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REVIEW

Genetics of coronary artery disease and myocardial infarction

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Abstract

Atherosclerotic coronary artery disease (CAD) comprises a broad spectrum of clinical entities that include asymptomatic subclinical atherosclerosis and its clinical complications, such as angina pectoris, myocardial infarction (MI) and sudden cardiac death. CAD continues to be the leading cause of death in industrialized society. The long-recognized familial clustering of CAD suggests that genetics plays a central role in its development, with the heritability of CAD and MI estimated at approximately 50% to 60%. Understanding the genetic architecture of CAD and MI has proven to be difficult and costly due to the heterogeneity of clinical CAD and the underlying multi-decade complex pathophysiological processes that involve both genetic and environmental interactions. This review describes the clinical heterogeneity of CAD and MI to clarify the disease spectrum in genetic studies, provides a brief overview of the historical understanding and estimation of the heritability of CAD and MI, recounts major gene discoveries of potential causal mutations in familial CAD and MI, summarizes CAD and MI-associated genetic variants identified using candidate gene approaches and genome-wide association studies (GWAS), and summarizes the current status of the construction and validations of genetic risk scores for lifetime risk prediction and guidance for preventive strategies. Potential protective genetic factors against the development of CAD and MI are also discussed. Finally, GWAS have identified multiple genetic factors associated with an increased risk of in-stent restenosis following stent placement for obstructive CAD. This review will also address genetic factors associated with in-stent restenosis, which may ultimately guide clinical decision-making regarding revascularization strategies for patients with CAD and MI.

Key words: Coronary artery disease; Myocardial infarction; In-stent restenosis; Genetics; Heritability; Genome-wide association study; Atherosclerosis

Core tip: This review provides the most comprehensive

summary of the genetics of coronary artery disease (CAD) and myocardial infarction (MI) research with a complete, up-to-date chromosomal map of all CAD and MI-susceptible genes. We discuss the existence and significance of protective genetic factors against atherosclerosis, CAD and MI. We also summarize the current status of constructing genetic risk scores to predict long-term risks of developing CAD and MI. In-stent restenosis is a new challenge in cardiology. The genetics of in-stent restenosis are also discussed in this article.

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INTRODUCTION

Coronary artery disease (CAD) remains the number one cause of death in industrialized society. CAD alone caused approximately 1 of every 6 deaths in the United States in 2010[1]. Atherosclerotic CAD comprises a broad spectrum of clinical entities that include asymptomatic subclinical atherosclerosis and its clinical complications, such as angina pectoris, myocardial infarction (MI) and sudden cardiac death. In the early 1930s, Carl Miller in Oslo reported the co-segregation of high plasma cholesterol, xanthoma and premature coronary heart disease, providing early clues regarding a genetic component of CAD and its association with cholesterol[2]. Family clustering of CAD and MI has subsequently been well recognized and documented. Large twin studies have estimated the heritability of CAD to be approximately 50% to 60%. Understanding the genetic basis of CAD and MI will not only provide insight regarding the pathogenesis of the disease but also a basis for the development of preventive and therapeutic strategies. Research investigating the genetic architecture of CAD has proven to be a difficult and costly task due to the heterogeneities of clinical CAD and MI and its multi-decade complex pathophysiological processes that involve both genetics and environmental factors and their interactions. Together with rapid advances in molecular technology and computational capacities in genetics and genomics, the recent decade has witnessed tremendous progress in genetic and genomic studies of CAD and MI. This article provides a comprehensive overview of the clinical heterogeneity of CAD and MI, which are often assessed in genetic studies; the heritability of CAD and MI; and achievements in gene discoveries related to CAD, MI, and in-stent restenosis. The development of a genetic risk score (GRS) based on genetic risk factors related to CAD and its initial success for predicting the life-long risk of CAD is also discussed.

HETEROGENEITY OF CAD

The heterogeneity of CAD and its clinical complications introduce significant complexity in genetic studies. Clinically, the presentation of atherosclerotic CAD ranges from completely asymptomatic (subclinical atherosclerosis), angina pectoris (typical or atypical, stable or unstable), and silent MI to acute myocardial infarction (AMI) or sudden cardiac death. The Framingham Heart Study (FHS) reported that one third of all MI are unrecognized[3]. Based on autopsy, up to 50% of sudden deaths are due to MI[4]. In addition to the broad spectrum of clinical presentations, the age of onset of clinical symptoms varies dramatically. The average age at the time of first MI is 64.9 years for men and 72.3 years for women[1]. Although AMI is not uncommon in young adults (< 40 years old), an initial diagnosis of severe atherosclerotic CAD in octogenarians is rather common and is often preceded by a long, asymptomatic disease state.

Coronary artery atherosclerosis is the most common underlying pathological process responsible for the majority of clinically significant CAD. Progressive narrowing of the arterial lumen due to negative remodeling and expansion of the atheroma causes myocardial ischemia and angina pectoris. The rupture of a vulnerable atherosclerotic plaque, local activation of thrombotic mechanisms with/without severe underlying stenosis, local thrombosis formation and arterial lumen closure are accepted as underlying mechanisms of AMI. Coronary embolization of the thrombus, spontaneous coronary dissection, myocardial bridging, an anomalous origin and course of coronary artery, and coronary spasm can cause clinical symptoms/presentations that are similar to those of AMI. In addition, some unusual clinical scenarios may cause coronary insufficiency and myocardial ischemia, such as adjacent tumor compression of coronary arteries and systemic vascularitis involving coronary artery beds. In addition, the locations of atherosclerotic stenosis along the coronary tree vary significantly. Isolated aorto-ostial stenosis (ostia of the left main or right coronary artery) and bifurcation lesions are more apparent in relation to turbulent flow and the endothelial response to the flow dynamics. Diffuse atherosclerosis is more commonly observed in patients with diabetes mellitus (DM). The heterogeneity of the location of CAD within the coronary tree may reflect a different set of genetic influences on atherogenesis. The location-dependent effects of PECAM-1 on atherogenesis in animal models have been reported[5], and the results suggest that the heterogeneity of the location of atherosclerotic CAD may represent different genetic influences of atherosclerosis under different dynamic flow conditions.

These heterogeneities of phenotypic characterization, pathological etiologies of CAD and MI and the complex molecular and cellular pathogenesis of atherosclerosis (summarized in Table 1) contribute to the difficulties associated with the identification of genes that are

Table 1 Heterogeneities in coronary artery disease/myocardial infarction

Clinical manifestation	Underlying pathology	Pathological processes of atherosclerosis
Asymptomatic stenosis	Atheroma positive remodeling	Endothelial injury
Stable or unstable angina pectoris	Atheroma negative remodeling	Lipid deposition
Silent MI	Plaque rupture/thrombosis	Oxidative stress/response
Acute MI (NSTEMI and STEMI)	Critical stenosis/thrombosis	Inflammation
Sudden cardiac death	Embolization	Cellular proliferation/apoptosis
	Spontaneous dissection	Foam cell formation
	Anomalous origin/course	Matrix deposition/degradation
	Coronary spasm	Plaque rupture/hematoma/thrombosis
	Myocardial bridging	Neovascular formation

MI: Myocardial infarction.

important for CAD and MI[6].

HERITABILITY OF ATHEROSCLEROTIC CAD

Clinical and population-based studies have demonstrated that genetic factors play important roles in CAD and MI. The phenomenon of family clustering of CAD was repeatedly reported in the 1950s and 1960s[7,8]. Slack and Evans demonstrated that a history of early onset ischemic heart disease (IHD) of first degree relatives was significantly associated with and predicted early onset IHD (< 55 in men and < 65 in women)[9]. The subsequent FHS confirmed that a family history of premature CAD, defined as the presence of a first degree relative with a diagnosis of CAD at < 55 years of age in men and < 65 years of age in women, is an independent risk factor for CAD[10]. The strength of hereditary in determining the risk of CAD increases with an increasing number of affected first-degree relatives and with a younger age of onset[11]. In a multivariate analysis, the extent of CAD based on coronary angiography was also strongly associated with the history of parental CAD independently of plasma lipids, obesity, hypertension, cigarette smoking and alcohol intake[12-15].

Twins have fascinated human communities and provided invaluable opportunities to identify the genetic component of diseases. Identical twins who concordantly develop early onset, angiographically proven CAD, in whom many of the same coronary arteries are even involved, provide highly suggestive information regarding the influence of genetics on CAD[16-20]. Early in 1967, Cederlöf *et al*[21] observed a concordance of 21.7% of CHD history in monozygotic twins, as compared with 6.1% in dizygotic twins. The Swedish Twin Registry and Danish Twins Registry are the two largest twin registries in the world. The Swedish Twin Registry has captured all of the twins born since 1886 and includes 20966 twins. A longitudinal follow-up of 36 years found that if one twin died of CAD, the relative risk of the development of fatal CAD in the second twin was 8.1 for monozygotic twins (MZ, identical twin)[22] and 3.8 for dizygotic twins (DZ, non-identical twin). The estimated heritability of CAD is 57% (50%-59%) in male twins and 38% (25%-50%) in female twins[23]. The influence of genetics is evident across the age range of 36 to 86 years. The Danish Twins Registry (8000 twin pairs) reported an increased incidence of CAD and CAD deaths in MZ twins of subjects with CAD compared with DZ twins (44% *vs* 14%), with an estimated heritability of 0.53 in males and 0.58 in females[24]. In general, CAD is widely accepted to have a heritability of 50% to 60%.

Large-scale prospective, population-based epidemiology studies, such as the Western Collaborative Group Study[25], Health Professional follow-up study[26], the Nurses' Health Study[27], the FHS[10], the British Regional Heart Study[28], the German PROCAM study[29], and the Utah Cardiovascular Genetic Research[30], confirmed the strong independent association among family, parental history of CAD and MI and the occurrence in offspring[31,32]. These genetic factors are independent of traditional risk factors (TRF) for the disease. TRFs, such as hypertension, diabetes mellitus, hypercholesterolemia, low physical activity, obesity, C-reactive protein, plasma homocysteine, and tobacco use are well known to have their own complex genetic components with individual heritability values that have been estimated in twin studies[33]. Figure 1 illustrates the contribution of genetic factors directly or through TRFs in the development and manifestation of CAD. The collective effects of genetic factors, environmental factors, and age determine the development of atherosclerotic CAD and its complications.

GENE DISCOVERY FOR CAD AND MI

Early candidate gene and linkage analyses have identified numerous causal genes and mutations that underlie rare, Mendelian monogenic CAD. Many of these genes and mutations are involved in lipid metabolism. Recently, a combination of a large pedigree of familial CAD and high-throughput genomic sequencing technology led to the discovery of a panel of new possible causal gene mutations for CAD. Table 2 summarizes the genes and mutations that are considered to be causal for atherosclerotic CAD.

Table 2 Genes and mutations identified as causal for monogenic familial coronary artery disease

Categories	Genes	Chrom	OMIM	Mutations	Ref.	GWAS[1]
Monogenic *CAD* genes	*ST6GALNAC5*	1p31.1	610134	G295A (p.*337Qext*20 stop-loss)	[52]	No
	CYP27A1	2p35	606530	G674A (p. Arg225His)	[51]	No
	MEF2A	15q26.3	608320	21-bp del in exon 11	[34,38]	No
	LRP6	12p13.2	610947	G1079A (p. Arg611Cys) T1298C (p. Asn433Ser)	[44,159]	No
Gene mutations cause high LDL	*LDL receptor*	19p13.2	606945	> 1000 variants	[55]	Yes
	PCSK9	1p32.3	603776	9 gain-of-function mutations	[63]	Yes
	ApoB-100	2p24.1	144010	C10580G (p. Arg3527Gln) C10800T (p. Arg3531Cys) rs515135	[59,60,84]	Yes
	LDLRAP1, ARH	1p36.11	603813	ARH1: 432 ins A (p. FS170stop) ARH2: G65A (p. Trp22ter)	[66]	No
Mutations cause low HDL	*ABCA1*	9q31.1	205400	Many ABCA1 LoF alleles Rs2230806 > A	[78,158]	Yes
	LCAT	16q22.1	606967	> 80 mutations Rs5923 ↑ CAD in Egyptians	[160]	Yes
Mutations cause high TG	*Apo C-II*	19q13.2	207750	ApoCII$_{St. Michael}$ p. Gln70Pro	[85,86]	No

[1]The association between the genetic variant and the risk of CAD and MI is also discovered in GWAS. GWAS: Genome-wide association studies; CAD: Coronary artery disease; MI: Myocardial infarction; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; TG: Triglyceride; OMIM: Online Mendelian Inheritance in Man.

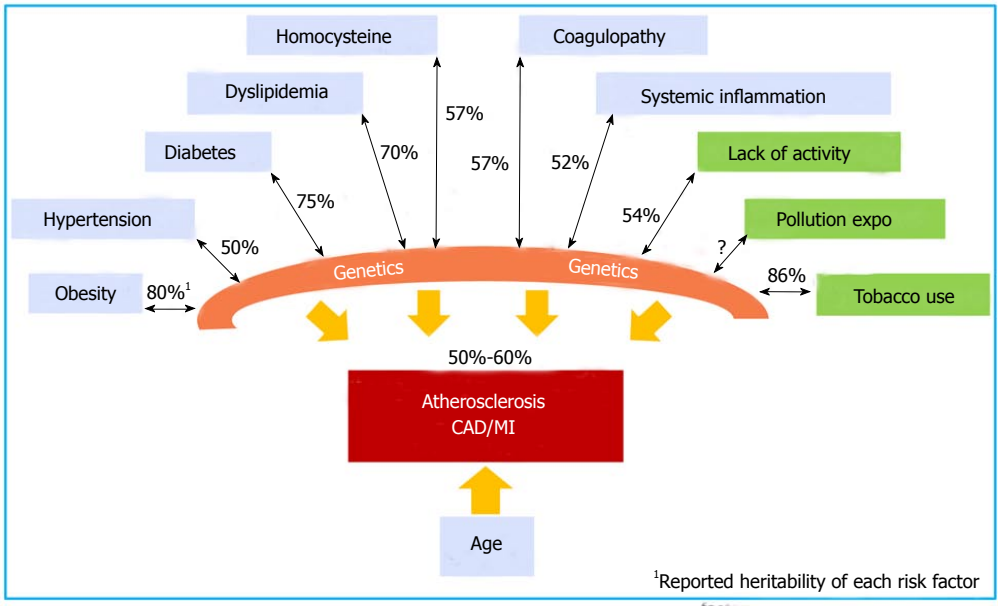

Figure 1 Atherosclerosis is a multi-decade pathological process involving complex interactions between genetics and environmental factors. The estimated heritability of CAD and MI is 50% to 60%. The heritability of each individual risk factor is indicated as a %. CAD: Coronary artery disease; MI: Myocardial infarction.

Monogenic CAD genes

Despite the clinical heterogeneity of CAD and MI as described above, the phenomenon of familial clustering of CAD and collections of large pedigrees with multiple members in multiple generations provided an opportunity to perform linkage analysis and gene discovery. In recent years, three potential causal genes and their responsible mutations for pedigrees with apparent Mendelian autosomal dominant (AD) CAD and MI have been identified (below and Table 2). The common feature of these mutations is co-segregation with the phenotype in the index kindred and a presence in unrelated cohorts. Functional analyses of these genes also supported their potential involvement in the pathogenesis of CAD and MI. However, the potential roles of these familial CAD causal genes and mutations in general population are unknown. Further validation with additional pedigrees and experimental models is warranted.

MEF2A: MEF2A is a transcription factor that belongs to the monocyte enhancer factor (MEF) family. MEF2A is expressed in blood vessels during embryogenesis as an early marker of vasculogenesis and interacts with a variety of molecules that are known to be involved in cardiovascular pathogenesis. Wang *et al*[34] performed a

genome-wide linkage analysis of a large kindred group consisting of 13 individuals and designated the first AD *CAD* gene (adCAD1) at chromosomal location 15q26 within a region containing approximately 93 genes including *MEF2A*. Considering the relevance of MEF2A in vasculogenesis, sequencing of the *MEF2A* gene revealed a 21-base pair deletion in exon 11 of the *MEF2A* gene that was present in all 10 affected living members but not in unaffected individuals[34]. This D7aa *MEF2A* mutation co-segregated with the CAD phenotype in an AD manner in the index pedigree. Interestingly, the same exon 11 deletion in *MEF2A* was reported in other CAD individuals from different ethnic backgrounds[35-37]. Missense mutations in exon 7 of *MEF2A*, resulting in a loss-of-function of MEF2A, were also found in premature CAD individuals, but not in age-, ethnicity- and BMI-matched controls lacking angiographic evidence of CAD[38,39]. Further studies have demonstrated that the deletion of 7 amino acid leads to defective trafficking of MEF2A in a dominant-negative manner. Consequently, MEF2A entry into the nucleus is blocked, which is crucial for the ability of MEF2A to regulate gene expression. It is plausible that functional abnormalities in D7aa MEF2A lead to cellular abnormalities in endothelial cells and vascular smooth muscle cells, which in turn participate in processes associated with atherogenesis. The discovery of the mutation in *MEF2A* in CAD resulted in significant hope of genetic testing for CAD. However, conflicting reports demonstrating the lack of an association between *MEF2A* gene mutations and CAD in other cohorts has raised doubts concerning a causal role of *MEF2A* in CAD[40-42]. In particular, two individuals carrying the D7aa *MEF2A* mutation did not appear to have CAD before the reported age of CAD development, while members of the same family who developed CAD carried the normal *MEF2A* gene[41]. However, potential genetic or environmental modifiers may reduce the phenotypic penetration. Polymorphisms that do not change *MEF2A* transcriptional activation are not associated with an increased risk of CAD[43], and the actual prevalence of functional *MEF2A* mutations in the general population is not yet known.

Low-density lipoprotein receptor-related protein 6: Mani *et al*[44] studied a group of extreme outlier kindred with an extraordinary prevalence of premature CAD presenting an almost uniform presence of hypertension, hypercholesterolemia, type Ⅱ DM, obesity and an absence of cigarette smoking in affected individuals. The extreme familial clustering and segregation of phenotypes (both premature CAD and risk factors) was transmitted as a highly penetrant AD trait[44]. Genome-wide linkage analysis revealed strong linkage between the familial trait and markers of chromosome 12p, which spans 750 kb and contains only six annotated genes [*ETV6, BCL2L14,* low-density lipoprotein receptor-related protein 6 (*LRP6*), *MANSC1, LOH12CR1* and *DUSP16*]. Sequencing of the candidate gene *LRP6* revealed the causal variant, a missense substitution of R611C in a conserved EGF-like domain of LRP6. LPR6 functions as a co-receptor with Frizzle proteins for Wnt ligands. Functional studies of the *LRP6*$_{R611C}$ mutation revealed a dominant-negative decrease in Wnt signaling. Although there was complete linkage of LRP6$_{R611C}$ and hypertension, high low-density lipoprotein (LDL), TG and a prevalence of DM2 in the index kindred, the frequency of *LRP6*$_{R611C}$ was very rare in general population. Recently, a polymorphism in *LRP6* intron 2 was found to be associated with the presence and severity of angiographic CAD in a Chinese case-control study[45]. A common variant of *LRP6*, rs2302685 (a non-synonymous coding sequence SNP in exon 14, T>C, p Ile1062Val), was initially found to be associated with late-onset Alzheimer's disease in Caucasians[46] followed by carotid artery atherosclerosis[47] and, very recently, CAD[48]. Ilr1062Val variant reduces Wnt/β-catenin signaling and anti-apoptotic activities in cultured cells and arterial walls. Additional missense mutations in the *LRP6* gene that correlate to its extracellular domain have been identified by the sequencing of exons and the promoter of *LRP6* in premature CAD patients and controls in different Chinese cohorts. All of these missense mutations cause loss of function (LoF) *via* reduced Wnt signaling activity and attenuated human umbilical vein endothelial cell proliferation *in vitro*[48].

CYP27A1: A large pedigree with well-defined familial traits together with massive parallel sequencing technology and bioinformatics computational and statistical tools has dramatically accelerated the pace of the discovery of disease-causing genes[49]. The identification of potential causative mutations in the *CYP27A1* gene that co-segregated with a familial AD CAD phenotype is one recent example. Inanloorahatloo *et al*[50] performed whole-exome sequencing of two affected members in a large group of AD kindred with premature CAD. An *in silico* un-biased algorithm identified two candidate variants, c. G674A (p. Arg225His) in *CYP27A1* and c. A241T (p.Ile81Phe) in NTRK2, which were further sequenced in all of the available members of the kindred. The variant c.G674A (p. Arg225His) in *CYP27A1* co-segregated with the CAD status. The *CYP27A1* gene encodes the sterol 27-hydroxylase involved in cholesterol and 25-hydroxy vitamin D3 synthesis. The amino acid p. Arg 225 that was affected by the identified variant is highly conserved in paralogous and orthologous proteins, suggesting its functional importance. This variant was not observed in 500 ethnically matched controls without a history of cardiac disease. Furthermore, an additional four disease-specific variants in the *CYP27A1* gene were discovered by sequencing the *CYP27A1* exons in 7 out of 100 unrelated CAD patients. Although disease-causing variants of the *CYP27A1* gene were considered relatively rare, potential disease-causing variants reached up to 7% in Iranian patients with CAD. To date, potential CAD-causing *CYP27A1* variants have not been reported in other populations, and the prevalence of

these variants in the general population is unknown. The mechanism underlying the possible causal role of mutant *CYP27A1* in atherosclerotic CAD remains uncharacterized. Recently, *CYP27A1*-deficient mice in an ApoE-deficient background exhibited a 10-fold reduction of aortic atherosclerosis after challenge with a high-fat diet associated with a 2-fold reduction of total plasma cholesterol, LDL, and very low-density lipoprotein (VLDL) as well as a 2-fold elevation of high-density lipoprotein (HDL). These results suggested that CYP27A1 regulates cholesterol homeostasis, and alterations of its activities may subsequently lead to atherosclerosis[51].

ST6GALNAC5: The *ST6GALNAC5* gene is the newest addition to the group of causal genes for familial CAD. InanlooRahatloo *et al*[52] studied a highly inbred Iranian pedigree of AD premature CAD. Unbiased GWAS combined with whole-exome sequencing of two affected members identified a polymorphism, G295A, in the *ST6GALNAC5* gene that resulted in a p. Val99Met mutation. Targeted sequencing of all of the available members confirmed the co-segregation between this variant and the CAD phenotype. A search of *ST6GALNAC5* mutations in other Iranians with confirmed CAD revealed a p.*337Qext*20 mutation in two unrelated patients with CAD (2 out of 160). Interestingly, one of the patients who carried this p.*337Qext*20 stop-loss mutation had one sibling with CAD and two unaffected siblings; a genetic analysis of the family again showed co-segregation of the mutation with disease status. *ST6GALNAC5* encodes sialyltransferase 7e, a member of the sialyltransferase family. Sialyltransferases add sialic acids (acetylated derivatives of neuraminic acid) to the termini of carbohydrate chains in glycoproteins and glycolipids. Elevated sialyltransferase activity in blood cells and serum sialic acid levels[53] are associated with atherosclerosis and CAD. *In vitro* functional studies of proteins encoded by these two mutated *ST6GALNAC5* genes revealed a two-fold increase in sialyltransferase 7e enzymatic activity[52]. Given that: (1) an un-biased approach was applied in the identification of the *ST6GALNAC5* mutation in a large CAD pedigree; (2) convincing evidence demonstrates the co-segregation of the *ST6GALNAC5* mutation with the familial CAD/MI phenotype; (3) additional functional mutations have been identified in the *ST6GALNAC5* gene in unrelated CAD/MI patients and families; (4) no functional variations were identified in affected family members and unrelated controls; and (5) the available evidence supports the notion that sialic acid and sialyltransferase activity are involved in the pathogenesis of atherosclerotic arterial disease, it is reasonable to conclude that gain-of-function mutations in ST6GALNAC5, such as p. Val99Met and p.*337Qext*20, are monogenic causal genes for CAD. The prevalence of functional *ST6GALNAC5* gene mutations in the general population and in patients with CAD is unknown. The mechanism by which mutant ST6GALNAC5 causes atherosclerosis and CAD and its potential role in targeted therapy or in the prevention of CAD remain unknown.

Monogenic lipid disorders

Serum lipid levels, particularly elevated LDL cholesterol and HDL, are important risk factors for the development of atherosclerotic CAD. Mutations in genes involved in lipid metabolism have been identified and demonstrated to be causal for dyslipidemia and related atherosclerotic CAD and MI with variable penetration. These genes and their mutations in association with CAD and MI have been extensively reviewed in the literature[54] and are presented in Table 2. Depending on the primary abnormality in lipid metabolism and its effects on CAD, monogenic lipid disorders can be categorized into primary elevated LDL (LDL receptor, ApoB-100, PCSK9, and LDLRAp or ARH), a primary reduction of HDL (ApoA1 in primary hypoalphalipoproteinemia, ABCA1 in Tangier disease, and the lecithin:cholesterol acyltransferase (*LCAT*) gene in Norum disease and Fish-Eye disease), and primary elevated triglycerides (TGs) (LPL, ApoC-Ⅱ in type Ib hyperlipoproteinemia and the *ABCG5/8* gene in Sitosterolemia).

Genes and variants that are the primary cause of high LDL cholesterol: Mutations in genes encoding the LDL receptor, apolipoprotein B-100 (an LDL receptor ligand) and the pro-protein convertase subtilisin kexin type 9 (PCSK9) cause AD familial hypercholesterolemia (FH). Patients who harbor homozygous [low-density lipoprotein receptor (LDLR)] mutations (1 in 1 million) display a 6- to 10-fold increase in plasma LDL-C from birth and experience CAD/MI in early childhood. The early atherosclerosis observed in children who are homozygous for FH is not associated with any other risk factors that suggest that elevated LDL alone can produce atherosclerosis in humans. Carriers of heterozygous LDLR mutations, demonstrating a frequency of 1/500 in the general population, display a 2-fold increase in low-density lipoprotein cholesterol (LDL-C) levels from birth and are at risk to suffer CAD and MI at 30s years of age. Approximately 5% patients with CAD and MI under the age of 60 years carry heterozygous LDLR mutations. A total of 1741 sequence variants (1122 unique variants) have been recorded in the British Heart Foundation LDLR database[55] (http://www.ucl.ac.uk/ldlr/Current/summary.php?select_db=LDLR&show=sum). These mutations are present in the form of exonic substitutions, small exonic rearrangements, large rearrangements, promoter variants, intronic variants, variant sin the 3' untranslated sequence, point mutations, splice site mutations, and large deletions. These mutations are equally distributed throughout the gene[56,57]. Genetic testing of all known LDLR variants is available. This test is often considered as the first step in a stepwise genetic analysis for FH followed by tests to assess the *ApoB-100* and *PCSK9* genes[58].

Apo B-100 is a unique protein component in lipoproteins originating from the liver (VLDL, IDL, and LDL). Apo B-100 is also required for the synthesis, assembly, and secretion of hepatic TG-rich lipoproteins, and it binds to heparin and various proteoglycans found in arterial walls. The most important function of Apo B-100 is to bind the LDLR *via* its LDLR-binding domain to mediate the clearance of LDL from plasma. Two mutations in the *Apo B-100* gene, C10580G (p. Arg3527Gln)[59] and C10800T (p. Arg3531Cys), result in the alteration of LDLR binding affinity. In addition, these mutations cause familial ligand-defective hypercholesterolemia (OMIM 144010) and are associated with early atherosclerotic arterial disease[60]. The frequency in the unselected general population of the Arg3527Gln and Arg3531Cys mutations is approximately 1 in 500 and 1 in 3000, respectively. Most recently, by taking advantage of whole-exome sequencing and linkage analysis of an AD hypercholesterolemia pedigree, a third mutation (p. Arg50Trp) was identified[61].

Linkage analysis of two large French ADH pedigrees resulted in the identification of two mutations in the *PCSK9* gene (1p34.1-1p32), which encodes a protein that is also known as a neural apoptosis-regulated convertase 1 (NARC-1)[62]. A total of 9 gain-of-function mutations in *PCSK9* genes in families with ADH have been reported[63]. These mutations cause a decreased number of LDLR, elevated levels of serum total and LDL cholesterol, and phenotypes of tendon xanthomas, premature CAD, MI and stroke. SNP rs11206510 (risk allele T) located in the *PCSK9* gene is also associated with an increased risk of CAD and MI in an unbiased GWAS study[64]. However, loss-of-function mutations in *PCSK9* identified by exome sequencing of individuals with extremely low LDL levels in the Atherosclerosis Risk in Communities study (ARIC) and Dallas Heart Study cohorts revealed that these mutations led to hypocholesterolemia and were protective against CAD and MI[65]. Secreted PCSK9 protein functions as an LDLR chaperone, binds to the EGF-A domain of the LDLR, decreases receptor recycling to the cell surface and promotes lysosomal degradation. Although the contribution of the PCSK9 gain-of-function mutation in ADH is rather small (< 3%), elucidation of the PCSK9 gain-of-function in ADH has shed light on the potential for the development of cholesterol-lowering agents by reducing the circulatory level of PCSK9 (PCSK9 inhibitors). These discoveries have resulted in the development of PCSK9 inhibitors as novel cholesterol-lowering agents.

Approximately 50 individuals of Mediterranean or Middle Eastern origin carry homozygous mutations in the autosomal recessive hypercholesterolemia (*ARH*) gene. *ARH* (1p34-1p35) was subsequently cloned and named LDL receptor adaptor protein 1 (LDLRAP1), which encodes a phosphotyrosine-binding domain protein and is required for LDLR internalization in hepatocytes. Two mutations, 432insA in exon 4 causing FS170Stop (*ARH1*) and the nonsense mutation G65A in exon 1 (p. trp22ter), account for most of the known cases of ARH in Sardinia[66]. The third mutant was a result of an ancient recombination between *ARH1* and *ARH2*. In addition, 4 Italian ARH individuals from the mainland carried homozygous *ARH1*. Overall, ARH mutations are rare[67].

Genes and variants that are primary causes of low HDL cholesterol: Approximately 40% of patients with CAD have a low level of high-density lipoprotein cholesterol (HDL-C; < 40 mg/dL per current guidelines or age and sex-adjusted plasma HDL-C levels below the 10th percentile). Prospective cohort studies also suggest that low HDL-C is a significant, independent risk factor for CAD. An estimated 50% to 70% of the variations in HDL-C in the human populations are due to genetic factors, and the majority remain undefined[68].

Apolipoprotein A1 (Apo AI) is the major apolipoprotein in HDL-C and is a key determinant of the levels and metabolism of HDL-C. Apo AI functions as a cofactor for LCAT, which is responsible for the formation of most cholesterol esters in the plasma. Apo AI also promotes the efflux of cholesterol from cells. *ApoAI* mutations cause AD familial hypoalphalipoproteinemia. The homozygous loss of *ApoAI* leads to a complete absence of Apo AI and HDL-C levels < 5 mg/dL with normal LDL-C and TG levels. Heterozygous LoF Apo AI carriers have HDL-C levels that are approximately 50% less than normal HDL-C levels. ApoAI gene polymorphisms are associated with decreased HDL and an increased risk of premature CAD[69]. Yamakawa-Kobayashi *et al*[70] analyzed sequence variations in the *ApoAI* gene in Japanese children with low levels of HDL (below the first percentile in the general population) and found 3 frameshift and 1 splice site mutation with possible deleterious effects. They estimated the frequency of hypoalphalipoproteinemia due to *ApoAI* mutations to be 6% in subjects with low HDL cholesterol and 0.3% in the general Japanese population[70]. The A164S variant of the *ApoAI* gene identified by sequencing of the *ApoAI* gene in 190 Copenhagen City Heart Study participants predicts an increased risk of IHD [hazard ratio (HR) 3.2, 95%CI: 1.6-6.5], MI (5.5, 95%CI: 2.6-11.7) and overall mortality (2.5, 95% CI: 1.3-4.8). Despite comparable levels of plasma lipids and lipoprotein, including HDL-C and *ApoAI*, in A164S heterozygotes, heterozygous A164S carriers exhibit a decrease in survival by more than 10 years ($P < 0.0001$) compared with non-carrier controls[71,72]. In addition, two *ApoAI* variants (*ApoAI$_{Paris}$* and *ApoAI$_{Milano}$*) were associated with a reduced risk of CAD, suggesting the occurrence of cardioprotective effects[73].

The ATP-binding cassette transporter (ABCA1) is involved in the initial phase of reverse cholesterol transport and the egress of free intracellular cholesterol and phospholipids from extrahepatic cells. Homozygous LoF *ABCA1* variants are causal factors for the rare Tangier disease, which results in extremely low HDL-C

levels, a 40% reduction of LDL-C compared with the general population, and an increased risk of early CAD[74,75]. A total of 200 LoF mutations in the *ABCA1* gene have been reported (http://www.hgmd.cf.ac.uk/ac/gene.php?gene=ABCA1, last accessed on August 6, 2014). Heterozygous carriers of the ABCA1 mutation exhibit an approximately 50% reduction in HDL-C without alterations in the levels of LDL-C and an increased risk of premature CAD[76]. The frequency of heterozygous carriers of *ABCA1* mutations is estimated as approximately 3:1000 in the general population[77]. The R219K polymorphism in the *ABCA1* gene is associated with a reduced risk of CAD, suggesting that this polymorphism provides protective effects against the disease[78].

LCAT catalyzes the esterification of free cholesterol with acyl groups derived from lecithin as an essential step in the maturation of HDL-C. Homozygous LoF in the *LCAT* gene causes rare autosomal recessive Norum disease with very low HDL (< 5th percentile), elevated TGs and decreased LDL-C. Greater than 80 genetic variants in the *LCAT* gene have been identified and reported to be associated with 29% of the individuals with low levels of HDL-C in the Netherlands[79]. However, the association between low levels of HDL-C caused by *LCAT* deficiency and an increased risk of CAD is not as certain as the associated risk of ApoAI[80]. This phenomenon may be explained by the observation that LCAT deficiency mainly causes decreased levels of ApoAII. HDL particles containing ApoAI, but not ApoAII, possess "anti-atherogenic" effects.

Genes and variants that are primary causes of elevated TGs: Plasma TGs predominantly occur in the form of intestinally synthesized chylomicrons (CMs), remnants in the postprandial state and hepatically synthesized VLDL in the fasted state. Plasma TG levels are a polygenic trait and is influenced by environmental factors and lifestyles, *i.e.*, diet, physical activities and tobacco use. Large epidemiological studies have demonstrated that plasma TG concentrations are a strong independent risk factor for CAD[81].

Lipoprotein lipase (LPL) is the rate-limiting enzyme in converting VLDL to LDL. Homozygous LoF mutations in *LDL* genes cause LPL deficiency in rare (approximately 1 in a million) AR type Ⅰ hyperlipoproteinemia characterized by marked hypertriglyceridemia with a decrease in HDL and LDL, eruptive xanthoma, hepatosplenomegaly, recurrent pancreatitis, and in some cases, premature atherosclerotic arterial disease. Greater than 100 LoF variants have been identified[82]. Sequencing data have suggested that rare LPL variants are actually common in patients with elevated TG levels[83]. Variants of LPL genes that are negatively associated with plasma levels of TG, positively associated with HDL and inversely associated with a risk of CAD have also reported, suggesting potential protective genetic variants against CAD[84]. ApoC-Ⅱ is an activator of LPL. A homozygous LoF ApoC-Ⅱ deficiency results in rare AD type Ⅰb hyperlipoproteinemia with extremely elevated TG and chylomicron levels in the plasma, causing recurrent pancreatitis and, in some cases, ApoCII$_{St.\ Michael}$ (Gln70Pro)[85] and other conditions[86], leading to premature ischemic vascular disease. The significance of these mutations in general population remains to be explored.

Sitosterolemia is characterized by hyperabsorption and the retention of dietary cholesterol and sterols, including plant and shellfish sterols, leading to high levels of plant sterols in the plasma, the development of tendon and tuberous xanthomas, accelerated atherosclerosis, and premature CAD. LoF mutations in ABCG5 (encoding sterolin-1) and ABCG8 (encoding sterolin-2) cause sitosterolemia. All of the probands identified in the sitosterolemia pedigree have homozygous mutations in either ABCG5 or ABCG8[87]. The prevalence of ABCG5 and ABCG8 heterozygous carriers and their effects on cholesterol metabolism and atherosclerotic disease in the general population remain unclear.

Genes and polymorphisms associated with CAD

Monogenic traits and their causal genetics only explain a small proportion of the genetics of CAD and MI. Prior to the completion of human genome sequencing, *CAD* and *MI* gene discovery largely employed pedigree-based linkage analysis and positional cloning with the limited availability of genomic markers. The Human Genome Project, HapMap project, and 1000 Genomes Project provided a reference of 3.2 billion nucleotide base pairs of the human genome and 3 million single nucleotide polymorphisms (SNPs) distributed throughout the genome. These SNPs serve as high-density genomic markers for the entire genome. The developments of high-density microchips containing millions of SNPs, high-throughput analytic technology, and powerful biostatistics data mining tools have permitted genome-wide association studies (GWAS). GWAS is a non-hypothesis-driven, unbiased analysis of the potential associations between traits of interest (disease, phenotypes, *etc*.) and genomic markers (SNPs) consisting of tens of thousands of cases and controls[88]. In 2007, SNPs located in 9p21 were identified as strongly associated with CAD and MI based on the results of four nearly simultaneous publications. Numerous GWAS studies have been subsequently conducted, involving tens of thousands of CAD and MI cases and controls inclusive of a large spectrum of demographic, geographic and ethnic backgrounds. The largest meta-analysis of GWAS data reported by the CARDIoGRAMplusC4D Consortium included a total of 63746 CAD cases and 130681 control subjects and confirmed/identified 46 CAD susceptibility loci[84]. Together with a 6q21 locus that was identified in the Chinese Han population by Wang *et al*[89] and an additional 3 CAD susceptibility variants identified by IBC 50K[90], which were not confirmed in the CARDIoGRAMplusC4D Consortium study, a total of 50 GWAS-identified CAD susceptibility genomic loci were

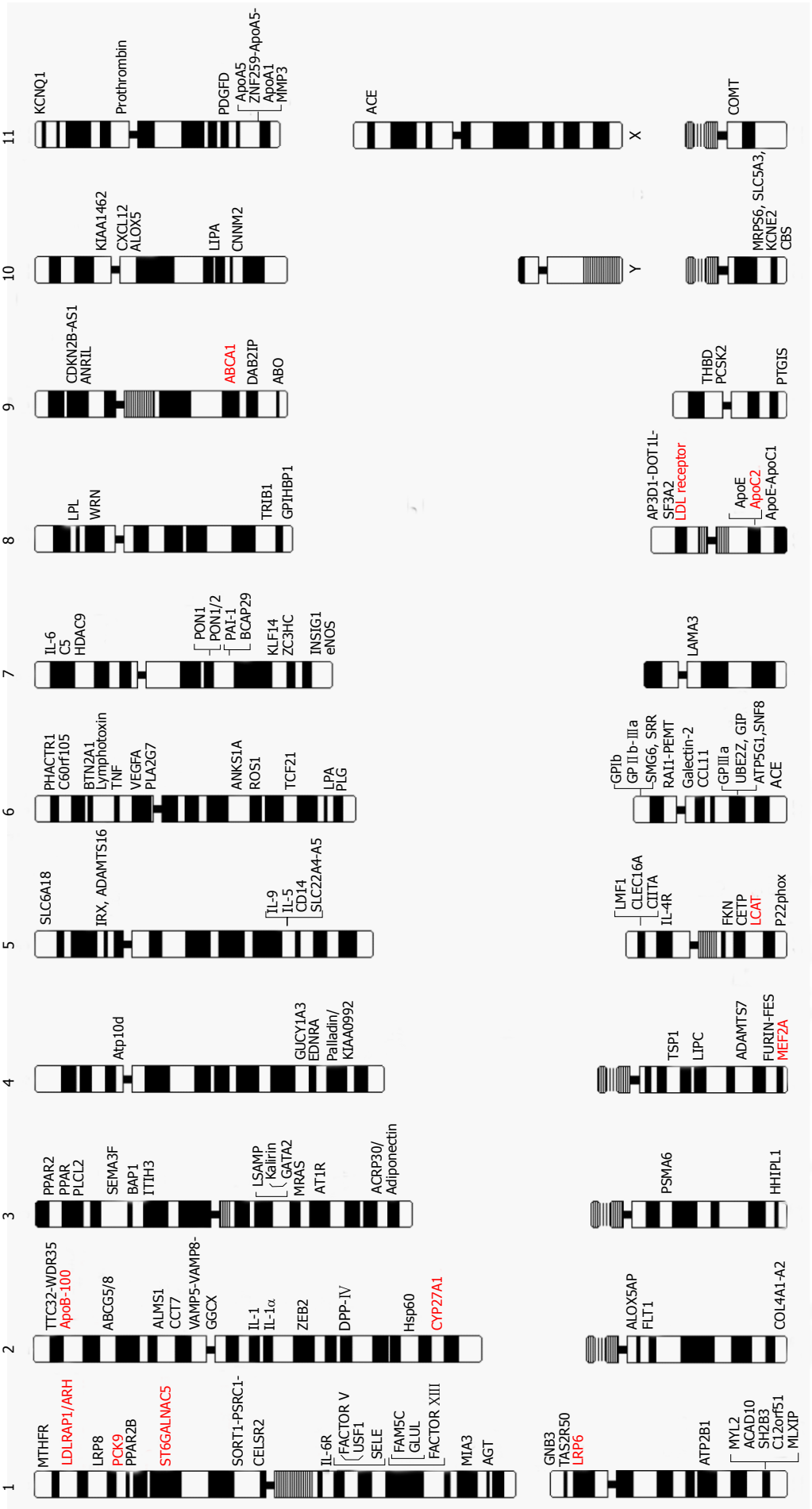

Figure 2 Chromosome map of genes reported to be causal for, susceptible to and associated with coronary artery disease and myocardial infarction in the literature. Genes in red are causal genes for monogenic familial CAD and MI. CAD: Coronary artery disease; MI: Myocardial infarction.

reported. Recent reviews have focused on GWAS discovery of CAD and MI susceptibility loci[91-95].

The journey to understand genetic/genomic architecture of CAD and MI continues with steady progress. Figure 2 provides a complete map of the genes and loci that are reported in literature to be causal for, susceptible to, or associated with the risk of CAD and MI identified by either linkage analysis and/or association analyses with

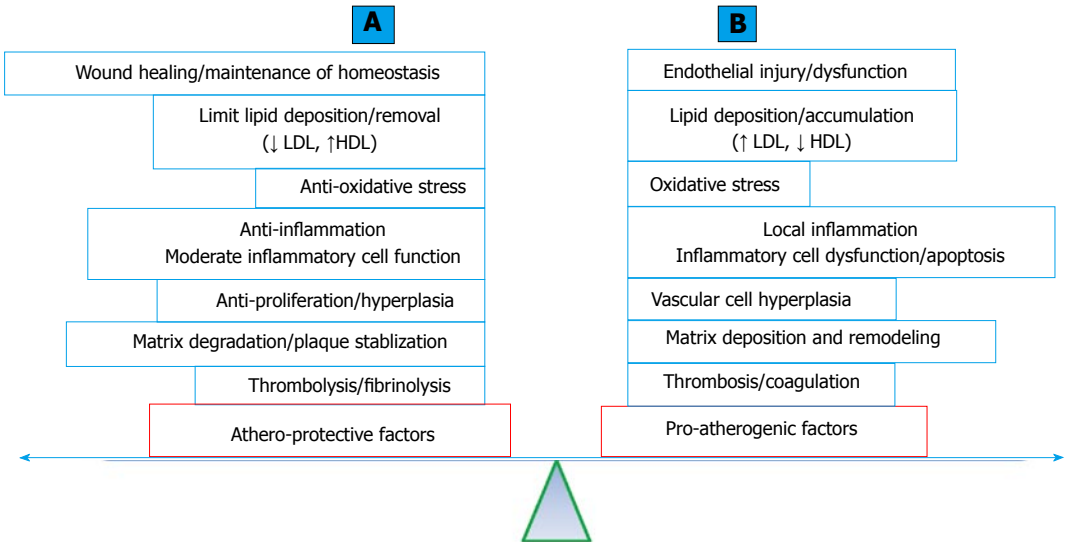

Figure 3 The balance between athero-protective (A) and pro-atherogenic (B) factors involved in the development of atherosclerosis. Obstructive atherosclerotic arterial disease results from the loss of balance between these two factors. A: A list of factors and processes that provide protective effects against atherogenesis; B: A list of factors and processes that promote atherogenesis. HDL: High-density lipoprotein; LDL: Low-density lipoprotein.

either candidate-gene or genome-wide approaches. The genes and mutations that are potentially causal for monogenic CAD and MI families are also presented in Table 2.

Post-GWAS challenges in CAD genetics

The ultimate goals of the study of the genetics of CAD and MI are to reveal genes and their products involved in the development of CAD and MI, understand the molecular and cellular pathophysiology and subsequently establish risk stratification strategies to direct prevention and also develop effective therapeutic approaches. Despite the total of 147 genes (Figure 2) with variants that are causative for or associated with CAD and MI, these genes only explain less than 20% of the heritability of CAD and MI. Furthermore, the biological functions and pathophysiological roles of most of the gene variants and genomic loci are not fully understood. Early attempts to use genetic risk markers of CAD to predict long-term outcomes were not successful, and many challenges remain before the ultimate goal of understanding the genetics of CAD can be realized.

Searching for unexplained heritability: GWAS is based on the hypothesis of a "common disease, common variant". The sensitivity of GWAS in detecting a significant association between genetic variants and traits is limited to high frequency variants (5%)[96]. Regarding CAD and MI, most of the GWAS-identified variants individually or in combination confer relatively small increments in risk (1.1- to 1.5-fold) and explain only a small proportion of heritability. The well-recognized sources for the missing heritability of complex traits[97-99] include: (1) larger numbers of variants with a smaller effect that remains to be identified; (2) a low minor allele frequency (0.5%-5%) or rare variants (< 0.5%) with a larger frequency that are not detectable using the available arrays; (3) structural variants (*i.e.*, copy number of variants due to insertion or deletions, inversions, or translocation) are poorly captured by SNPs; (4) a low power to detect gene-gene interactions; and (5) an inability to detect gene-environment interactions using the current GWAS methodology. Strategies have been suggested and explored to overcome these pitfalls, including: (1) analyzing phenotypically well-defined cases and controls[100], increasing the numbers of participants[84], and utilizing extreme phenotype groups[54,101]; (2) developing powerful biostatistics tools to enrich the signal and detect sensitivities and to capture the additive effects of variants, gene-gene interactions and rare variants[102,103]; (3) integrating available functional information, *i.e.*, eQTLs, protein structure/function predictions, and known pathways and networks related to the traits, to prioritize GWAS signals[104] and performing integrative analyses[105]; (4) customizing fine mapping SNPs or use next-generation sequencing regions of interest to capture rare variants and structural variants; and (5) considering the epigenomic regulation of gene expression.

Many current phenotypes are subjectively measured and may represent numerous underlying biological processes. Misclassifying a phenotype can reduce power in GWAS relative to expectations based on power calculations of idealized homogeneous populations. Strong genotypic effects that are important in a small homogeneous subgroup could have a small or even negligible effect within an entire population[106].

Functional annotation of known genes and variants: Numerous genes and variants associated with CAD and MI have been explored in the last two decades. Candidate gene approaches (positional cloning, linkage analysis, and candidate-gene asso-

Table 3 Genetic variants associated with a reduced risk of coronary artery disease/myocardial infarction (protective factors against coronary artery disease/myocardial infarction)

Chr	Gene	Protective alleles	Ref.
1p13	*Rs599839 A>G Rs646776 T>C*	C/G haplotype	[161,162]
1q22	*E-selectin*	G2692A; C901T	[163]
1q31	*GLUL*	Rs10911021 T>C, TT allele	[164]
1q31	*IL-10*	G(-1082)A, GG genotype	[165]
1p34	*LRP 8*	TCCGC	[166]
2p21	*ABCG 5/8*	Rs41360247	[167]
3p25	*PPARγ2*	Pro12Ala homo	[168-170]
3p25	*PPARγ*	C161T	[171]
3q27	*Adiponectin*	Rs1501299 (G276T), TT allele	[172-174]
8q21	*FABP4*	Rs77878271	[175]
6p12.3	*PLA2G7*	R92H	[176]
6p25.3	*FXIII*	Val34Liu	[177,178]
7q21.3	*PON1/2*	Gln192Arg	[112,116]
7q32.3	*KLF14*	Rs4731702 T/T allele	[179]
7q36	*INSIG1*	Hap3 (T/G/A)	[180]
9q31.1	*ABCG1*	G1051A, r219K, KK allele	[78]
11q23.3	*APOC3*	R19X	[181]
13q34	*FVII*	R353Q; QQ allele A2 allele (without a 10 bp insertion)	[182]
16q13	*FKN*	T280M allele; Rs4329913; Rs7202364	[183,184]
16q24	*NADPH p22phox*	C242T	[185,186]
17p13.2	*GP1ba*	Thr/Th; TT haplotype	[187]
21q22.1	*MRPS6*	C699T (TT) or T1080C (CC)	[64]

ciation analysis) provide a direct link between the pathogenesis of CAD/MI and candidate genes. Variants or chromosomal loci identified by GWAS however do not associate with specific genes or pathways. Only one-third of the 45 CAD loci reported in the largest CAD and MI GWAS study contain a known functionally relevant candidate gene[84]. The 9p21 locus is the CAD locus discovered by GWAS and remains the strongest association with CAD in the human genome. However, the SNPs defining the 9p21 association with CAD are all located in intergenic locations rather than in coding or regulatory regions. Functional annotation of the 9p21 locus in association with CAD has focused on the two closest protein-coding genes, *CDKN2A* and *CDKN2B*, and an additional *CDKN2B* antisense noncoding RNA (ANRIL). The systematic functional annotation of these *CAD* and *MI* gene variants and loci will provide insight regarding the pathophysiology of the disease. These functional studies will require a combination of tissue, cell and animal model systems as well as assessments at the levels of gene expression, protein modification and metabolism[107,108].

Protective genetic factors against CAD and MI: Atherosclerosis is a multi-decade pathological process. A simplified pathologic process (Figure 3A) includes: (1) endothelial injury; (2) lipid particle deposition (fatty streak formation); (3) local cellular and inflammatory responses (early atheroma formation). The process is followed by (4) atheroma progression with the formation and expansion of the necrotic core, fibrous cap, matrix accumulation and various degrees of plaque instability; and (5) intertwined with various degrees of thrombosis formation[109]. The standard human genetic approach to CAD involves searching for genetic risk factors or susceptibility genes for the disease. Could genetic factors be protective against atherosclerosis and CAD and MI? Protective genetic factor against CAD and MI may antagonize the effects of genetic risk factors and potentially explain a portion of the missing heritability. The presence of protective genetic factors will alter the predictive value for CAD and MI using risk variants. The identification of protective genetic factors may shed light on the mechanisms of CAD and MI and further guide the development of strategies or therapy.

Clinical practice often encounters individuals of an advanced age with multiple TRF for CAD and MI without demonstrated angiographic evidence of CAD. The offspring of centenarians have a significantly reduced rate of cardiovascular complications[110]. The current understanding of the pathophysiology of atherosclerosis and CAD and MI supports the notion that the development and progression of atherosclerosis is an accumulating effect of the imbalance between athero-protective and pro-atherogenic processes (Figure 3B). Approximately 500 genes reported in the literature have been tested for their effects on atherogenic processes in atherosclerosis-prone mouse models (ApoE deficiency or LDL receptor deficiency with a high-fat diet) with transgenic (gain-of-function), knockout (LoF) or both genetic modifications. LoF mutations in approximately half of these genes accelerate atherosclerosis in a mouse model, whereas gain-of-function mutations significantly reduced atherosclerosis. It is plausible to suggest that these genes normally function as protective factors against atherosclerosis. In contrast, the remaining half of these reported genes exert pro-atherogenic effects that are normal or consistent with their gain-of-function mutations[111] (a complete list of these genes is available from the authors upon request).

Most genomic association studies have been designed to identify CAD/MI susceptibility genes or polymorphisms. The largest genetic study to assess the impact of common genomic variation on the risk of CAD reported a total of 45 CAD susceptibility loci and an additional 104 likely independent SNPs that were associated with an increased risk of CAD and MI, explaining approximately 10.6% of the heritability. No protective variants were reported[84]. Candidate gene-based association studies identified polymorphisms that are significantly associated with a reduced risk of CAD and MI (Table 3). However, the results obtained for many of these potentially protective genetic loci against CAD are conflicting.

HDL provides protection against atherosclerotic CAD partially through its anti-oxidative effects. Serum paraoxonase is responsible for most of the antioxidant

properties of HDL. Human paraoxonase is encoded by the family of *PON1, PON2* and *PON3* genes. Low serum PON1 activity is associated with an increased risk of CAD and its severity[112,113]. Many candidate gene association studies have revealed that *PON1* (Leu55Met, Gln193Arg) and *PON2* (Ser311Cys) polymorphisms are associated with the risk of CAD[114] and its angiographic severity[115]. For example, an association study in a single center of consecutive patients who underwent coronary angiography revealed a significant dose-dependent association of the *PON1* genotypes (192 Q/R) and serum PON1 (QQ192 > QR192 > RR192) as well as an inverse association with systemic indices of oxidative stress. In addition, 192 Q (QQ and QR) was associated with a decreased risk of cardiovascular and all-cause mortality[116]. The *PON1/PON2* haplotype comprising M55, Q1192 in PON1 and Cys 311 in *PON2* is associated with a significant protective effect against the risk of MI[117]. PON1-deficient mice in an $ApoE^{-/-}$ background fed a high-fat diet exhibit significantly exaggerated atherosclerosis compared with $ApoE^{-/-}$ mice carrying the wild type *PON1* gene[118,119]. Germline transgenic or transient adenoviral vector-mediated overexpression of atheroprotective PON1 (55L/192Q) in $ApoE^{-/-}$ mice revealed protective effects against atherosclerosis with $ApoE^{-/-}$ without transgenic PON1[120,121]. Multiple layers of evidence suggest that genetic polymorphisms in *PON1* and *PON2* lead to an increase in serum paraoxonase activity that may provide protective effects against CAD. However, the frequency of these variants in the general population remains to be determined.

GENETIC RISK SCORE TO PREDICT THE RISK OF CAD AND MI

Primary prevention of CAD is gauged based on the risk categories derived from the risk assessment with TRFs, such as the Framingham risk score (FRS) in the United States[122], the SCORE risk equation in Europe[123], the Reynolds risk score for women[124] and the PROCAM risk score in Germany[29]. The discovery of causal genetic factors for monogenic CAD and MI, such as monogenic lipid disorders, have made it possible to perform clinical genetic screening of family members and to provide enhanced primary prevention to carriers of causal mutations. This approach has been shown to be cost-effective[125]. The association between genetic polymorphisms and the risk of CAD and MI provides an opportunity to use genetic information and develop a GRS to improve the risk prediction of CAD and MI in the general population and subsequently guide preventive strategies. The GRS is calculated either in an un-weighted manner by adding allele numbers (0 for no risk allele, 1 for one allele and 2 for both alleles) with a weighted GRS typically by using the reported effect sizes from the reference studies as weights for the risk allele counts or with a weighted GRS mean, which is derived by dividing the sum of the weighted GRS allele counts by the number of the SNPs. The association of GRS with the risk of the CAD endpoint has been assessed. Thus, GRS is evaluated if the addition of GRS to the traditional risk scoring model improves the discrimination measured using AUC or C statistics or results in risk category net reclassification improvement (NRI). To be clinically applicable, GRS must eventually be validated in independent prospective studies. The expectations are high[126]. Research on this topic is growing. The scientific community has provided guidelines regarding the design, performance and reporting of studies investigating genetic risk prediction[127,128]. However, the outcomes have been mixed.

Early in 2004, Humphries *et al*[126] reported a non-significant improvement of the risk prediction power to *PROCAM* risk score with the addition of ApoE genotype information in the Northwick Park Heart Study Ⅱ (NPHSⅡ) cohort (ROC increased from 0.65 to 0.67, $P = 0.11$). The addition of genetic variants of *IL6* and *PPARα* did not result in any improvement of the CAD prediction power of the PROCAM score[126]. Chromosome 9p21.3 has demonstrated the strongest association with CAD in GWAS studies. The addition of the genotype of SNP rs10757274 A>G in the 9p21.3 locus did not significantly improve the predictive value of the FRS, but it improved the reclassification of coronary heart disease (CHD) risk and guided primary prevention for a high-risk population in a prospective study[129]. This conclusion was subsequently confirmed in studies using independent cohorts[130-133]. Statistical modeling revealed that larger numbers of genetic variants, higher odds ratios (OR) and the genotype frequency of individual variants can improve the discriminative accuracy of area under the receiver operating characteristic curve (AUC) using the genetic score to predict the risk of CAD and MI[134,135]. The application of 100 established variants with ORs ranging from 1.13 to 1.42 can achieve an AUC of 0.76, which is comparable to most of the currently used conventional risk scoring systems[135]. A rapid increase in the number of studies reporting the development and validation of GRS to predict the risk of CAD has been recently noted[136,137].

Morrison *et al*[138] calculated the GRS based on the number of risk alleles of 11 CAD-associated SNPs identified in the Atherosclerosis Risk in Communities Study (ARIC) cohort and combined the results with the ARIC Cardiovascular Risk Score (ACRS) to predict CAD. These researchers found that the addition of GRS to the traditional risk score significantly increased the AUC to predict the risk of CAD in blacks and suggested improved CAD risk prediction in whites[138]. In a large prospective cohort study with a median of 10.7 years of follow-up, Ripatti *et al*[139] found that individuals with a GRS in the top quintile derived from 13 multi-locus SNPs of CHD exhibited a 1.66-fold increased risk of CHD adjusting for TRF. However, the GRS did not improve the C index over the TRFs and family history or the net reclassification of risk categories. Paynter *et al*[140] prospectively studied GRS from 101 SNPs in the

large Women's Genome Health Study with a median follow-up of 12.3 years and found that the GRS did not improve the discrimination or reclassification of the ATP Ⅲ risk score. Most recently, by choosing SNPs that were repeatedly and reproducibly confirmed in multiple GWAS studies using improved statistics tools and systematic risk stratifications of TRFs, GRS added significant predictive value to improve risk predictions[141-146]. For example, Thanassoulis *et al*[142] constructed a GRS with 13 CAD risk SNPs and assessed participants in the FHS. These researchers not only confirmed the association between GRS and incident CHD and a high coronary artery calcium score (CAC) but also demonstrated that GRS modestly but significantly improved the risk reclassification for incident CHD and significantly improved the discrimination for a high CAC[142]. However, the addition of 16 newly discovered SNPs to the GRS (total of 29 SNPS) did not improve the performance of the GRS in contrast to previous *in silico* computations[135]. Tikkanen *et al*[146] derived a weight GRS using 28 SNPs associated with risk for CAD and MI in the large FINRISK study cohort with up to 19 years of follow-up for CHD. These researchers discovered a highly significant independent association between GRS and the risk of CHD. The addition of GRS to TRF with and without a family history significantly improved both the risk discrimination for all end points and the reclassification of individuals in the intermediate-risk category (clinical NRI = 27%). Similar results were validated in additional independent cohorts. Furthermore, this GRS was used as a novel risk marker in the 2-stage population screening study Emerging Risk Factors Collaboration. The addition of GRS screening of individuals with intermediate risk per TRF screening reclassified 19% of the group into the low- and 12% into the high-risk category, who thus became eligible for more aggressive primary prevention[146].

GRS derived from genetic variants associated with TRF for CAD is generally confirmed by an association with the disease, but it does not improve the discrimination of CAD and MI derived from the TRF assessment[142]. Kathiresan *et al*[147] calculated genetic scores for 5414 subjects in the Malmo Diet and Cancer Study based on the number of unfavorable alleles of nine SNPs with associations with LDL or HDL cholesterol levels. In this study, the genetic score was an independent risk factor for incident CVD over a median of 10.6 years of follow-up and modestly improved the clinical risk reclassification (Adult Treatment Panel Ⅲ, ATP Ⅲ classification) for individuals in the intermediate-risk category (26% rate of reclassification). However, this genetic score did not improve the risk discrimination[147]. Isaacs *et al*[148] derived a GRS from 95 blood lipid loci with common genetic variants with confirmed cumulative effects on subclinical atherosclerosis and clinical CAD and MI, but the score did not improve the clinical AUCs in combination with FRS. Similarly, Guella *et al*[149] analyzed a weighted GRS based on the top SNPs in 12 loci in the hemostatic gene pathway and found a 2.69-fold increased risk of early onset MI in subjects in the highest GRS quintile compared with those in the lowest quintile[149]. The predictive value of this weighted GRS has not been studied in a prospective study.

Compared with traditional risk assessment, the advantages of GRS are evident and include the following characteristics: (1) GSR is highly stable over a life time. This information permits the early identification of individuals who are at risk and the implementation of early intervention; (2) Current technology allows the simultaneous measurement of large numbers of genetic variants; (3) The presence of specific genetic risk alleles may provide information regarding targeted preventive intervention; and (4) Most of the SNPs identified by GWAS do not correlate with known TRFs. SNP-based GRS offers complementary information for risk prediction. GRS derived from CAD-associated SNPs provides significant additional predictive power that exceeds TRFs based on both AUC and NRI criteria. Genomic technology has also reduced the cost associated with genotyping a large number of SNPs. It is reasonable to predict that the GRS of CAD will eventually be a component of clinical practice. A number of questions remain to be addressed: (1) The potential difference of predictive values among candidate gene approach identified variants *vs* GWAS variants. Genetic association studies using a candidate gene approach often consist of a small sample size and cannot be replicated in different populations. The minimal criteria for a genetic variant to be included in CVD clinical risk management is recommended, including a meta-analysis based on the data from a minimum of three different independent studies that comprise at least a total of 1000 cases[126]. Potential causal variants for familial CAD and MI (Table 2) are low frequency, high impact variants. The allele frequencies in the general population remain to be determined. The appropriate techniques to incorporate these variants into the GRS remain to be addressed; (2) Protective genetic variants against CAD and MI can potentially attenuate predisposing effects of risk alleles. The number and frequency of protective genetic factors against CAD and MI in the population remain be determined. It will be interesting to evaluate how these protective variants influence the GRS calculation and its predictive power; (3) Gene-gene interactions: The synergistic effects between genetic variants have been reported in association with the risk of CAD[150,151]. Consideration of the combined effects in the GRS model may facilitate risk prediction; and (4) Gene-environmental interactions. The effects on the risk of CAD and MI by certain environmental factors depend on genetics in a "context dependency" fashion. In addition to the overall calculated GRS, information about specific genetic variants may guide personalized preventive intervention. For example, the information obtained for the *ApoEe4* allele is associated with exaggerated CAD and MI risk in tobacco smoker but not in non-smoker.

Table 4 Genetic variants associated with the risk of in-stent restenosis

Chr locations	Gene symbols	Genetic polymorphisms	Effects on risk of ISR	Pathway involved	Ref.
1p36.3	*MTHFR*	C677T	↑ ISR	Metabolism	[188]
1q32.1	*IL10*	G(-2849)A; G(-1082)A; A4259G	↑ ISR	Inflammation	[189]
1p35.1	*CX37*	C1019T	↑ ISR in men	Inflammation	[190,191]
2q14	*IL 1B*	C(-511)T	↑ ISR	Inflammation	[192]
2q14.2	*IL-1RN*	T8006C	↓ ISR	Inflammation	[154]
3p21.3	*GPx-1*	C599T (rs1050450)	↑ ISR	Thrombosis	[193]
		rs8179164 A>T	↑ ISR		[194]
3p24	*KAT2B*	rs6776870 G>C; rs2929404 T>C; rs17796904 T>C; rs4858767 G>C	↑ ISR	Epigenetic/gene expression	[194]
3q24	*AGTR1*	rs5182 T>C	↑ ISR	Vascular homeostasis	[194]
3q24	*P2RY12*	P2Y12 Haplotype H1 (5 P2Y12 ht-SNPs)	↑ ISR	Thrombosis	[195]
3q27	*Adiponectin*	T(+45)G rs2242766	↑ ISR	Inflammation	[196]
4q13	*IL-8*	A(-251)T + C(781)T	↑ ISRS	Inflammation	[197]
4q28	*FGB*	rs1044291 T>C	↑ ISR	Thrombosis	[194]
5q12	*CCNB1*	rs350099 C>T (TT); rs350104 T>C (CC); rs164390 T>G (GG); TT/CC/GG haplotype	↑ ISR ↑↑ ISR	Cell cycling	[198]
5q31.1	*CD14*	C(-260)T	↑ ISR	Inflammation	[199]
5q34	*miRNA-146a*	rs2910164>G (G/C)	↑ ISR	Inflammation	[200]
		rs2910164>G (C/C)	↓ ISR		
6p21.3	*TNFa*	T (-857)C +C(-1031)T	↑ ISR	Inflammation	[201]
6p21.3	*RAGE*	T(-374)A	↓ ISR	Inflammation	[202]
6q25.1	*aER*	PvuII (C/T) > (TT)	↑ ISR in women	Cell cycling	[203]
7q22.1	*PAI-1*	5G/5G	↑ ISR (smoker) ↓ ISR (nonsmoker)	Thrombosis	[204]
7q36.1	*eNOS*	298C/T (p. Glu298Asp)(rs1799983>T); T(-786)C	↑ ISR	Cell proliferation	[193,205,206]
11q22.3	*MMP12*	rs12808148 C>T; rs17099726 G>T	↑ ISR	Matrix deposition	[194]
11q22.2	*IL-18*	G(-137)T	↑ ISR	Inflammation	[207]
11q13.4	*UPC3*	C(-55C)T	↑ ISR	Metabolism	[208]
12p13.1	$p27^{kip1}$	(-838)AA	↓ ISR	Cell cycling	[209]
12q13.11	*VDR*	Block 2 AA haplotype	↑ ISR	Metabolism	[210]
		rs11574027 T>G; rs11574077 G>A	↑ ISR		[194]
13q12	*ALOX5AP*	rs10507391 T>A; rs17216473 G>A	↑ ISR	Lipid metabolism	[211]
		rs17222814G>A	↓ ISR		
17p13.1	*p53*	Arg72Pro	↑ ISR	Cell cycling	[212]
17q23.3	*ACE*	D allele: no 287-bp Alu repeats insertion in intron 16	↑ ISR	Cell cycling	[29-32,213-215]
19p13.2	*ICAM-1*	K469E	↑ ISR	Cell-cell interaction	[216]
21q22.3	*CD18*	C1323T	↓ ISR	Inflammation	[217]
22q13.1	*HO-1*	> 29 TG repeats in promoter	↑ ISR	Oxidative stress	[218]

ISR: In-stent restenosis.

It would be particularly important to advise smoking cessation in *ApoEe4* carriers[126]. Although, the inclusion of *ApoEe4* in the GRS calculation may overestimate the risk for non-smokers.

GENETICS OF IN-STENT RESTENOSIS

Percutaneous coronary intervention (PCI), an effective and safe alternative treatment modality for obstructive CAD, has become one of the most commonly performed therapeutic medical procedures since it was first performed by Grüntzig *et al*[152] in 1977 (http://www.ptca.org/nv/timeline.html. Last accessed on 8/30/3014). Restenosis, which is defined as a renarrowing of the treated vessel area that equals or exceeds 50% of the lumen in the adjacent normal segment, is an entity that is produced with the birth of PCI. The process often results in recurrent symptoms that require repeated intervention. Early experiences in balloon angioplasty revealed a restenosis rate of greater than 50%. The implantation of bare metal stents reduces the restenosis rate to 20% to 30%, mainly *via* the elimination of early elastic recoil and negative remodeling. The development of drug-eluting stents (*i.e.*, silorimus and paclitaxel as prototype-eluting drugs) further reduced the rate to 5% to 15%, as demonstrated in large randomized controlled trials[153]. Despite the advancement of PCI equipment and technology, late luminal loss due to in-stent restenosis (ISR) remains the "Achilles heel" for interventional cardiologists treating CAD.

ISR is a complex disease. Patient factors, such as older age, hypertension, diabetes mellitus and a history of restenosis, increase the risk of ISR[154], whereas tobacco use decreases the risk. Lesion characteristics, such as chronic total occlusion, a small vessel diameter, long lesions, the degree of calcification, ostial/bifurcation

lesions, and restenosis lesions, are associated with an increased risk of restenosis. Procedural-related factors, such as multiple stents, bare metal stents, small diameter and/or long stents, stent fracture, under-expansion, and the presence of edge dissection, increase the risk of restenosis[155]. The pathophysiology of ISR is not fully understood. Compared with balloon angioplasty, stent placement achieves greater acute gain (greater lumen caliber), prevents acute elastic recoil and plaque prolapse, and reduces negative remodeling. However, greater injury to the deeper arterial layers, de-endotheliarization and accumulating layer of platelets and fibrin on the stent surface in association with stent deployment trigger an increased inflammatory response and wound healing process, which includes leukocyte infiltration, cytokine and growth factor release, VSMC activation and proliferation, and matrix production. These processes result in neointimal hyperplasia, the main process of ISR, and neo-atheroma formation during late luminal loss[156]. It is well known that these processes, in particular the cell cycle regulation and inflammatory responses, involve a sophisticated regulatory network consisting of a multitude of proteins. The abundance, modification, and temporal and spatial expression of these proteins are controlled by genetic elements. Genetic factors are hypothesized to influence the risk of ISR for individuals undergoing PCI with stent placement.

Traditional epidemiological genetics has not yet established the heritability of ISR. Candidate gene association analyses using genetic markers, genomic polymorphisms or SNPs have revealed many important associations between genomic variants and the risk of ISR. Table 4 summarizes the published gene polymorphisms associated with the risk of ISR. These genes participate in the regulation of the cell cycle [CCNB1, p27kip1, eNOS, miRNA-146a and p53); inflammation (IL1B, IL1RN, IL8, IL18, TNFα, CD18, CD14, ICAM1 and CX37]; oxidative stress (RAGE, eNOS and HO-1); metabolism/hormonal regulation (ALOX5AP, vitamin D receptor (VDR), α-estrogen receptor (αER), methylenetetrahydrofolate reductase (MTHFR), adiponectin, UPC3, and FBG) and coagulation/thrombosis [factor V leiden, fibrinogen beta chain (FGB), GPx-1, PAI-1, and P2RY12]; epigenetic regulation of gene expression (KAT2B), matrix deposition and degradation (MMP12); and the renin-angiotensin-aldosterone system (RAAS) system (ACE and AGTR1), which is also related to the maintenance of vascular hemostasis (ICAM-1). Although most of the polymorphisms identified in these genes are associated with an increased risk of ISR, some genetic variants were found to have protective effects against ISR, such as the TT genotype in exon 11 of CD18 (ITGB2), the A allele of *ALOX5AP*, the A allele of the $p27^{kip1}$ gene, the AA genotype at position -374 of the RAGE promoter, the CC alleles in miRNA-146a, and allele 2 (C allele) in the *IL-1RN* gene. There are discrepancies in the literature reporting candidate gene-based association analyses and unbiased GWAS studies that involve significantly heterogeneous cases and controls as well as relatively small sample sizes[157]. Further validation and physiological annotation of most of these associations between polymorphisms and the risk of ISR in future studies will be essential.

Discoveries of genetic factors associated with the risk of ISR will not only provide insight regarding the molecular mechanisms underlying the pathogenesis of ISR but also facilitate the development of novel strategies or agents to prevent ISR. More importantly, a complete understanding of genetic risks for ISR will provide clinicians with prognostic information to tailor revascularization strategies, PCI with stenting or coronary artery bypass grafting (CABG). Understandably, patients, in particular younger patients with significant CAD who possess genetic risk factors for ISR, will theoretically benefit more from CABG, and patients carrying protective genetic factors for ISR may benefit from PCI stenting to avoid surgery.

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REVIEW

Population-level differences in revascularization treatment and outcomes among various United States subpopulations

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Abstract

Despite recent general improvements in health care, significant disparities persist in the cardiovascular care of women and racial/ethnic minorities. This is true even when income, education level, and site of care are taken into consideration. Possible explanations for these disparities include socioeconomic considerations, elements of discrimination and racism that affect socioeconomic status, and access to adequate medical care. Coronary revascularization has become the accepted and recommended treatment for myocardial infarction (MI) today and is one of the most common major medical interventions in the United States, with more than 1 million procedures each year. This review discusses recent data on disparities in co-morbidities and presentation symptoms, care and access to medical resources, and outcomes in revascularization as treatment for acute coronary syndrome, looking especially at women and minority populations in the United States. The data show that revascularization is used less in both female and minority patients. We summarize recent data on disparities in co-morbidities and presentation symptoms related to MI; access to care, medical resources, and treatments; and outcomes in women, blacks, and Hispanics. The picture is complicated among the last group by the many Hispanic/Latino subgroups in the United States. Some differences in outcomes are partially explained by presentation symptoms and co-morbidities and external conditions such as local hospital capacity. Of particular note is the striking differential in both presentation co-morbidities and mortality rates seen in women, compared to men, especially in women $\leqslant$ 55 years of age. Surveillance data on other groups in the United States such as American Indians/Alaska Natives and the many Asian subpopulations show disparities in risk factors and co-morbidities, but revascularization as treatment for MI in these populations has not been adequately studied. Significant research is required to understand the extent of disparities in treatment in these subpopulations.

Key words: Revascularization; Myocardial infarction; Cardiovascular; Disparities; Minorities

Core tip: Disparities persist in the care of myocardial infarction (MI) in women and racial/ethnic minorities in the United States. They arrive at the hospital later, present with more risk factors and co-morbidities, and are less likely to receive guideline treatments. Women and blacks are less likely to receive revascularization. Younger women have more in-hospital mortality, and both blacks and women have greater long-term risk for death, recurrent MI, and re-hospitalization. Disparities in risk factors and co-morbidities among Hispanics/Latinos are complicated by the many subgroups. American Indians/Alaska Natives and Asian subpopulations have been much less studied, but surveillance data indicate more risk factors and co-morbidities among these subgroups.

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INTRODUCTION

Despite recent general improvements in health care, significant disparities persist in the cardiovascular care of women and racial/ethnic minorities, even when income, education level, and site of care are taken into consideration[1]. A lack of significant improvements in cardiometabolic risk factors, including hypertension, dyslipidemia, obesity, and cardiorenal metabolic syndrome, combined with increased prevalence of diabetes among blacks, accounts for much of the observed racial differences. Eliminating racial/ethnic disparities alone could prevent an estimated 1.1 million hospitalizations a year[2].

Explanations suggested for the observed continued disparities include socioeconomic considerations and elements of discrimination and racism that affect socioeconomic status and access to adequate medical care.

Socioeconomic status

Patients with acute myocardial infarction (AMI) living in poorer regions were of advanced age and more likely to be non-white and presented with more co-morbidities and were more likely to be smokers. Lower education was associated with more mature age, nonwhite race, more co-morbidity, and lower ejection fraction[3]. In the PREMIER study, lower levels of socio economic status were associated with higher risk of mortality and re-hospitalization in patients hospitalized for AMI. Patients with lower income levels had worse initial overall symptoms and clinical presentation at admission and worse quality of care. Baseline clinical status largely explained the excess mortality but not re-hospitalization[4].

Achieving less than a high school level of education was linked with a 67% increase in one to five-year mortality in women and a 37% increase in men among nearly 16000 Medicare patients admitted for myocardial infarction (MI) from 1991 to 2001, adjusting for a number of clinical factors. Education level was associated with 1- to 5-year MI recurrence in men only[5]. Patients with high financial stress had worse physical and psychological health, worse disease-specific overall quality of life, and more angina 1 year after hospitalization than patients without such stress in a study of 2344 AMI patients discharged in 2003 and 2004. Four-year mortality rates did not differ[6].

Current cardiovascular health disparities

Cardiovascular disease (CVD) health disparities continue to exist among women and minorities. Krieger[7] proposed an "ecosocial" approach to the study of discrimination and health. She posited that inequitable race relations simultaneously benefit the group claiming racial superiority at the expense of those deemed inferior[7]. Minority patients with acute coronary syndrome (ACS) are at greater risk for the full spectrum of cardiac disease including MI, re-hospitalization, and mortality than non-minority patients[8,9]. American Indians/Alaska Natives (AI/AN) have significantly higher rates of obesity, diabetes, CVD, CHD, stroke, and stroke-related death than the general United States population. AI/AN women are particularly at risk[10].

Interventional studies designed to reduce disparities in CVD risk factors and outcomes have included hypertension, hyperlipidemia, tobacco cessation, physical inactivity, and heart failure management. These studies were few, limited by not enough patients, had short follow-up times, and showed only modest clinical gains[11]. Investigators have found "compelling evidence" of disparities in cardiac interventions between whites and blacks. These are not explained by confounding factors such as insurance coverage and disease severity[12].

Table 1 provides a current summary of racial and gender cardiovascular disparities.

REVASCULARIZATION

Revascularization is an accepted treatment for MI, with recommendations available on the use of CABG *vs* PCI, including anatomical considerations[14]. Although ST-segment elevation myocardial infarction (STEMI) incidence decreased between 2001 and 2010, PCI for STEMI increased by 33.5% among patients aged 65 to 79 years and by 22% for those ⩾ 80 years[15].

PCI has continued to be inferior to CABG for anatomical conditions such as left main disease. Despite advances in both procedures, risk for repeat revascu-

Table 1 Summary of current minority disparities related to cardiovascular disease[13]

Total CVD prevalence and total CVD mortality are higher in females than in males
Black males have higher prevalence than white males (44.4% *vs* 36.6%) and higher mortality (369.2/100000 *vs* 278.4/100000)
Black females have higher prevalence than white females (48.9% *vs* 32.4%) and higher mortality (260.5/100000 *vs* 192.2/100000)
Mexican American males have lower prevalence than white males (33.4% *vs* 36.6%)
Mexican American females have lower prevalence than white females (30.7% *vs* 32.4%)
The prevalence of having ≥ 2 risk factors is highest among blacks (48.7%), followed by AI/AN (46.7%), and lowest among Asians (25.9%). The prevalence is similar among men (37.8%) and women (36.4%)
The prevalence of having ≥ 2 risk factors is lower among college graduates (25.9%) than among those with less than a high school diploma (52.5%); a similar disparity in prevalence of risk factors is seen among those making ≥ $50000/yr (28.8%) *vs* those making < $10000/yr (52.5%)
Among older Americans (≥ 65 yr), hypertension is more prevalent in women than in men (57% *vs* 54%) and women have a significantly lower rate of hypertension control
Hypertension increased from 1988 through 2002 in both blacks and whites: From 35.8% to 41.4% in blacks (44.0% among black females) and from 24.3% to 28.1% in whites
Blacks develop hypertension earlier in life and have higher average blood pressures. As a result, blacks have a non-fatal stroke rate 1.3 times that of whites and a fatal stroke rate 1.8 times that of whites. Blacks also have a rate of death attributable to hypertension 1.5 times greater than that of whites and a 4.2-times-higher rate of end-stage kidney disease
Black and Mexican American males have higher mean LDL levels than white males (blacks, 115.9 mg/dL; Mexican Americans, 119.7 mg/dL; whites, 115.1 mg/dL); both black and Mexican American females have lower mean LDL levels than white females (blacks, 114.2 mg/dL; Mexican Americans, 115.0 mg/dL; whites 115.7 mg/dL)
Among men, non-Hispanic blacks (38%) and Mexican Americans (36%) are more likely than non-Hispanic whites (34%) to be obese. Among women, non-Hispanic blacks (54%) and Mexican Americans (45%) are more likely to be obese than non-Hispanic whites (33%)
The prevalence of physician-diagnosed diabetes mellitus in adults > 20 yr is highest in non-Hispanic blacks (12.6%) followed by Hispanics (11.8%), Asian Americans (8.4%), and non-Hispanic whites (7.1%). The prevalence of diagnosed diabetes in adult Asian Indians is more than twice as high (14%) as that in Chinese (6%) or Japanese (5%) Americans. Death rates per 100000 attributable to diabetes mellitus are 23.1 for white males, 43.6 for black males, 15.6 for white females, and 35.1 for black females
The age-adjusted prevalence of diabetes in AI/AN adults aged < 35 yr rose from 8.5% to 17.1% between 1994 and 2004; the rate was higher in females in all age groups

LDL: Low-density lipoprotein; CVD: Cardiovascular disease; AI/AN: American Indians/Alaska Natives.

larization still appears to be higher with PCI[16]. Mohr *et al*[17] found no significant differences between CABG and PCI in all-cause death or stroke, but patients with intermediate or high SYNTAX scores treated with PCI had more serious adverse cardiac and cerebrovascular events at 5-year follow-up. CABG, compared to PCI, offered significant protection from long-term mortality[18], but PCI offers advantages in accessibility. A recent expert consensus found no difference in either in-hospital or 30-d mortality with primary PCI between sites with and without on-site surgical backup[19].

Coronary revascularization has become one of the most common major medical interventions in the United States, with over 1 million procedures yearly[20]. Even so, revascularization is used less in both female and minority patients[21,22]. Local hospital capacity helps to explain the revascularization disparities between black and white AMI patients[23].

This review presents recent data on disparities in co-morbidities and presentation symptoms, care and access to medical resources, and outcomes in revascularization as treatment for ACS.

WOMEN

Co-morbidities and presentation symptoms

Among 6746 STEMI patients undergoing primary PCI, stratified by age (< 65 years, ≥ 65 years), hypertension was higher in both groups of women than in men, and younger women had a higher likelihood of being current smokers. Older women also had more diabetes than men[24]. In a cohort that included 15120 women, women were less likely than men to be taking cardioprotective medications in the first year after their diabetes diagnosis[25]. The impact of this lack of adherence to medications on cardiovascular disparities is difficult to estimate, but crude mortality in MI patients has been found to be highest in those with diabetes[26].

In the Variation in Recovery: Role of Gender on Outcomes of Young AMI Patients (VIRGO) study, younger female AMI patients (18 to 55 years) had worse pre-event health than men, including more diabetes, dyslipidemia, and obesity. They also had significantly more angina, stroke, and congestive heart failure, worse physical function, and poorer quality of life than male AMI patients in the same age group[27,28]. Similar results were found in a cohort of younger AMI patients (≤ 55 years) from the Translational Research Investigating Underlying disparities in Acute Myocardial infarction Patients' Health Status (TRIUMPH) study[29,30]. Lower resting metabolic rates in black women may contribute to the higher levels of obesity seen in black women compared to white women[31].

Between 1997 and 2009, awareness of CVD as the leading cause of death in women increased significantly, but black and Hispanic women still had significantly less awareness than white women. Only 53% of the women interviewed would call 9-1-1 if they thought they had symptoms of a heart attack[32]. Hispanic women were also less likely to know the symptoms of a heart attack and more likely to underestimate their weight[33].

Chest pain is critical in the decision to initiate dia-

gnostic testing for ACS upon presentation, yet up to 35% of AMI patients do not report chest pain, which can lead to misdiagnosis and a higher risk of death. Female ACS patients aged 55 years or younger had a higher probability of presenting without chest pain and with NSTEMI. This was not associated with markers of coronary disease severity[34,35]. However, women aged 65 and older were actually less likely to present without chest pain than similarly aged men[36]. African American women were more likely to present with stomach associated symptoms and less chest related signs than white women and had significantly greater all-cause and cardiovascular mortality[37].

Women with STEMI have increased left ventricular filling pressures during acute STEMI *vs* men, independent of age, high blood pressure, and size of the infract. This suggests that pulmonary capillary wedge pressure may mediate the effect of sex on outcomes post-STEMI[38].

Seeking better risk estimates for women, Cook *et al*[39] compared the Adult Treatment Panel Ⅲ (ATP-Ⅲ) score, the Framingham risk score and the Reynolds Risk Score CVD model. The ATP-Ⅲ overestimated the risk for coronary heart disease and the Framingham CVD model overestimated the risk for major CVD. After recalibration, the Reynolds Risk Score was better calibrated for both black and white women than either of the Framingham-based models[39]. A high-sensitivity troponin assay that incorporated diagnostic thresholds that were specific for women and men increased the ability to diagnose MI in women compared to a single-threshold contemporary assay, but this was not as effective in men. Women with MI identified by the high-sensitivity assay or by both assays had the highest risk for death or recurrent MI at 12 mo[40]. Independent predictors of obstructive CAD in women with chest pain and an abnormal stress test included body mass index (BMI) < 30 kg/m^2, a history of smoking, low high-density lipoprotein (HDL), a significant family history of early heart disease, age ⩾ 55 years, lateral abnormality on stress imaging, and exercise capacity < 5 metabolic equivalents. the risk score had a negative predictive value of 80%[41].

Care/medical resources

Disparities in care for AMI among women fall largely into three categories: The likelihood of hospitalization, the time to hospital or to guideline treatment from onset of symptoms, and the administered treatments themselves.

Between 1992 and 2010, rates of hospitalization for AMI per 10000 Medicare enrollees were significantly lower in both black and white women, persisting as hospitalization rates for AMI in general declined. Rates of PCI within 30 d of AMI continued to be significantly lower in both black and white women. Mortality differences by race declined, but remained higher in women[42].

Between 1960 and 2008, women had consistently longer prehospital delay from symptom onset (median 1.8 to 7.2 h *vs* 1.4 to 3.5 h in men). The characteristics associated with delay in females included being older, not being married, having a previous history of MI, being alone during symptom onset, and not wanting to bother anyone[43]. The time from the first appearance of symptoms-to-balloon time was also significantly longer in women than in men, largely driven by later presentation to the hospital. Women were more often treated with just medical management and were more likely to receive medications such as a diuretic or warfarin on discharge, whereas men more often received b-blockers and statins. Compared with men, women had significantly higher levels of major adverse cardiovascular events; major bleeding; death; and target vessel revascularization for ischemia in-hospital and at 30 d. In women, higher rates at these end points persisted at 3 years[44]. At hospital arrival, female STEMI patients had delays in both door-to-code and code-to-balloon times. Independent determinants of delays in door-to-balloon times included female sex, hypertension, maximum ST-elevation, office hours, and triage category[45].

Among ACS patients aged 18 to 55 years, women had significantly less income; more diabetes mellitus, hypertension, family history of CVD, and previous CVD events; and more depression and anxiety before symptom onset. Females were less likely to have a diagnosis of STEMI and more likely to have a diagnosis of unstable angina. Women were less likely to receive ECG or fibrinolytic therapy within established time benchmarks but did not differ from men in timely PCI. Females with STEMI were less likely to have reperfusion therapy than males, and females with NSTEMI were less likely to have PCI, although the proportions of male and female patients with NSTEMI who had cardiac catheterization were similar. The determinants of poorer access to care included anxiety, more risk factors, and lack of chest pain at presentation[46].

STEMI patients aged ⩽ 45 years generally had more non-traditional cardiovascular profiles and had lower in-hospital mortality, but younger women had significantly poorer quality of care, with longer delay in door-to-thrombolytic time, and higher in-hospital mortality rates than younger men[47]. In patients receiving care for CVD in Veterans Health Administration facilities in 2010 and 2011, women had higher mean LDL cholesterol levels than men but were significantly less likely to receive statin treatment according to recent cholesterol guidelines[48]. Between 2008 and 2011, patients hospitalized for non-ACS indications who had in-patient STEMI were more likely to be older and female and less likely to undergo cardiac catheterization or PCI. These patients had more than 3-fold greater in-hospital mortality[49].

At 30 d after discharge, no difference was found by race/ethnicity since inception of the Medicare Part D

prescription drug benefit in usage of statins, β-blockers or ACE inhibitors but women were less likely than men to be using β-blockers and angiotensin-converting enzyme inhibitors. At 12 mo, black and Hispanic women were the least likely to be adherent, followed by white, Asian, and other women and by black and Hispanic men[50].

Golden *et al*[51] looked at cardiovascular testing after evaluation for chest pain. This analysis focused on the physician-patient discussions and how these affect patient decisions around cardiovascular testing. The primary outcomes were sex differences in recommendations for testing. Physicians were less likely to tell women their symptoms could result from heart disease or to recommend cardiovascular testing or cardiac catheterization. No patients in this study did not follow the recommendations of their doctors[51].

Hormone replacement and combined hormone contraception

A recent analysis of data from the large Women's Health Initiative, including 13 years of follow-up, found the risk for both CHD and stroke to be higher with combined estrogen plus progesterone in all age groups, but risk for MI was slightly reduced in the 50 to 59 year age group. Among women with previous hysterectomy taking estrogen alone, women aged 50 to 59 years had slightly less risk for CHD and MI, but not older women taking estrogen alone and the risk for stroke and venous thrombosis was higher. These findings do not support the use of hormone therapy, although it might be a reasonable option to manage menopause symptoms during early menopause[52]. A more recent Cochrane review of 19 trials largely confirmed these results[53].

The potential added risk of MI associated with combined hormonal contraceptives has also been controversial. Most women who take oral contraceptives take a combined estrogen-progestin preparation and today's contraceptives have much smaller doses of estrogen than earlier versions. In a very large Danish cohort, women taking doses of 30 to 40 μg ethinyl estradiol had a roughly 2-fold risk of both thrombotic stroke and MI, but risk varied with the type of progestin. Those taking 20 μg ethinyl estradiol had approximately a 1.5-fold risk of both thrombotic stroke and MI with all types of progestin except drospirenone, which offered no excess risk[54]. In a more recent but much smaller study in Turkey that also examined MI/PCI sequelae, women taking a contraceptive containing 30 μg ethinyl estradiol combined with drospirenone had increased risk for STEMI. Following PCI, patients had increased thrombus burden, were less likely to have complete ST resolution, and were more likely to develop congestive heart failure than women not taking the contraceptive. Confounding factors in this study included the small number of oral contraceptive users and the fact that women taking contraceptives were more likely to be smokers, suggesting that oral contraceptives should not be prescribed to smokers, especially if aged more than 35 years[55]. It has been noted that taking combined hormonal contraceptives is safer than pregnancy and delivery[56].

Outcomes

Age-adjusted CVD mortality rates in the United States from 1980 through 2002 declined more in men than women (52% among men and by 49% among women). However, between 2000 and 2002, the mortality rate in women aged 35 to 54 years increased by 1.5% despite declining in this group during the earlier study years. By contrast, in both men and women aged ⩾ 55 years, declines in mortality rate accelerated between 2000 and 2002[57].

In a decade long prospective study of STEMI patients undergoing primary PCI, hypertension was more prevalent in both younger (< 65 years) and older (⩾ 65 years) women than in men of the same age. Younger women were more likely to smoke, have less obstructive CAD, and to have a family history of CVD than younger men, whereas older women had more diabetes than older men but were less likely to smoke. Overall mortality was greater in women, but younger women had more risk of mortality at 30 d and at 1 year than men of the same age, whereas older women had significantly increased risk of mortality only at 30 d, not at 1 year[24].

In-hospital mortality was higher in women for both STEMI and NSTEMI but more so for STEMI patients. However, younger women actually were the main drivers in this difference in mortality. Among NSTEMI patients, in-hospital mortality rate differences reversed among women ⩾ 70 years, who had better in-hospital survival than men of the same age[58]. Similarly, women were older than men for both STEMI and NSTEMI diagnoses and were less likely to be treated with PCI or CABG for either. Female STEMI patients had more in-hospital mortality than men of similar ages in all age categories except 80 to 89 years. Female NSTEMI patients had higher rates of in-hospital mortality than men of the same age through age 69 years, but women ⩾ 70 years had better survival than men of the same age[59].

AMI hospitalization rates did not decline in either sex in United States patients aged 30 to 54 years between 2001 and 2010, but women had more co-morbidities, longer hospital stays, and more in-hospital mortality than men across all ages. In-hospital mortality declined significantly for women but not for men[60]. In adults ⩾ 20 years of age hospitalized for AMI, younger women had a higher rate of renal disease, diabetes, systolic heart failure, and malignancies than similarly aged men. Women ⩽ 55 years experienced a significant increase in AMI rates, which did not occur in men in this age group. Women also had higher 30-d mortality rates than men, although this declined in both sexes

over the 10 years of the study. Women 20-55 had 45% higher odds of 30-d mortality than men of the same age, which persisted over the study. Only women ⩾ 75 years of age had borderline better mortality rates than men[61]. In a systematic review of between-sex AMI mortality, unadjusted mortality was higher in women at both 5 and 10 years. Sex differences in long-term mortality after AMI were largely explained by differences in age, co-morbidities, and differential treatment usage by women compared with men[62].

An analysis of outcomes by sex and long-term outcomes by sex and type of stent found that women had more in-hospital complications, including mortality, MI, bleeding, and vascular complications. At 30 mo, women had a slightly lower adjusted risk for death, but there weren't any significant sex-related differences in adjusted rates of MI, bleeding, or revascularization. Males and females benefited similarly from the use of drug-eluting stents[63]. The most significant predictors of re-hospitalization for ACSs within 1 year were CABG prior to hospitalization for the AMI, female sex, and in-hospital PCI. No difference was found in risk of ACS re-hospitalization by type of stent, but the strongest predictors of revascularization were multi-vessel disease and in hospital PCI with a bare metal stent[64].

Significant pre-PCI predictors of 30-d re-admission comprised gender, age, Medicare or other government insurance, a history of heart failure and kidney disease. Predictors after PCI included not receiving a prescription for b-blocker upon discharge, vascular complications, and prolonged length of stay[65].

At age 45, the risk of death increased more significantly in white men than black men. White men had six times the increased risk of death compared to white women, whereas black males had only twice the increased risk of fatal CHD compared to black women. The risk of mortality between sexes equalized by age 95 in both blacks and whites. Adjustments for CHD risk factors did not explain this disparity between races in gender difference in CHD mortality[66].

Sex differences in perceived stress could be a central explanation for gender based differences in post-AMI recovery. Women had significantly higher baseline stress, mostly explained by co-morbidities, state of physical and mental health, intra-family conflicts, caregiving demands, and financial hardship. Higher stress was associated with worse female recovery at 1 mo post-AMI in angina, overall quality of life, and mental health[67]. A study to distinguish the effects of gender role *vs* biological sex on quality of life after ACS found that at baseline and at 1, 6, and 12 mo, women had clinically significant lower Health Related Quality of Life scores than men. Social support and gender-related variables such as housework responsibility were statistically significant predictors of physical limitation, angina frequency, and disease perception, but biological sex predicted only physical limitation[68].

The status of CVD in women internationally

Women in other countries with health care systems vastly different from that of the United States have been found to experience similar disparities. Recent studies in Spain, China, Germany, Vietnam, and Italy found equivalent differences in presentation symptoms and co-morbidities, access to treatments, and outcomes compared to men[69-73].

Table 2 summarizes disparities in women in presentation, treatment, and outcomes of acute coronary syndrome.

BLACKS

Co-morbidities and presentation symptoms

Differences between blacks and whites at presentation for ACS often fall into three categories: Demographic factors such as income and education, risk factors and co-morbidities, and symptoms.

A constellation of cardiometabolic risk factors, including high blood pressure, high cholesterol, obesity, diabetes mellitus, and chronic kidney disease, coupled with physical inactivity, smoking, and poor eating habits, is more prevalent in blacks and contributes to CVD disparities[2].

Black patients with NSTE ACS in the CRUSADE quality improvement initiative, from 2002 to 2003, were younger; had a higher prevalence of hypertension, diabetes mellitus, congestive heart failure, kidney failure and history of stroke than whites. African American patients had a lower rate of private insurance or primary cardiology care and more likely to be uninsured. Blacks were less likely to be prescribed clopidogrel and GP IIb/IIIa inhibitors or to have diagnostic cardiac catheterization or PCI than white patients. High-risk African Americans had a lower incidence of CABG than high-risk white patients[74].

African Americans in the PREMIER study[75] were more likely than white patients to have Medicaid, no education beyond high school, household income less than $10000, and a prior incidence of heart failure. Comparing rates of hypertension, hypercholesterolemia, diabetes, obesity, and current smoking, more blacks than whites had hypertension and diabetes within each age-sex group. Black men ⩾ 55 years were more likely to smoke, but no differences were observed in the group < 55 years of age. The prevalence of multiple cardiac risk factors was significantly higher for blacks, particularly black women, with 60% of older (⩾ 55 years) and 54% of younger (< 55 years) black women having three or more risk factors[76].

Black patients with confirmed ACS upon presentation were significantly younger and had less education and lower incomes, significantly longer prehospital delays, more hypertension, higher rates of diabetes, higher BMI, and reported more current tobacco use than whites. They were more likely to experience palpitations, chest pressure, and chest pain, and to

Table 2 Summary of disparities in acute myocardial infarction co-morbidities and presentation symptoms, care and access to medical resources, and outcomes in women

Co-morbidities and presentation symptoms
More hypertension and diabetes than men[24]
More diabetes, dyslipidemia, obesity, angina, stroke, and congestive heart failure; worse physical function; and poorer quality of life than men[28]
More hypertension, diabetes, lung disease, depression, and angina; worse general health scores; poorer physical function; and worse quality of life than men[30]
Women ≤ 55 yr of age more likely than men to present without chest pain or with NSTEMI[35]
Women < 45 yr of age more likely than men to present without chest pain, but this reversed with age[36]
Risk less likely to be accurately assessed by standard models or assays[39,40]
More likely than men to be older and have hypertension, hyperlipidemia, and congestive heart failure and less likely to have previous history of MI or revascularization[44]
Women ≤ 55 yr of age more likely to have low income, more diabetes, more hypertension, more family history of CVD, more previous CVD events, and more depression and anxiety; less likely to have diagnosis of STEMI and more likely to have NSTEMI or unstable angina[46]
Higher baseline stress than men[67]
Care/medical resources
Lower rates of hospitalization for AMI and lower rates of PCI as treatment for AMI compared to men[42]
Longer pre-hospital delay from onset of symptoms compared to men[43]
Longer symptom-onset-to-balloon time than men and more likely to be treated with medical management only; less likely to receive b-blockers and statins on discharge[44]
Greater delays than men in both door-to-code and door-to-balloon times[45]
Less likely than men to receive ECG or fibrinolytic therapy within guideline times, to have reperfusion therapy with STEMI, or to have PCI with NSTEMI[46]
Longer door-to-thrombolytic time than men[47]
Less likely than men to have statin treatment for high cholesterol[48]
Women with in-hospital STEMI less likely to have cardiac catheterization or PCI than men[49]
Less likely than men to be using ACE inhibitors, angiotensin receptor blockers, and β-blockers 30 d after discharge[50]
Less likely than men to be told their symptoms could be related to heart disease or to have cardiovascular testing or cardiac catheterization recommended[51]
Less likely than men to be treated with either primary PCI or CABG[73]
Outcomes
Greater mortality than men at 30 d and at 1 yr in women < 65 yr, but only at 30 d in women ≥ 65 yr[24]
Greater in-hospital mortality than men for both STEMI and NSTEMI in women ≤ 69 yr[58]
Greater in-hospital mortality than men for STEMI in women < 80 yr, and greater in-hospital mortality than men for NSTEMI in women ≤ 69 yr[59]
More in-hospital mortality for AMI than men[60]
Higher 30-d mortality rates for AMI than men up to age 75 yr[61]
Higher post-AMI mortality rates than men at both 5 and 10 yr[62]
More in-hospital complications than men, including mortality, MI, bleeding, and vascular complications[63]
More likely than men to be re-hospitalized for ACS within 1 yr[64]
Worse recovery than men at 1 mo post-AMI in angina, overall quality of life, and mental health[67]
Clinically significant lower health-related quality of life scores than men at 1, 6, and 12 mo following ACS event[68]
Higher re-hospitalization rates and lower quality of life than men at 6 mo after AMI[69]
Greater risk of 1-yr re-hospitalization for AMI and higher 1-yr mortality than men[93]

AMI: Acute myocardial infarction; CVD: Cardiovascular disease; STEMI: ST-segment elevation myocardial infarction; CABG: Coronary arterybypass grafting; PCI: Percutaneous coronary intervention; ECG: Electrocardiogram; ACE: Angiotensin converting enzymes; ACS: Acute coronary syndromes.

report more severe symptoms than whites. A higher percentage of black patients received lidocaine, but there was no other significant treatment difference. At 1 mo follow-up, blacks reported significantly more symptoms and more clinic visits than whites. Blacks continued to have more symptoms at 6 mo, but health service usage no longer differed[77].

Care/medical resources

Disparities in clinical care for blacks with AMI fall largely into two categories: The time to hospital or to guideline treatment from onset of symptoms, and the administered treatments themselves.

Black patients undergoing PCI were more apt to be younger and female and to have more hypertension and other chronic illnesses including prior MI, history of gastrointestinal bleeding, and worse baseline hemoglobin. They were also more likely to be on Medicaid or to be uninsured. No differences were found in treatment for STEMI between whites and blacks, but more black patients than white patients had PCI for NSTEMI and more white patients had emergent CABG. No difference was seen in in-hospital mortality rates between whites and blacks. In a propensity-matched subcohort of African American and white patients, blacks were not as likely to receive prasugrel or drug-eluting stents[78].

Time from first arrival to first drug was longest for blacks, but was actually significantly longer for all minority patients than for whites. Door-to-balloon times were significantly longer for blacks, Hispanics, and Asian/Pacific Islanders than for whites. The differences remained significant when controlling for specific hospitals[79]. Cavender *et al*[80] found insignificant differences in door-to-balloon times when comparing white, black, and Hispanics and similar in-hospital mortality rates between groups. However, after controlling for the usual confounding factors, black race was

associated with less likelihood of door-to-balloon time under 90 min (a quality-of-care indicator for treatment of STEMI) compared to white race[80]. Among Medicare beneficiaries with AMI admitted to hospitals without revascularization facilities in 2006, black patients were transferred to a PCI ready hospital more slowly than whites (median 1 d for whites, 2 d for blacks), but the risk-standardized mortality rate in the revascularization hospitals did not differ between races[81].

In a study of hospitalizations for ischemic heart disease in Massachusetts in the pre- and post-health care reform periods (November 2004 to July 2006, and December 2006 to September 2008), blacks had 30% less likelihood of receiving revascularization than whites in pre-health reform Massachusetts. This disparity has persisted post-reform, as have somewhat smaller disparities in Hispanics. Asians were slightly more likely to receive revascularization than whites. Patients living in more educated communities, men, and patients with private insurance were more likely to have revascularization treatment both before and after reform. The adjusted odds of in-hospital mortality were higher in the post-reform period than in the pre-reform period, but no differences were observed in 1-year mortality by race/ethnicity, education level, or sex[82].

Blacks were the least likely to be treated with revascularization in an analysis of data from 12555 patients admitted with AMI in New York city in 1996. Whites were older and more likely to have congestive heart failure. Hispanics were more likely to survive than whites, but blacks and whites did not differ significantly in survival. Non-revascularized blacks and Hispanics were more likely to be discharged alive than non-revascularized whites[83].

In an analysis of data from AMI patients with Medicare, private insurance, as well as those were uninsured or on Medicaid, in nine states (from 2000 to 2005). Blacks and Hispanics were significantly less likely than whites to be revascularized, regardless of insurance status. After adjusting for demographics, co-morbidities, and hospital clustering, blacks were approximately 25% less likely than whites with similar insurance to be treated with revascularization and Hispanics about 5% less likely[84].

The impact of hospital and physician effects on disparities in revascularization treatment was examined in 119386 initial episode AMI patients, aged ⩾ 65 years, and all fee-for-service Medicare recipients in Florida (from 1997 to 2005). Black and Hispanic patients were younger, more likely to be female, and more likely to have diabetes mellitus than white patients. The unadjusted rates of intervention were significantly higher in whites than in either blacks or Hispanics. Black-white disparities for these procedures persisted despite adjustment for age, gender, co-morbidities, socioeconomic status, and hospital characteristics. Hispanic-white disparities held for catheterization and PTCA, but were no longer significant for CABG. Hospital fixed effects were found to not be the full reason behind disparities in cardiac treatment. Physician fixed effects accounted for some disparities in treatment and entirely explained Hispanic treatment differences[85]. Li *et al*[23] assessed data for AMI patients in Pennsylvania from 1995 to 2006 and found African Americans were significantly less likely to be treated with either CABG or PCI within 3 mo of AMI. The PCI rate disparity was more in counties with the lowest AMI hospital capacity[23].

Improvements in process-of-care quality measures were assessed using more than 2 million AMI hospitalizations in 2005 or 2010. Despite significant narrowing of the racial/ethnic gap in performance rates among United States hospitals on these quality measures, the gap in PCI rates between blacks and whites in 2010 remained three times the size of the gap in PCI rates between Hispanics and whites[86].

Outcomes

Black Medicare beneficiaries, aged ⩾ 68 years, admitted with AMI from 2000 to 2005 to non-revascularization hospitals, were significantly less likely to be transferred to a hospital with PCI facilities or to receive revascularization, and had significantly higher 1-year mortality than white patients. After adjustment, disparities between transfer and revascularization rates remained significant. Black patients had lower mortality at 30 d, but significantly higher mortality thereafter, regardless of hospital type[87].

Black patients undergoing PCI had significantly more cardiovascular co-morbidity and had a higher likelihood of presenting with an AMI. At 6 mo, patients of both races had equivalent survival. However, at 5 years, blacks had significantly higher incidence of AMI, congestive heart failure, and mortality than white patients[88]. Nonwhite patients in the TACTICS-TIMI 18 randomized trial had a higher probability of death, MI, or re-hospitalization after adjustment for medical characteristics. Rates of protocol-guided angiography and revascularization were similar in white and non-white ACS patients, but nonwhite patients were significantly less likely to take their cardiac medications, to undergo non-protocol mandated angiography, and to receive a stent if undergoing PCI. They also had less procedural success with PCI. Nonwhite patients had significantly worse prognosis than white patients after adjustment for baseline characteristics[89]. In the BARI 2D trial Black, white, and Hispanic patients with diabetes treated similarly showed similar risk for death or risk for death, MI, or stroke at 5 years and in all, better risk factor control was associated with higher 5-year survival[90].

After adjusting risk in Medicare recipients aged ⩾ 65 years who had CABG performed in 2007 and 2008, using patient characteristics, socioeconomic status, and relative hospital quality, nonwhite patients had a 34% higher risk of death following CABG. Hospitals treating the largest proportion of nonwhite patients

had the highest risk-adjusted mortality for both white and nonwhite patients and hospitals treating the smallest proportion of nonwhite patients had the lowest mortality for both white and nonwhite patients[91]. In a retrospective study of revascularization outcomes in patients with left main CAD, black race and age were the only two independent predictors of adverse cardiac outcomes at 1 year following revascularization[92].

In a national sample of more than 2 million Medicare patients hospitalized for AMI from 1999 to 2010, the incidence of an index AMI declined from 1283 per 100000 person-years in 1999 to 830 in 2010, but the percentage of nonwhite patients increased from 11.0% to 12.7%. The risk of 1-year re-hospitalization for AMI declined in both white and black patients, but the decline was larger in whites (27.7%) than in blacks (13.6%), so that at the end of the study period, the discrepancy between whites and blacks actually increased. All-cause 1-year mortality declined in both sexes and both races between 1999 and 2010, but females had consistently higher 1-year mortality rates than males[93].

In the Family Cardiac Caregiver Investigation To Evaluate Outcomes (FIT-O) study[94], blacks and Hispanics were less likely to report statin use before admission, but statin use after discharge was not significantly different. Patients with a statin prescription at discharge were significantly less likely to be dead or readmitted at 30 d, independent of demographic characteristics or co-morbidity. At 1 year, blacks and Hispanics were 23% more likely than white/Asian patients to be dead or readmitted. This was not associated with statin prescription before or after hospitalization. After adjusting for co-morbidities, the investigators found that race/ethnicity did not predict death or re-hospitalization at 1 year, but age > 65 years, having a caregiver, and lacking health insurance remained significant predictors[95].

O'Neal *et al*[96] found that median survival for black CABG patients with pre-operative β-blockers was 14 years, compared with 11 years for black patients who did not have pre-operative β-blockers. White patients who had pre-operative β-blockers had median survival of 15 years *vs* 13 years for those without pre-operative β-blockers. Despite the absolute difference in median survival, the magnitude of the drugs' effect on survival was statistically similar for black and white patients[96].

Table 3 summarizes disparities in blacks in presentation, treatment, and outcomes of acute coronary syndrome.

HISPANICS

Co-morbidities and presentation symptoms

One challenge in preventing CVD in United States Hispanics is understanding the diversity within that community as it is not at all a homozygous population.

The population's genetics, exposures and related cultural experiences have tremendous variation[97]. Some recent studies that include results for Hispanics have already been presented in the sections on women and blacks.

The Hispanic Community Health Study/Study of Latinos includes individuals from a number of Hispanic backgrounds. The overall rate of high cholesterol was 52% among men (range: 48% in Dominicans and Puerto Ricans to 55% in Central Americans) and 37% in women (range: 31% in South Americans to 41% in Puerto Ricans). About 37% of men were obese (range: 27% in South Americans to 41% in Puerto Ricans) and 43% of women were obese (highest among Puerto Ricans). Approximately 26% of men actually smoking currently (highest in Puerto Ricans) and 15% of women were current smokers (21% in Cuban women, 32% in Puerto Rican women). Puerto Ricans had the highest rates of obesity and current smoking. Central American men and Puerto Rican women had the highest hypercholesterolemia. The presence of having ⩾ 3 risk factors was highest among Puerto Ricans and those who either were United States born or had lived in the United States for 10 or more years[98].

A higher level of education was linked with a higher probability of high blood pressure and large waist measurement in both male and female Mexican Americans born in the United States and those born abroad. The odds of diabetes increased with education among United States-born Mexican American women. Foreign-born Mexican American women who had lived in the United States for 5 to 19 years had the highest risk of diabetes. The odds of having hypertension were 26% lower among Mexican-born men residing in the United States under 5 years, 39% lower for Mexican-born men in the United States 5 to 19 years compared with Mexican-born men in the United States for ⩾ 20 years. Foreign-born males who had lived in the United States for fewer than 5 years had the least probability of diabetes and a large waist circumference[99].

Data from both the National Health and Nutrition Examination Study and the earlier Hispanic Health and Nutrition Examination Study looking at first- and second-generation Mexican Americans showed that first- and second-generation men did not differ in diabetes incidence, cholesterol levels and framingham risk score (FRS). Smoking levels were lower in second-generation men; they also had lower HDL cholesterol levels, and the degree of hypertension was higher than first-generation men. Neither FRS nor diabetes rates differed between first- and second-generation women. The levels of HDL cholesterol were higher in second-generation women and the rates of smoking and total cholesterol was also lower though rates of hypertension were higher than first-generation women[100].

Hispanic patients were more likely to be younger and have diabetes, and less likely to have previous MI or prior revascularization in a comparison to white STEMI patients enrolled in the Get with the Guidelines Registry. Hispanics had a higher probability of being uninsured. Hispanic patients experienced noteworthy time delays in

Table 3 Summary of disparities in acute myocardial infarction co-morbidities and presentation symptoms, care and access to medical resources, and outcomes in blacks

Co-morbidities and presentation symptoms
More likely than whites to have dyslipidemia, hypertension, obesity, insulin resistance, hyperglycemia, diabetes, and chronic kidney disease and to be physically inactive, smoke, and have poor eating habits[2]
More likely than whites to be younger and female and to have hypertension, diabetes, congestive heart failure, renal insufficiency, and history of smoking and stroke; less likely to have private insurance or cardiology care and to be uninsured[74]
More likely than whites to have Medicaid as insurer; to have no education beyond high school; to have low income; and to have a history of congestive heart failure, hypertension, and diabetes[76]
Likely to be younger and to have less education than whites; to have more hypertension, diabetes, higher BMI, and more current tobacco use; also more likely to experience palpitations, chest pressure, and chest pain[77]
More likely than whites to be younger and female and to have more hypertension, diabetes, renal insufficiency, history of smoking, congestive heart failure, previous MI, history of gastrointestinal bleeding, and lower baseline hemoglobin; also more likely to be on Medicaid or uninsured[78]
Care/medical resources
Less likely to be treated with either PCI or CABG within 3 mo of AMI than whites[23]
Longer door-to-drug and door-to-balloon times than for whites[79]
Less likely than whites to have door-to-balloon times < 90 min[80]
Likely to be transferred to a revascularization hospital more slowly than whites[81]
Less likely than whites to receive revascularization treatment[82]
Less likely than whites or Hispanics to receive revascularization treatment[83]
Less likely to be treated with revascularization than whites regardless of insurance status[84]
Less likely than whites to receive cardiac catheterization, PTCA, or CABG[85]
Persistently lower PCI rates in blacks compared to whites[86]
Less likely than whites to be transferred to a hospital with revascularization services or to be revascularized[87]
Less likely than whites to take their cardiac medications, to undergo non–protocol mandated angiography, or to receive a stent if undergoing PCI; less procedural success with PCI[89]
Outcomes
More likely to be discharged alive when not treated with revascularization than whites not receiving revascularization[83]
Lower mortality than in whites at 30 d post-AMI but higher thereafter[87]
Higher rates of recurrent AMI, congestive heart failure, and mortality than whites at 5 yr post-PCI[88]
Higher risk of death, recurrent MI, or re-hospitalization than whites[89]
Higher risk of death than whites following CABG[91]
More likely than whites to have adverse cardiac outcomes at 1 yr post-revascularization[92]
Consistently more likely than whites to have AMI re-hospitalization at 1 yr[93]
Both with and without pre-operative β-blockers, shorter median survival times with CABG than white patients[96]

PTCA: Percutaneous transluminal coronary angioplasty; AMI: Acute myocardial infarction; BMI: Body mass index; CABG: Coronary arterybypass grafting; PCI: Percutaneous coronary intervention.

triage and subsequent related reperfusion, but the use of acute medications and primary PCI was the same in the two groups. Mean in-hospital stay was longer for Hispanics, but in-hospital mortality did not differ significantly. Hispanic patients had less evidence-based discharge care. Despite these disparities, Hispanics had clinical outcomes that did not differ significantly from those of non-Hispanic whites[101].

In STEMI patients who received PCI between 2004 and 2007, patients receiving a bare metal stent (BMS) were more likely to be Hispanic and uninsured; had higher rates of surgical or PCI revascularization, peripheral vascular disease, and diabetes; and had significantly longer hospital stays and a trend toward higher all-cause mortality. Hispanic ethnicity was not an independent predictor of BMS use[102].

Among Mexicans, Hispanics, and non-Hispanic whites presenting with NSTE ACS, Mexicans were younger; had less hypertension, hyperlipidemia, renal failure, and prior revascularization; and were more likely to smoke than Hispanic and non-Hispanic white patients. Mexicans and Hispanics had a significantly higher incidence of diabetes. Acute medication use was similar in all three groups, but Mexican patients were less likely to have revascularization. Mortality was similar in all three groups[103].

Care/medical resources

The literature on disparities in AMI treatment for Hispanics is sparse. Some pertinent data were presented in the previous section, and we here briefly reiterate specific results for Hispanics from studies already cited in earlier sections. These disparities are primarily in the time to treatment and the specific treatments Hispanics received.

Door-to-drug and door-to-balloon times were significantly longer for Hispanic patients than for white patients when receiving primary PCI for STEMI; some of this disparity was explained by the hospitals in which Hispanics were treated[79]. Cavender *et al*[80] found that median door-to-balloon time was marginally longer for Hispanics than for whites. Hispanic ethnicity was not associated with lower odds of door-to-balloon times ⩽ 90 min. There was no association between race/ethnicity and in-hospital mortality.

Hispanics were not as likely as non-Hispanic whites to get in-hospital revascularization regardless of insurance (Medicare, private insurance, uninsured/

Table 4 Summary of disparities in acute myocardial infarction co-morbidities and presentation symptoms, care and access to medical resources, and outcomes in Hispanics

Co-morbidities and presentation symptoms
More likely than non-Hispanic whites to have hypertension, diabetes, and renal failure and to lack health insurance[95]
More likely than non-Hispanic whites to be younger and to have diabetes, but less likely to have previous MI or prior revascularization[101]
More likely than non-Hispanic whites to have diabetes[103]
Care/medical resources
Longer door-to-drug and door-to-balloon times than for whites[79]
Longer door-to-drug and door-to-balloon times than for whites[79]
Less likely than whites to receive catheterization or PTCA[104]
Outcomes
Hispanic patients with diabetes somewhat less likely at 5 yr to be dead, have MI, or have stroke than white patients with diabetes[90]
More likely to be dead or re-hospitalized at 1 yr than non-Hispanic whites[95]
In-hospital mortality increases with age and is higher among Hispanic females[105]

MI: Myocardial infarction; PTCA: Percutaneous coronary angioplasty.

Medicaid) but were more likely than black patients to receive revascularization[84]. Hispanics were less likely than whites to receive catheterization or PTCA, whereas black patients were less likely than white patients to receive catheterization or CABG and were somewhat less likely to have a stress test or echocardiogram[104]. Disparities in the treatment of Hispanic patients *vs* white patients dropped significantly between 2005 and 2010, indicating more equitable care in the same hospital[86].

Outcomes

Data are very limited on clinical outcomes in Hispanic patients treated for AMI. We here briefly reiterate data from studies already cited, but with specific reference to Hispanics, and note one additional recent study of Puerto Rican patients.

Patients with first MI hospitalized in 2007 in San Juan, Puerto Rico, had an average age of 64 years. Women made up 45% of the study population, but the incidence rate per 100000 was significantly higher for men (198) than for women (134). Women were less likely to receive medications such as aspirin, recommended statins, ACE inhibitors, β-blockers, or to have interventional procedures[105].

Hispanic patients with diabetes treated intensively for cardiac risk factors had a smaller risk of death/MI/stroke at 5 years than white diabetics with similar treatment, but the differences were not significant[90]. Hispanic patients with pre-existing coronary heart disease, admitted to a cardiovascular service, were less likely to report statin use before admission and more likely to be dead or re-hospitalized at 1 year than white patients. They also had higher rates of high blood pressure and diabetes and less likely to have health insurance[97].

Table 4 summarizes disparities in Hispanics in presentation, treatment, and outcomes of acute coronary syndrome.

OTHER GROUPS

Recent data are largely lacking on CVD risk factors in general, on CVD health status, and especially on revascularization as treatment for AMI among minority groups other than blacks and Hispanics. A few studies have already been discussed that either originally included some groups but tossed those study participants from the analyses because they were too few to lead to any conclusions or simply added them to other populations (*e.g.*, whites/Asians). Here we include a brief look at some recent attempts to elucidate risk factors, treatment status, or outcomes among other minority groups.

A study of the prevalence of dyslipidemia among minority populations in the United States included Asian Americans, Mexican Americans, and blacks, compared to non-Hispanic whites. Outcome measures were elevated levels of triglyceride, low HDL and high LDL cholesterol levels. Hispanic/Latino patients from subgroups other than Mexican Americans were excluded because of small numbers. Filipino and Mexican American women had the highest prevalence of high triglyceride levels and high LDL cholesterol levels. Asian Indian and Mexican American women had the highest prevalence of low HDL cholesterol levels. Mexican American women and all Asian subgroups except Korean women had higher prevalence of high triglyceride levels than white patients, but black patients had the lowest prevalence of high triglyceride levels (18.1%). In general, the prevalence rates of all three dyslipidemia types were higher in men[106].

Among Chinese, South Korean, Asian Indians, Japanese, Filipinos, and Vietnamese-the six largest Asian subgroups in the United States-Asian Indian men and women and Filipino men had the largest proportionate mortality burden from ischemic heart disease relative to non-Hispanic whites. The mortality impact of hypertension and cerebrovascular disease, namely hemorrhagic CVAs, was more elevated in every Asian-American subgroup than in whites[107].

AI/ANs have higher rates of obesity than any other group, and they are rising at a faster rates compared with non-Hispanic whites. Metabolic syndrome was found in higher rates in AI/AN men and women,

compared with the general population. The prevalence of diabetes among AI/ANs is almost three times the prevalence of diabetes among non-Hispanic whites. The rates of self-reported heart disease, stroke, and cardiovascular mortality were higher in AI/ANs than in whites. Differences in the prevalence of hypertension and hyperlipidemia were more equivocal. English surveys may underestimate the prevalence of these risk factors[10].

Bradley *et al*[79] used time between hospital arrival and reperfusion therapy as their main outcome measure in an analysis of individuals being treated for STEMI. Black patients had the longest door-to-drug time, followed by Asians/Pacific Islanders and Hispanics; all had significantly longer door-to-drug times than white patients. Minorities on a whole had significantly longer door-to-balloon times than whites.

Despite a vastly different health care system, a study in the Netherlands found disparities among minority populations there similar to those observed in the United States Investigators looked at differences between first-generation ethnic minority groups (Antillean, Chinese, Indonesian, Moroccan, South Asian, Surinamese, and Turkish) and the ethnic Dutch population after first hospitalization for AMI or congestive heart failure. Mortality rates at 28 d and 5 years were significantly higher among the migrant groups than in the ethnic Dutch. The rate of AMI re-admission for the migrant groups was nearly a third larger than for ethnic Dutch. Mortality rates for migrants after congestive heart failure differed, with a lower 28-d mortality rate among Moroccans and Turks and a higher 5-year mortality rate among Surinamese, Chinese, and South Asians. Re-admission rates for congestive heart failure were generally higher among migrant groups than in the ethnic Dutch population[108].

CONCLUSION

As this review documents, disparities persist in risk factors, health status, and co-morbidities at presentation; in the allocation of treatments; and in outcomes in revascularization as treatment for MI and, more generally, outcomes associated with CVD between female and minority patients and the general white patient population.

Women, for example, typically have more risk factors and are likely to present with more co-morbidities such as diabetes, dyslipidemia, and obesity than men. This is exacerbated among minority female groups compared with white women. Models intended to assess and estimate risk do not estimate women's risk accurately. Women have longer pre-hospital delay, and once admitted, have more limited access to guideline treatments such as PCI than men. Younger women especially have substantially higher rates of in-hospital and early and long-term mortality than men and are more likely to be re-admitted. These differences decline with age.

Blacks similarly have more risk factors such as dyslipidemia, hypertension, and obesity, and are more likely to present with co-morbidities, especially diabetes. Black patients have poorer access to guideline treatments such as PCI or CABG and experience more long-term mortality, congestive heart failure, and re-admission for AMI.

Disparities among Hispanics are more challenging to characterize, not least because so many Hispanic/Latino groups are represented in the United States population. The range of risk factors and co-morbidities seen across these various groups makes generalizing very difficult. Furthermore, in several studies, Hispanics seemed to have access to comparable care and to have outcomes that are comparable or slightly better than those in white patients, even if their initial presentation does not seem as promising.

The data show many disparities in all three of these groups but offer little explanation for these disparities. One thing women, blacks, and Hispanics often have in common in the United States is lower incomes, which can translate into less access to health insurance and thus less continuity of care. These groups often live in poorer neighborhoods and, for a variety of reasons, may have poorer health habits than their wealthier neighbors. Residential location can mean care in less-than-optimal hospital settings. Several studies reviewed here showed that hospital quality can have a major impact on the quality of treatments and on outcomes. The logical expectation that better access to coverage would translate into better care and better outcomes does not seem to be borne out in the early results from Massachusetts, where health care reform implementation is nearly 10 years old.

Huge knowledge gaps still exist, especially in studies of treatments for AMI and outcomes in minority groups beyond blacks and Hispanics. Little is known about revascularization as treatment for AMI/ACS in AI/ANs or the several Asian subpopulations in the United States or, for that matter, in Hispanic subpopulations. With advances in revascularization techniques and particularly the promising results obtained with drug-eluting stents, new randomized trials and comparative treatment studies that oversample these groups are needed. Admittedly, these can be difficult groups to study because of small numbers, but much too little is known about how to better treat these populations and how to resolve disparities in outcomes.

We'd like to end on a positive note by pointing out that racial/ethnic gaps in treatment quality measures are narrowing and that where rigorous adherence to treatment guidelines is enforced for study purposes, benefits to patients are uniform regardless of race or ethnicity. The news does not seem to be so good for women, however, and much research is still needed to understand observed disparities in outcomes among

younger female patients.

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REVIEW

Surgical perspectives in the management of atrial fibrillation

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Abstract

Atrial fibrillation (AF) is the most common cardiac arrhythmia and a huge public health burden associated with significant morbidity and mortality. For decades an increasing number of patients have undergone surgical treatment of AF, mainly during concomitant cardiac surgery. This has sparked a drive for conducting further studies and researching this field. With the cornerstone Cox-Maze III "cut and sew" procedure being technically challenging, the focus in current literature has turned towards less invasive techniques. The introduction of ablative devices has revolutionised the surgical management of AF, moving away from the traditional surgical lesions. The hybrid procedure, a combination of catheter and surgical ablation is another promising new technique aiming to improve outcomes. Despite the increasing number of studies looking at various aspects of the surgical management of AF, the literature would benefit from more uniformly conducted randomised control trials.

Key words: Atrial fibrillation; Cardiac surgery; Surgical management; Surgical ablation; Minimally invasive

Core tip: The surgical management of atrial fibrillation (AF) is a rapidly developing field. Existing surgical

techniques are constantly evolving in order to achieve more minimally invasive procedures. Additionally, the relatively new ablative modalities are being increasingly used, either alone or in conjunction with surgical techniques; attempting overall better and less invasive results. This review looks at the current surgical techniques and ablative modalities available for managing AF, where each section is re-enforced with the current most up to date guidelines on the use of each of these modalities.

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INTRODUCTION

Atrial fibrillation (AF) is the most common cardiac arrhythmia seen in clinical practice and it has been associated with substantial morbidity and mortality. The lifetime risk of AF between the ages of 40-95 is 1 in 4, as demonstrated by the Framingham study[1]. In the general population AF has been shown to occur in around 1%-2%[2].

Patients suffering from AF are at risk of thromboembolic events, including stroke leading to disability or death. One out of every five strokes is secondary to AF, with those resulting from AF being more disabling and having increased clinical significance[1,3].

The first-line treatment of AF has traditionally been anti-arrhythmic drugs, whether attempting rate and or rhythm control. However, long-term anticoagulation is not without risks as it can interfere with quality of life and increase morbidity. There is still considerable variation in the pharmacological treatments of AF in clinical practice[2].

Catheter based ablation is an alternative to medical therapy, as a minimally invasive intervention which can provide relatively good results[4].

The role of surgery in the management of AF has been introduced following the ground-breaking "Maze" procedure described and developed by Cox *et al*[5] in a series of publications. The "Maze" procedure has been the cornerstone of surgical management of AF[3-8]. The Cox-Maze Ⅲ procedure is regarded as the gold-standard surgical treatment of AF having the highest success rates; greater than or equal to 90% long-term freedom from AF[4,9,10]. However, the procedure is highly invasive and technically difficult, requiring a high level of surgical expertise, thus limiting its use to a few specialist centres[9].

These limitations have fuelled further research in the field of surgical management of AF with a view to develop less invasive but equally effective alternative techniques.

This has led to the development and use of multiple ablative devices using various energy sources, as well as less surgically invasive Cox-Maze lesions allowing replacement of incisions with ablation lines[2]. There is still on-going research and development of new techniques, within this rapidly evolving field.

AF BACKGROUND AND DEFINITIONS

Electrophysiological basis of AF

In 1998, Haïssaguerre *et al*[9] made an important discovery regarding the origin of atrial ectopic beats in paroxysmal AF. At the time it was known that chronic AF was the result of re-entrant circuits, though no information was available about its origin.

The spontaneous initiation of AF was studied using intra-cardiac monitoring, angiography and fluoroscopy looking specifically at the electrical activity preceding the onset of AF. A total of 69 foci were identified as being responsible for the origin of atrial ectopic beats, in a study of 45 patients. The striking majority (94%) of the foci were found to be in the pulmonary veins with others including the right and left atria. Radiofrequency catheter ablation was subsequently utilised to ablate those foci in order to abolish spontaneous depolarisation. Sinus rhythm was achieved and maintained in 28 patients (62%) at a follow up period of 8 ± 6 mo[9]. This discovery led to the pulmonary vein isolation (PVI) approach.

The identification of abnormal depolarisation foci, helped in understanding the origin and development of AF. It became apparent that ectopic atrial depolarisation is responsible for the initiation of AF, whilst macro re-entrant circuits are responsible for its propagation (Figure 1)[10].

Definition and classification of AF

AF is defined as a supra-ventricular arrhythmia where asynchronous atrial activation occurs, leading to worsening atrial mechanical function[2,4,11].

According to the definitions given by ACC/ESC/AHA 2006, Society of thoracic surgery (STS), ESC and EACTS clinical guidelines committee, there are five types of AF. These are defined as: First diagnosis, paroxysmal, persistent, long-standing persistent and permanent AF (Table 1).

AF can also be classified as primary or secondary according to its origin. Primary AF occurs in patients with no underlying cardiac disease whilst secondary AF occurs as a result of pre-existing cardiac disease. This has implications when looking at the surgical management of AF. Whilst patients with secondary AF benefit from concomitant treatment alongside other cardiac surgical procedures, catheter ablation alone is a more suitable treatment modality for paroxysmal primary AF[12-15].

SURGICAL MANAGEMENT OF AF

Correct nomenclature for surgical procedures used in AF management

According to 2012 HRS/EHRA/ESC guidelines the term

Table 1 The five types of atrial fibrillation as classified by European Heart Rhythm Association and European Association For Cardio Thoracic Surgery

Type of AF	Duration	Definition
First diagnosis	-	First episode of AF irrespective to duration or severity
Paroxysmal	48 h	Self-terminating (usually within 48 h); may continue for up to 7 d. After 48 h it is unlikely that spontaneous conversion will occur Anticoagulation must be considered
Persistent	> 7 d	Requires termination by cardio-eversion with drugs or direct current
Long standing persistent	⩾ 1 yr	Rhythm control strategy
Permanent	-	Presence of arrhythmia is accepted and rhythm control interventions are not pursued[1]

[1]In case of rhythm control interventions, the permanent AF should be re-designated as long standing persistent AF. AF: Atrial fibrillation.

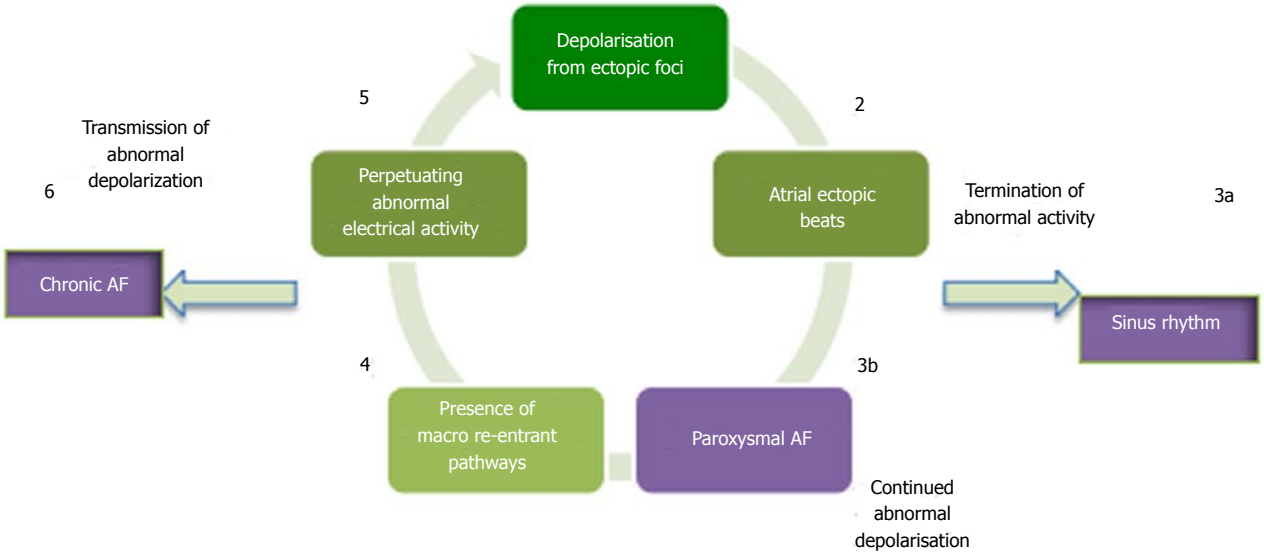

Figure 1 Electrophysiological basis of paroxysmal and chronic atrial fibrillation. AF: Atrial fibrillation.

"Maze" procedure should only be used to refer to the Cox-Maze Ⅲ lesion set. The above term should not be used for other less extensive lesion sets. Furthermore, the suggested terminology for ablative procedures is as follows: (1) full Cox-Maze lesion set; (2) left atrial appendage (LAA) lesion set; and (3) PVI[4,14].

The Cox-Maze "cut and sew" procedure

Cox-Maze Ⅰ and Ⅱ: Cox *et al*[6] first described the Cox-Maze procedure in 1991. The Cox-Maze Ⅰ (CM-Ⅰ) procedure was initially developed, consisting of a set of lesions generating an "electrical maze" through the atria. The linked atrial segments were created surgically by cutting and sewing in order to interrupt and eliminate macro re-entrant circuits[7-10]. The Maze Ⅰ procedure had several limitations including left atrial dysfunction and failure to generate sinus tachycardia on exertion. The Cox-Maze Ⅱ (CM-Ⅱ) procedure was subsequently developed aiming to overcome those limitations. In CM-Ⅱ a revised lesion set was used, in an attempt to improve conduction between the atria. However, this led to a technically more challenging procedure with the same drawbacks as CM-Ⅰ[7-10].

Cox-Maze Ⅲ: The Cox-Maze Ⅲ (CM-Ⅲ) procedure shortly followed which overcame the limitations of the previous two procedures. Atrial transport function was preserved allowing depolarisation from sinoatrial node to atrioventricular node for efficient atrial contraction. CM-Ⅲ achieved 93% freedom from AF during an 8.5 year follow up, with successful cardioeversion of all cases on one anti-arrhythmic drug. Additionally, the need for pacemaker was abolished and recurrence of AF reduced[7-10]. Equally encouraging results from the CM-Ⅲ were generated by the Cleveland Clinic and Mayo Clinic[16,17].

Despite its high success rates the procedure remained technically challenging and highly invasive. A median sternotomy and cardiopulmonary bypass (CPB) is required for CM-Ⅲ, limiting its use to patients undergoing concomitant heart surgery, as it is deemed to be too invasive to be solely performed for AF treatment.

The Cox-Maze Ⅳ: A few years later, the Cox-Maze Ⅳ (CM-Ⅳ) was developed initially described by Gaynor *et al*[18] in 2004. A different lesion set to CM-Ⅲ was used and the traditional "cut and sew" technique was replaced with the use of ablative devices. Namely, the combined use of bipolar radiofrequency ablation together with

cryoblation was used in that study. Moreover, CM-Ⅳ had the added advantage of being technically simpler than CM-Ⅲ, meaning that it could be used in a greater number of centres. The lesion set used was similar to CM-Ⅲ and it still had to be performed under CPB[18,19].

Widespread variation has been observed in the lesion sets used to treat AF. Since the publication of CM-Ⅲ the lesion sets have been altered slightly in CM-Ⅳ and are continuously being altered in the current literature. The main reason for the constant alteration of the lesion sets is that surgeons are striving to achieve minimally invasive procedures, with the best clinical outcomes possible[12].

PVI

The PVI approach was developed following the discovery of the pulmonary veins being a key area of ectopic depolarisation, resulting in atrial ectopic beats and ultimately leading to AF. The PVI approach has been used in a number of trials and was shown to produce good results in paroxysmal AF.

When first performed by Haïssaguerre *et al*[9] 62% of patients were free from AF in a median follow up of 7 mo. In studies that followed, empirical isolation of the pulmonary veins became the most common approach as it was observed that the ectopic foci contributing to AF were often variable.

In the study by Haïssaguerre *et al*[9], 94% of the ectopic foci were found in the pulmonary veins. Thus, one would expect that by ablating those foci freedom from AF would be close to 90%. However, this has not been the case in studies looking at long term (5 year) freedom from AF using PVI, with the success rate being as low as 30%-50% and the recurrence rate up to 70%[20,21].

The reduced effectiveness of PVI can be attributed to incomplete transmural lesions and pulmonary vein reconnection. Another reason for the low success rates is the fact that the pulmonary veins are not the only triggers of AF. Exclusively using PVI may not be sufficient in patients with persistent and long-standing AF, as demonstrated by studies where ablation of additional areas improved the outcomes[22-24]. However, due to large inter-study variation in ablation methodology it is difficult to assess the effectiveness of PVI alone.

Exclusion of LAA

The LAA has been associated with occurrence of stroke in patients with AF. Studies have demonstrated that around 90% of the thrombi are found in the LAA, making it the primary source of emboli. This has led to the conclusion that successful closure of the LAA would reduce the risk of such thromboembolic events[25,26]. Several studies have investigated the link between LAA exclusion and reduction in stroke in patients with AF.

Healey *et al*[27] (2005) performed an RCT of 77 patients undergoing CABG where 52 of them underwent LAA occlusion. However, occlusion was successful in just 66% of the patients. One patient had an intraoperative ischaemic stroke and another had a TIA. Twelve percent of the patients had subsequent self-reported strokes on follow-up done *via* a questionnaire.

Kanderian *et al*[28] (2008) demonstrated that 55% of 137 patients who underwent LAA closure had a successful procedure. Eleven percent of the patients that had a successful closure had a subsequent stroke or TIA compared to 15% of those with unsuccessful procedure. These results were nevertheless found to be non-significant.

García-Fernández *et al*[29] (2003) looked at 205 patients undergoing mitral valve surgery, with 58 of them having LAA ligation. Successful ligation was seen in 89.7% of patients. Absence of LAA ligation was found to be an independent predictor of thromboembolism following mitral valve surgery. Systemic emboli occurred more frequently in the group of patients that did not receive ligation.

Contrasting the above studies, Almahameed *et al*[30] (2007) found a significantly increased rate of stoke in patients with LAA occlusion, looking at 136 patients that underwent LAA ligation during mitral valve surgery.

The above studies demonstrate the heterogeneity of existing results when looking at LAA exclusion. Success rate is variable between the studies, ranging from 55% to 93%. According to the EACTS guidelines, there is insufficient evidence to prove that LAA exclusion has a benefit in terms of stroke reduction or mortality[2].

ABLATION USING ENERGY SOURCES

Various energy sources have emerged over the last decade striving to replace the traditional "cut and sew" technique by replicating the transmural lesions whilst using a less invasive approach[31]. Nevertheless, the vital pre-requisite for successful AF ablation, as demonstrated by the CM-Ⅲ lesion set, is that the lesions need to be completely transmural and contiguous bilaterally. In addition, it is fundamental that the lesions are placed in the correct pattern[10,12,18]. Therefore, an important caveat when looking at new ablation techniques is the ability to achieve complete transmurality of lesions. The ablative energy modalities available for surgical treatment of AF are compared in Table 2.

Radiofrequency ablation

Radiofrequency ablation (RFA) works by conducting an alternating electrical current through the myocardium. The energy from this electrical current gets dissipated through the myocardial tissue as heat, causing coagulative necrosis and resulting in an area of non-conducting myocardium. Complications of RFA include injury to collateral structures such as the pulmonary veins, oesophagus and coronary arteries[14,25].

Unipolar RFA

The effectiveness of unipolar RFA during concomitant cardiac surgery has been investigated by several studies.

Table 2 Comparing and contrasting the various available ablation modalitie

Ablation modality	Mode of action	Advantages	Complications	Transmural lesions	Current limitations
RFA	Controlled thermal damage and lesions caused by electrical current	Less operating time Reduced technical difficulty	Intercavity thrombus Pulmonary vein stenosis Oesophageal and coronary artery injury	Variable	Confirmation of transmurality Variation between instruments
Cryoablation	Targeted scarring by cooling tissue using high-pressure argon and helium Initial cellular destruction followed by fibrosis and full thickness disruption	Visual confirmation of transmurality Less damage to surrounding tissues and vascularity Less endocardial thrombus Electrical isolation of atria	Coronary artery and phrenic nerve injury Atrioesophageal fistula	Yes	Variable success rate
Microwave	Production of lesions by thermal injury	Minimal collateral damage Minimal scar formation Lower risk of VTE	Coronary artery damage potential	Variable	Less effective compared to other modalities Limited evidence
HIFU	Creation of localised hyperthermic lesions using a focused beam of ultrasound energy	Fast epicardial lesions Future potential advantage visualisation of thickness by ultrasound and tailor made lesions	Atrioesophageal fistula Pericardial effusion Phrenic nerve injury	Yes endocardial only	High rate of complications Limited evidence currently not recommended outside trials
Laser	Use of high energy optical beams to create thermal lesions	Well demarcated lesions Non-arrythmogenic Rapid lesions	Crater formation Perforation Tissue loss Poor visibility of scar	Yes	Limited evidence currently not recommended outside trials

RAF: Radiofrequency ablation; HIUF: High intensity focused ultrasound.

Johansson *et al*[32] (2008) looked at patients undergoing CABG in combination with unipolar RFA. Patients were followed up for 32 ± 11 mo (with intermediate follow up at 3 and 6 mo) looking for sinus rhythm. In the RFA group 62% of patients were in sinus rhythm compared to 33% in the non-RFA group. Patients who were in paroxysmal or persistent AF were more likely to remain in sinus rhythm than patients with permanent AF. The presence of sinus rhythm at 3 mo was found to be a high predictor of the patient remaining in sinus rhythm at further follow up.

Khargi *et al*[33] (2005) looked at a cohort of patients with permanent AF undergoing open-heart surgery (CABG, aortic and mitral surgery) together with unipolar RFA. Sinus rhythm was observed in 79% of patients undergoing CABG/aortic surgery and 71% of mitral surgery patients. Notably, adding RFA did not increase mortality compared to cardiac surgery alone.

Bukerma *et al*[34] (2008) looked at patients fulfilling the criteria for permanent AF who underwent concomitant cardiac surgery and unipolar RFA. Contrasting the high success rates seen at the aforementioned studies, just 52% of patients maintained sinus rhythm at 5-year follow up.

All of the above studies used 24 h outpatient holter ECG monitoring to detect the presence of sinus rhythm. An important pitfall is that asymptomatic AF can be easily missed, as the monitoring is not continuous during the follow up period. This needs to be taken into account when designing future studies[2].

Unipolar RFA combined with concomitant cardiac surgery is considered to be effective in restoring sinus rhythm. Higher degrees of success rates are seen in paroxysmal or persistent AF, young age and smaller LAD[2].

Bipolar RFA

The effectiveness of bipolar RFA during concomitant surgery has also been explored.

A meta-analysis conducted by Chiappini *et al*[35] (2004) looked at 6 non-randomised studies of patients with AF undergoing RFA as an adjunct to cardiac surgery, where 76% freedom from AF was achieved at 13.8 mo follow up with the overall survival rate being 97.1%.

Similarly, von Oppel *et al*[36] (2009) looked at patients with persistent AF undergoing concomitant cardiac surgery and bipolar RFA compared to cardiac surgery alone. Seventy-five percent of patients in the RFA group were free of AF at a 1-year follow up with more than 60% of patients having restoration of left atrial contraction.

A best evidence topic on the effectiveness of bipolar RFA during concomitant cardiac surgery conducted by Basu *et al*[37] (2012), revealed that bipolar RFA was more successful in restoring sinus rhythm for at least 1 year when performed together with cardiac surgery. In addition, a high survival rate was observed and the procedure required an average of 15 additional minutes of cross clamp time.

Bipolar RFA used in conjunction with cardiac surgery has a higher success in restoration of sinus rhythm compared to cardiac surgery alone. There is limited evidence to conclude whether bipolar RFA is more

effective than unipolar RFA. Further studies comparing the two modalities are needed[2].

Cryoablation

Cryoablation works by cryothermal energy, generated by the use of pressurised liquid nitrous oxide resulting in cooling of the surrounding tissue. Tissue injury occurs by the creation of ice crystals within the cells disrupting the cell function and electrical conductivity. Additionally, microvascular disruption ensues resulting in cell death. Complications of cryoablation include phrenic nerve injury, atrioesophageal fistulas and coronary artery injury[14,24]. Several studies have proved the efficacy of cryoablation in the treatment of AF.

The PRAGUE 12 (2012) was a randomised multi-centre trial that is considered a milestone trial for AF. It looked at 224 patients with AF undergoing valve replacement or coronary surgery. The patients were randomised in two groups with group A undergoing surgical ablation and group B having no ablation. In the ablation group, 96% had treatment with a cryoprobe. The procedure performed consisted of PVI, mitral annulus lesion, LAA lesion and a connecting lesion. At 1 year follow up 60% of patients that underwent ablation were in sinus rhythm compared to 36% in the untreated group. At 1 year follow up no clinical benefits were seen in patients who underwent AF surgery; however the study is still ongoing and results for the 5-year follow up are yet to be published[38].

Camm *et al*[39] (2011) conducted a best evidence topic looking at the effectiveness of cryoablation during concomitant cardiac surgery. Nine studies were reviewed, including RCTs and retrospective studies. Cryoablation was found to be an acceptable surgical intervention, achieving sinus rhythm in 60%-82% of patients at 12 mo follow up.

Blomström-Lundqvist *et al*[40] (2007) conducted a RCT looking at patients undergoing concomitant AF surgery and mitral valve repair. The results demonstrated that undergoing cryoablation for AF treatment significantly increased the return to sinus rhythm. 73.3% of patients in the cryoablation group were found to be in sinus rhythm compared to 42.9% of those undergoing mitral valve surgery alone. However, it is worth noting that patients in the cryoablation group had an increased rate of complications. No significant increase in the mortality or morbidity was seen in either group.

Cryoablation during concomitant cardiac surgery has been proven to achieve good rates of sinus rhythm and it is more successful in patients with paroxysmal AF as opposed to permanent AF. Increased complication rates from cryoablation were seen in just one study. Finally, a lack of 24 h monitoring meant that accurate assessment of AF resolution was difficult[2,4].

Microwave ablation

Microwave ablation works by producing a well-demarcated lesion through thermal injury. Its main advantage is that it produces good epicardial lesions and can be used in minimally invasive techniques.

MacDonald *et al*[41] (2011) conducted a best evidence topic regarding the effectiveness of microwave ablation for AF treatment during concomitant heart surgery. Eleven studies were reviewed with a large degree of heterogeneity observed between the studies. The success rate ranged between 65%-87% over a variable follow up period between 6-12 mo. The conclusion was that microwave ablation is not currently recommended due to limited evidence and unclear long-term success rates.

Lin *et al*[42] (2010) compared microwave ablation to bipolar RFA. A RCT was conducted where patients were randomised to a radiofrequency or a microwave ablation group. Patients were then followed up at 3, 6, 9 and 12 mo and then annually. With a mean follow up of 24 mo, freedom from AF in the radiofrequency group was 88.7% compared to 71.2% in the microwave ablation group (P = 0.0008). Thus bipolar radiofrequency ablation was demonstrated to be superior to microwave ablation.

Kim *et al*[43] (2010) compared cryoablation to microwave ablation in patients with mitral disease and AF. They demonstrated a 5-year freedom rate from AF of 61.3% in the microwave group compared to 79.9% in the cryoablation group. Additionally, microwave ablation was associated with more frequent AF recurrence rates.

Microwave ablation is currently considered to be less effective than other ablation modalities, based on the limited evidence[2]. Further studies are needed to investigate the effectiveness of microwave ablation as a definite treatment of AF.

High intensity focused ultrasound ablation

High intensity focused ultrasound (HIFU) is a relatively new ablative modality and works by creating a localised thermal lesion using a focused beam of ultrasound energy. HIFU has been proven to create permanent transmural lesions when applied epicardially. It has the advantage that CPB is not needed and can be performed on the beating heart. HIFU can also be delivered *via* a balloon catheter in order to facilitate circumferencial ablation of pulmonary veins[44].

Neven *et al*[45] (2011) performed PVI using HIFU and subsequently followed up the patients for 2 years. An oesophageal temperature-guided safety algorithm was used in an attempt to minimise the complications. At 2 year follow up the success rate from the procedure was comparable to that of radiofrequency ablation. However, severe complications were not prevented despite the use of a safety algorithm. Complications included atrioesophageal fistula, pericardial effusion and phrenic nerve palsy. They concluded that HIFU did not meet the safety standards required for AF treatment, mainly because phrenic nerve palsy and atrioesophageal fistula were still common severe complications. The clinical use of HIFU has currently been halted.

Davies *et al*[46] (2013) followed up 110 patients undergoing HIFU ablation for AF treatment. At a 2-year

follow up 49% of patients remained in sinus rhythm. The percentage of patients in sinus rhythm was given for each of the pre-operative AF types: 81% for paroxysmal AF, 56% for persistent AF and 18% for long standing AF. The conclusion was that HIFU is safe and effective for use in paroxysmal AF, however alternative ablation strategies should be considered for persistent and long standing AF.

Klinkenberg *et al*[47] (2009) and Schmidt *et al*[48] (2009) have also demonstrated that despite relatively high percentages of freedom from AF there is a high complication rate when using HIFU ablation. They have concluded that further research is needed to assess optimal ablation techniques.

HIFU ablation is currently not recommended outside trials due to the high rates of complications reported and its success rates being inferior to other ablative modalities[2]. Further studies are looking at the success rates of HIFU combined with cardiac surgery are needed, as the evidence available is currently limited.

Laser ablation

Laser ablation for AF treatment works by using laser energy to create localised hyperthermic lesions[14,20].

Gal *et al*[49] (2015) used an endoscopic laser balloon ablation system to perform PVI with 58% of patients remaining free from AF at follow up with no anti-arrhythmic drugs. They concluded that laser ablation has a low risk of complications and its success rate was comparable to other ablation modalities.

Šedivá *et al*[50] (2014) performed PVI using visually guided laser ablation in 194 patients. In 1 year follow up 82.3% of patients remained free from AF in the paroxysmal AF group and 75% in the persistent AF group; this percentage remained close to 75% in 3 and 4-year follow up. They concluded that visually guided laser ablation is an effective and safe modality to be used in clinical practice with good clinical outcomes and low rates of complications.

Hamman *et al*[51] (2009) used a diode pumped laser to perform a left modified or complete CM-III lesion set. The results observed were very encouraging with a 95% freedom from AF and 76% freedom from all tachyarrhythmias. However, it needs to be noted that the study was only a small one, consisting of 28 patients.

Currently, laser ablation is not approved for clinical use outside trials due to limited available evidence to support its effectiveness and safety.

CATHETER ABLATION, SURGICAL ABLATION AND HYBRID APPROACH

As well as using different devices for AF ablation, there are several methods to perform the ablation procedure. Traditionally the two options were catheter and surgical ablation.

Surgical ablation can be performed with the conventional surgical approach during concomitant cardiac operations or with less invasive approaches such as mini sternotomy, mini thoracotomy or VATS.

Catheter ablation is considered to be the least invasive approach and it is used to create endocardial lesions. In some studies catheter ablation for AF has been shown to be 80% effective, with 70% of patients not requiring any anti-arrhythmic drugs at intermediate follow up[52].

The hybrid approach consists of a combination of surgical and catheter procedures. This has emerged in an attempt to ensure good epicardial and endocardial transmurality of lesions as well as attempting to enhance the long-term success of AF ablation. In essence, this approach aims to overcome the limitations of surgical and catheter procedures alone.

The hybrid procedure can be performed as a single or a two-stage procedure with advantages to each. When performing a single procedure undergoing anaesthesia twice and having further hospital admission are avoided. In contrast, when performing a two-stage approach with an average interval of 1-3 mo, the lesions are more likely to have healed and have stable conductive properties (Figure 2)[53].

Gaita *et al*[54] (2013) looked at a hybrid approach involving surgical cryoablation and transcatheter RFA in order to perform PVI and left atrial isolation. The procedure was performed in 33 patients, 73% of which were in sinus rhythm, at a mean follow up of 10 ± 3.1 years. At the end of the follow up period 81% of patients with a complete lesion set were in sinus rhythm compared to 43% of those with an incomplete lesion set. Electrophysiological evaluation of lesion transmurality of was used, aiding in significant improvement of outcomes.

Kumar *et al*[55] (2014) used a hybrid approach consisting of bipolar radiofrequency devices epicardially and cryoballoon endocardially. This approach was found to be feasible and safe, though the results should be interpreted with caution as the study consisted of only 7 patients.

Bulava *et al*[56] (2015) combined surgical thoracoscopic RFA with catheter RFA performed 6-8 wk later in a staged hybrid method. At 12 mo follow up after a completed hybrid ablation 94% of patients were in sinus rhythm.

A systematic review by Je *et al*[57] (2015) compared the endocardial Cox-Maze procedure, epicardial surgical ablation and hybrid procedure. The results demonstrated that minimally invasive Cox-Maze procedure with CPB support was the most effective treatment for stand-alone AF with a higher success rate seen at 12 mo following the procedure.

The hybrid approach is a promising new procedure that could significantly improve outcomes for patients undergoing surgical treatment for AF. It has been shown to have a mortality rate close to 0% with long-term success rates approaching 95% similar to the cut and sew Cox maze procedure. Thus, in the mildly symptomatic lone AF population, the hybrid procedure could become the standard of care in the near future[58].

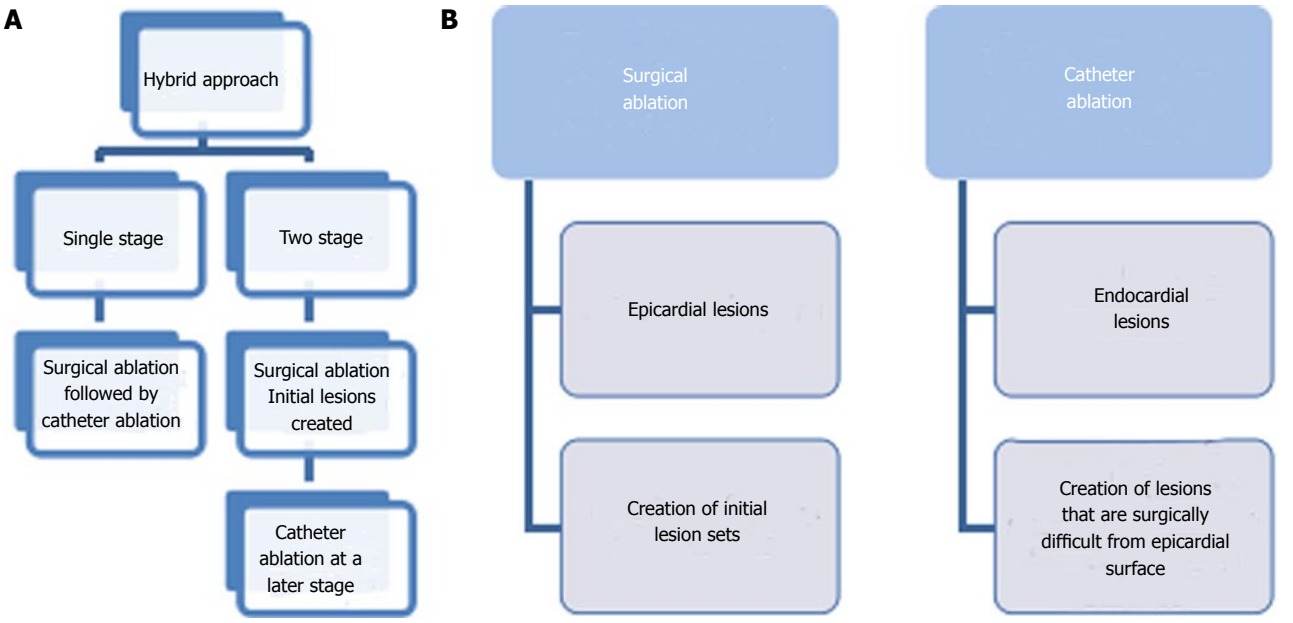

Figure 2 Schematic representation of the hybrid approach and the two stages of the hybrid approach (A and B).

Further studies would be essential in order to identify the combination of modalities that yields the most successful results when performing a hybrid procedure.

CONCOMITANT HEART SURGERY AND SURGICAL TREATMENT OF AF

Surgical treatment of AF can be performed alone as well as in conjunction to cardiac surgery. Several studies have compared the efficacy of concomitant cardiac and AF surgery to cardiac surgery alone. Mitral valve surgery is the most common procedure that has been combined with AF ablation. It is known that 30%-50% of patients undergoing mitral valve surgery present with AF, which itself leads to increased risk of stroke and reduction in survival rates[59].

Phan *et al*[59] (2014) conducted a meta-analysis on surgical ablation for AF during mitral valve surgery. The results demonstrated that the addition of AF ablation led to a significantly greater number (64.4% *vs* 17.9%, $P < 0.00001$) of patients in sinus rhythm at a follow up period of > 12 mo. There was no increase in mortality, need for pacemaker implantation, stroke or thromboembolism risk.

A RCT conducted by Gillinov *et al*[60] (2015) consisted of a group of 260 patients with persistent or long-standing persistent AF. It compared patients undergoing mitral valve replacement therapy either with or without surgical ablation. The results showed that addition of AF ablation to mitral valve surgery led to a significant increase ($P < 0.001$) in the rate of freedom from AF in 1 year. The control group had 29.4% freedom from AF when compared to 63.2% in the ablation group.

The Left atrial radiofrequency ablation during mitral valve surgery: A prospective randomized multicentre study (SAFIR)[61] study (2009) was a multi-centre double-blinded centrally randomised trial involving four university hospitals. It compared patients undergoing left atrial RFA combined with mitral valve replacement to those undergoing mitral valve replacement alone. The results were in favour of the combined ablation and mitral valve replacement. At 12 mo follow up the freedom from AF was 95.2% in the combined group *vs* 33.3% in the control ($P < 0.005$).

The Surgical Atrial Fibrillation Suppression Study (2011) was a RCT that looked at patients undergoing RFA performed in conjunction to cardiac surgery. They concluded that surgical RFA for AF during concomitant cardiac surgery significantly reduces AF burden. However, 13% of patients had asymptomatic AF episodes only identified on continuous monitoring. This was deemed to have significant implications for the definition of successful surgical AF ablation as well as the need for post-operative anti-arrhythmic and anticoagulants[62]. Potential disadvantages of this combined approach are the increased rates of permanent pacemaker insertion and increased operative time[27,59-62].

The use of energy sources for AF ablation is recommended in concomitant cardiac surgery because of good evidence supporting the efficacy of the combined procedure[2]. However, further studies are needed to investigate combination of surgical AF ablation with specific cardiac operations. This will help in identifying the combination of ablative modality and cardiac surgery yielding the best results.

Tables 3-9 summarise the studies discussed in the sections above, looking at each modality available for surgical AF ablation.

POST-OPERATIVE ANTICOAGULATION AND FOLLOW UP

Post-operative anticoagulation

A best evidence topic was conducted by Michael Gray

Table 3 Adapted from 2012 Heart Rhythm Society/European Heart Rhythm Association/European Society of Cardiology guidelines

Indications for concomitant surgical ablation of AF
Symptomatic AF refractory or intolerant to at least one Class 1 or 3 antiarrhythmic medication
Paroxysmal: Surgical ablation is reasonable for patients undergoing surgery for other indications (IIa, C)
Persistent: Surgical ablation is reasonable for patients undergoing surgery for other indications (IIa, C)
Longstanding persistent: Surgical ablation is reasonable for patients undergoing surgery for other indications (IIa, C)
Symptomatic AF prior to initiation of antiarrhythmic drug therapy with a Class 1 or 3 antiarrhythmic agent
Paroxysmal: Surgical ablation is reasonable for patients undergoing surgery for other indications (IIa, C)
Persistent: Surgical ablation is reasonable for patients undergoing surgery for other indications (IIa, C)
Longstanding persistent: Surgical ablation may be considered for patients undergoing surgery for other indications (IIb, C)
Indications for standing alone surgical ablation of AF
Symptomatic AF refractory or intolerant to at least one Class 1 or 3 antiarrhythmic medication
Paroxysmal: Stand alone surgical ablation may be considered for patients who have not failed catheter ablation but prefer a surgical approach (IIb, C)
Paroxysmal: Stand alone surgical ablation may be considered for patients who have failed one or more attempts at catheter ablation (IIb, C)
Persistent: Stand alone surgical ablation may be considered for patients who have not failed catheter ablation but prefer a surgical approach (IIb, C)
Persistent: Stand alone surgical ablation may be considered for patients who have failed one or more attempts at catheter ablation (IIb, C)
Longstanding persistent: Stand alone surgical ablation may be considered for patients who have not failed catheter ablation but prefer a surgical approach (IIb, C)
Longstanding persistent: Stand alone surgical ablation may be considered for patients who have failed one or more attempts at catheter ablation (IIb, C)
Symptomatic AF prior to initiation of antiarrhythmic drug therapy with a Class 1 or 3 antiarrhythmic agent
Paroxysmal: Stand alone surgical ablation is not recommended (III, C)
Persistent: Stand alone surgical ablation is not recommended (III, C)
Longstanding persistent: Stand alone surgical ablation is not recommended (III, C)

AF: Atrial fibrillation.

Table 4 Adapted from the surgical treatment of atrial fibrillation guidelines by the European Association for Cardio-Thoracic Surgery Clinical Guidelines Committee guidelines

Use of ablative modalities
Unipolar radiofrequency ablation
Concomitant unipolar RFA for AF treatment together with cardiac surgery is effective in restoration of sinus rhythm
Success rates vary between 54%-83% at medium term follow up (at least 12 mo)
Safe procedure - no additional risks
Success rates are higher with: paroxysmal or persistent AF, younger age, smaller LAD
Class IIa recommendation based on multiple small retrospective studies (Level C)
Bipolar radiofrequency ablation
Higher success rates in restoring sinus rhythm compared to no ablation in concomitant cardiac surgery
On average the cross clamp time is increased by 15 min
There is limited evidence to suggest superiority of bipolar over unipolar RFA
1 prospective trial has provided evidence demonstrating superiority of bipolar RFA over microwave ablation
Class I recommendation based on 3 RCTs and multiple small prospective studies (Level A)
Cryoablation
Acceptable intervention for AF treatment during concomitant surgery with acceptable sinus rhythm conversion rates between 60%-82% at 12 mo
Cryoablation is most successful in patients suffering from paroxysmal as opposed to permanent AF (suggested by 6 out of 9 studies reviewed)
Class IIa recommendation based on 1 small RCT and multiple prospective and retrospective studies (Level B)
Microwave ablation
Less effective intervention for AF treatment based on the limited evidence
Success rates in the longer term are less clear - the only RCT to date has found outcomes inferior to RFA
Class III recommendation based on 1 small RCT and multiple small prospective and retrospective studies (Level B)
HIFU
Currently not recommended as an intervention for the treatment of AF during concomitant surgery outside clinical trials due to limited evidence
Success rates seem to be inferior to those of other devices
Significant concerns have been reported
Class III recommendation based on cohort studies (Level C)
Exclusion of laa and standing alone surgical ablation
Exclusion of LAA
No proven benefit of surgical LAA exclusion in terms of stroke reduction or mortality
Ineffective LAA occlusion and potentially increased stroke risk due to poor technique was seen in many studies
Devices designed for LAA exclusion should be preferentially used rather than a cut and sew or stapling technique, if LAA is to be performed
Class IIa recommendation based on multiple cohort studies and one pilot RCT (Level B)
Stand alone surgical ablation
Surgery can be considered for symptomatic patients who are refractory or intolerant to at least 1 anti-arrhythmic medication
Considered for patients with paroxysmal, long standing and persistent AF who prefer surgery to catheter ablation or have failed catheter ablation
Results of both catheter-based and surgery-based ablation should be discussed with the patient
Class IIa recommendations based on 1 RCT and multiple cohort studies (Level B)

RFA: Radiofrequency ablation; AF: Atrial fibrillation; LAD: Left anterior descending; RCT: Randomized controlled trial; HIFU: High intensity focused ultrasound; LAA: Left atrial appendage.

Table 5 Summary of results from studies included looking at Cox-Maze procedures

Procedure	Ref.	Sample size	Mean follow-up period	Outcome	Important findings
Cox-Maze	Cox *et al*[7]	178 patients	8.5 yr	93% freedom from AF	Cox-Maze procedure developed
Cox-Maze	McCarthy *et al*[16]	100 patients	3 yr	90.4% in sinus rhythm or atrial pacing	Associated with low perioperative and late morbidity rates
Cox-Maze	Schaff *et al*[17]	221 patients	6 yr	90% in sinus rhythm	CM procedure was useful in patients requiring valvuloplasty for mitral regurgitation
Modified Cox-Maze with bipolar RFA	Gaynor *et al*[18]	40 patients	6 mo	91% in sinus rhythm	Modification of CM-III shortened and simplified the procedure with no change in short-term efficacy

RFA: Radiofrequency ablation; AF: Atrial fibrillation.

Table 6 Summary of results from studies included looking at pulmonary vein isolation and left atrial appendage

Procedure	Ref.	Sample size	Mean follow-up period	Outcome	Important findiNGS
PVI	Haïssaguerre *et al*[9]	45 patients	8 ± 6 mo	Sinus rhythm achieved in 28 patients (62%)	69 foci identified as the source of ectopic atrial beats in 45 patients
PVI	Chao *et al*[21]	88 non-paroxysmal AF patients	36.8 mo	The long-term freedom period of AF was 28.4% after a single procedure	CHADS2 score of >/3 and left atrial diameter found to be significant predictors of recurrences
LAA obliteration	Healy *et al*[27]	RCT - 77 patients with risk factors for stroke	8 wk follow-up with trans-oesophageal echocardiography	Complete occlusion achieved in 45% (5/11) of patients through the use of sutures and in 72% (24/33) using a stapler	Surgical LAA can be safely done during a routine CABG; expertise is key to its success rates
LAA excision or exclusion	Kenderian *et al*[28]	137 patients	Post-operative trans-oesophageal echocardiography	Successful LAA closure 73% with surgical excision and 23% with suture exclusion. Evidence of stroke in 11% of successful LAA closure and 15% of unsuccessful LAA closure (P = 0.61)	High proportion of surgical LAA closure. LAA excision more successful than exclusion
LAA obliteration + Mitral valve replacement	García-Fernández *et al*[29]	58 patients	69.4 mo trans-oesophageal echocardiography	46% of patients had an embolism. Risk of embolism increased by 11.6 in incomplete/absence of LAA ligation	Absence of LAA ligation and presence of left atrial thrombus identified as independent predictors for stroke
LAA exclusion during mitral valve surgery	Almahameed *et al*[30]	136 patients	3.6 ± 1.3 yr	12.3% of patients had thromboembolic events, 71% of which occurred in patients undergoing mitral valve repair	There were more thromboembolic events in patients not prescribed warfarin on discharge

PVI: Pulmonary vein isolation; LAA: Left atrial appendage.

et al[63] looking at the safety of stopping anticoagulants following successful surgery for AF.

Looking at compiled data of 10 000 patient-years follow up, they concluded that discontinuation of warfarin following AF surgery is safe. An annual thromboembolic stroke rate of 0.3%-8% in patients who were discontinued off warfarin was seen in these studies, where warfarin was stopped after AF surgery at a mean of 3.6 mo (0-8 mo) after AF surgery. It is worth noting here that care needs to be taken when interpreting those results, since the scarcity of good quality RCTs means that their conclusion was mainly based on low quality evidence such as observational studies.

Stroke risk also varied according to the procedure performed. PVI performed as an isolated procedure, as well as being the procedure most extensively evaluated, was shown to have the lowest stroke risk off warfarin (0%-0.4% per annum). In contrast, concomitant cardiac surgery such as mitral valve repair was found to considerably increase the thromboembolic stroke rate. Thus, mitral valve surgery was found to be risk factor for late thromboembolic stroke in patients undergoing concomitant AF surgery.

In summary, the best evidence topic concluded that discontinuation of warfarin at 3 mo post-operatively would be feasible in selected patients, following consi-

Table 7 Summary of results from studies included looking at radiofrequency ablation

Procedure	Ref.	Sample size	Mean follow-up period	Outcome	Important findings
Concomitant RFA	Johansson *et al*[32]	39 patients undergoing CABG	32 ± 11 mo	62% freedom from AF in ablation group compared to 33% in non-ablation group	Sinus rhythm at 3 mo was highly predictive of long-term sinus rhythm
Concomitant RFA	Khargi *et al*[33]	128 patients in permanent AF (Group 1: mitral valve surgery, group 2: aortic valve surgery or CABG)	3, 6 and 12 mo ECG and sinus rhythm confirmed with 24hrs ECG	71% post-operative sinus rhythm in group 1 *vs* 79% in group 2	Concomitant RFA in mitral valve surgery and aortic valve surgery or CABG is equally effective
Concomitant RFA	Beukema *et al*[34]	258 patients with permanent AF	43.7 ± 25.9 mo	Sustained sinus rhythm in 69% of patients at 1 yr, 56% at 3 yr, 52% at 5 yr and 57% at the latest follow up	RF modified maze procedure abolished AF in the majority of patients
Concomitant RFA	Chiappini *et al*[35]	Review of 6 studies - 451 patients in total	13.8 ± 1.9 mo	97.1% overall survival rate, 76.3% ± 5.1% overall freedom from AF	RFA is a safe and efficient procedure to cure AF in patients undergoing concomitant heart surgery
Concomitant RFA	Von Opell *et al*[36]	49 patients with AF of more than 6 mo duration	At discharge, 3 and 12 mo post procedure	Return to sinus rhythm 29% 57% and 75% (at discharge, 3 mo and 12 mo post-procedure) in the cardioblate group *vs* 20%, 43% and 29% respectively in the control group	Concomitant RFA resulted in 75% conversion rate to sinus rhythm compared to the control group (39%)
Concomitant RFA	Budera *et al*[38]	Multicentre RCT involving 224 patients with AF undergoing cardiac surgery with (n = 117) or without ablation (n = 107)	30 d	At 1 yr follow up, 60.2% of patients were in sinus rhythm in the ablation group compared to 35.5% in the control group. 1 yr mortality was 16.2% and 17.4% respectively	Concomitant ablation increases postoperative sinus rhythm with no effect on peri-operative complications
Concomitant RFA	Blomström-Lundqvist *et al*[40]	Double-blind randomized study of 69 patients undergoing mitral valve surgery with or without epicardial left atrial cryoablation	6 and 12 mo	At 6 mo follow-up, 73.3% of patients in the cryoablation group regained sinus rhythm *vs* 45.7% of patients with mitral valve surgery alone (P = 0.024). At 12 mo follow-up, the results were 73.3% *vs* 42.9% respectively (P = 0.013)	Concomitant left atrial epicardial cardioablation is significantly better in regaining sinus rhythm in patients with permanent AF compared to mitral valve surgery alone
Concomitant RFA	Chevalier *et al*[61]	Prospective, multicentre, double-blinded RCT involving 43 patients with mitral valve disease and permanent AF	12 mo	At 12 mo, sinus rhythm was maintained without any arrhythmia recurrences in 57% of patients in the RFA group *vs* 4% in the control group (undergoing mitral valve surgery only)	Left atrial RFA is an effective procedure in patients suffering with long-term AF and co-existing valvular disease
Concomitant RFA	Veasey *et al*[62]	100 patients in paroxysmal or persistent AF undergoing cardiac surgery were enrolled	6 mo	75% freedom of AF at 6 mo follow-up post concomitant RFA. The AF burden decreased from 56.2% post-operatively to 27.5% at 6 mo post-operatively. 13% of patients had asymptomatic AF episodes identified *via* continuous monitoring	Concomitant RFA successfully reduces AF burden but based on these results, the importance of post-operative antiarrhythmic medication and anticoagulation should be evaluated

RFA: Radiofrequency ablation; AF: Atrial fibrillation; ECG: Electrocardiogram; CABG: Coronary artery bypass grafting.

deration of the patient's individual risk factor profile[63].

The above is in agreement with the 2012 HRS/EHRA/ESC Guidelines, which concluded that surgical intervention for AF is not recommended solely to discontinue warfarin or other anticoagulants. Furthermore, cessation of anticoagulants in patients post-ablation is not recommended if the stroke risk is high as measured on CHAD52. However, if a patient is not high risk on CHAD52 and has been in sinus rhythm for a significant continuous period they could change their warfarin to aspirin alone[14].

The EACTS clinical guidelines committee also recommend cessation of anticoagulants at 3 mo following established AF ablation procedures; provided that the patient is in sustained sinus rhythm and that their stroke-risk profile has been considered and deemed to be low[2].

POST-OPERATIVE FOLLOW UP

The STS workforce on evidence-based surgery published a document on reporting results from AF surgery. This included reporting regular interval ECG assessments and encouraging the widespread use of implantable recording devices to assess AF[64].

The STS workforce in accordance with 2012 HRS/EHRA/ESC Guidelines, recommend that the entrance and exit block should be reported and demonstrated intra-operatively[14,63]. Additionally, the 2012 HRS/EHRA/ESC Guidelines recommend follow-up of at least one

Table 8 Summary of results from studies included looking at high intensity focused ultrasound

Procedure	Ref.	Sample size	Mean follow-up period	Outcome	Important findings
HIFU	Neven *et al*[45]	Two-year follow-up of 28 people with paroxysmal AF 9 (n = 19) and persistent AF (n = 9) undergoing	Median follow-up 738 d	Following a median follow-up of 738 d, 79% of patients were free of AF. Following a repeat procedure with radiofrequency ablation, 18% of patients maintained freedom of AF	Success rates of HIFU are comparable to radiofrequency ablation but complication rates remain higher for HIFU
HIFU	Klinkenberg *et al*[47]	15 patients with AF refractory to antiarrhythmic medication underwent HIFU for PVI	24 mo	At 6 mo 40% of patients with 1 epicardial PVI gained sinus rhythm. After 1.3 ± 0.6 yr, 27% of patients had sinus rhythm after 1 epicardial pulmonary vein isolation	Success rate was low in epicardial pulmonary vein isolation done through right-sided VATS using HIFU and was associated with substantial complications
HIFU	Schmidt *et al*[48]	22 patients with paroxysmal AF who underwent PVI using HIFU	median follow-up of 342 d	71% of patients remained free of any AF/AT recurrence without antiarrhythmic drugs after a procedure	The 12F-HIFU induces a very rapid pulmonary venous isolation in patients

HIFU: High intensity focused ultrasound; PVI: Pulmonary vein isolation; LAA: Left atrial appendage.

Table 9 Summary of results from studies included looking at the hybrid approach

Procedure	Ref.	Sample size	Mean follow-up period	Outcome	Important findings
Hybrid approach	Kuman *et al*[55]	A cohort of 7 patients with AF undergoing a hybrid procedure	Follow-up at 3, 6, 9 and 12 mo post-procedure	After a follow-up of 40 ± 3 mo, 6 out of 7 patients were in sinus rhythm	The hybrid approach is a safe and feasible technique to AF ablation
Hybrid approach	Bulava *et al*[56]	50 consecutive patients with long-standing AF who underwent the procedure	Follow-up at 3, 6, 9 and 12 mo post-procedure and thereafter after every 6 mo	94% of patients were in sinus rhythm, 12 mo after the procedure No arrhythmias were present in any patient after 12 mo	The hybrid approach is extremely effective in maintaining sinus rhythm compared to radiofrequency catheter ablation or surgical ablation alone
Hybrid approach *vs* Cox-Maze *vs* epicardial ablation	Je *et al*[57]	Systematic review of 37 studies with a total of 1877 patients	12 mo	Operative mortality for the Cox-Maze, epicardial ablation and hybrid approach were 0%, 0.5% and 0.9% At 12 mo, rates of sinus rhythm restoration for the above were 93%, 80% and 70% respectively	The Cox-Maze procedure with cardiopulmonary bypass revealed the highest success rate 12 mo post-procedure compared to the hybrid approach and epicardial approach

AF: Atrial fibrillation.

year with a minimum of 24-72 h holter monitoring, trans-telephonic monitoring, 30 d auto event triggered monitoring or outpatient telemetry[2,14].

The EACTS Guidelines recommend routine testing of entrance and exit block after AF surgery to establish creation of effective lesion sets. They also recommend following the 2012 HRS/EHRA/ESC Guidelines for reporting results of surgery and in publications[2].

CURRENT GUIDELINES IN SURGICAL MANAGEMENT OF AF

The 2012 HRS/EHRA/ESC Guidelines have summarised the indications for surgical interventions of AF. Their statements were in accordance with their 2006 guidelines and their subsequent updates. The guidelines include the indications for concomitant surgical ablation of AF (Table 3) and the use of ablative modalities in each AF category (Table 4)[14].

LIMITATIONS AND FUTURE CONSIDERATIONS

The surgical management of AF is a rapidly evolving field with multiple studies exploring the various surgical options available. The current literature includes a few RCTs as well as several prospective, retrospective and cohort studies. When looking at these studies, there are certain limitations that need to be considered.

First, there is a variable definition of "success" when reporting results. This is often vaguely described as "freedom from AF" though not being further defined. Conversely, a few studies report "success" as patients being in sinus rhythm at follow up. Standardisation on reporting the outcomes of studies would be invaluable when looking at results from different studies. This

would enable accurate comparisons in order to draw reliable conclusions. Guidelines aiding standardisation of results reporting have been published by STS[64] and following them has been recommended by EACTS and HRS/EHRA/ECAS[2,14].

Secondly, there is vast heterogeneity regarding the follow up periods used in each study. Follow up periods ranging from 1 mo to 5 years have been seen across different studies. The lack of a standardised follow up interval makes it very difficult to reliably compare results. The STS workforce has published a document regarding the reporting of results and recommended follow up periods in surgery for AF[64].

When looking at the current literature it is evident that an array of lesion sets is being used when performing AF surgery. An explanation for this can be the move towards minimally invasive surgery attempting to yield good results, whilst using less invasive techniques. Additionally, it is widely accepted that the CM-Ⅲ procedure has a limited use due to its technically challenging nature. This has led to the development of other lesion sets that are less invasive and easier to perform. It would be worthwhile establishing some common lesion sets that could be used in studies. Currently, the EACTS recommended using the terminology "Maze" procedure, "PVI" and "LAA" when describing the different lesion sets[2]. This would eliminate the bias of using slightly different lesion sets in each study and enable the results of the studies to be compared accurately.

Furthermore, there is limited data available on the comparison of different energy sources in AF ablation. Several studies have looked at the use of individual ablative modalities for AF treatment during concomitant cardiac surgery[59-62]. However, very few studies compared the ablative modalities to each other[42,43]. Future studies performing this comparison would be vital, as evidence is needed in order to identify the ablation modalities with the highest success rates and least complications.

Looking at the patient population recruited in the studies, there is a large variation between AF types in the patients included. A few studies have included a population with a single AF type such as permanent AF and looked at ablation modalities in that population[33,34,36,50]. More studies looking at patient populations with specific AF types would be useful in finding out which ablation modality works better for each AF type.

Additionally, the hybrid approach is a promising new procedure that could potentially improve success rates in the surgical management of AF. Over the recent years an increasing number of studies have been looking at this new approach[53-57]. More studies exploring the hybrid approach are needed in order to obtain reliable results as to whether the hybrid procedure should be clinically recommended for the surgical management of AF, as well as identify the best combination of modalities to be used in this procedure.

Finally, an important consideration for future studies is the big gap in literature when looking for RCTs, in order to obtain reliable results and be able to make good clinical recommendations. There is definitely a need for more, well-conducted prospective RCTs looking the various ablative modalities[65].

CONCLUSION

In conclusion, AF is a public health burden associated with substantial morbidity and mortality. Surgical management of AF is currently recommended in paroxysmal or persistent AF during concomitant heart surgery. Stand alone surgical ablation for AF can be considered with caution in patients who are intolerant or refractory to antiarrhythmic medication. Several studies have produced promising results using the new ablative modalities, which emerged over the last few years. Nevertheless, there is still a requirement for additional high quality RCTs in order to be able to make reliable evidence-based recommendations regarding the surgical management of AF.

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REVIEW

Ventricular repolarization measures for arrhythmic risk stratification

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Abstract

Ventricular repolarization is a complex electrical phenomenon which represents a crucial stage in electrical cardiac activity. It is expressed on the surface electrocardiogram by the interval between the start of the QRS complex and the end of the T wave or U wave (QT). Several physiological, pathological and iatrogenic factors can influence ventricular repolarization. It has been demonstrated that small perturbations in this process can be a potential trigger of malignant arrhythmias, therefore the analysis of ventricular repolarization represents an interesting tool to implement risk stratification of arrhythmic events in different clinical settings. The aim of this review is to critically revise the traditional methods of static analysis of ventricular repolarization as well as those for dynamic evaluation, their prognostic significance and the possible application in daily clinical practice.

Key words: Ventricular repolarization; Arrhythmias; QT interval; Cardiovascular diseases; Drugs

Core tip: The analysis of the role of ventricular repolarization perturbations as potential triggers of malignant arrhythmias has increasingly gained interest, particularly as a potential tool for the risk stratification of arrhythmic events in different clinical settings. Several measures of ventricular repolarization have been developed and tested in clinical practice. This review critically revises the traditional methods of static analysis as well as those for dynamic evaluation, their prognostic significance and the possible application in daily clinical practice.

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INTRODUCTION

The electrocardiogram (ECG) is widely used in clinical practice for the diagnosis of cardiac arrhythmias, conduction disturbance, structural changes of the myocardium, myocardial ischemia, drug effects, and electrolyte and metabolic disorders. The ECG waveforms are the expression of transmembrane action potentials (APs) of atrial and ventricular myocytes[1].

ECG recording in a normal cardiac cycle is composed of two basic processes: Depolarization and repolarization. Ventricular depolarization and activation is represented by the QRS complex, whereas ventricular repolarization (VR) is expressed as the interval from the beginning of the QRS complex to the end of the T wave (QT interval). VR is a complex electrical phenomenon which has been studied in detail[2,3].

It is a crucial step in cardiac electrical activity consisting of a recovery period with the return of the ions to their previous resting state, which corresponds with the relaxation of the myocardial muscle, thus setting the stage for the next depolarization and contraction. On the surface ECG, VR is made up of the J-wave, ST-segments, and T and U waves[1]. Over the years previous studies have emphasized the role of VR alterations in predisposing to lethal arrhythmias[4,5] and thus the analysis of VR has increasingly gained interest, particularly as a potential tool for the risk stratification of arrhythmic events[6,7], integrating other well-established parameters[8].

This review aims to critically revise the available static and dynamic methods of VR analysis and their application in clinical practice.

PATHOPHYSIOLOGICAL BACKGROUND OF VENTRICULAR REPOLARIZATION MEASURES

VR measures have been proposed to stratify arrhythmic risk due to their ability to reflect abnormalities in cardiac electrical activity predisposing to the occurrence of malignant arrhythmias. Cardiac structural and electrical alterations may cause abnormalities in APs, and in the refractory period and conduction velocities of adjacent myocardial areas, thus leading to spatial heterogeneity and temporal fluctuations in repolarization and favoring the onset of arrhythmias[9,10]. Furthermore, it has been demonstrated that autonomic nervous system (ANS) activity can interact with structural heart diseases, affecting the VR and promoting the onset of arrhythmias. Moreover, the modulation of VR by ANS is not limited to its influence on sinus node regulation and on heart rate (HR). In fact, there is a direct regulation by ANS on APs through the regulation of the activity of ion channels[11]. Furthermore, the effects of vagal and sympathetic systems should not be considered singularly. Sympathovagal interactions are fundamental in regulating heart function and conditions which alter the sympathovagal balance, facilitate cardiovascular instability and can lead to arrhythmias[8].

Finally, several drugs have been showed to affect VR and prolong the QT interval, inducing alterations which can predispose to ventricular arrhythmias[12,13]. From these considerations, the importance of the analysis of VR and the QT interval in the evaluation of arrhythmic risk, drug effects and liability of the ventricular arrhythmias is clear (Figure 1). Since the earliest demonstrations that a prolonged corrected QT interval (QTc) is associated with an increased risk of ventricular arrhythmias and sudden cardiac death (SCD), in patients with myocardial infarction[14], as well as in patients taking QT-prolonging drugs[15], interest in the assessment of QT prolongation grown. At the same time, the role of QTc prolongation as a marker for arrhythmic risk is controversial[16] and measures of QT dispersion at ECG did not always demonstrate the ability to predict the risk of arrhythmic events[17]. Thus, as an alternative to "static evaluation" of the QT interval, different measures of QT variability and dynamicity have been proposed, better representing the complex interactions between arrhythmic substrate, HR and ANS activity and offering a more complete assessment of VR and estimation of arrhythmic risk[18].

MEASUREMENT OF QT INTERVAL

The measurement of the QT interval represents the traditional approach to the analysis of VR.

Methodological aspects

The QT interval is calculated as the distance between the first deflection of the QRS and the end of the T wave on the surface ECG. Measurement of the QT interval by surface ECG can be performed either manually or automatically[11,19-22].

In the manual measurement, the end of the T wave is determined as the intersection between the tangent to the steepest down-slope of the T wave and the isoelectric line[22], but this method can be time-consuming and is liable to inter-reader variability. Recommendations concerning QT measurement have not proposed a single defined lead (lead Ⅱ or the lead with the largest T wave) or a mean QT derived from an arbitrary subset of leads. As consequence of this lack of a systematic approach, there is a variation in sensitivity and specificity for single lead measurement of the QT interval in predicting the risk of major arrhythmic events. The interlead QT variation associated with the observation that in healthy individuals the longest QT interval is most frequent in leads V2 to V5 and that the QT interval is

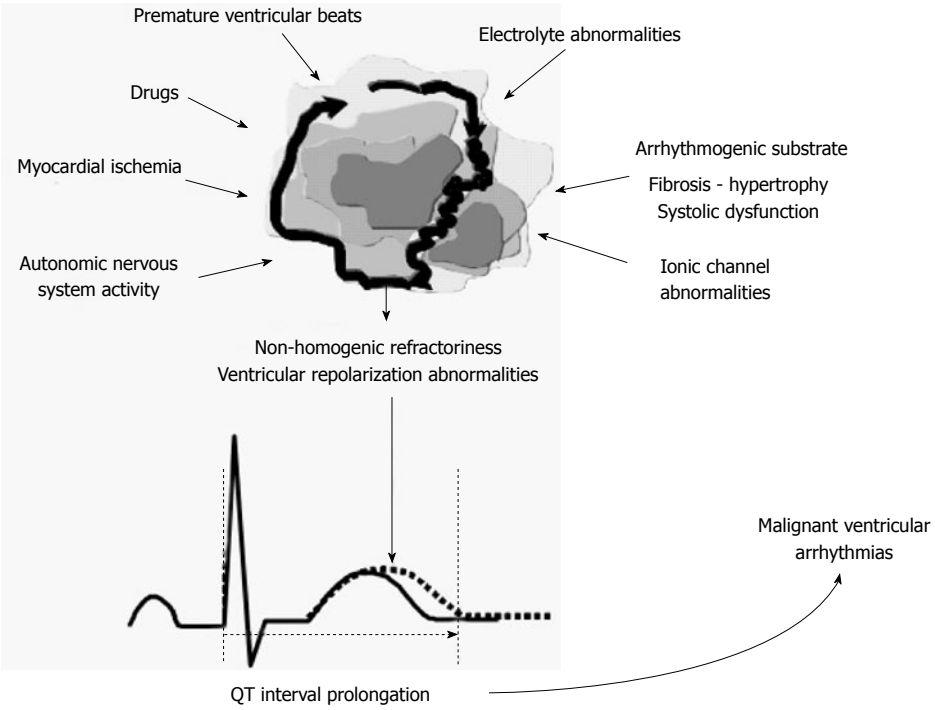

Figure 1 Structural and functional cardiac abnormalities and interaction with the other factors are able to induce non-homogenic refractoriness and abnormalities in ventricular repolarization leading to QT interval prolongation.

not closely related to T wave height makes it difficult assessing ventricular recovery by measuring a single QT interval[23-26]. The measurement of the QT dispersion addresses this challenge as subsequently explained. It is widely recognized that the typical measurement of the QT interval is subject to different interpretations due to different factors, such as autonomic tone, electrolytes imbalance, technical aspects, variations in T wave morphology, presence of U waves, and noisy baseline. The absence of agreement among experts and of a standardized measure of the QT interval contributes to interobserver variability[27,28].

The main problems regarding the automated measurement are related to the T wave morphology (flat, bifid, biphasic) and to the presence or absence of the U wave. Consequently, the measurement of the QT interval requires a lot of experience and a good interpretation of the ECG signal[29]. In addition, some of the automated QTc interval monitoring strategies are labor-intensive, and dependent on expensive technology[30] and experts disagree on the utility and efficacy of automated readings when compared with careful manual measurements[31]. The other relevant aspect in the measurement of the QT interval is its dependence on HR, the main physiological factor influencing VR. The QT interval is inversely correlated with HR prolonging at a slower HR and shortening at faster one. In order to minimise the influence of this factor on the measurement, it is essential to make a correction of the QT interval for HR (QTc). Different formulas have been developed in order to adjust QT for HR. Those most commonly used are Fridericia's formula: QTc: $QTxRR^{-1/3}$[32], and Bazett's formula: QTc: $QTxRR^{-1/2}$[33], where RR means the time interval and QT means the distance. However different opinions exist as to the best and most useful correction for HR and the evidences remain unclear and contrasting[34-36]. The normal range of QTc has been assessed by Straus *et al*[37] who established the gender-specific variability of QTc measurement. The authors subdivided the Bazett-corrected QTc interval into gender-specific groupings and further subdivided the QTc interval into normal, borderline, and prolonged categories.

Considering the lack of standardization and recommendations for the best method to measure QT, a broad of experts proposed guidelines for measuring the QT interval[31].

The expert group from the American Heart Association (AHA) and American College of Cardiology Foundation (ACCF) recommends that a QT_c over the 99th percentile should be considered abnormally prolonged. Approximate 99th percentile QT_c values for otherwise healthy postpubertal individuals are 470 ms for males and 480 ms for females[38].

Clinical implications

Marked prolongation of the QT interval is a well-established pro-arrhythmic risk factor in the general population[39] in patients with coronary artery disease[40], hypertrophic cardiomyopathy (HCM)[41], or heart failure (HF)[42] and in patients taking QT-prolonging drugs[43]. However, the clinical usefulness of QT measurement has mainly been demonstrated in both congenital[43] and acquired long QT syndrome (LQTS)[44].

Congenital LQTS

The congenital LQTS was described for the first time in 1957 and since then remarkable efforts have been made to define its pathogenesis, diagnosis and treatment[45]. Genetic studies have shown that LQTS is caused by pathogenic mutations in 15 genes encoding cardiac ion channels or membrane adaptors and thus different LQTS genotypes have been identified. Pathogenic mutations identified in the *KCNQ1* and *KCNH2* genes as well as in the sodium channel, encoded by SCN5A, are responsible for nearly 80% of all clinically diagnosed cases. All other genes together account for less than 5% of LQTS cases[46]. LQTS 1, 2 and 3 are the most common genotypes, representing 80%-90% of the total cases of inherited LQTS[47,48]. Due to limitations of space and the different purposes of this article, our focus is mainly on the diagnostic criteria of the congenital LQTS. However, details about specific triggers, clinical presentation, prevalence and genetic aspects, risk stratification and therapeutic advances are available in the literature[49-53]. As regards the diagnosis of LQTS, a scoring system, updated in 2011, and including symptoms, family history and ECG findings was proposed by Schwartz *et al*[54]. In 2013 an expert consensus, incorporating the Schwartz score, drafted the following recommendation for the diagnosis of LQTS[50]. Congenital LQTS is diagnosed when the LQTS risk score is $\geqslant$ 3.5, in the absence of a secondary cause for QT prolongation and/or in the presence of an unequivocally pathogenic mutation in one of the LQTS genes, or it can be diagnosed in the presence of a corrected QT interval for HR using Bazett's formula (QTc) $\geqslant$ 500 ms in repeated 12- lead ECG and in the absence of a secondary cause for QT prolongation. Moreover LQTS can be diagnosed in the presence of a QTc between 480 and 499 ms in repeated 12-lead ECGs in a patient with unexplained syncope in the absence of a secondary cause for QT prolongation and in the absence of a pathogenic mutation[50].

Short QT syndrome

Short-QT syndrome (SQTS) is a clinical entity originally described by Gussak *et al*[55] in 2000 as an inherited syndrome in a family with paroxysmal atrial fibrillation and constantly shortened QT intervals.

Subsequently, a high familial risk for sudden cardiac death associated with a short QT interval was demonstrated by Gaita *et al*[56] in the members of a family with a history of syncope or palpitations, as well as one case of sudden death resuscitation. A strong family history of sudden death, present in 4 generations, was detected. The family members had a very short QT interval at ECG, which never exceeded 280 and 290 ms when corrected for HR with Bazett's formula (QTc). The authors provided a definition of SQTS as characterized by familial sudden death, short refractory periods, and inducible ventricular fibrillation. The definition of SQTS became a possible diagnosis for yet unexplained SCD in patients without structural heart disease. Details of possible pathophysiological mechanisms, related genetic mutations and other possible explanations, besides the well-known channelopathy, are available in the literature[57-59].

Acquired long QT syndrome

In daily clinical practice, one of the most frequent application of QTc measurement is the monitoring of drug-induced QTc prolongation, the aim of which is to mitigate the risk of Torsade de Pointes (TdP) and other ventricular arrhythmias and prevent SCD. Several drugs have been shown to induce perturbation of VR and prolongation of QT interval, increasing the risk of ventricular arrhythmias such as TdP and SCD. There has been increased research into the mechanisms involved in drug-induced LQTS in patients in treatment with these drugs. Those generally involved in acquired LQTS are cardiac drugs such as class ⅠA and Ⅲ antiarrhythmic drugs, while the non-cardiac ones include antibiotics, antihistamines, antidepressants, antipsychotic and methadone. An updated list of drugs that can potentially cause QT prolongation is available on the Internet where they are classified into the following four categories: (1) drugs with known risk of TdP; (2) drugs with possible risk of TdP; (3) drugs with conditional risk of TdP; and (4) drugs to avoid in congenital LQTS (https://www.crediblemeds.org/new-drug-list/). Medications that cause QT prolongation generally act by blocking Ikr, a potassium-channel protein that regulates an important rapid delayed repolarizing current in phase 3 of the cardiac AP. This protein is encoded by the human ether-a-go-related gene (HERG), mutated in the LQT2 form of the congenital syndrome[60]. The blocking of Ikr causes a lenghthening of AP in cardiac myocytes and QT interval, thus increasing the risk of ventricular arrhythmias and SCD[16,61]. However many drugs blocking the Ikr current do not seem to cause TdP (*e.g.,* amiodarone). Other mechanisms involved in drug-induced LQTS have been described and concern the loss of K channels (*e.g.,* fluoxetine) and an increased inward sodium current, such as that produced by cisapride and antimony[62-65]. However, drug-induced LQTS is not easy to predict in any given individual and the same medication does not exhibit the same pro-arrhythmic effects in different individuals[16]. Indeed, some individuals taking QT prolonging drugs, may develop QTc prolongation with or without TdP, or may not experience QTc prolongation, while several authors have also demonstrated genetic predisposition to acquired LQTS[61,66]. However, only a small proportion of patients taking QT prolonging drugs experience TdP and, at the same time, TdP can develop in patients with a normal QTc interval[27]. Additional risk factors causing QT prolongation and favoring drug-induced VR alterations and TdP have been identified. They include hypokalemia, drug-drug interactions, the female gender, advancing age, genetic predisposition, hypomagnesemia, heart failure, bradycardia, and baseline QTc interval prolongation. Many risk factors are potentially modifiable and should be corrected in

those patients at risk for QT interval prolongation. It has been reported that all patients with TdP secondary to non-cardiac drugs have established risk factors. Most patients manifestating drug-induced LQTS have at least one identifiable risk factor in addition to drug exposure[13,27,67]. Female gender is the most common risk factor[68]. Age has also been detected as a risk factor for QT prolongation, particularly when combined with additional risk factors, such as female gender, personal or family history of pre-syncope or syncope, electrolyte disturbances or cardiovascular disease[69]. Impaired glucose tolerance and diabetes were observed to be associated with an increased likelihood of prolonged QTc independent of age, race, gender, education, and heart rate. In addition, persons with diabetes and multiple cardiovascular disease risk factors were more likely to have a prolonged QTc than those with Normal Glucose Tolerance and no additional risk factors, suggesting that this group may be at increased risk for cardiac arrhythmia and sudden death[70]. Hypokaliemia is a very common QT-prolonging factor and is often detected in patients with drug-induced QT prolongation and TdP and some proposals have been made as to the different mechanisms that may potentially be involved[61,71]. Other metabolic conditions correlated with QT-prolongation are hypothyroidism, hypocalcemia and hypomagnesemia as well as hepatic diseases[72,73]. The "five-year cross-sectional ECG screening Outcome in psychiatry study" revealed that patients with drug-induced LQTS had a significantly higher frequency of hypokaliemia, hepatitis C virus infection and abnormal T wave morphology. The drugs mostly involved in QT prolongation were haloperidol, clotiapine, phenothiazines and citalopram[74]. Another recognized risk factor is represented by the polytherapy and the concomitant use of medications known to prolong QT[13,75]. A prospective observation study carried out in the United States demonstrated the high prevalence of QTc prolongation in patients admitted to cardiac units, with 28% of patients presenting with QTc prolongation (defined as $\geqslant$ 470 ms in males and $\geqslant$ 480 ms in females) and 18.2% with a QTc > 500 ms at admission. The study revealed that of 251 patients admitted with QTc interval prolongation, 87 (34.7%) were subsequently administered QT interval-prolonging drugs, and 166 of the patients admitted with QTc interval > 500 ms, 70 (42.2%) were subsequently administered QT interval-prolonging drugs. Moreover additional QTc interval prolongation $\geqslant$ 60 ms occurred in 57.1% of these patients[76]. The authors also suggested that hospitalized patients are more prone to develop QTc prolongation due to the presence of other risk factors such as heart disease, electrolyte imbalance, and advanced age associated with the administration of QTc prolonging drugs. The statement from the AHA/ACCF underlined the importance of collecting the medical history and the risk factors of each single hospitalized patient in order identify those at higher risk and minimize the possibility of QTc prolongation and TdP. According to the AHA's practice standards for ECG monitoring in hospital settings, the indications for QT-interval monitoring include the following: (1) initiation of a drug known to cause TdP; (2) overdose from potentially proarrhythmic agents; (3) new-onset bradyarrhythmias; and (4) severe hypokalemia or hypomagnesemia. Due to the lack of clarity regarding the types and amounts of drugs taken in an intentional overdose situation, it is prudent to monitor QT intervals in all overdose victims[38]. To achieve a long-term reduction in the risk of drug-induced QTc prolongation and TdP in hospitalized patients, a risk score has been developed and validated. The authors suggested that, by using easily obtainable risk factors, the risk score can identify patients at highest risk for in-hospital QTc prolongation and, thus, could be incorporated into clinical decision support system to guide monitoring and treatment decisions[30].

Acquired LQTS and antipsychotic: An unclear scenario

Among the drugs known to cause QT-prolongation, antipsychotic agents are probably the most studied. Since the development and marketing of the first molecules, a close relation has been found with QTc prolongation and an increased risk of major arrhythmic events such as TdP[77,78]. Antipsychotic drugs are widely used in the treatment of schizophrenia, mood disorders and somatic symptoms.

Conventional or first generation antipsychotics have been widely recognized as being associated with an increased risk of cardiac arrhythmias, TdP and SCD[79].

Since the early 1960s, sudden unexpected deaths with antipsychotic use have been reported[77].

Among the first generation antipsychotics, the described association between thioridazine and haloperidol with TdP or SCD led to the withdrawal of thioridazine from the market by its producer in 2005 and to the use of label warnings by the Food and Drug Administration for intravenous haloperidol[80,81]. However, the rate of ventricular arrhythmia, sudden death, and unexplained or unattended death did not appear to increase with the dosage for either thioridazine or haloperidol, suggesting that low-doses of these drugs have similar cardiac safety[82]. As in the case of thioridazine and haloperidol, data on the safety profile and possible link of other first generation antipsychotics with severe arrhythmias are contradictory[83-85]. When first introduced, atypical or second generation antipsychotics were considered to be safer than first generation antipsychotics as regards the QTc prolongation and arrhythmic risk[84,86,87]. However these promising data were not univocally confirmed[88]. Among the second generation antipsychotics available, lurasidone and aripiprazole seem to have minimal effect on QTc interval[89-91]. It should be noted that patients with schizophrenia are more likely to experience SCD and QTc prolongation than individuals from the general population because of treatment-related metabolic disorders and autonomic dysfunction linked to the

underlying psychiatric illness[92,93]. Given all of these evidence, and considering the contradictory and inconclusive data available, it is easy to imagine how difficult the assessment of the individual risk in patients taking antipsychotic agents must be. In fact, drug-induced LQTS is unpredictable in any given individual. Because of all the possible medical complications associated with antipsychotics, Nachimuthu *et al*[62] and Shulman *et al*[94] highlighted the importance of a multidisciplinary approach which takes into account pre-existing heart or other diseases, personal or family history of ventricular arrhythmias or syncope, metabolic and endocrine disorders such as hypothyroidism and hypokalemia in order to reduce the risk of adverse events. Some authors recommend performing an ECG before and shortly after initiation of treatment with an antipsychotic drug in order to screen for existing or emergent prolongation of the QT interval[95]. The majority of authors recommend a baseline ECG for patients with personal or family history of cardiovascular disease or signs of arrhythmias, such as syncope, and for those patients taking another agent known to prolong QTc[96]. De Hert *et al*[97] performed a systematic review of the practice guidelines for the screening and monitoring of cardiometabolic risk in patients with schizophrenia and related psychotic disorders using the Appraisal of Guidelines for Research and Evaluation. The authors concluded that four European guidelines can be recommended for clinical use in daily clinical practice and proposed a monitoring protocol to manage cardiovascular disease risk. After a careful research of the literature, Trinkley *et al*[13] concluded that it is necessary to perform a careful and systematic monitoring of ECG and electrolytes, after the initiation of QT-interval-prolonging drugs. Where there are risk factors for QTc prolongation, patients should be trained to go to the emergency room in case of palpitations, lightheadedness, dizziness or syncope. When the QTc interval is 470-500 ms for males, or 480-500 ms for females, or the QTc interval increases by 60 ms or more from pretreatment values, dose reduction or discontinuation of the offending drug should be considered if possible, and electrolytes corrected as needed. Furthermore, if the QTc interval is $\geqslant$ 500 ms, the drug should be discontinued, and continuous ECG telemetry monitoring should be performed, or a 12-lead ECG should be repeated every 2-4 h, until the QT interval has normalized[13]. The American Psychiatric Association practice guidelines report that an absolute QTc interval > 500 ms or an increase of 60 ms from baseline requires dosage reduction or discontinuation of the agent. Serum potassium levels and an ECG should be obtained before initiating treatment with thioridazine, mesoridazine and pimozide and in the presence of cardiac risk factors, known heart disease, personal history of syncope, a family history of sudden death under 40 years age or LQTS before treatment with ziprazidone. An ECG should be performed again after a significant change in the dose of thioridazine, mesoridazine and pimozide or in the presence of cardiac risk factors, ziprasidone, or following the addition of another QT-prolonging medication[98,99]. Based on a relevant literature research, Shah *et al*[100] recently provided clinical practice guidelines for monitoring QTc intervals in patients being treated with antipsychotics. The authors reported that antipsychotics can be prescribed without pre-treatment ECG and without ECG monitoring, with the exception of patients with increased cardiac risk, antipsychotics with known risk of TdP and SCD, patients with an overdose of antipsychotic agents. In these cases ECG monitoring is recommended. If a pre-treatment ECG indicates a prolonged QTc, the ECG should be repeated and risk factors assessed and it is advisable to use lusaridone, which is the agent with minimal QTc prolongation. If QTc prolongation is assessed during antipsychotic treatment, the ECG should be repeated and monitored in case of continuous QTc prolongation in association with evaluation and correction of serum electrolytes. If a patient being treated complains of syncope or palpitations, discontinuation of the antipsychotic can be considered.

Prognostic significance in cardiovascular disease

As already outlined, several cardiovascular diseases are associated to QTc prolongation. Those known to predispose to QT-prolongation are HF, cardiac arrhythmias, bradycardia, myocardial ischemia, and HCM[40-42]. Prolonged QTc reflects cardiac repolarization prolongation and/or increased repolarization inhomogenity known to be associated with an increased risk of arrhythmias[101].

QTc prolongation has been widely observed in patients with myocardial infarction and it has been suggested as one of the earliest ECG abnormalities in transmural ischemia[102] and a prognostic marker of arrhythmic events[103].

Thus, for some time, the assessment of QTc interval has been considered an interesting tool in the evaluation of the arrhythmic risk[104,105] improving the accuracy of the personalized cardiovascular prognosis when associated to conventional risk models for cardiovascular diseases[106].

However, data available in literature concerning the role of QTc prolongation in the risk assessment are not univocal. The QTc interval did not seem a useful prognostic tool after acute myocardial infarction[107] and reduced left ventricular ejection fraction (LVEF) and frequent ventricular premature complexes were found to be the most important factors for predicting subsequent SCD after acute myocardial infarction[108].

Similarly in patients with HF, baseline QTc interval within normal limits seems to be associated with a marked reduction in mortality, suggesting its possible usefulness in identifying patients who might benefit from prophylactic treatment with antiarrhythmic drugs[109]. Prolonged QTc interval has been found to be a strong, independent predictor of adverse outcomes in patients with advanced HF with BNP levels > 400 pg/mL[110].

At the same time, prolonged QRS interval, but not prolonged QTc interval, was observed to be associated with increased long-term mortality in patients with acute decompensated HF[111].

Moreover, the role of QTc prolongation as a marker of arrhythmic risk is not widely confirmed, sometimes judged "imperfect", and nowadays its role remains controversial[112,113].

Despite the large number of studies on the evaluation of QTc in cardiovascular diseases, data about its utility are not consistent and the measurement of QTc interval in daily clinical practice is not widely carried out. Based on this background, other strategies to assess abnormalities of VR in cardiovascular diseases have been proposed.

QT DISPERSION

The "simple" measurement of QT interval cannot always permit a complete assessment of the arrhythmic risk. The analysis of the QT dispersion seems to more accurately represent the non-uniform prolongation of APs and heterogeneity of the duration of the refractory periods and the conduction velocities of adjacent myocardial areas, thus better analyzing the perturbation of VR.

Various experimental studies have highlighted the close relationship between the dispersion of the myocardial repolarization and the development of ventricular arrhythmias[114-116].

A non-invasive method to highlight the inhomogeneity of myocardial repolarization time has been proposed, *i.e.*, the measurement of the variability of the QT interval duration in the different leads of the standard 12-lead ECG[117,118].

Methodological aspects

QT dispersion (QTd) is the measurement of the variability of the QT interval on the 12-lead surface ECG, defined as the difference between the maximum QT and minimum QT calculated[119]. This phenomenon was described by Campbell *et al*[24] who demonstrated small but significant differences between the QT intervals of different leads measured by a digitizer program. The normal value of QTd is less than 50-70 ms. The standard deviation of repeat measurements is approximately 6 ms when an experienced observer measures from recordings made at 50 mm/s and 10 mV/cm. When the digitizer is used the normal rate-corrected values for QTd are between 20 ms and 50 ms with values after infarction rising to 60-100 ms and to as high as 150-200 ms in patients with LQTS[26].

There are more discrepancies about the determination of the end of the T wave, the lead group to be used, and the use of manual or automatic measurements. Surely, the greatest difficulties in the assessment of electrocardiographic VR are based essentially on the lack of universally accepted criteria for defining the end of the T wave. In particular, Kautzner *et al*[119] concluded that in the absence of more objective criteria for the separation of the T wave and U wave, measuring the QT dispersion appears to be unstable and its statistical validity is disputable.

New measurements have gradually been added to the traditional measurement of QT dispersion, among which are the following: (1) QTd in the precordial leads: The measurement is carried out only in the precordial leads, considered closer to the heart and, therefore, more reliable; (2) QTc-d in the 12 leads and in the precordial leads: The measurement is performed using the values of QTc (Bazett's formula)[120]; (3) QT "adjusted": The value of QT dispersion is adjusted to the number of leads on which the calculation is made (QTd/numbers of leads); (4) and QT "relative" and QTc "relative": Respectively, the standard deviation of the QT/QT average x 100 ratio and the standard deviation of the QTc/QTc average x 100 ratio on the 12-lead ECG.

Clinical implications and prognostic significance

The electrophysiological mechanisms through which the dispersion of ventricular repolarization may induce ventricular arrhythmias are different. Kuo *et al*[116] identified at least three: The formation of an ectopic focus; the creation of a reentry circuit facilitated by conduction from an area with long refractoriness to an area with short refractoriness; and the creation of a reentry circuit facilitated by an area with short refractoriness to an area with prolonged refractoriness. The increase in the QTd has been associated to vulnerability in the development of ventricular tachycardia (VT), particularly in patients with previous myocardial infarction[121]. A cross sectional American study compared 100 patients with coronary artery disease and a history of arrhythmia events with 70 patients with previous myocardial infarction. QTd was measured in all cases.

It was observed that QTc and QTd were consistently higher in patients with susceptibility to episodes of sustained and unsustained VT as well as in the post infarction patients[122].

The mechanism underlying the origin of VT in post infarction has been recognized to be a mechanism of reentry[122-125]. The role of increased dispersion of repolarization in the genesis of ventricular fibrillation has also been generally accepted[126] and infarct scar and reentrant circuits are known to be substrates in the pathogenesis of sustained monomorphic VT[127]. Strong evidence supports the hypothesis that dispersion of refractoriness and repolarization provides a pathophysiologic basis for reentry[128,129]. Furthermore, QTd has been shown to reflect the dispersion of recovery times and repolarization. Thus, increased QTd suggests the presence of a substrate for ventricular tachy-arrhythmias, more realistically by a reentry mechanism[117,118,121,122]. Changes in QTd evaluated in a population of patients after percuteneous coronary intervention were predictors of long-term cardiac mortality, confirming how a defective QTd recovery suggests the

persistence of repolarization inhomogeneities[130].

QT DYNAMICITY AND QT VARIABILITY

Measures of QT variability and dynamicity have been proposed as an alternative to the "static" evaluation of VR and seem to offer a more complete picture of the complexity of VR components.

Methodological aspects

Several kinds of softwares have been developed in order to dynamically analyse the QT interval and QTd from 24-h Holter recordings. Compared to the ECG static evaluation, dynamic assessment of VR allows the analysis of the relationship between the duration of the QT interval and HR changes and the effects of the ANS on both these elements. Moreover, through the measurement of the variability of VR duration and not its duration in absolute terms, this kind of analysis allows technical difficulties related to the exact definition of the T wave end to be reduced.

Dynamic behaviour of repolarization may translate in beat-to beat changes in repolarization duration and morphology[18,131].

QT-RR relationship and QT variability reflect an increased vulnerability of the myocardium and changes in autonomic HR control, which are conditions related to the increased risk of SCD[132]. The automatic assessment of VR dynamicity is based on the measure of: QT apex (QTa): The interval between the Q wave start and the T wave apex. The T-wave apex is identified by interpolation of a parabola with the peak of the T-wave.

QT end (QTe): The interval between the Q wave start and the T wave end, T-wave end is determined by the intersection of the tangent of the downslope of the T-wave with the isoelectric baseline[7]. It has been shown that the QTa is more influenced by HR changes than QTe. The interval between the apex and the end of the T wave is rate independent and is probably influenced by the ANS and by activity of M cells that seem to be the cells involved in arrhythmogenesis[133,134].

QT dynamicity is generally assessed by 24 h ECG recordings which are analyzed by a specific software able to automatically calculate, in a template of 30 s the QTa, the QTe and the correspondent RR interval. By interpolating each measure obtained the software also computes the slopes of the linear regressions between QTe and QTa and the corresponding RR interval (QTe/RR and QTa/RR). A steeper slope reflects a greater variation of QT interval for changes in RR intervals (Figure 2).

QT-RR slope, *i.e.,* the slope of the regression line between QT end and RR during a 24 h period, is considered an index of QT dynamicity related to arrhythmic events.

The automatic measure of VR by ELA system was validated by Copie *et al*[135] in a study that did not show significant differences between this kind of measurement and the manual measurement.

The QT-RR slope is highly individual. Generally the QT-RR slope is steeper in women than men and has higher values during the day than at night due to the ANS influence[136]. A steeper QTe slope indicates that the QT interval is more prolonged with longer RR intervals and shortens more with shorter RR intervals. The steeper the QTe-slope, the greater the arrhythmic risk[18]. Another parameter of QT dynamicity, QT/RR variability ratio, was proposed by Jensen *et al*[137]. This is the ratio between the standard deviation of all QT intervals and the standard deviation of all RR intervals. Whereas QT dynamicity is based on the analysis of QT/RR relationship, "QT variability" is based on the analysis of beat to beat changes in duration and the morphology of VR. HR and ANS can influence QT variability, but do not entirely explain beat to beat repolarization changes. These can depend on fluctuations in ion channel activity and number[18]. QT variability can be measured during a short-term (256 s or 30 beats) or 24-h period, distinguishing into short term and long term variability. Its measurement is not standardized, so several algorithms have been developed in order to quantify it. In 1997, Berger *et al*[9] proposed a first semiautomated algorithm able to measure temporal beat-to-beat lability of repolarization. In this instance, the operator selects the start and the end of the QT interval of one beat and the algorithm by stretching or compressing the JT segment identifies the QT interval of all other beats. Moreover, Berger *et al*[9] developed an index, called the QT variability index (QTVI), that is the log ratio between the QT interval and HR variability, both normalized by their mean values.

Most studies use this method in order to evaluate QT variability, but other algorithms have been proposed.

Burattini *et al*[138] proposed a time domain method which is able to quantify beat-to-beat variability of repolarization morphology without the need to exactly define the T wave end.

Starc *et al*[139] proposed a fully automated time-shifting algorithm that estimates the QT interval constructing separate QRS and T wave templates and shifting them in time. This algorithm has been shown to be the best method in order to measure QT variability[140]. On the basis of these considerations the assessment of QT dynamicity and/or variability allows a more complete evaluation of ventricular repolarization because they reflect the interaction between the arrhythmic substrate, the increased vulnerability of the myocardium, HR and ANS activity.

Prognostic role of QT dynamicity and variability

The increased QT variability and dynamicity probably build up repolarization heterogeneity inducing the onset of arrhythmias. Therefore a number of studies have investigated the role of an increased QT dynamicity and variability as predictor of arrhythmic events in different clinical settings. QT dynamicity was demonstrated to be able to predict major arrhythmic events in patients with both idiopathic and ischemic dilated cardiomyopathy,

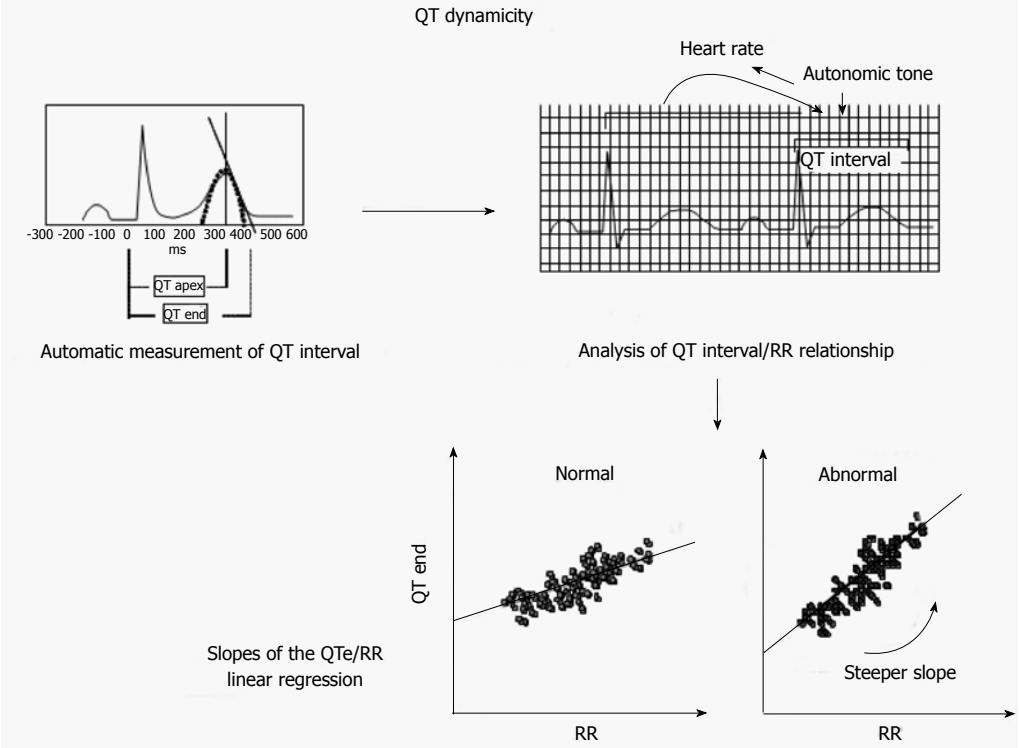

Figure 2 QT dynamicity analysis is based on automatic measurement of QT interval (QT apex and QT end) during 24 h electrocardiogram monitoring. The relationship between these measures and the corresponding RR intervals allows a slope of regression analysis to be obtained. A steeper slope reflects a wider QT variability suggesting abnormalities in ventricular repolarization.

improving the accuracy in stratifying the arrhythmic risk of these patients. Our group evaluated the role of the QT slope as a predictor of a greater risk of ventricular arrhythmias in a population of patients affected by non-ischemic dilated cardiomyopathy. At univariate analysis, QTe-slope, LVEF, non-sustained VT, and standard deviation of RR intervals (SDNN) were the variables significantly related to major arrhythmic events. At multivariate analysis only the QTe-slope, LVEF and non-sustained VT remained significantly associated with these events, independently of SDNN, a QRS duration > 120 ms or beta-blocker therapy. Combining LVEF (< 35% *vs* > 35%), non-sustained VT and QTe-slope (> 0.19 *vs* < 0.19), patients with non-sustained VT and LVEF < 35% and patients with LVEF < 35% and a steeper QTe slope presented a greater risk of arrhythmic events than patients with a higher LVEF and non-sustained VT or steeper QTe slope. Considering these variables together, the population of patients with low LVEF and presence of non-sustained VT and a QTe slope > 0.19 represented the subgroup with the highest probability of arrhythmic events[7]. Chevalier *et al*[141] showed the association between a steeper QTe slope and a greater arrhythmic risk in a population of patients with ischemic cardiomiopathy. They found that QTe slope was a more powerful independent predictor of sudden death than LVEF, HR variability and late potentials in these patients. Another parameter of QT dynamicity, QT/RR variability ratio has been shown by Jensen *et al*[137] to be related to the sudden arrhythmic death risk in a population of post-acute myocardial infarction patients. Moreover, QTe slope was shown to be important in arrhythmic risk stratification also in patients with HF, regardless of etiology, both with relatively preserved LVEF (> 35%)[142] and with reduced LVEF[143]. Recently Quinteiro *et al*[144] evaluated the role of QTe slope in arrhythmic risk stratification in a small population of patients with HCM. They found that these patients presented an impaired QT dynamicity and QT slope was helpful in order to identify high risk patients. Several studies have also demonstrated the prognostic role of "beat to beat" QT variability. Berger *et al*[9] showed that there was an increased repolarization variability in a group of patients with ischemic and non-ischemic dilated cardiomyopathy, compared with control subjects, regardless of HR. Subsequent studies confirmed the increased repolarization variability in ischemic and non-ischemic cardiomyopathy and in different clinical settings, including acute myocardial ischemia, left ventricular hypertrophy, HCM, left ventricular dysfunction and LQTS[145]. Atiga *et al*[146] demonstrated the relation between an increased QTVI and arrhythmic risk in a population of patients presenting for electrophysiologic study. The QTVI had greater values in patients with ischemic or non-ischemic heart disease than in healthy subjects, and among patients with cardiac disease those with SCD had the highest values. A QTVI $\geqslant$ 0.1 was a predictor of a higher risk of arrhythmias. Therefore the authors concluded that this index identified patients with SCD, and predicted arrhythmia-free survival. The same group also investigated the prognostic role of QT variability

in a population of patients with HCM, concluding that patients with HCM presented the increased repolarization variability and had a greater risk of SCD. The highest QTVI values were found in patients with b-MHC gene mutation, a mutation associated with a worse prognosis[147]. In a substudy of the MADIT trial, Haigney *et al*[6] have shown that, in a wide population of postinfarction patients with a low LVEF, increased QT variability was associated to the occurrence of malignant ventricular arrhythmias (VT/ventricular fibrillation). Piccirillo *et al*[148] also evaluated the role of QT variability in a population of patients with ischemic cardiomyopathy but with a LVEF between 35 % and 40% and in NHYA class Ⅰ. A QTVI greater than or equal to the 80th percentile identified a high risk of SCD, therefore this parameter might be useful to stratify the risk of sudden death in this population of patients who do not currently meet the criteria for ICD implantation for primary prevention. Tereshchenko *et al*[149] investigated the role of QT variability in a population of patients with cardiac structural disease who had undergone ICD implantation for primary or secondary prevention of SCD. This study confirmed the prognostic utility of the increased repolarization variability, able to predict the malignant arrhythmic events risk in this population of patients. Nevertheless, the same group more recently investigated the prognostic role of QT variability in a population of patients with chronic HF (NYHA class Ⅱ-Ⅲ), both with preserved and reduced LVEF and found that an increased QTVI was a predictor of cardiovascular mortality, but not of SCD, regardless of LVEF. The hypothesis of the authors was that in these patients the elevated QTVI was due to depressed HR variability, a predictor of cardiovascular mortality, and not to an increased QT beat to beat variability[150]. In a heterogeneous population of patients with mild to moderate HF, the role of QTVI in predicting increased cardiovascular mortality has been investigated. The authors observed that QTVI, as an expression of increased repolarization liability, is a marker of increased risk of cardiovascular mortality[151]. Finally, a very recent study on a population of patients with ischemic dilated cardiomyopathy, both with reduced and with preserved LVEF, confirmed the utility of QT variability in order to identify the patients with a higher risk of SCD[152]. Therefore increased QT/RR slopes and an increased QT variability can reflect a greater vulnerability of the myocardium and predispose the development of malignant arrhythmias. Thus the dynamic analysis of VR represents an interesting tool to improve the accuracy in stratifying the risk of arrhythmic events.

MICROVOLT T WAVE ALTERNANS

Definition and prognostic role

Electrical alternans is defined as a change of the amplitude of the waves of the ECG which manifests itself at alternate heartbeats. It was described for the first time by Hering[153] in 1908. Much of the interest in the alternans phenomenon has focused on alternans occurring during the repolarization phase of the cardiac APs, also known as repolarization alternans and in particular in microvolt level beat-to-beat alternation in T-wave morphology: The microvolt T wave alternans (MTWA). That has been recognized as being a strong predictor of ventricular arrhythmias, as assessed in a variety of clinical and experimental studies[154-157]. There are two main theories that explain this mechanism. The first refers to a spatial dispersion of refractoriness which results in changes in the impulse propagation and repolarization. In this case the alternation of repolarization would be secondary to the alternation in the propagation of the impulse. This would occur when the refractory period of the cell is shorter than the time between two successive activations. It would block one-way and re-entry. This hypothesis was supported by an experimental study. According to the second hypothesis MTWA would be caused by an alternation in repolarization of the APs resulting in a secondary propagation of alternans APs[158-160].

Methodological aspects

The analysis is based on the alignment of ECG cycles to the QRS complex and on the measurement of T-wave amplitude. The beat-to-beat fluctuations of the T-wave are then analyzed using fast Fourier transformation and MTWA is represented by the pronounced peak visible in the spectrum at 0.5 cycles/beat. The MTWA is considered significant when the alternans voltage exceeds a threshold (usually 1.9 microV) and if the alternans ratio K is $\geqslant$ 3. In general, we can judge as positive an alternans lasting more than 1 min, at a HR $\leqslant$ 110 beats/min[161]. Because of the strong correlation between the phenomenon of MWTA and the occurrence of ventricular re-entrant arrhythmias, its identification was proposed as a test to stratify the risk of ventricular arrhythmias[162,163].

The phenomenon is dependent on the HR. The treadmill test, a non-invasive and inexpensive test, is generally used for recognition. However, there are discordant opinions on the fact that a negative MTWA test can really identify a group of patients at extremely low risk of SCD or cardiac arrest[164-167].

Prognostic significance

Hohnloser *et al*[168] found that MWTA is predictive of major ventricular arrhythmias with a very low event rate among patients with a negative MWTA. In another meta-analysis, a positive MTWA was associated with a 2.5-fold higher risk of cardiac death and severe arrhythmias in both ischemic and non-ischemic cardiomyopathy[169]. The Alternans Before Cardioverter Defibrillator (ABCD) trial demonstrated the role of MWTA in guiding the ICD implantation for primary prevention in patients with LVEF $\leqslant$ 40%, coronary artery disease and non-sustained VT[170]. The analysis of data from five studies involving 2883 patients without ICD demonstrated that in patients with a LVEF >

35%, a positive MWTA identified those more prone to experience major arrhythmic events and SCD[171].

Despite the evidence suggesting a possible role of MWTA in predicting the arrhythmic risk, discordant data are available in the literature. Gupta *et al*[172] demonstrated that spectrally derived MTWA testing has limitations in its feasibility and is not specific enough to evaluate the arrhythmic risk and to guide strategic clinical decisions. In a population of patients with HF, Kraaier *et al*[173] observed that MTWA testing could be carried out only in a half of the population, and often resulted indeterminate. The authors concluded that MTWA treadmill testing is not suitable to stratify the risk of SCD in patients with HF.

CONCLUSION

There is much evidence that underlines the role of VR alterations in predisposing to lethal arrhythmias and the analysis of VR has become an interesting tool to refine the risk stratification of arrhythmic events. Different cardiac structural and electrical alterations may cause abnormalities in APs and in refractory period leading to perturbations of repolarization that can favor the onset of severe ventricular arrhythmias. Several measures of ventricular repolarization have been suggested with the aim of stratifying the arrhythmic risk allowing identification of those patients more prone to experiencing major arrhythmic events.

The measure of QT interval has gained growing interest since the first description of congenital LQTS and SQTS. Moreover, several factors such as drugs, advanced age, female sex, personal medical history, metabolic and electrolyte disorders can cause QTc prolongations and predispose to arrhythmic events. However, despite the vast number of studies evaluating the role of prolonged QTc as a marker of arrhythmic risk, opinions on the utility of QTc measurement in daily clinical practice are not univocal.

In order to overcome some of the limitations of QTc assessment, other strategies evaluating VR have been proposed. The analysis of the QTd seems to more accurately represent the non-uniform prolongation of APs and heterogeneity of the duration of the refractory periods and the conduction velocities of adjacent myocardial areas, allowing a better analysis of VR. The role of QTd analysis as an arrhythmic risk predictor has been well-established, but this evaluation of VR has not always been effective in identifying patients at higher risk of arrhythmic events. Moreover there are no recommended cut-off values for QTd.

Therefore, dynamic measures of VR, such as QT dynamicity and variability, reflecting the dynamic behaviour of VR, were developed as prognostic markers of arrhythmic risk. In addition, MWTA, another ECG parameter expression of alternans during VR, has been shown to predict arrhythmic events, although there are limitations in its feasibility. However there are no recommendations for the routine use of these parameters.

In conclusion, several measure of VR have been proposed but, despite the first studies concerning VR being nearly outdated, their role as a predictor of ventricular arrhythmias is not always clear and definite recommendations on their use in different clinical settings and for each single patient are still lacking and unfocused.

More attention should be paid to collecting a complete medical history of the patient and detecting the presence of well-established risk factors, cardiovascular conditions and medications known to cause QTc prolongation.

In the absence of one-size-fits all approach to the risk stratification of arrhythmic events, it is desirable to combine different measures of VR with other predictors in each specific clinical setting.

Further robust and tailored studies are required to settle the existing issues and provide useful prognostic tools for clinician.

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Cardiovascular drugs in the treatment of infantile hemangioma

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Abstract

Since the introduction of propranolol in the treatment of complicated infantile hemangiomas (IH) in 2008, other different beta-blockers, including timolol, acetabutolol, nadolol and atenolol, have been successfully used for the same purpose. Various hypotheses including vasoconstriction, inhibition of angiogenesis and the induction of apoptosis in proliferating endothelial cells have been advanced as the potential beta-blocker-induced effect on the accelerated IH involution, although the exact mechanism of action of beta-blockers remains unknown. This has generated an extraordinary interest in IH research and has led to the discovery of the role of the renin-angiotensin system (RAS) in the biology of IH, providing a plausible explanation for the beta-blocker induced effect on IH involution and the development of new potential indications for RAS drugs such as angiotensin-converting enzyme inhibitors and angiotensin-receptor blockers in the treatment of IH. This review is focused on the current use of cardiovascular drugs in the treatment of IH.

Key words: Infantile hemangioma; Beta-blockers; Renin-angiotensin system; Angiogenesis

Core tip: This article aimed to review the different beta-blockers used in the treatment of children with infantile hemangioma, the pre-treatment cardiologic work-up required and the potential side-effects associated with beta-blockers therapy in such a young population. Other cardiovascular drugs with potential effects on infantile hemangioma including angiotensin-converting enzyme inhibitors and angiotensin-receptor blockers are also reviewed.

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INTRODUCTION

Infantile hemangiomas (IH) are not only the most common vascular tumors in children, but also the most common soft-tissue tumors in this population, occurring in 5% to 10% of infants[1,2]. Evolution of IH is characterized by a proliferation phase, stabilization, and a progressive spontaneous involution in the first 2-10 years of age[3]. Only 10%-15% of IHs results in complications requiring treatment[4]. Beta-blockers, especially propranolol, have emerged as first-line therapy and have dramatically changed the therapeutic approach for complicated IH, leaving systemic glucocorticoids as the second-line therapy. After the first publication in 2008[5] about the efficacy of propranolol in IH, more than 500 reports in the medical literature have supported its use as first-line therapy[6-10]. The largest, randomized, placebo controlled trial involving patients with complicated IHs treated for up to 24 wk with a pediatric oral propranolol solution has been recently published[6]. Other pharmacological agents including angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin-receptor blockers (ARBs) implicated in the renin-angiotensin system (RAS) have been tested for IH[11-13] (Table 1). This article aimed to review the current indications for beta-blockers in IH, the potential effects of RAS drugs in the treatment of IH and their role as antiangiogenic agents.

BETA-BLOCKERS

Beta adrenergic receptor blockers are a class of medications which exerts their action by blocking B1 and/or B2 adrenergic receptors that exist throughout the body. B1 are primarily represented in the myocardium and kidneys while B2 receptors are the predominant beta receptor in the extracardiac vasculature, skeletal muscle and lungs. Multiple forms of beta-blockers exist including B1 selective and nonselective beta-blockade. Beta-blockers cardiac function is by partially activating the beta receptors and thus not allowing norepinephrine or epinephrine to bind to the receptor. This causes a decreased amount of G stimulatory protein activation leading to decreased intracellular cyclic adenosine monophosphate (cAMP) which then decreases phosphorylation by protein kinase A. This in the myocardium leads to decreased heart rate and contractility. In the vasculature, B2 receptors are also coupled to G stimulatory proteins which when stimulated by norepinephrine or epinephrine lead to increased cAMP and intracellular calcium loading which yields smooth muscle relaxation. B2 antagonism therefore is associated with a small degree of vasoconstriction in many vascular beds. Beta-blockers have also been found to decrease vascular endothelial growth factor (VEGF) as well as bFGF through unknown mechanisms[14]. B antagonism has also been shown to decrease the renin formation in renal cells as cAMP signaling subsequent to B receptor activation is critical for basal expression of vessel associated renin[15].

ANGIOTENSIN-CONVERTING ENZYME INHIBITORS

ACEIs function by preventing the angiotensin-converting enzyme (ACE) from cleaving angiotensin Ⅰ (AT Ⅰ) to create AT Ⅱ. Normally, renin produced in the kidney as a result of sympathetic stimulation, hypotension or decreased sodium delivery to the nephrons cleaves the protein angiotensinogen to form AT Ⅰ which is then converted by ACE to AT Ⅱ. AT Ⅱ then binds to AT I-receptors in smooth muscle and cause vasoconstriction. AT Ⅱ also causes release of norepinephrine as well as preventing the reuptake of norepinephrine in sympathetic nerves. In addition, AT Ⅱ causes an increase in the circulating aldosterone levels. By blocking these mechanisms, ACEIs therefore cause vasodilation of the vasculature with a resultant decrease in cardiac preload and afterload as well as decreasing the systemic blood pressure. ACEIs also down-regulate the sympathetic tone by preventing the release of norepinephrine in the sympathetic nerves. ACEIs additionally increase naturesis by helping to decrease aldosterone levels[11,12,16].

ANGIOTENSIN-RECEPTOR BLOCKERS

ARBs also work on the renin-angiotensin-aldosterone pathways but by a competitive antagonism of AT Ⅱ binding to the AT Ⅰ receptors. This results in the same decrease in vascular tone, sympathetic/norepinephrine release and aldosterone release. ARBs have also been shown to block transforming growth factor beta which is known to have angioproliferative properties[13,17].

BETA-BLOCKERS AND ANGIOGENESIS

Since the serendipitous discovery of the use of propranolol in the treatment of complicated IHs in 2008[5], an interest in the role of beta-blockers in hypoxia-induced angiogenesis has been raised. Other conditions, including retinopathy of prematurity (ROP) and cancer, are also characterized by the presence of hypoxia-induced angiogenesis and a potential role for beta-blockers has been advocated[18]. Most IHs do not present a premonitory mark and they become apparent 1-3 wk after birth. A blanched area, a telangiectatic patch or a bruiselike lesion may be seen as a premonitory mark in the early neonatal period in some patients. A rapid growth of IH is normally seen in the first 3-4 mo after birth, followed by a slow growth or stable phase until the age of 1 year. Spontaneous involution occurs over the next several years[2,4]. However, the growth pattern differs from each patient and lesion. Deep IHs often appear later and continue to grow for a longer time than superficial IHs. The origin of IH remains unknown, but some authors support the hypothesis that IH

Table 1 List of publications on the role of beta-blockers, angiotensin-converting enzyme inhibitors and angiotensin-receptor blockers in infantile hemangioma

Ref.	Study type	*n*	Median age (range)	CV drugs	Conclusions
Léauté-Labrèze *et al*[6]	Prospective, clinical trial	456	103.8 ± 31.0 d	Propranolol	Propranolol was effective at a dose of 3 mg/kg per day for 6 mo
Abarzua-Araya *et al*[48]	Randomized double-blind controlled trial	23	5.2 ± 3.5 mo (2-14 mo)	Atenolol *vs* Propranolol	Atenolol appears to be as effective as propranolol
Léauté-Labrèze *et al*[10]	Randomized double-blind controlled trial	14	12.5 wk	Propranolol	Propranolol may be given very early in infants with IH, to stop IH growth and thus prevent disabling scarring
Blanchet *et al*[47]	Case series	4	2 mo (1.5-3 mo)	Acebutolol	Acebutolol seems to present advantages for use in treating subglottic hemangiomas
Bauman *et al*[43]	Randomized investigator-blind controlled trial	19	2 wk-6 mo	Propranolol *vs* Prednisolona	Both medications show similar efficacy. Propranolol should be the first line of therapy for symptomatic IH unless contraindicated or unless future studies demonstrate severe adverse effects
Chan *et al*[45]	Randomized controlled trial	41	2.5 mo (5-24 mo)	Timolol	Topical timolol maleate 0.5% gel with a maximum dose of 0.5 mg per day is a safe and effective option for small superficial IHs that have not ulcerated and are not on mucosal surfaces
Pope *et al*[46]	Cohort- blinded study	19	4.5 mo (1-92 mo)	Nadolol *vs* Propranolol	Patients with proliferative IH, treated with oral nadolol for 6 mo, experienced almost complete involution of their tumor, which was significantly different from patients treated with propranolol
Tan *et al*[11]	Open-labelled observational trial	8	12.9 wk (5-22 wk)	Captopril	The response of IH to an ACEI supports a critical role for the RAS proteins in IH
Cristou *et al*[12]	Retrospective case series	17	7.5 mo (4.5-15 mo)	Captopril	The striking improvement observed with propranolol has not been replicated with captopril. ACEI is not involved in IH involution and the mechanism of action
Itinteang *et al*[13]	Basic research-*In vitro*	6	6 mo (4-8 mo)	Ramipril Losartan	Findings suggest a key regulatory role of AT I and AT II in promoting cellular proliferation in IH, and establish a role for ACEIs and ARBs in the proliferation of IH

ACEI: angiotensin-converting enzyme inhibitors; ARBs: Angiotensin-receptor blockers; AT I: Angiotensin I; IH: Infantile hemangioma.

may actually be a response to local tissue hypoxia, a homeostatic attempt to revascularize relatively hypoxic tissue with new blood vessels[19-23]. A well-known risk factor for IH is placental insufficiency and this might be the cause of prenatal hypoxia that triggers the angiogenesis process and the development of IH[24,25]. Glucose transporter, type 1 (GLUT-1), a glucose transporter in the erythrocyte membrane, is recognized as a specific immunohistochemical marker for IH and an important sensor of hypoxia. GLUT-1 is present in IH during proliferation and involution phases and it has been recently demonstrated to be upregulated within hypoxic zones of mesenchymal tumors[26,27]. Another condition associated with hypoxia is the ROP, which is known to be related to an initial microvascular ischemic insult followed by abnormal hypoxia-induced neovascularization[28,29]. Both, IH and ROP, have a higher incidence and severity in neonates with lower gestational age and birth weight. Interestingly, both conditions occur in the early neonatal period and most of them resolve spontaneously without sequelae. VEGF is overexpressed in response to hypoxia and ischemia. Both, IH and ROP, have an overexpression of VEGF. Particularly in the retina, VEGF induces a pathological blood vessel formation at the junction between the vascularized retina and the avascular zone of the retina, also into the vitreous[30]. Anti-VEGF drugs, including bevacizumab and ranibizumab, have showed similar efficacy in the regression of ROP[31,32]. Kong *et al*[33] measured serum levels of bevacizumab and VEGF in premature infants with ROP and treated with intravitreal injection of bevacizumab and they concluded that clearance of bevacizumab from the bloodstream takes at least 2 mo in this age population. Because VEGF is crucial in the fetal organogenesis, concern about the anti-VEGF effect mediated by bevacizumab in premature infants exists. Beta-blockers have demonstrated to have a safer pharmacological profile in the pediatric population. Ristori *et al*[34] published the first demonstration that beta-blockers were protective against retinal angiogenesis in an animal model. Filippi *et al*[35] evaluated the safety and efficacy of oral propranolol administration in preterm newborns affected by an early phase of ROP and they concluded that propranolol counteracts the progression of ROP with a high incidence of adverse effects. The preterm infant with IH may not be the appropriate candidate for systemic propranolol use and instead a topical beta-blocker may be an alternative selection in this specific population. Topical ocular instillation of propranolol has

shown to be safe in animal models and on-going studies will define its role in ROP[36]. For periocular IH, timolol, another beta-antagonist, has also been reported to be effective and may be a viable alternative to systemic propranolol therapy[37].

New anti-cancer agents are being developed in response to tumor chemoresistance and severe side effects of standard chemotherapeutic agents. Several drugs, including beta-blockers, ACEIs and ARBs, were originally approved for indications other than malignancies treatment, but recent investigations support their role as cytostatic agents[38]. Adrenergic activation may play a role in carcinogenesis and tumor progression by promoting production of VEGF. Expression of beta-adrenergic receptors has been demonstrated in several tumor types, including colon cancer, hepatocellular carcinoma, lung adenocarcinoma, prostate cancer and breast cancer[39]. Recent studies have suggested that angiotensin and beta-adrenergic blockade may modulate the development and progression of cancer. Engineer *et al*[40] evaluated 262 patients with colon cancer who were exposed to ACEIs, ARBs and beta-blockers and they concluded that exposure to a combination of beta-blockers and ACEIs/ARBs is associated with decreased tumor progression, decreased hospitalizations, and increased survival in patients with advanced colorectal cancer.

BETA-BLOCKERS AND INFANTILE HEMANGIOMA

The use of beta-blockers for the treatment of IH was serendipitously discovered when a patient with a large infantile hemangioma was treated for cardiomyopathy with propranolol which prompted a change in color, softening and decrease in size of the lesion in 2008[5]. The group from France then treated 10 other patients with propranolol resulting in similar decrease in size of the IH. There have been multiple retrospective, single-institution case series reporting the benefit of propranolol in treating IH. A meta-analysis from 2013 reviewed 1162 publications and included 41 studies in the analysis comparing corticosteroids and propranolol for the treatment of cutaneous IHs[41]. Sixteen reported the outcomes from corticosteroid use in 2629 patients and 25 examined propranolol use in 795 patients with a pooled response rate of 69% for corticosteroids and 97% for propranolol (P = 0.001).

There have been three randomized controlled trials addressing propranolol use in a few different manners. The first was a small study, which randomized 40 patients to propranolol at 2 mg/kg (divided three times daily) or placebo for 6 mo[42]. Propranolol halted growth after 4 wk of use and decreased volume, color and elevation when compared to placebo. Major side effects such as hypoglycemia, hypotension and bradycardia were not reported. The next randomized trial evaluated the difference between treatment with corticosteroids and propranolol in 19 patients at 3 vascular anomalies centers[43]. Treatment occurred until toxicities developed or clinical response was achieved. The corticosteroid group had quicker decrease in size of the lesion but also had more frequent severe adverse events limiting the length of treatment. No difference in response rate to the medications of the IH was found after 4 mo of treatment though all 11 patients had discontinued the steroids due to toxicity. A third randomized trial explored the possible additive effect corticosteroids and propranolol[44]. Thirty patients were randomized to one of three groups: Propranolol (2-3 mg/kg per day), prednisolone (1-4 mg/kg per day) or combination therapy all for 3 mo. The group treated with propranolol had superior results to the prednisolone group and similar results to the combination therapy. Again, most patients treated with prednisolone stopped taking the drug early due to adverse events. The largest and most recent randomized trial examined the effect of propranolol at different doses and lengths of treatment[6]. In 456 patients, the optimal dosing was identified at 3 mg/kg per day for 6 mo with a response rate of 60% *vs* 4% for placebo. Response was defined as complete or near complete resolution of the lesion at 24 wk of treatment. After 5 wk of treatment, 88% of patients in the higher propranolol dosing group had a response to the medication. The known adverse events of hypoglycemia, hypotension, bradycardia and bronchospasm were infrequent and equivalent in both groups.

Other beta-blockers, including timolol, acetabutolol, nadolol and atenolol, have been successfully used in the treatment of IH. Topical treatment with timolol maleate gel has also been well studied with a randomized controlled trial published in 2013[45]. Forty patients with superficial hemangiomas without ulceration or mucosal involvement were randomized to topical timolol gel 0.5% (twice daily) *vs* placebo. The treated group had smaller than expected lesions and improved color at 24 wk of treatment though minimal differences were identified at earlier time points. No adverse events were discerned in the treatment group.

Since propranolol is a lipophilic nonselective beta-blocker that crosses the blood-brain barrier, sleep disturbances have been associated with its use, being less frequent with hydrophilic drugs such as atenolol and nadolol. Some investigators have highlighted the importance of the beta-adrenergic system in memory modulation and the potential long-term memory loss of children with prolonged propranolol use. A pilot, cohort study by Pope *et al*[46] compared 10 patients in the nadolol group *vs* 9 historic controls in the propranolol group, matched on age and sex. The nadolol group had a superior response at 4, 12 and 24 wk assessments, decreasing sleep disturbances and potential concerns about long-term memory loss. The difference in response may be related to the longer half-life of nadolol, which may increase compliance and steady

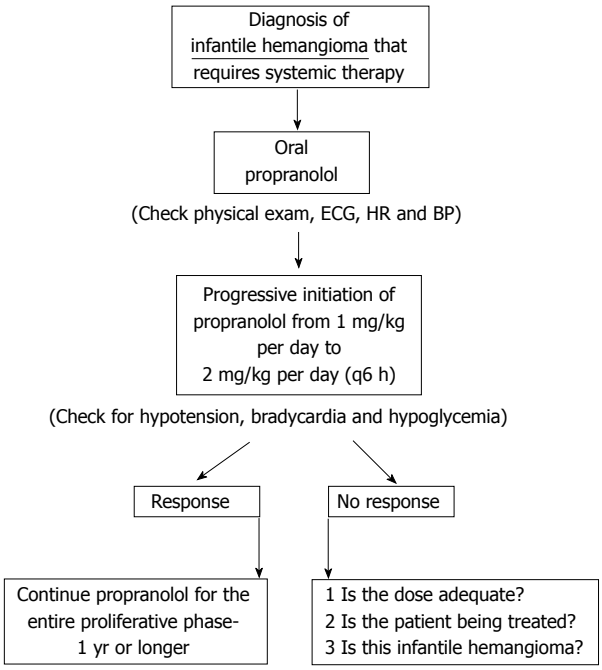

Figure 1 Therapeutic algorithm for oral propranolol treatment in infantile hemangioma. BP: Blood pressure; ECG: Electrocardiogram; HR: Heart rate.

state effect of the drug. Blanchet *et al*[47] reported good results in 3 cases of subglottic hemangioma treated with acebutolol, a cardioselective beta-blocker. Acebutolol should theoretically have less adverse effects than propranolol due to it cardioselectivity, but more studies are necessary to compare the efficacy of this agent. Atenolol is a selective, cardiac beta-blockers and may decrease possible respiratory side effects. A small study, which randomized 23 patients to treatment with atenolol or propranolol revealed equivalent response rates, 54% *vs* 60%[48]. Prospective clinical trials are required to better define the role of each beta-antagonist and the agent selection according to the patient characteristics and the type of lesion.

Cardiology evaluation prior to starting propranolol has been routinely performed; however, there is no uniform evaluation. Most centers utilize an electrocardiogram and echocardiography in infants prior to starting treatment. Although are few limitations to starting therapy with propranolol based on abnormalities found on these studies, there can be other cardiac related issues found prior to starting which may require additional treatments. One study showed 21% of patients with IH had an additional cardiac abnormality found on echocardiography[49]. Another study has shown that pretreatment electrocardiogram is of limited value for patients with an unremarkable cardiovascular history and a normal heart rate and blood pressure[50]. The duration of treatment also can vary based off of multiple factors (Figure 1). Not all infantile hemangiomas will respond to beta-blocker therapy and may not require long term treatment. Most, however, recommend at least 3 mo prior to determining that there is no effect from the beta-blocker. The long term therapy in those who respond should be at a minimum of 6 mo. If there is a significant decrease in size of the hemangioma but not complete resolution, this can be continued for 12 mo. Routine cardiac follow-up should be determined by growth that is expected to occur for that age. Infants increase their weight and thus need dose adjustments more frequently than toddler age children and therefore require more frequent evaluation. These follow-up evaluations however should consist of monitoring for symptoms secondary to the beta-blocker, dosage adjustment for weight gain, and determination of effect of treatment.

Side effects of beta-blockers include hypotension, bradycardia, hypoglycemia, seizure, nightmares, bronchoconstriction, diarrhea and somnolence[51]. The hypotension and bradycardia seen is often asymptomatic and typically associated with the first dose. Most symptomatic hypoglycemia is associated with concomitant illness or poor oral intake around the time of seizure. This is usually seen within the first few days of therapy but may occur at any time assuming the dietary intake changes. Nonselective beta-blockers are thought to prevent catecholamine induced glycogenolysis, gluconeogenesis and lipolysis which lead to hypoglycemia. Seizure is thought to be related to the hypoglycemia. Bronchoconstriction is related to the effects on the smooth muscle in the bronchi which beta agonist cause bronchorelaxation and therefore this mechanism is blocked with beta-blockers. Sleep disturbances can be very difficult to evaluate in this patient population.

ANGIOTENSIN-CONVERTING ENZYME INHIBITORS AND INFANTILE HEMANGIOMA

After the demonstration of the RAS components in the endothelium of IH, a greater interest on the role of cardiovascular drugs in the management of proliferating IH has emerged. It has been proposed that modulation of products of the RAS such as AT Ⅰ, ACE, or AT Ⅱ could represent an alternative therapeutic target. Tan *et al*[11] published an open-labelled observational clinical trial using captopril, an ACEI, in the treatment of problematic proliferating IH in 8 patients. All the lesions responded to captopril at a dosage of 1.5/kg per day with a transient mild renal impairment occurred in one patient. Treatment was discontinued at the age of 14 mo, except for one patient. In contrast, Christou *et al*[12] reported the results of 17 patients with IH who were treated with oral corticosteroid therapy and developed hypertension requiring treatment with captopril. They concluded that captopril alone did not sustain the corticosteroid-induced involution. Further clinical trials are required to

better define the role of these cardiovascular drugs.

ANGIOTENSIN-RECEPTOR BLOCKERS AND INFANTILE HEMANGIOMA

A recent study aimed to investigate the effect of the angiotensin peptides and their agonists and antagonists on cellular proliferation in proliferating IH *in vitro* samples. A significant increase in cellular proliferation in the AT Ⅰ and AT Ⅱ treated IH tissues compared with control samples was found, suggesting a potential role for ACEIs and ARBs in the proliferation phase of IH[12].

CONCLUSION

Although very few reports have been published on the role of the RAS and some cardiovascular drugs such as beta-blockers, ACEIs and ARBs in the management of IH, clinical evidence supports the use of propranolol as first-line agent for complicated lesions. More basic and clinical studies are needed to investigate the potential effectiveness of other cardiovascular drugs.

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MINIREVIEWS

Pulmonary vein stenosis: Etiology, diagnosis and management

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Abstract

Pulmonary vein stenosis (PVS) is rare condition characterized by a challenging diagnosis and unfavorable prognosis at advance stages. At present, injury from radiofrequency ablation for atrial fibrillation has become the main cause of the disease. PVS is characterized by a progressive lumen size reduction of one or more pulmonary veins that, when hemodynamically significant, may raise lobar capillary pressure leading to signs and symptoms such as shortness of breath, cough, and hemoptysis. Image techniques (transesophageal echocardiography, computed tomography, magnetic resonance and perfusion imaging) are essential to reach a final diagnosis and decide an appropriate therapy. In this regard, series from referral centers have shown that surgical and transcatheter interventions may improve prognosis. The purpose of this article is to review the etiology, assessment and management of PVS.

Key words: Pulmonary vein stenosis; Pulmonary vein stenosis etiology; Pulmonary vein stenosis causes; Pulmonary vein stenosis diagnosis; Pulmonary vein stenosis management; Pulmonary vein stenosis treatment

Core tip: Several papers in literature focus either on

the causes, diagnosis or treatment of pulmonary vein stenosis. However this is simple yet complete and updated review of all these matters that may guide physician's decision making when facing a suspected or confirmed case of this unusual disease.

Pazos-López P, García-Rodríguez C, Guitián-González A, Paredes-Galán E, Álvarez-Moure MADLG, Rodríguez-Álvarez M, Baz-Alonso JA, Teijeira-Fernández E, Calvo-Iglesias FE, Íñiguez-Romo A. Pulmonary vein stenosis: Etiology, diagnosis and management. *World J Cardiol* 2016; 8(1): 81-88 Available from: URL: http://www.wjgnet.com/1949-8462/full/v8/i1/81.htm DOI: http://dx.doi.org/10.4330/wjc.v8.i1.81

INTRODUCTION

Despite pulmonary vein stenosis (PVS) is an uncommon entity (estimated incidence about 2-3 cases per year in large centers)[1] its morbidity and mortality rates are high at advance stages[2]. The condition, linked in the past to congenital heart diseases in childhood and mediastinal processes (*i.e.,* tumors) in adults, is nowadays firstly associated to injury from radiofrequency ablation (PVA) for atrial fibrillation (AF). It is essential to consider the possibility of the disease in patients at-risk to guarantee early detection (image techniques play a key role in this regard) and treatment. The aim of this article is to review the etiology, assessment and management of PVS.

ETIOLOGY

Congenital PVS

Congenital PVS is an exceptional abnormality (0.4% of congenital heart diseases) consequence of a failed incorporation of the common right and/or left PV into the left atrium (LA) during the embryologic development of the vessel that leads to partial or complete obliteration of the PVs on one or both sides[3]. From a histological point of view its main feature is an overgrowth of connective tissue with medial hypertrophy and intimal fibrosis which results in obstruction. Even though diagnosis is usually made within the first 3 years of life, it may be delayed till adulthood in some cases[3]. Congenital PVS is frequently associated (50%) with other cardiac defects[4,5], hence imaging examination protocols applied to patients with congenital heart diseases should include a systematic evaluation of the PVs (Table 1).

ACQUIRED PVS

PVA for AF

At the present time PVA for AF has become the principal cause of PVS. Incidence derived from recent studies reaches a mean and median of 2% and 3.1%, respectively. These figures represent a significant reduction in comparison with those reported in pioneer series (mean: 6.3% and median: 5.4%, estimated from papers published between 1999 and 2004)[5]. Main factors contributing to this finding are operator experience and improvements in the procedure [changing of ablation site from the PVs antra to ostia, reduction of temperature applied to tissue, cryoablation and intracardiac echocardiography (ICE) guidance][2]. However real occurrence of PVS is probably underestimated as screening is only performed within the first 3 mo in some centers (it has been demonstrated that PVS can occur over this time period)[6] and asymptomatic patients are not always imaged.

Table 1 Causes of pulmonary vein stenosis

Congenital
Cardiac defects associated:
Total anomalous pulmonary venous return
Septal defects
Transposition of the great vessels
Acquired
Pulmonary vein ablation
Sarcoidosis
Neoplasm
Fibrosing mediastinitis
Post cardiovascular surgery

Mediastinal processes

Extrinsic compression by lymphadenopathies or granulomatous involvement may cause PVS in sarcoidosis[7,8].

Fibrosing mediastinitis, a rare complication of tuberculosis and Histoplasma capsulatum infection, characterized by uncontrolled fibrosis around the affected mediastinal lymph nodes, may lead to invasion and obstruction of the surrounding PVs[9].

Neoplasm adjacent to the PVs may cause stenosis due to compression or infiltration[10,11].

Cardiovascular surgery

Clinically significant PVS in pediatric population is most frequently seen after total anomalous pulmonary venous return repair (estimated incidence approximately equal 10%)[12,13]. Obliteration may be localized either at the level of the anastomosis of the PV into the LA or further into the center of the vessel. Isolated cases of PV injury leading to obstruction after myxoma resection[14], suture repair of a PV cannulation site[15] and lung transplantation[16] can be found in literature.

ASSESSMENT

PVS may be symptomatic when vein caliber is reduced significantly (> 50% stenosis), as a consequence of a raise in lobar wedge pressure, or lung perfusion is decreased by > 20%-25%[17-19]. Clinical manifestations, which in case of PVA normally appear 3-6 mo after the procedure, are clearly related to the number of PVs affected and include progressive exertional dyspnea, cough, chest pain (frequently following a

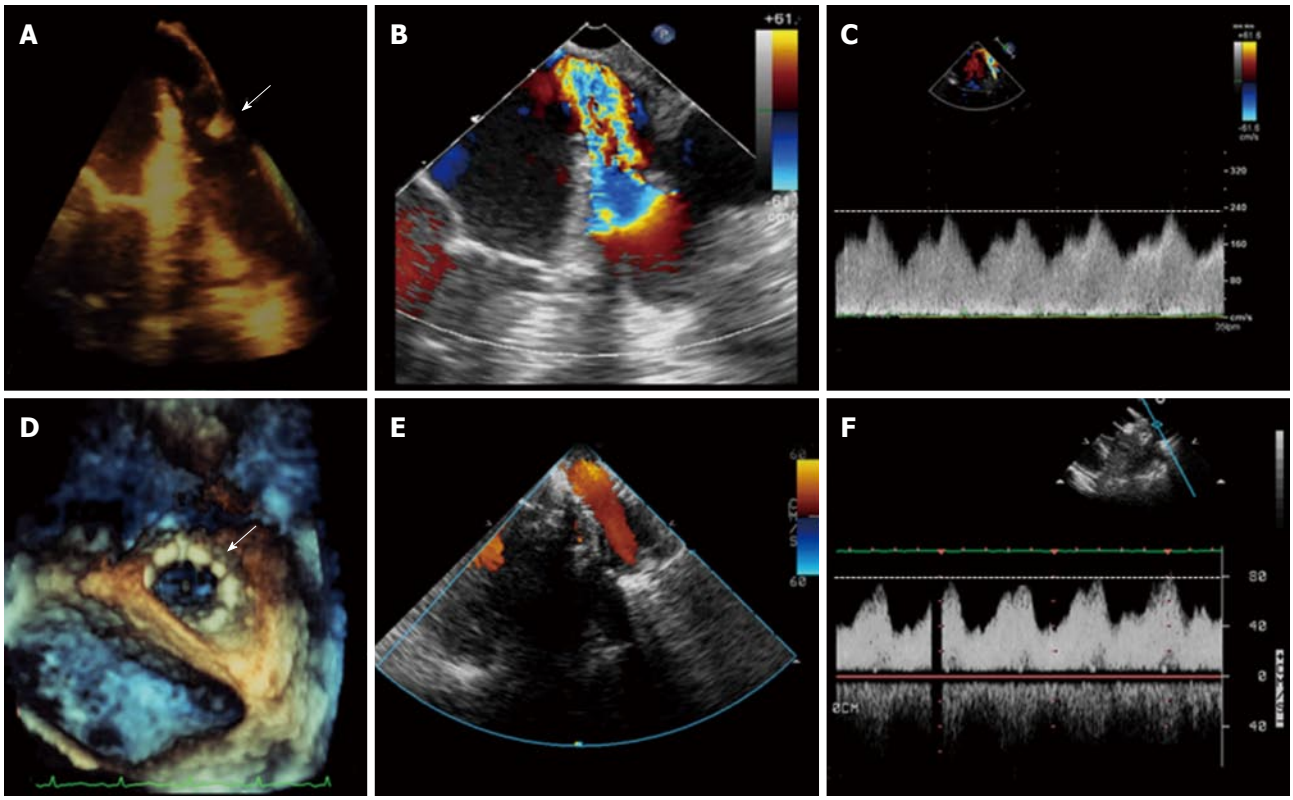

Figure 1 Transesophageal echocardiography of a patient with a recent left lung transplantation and severe congestion in the graft. A: Narrowing in the common trunk of the left PVs at the level of the sutures (arrow). Color Doppler and Continuous Wave Doppler demonstrate turbulent flow (B) and high velocity (C: peak velocity 2.4 m/s; peak gradient 23 mmHg) across the vessel which is consistent with a significant stenosis. A stent was successfully implanted at the level of the stenosis (D: "en face" 3D echo image view; arrow). Laminar flow (E) and normal velocities (F: peak velocity 0.8 m/s; Peak gradient 2.5 mmHg) were seen after the procedure.

pleuritic profile) and hemoptysis. Chest X ray may demonstrate signs of congestion (peribronchovascular and septal thickening, Kerlley B lines, alveolar edema) either diffuse or localized (mimicking other processes such as pneumonia), depending on the PVs involve[6]. Other findings can be found depending on the cause of the stenosis (*i.e.,* lung size reduction in congenital PV atresia, a thoracic mass in the case of a tumor, mediastinal calcifications in fibrosing mediatinitis or calcified mediastinal lymph nodes in sarcoidosis). As the clinical picture is nonspecific, collateral flow development may mitigate symptoms[17], and occasionally physicians do not bear in mind the possibility of the disease, the diagnosis is commonly missed or delayed. Therefore screening with available imaging modalities in patients at risk (especially those with history of PVA) who develop respiratory symptoms is warranted.

Echocardiography

Transesophageal echocardiography (TEE) is a useful tool for PV investigation. Studies have shown high diagnosis accuracy for detection of PVS after PVA (sensitivity: 82%-100%, specificity: 95%-100%) compared to other techniques [computed tomography (CT), magnetic resonance imaging (MRI) and angiography][20]. Advantages of TEE are its wide availability, avoidance of radiation exposure, low cost, and applicability to patients with ferromagnetic implanted devices (*i.e.,* pacemakers, defibrillators). There is no standard definition of PVS, nevertheless it seems that an increased maximum PV Doppler flow velocity (> 1.1 m/s) combined with color Doppler turbulence may be a reliable index[21] (Figure 1). TEE poses however noteworthy limitations including need of sedation, technical difficulties to visualize all PVs if performed by not experienced operators, non-volumetric but planar acquisition, inadequate assessment of paracardial structures, imprecise delimitation of LA-PVs junction (makes PVs ostial size a non-reliable anatomical parameter) and, even low, risk of esophageal perforation and pulmonary aspiration. 3D TEE may overcome some of these limitations.

ICE has been successfully used to guide PVA and evaluate PV ostial narrowing. The invasive nature of the technique restricts however its use to patients undergoing a redo PVA. Although diagnostic accuracy of ICE has not been investigated, an increased peak Doppler flow velocity over 1.6 m/s is consistent with PVS according to initial experiences[22].

CT

CT allows assessment of the extension of mediastinal neoplastic and non tumoral diseases infiltrating or compressing the PVs and enables the diagnosis of PVS after PVA by directly depicting vessel diameter (significant stenosis > 50%)[3,4] (Figure 2). Although the choice of CT protocol depends on daily practice in every center ECG gated scanning improves quality and allows postprocessing with 3D reconstruction software which

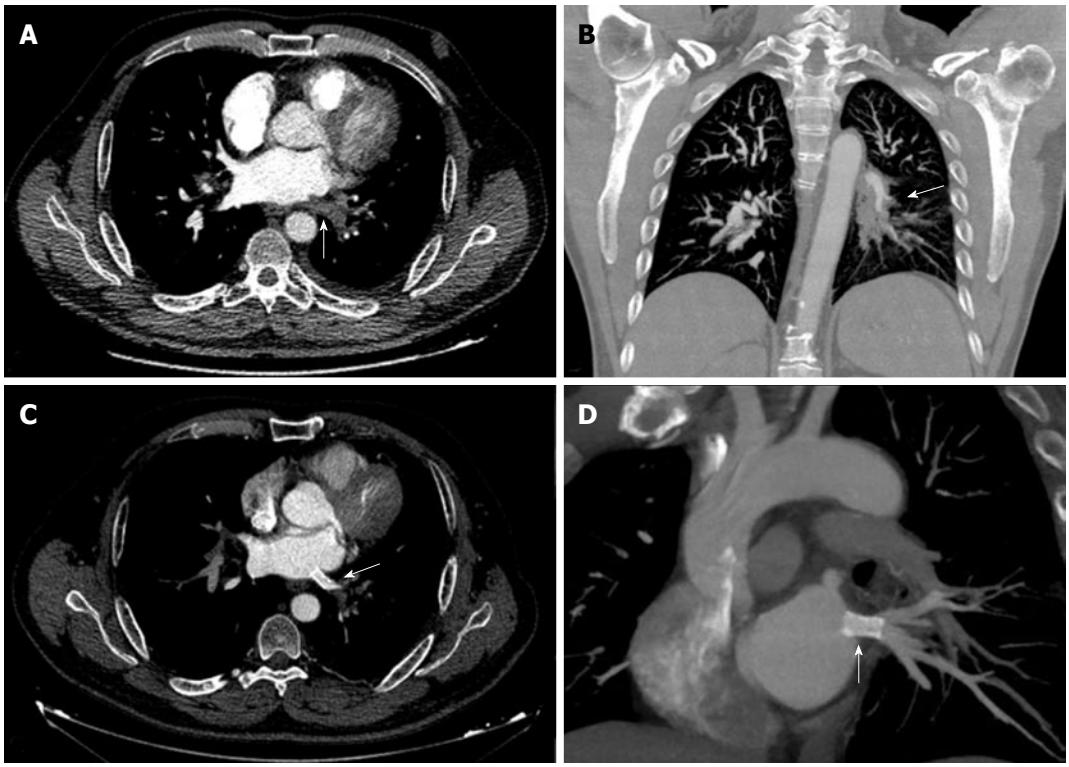

Figure 2 Computed tomography of a patient undergone radiofrequency ablation two months before and recent onset of dyspnea on exertion. A: Absent of contrast (arrow) in the left lower pulmonary vein (complete occlusion); B: Extensive infiltrate within the left lung (arrow) cause by localized edema; C and D: After stent implantation (arrows) flow was successfully restored.

permits better evaluation of the PVs ostia. The main benefits of CT are short examination time, multiplanar views and high spatial resolution, whereas disadvantages include patient exposition to ionizing radiation and need of intravenous iodine contrast agents that might impair renal function in vulnerable individuals. PVs (typically the left inferior) can be compressed between the LA and the descending aorta appearing stenotic (pseudostenosis). Differential diagnosis can be made measuring PV caliber in every phase of the cardiac cycle (fixed in cases of true PVS and variable in pseudostenosis) or imaging the patient in prone position (this maneuver eliminates LA compression and therefore pseudoestenosis) when either a multiphase scan has not been performed or findings are inconclusive[23].

MRI

MRI is diagnostic in most cases by analyzing PV anatomy (MR angiography) and flow dynamics (MR phase contrast imaging; velocity and gradients across the vessel)[24,25] (Figure 3). This modality can be also used to evaluate congenital cardiopathies and processes in the vicinity of the heart associated with a PVS (*i.e.,* neoplasm). The main advantage of MRI over CT is that it does not expose the patient to radiation. Nevertheless drawbacks are considerable: Spatial resolution is lower than CT, it is contraindicated in patients with implanted non-compatible metal devices, and it may not be possible to perform in individuals with claustrophobia, unable to cooperate, large body habitus or severe renal impairment when gadolinium contrast is needed. Additionally, scanning time is considerably long.

Perfusion imaging

Perfusion of a pulmonary lobe draining to a PV with a significant stenosis may be decreased and detected using radionuclide quantitative pulmonary flow imaging (TC99m macroaggregated albumin) (Figure 4). This test however is not valuable for an etiological diagnosis of a PVS, may be altered in other pathologies that decreased lobar perfusion (*i.e.,* pulmonary thromboembolism), is not suitable for detection of < 50% stenosis[26] and may be inaccurate if significant compensating ipsilateral PV flow is present. Moreover, even small, it implicates radiation exposure (Table 2).

Summing up, clinical manifestations and imaging test are the key elements in PVS assessment. Choice of imaging modality depends on availability, experience, and patient characteristics. Despite current guidelines do not provide a recommendation for frequency and duration of imaging screening in case of PVA most electrophysiology (EP) labs suggest a follow up test within 3-6 mo after the procedure in order to detect significant iatrogenic PVS at an early stage and avoid its sequelae.

MANAGEMENT

PVS in pediatric population

Mild and asymptomatic PVS may not need intervention;

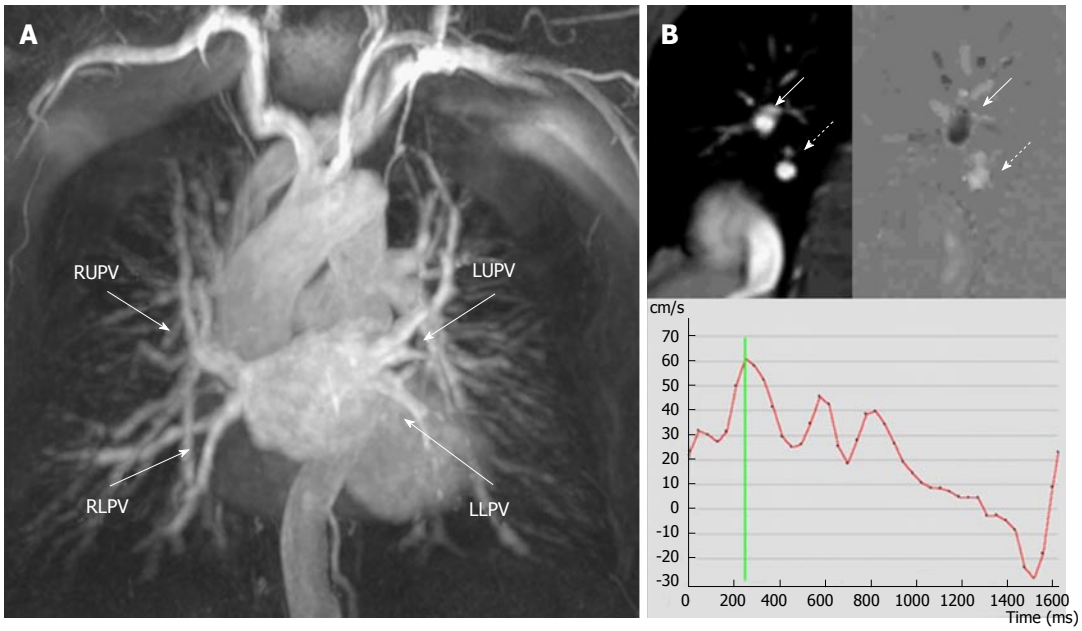

Figure 3 Magnetic resonance scan of a patient with a radiofrequency ablation procedure one month before, mild hemoptysis and fever. A: Angiography shows normal caliber of the four PVs; B: Phase contrast imaging of the right lower PV. Top left: right pulmonary artery (arrow) and right lower PV (dashed arrow). Top right: Flow map. Black or white signal depends on the direction of the flow. The PV "white flow" (dashed arrow) compares with the opposite direction of flow in the pulmonary artery seen in the same image that is "black" (arrow). Bottom: the resulting velocity-time curve demonstrates normal flow morphology and velocities in the PV. Significant PVS was excluded. RUPV: Right upper pulmonary vein; RLPV: Right lower pulmonary vein; LUPV: Left upper pulmonary vein; LLPV: Left lower pulmonary vein; PV: Pulmonary vein.

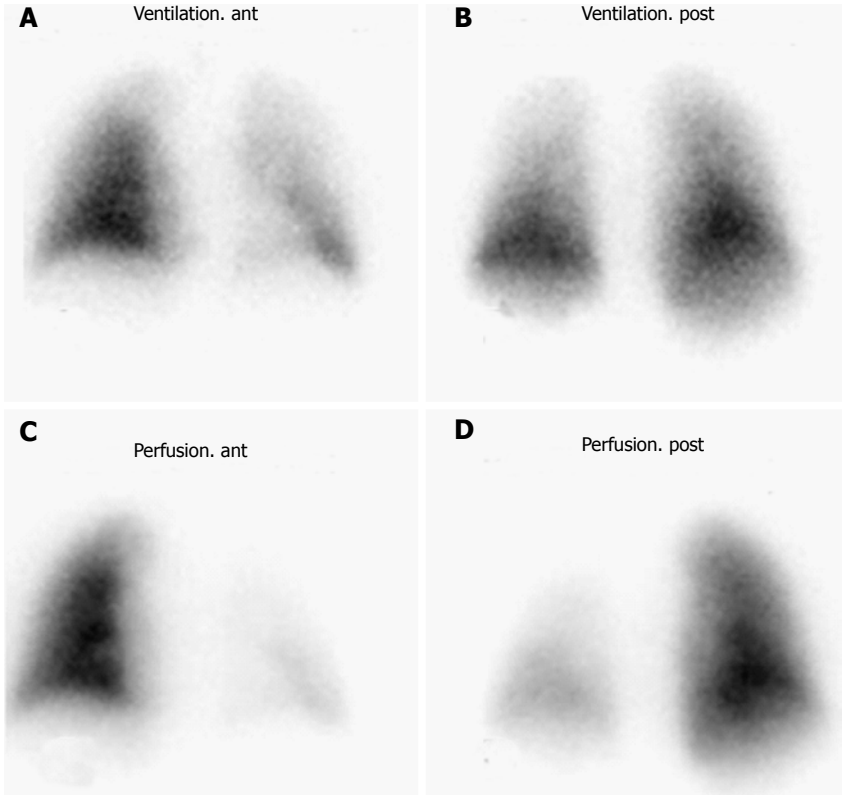

Figure 4 Radionuclide lung ventilation/perfusion scan performed three months after radiofrequency ablation in a patient with shortness of breath. A and B: Normal ventilation; C and D marked hypoperfusion within the left lung consistent with significant left PV stenosis which was demonstrated on a CT scan. PV: Pulmonary vein; CT: Computed tomography.

clinical and image surveillance is advised as the disease can evolve over time. Surgery is the preferred approach in most congenital or acquired significant symptomatic PVS. The conventional interventions

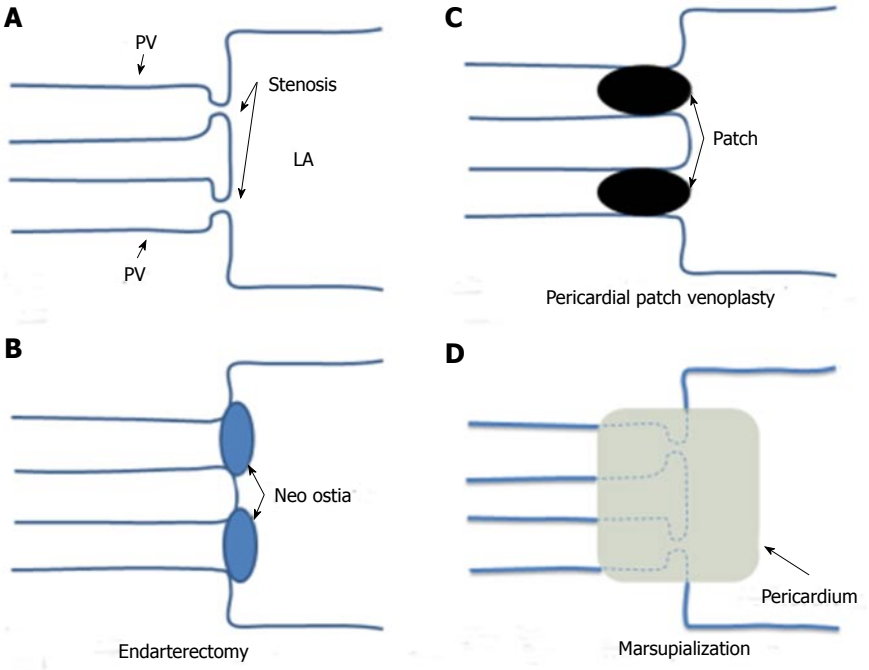

Figure 5 Surgical techniques for pulmonary veins. A: Schematic representation of a bilateral pulmonary vein stenosis at the ostia of the vessels; B: Endarterectomy; the stenotic tissue has been excised and the PVs directly anastomosed to the LA; C: Pericardial patch venoplasty; the stenotic tissue has been resected and a pericardial patch anastomosis has been used to enlarge the tightened ostia of the vessels; D: Sutureless marsupialization: the veins ostia have been incised longitudinally, excess fibrotic tissue has been excised and *in situ* pericardial flaps have been sewn directly to the left atrium so direct stiches over the cut edges of the pulmonary veins are avoid. PV: Pulmonary vein; LA: Left atrium.

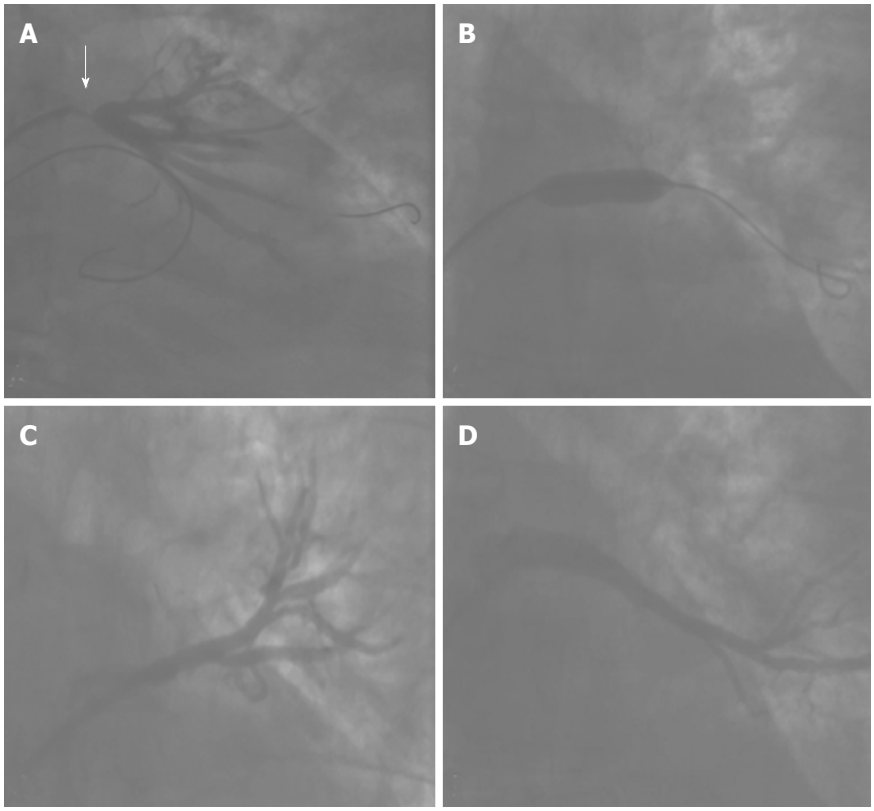

Figure 6 Stent implantation in a pulmonary vein stenosis. A: Angiography showing a critical stenosis in the ostium of the left lower pulmonary vein; B: Bare metal stent release; C and D: Final result. The stenosis was resolved. Normal flow can be seen in the main superior (C) and inferior (D) branches of the vein.

(Figure 5) include: (1) endarterectomy (excision of the stenotic ring and direct anastomosis of the PV to the LA endocardium); and (2) pericardial patch venoplasty (resection of the stenotic tissue and patch anastomosis

Table 2 Advantages of imaging modalities used for pulmonary vein stenosis evaluation

	TEE	CT	MRI	VQ
Availability	Yes	Yes	No	No
Non-invasive	No[1]	Yes	Yes	Yes
Caliber assessment	No	Yes	Yes	No
Functional assessment	Yes	No	Yes	Yes
Evaluation of surrounding tissues	No	Yes	Yes	No
Radiation avoidance	Yes	No	Yes	No

[1]TEE is generally considered a semi-invasive technique. TEE: Transesophagueal echocardiography; CT: Computed tomography; MRI: Magnetic resonance imaging; VQ: Ventilation perfusion scan.

to enlarge the tightened segment). The newer sutureless marsupialization technique (the pericardium surrounding the affected PV is directly attached to the LA so direct stiches over the cut edges of the vessel are avoided) can help to prevent deformation of the suture line and reduce tissue growth stimulus decreasing therefore restenosis risk[27]. Overall, published surgical outcomes are modest; only half of cases are free from reintervention or death at 5 years[27,28]. Pneumectomy may be mandatory in cases of severe or uncontrolled hemoptysis and lung transplantation has been performed in patients with relentless PVS progression and severe pulmonary hypertension[29]. There is limited experience with percutaneous interventions in childhood; angioplasty is technically challenging (high pressures are needed to released stenosis and in case of stent implantation prosthesis should allow future expansion to adult dimension (> 12 mm) and results are suboptimal (repeated dilatations are frequently needed as instent restenosis rate is high)[30].

PVS in adult population

Transcatheter therapy is the most common chosen approach (Figure 6). While evidence of treatment of PVS due to extrinsic compression, infiltration or cardiac surgery is restricted to cases reports in literature[16] several small studies have evaluated the efficacy of percutaneous interventions for PVS after PVA. There are discrepancies among EP labs about management of asymptomatic PVS. Despite most authors recommend clinical and imaging monitoring every 3-6 mo in patients with 50%-85% stenosis, some promote angioplasty if a single stenosis > 75%[17] and others in cases of a cumulative stenosis index (average stenosis of the PVs of one site) > 75%[18]. Main arguments for early intervention are: Inadequate recovery of lung perfusion at advance stages caused by fixed venoconstriction leading to permanent pulmonary hypertension; and fast progression to PV occlusion in some cases which may be difficult to amend. Regarding the technique itself stenting appears better than isolated balloon venoplasty in terms of vessel restenosis (60% *vs* 36% for PV over 8 mm)[5]. Mid to long term patency is directly related to vessel size with higher rates of restenosis observed in PV < 1 cm. Drug eluting stents may have a better restenosis profile than conventional bare metal stent however studies regarding their use this scenario are scarce[31].

Limited data about antithrombotic regimes are available: (1) anticoagulation with warfarin, with an international normalized ratio target of 2-3, is generally recommended for at least 12 mo in the case of stents > 1 cm and indefinitely for those smaller[19]; (2) dual antiplatelet therapy, added to anticoagulation, with aspirin plus clopidogrel is usually prescribed for a minimum of 3 mo, however optimal duration is not known; and (3) new oral anticoagulants (dabigatran, rivaroxaban, apixaban) or antiaggregants (prasugrel, ticagrelor) have not been tested.

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ORIGINAL ARTICLE

Basic Study

Bicuspid aortic valve hemodynamics does not promote remodeling in porcine aortic wall concavity

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Abstract

AIM: To investigate the role of type-I left-right bicuspid aortic valve (LR-BAV) hemodynamic stresses in the remodeling of the thoracic ascending aorta (AA) concavity, in the absence of underlying genetic or structural defects.

METHODS: Transient wall shear stress (WSS) profiles in the concavity of tricuspid aortic valve (TAV) and LR-BAV AAs were obtained computationally. Tissue specimens excised from the concavity of normal (non-dilated) porcine AAs were subjected for 48 h to those stress environments using a shear stress bioreactor. Tissue remodeling was characterized in terms of matrix metalloproteinase (MMP) expression and activity *via* immunostaining and gelatin zymography.

RESULTS: Immunostaining semi-quantification results indicated no significant difference in MMP-2 and MMP-9 expression between the tissue groups exposed to TAV and LR-BAV AA WSS (P = 0.80 and P = 0.19, respectively). Zymography densitometry revealed no difference in MMP-2 activity (total activity, active form and latent form) between the groups subjected to TAV AA and LR-BAV AA WSS (P = 0.08, P = 0.15 and P = 0.59, respectively).

CONCLUSION: The hemodynamic stress environment present in the concavity of type-I LR-BAV AA does not

cause any significant change in proteolytic enzyme expression and activity as compared to that present in the TAV AA.

Key words: Bicuspid aortic valve; Fluid shear stress; Aortopathy; Remodeling; Matrix metalloproteinases

Core tip: The bicuspid aortic valve with left-right cusp fusion (LR-BAV) generates a stress overload on the ascending aorta (AA) convexity, which promotes aortic medial degeneration and aortic dilation. While the wall concavity is generally spared from the disease, the protective role of the local hemodynamics has not been demonstrated. This study aimed at comparing matrix metalloproteinase biology in AA concavity tissue subjected to the local hemodynamic stresses generated by a tricuspid aortic valve (TAV) and a LR-BAV. The results suggest that the fluid stresses in the TAV AA and LR-BAV AA concavity result in similar MMP expressions and activities.

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INTRODUCTION

The bicuspid aortic valve (BAV) is present in 1%-2% of the general population[1-3] and is the most common cardiac anomaly. Despite its seemingly low incidence, the BAV is responsible for causing more valvular and vascular disease compared to all other congenital heart defects combined[4]. Unlike the normal tricuspid aortic valve (TAV) which consists of three leaflets, the BAV forms with only two[5-7]. While there are different BAV morphogenic phenotypes[8-10], the most common is referred to as the type-I BAV and is characterized by the presence of two cusps of unequal size and one fibrous raphe marking the site of fusion on the larger leaflet[5]. Type-I BAV patients not only have a higher susceptibility to develop valvulopathies that usually require surgical intervention and valvular replacement, they are also associated with increased risk of aortopathies such as aortic dilation, dissection and aneurysm[11-13]. In particular, type-I BAVs with fusion between the left- and right-coronary cusps (LR subtype) has emerged as the most aggressive in terms of risk for secondary aortopathy[14-16]. This subtype tends to result in asymmetric dilation patterns that localize to the convex region of the thoracic ascending aorta (AA) but spare the wall concavity[14,15,17].

Previous clinical studies have demonstrated that the degenerative remodeling of the aortic wall in type-I BAV patients is accompanied by increased expression of matrix metalloproteinase-2 (MMP-2) and MMP-9[16,18-20] in the disease-prone wall convexity relative to the wall concavity[14,15,21]. Those proteolytic enzymes degrade key extracellular matrix components such as collagen and elastin[22]. The respective expression and activity of those enzymes and their tissue inhibitors regulate the balance between extracellular matrix synthesis and resorption[23]. A perturbation of this delicate equilibrium can result in the progressive degeneration of the vascular wall and the loss of vessel wall integrity[24].

Interestingly, type-I LR-BAVs have been shown to generate perturbed hemodynamics characterized by a valvular jet skewed toward the non-coronary leaflet and increased shearing friction force [*i.e.,* wall shear stress (WSS)] on the convexity of the thoracic AA[25-31]. While those observations suggest a role for hemodynamics in the pathogenesis of BAV aortopathy[32-34] and despite the clear evidence for the existence of flow abnormalities in BAV aortic wall regions vulnerable to dilation, the causative effects of those abnormalities on the local weakening of the aortic wall have not been fully established. Underlying challenges hampering the *in vivo* assessment of this hemodynamic theory include the possible existence of genetic anomalies in the aortic wall, as well as the paucity of hemodynamic data in non-dilated BAV aortas. To circumvent those issues, *ex vivo* methodologies enabling the replication of the native BAV AA WSS environment on genetically normal and non-dilated AA tissue have been developed.

In our previous *ex vivo* study[35], we isolated the impact of TAV and LR-BAV hemodynamic stresses on the remodeling of the AA convexity. The WSS environments in the convex region of a TAV AA and a normal (non-dilated) LR-BAV AA were quantified computationally[28,35] and replicated in the laboratory using a shear stress bioreactor[36,37]. The remodeling response of porcine aortic tissue extracted from the AA convexity and exposed to those environments for 48 h was investigated *via* immunostaining, immunoblotting and zymography. Exposure of normal aortic tissue to BAV AA WSS resulted in increased MMP-2 and MMP-9 expressions and MMP-2 activity but similar fibrillin-1 content relative to the TAV AA WSS treatment. While this study demonstrated the susceptibility of the hemodynamic stresses experienced by the BAV AA convexity to focally mediate aortic medial degradation, the apparent protective effects of the LR-BAV hemodynamics on the AA concavity and the asymmetric development of dilation in the LR-BAV AA require further investigation. Therefore, the objective of the present study was to isolate *ex vivo* the impact of LR-BAV hemodynamic stresses on the remodeling of the disease-protected AA concavity, with a focus on MMP expression and activity.

MATERIALS AND METHODS

WSS characterization and in vitro generation

The temporal WSS variations experienced by the

Table 1 Wall shear stress signal characteristics in the concavity of the tricuspid aortic valve and left-right bicuspid aortic valve ascending aorta

	Maximum (Pa)	Minimum (Pa)	TSM (Pa)	OSI
TAV AA WSS	3.2	-2.75	0.77	0.49
LR-BAV AA WSS	3.3	-3.63	1.06	0.18

WSS: Wall shear stress; LR-BAV: Left-right bicuspid aortic valve; TAV: Tricuspid aortic valve; AA: Ascending aorta; OSI: Oscillatory shear index; TSM: Temporal shear magnitude.

concave region of a TAV AA and LR-BAV AA were obtained computationally using a previously published and validated fluid-structure interaction (FSI) model of a human aorta subjected to idealized TAV and LR-BAV flows[28]. Briefly, a realistic model of a human aortic arch was reconstructed based on histological slices (Visible Human Project, National Library of Medicine). 3D transient velocity profiles matching physiologic TAV and LR-BAV average flow rates were prescribed at the model inlet. The dynamic WSS profiles experienced by the TAV AA and LR-BAV AA concavity were captured in a rectangular region (dimensions: 8 mm × 15 mm) centered on the wall concavity and located 1 cm above the left-coronary leaflet (Figure 1A). The two WSS waveforms share important similarities both qualitatively and quantitatively, as indicated by their peak values and average magnitude temporal shear magnitude (TSM) over one cardiac cycle (Table 1). Importantly, as compared to the TAV, which generates a nearly perfectly sinusoidal WSS signal, the LR-BAV generates a double negative WSS peak, which tends to lower the signal oscillatory shear index (OSI).

The two WSS environments were replicated in the laboratory using our previously described and validated cone-and-plate bioreactor[35,37]. Briefly, the device consists of a cylindrical chamber filled with culture medium and containing a cone rotating above a stationary mounting plate (Figure 1B). The rotation of the cone generates a flow and thus, a WSS on the surface of the plate, whose intensity τ at a radial location r is directly proportional to the cone angular velocity ω:

$$\omega = [(h + r\alpha)/\mu r]\tau \quad (1)$$

where μ is the dynamic viscosity of the culture medium (0.95×10^{-3} kg/m per second), α is the cone half angle (0.5°), and h is the distance between the cone apex and the mounting plate (200 μm)[36]. The two angular velocity waveforms producing the TAV AA and LR-BAV AA WSS profiles obtained computationally were programmed into the servo drive (Gemini GV6k, Parker Hannafin) controlling the cone motion. The details of this protocol have been previously published[35].

Tissue harvest and preparation

The experiments were conducted on porcine aortas (6-12 mo) acquired from a local abattoir (Martin's Custom Butchering, Wakarusa, IN, United States) due to their structural similarities with human aortas and their well-characterized antibody specificities. Aortic tissue was harvested after on-site dissection of the hearts within 10 min of slaughter and was transported to the laboratory in sterile, ice-cold Dulbecco's Phosphate Buffered Saline (PBS, Sigma-Aldrich). This protocol has been previously implemented in our laboratory and has been shown to preserve endothelium integrity and cellular viability[35,36,38]. All subsequent procedures were performed in a sterile flow hood. Upon arrival to the laboratory, the aortas were cut longitudinally in order to expose the inner endothelial surface. Consistent with our previous study on the effects of BAV flow on AA convexity[35], two circular specimen (7-mm diameter) were excised from the AA concavity, 8 and 15 mm above the sinus of the left-coronary leaflet (*i.e.,* region least prone to dilation[14,15,39]). Samples were then randomized into fresh controls and experimental samples. Six samples were mounted to the circular plate using a button suturing technique, which has been shown not to affect the WSS level generated on the tissue[35]. The native orientation of the tissue relative to blood flow was maintained by aligning the longitudinal axis of the samples with the direction of cone motion (*i.e.,* tangential direction). Tissue conditioning to WSS was performed in an incubator maintaining a temperature of 37 ℃ and a CO_2 level of 5% for 48 h (duration sufficient for acute mechanosensitive remodeling processes to become evident in aortic tissue[34,35,40]). The system was continuously perfused with standard culture medium (Dulbecco's Modified Eagle's Medium supplemented with 10% fetal bovine serum, 3.7 g/L sodium bicarbonate, 0.05 g/L ascorbic acid, 10% non-essential amino acid solution and 1% penicillin-streptomycin; all from Sigma-Aldrich) at a rate of two bioreactor volumes per hour. The perfusion system was flushed and replenished with fresh medium every 12 h.

Groups

Two experimental groups and one control group were considered to isolate the impact of TAV AA and LR-BAV AA hemodynamics on the acute remodeling response of the AA concavity: (1) fresh porcine tissue excised from the concavity of the ascending aortic wall (control); (2) fresh porcine tissue excised from the concavity of the ascending aortic wall and subjected to the local TAV AA WSS; and (3) fresh porcine tissue excised from the concavity of the ascending aortic wall and subjected to the local BAV AA WSS.

Biological analyses

Following WSS conditioning, the samples were harvested and washed three times with sterile PBS. The samples were then either frozen in optimal cutting medium for future immunostaining analysis flash frozen in liquid nitrogen for future gelatin zymography analysis.

Immunostaining: The OCT blocks were cut into

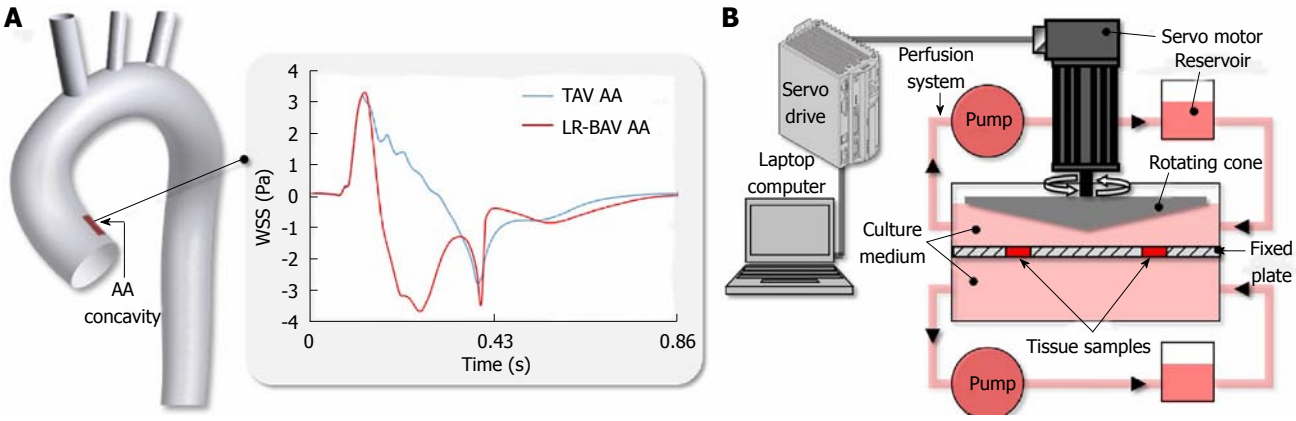

Figure 1 ***Ex vivo* methodology.** A: Temporal wall shear stress (WSS) signals captured computationally in the concavity of the tricuspid aortic valve (TAV) ascending aorta (AA) and left-right bicuspid aortic valve (LR-BAV) AA (adapted from Cao *et al*[28]); B: Shear stress bioreactor used to condition porcine AA tissue to TAV AA and BAV AA WSS.

5-μm sections using a Microm 505E cryostat (Microm International GmbH) and mounted on glass slides. The region occupied by the tissue section was circled with a fluid block pen (Immunotech) after 20 min on a heater at 37 ℃. Sections were then rinsed for 20 min in PBS. Blocking [10% Goat Serum (Sigma), 0.2% TritonX-100 (Sigma), 1% dimethyl sulfoxide (Thermo Fisher Scientific)] was performed at room temperature for 1 h. Next, MMP-2 (1:200, EMD Millipore) or MMP-9 (1:200, EMD Millipore) primary antibody was diluted in blocker and slides were incubated overnight at 4 ℃ with shaking. The following day, PBS was used to rinse the sections 3 times and secondary antibody (1:100, Santa Cruz) was incubated for 2 h at room temperature in PBS. Sections were rinsed 3 more times in PBS for 5 min each before counterstaining with 1 4′,6-Diamindino-2-phenylindole (DAPI, Sigma) and mounted with fluorescence mounting medium (Dako). Coverslipped sections were stored at 4 ℃. Fluorescence immunohistochemistry (IHC) performed on a Nikon E600 microscope was used to identify regions positively stained for MMP-2 and MMP-9 on each slide. MMP-2 and MMP-9 expression was assessed semi-quantitatively using ImageJ (National Institutes of Health, Bethesda, MD) over three image fields per sample, following our previously published methodology[38,41-43]. The overall intensity of MMP immunopositive expression was measured and normalized by the total number of cells present over each image field.

Gelatin zymography: Proteolytic activity of enzymes MMP-2 and MMP-9 was quantified using gelatin zymography. The collected supernatant protein content was quantified using a bicinchoninic acid protein assay (BCA, Pierce). Tissue lysates were loaded in equal amounts (20 μg) on a 10% zymogram gel (Bio-Rad). Gels were resolved by sample buffer (Bio-Rad) followed by 1 h incubation in developing buffer (Bio-Rad) at 37 ℃ and 5% CO_2. Stain solution (G-Biosciences) was added at room temperature, then gels were destained in deionized water at room temperature. Gels were scanned and the digital images were converted to 8-bit grayscale images before being processed in ImageJ for densitometric analysis following our previously published protocol[42,43].

Statistical analysis

Consistent with our previous study, each analysis was performed on a sample size of $N = 3$ and was quantified as mean ± SE. This sample size was shown previously to generate significant biological differences between convexity tissue specimens subjected to TAV and BAV flows[35]. Normalization to the fresh control was performed in all experimental groups. Significance was determined using ANOVA followed by a Bonferroni post-hoc test using the software SAS (SAS Institute Inc). The threshold for statistical significance was set at a P value of 0.05. Those analyses were reviewed by a biomedical statistician (Dr. Ick H Jin, Department of Applied and Computational Mathematics and Statistics, University of Notre Dame, Notre Dame, IN, United States).

RESULTS

TAV and LR-BAV hemodynamic stresses generate similar MMP expression levels in AA concavity tissue

MMP-2 and MMP-9 immunostaining results are shown in Figure 2. In fresh tissue, MMP-2 and MMP-9 expressions were moderate and consistently localized in the medial layer (Figure 2A). While MMP-2 and MMP-9 were also detected in the same region in specimens subjected to WSS, MMP-9 expression was reduced in the samples subjected to BAV AA WSS. Semi-quantification of the IHC images (Figure 2B) revealed statistically similar MMP-2 expression across the different groups (TAV AA WSS: 1.2-fold increase *vs* control, $P = 0.73$; BAV AA WSS: 1.1-fold increase *vs* controls, $P = 0.95$) and no statistical difference between the two experimental groups subjected to WSS ($P = 0.80$). While MMP-9 semi-quantification indicated a significant reduction in MMP-9 expression in tissue exposed to BAV AA WSS (0.3-fold increase *vs* control, $P = 0.01$), it revealed no statistical difference between the fresh controls and the

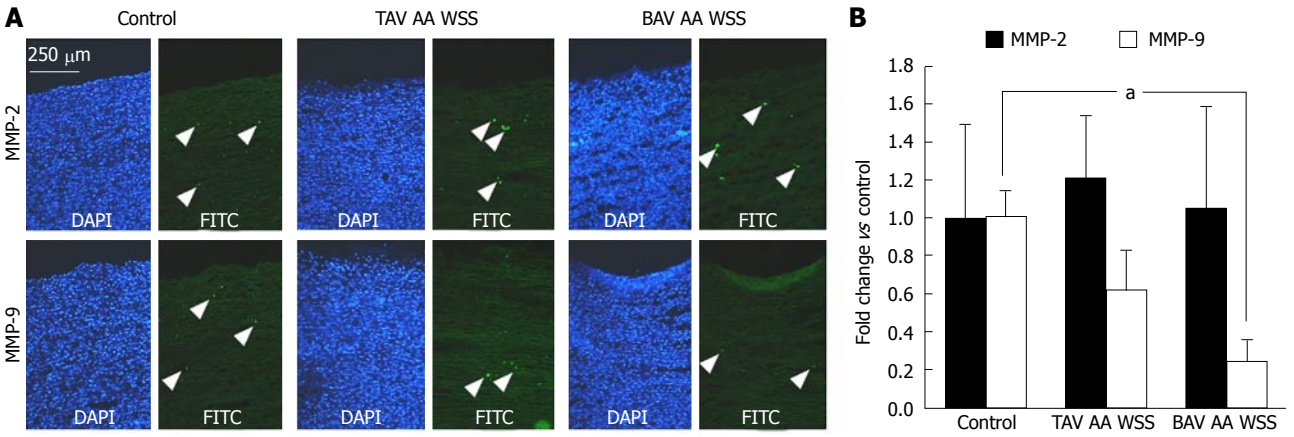

Figure 2 Matrix metalloproteinase immunohistochemistry. A: Matrix metalloproteinase (MMP)-2 and MMP-9 immunostaining with DAPI and FITC filters (blue cell nuclei, green positively stained cells); B: Semi-quantitative results ($^{a}P < 0.05$ *vs* control). DAPI: 4',6-diamidino-2-phenylindole; FITC: Fluorescein isothiocyanate.

specimens subjected to TAV AA WSS (0.6-fold increase *vs* control, $P = 0.20$) or between the two conditioned groups ($P = 0.19$).

TAV and LR-BAV hemodynamic stresses generate similar MMP activities in AA concavity tissue

MMP-2 and MMP-9 zymography results are shown in Figure 3. MMP-9 was undetectable in the zymograms. While the active form of MMP-2 was hardly detectable in the fresh controls, both latent and active MMP-2 were found in both experimental groups subjected to WSS (Figure 3A). Neither latent nor active form of MMP-9 was detected in the zymogram. Therefore, the densitometric quantification of MMP activity was only performed on MMP-2. Total MMP-2 activity was quantified as the sum of active and latent forms of MMP-2 (Figure 3B). Tissue specimens subjected to TAV AA WSS exhibited a significant increase in total MMP-2 activity relative to the fresh controls (1.5-fold increase, $P = 0.02$). While BAV AA WSS also resulted in increased total MMP-2 activity relative to the fresh controls (1.5-fold increase), the difference was not statistically significant ($P = 0.37$). No significant difference was also detected between the two experimental groups subjected to WSS ($P = 0.08$). Although the densitometric analysis performed on the latent form of MMP-2 (Figure 3C) indicated lower contents in groups subjected to TAV AA WSS (0.76-fold increase) and tissue subjected to BAV AA WSS (0.69-fold increase) relative to fresh tissue, the differences were not statistically significant ($P = 0.17$ and $P = 0.12$, respectively). No statistical difference was found between the two experimental groups subjected to WSS ($P = 0.59$). Lastly, tissue conditioning to WSS resulted in a dramatic increase in expression of active MMP-2 relative to the fresh controls, in which active MMP-2 expression was hardly detectable (TAV AA WSS: 5713-fold increase *vs* controls, $P = 0.004$; BAV AA WSS: 3877-fold increase *vs* controls, $P = 0.0008$; Figure 3D). The difference in active MMP-2 expression between the two conditioned groups remained non-significant ($P = 0.15$), but both groups exhibited a conversion from pro-(latent) to active MMP-2 after 48 h of conditioning.

DISCUSSION

We conducted an *ex vivo* study to investigate the isolated effects of BAV hemodynamic stresses on the biological remodeling of porcine AA tissue excised from the concavity of the aortic wall. The primary contribution of this study is the indication that, in the absence of any underlying congenital defect, the local hemodynamics experienced by the LR-BAV AA concavity does not trigger any acute upregulation of enzymatic protease expression or activity in the aortic medial layer.

The immunostaining and zymography analyses evidenced the absence of significant change in MMP expression and activity between the aortic wall specimens subjected to TAV AA and LR-BAV AA WSS. Those results complement our previous study on the effects of BAV flow on the biology of the AA convexity, which revealed the susceptibility of the WSS overload experienced by the convexity of the LR-BAV AA to promote aortic medial degradation *via* MMP-dependent pathways[34,35,40]. Those observations are consistent with the asymmetric presentation of aortic dilation observed in type-I LR-BAV patients and the higher vulnerability of the AA wall convexity to aortopathy[14,15,44]. The similarities in the hemodynamic stress environments present in the concavity of the TAV AA and LR-BAV AA evidenced in the present study, combined with the absence of difference in the remodeling activity of tissue exposed to those environments support a hemodynamic etiology of BAV aortopathy.

The demonstration of causality between the asymmetric BAV flow patterns and the asymmetric expression of secondary BAV complications has already been established in the context of BAV calcification, which typically affects primarily the fused leaflets exposed to WSS overload but spares the non-coronary leaflet subjected to relatively normal WSS levels[42,45]. Therefore, while the involvement of underlying genetic

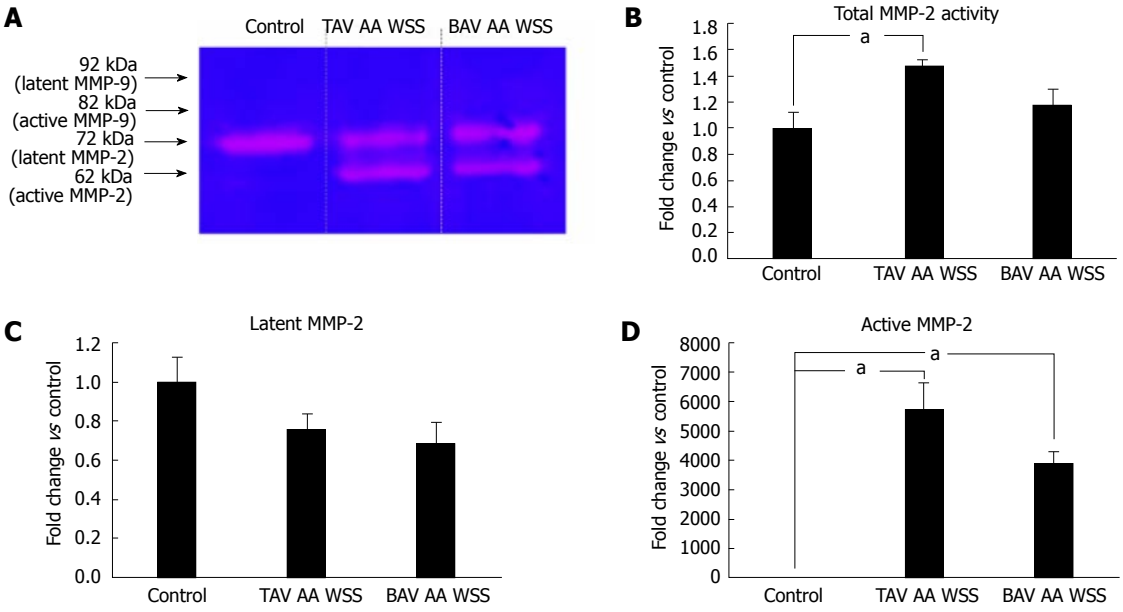

Figure 3 Matrix metalloproteinase gelatin zymography. A: Zymogram showing latent and active forms of matrix metalloproteinase (MMP)-2 and MMP-9 in fresh controls and tissue conditioned to tricuspid aortic valve (TAV) ascending aorta (AA) and bicuspid aortic valve (BAV) AA wall shear stress (WSS); B: Densitometry results for total MMP-2 enzymatic activity; C: Latent MMP-2; D: Active MMP-2 ($^aP < 0.05$ *vs* control; MMP-9 data not shown as MMP-9 was absent from the protein lysates).

abnormalities in BAV leaflets and BAV AA tissue cannot be ruled out, the present study provides one more evidence in support of the key role played by blood flow and hemodynamic stresses in BAV disease.

While no difference in protease expression and activity was detected between the tissue groups subjected to TAV AA and BAV AA WSS, some changes were measured between the fresh controls and the conditioned groups. First, tissue subjected to WSS exhibited a significant upregulation of active MMP-2 relative to fresh tissue. Although this result requires further investigation, it is important to note that, while the bioreactor was able to subject the samples to WSS, it eliminated all other forces normally present in the native environment, such as stretch and pressure. Those forces have been shown to play a critical role in the maintenance of vascular homeostasis and MMP-2 regulation[46,47]. Second, tissue exposure to LR-BAV WSS resulted in a significant MMP-9 downregulation relative to the fresh controls as suggested by immunostaining, while MMP-2 levels remained unchanged. This difference in biological response may be related to the specific mechanosensitivity of the aortic endothelium to WSS. In fact, studies conducted in our laboratory in the context of valvular tissue have demonstrated the differential sensitivity of valvular endothelial cells to WSS magnitude, directionality and frequency[41,43,48]. Following the same concept, the cells lining the aortic wall may be able to detect changes in different WSS characteristics and transduce them into different biological responses. As a result, despite the qualitative similarity between the WSS waveforms captured in the concavity of the TAV AA and LR-BAV AA, the minor differences in magnitude and directionality, as quantified by the TSM and OSI (Table 1), may be sufficient to drive a differential biological response.

MMP-9 expression was below detection level in tissue lysates and zymograms. The near absence of MMP-9 expression following exposure of aortic concavity tissue to WSS proves to be an interesting phenomenon. Animal models have indicated that MMP-2 and MMP-9 work synergistically to promote aneurysm formation[49] and that MMP-9 knockout mice are unable to develop aneurysms even under the presence of increased MMP-2 activity[50]. Therefore, the absence of MMP-9 in fresh tissue and tissue subjected to TAV AA and BAV AA WSS, which prevents the possible downstream pathological effects of MMP-2/MMP-9 synergies, may protect the aortic wall against dilation and aneurysm formation. Further *ex vivo* investigations on the combined effects of WSS, MMP-2 and MMP-9 and the modulation of the remodeling response through MMP-2/MMP-9 synergies will be necessary to test this hypothesis.

Although relationships between WSS abnormalities and biological perturbations in the aortic endothelium have been previously evidenced[51-54], more work needs to be done to isolate the impact of hemodynamic stress abnormalities on tissue remodeling. The results collected from the present study combined with those from our previous study[35] on the local effects of TAV and LR-BAV AA hemodynamic stresses on AA remodeling suggest the susceptibility of BAV hemodynamic stresses to mediate aortic medial degradation on the disease-prone wall convexity, while sparing the wall concavity. These observations suggest a critical role played by hemodynamic stresses in the development of BAV asymmetric aortopathies.

Finally, several limitations should be discussed.

The demonstration of a role for WSS in the differen-

tial remodeling state of the BAV AA convexity and concavity relied on the retrospective comparison of the present data obtained with AA concavity tissue with our previous data obtained with AA convexity tissue[35]. While ideally both sets of experiments should have been carried out using tissue specimens from the same animal, the availability of a single shear stress bioreactor prevented such mode of operation. However, the same methodology (sample size, culture techniques, biological endpoints, assays) as in the previous study was implemented to allow for the direct comparison of the results.

Second, the study only focused on the effects of WSS and neglected other important mechanical signals (stretch, pressure) normally found in the native environment. This choice is justified by two arguments. First, the objective of the study was to isolate the potential role played by WSS in the remodeling of the BAV AA concavity, in the absence of any other biochemical and mechanical signals. Second, the mechanical characterization of the TAV and BAV aortic wall provided by the FSI model revealed the absence of substantial differences in circumferential stretch and pressure between the TAV AA and BAV AA (average pressure difference: 0.4% in the convexity and 0.5% in the concavity; average stretch difference: 0% in the convexity and 0.3% in the concavity). The analysis of the WSS in both anatomies revealed more contrasted environments (TSM difference: 94% in the convexity and 38% in the concavity), which motivated and justified the investigation of their mechanobiological impact.

Third, while the study would benefit from a larger sample size, the absence of significant differences in the remodeling response of TAV AA and BAV AA concavity tissue is in agreement with the data reported in larger clinical studies that examined the asymmetric nature of aortic dilation and the spatiotemporal patterns of MMP expression in BAV AAs[14-16,55,56]. In addition, the same sample size in our previous study was able to demonstrate statistically significant biological differences between convexity specimens subjected to TAV AA and BAV AA WSS. In this context, the absence of statistical differences in the remodeling response of concavity tissue samples subjected to TAV AA and BAV AA flow is likely to be a reflection of the low impact of the concavity WSS environment on the local tissue biology rather than the consequence of a small sample size.

COMMENTS

Background

The asymmetric dilation of the ascending aortic (AA) wall downstream of the bicuspid aortic valve (BAV) is marked by aortic medial degeneration through upregulation of matrix metalloproteinase (MMP) expression and enzymatic activity. BAV AA dilation typically localizes to the AA wall convexity, which is the region impinged by the skewed BAV orifice jet and subjected to abnormally high hemodynamic wall shear stress (WSS). While previous studies have established a link between the WSS overload on the AA wall convexity and the upregulation of remodeling activity, the ability of the hemodynamic environment present in the BAV AA concavity to maintain vascular homeostasis has not been formally demonstrated.

Research frontiers

The common classification of BAV aortopathy as an inherited disorder has guided the implementation of aggressive surgical modalities including reduction aortoplasty, aortic root replacement and AA replacement. However, those procedures have been associated with a significant mortality rate when treating aortic dilation in BAV patients. Such outcome questions the suitability of those surgical approaches and justifies the need to elucidate the etiology of BAV aortopathy. The characterization of the remodelling pathways involved in the disease and the interacting mechanisms of micro-scale mechanotransduction and macro-scale hemodynamics are current hotspots in BAV and vascular research.

Innovations and breakthroughs

The authors' previous *ex vivo* characterization of the isolated effects of tricuspid aortic valve (TAV) AA and BAV AA WSS on the biology of the AA convexity revealed the ability of BAV AA hemodynamic abnormalities in the wall convexity to promote aortic medial degeneration *via* MMP-2 and MMP-9-dependent pathways. The present study is a logical extension of the authors' previous work as it investigates the contribution of the WSS environment in the seemingly disease-protected concavity of the LR-BAV AA on MMP biology. The absence of difference in the remodeling response of tissue subjected to the local WSS normally present in the TAV AA and LR-BAV AA concavity justify at least partially the asymmetric dilation pattern typically observed in LR-BAV patients and isolate, for the first time, the key role played by hemodynamic stresses in BAV aortopathogenesis.

Applications

The demonstration of a hemodynamic pathway of BAV aortic dilation may switch the clinical focus from developing aggressive surgical procedures aimed at eliminating the presumed genetically weakened AA wall to investigating new modalities aimed at normalizing BAV aorta hemodynamics or inhibiting pharmacologically the pathological remodeling cascade at an early age.

Terminology

The BAV is the most common cardiac anomaly and consists of two leaflets instead of the three present in the normal TAV. The most common LR-BAV morphotype results from the fusion between the left- and right-coronary cusps. WSS is the frictional fluid force resulting from the relative motion between the aortic wall and the surrounding blood flow. MMP-2 and MMP-9 are two proteolytic enzymes that degrade collagen, elastin and fibronectin, which are fundamental protein components of the aortic media.

Peer-review

The manuscript by Atkins *et al* proposes an *ex-vivo* model of wall shear stress applied to the lesser curvature (concavity) of porcine thoracic aorta. The *ex-vivo* model reproduces in a bioreactor the shear stress generated by a TAV and by a LR-BAV, with the aim of dissecting the role played by this single local hemodynamic factor on vascular wall remodeling of aortic concavity.

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META-ANALYSIS

Percutaneous assist devices in acute myocardial infarction with cardiogenic shock: Review, meta-analysis

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Abstract

AIM: To assess the impact of percutaneous cardiac support in cardiogenic shock (CS) complicating acute myocardial infarction (AMI), treated with percutaneous coronary intervention.

METHODS: We selected all of the studies published from January 1st, 1997 to May 15st, 2015 that compared the following percutaneous mechanical support in patients with CS due to AMI undergoing myocardial revascularization: (1) intra-aortic balloon pump (IABP) *vs* Medical therapy; (2) percutaneous left ventricular assist devices (PLVADs) *vs* IABP; (3) complete extracorporeal life support with extracorporeal membrane oxygenation (ECMO) plus IABP *vs* IABP alone; and (4) ECMO plus IABP *vs* ECMO alone, in patients with AMI and CS undergoing myocardial revascularization. We evaluated the impact of the support devices on primary and secondary endpoints. Primary endpoint was the inhospital mortality due to any cause during the same hospital stay and secondary endpoint late mortality at 6-12 mo

of follow-up.

RESULTS: One thousand two hundred and seventy-two studies met the initial screening criteria. After detailed review, only 30 were selected. There were 6 eligible randomized controlled trials and 24 eligible observational studies totaling 15799 patients. We found that the inhospital mortality was: (1) significantly higher with IABP support *vs* medical therapy (RR = +15%, *P* = 0.0002); (2) was higher, although not significantly, with PLVADs compared to IABP (RR = +14%, *P* = 0.21); and (3) significantly lower in patients treated with ECMO plus IABP *vs* IABP (RR = -44%, *P* = 0.0008) or ECMO (RR = -20%, *P* = 0.006) alone. In addition, Trial Sequential Analysis showed that in the comparison of IABP *vs* medical therapy, the sample size was adequate to demonstrate a significant increase in risk due to IABP.

CONCLUSION: Inhospital mortality was significantly higher with IABP *vs* medical therapy. PLVADs did not reduce early mortality. ECMO plus IABP significantly reduced inhospital mortality compared to IABP.

Key words: Intra-aortic balloon pump; Impella; TandemHeart; Extracorporeal membrane oxygenation; Cardiogenic shock; Meta-analysis

Core tip: Meta-analyses from observational studies represent an area of innovation in statistical science. In the present review, we identified only a small number of randomized trials, which by themselves were underpowered to assess the efficacy of the support devices on inhospital mortality. To increase the power of the analysis we included observational data, which enabled us to add 14909 additional patients to the 890 from the randomized controlled trials selected. The results of the analysis showed that: (1) intra-aortic balloon pump (IABP) used alone was associated with significant increase in inhospital mortality compared to Medical therapy; (2) percutaneous left ventricular assist devices increased, although non significantly, the mortality as compared with IABP; and (3) extracorporeal membrane oxygenation (ECMO) plus IABP had significant protective effect compared to IABP or ECMO alone.

Romeo F, Acconcia MC, Sergi D, Romeo A, Francioni S, Chiarotti F, Caretta Q. Percutaneous assist devices in acute myocardial infarction with cardiogenic shock: Review, meta-analysis. *World J Cardiol* 2016; 8(1): 98-111 Available from: URL: http://www.wjgnet.com/1949-8462/full/v8/i1/98.htm DOI: http://dx.doi.org/10.4330/wjc.v8.i1.98

INTRODUCTION

Cardiogenic shock (CS) occurs in 5% to 15% of patients with acute myocardial infarction (AMI). Despite major technical advances the inhospital mortality of these patients continues to remain unacceptably high at over 40%[1-4]. To date immediate myocardial revascularization represents the only intervention of proven benefit. Emergency percutaneous coronary intervention (PCI) is recommended if coronary anatomy is amenable and emergency surgical revascularization is recommended in case coronary anatomy is not amenable for PCI (AHA/ACC and ESC/EACTS indication: Class Ⅰ, Level B)[5-7]. In order to maintain hemodynamic stabilization before and/or after early revascularization, mechanical support with devices such as intra-aortic balloon pump (IABP), percutaneous left ventricular assist devices (PLVADs) and complete extracorporeal life support with extracorporeal membrane oxygenation (ECMO) are often considered[8]. It is known that IABP support provides significant benefit when used in association with thrombolysis; however, it is of no benefit when used in association with PCI[4,9,10].

It is of note that current guidelines do not recommend routine use of IABP in AMI patients with CS complicating AMI (AHA/ACC and ESC/EACTS indication: Class Ⅲ, Level A), but IABP use may be considered in these patients when CS is secondary to mechanical complications (AHA/ACC indication: Class Ⅱa, Level C). Further, it is recommended that the use of LV assist devices should be restricted for short-term circulatory support (AHA/ACC and ESC/EACTS indication: Class Ⅱb, Level C)[5-7].

Because the sickest patients are often excluded from randomized controlled trials (RCTs), only few RCTs of circulatory assist devices have been conducted thus far. On the other hand, there are some data from clinical observational studies[11-15].

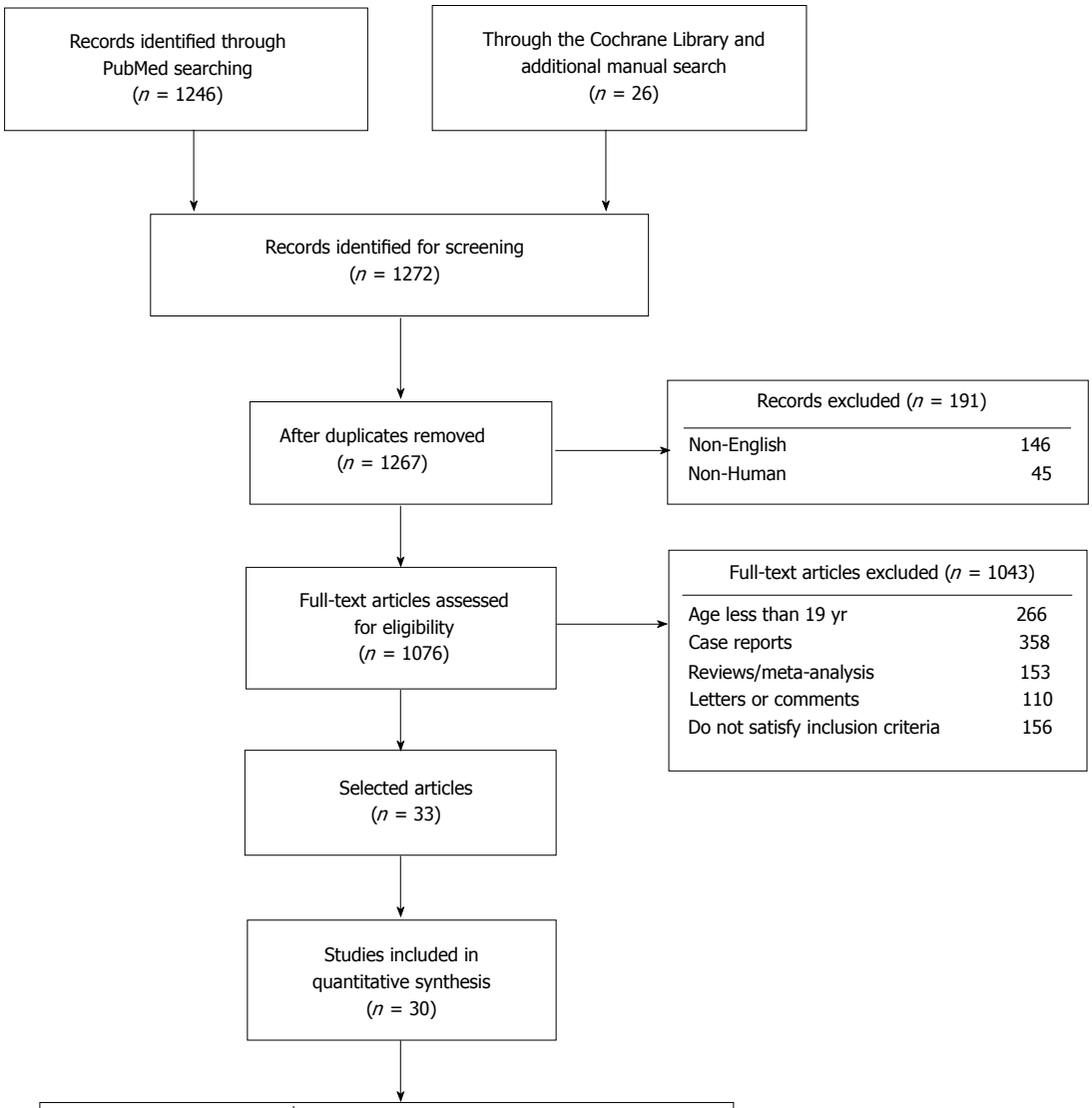
We present here a meta-analysis of available data, based on RCTs and observational studies, on the use of support devices in AMI patients with CS undergoing PCI with regard to inhospital and late mortality.

MATERIALS AND METHODS

Study definition (search and data extraction)

We performed a systematic PubMed and the Cochrane Library literature search using the terms relating to the intervention of interest "IABP" or "IABC", "Impella", "Tandemheart", "PLVADs" "ECMO" or "extracorporeal life support" or "ECLS" or "CPS" in the setting of CS in patients with AMI undergoing percutaneous coronary revascularization. We performed additional manual literature search through: (1) the reference lists of retrieved articles and published reviews; and (2) the abstracts presented at recent (last five years) International Conferences.

Two investigators independently examined the designs, patient populations and interventions used, aiming to include only studies designed to test the effect of the percutaneous support in patients with CS due to AMI and undergoing myocardial revascularization. The



Comparison	No. of studies	Inhospital mortality				Total
		Experimental group		Control group		
		Events	Total	Events	Total	
IABP *vs* medical therapy	13	2016	4360	1783	4431	8791
PLVADs *vs* IABP	6	66	118	73	153	271
ECMO + IABP *vs* IABP	3	32	88	46	76	164
ECMO + IABP *vs* ECMO	6	116	196	72	105	301
Total	28	2230	4762	1974	4765	9527
		Late mortality				
IABP *vs* medical therapy	6	1816	3491	1396	3550	7041
Overall	30	3851	7865	3167	7934	15799

Figure 1 Flow-chart of the study selection process. IABP: Intra-aortic balloon pump; PLVADs: Percutaneous left ventricular assist devices; ECMO: Extracorporeal membrane oxygenation.

search was restricted to English-language journals and excluded studies on non-human subjects as well as articles unrelated to the topic.

The study selection process is outlined in Figure 1. The exclusion criteria were data from registries or studies with lack of a control group, the absence of mortality data, the presence of different timing for the outcome or, more generally, insufficient data for risk estimation. Disagreements were resolved by asking the opinion of a third reviewer to reach consensus at each stage of the screening process. We selected all of the studies published from January 1st, 1997 to May 15st, 2015 that compared the following percutaneous mechanical support in patients with CS due to AMI undergoing myocardial revascularization: (1) IABP *vs* Medical therapy; (2) PLVADs *vs* IABP; and (3) ECMO plus IABP *vs* IABP or ECMO. CS was defined by: (1) a decrease in systolic blood pressure to $\leqslant$ 90 mmHg for more than 30 min, in the absence of hypovolemia, or requiring vasopressor support; (2) a reduction of cardiac

index to 1.8 L/min per square without support or to 2.0–2.2 L/min per square with support; and (3) elevated left ventricular filling pressures[16,17]. Moreover, profound shock was defined as systolic blood pressure less than 75 mmHg-despite receiving an intravenous inotropic agent that was associated with altered mental status and respiratory failure[18]. The acronym PLVADs included the Impella®2.5 (Abiomed, Danvers, MA, United States) and the TandemHeart (Cardiac Assist Inc., Pittsburgh, PA, United States)[14,15]. The acronym of ECMO included a modified heart-lung machine, generally consisted of a centrifugal pump, a heat exchanger and a membrane oxygenator[15,18-22].

Study outcomes

Primary and secondary endpoints: We evaluated the impact of the support devices on primary and secondary endpoints. Primary endpoint was the inhospital mortality due to any cause during the same hospital stay and secondary endpoint late mortality at 6-12 mo of follow-up.

Statistical analysis

Meta-analysis was performed separately for observational studies and RCTs comparing the following groups of patients: (1) IABP (experimental) *vs* Medical therapy (control); (2) PLVADs (experimental) *vs* IABP (control); (3) ECMO plus IABP (experimental) *vs* IABP (control); and (4) ECMO plus IABP (experimental) *vs* ECMO (control). We computed the risk ratio (RR) with 95%CI, using the Mantel-Haenszel random-effect model to take into account possible heterogeneity among the individual studies beyond that expected from chance, to point out the relative effect of the mechanical assist devices under study. We used the Forest plot to present the results graphically, to report the effect estimates for the individual studies together with the overall measure of effect. We computed the Cochran's *Q* test and I^2 statistics to quantify the homogeneity/heterogeneity among the selected studies within and between subgroups[23]. A Funnel Plot was designed as visual aid for detecting bias or systematic heterogeneity among the studies included in the meta-analysis (publication bias). A sensitivity analysis was then performed by repeating the meta-analysis after exclusion of the study(ies) falling out the 95%CI.

The meta-analysis was performed using Review Manager (RevMan) (Computer program) Version 5.3. Copenhagen: The Nordic Cochrane Centre, the Cochrane Collaborations, 2014[24].

We performed Trial Sequential Analysis using the program provide by "The Copenhagen Trial Unit, Center for Clinical Intervention Research CTU, Denmark; version 0.9 beta; available at www.ctu.dk/tsa" in order to assess if the studies enclosed in the meta-analysis reached the required number of participants (information size), and to construct the monitoring boundaries to detect significance and futility of the primary and secondary endpoints[25,26]. Trial Sequential Analysis was done using the effective difference in risks between the experimental (intervention risk) and control groups (basal risk) with a risk of a type I error of 5% and a power of 80%. The relative risk reductions (RRR) observed were linked to the number of patients to be treated (NNT) or to be harmed (NNH), to assess the clinical benefit or the detrimental effect corresponding to each level of RRR. All statistical tests were two-sided and α error of $\leqslant$ 0.05 was defined as statistically significant.

The statistical methods of this study were reviewed by Flavia Chiarotti, Biostatistician, Research Director from the Italian National Institute of Health.

RESULTS

One thousand two hundred and seventy-two records met the initial screening criteria. After detailed review, only 30 were selected[4,18,21,27-54]. There were 6 eligible RCTs[4,27-31] and 24 eligible observational studies[18,21,32-54] totaling 15799 patients. The main characteristics of the selected studies are reported in Table 1.

IABP vs medical therapy

In the comparison between IABP and Medical therapy, we analysed a total of 15063 patients (14273 from 12 observational studies[32-44] and 790 form 3 RCTs[4,27,31]). The data provided us by French *et al*[31] and Kunadian *et al*[44] contributed only for the analysis of the secondary outcome.

Primary endpoint: Primary endpoint was assessed in 8791 patients (8153 from 11 observational studies[32-43] and 638 from 2 RCTs[4,27]). The inhospital deaths occurred in 46.24% of patients in the experimental group and 40.24% of patients in the control. The NNH was 16 (6 more deaths every 100 patients treated with IABP). The overall analysis showed a significant risk increase (+18%, P = 0.002) in the IABP group (Figure 2). More specifically, we observed a significant risk increase in observational studies (RR = +21%, P = 0.0008) and a nonsignificant risk reduction in RCTs (RR = -3%%, P = 0.78) (Figure 2). The test for subgroup differences showed high heterogeneity among observational studies (I^2 = 63%) and between observational and RCTs (I^2 = 73.9%), providing a significantly different estimate of the IABP effect (Figure 2). In the Funnel plot, the studies by Gu *et al*[37] and by Zeymer *et al*[39] fell out of the 95%CI, thus appearing to be the potential source of bias. After the sensitivity analysis, heterogeneity decreased to a lower level among the observational (I^2 = 19%), but persisted at high levels between observational studies and RCTs (I^2 = 68.2%) (Table 2). Furthermore the overall risk in the experimental group slight decreased (RR = +15%) (Table 2). The NNH was equal to 18 (5 more deaths every 100 patients treated with IABP) (Table 3). Trial Sequential Analysis showed that the required number of participant was reached and the monitoring boundaries,

Table 1 Main characteristics of the selected studies

Ref.	Setting	Study design	Etiology of CS	Cardiac arrest	Treatment	Period	No. of pts
IABP *vs* medical therapy							
Anderson *et al*[32], 1997 (GUSTO-I)	United States, Europe	Obs.; multicenter	STEMI	No	PCI	1990-1993	37
Sanborn *et al*[33], 2000 (SHOCK Registry)	United States, Canada, Europe, New Zealand	Obs.; multicenter registry	AMI	No	PCI or CABG	1993-1997	383
Barron *et al*[34], 2001 (NRMI-2)	United States	Obs.; multicenter registry	AMI	No	PCI	1994- < 2000	2990
French *et al*[31], 2003 (SHOCK Trial 12-mo survival)	United States, Canada, Europe, New Zealand	RCT; multicenter	AMI	No	PCI or CABG	1993-1998	152
Vis *et al*[35,36], 2007 (AMC CS)	Europe	Obs.; single-center	STEMI	No	PCI	1997-2005	292
Gu *et al*[37], 2010	Asia	Obs.; single-center	STEMI	No	PCI	2003-2008	91
Prondzinsky *et al*[27], 2010 (IABP-SHOCK)	Europe	RCT; single-center	AMI	No	PCI	2003-2004	40
Stub *et al*[38], 2011	Europe	Obs.; multicenter registry	ACS	No	PCI	2004-2010	410
Zeymer *et al*[39], 2011 (Euro Heart Survey PCI)	Europe	Obs.; multicenter registry	STEMI or NSTEMI	No	PCI	2005-2008	653
Thiele *et al*[4], 2012 (IABP-SCHOCK II)	Europe	RCT; multicenter	AMI	No	PCI (95.8%), CABG (3.5%), PCI and CABG (0.7%)	2009-2012	598
Zeymer *et al*[40], 2013 (ALKK-PCI)	Europe	Obs.; multicenter registry	STEMI or NSTEMI	No	PCI	2006-2011	1913
Dziewierz *et al*[41], 2014 (EUROTRANSFER registry)	Europe	Obs.; multicenter registry	STEMI	No	PCI (49 pts), CABG (2 pts)	2005-2007	51
Kunadian *et al*[44], 2015 (BCIS registry)	Europe	Obs.; multicenter registry	ACS	No	PCI	2005-2011	6120
Kim *et al*[42], 2015 (KAMIR)	Asia	Obs.; multicenter registry	AMI	Yes	PCI	2005-2014	1214
Suzuki *et al*[43], 2015 (Tokyo CCU Network Scientific Council)	Asia	Obs.; multicenter registry	STEMI	No	PCI	2009-2011	119
PLVADs (TandemHeart, Impella® 2.5) *vs* IABP							
Thiele *et al*[29], 2005[1]	Europe	RCT; single center	AMI	No	PCI (49 pts), CABG (2 pts)	2000-2003	41
Burkoff *et al*[28], 2006[1]	United States, Europe	RCT; multicenter	AMI (70%)	No	PCI (22 pts), CABG (3 pts)	2002-2004	33
Seyfarth *et al*[30], 2008[2] (ISAR-SHOCK)	Europe	RCT; two-center	AMI	No	PCI (22 pts)	2004-2007	26
Schwartz *et al*[46], 2012[1,2]	United States	Obs.; single center	68% STEMI, 11% OHCA	Yes	PCI (63 pts), CABG (5 pts)	2008-2010	76
Shah *et al*[47], 2012[1,2]	United States	Obs.; single center	STEMI or UA/NSTEMI	No	PCI	2007-2009	17
Manzo-Silberman *et al*[45], 2013[2]	Europe	Obs.; single center registry	ACS (mainly), OHCA	Yes	PCI (54 pts)	2007-2010	78
ECMO plus IABP *vs* IABP							
Sheu *et al*[18], 2010	Asia	Obs.; single center	STEMI	No	PCI	1993-2009	71
Tsao *et al*[21], 2012	Asia	Obs.; single center	AMI	No	PCI	2004-2009	58
Perazzolo Marra *et al*[48], 2013	Europe	Obs.; single center	AMI	No	PCI	2010-2012	35
ECMO plus IABP *vs* ECMO							
Yamauchi *et al*[49], 2009	Asia	Obs.; single center	AMI	No	PCI	2000-2007	16
Chung *et al*[50], 2011	Asia	Obs.; multicenter	AMI, INCA (14 pts)	Yes	PCI (7 pts), CABG (13 pts)	2206-2009	20
Kagawa *et al*[51], 2012	Asia	Obs.; multicenter	ACS, INCA, OHCA	Yes	PCI	2004-2011	73
Aoyama *et al*[52], 2014	Asia	Obs.; single center	AMI, INCA (2 pts, OHCA 7 pts)	Yes	PCI (34 pts), CABG (4 pts)	1993-2000	38
Park *et al*[53], 2014	Asia	Obs.; single center	AMI	No	PCI (78 pts), PCI e/o CABG (10 pts), medical treatment (8 pts)	2004-2011	96
Kim *et al*[54], 2014	Asia	Obs.; multicenter	ACS	No	PCI (53 pts), CABG (5 pts)	2010-2013	58

ACS: Acute coronary syndrome; AMI: Acute myocardial infarction; CABG: Coronary artery bypass grafting; CS: Cardiogenic shock; ECMO: Extracorporeal membrane oxygenation; IABP: Intra-aortic balloon pump; INCA: In-of-hospital cardiac arrest; NSTEMI: Non-ST-elevation myocardial infarction; PCI: Percutaneous coronary intervention; PLVADs: Percutaneous left ventricular assist devices with ([1]TandemHeart, or [2]Impella® 2.5); pts: Patients; Obs.: Observational study; OHCA: Out-of-hospital cardiac arrest; RCT: Randomized controlled trial; STEMI: ST-elevation myocardial infarction; UA: Unstable angina.

Table 2 Meta-analysis before and after sensitivity analysis

Comparison/subgroup	RR							
	Before				After			
	n	I^2 (%)	Estimate (95%CI)	*P*	*n*	I^2 (%)	Estimate (95%CI)	*P*
Inhospital mortality								
IABP *vs* medical therapy								
Observational studies	11	63	1.21 (1.08, 1.36)	0.0008	9	19	1.17 (1.09, 1.26)	< 0.0001
RCTs	2	0	0.97 (0.81, 1.18)	0.78	2	0	0.97 (0.81, 1.18)	0.78
Overall effect	13	62	1.18 (1.06, 1.32)	0.002	11	24	1.15 (1.07, 1.24)	0.0002
Test for subgroup differences[1]		χ^2 = 3.83, df = 1 (P = 0.05), I^2 = 73.9%				χ^2 = 3.14, df = 1 (P = 0.08), I^2 = 68.2%		
ECMO plus IABP *vs* ECMO								
Observational studies	6	12	0.78 (0.65, 0.94)	0.008	5	0	0.80 (0.68, 0.94)	0.006
Late mortality								
IABP *vs* medical therapy								
Observational studies	3	90	0.92 (0.51, 1.67)	0.78	2	60	1.16 (0.69, 1.95)	0.57
RCTs	3	32	1.16 (0.86, 1.58)	0.34	2	0	1.56 (0.97, 2.52)	0.07
Overall effect	6	85	1.08 (0.82, 1.41)	0.60	4	0	1.38 (1.30, 1.46)	< 0.00001
Test for subgroup differences[1]		χ^2 = 0.48, df = 1 (P = 0.49), I^2 = 0%				χ^2 = 0.68, df = 1 (P = 0.41), I^2 = 0%		

[1]Between observational studies and RCTs. IABP: Intra-aortic balloon pump; RCT: Randomized controlled trial; ECMO: Extracorporeal membrane oxygenation.

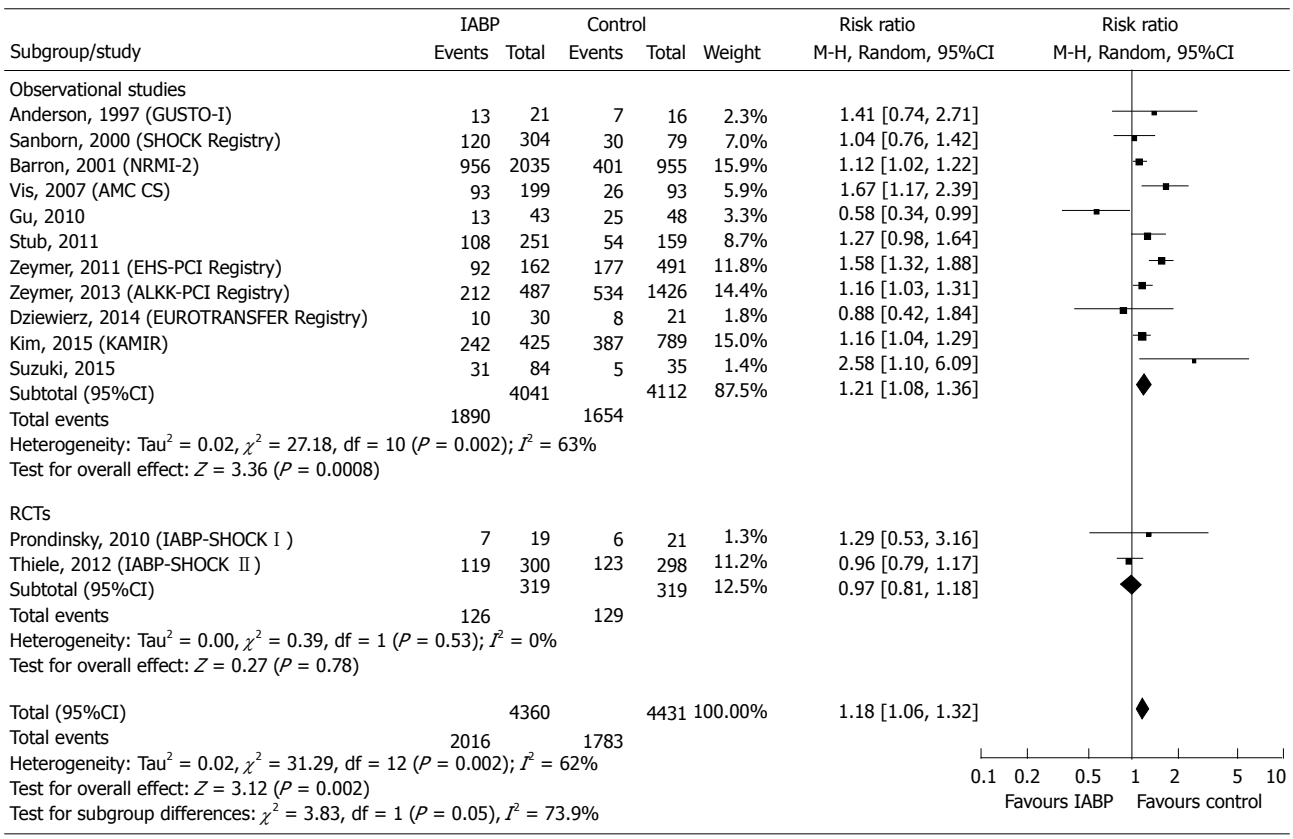


Figure 2 Meta-analysis on risk ratio of inhospital mortality between the patients with intra-aortic balloon pump *vs* medical therapy.

constructed to detect significance, were crossed by the z-curves, demonstrating a detrimental effect of IABP (Table 3, Figure 3).

Secondary endpoint: The late mortality was assessed in 7041 patients (6262 from 3 observational studies[37,41,44] and 779 from 3 RCTs[4,27,31,55,56]). Mortality rate was higher, but not significantly, in the IABP group respect to control (52.02% *vs* 39.32%). IABP reduced mortality (-8%, P = 0.78) in observational studies and increased mortality (+16%, P = 0.34) in RCTs (Figure 4). In the Funnel plot the studies by Gu *et al*[37] and by Thiele *et al*[56] fell out of the 95%CI, appearing to be the potential source of bias. When we applied the sensitivity analysis by excluding the study by Gu *et al*[37] from observational studies and the study by Thiele *et al*[56]

Table 3 Benefit - harm observed in the experimental group and result of Trial Sequential Analysis

Groups			Mortality rate (%)		RRR	Effect of experimental support				Trial Sequential Analysis	
Experimental		Control	Experimental	Control		NNT	NNH	Harm[1]	Benefit[1]	Required information size	Results
Inhospital mortality											
IABP[2]	*vs*	Medical therapy[2]	45.99	40.62	-13.22		18	5.37		2174	Conclusive
PLVADs	*vs*	IABP	55.93	47.71	-17.23		12	8.22		1161	Inconclusive
ECMO + IABP	*vs*	IABP	36.36	60.53	39.92	5			24.16	150	Conclusive
ECMO + IABP[2]	*vs*	ECMO[2]	61.29	66.67	8.06	19			5.38	Not calculable	Inconclusive
Late mortality											
IABP	*vs*	Medical therapy	52.02	39.32	-32.28		7	12.70		5984	Futility
IABP[2]	*vs*	Medical therapy[2]	52.08	37.68	-38.22		6	14.40		168	Conclusive

[1]Number of patients out of 100; [2]Comparison after sensitivity analysis.

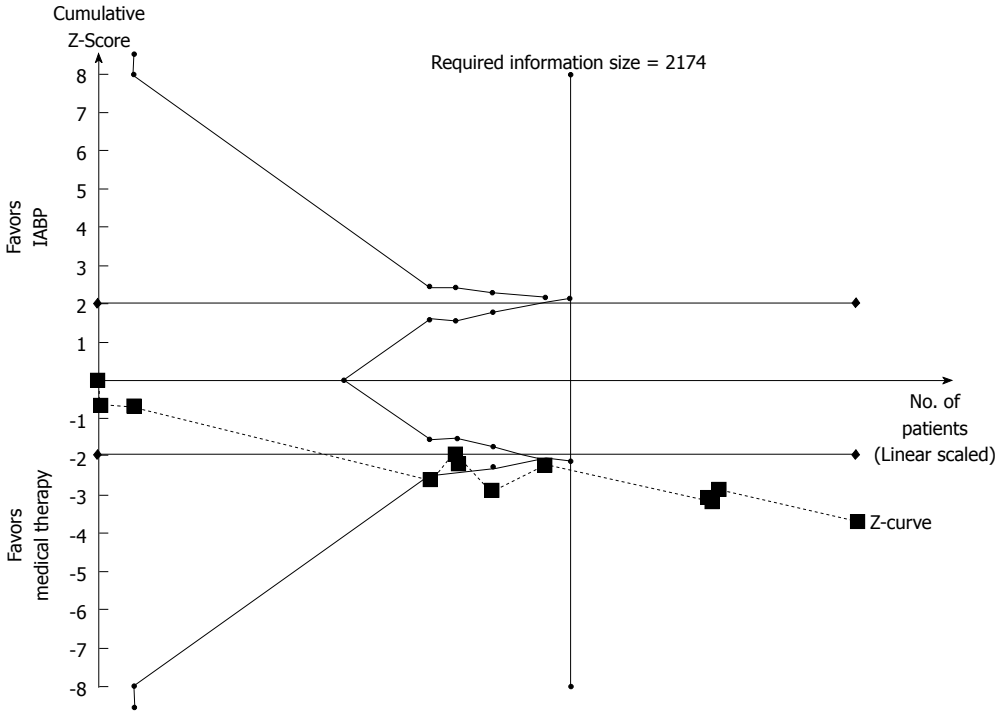


Figure 3 Intra-aortic balloon pump *vs* medical therapy: Trial Sequential Analysis on inhospital mortality. IABP: Intra-aortic balloon pump.

from RCTs, the overall I^2 decreased from 85% to 0% (Table 2). Moreover, the test for subgroup differences showed that the heterogeneity between observational and RCTs was lower (I^2 = 0%) and an overall significant detrimental effect of IABP was found (Table 2). Trial Sequential Analysis was performed: (1) by including all studies; and (2) by excluding the study by Gu *et al*[37] and that by Thiele *et al*[56] according to the sensitivity analysis (Table 3). With inclusion of all studies, there was a 32.28% mortality increase in the IABP group with about 13 more deaths every 100 treated patients. When studies by Gu *et al*[37] and Thiele *et al*[56] were excluded, IABP support resulted in a 38.22% risk increase, and Trial Sequential Analysis showed that data were sufficient to highlight the harmful effect of IABP support on the late mortality (Table 3).

PLVADs vs IABP

We compared the effect of PLVADs *vs* IABP in 271 patients; 171 from 3 observational studies[45-47] and 100 from 3 RCTs[28-30].

Primary endpoint: The overall inhospital mortality increased although not significantly, in PLVADs group compared to IABP group, both in the observational studies (+16%, P = 0.20) and the RCTs (+6%, P = 0.80) (Figure 5). The test for subgroup differences did not show significant differences between observational studies and RCTs (χ^2 = 0.13, P = 0.72, I^2 = 0%). Indeed, in the Forest plot the confidence intervals overlapped, P values of the χ^2 tests were all greater than 0.10 and the I^2 statistics were all equal to zero, showing the homogeneity among the studies within both

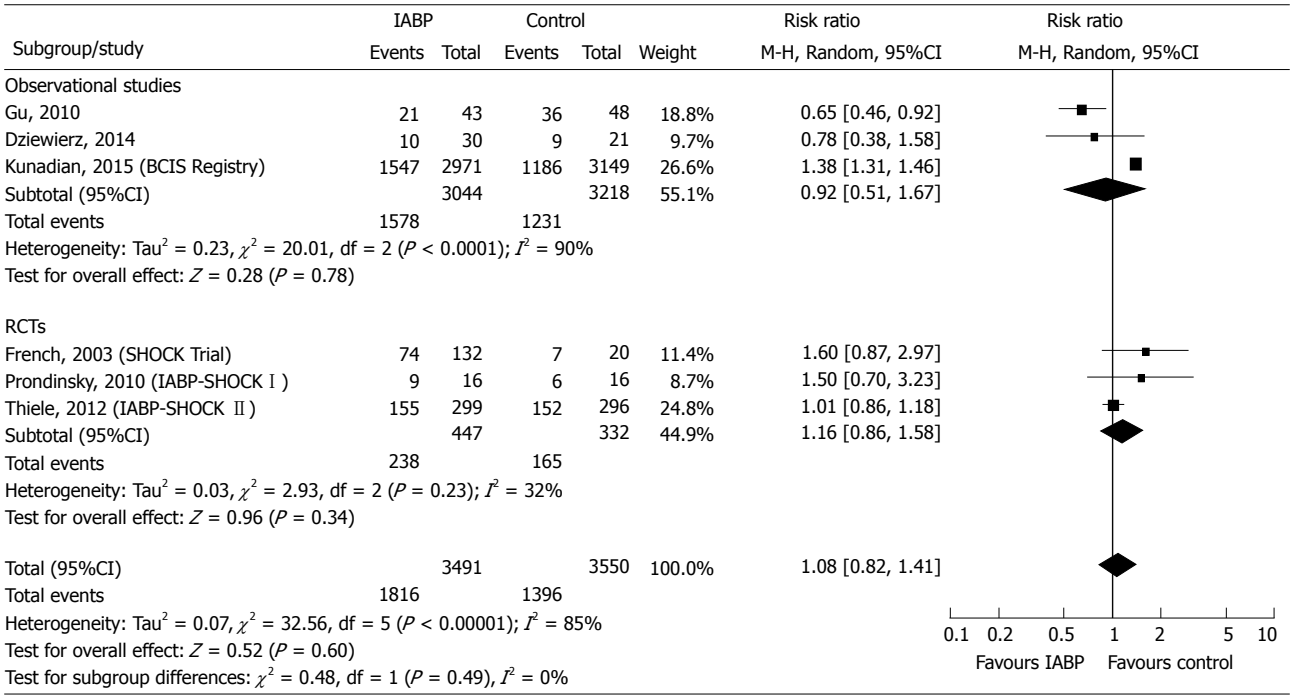


Figure 4 Meta-analysis on risk ratio of late mortality between the patients with intra-aortic balloon pump *vs* medical therapy.

observational and RCTs (Figure 5). In the Funnel plot, all studies were enclosed into 95%CI and the larger studies were plotted at the central top of the graph, demonstrating a convergence in risk estimation while increasing the sample size. RRR equaled -17.23%; when translated into clinical terms, use of PLVADs resulted 8 more deaths every 100 patients treated. For appropriate Trial Sequential Analysis, more patients would have to be included (Table 3).

ECMO plus IABP vs IABP

Primary endpoint: We compared the effect of ECMO plus IABP *vs* IABP in 164 patients from 3 observational studies[18,21,48]. We did not find any RCTs on the topic. In the Forest plot the χ^2 test and the I^2 statistics detected the absence of significant heterogeneity (I^2 = 7%). In the Funnel plot analysis, all studies within 95%CI were included. The inhospital mortality was higher when IABP was used alone rather than in combination with ECMO (60.53% *vs* 36.36%, respectively). ECMO plus IABP group showed a 44% reduction in mortality (Figure 6). The observed RRR was 39.92%, which means that there were 24 fewer deaths for every 100 treated patients. Trial Sequential Analysis showed that the cumulative Z-curve crossed the alpha-spending boundaries, demonstrating that a significant RRR was obtained when ECMO support was used in association with IABP (Figure 7). The required numbers of patients was reached and the meta-analysis could be considered conclusive (Table 3, Figure 7).

ECMO plus IABP vs ECMO

Primary endpoint: We compared the effect of ECMO plus IABP *vs* IABP in 301 patients from 6 observational studies[49-54]. We did not find any RCTs that analyzed this topic. We found a significantly lower inhospital mortality (RR = -22%, P = 0.008) in the group of patients treated with ECMO plus IABP compared to ECMO alone (Figure 6). In the Funnels plot analysis, only the study by Yamauchi *et al*[49] could be a potential source of bias. After the sensitivity analysis I^2 decreased to 0% while the significant effect of ECMO plus IABP *vs* ECMO remained substantially unchanged (RR = -20%, P = 0.006) (Table 2). Despite these results, Trial Sequential Analysis could not be performed because of the small number of patients included (Table 3).

DISCUSSION

All recent reviews on the use of support devices in AMI patient with CS undergoing PCI thus far show lack of a meta-analytic estimates[11-15], probably because the results were based mainly on registry data.

Meta-analyses of data from observational studies represent an area of innovation in statistical science. This analysis can be performed when the question of interest cannot be answered by a review of randomized controlled trials. Even though observational studies are prone to bias (including confounding variables), strategies to adjust for unmeasured confounding variables can be adopted[23]. In the present review, we identified only a small number of randomized trials, which by themselves were underpowered to assess the efficacy of the support devices on inhospital mortality. To increase the power of the analysis we included observational data, which enabled us to add 14909 additional patients to the 890 from the RCTs selected. Further, to avoid bias we used the Funnel plot analysis,

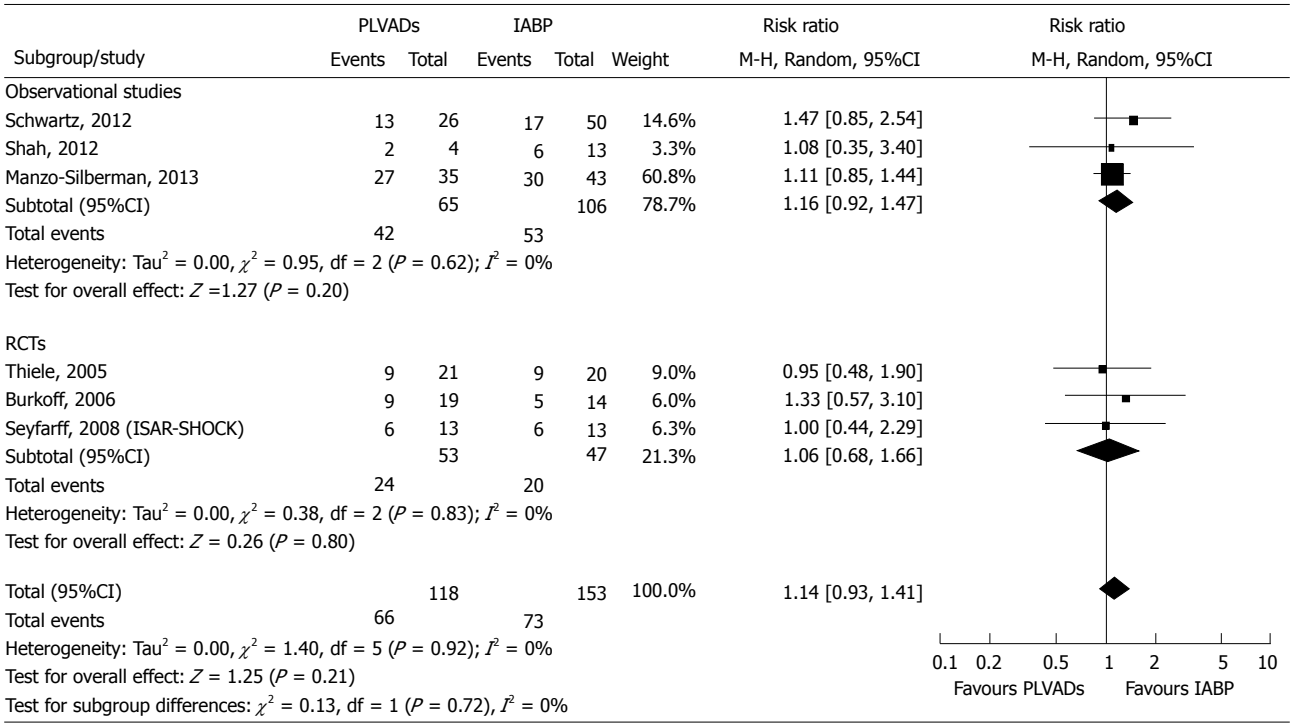


Figure 5 Meta-analysis on risk ratio of inhospital mortality between the patients with percutaneous left ventricular assist devices *vs* intra-aortic balloon pump. IABP: Intra-aortic balloon pump; PLVADs: Percutaneous left ventricular assist devices.

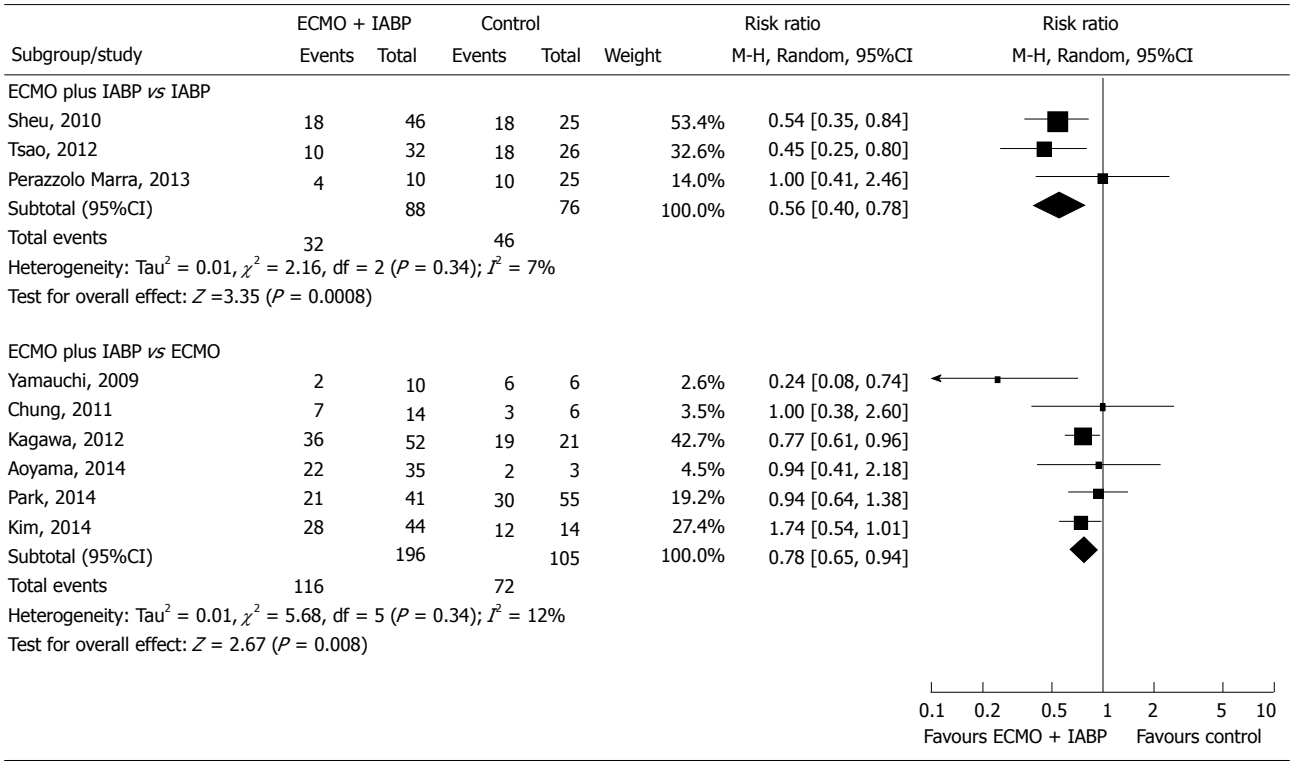


Figure 6 Meta-analysis on risk ratio of inhospital mortality between the patients with extracorporeal membrane oxygenation plus Intra-aortic balloon pump *vs* intra-aortic balloon pump or extracorporeal membrane oxygenation alone. IABP: Intra-aortic balloon pump; ECMO: Extracorporeal membrane oxygenation.

the Cochran's *Q* test and I^2 statistics to test differences between groups and subgroups. The sensitivity analysis allowed us to make comparisons not affected by excessive heterogeneity.

From the meta-analysis we can make the following conclusions

First, in the comparison between IABP *vs* Medical therapy, the analysis confirmed that IABP support

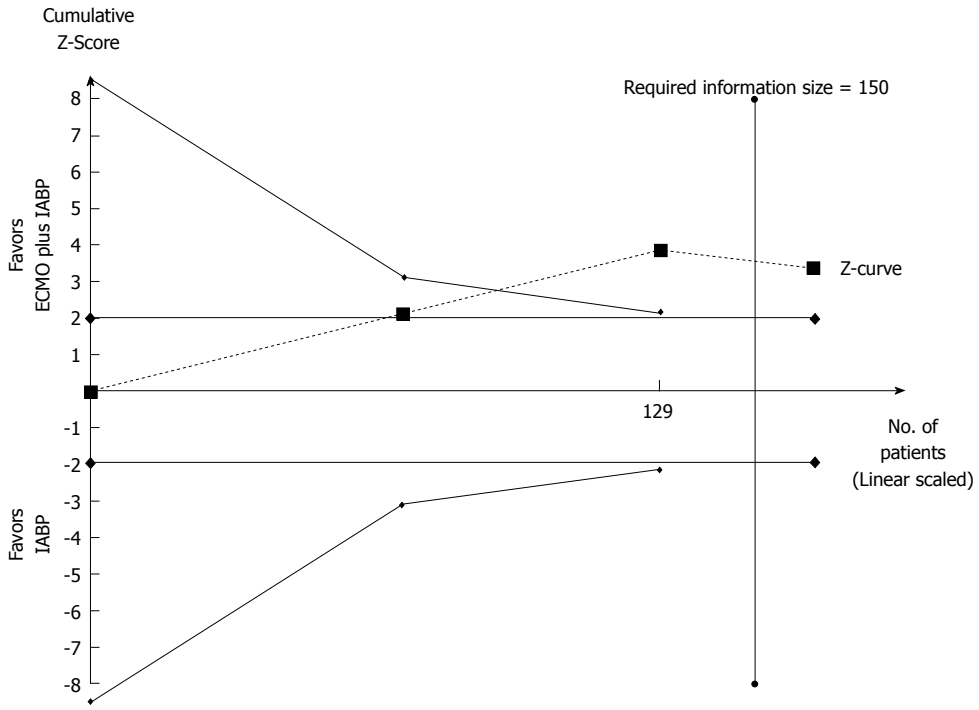


Figure 7 Extracorporeal membrane oxygenation plus Intra-aortic balloon pump support *vs* Intra-aortic balloon pump alone: Trial Sequential Analysis on inhospital mortality. IABP: Intra-aortic balloon pump; ECMO: Extracorporeal membrane oxygenation.

was associated with a significant increase inhospital mortality (Figure 2). The results of RCTs were marginal probably because of the small sample size and the results could be considered a chance occurrence (Figures 2 and 4). When we included the data from observational studies and applied the sensitivity analysis the results were affected only low heterogeneity (I^2 = 19%). Trial Sequential Analysis showed that the *Z*-curves surpassed not only the conventional boundaries but also the alpha-spending boundaries, constructed to control for type 1 error as the source of bias. Thus, the meta-analysis can be considered conclusive in terms of showing a detrimental effect of IABP (Figure 3). With regard to late mortality, we did not identify any difference in both observational studies or in RCTs. However, after sensitivity analysis a significantly higher late mortality was observed in IABP-treated patients and was confirmed by Trial Sequential Analysis, that was conclusive (Table 3).

Second, relative the comparison between IABP *vs* PLVADs, recently reported studies have failed to show a hemodynamic or survival benefit of mechanical support in AMI patients with CS and undergoing PCI. The meta-analysis by Cheng *et al*[57] dates back to 2009, performed on 3 RCTs and included 100 patients, showed that although PLVADs provided superior haemodynamic support in patients with CS compared to IABP, the use of these more powerful devices did not significantly improve early survival. Afterwards only observational studied were performed on this topic. O'Neill *et al*[58] suggested that early initiation of hemodynamic support prior to PCI with Impella 2.5 was associated with more complete revascularization and improved survival in the setting of refractory CS complicating AMI.

In our analysis, the PLVADs increased, although non significantly, the mortality as compared with IABP. The Trial Sequential Analysis showed that 1161 patients will need be analyzed in order to demonstrate its detrimental effect. Our meta-analysis was as such inconclusive and additional perspective investigations would be needed to definitive conclusion.

Third, relative to comparisons of ECMO plus IABP *vs* IABP or ECMO plus IABP *vs* ECMO, the meta-analysis showed a significant protective effect of ECMO plus IABP on inhospital mortality compared to IABP or ECMO used alone (Figure 6). Moreover, Trial Sequential Analysis showed that in the comparison ECMO plus IABP *vs* IABP the required numbers of patients was reached and the meta-analysis could be considered conclusive (Figure 7).

Potential limitation

The main limitation of this meta-analysis is the inclusion of the observational studies, since they are viewed as having less validity than RCTs, due to the absence of randomization. Indeed, we cannot exclude that CS was more severe in the IABP group compared to Medical therapy in some observational studies included in our meta-analysis. However, we repeated the analysis, including only the observational studies, between IABP *vs* control group, selected according to the same severity of shock. The results were substantially unchanged (RR = 1.11, 95%CI = 1.02 to 1.21), significantly in favour of Medical therapy. The heterogeneity was absent (I^2 = 0%). If RCTs were

added to the analysis, the heterogeneity appeared equally low (I^2 = 38%). Moreover, RCTs conducted to assess the role of haemodynamic support in patients with CS complicating AMI reported in the scientific literature are few, perhaps due to ethical issues and feasibility, involving randomization of very severely sick patients. Thus, the inclusion of well-performed observational studies may be acceptable to allow for risk estimation in such situations. Concato *et al*[59] analyzed published meta-analyses based on randomized clinical trials and observational studies that examined identical clinical topics and found that the average results of well-designed observational studies (with either a cohort or a case-control design) were markedly similar to those of the RCTs. Therefore, an integrated approach should be adopted using both experimental and observational studies, as long as well-designed and conducted. Finally, "discarding observational evidence when randomised trials are available is missing an opportunity. Conversely, abandoning plans for randomised trials in favour of quick and dirty observational designs is poor science[60]".

Another limitation was the lack of the analysis of the baseline characteristics (such as age, gender, race, *etc*.) that are recognized markers of risk. Unfortunately, these data available at baseline were not reported in the outcome.

Conclusion

The results of our meta-analysis showed that in AMI patients with CS and undergoing PCI: (1) the inhospital mortality was significantly higher with IABP support *vs* Medical therapy; (2) PLVADs increased, although non significantly, the mortality as compared with IABP; and (3) ECMO plus IABP had significant protective effect compared to IABP or ECMO alone. Trial Sequential Analysis of data on inhospital mortality in IABP *vs* control and ECMO plus IABP *vs* IABP showed that the analyses were sufficient to highlight the harmful effect of IABP and further studies would no longer be needed. Based on the results we can conclude that in CS complicating AMI: (1) routinely use of IABP and PLVADs is not recommended; and (2) the beneficial effect of the reduction inhospital mortality provided by ECMO plus IABP could be attributed to the synergistic action of the two devices in supporting the failing heart. IABP decreasing afterload and myocardial oxygen consumption, can avoid the negative effects on myocardial protection that can occur when using ECMO alone.

COMMENTS

Background

Despite major technical advances the inhospital mortality of patients with cardiogenic shock (CS) complicating AMI continues to remain high. To support the failing heart [intra-aortic balloon pump (IABP)], percutaneous left ventricular assist devices (PLVADs) and extracorporeal membrane oxygenation (ECMO) are used. Unfortunaletely randomized controlled trials (RCTs) on this issue are performed in small numbers, perhaps due to ethical issues and feasibility, involving randomization of patients with CS.

Research frontiers

The question of impact of cardiac support percutaneous devices cannot be answered by a review of RCTs alone. Meta-analyses of observational studies increase the power of the analysis by adding more data to the RCTs to have more comprehensive results.

Innovations and breakthroughs

In the present study, the authors investigated the impact of IABP, PLVADs and ECMO on inhospital mortality and late survival in patients with CS complicating acute myocardial infarction (AMI) undergoing percutaneous coronary intervention (PCI). Meta-analysis of observational studies in addition to the RCTs enabled them to increase the power of the analysis.

Applications

The results of the meta-analysis allow us to understand the impact of percutaneous cardiac support with IABP, PLVAD and ECMO in patients with CS complicating AMI undergoing PCI.

Terminology

This is a systematic review and meta-analysis of observational studies and RCTs.

Peer-review

In this study, the authors collected the data from 30 published research papers (total 15799 patients) and used meta-analysis to analyze in hospital and late mortality of percutaneous mechanical support. This is an interesting study. The findings in this study have the potential to help the clinical doctor work out the guideline for reducing mortality in acute myocardial infarction complicated by cardiogenic shock.

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Electrophysiologic testing guided risk stratification approach for sudden cardiac death beyond the left ventricular ejection fraction

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Abstract

Sudden cardiac death threats ischaemic and dilated cardiomyopathy patients. Anti- arrhythmic protection may be provided to these patients with implanted cardiac defibrillators (ICD), after an efficient risk stratification approach. The proposed risk stratifier of an impaired left ventricular ejection fraction has limited sensitivity meaning that a significant number of victims will remain undetectable by this risk stratification approach because they have a preserved left ventricular systolic function. Current risk stratification strategies focus on combinations of non invasive methods like T wave alternans, late potentials, heart rate turbulence, deceleration capacity and others, with invasive methods like the electrophysiologic study. In the presence of an electrically impaired substrate with formed post myocardial infarction fibrotic zones, programmed ventricular stimulation provides important prognostic information for the selection of the patients expected to benefit from an ICD implantation, while due to its high negative predictive value, patients at low risk level may also be detected. Clustering evidence from different research groups and electrophysiologic labs support an electrophysiologic testing guided risk stratification approach for sudden cardiac death.

Key words: Electrophysiologic study; Risk stratification; Sudden cardiac death; Myocardial infarction; Preserved ejection fraction

Core tip: There is a growing need for more effective risk stratification approach in order to detect those post myocardial infarction and dilated cardiomyopathy patients at high risk for sudden cardiac death (SCD) at early or even asymptomatic stage of heart failure with relatively well preserved left ventricular ejection fraction (LVEF). Although in an individual basis the SCD risk is lower among the patient population compared to the one observed among to those with a severely impaired

LVEF, epidemiologically there is a large such patient pool at risk in the community. Based on preliminary evidence these patients could be effectively and timely identified by applying a combined electrophysiologic guided approach using non-invasive electrocardiogram-related markers of risk leading to programmed ventricular stimulation testing. Using this approach, we could select those with inducible ventricular tachyarrhythmias as suitable candidates for implantable defibrillator therapy.

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TO THE EDITOR

Hilfiker *et al*[1] report on their experience with the electrophysiologic (EP) studies as risk stratifier for sudden cardiac death (SCD) surrogates among a cohort of patients with mostly organic heart disease and different levels of left ventricular ejection fraction (LVEF). They found that both the EP results as well as a reduced LVEF were significant predictors among those patients with a LVEF ⩽ 35% while the ventricular stimulation results were much more promising among those with LVEF > 35%. The latter is confirmed in our own database of post myocardial infarction (post-MI) and dilated cardiomyopathy patients who were risk stratified with EP studies for the primary prevention of SCD when presenting with a worrisome risk profile of either non sustained ventricular tachycardia or/and pre and syncope episodes despite a well maintained LVEF > 35%-40%[2-4]. This is based on a risk stratification approach aiming to define the high risk profile patient with organic heart disease beyond the reduced LVEF. Indeed there is preliminary evidence that such a mixed non-invasive[5] and invasive EP guided[4] approach may identify in a much more cost effective way not only those high risk patients with impaired LVEF but also those high risk patients with well maintained LVEF who may benefit from the prophylactic implanted cardiac defibrillators implantation timely. Such a patient population with relatively well preserved LVEF were the majority of SCD victims both in the Maastricht[6] as well as in the Oregon[7] out of hospital cardiac arrest registries. In this context we currently recruit post-MI patients at high risk for SCD despite the well maintained LVEF based on a combined non invasive and invasive EP guided approach in the ongoing prospective observational PRESERVE-EF study[8]. Is it time for a more rational EP guided risk stratification approach considering the limitations of the LVEF as a risk stratifier for SCD[9,10]?

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EDITORIAL

Omega 3 and atrial fibrillation: Where are we?

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Abstract

Anti-arrhythmic properties of n-3 polyunsaturated fatty acids, at least in part mediated by anti-oxidant, anti-inflammatory and anti-fibrotic power, have been widely proved. Effect of fish oil on atrial fibrillation, both in primary and in secondary prevention and after cardiac surgery, are controversial, mostly due to lack of homogeneity between studies but also due to individual variability in response to fatty acids administration. Inclusion of measurement of incorporation of fish oil into cell membranes, appears to be essential in future studies, to assess their antiarrhythmic effect.

Key words: N-3 polyunsaturated fatty acids; Atrial fibrillation; Upstream therapy; Omega-3 index; Cardiac surgery

Core tip: Individual variability in response to fish oil administration, in terms of eicosapentaenoic and docosahexaenoic acids in corporation into cell membranes, is responsible for controversial results of n-3 poly-unsaturated fatty acids administration in patients suffering atrial fibrillation.

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INTRODUCTION

N-3 poly-unsaturated fatty acids (PUFA) anti-arrhythmic effects have been debated for several years, since their electrophysiological properties have been recognized.

Through direct interaction with membrane bound proteins and thanks to incorporation into the phospholipid bilayer, n-3 PUFA are well known to influence ion channels and transmembrane pumps[1] to modulate signal transduction, protein trafficking and ion channels kinetic and to regulate gene expression[2]. N-3 PUFA can also exert anti-

Table 1 Clinical studies investigating the effect of n-3 poly-unsaturated fatty acids on primary prevention for atrial fibrillation

Study design	Population	PUFA administration	PUFA quantification	AF diagnosis	Results
Prospective cohort[5]	4815 individuals; age 72.8 yr; United States	Broiled/backed fish assessment. FU: 12 yr	FFQ	Annual ECG; hospital discharge diagnoses	Lower AF risk of 31% with fish intake ⩾ 5 times/wk *vs* < 1/mo. $P = 0.008$
Prospective cohort[12]	2174 subjects; mean age: 52.8 yr; Finland	Serum EPA and DHA and dosage. FU: 17.7 yr	DHA, EPA serum dosage	National computerized hospitalization registry	Lower AF risk of 38% for higher DHA levels. $P = 0.02$
Prospective cohort[6]	3326 subjects; age: 74.1 yr; United States	Serum EPA, DHA dosage	DHA, EPA serum dosage	Annual ECG; telephonic contact 2/yr; hospitalizations	Lower AF risk for top *vs* lowest quartile of PUFA/DHA levels
Population study[7]	3242 subjects affected by acute myocardial infarction; age: 54.1 yr; Italy	Previous PUFA intake *vs* not. FU: 360 d	FFQ	AF episodes during hospitalization	Lower risk of AF with fish oil
Prospective cohort[8]	47949 subjects; age: 46 yr; Denmark	Fish-oil intake assessment. FU: 5.7 yr	FFQ	Danish national hospitalization registry	Higher AF risk for top *vs* lowest quintiles of fish intake
Prospective cohort[9]	5184 subjects; age 67.4 yr; the Netherland	Fish-oil intake assessment. FU: 6.4 yr	FFQ	Two ECGs during FU; clinical data from general practitioners	No AF risk reduction in the highest tertile of fish intake
Prospective cohort[10]	44720 female; age: 63 yr; United States	Fish intake assessment. FU: 6 yr	FFQ	ECG at baseline and at the third and sixth years	No lower AF risk for higher fish intake
Prospective cohort[11]	4526 individuals; age: 62 yr; United States	Fish intake assessment. FU: 4 yr	FFQ	Two ECGs every 4 yr of FU; hospitalizations	No AF risk reduction in the top *vs* the lowest tertile of fish intake
Post-hoc analysis of a RCT (Aleksova)[13]	5835 systolic heart failure-subjects	N-3 PUFAs 1 g/d *vs* placebo; FU 3.9 yr	No PUFA dosage	ECG during FU visits	No AF risk reduction with n-3 PUFA

FU: Follow-up; FFQ: Food frequency questionnaires; AF: Atrial fibrillation; EPA: Eicosapentaenoic acid; DHA: Docosahexaenoic acid; RCT: Randomized controller trial; PUFA: Poly-unsaturated fatty acids.

inflammatory effects by antagonizing pro-inflammatory prostaglandin formation[2], and exert anti-fibrotic effects[3], as well as cardiac autonomic modulation[4].

In particular, the influence of n-3 PUFA on atrial fibrillation (AF) primary and secondary prevention, including post-operative AF (POAF) has also been the object of numerous clinical studies.

N-3 PUFA in primary and secondary prevention and in POAF

Primary prevention: With regard to primary prevention of AF (Table 1), two studies involving elderly subjects[5,6] and one focusing on patients affected by acute myocardial infarction[7] proved n-3 PUFA to be protective against AF, while other studies[8-12], showed no benefit. The influence of various diet habits, including fish consumption[8,9], can possibly explain different results, as well as different methodologies used for assessment of fish intake and for AF diagnosis. In particular, positive studies, generally included elderly individuals[5-7], suggesting benefit from antifibrotic properties of fish-oil. However, a post-hoc analysis of the randomized controlled trial GISSI-HF[13] showed no effect of long-term PUFA administration on AF development in heart failure patients, thus allowing no conclusions for the role of n-3 PUFA in AF primary prevention.

Post-operative AF: The effect of n-3 PUFA in the context of POAF, that is characterized by inflammation, electrolyte disturbances and hemodynamic instability secondary to cardiac surgery, have also been also widely investigated. An open label study[14] firstly observed a short-term n-3 PUFA administration-related decrease in POAF incidence after coronary artery bypass grafting. Two papers[15,16] also gained benefit from various fish-oil preparations and administration timings (Table 2). A recent randomized-controlled trial (RCT)[17] also observed reduction of POAF with n-3 PUFAs plus vitamins C and E administration in comparison to placebo, in 203 patients scheduled for cardiac surgery. Further studies however, failed to prove both prevention of AF[18,19] and decrease of inflammation[20] from higher serum levels of n-3 PUFA, eicosapentaenoic acid (EPA), or docosahexaenoic acid (DHA), and from higher n3-PUFA atrial content[21,22]. Recently, the multicenter double-blind RCT "OPERA"[23] showed no influence on POAF occurrence, from short-term n3-PUFA administration. The effect was unrelated to patients characteristics, kind of cardiac-surgery, antiarrhythmic drugs, fish intake and serum n-3 PUFA. In a substudy of this trial indeed[24], including 564 subjects receiving short-term PUFA or placebo before surgery, the risk of POAF was unrelated to fish oil concentrations at enrollment and day of surgery. Interestingly, PUFA increase, was characterized by significant inter-individual variableness (0.7%-7.5% after 5 d of supplementation). Finally, Metcalf *et al*[25], by using combined data from previous RCTs, demonstrated less incidence of POAF among subject within the fourth quintile of red blood cell

Table 2 Principal clinical studies investigating the effect of n-3 poly-unsaturated fatty acids on post-operative atrial fibrillation

Study design	Population	PUFA administration	PUFA quantification	AF diagnosis	Results
Randomized, open label[14]	160 CABG pts; age: 66.2 yr; Italy; BB approximately 57%; statins approximately 58%	N-3 PUFA 2 g/d (EPA/DHA: 1:2) ⩾ 5 d before CS, until discharge *vs* not	No PUFA dosage	Continuous 5 d monitoring + daily ECG up to discharge. AF: > 5 min/requiring therapy	Lower AF risk. $P = 0.013$
Prospective observational[15]	530 CS pts; age: 66.4 yr; Italy. BB: 53%; statins: 46%	N-3 PUFA 1 g/d (EPA/DHA: 0.9:1.5) 5 d pre-CS *vs* not	No PUFA dosage	Continuous monitoring during ICU-stay. AF: ⩾ 5 min	Lower POAF during ICU stay. $P = 0.006$
Double blind-RCT[16]	102 CABG pts; age: 67 yr; Germany	Iv 100 mg fish oil/kg per day during ICU-stay *vs* soya oil	No PUFA dosage	Continuous monitoring during ICU-stay	Lower AF risk with PUFA. $P < 0.05$
Prospective cohort[19]	125 CABG pts; age: approximately 68 yr; Iceland. BB: 77.4%; statins: 84%	N3-PUFA (EPA/DHA: 1.2:1) 2.2 g/d 7 d pre-CABG *vs* placebo	PUFA dosage basally, before, 3 d after CS	Continuous monitoring during hospital stay. AF: ⩾ 5 min	Positive DHA/POAF association (U-curve relationship)
Double blind-RCT[23]	1516 CS pts; age: 64 yr; Italy-United States-Argentina. BB: 76.9%; statins: 57.5%	N3-PUFA (EPA/DHA: 4.6:3.7) 2 g/d 5 d pre-CS up to discharge *vs* placebo	Serum PUFA dosage basally, before CS	Continuous 5 d monitoring. AF: ⩾ 30 s	No lower AF despite 40% higher plasmatic PUFA
Double blind-RCT[18]	243 CS pts; age: 62.7 yr, United States. BB: 79%; statins: 73%	N-3 PUFA 2 g/d *vs* corn oil	Basal serum PUFA dosage, before, 3 d post CS	Continuous ECG during hospital stay; FU: 1 mo. AF: Episodes requiring treatment	No lower AF; plasma PUFA increase
Double blind-RCT[20]	170 CS pts; age: 67 yr; Iceland. BB approximately 76%	N3-PUFA (EPA/DHA: 1.2:1) 2 g/d 1 wk before and 2 after CS *vs* olive oil	Serum DHA, EPA dosage basally, pre 3 d post CS	Continuous monitoring during hospital stay. AF: ⩾ 5 min	No lower AF; plasma n-3 PUFA increase
Double blind-RCT[22]	200 CS pts; age: 64 yr; Australia, BB: 43%; statins: 73%	N-3 PUFA oil (EPA/DHA: 2.7:1.9) for 3 wk *vs* placebo	Dosage of serum PUFA basally, pre-CS; atrial PUFA	Continuous 72 h monitoring. AF/flutter ⩾ 10 min/requiring treatment	No lower AF risk; increase in serum and atrial PUFA
Double blind RCT[21]	108 CABG pts; age: 64 yr; United Kingdom; BB: 88%; statins: 98%	N-3 PUFA (EPA/DHA: 1.2:1) 2 g/d for approximately 16 d *vs* olive oil	Dosage of serum PUFA basally, 3 d post CS; atrial PUFA	Continuous 5 d monitoring + daily ECG. AF: > 30 s	No lower AF risk; higher serum and atrial PUFA

CABG: Coronary artery bypass grafting; pts: Patients; BB: Beta blockers; CS: Cardiac surgery; ICU: Intensive care unit; PUFA: Poly-unsaturated fatty acids; EPA: Eicosapentaenoic acid; DHA: Docosahexaenoic acid; AF: Atrial fibrillation.

n-3 DHA, thus suggesting a U-shaped relation between n-3 PUFA intake and POAF. Four recent meta-analyses of the previously presented studies showed in turn, overall protective or neutral effect on POAF from n-3 PUFA[26-29] (Table 3). Of note, none of these meta-analyses has assessed n-3 PUFA treatment duration to surgery as a covariate in a meta-regression analysis.

Dissimilarities may be explained by various study designs and populations, AF definitions, cardiac surgery, co-administration of anti-arrhythmic or anti-inflammatory drugs, dietary PUFA intake, EPA/DHA ratios and fish oil-administration modes (*i.e.*, intravenous or through nasogastric tube) and fish-oil administration time courses. Conversely, no effects of n-3 PUFA administration on myocardial infarction and bleeding after cardiac surgery, eventually influencing POAF occurrence, have been demonstrated[27].

Interestingly, all RCTs that failed to demonstrate a beneficial effect, used a formulation containing 1.24 EPA: DHA ratio[18,20,23]. In contrast, Rodorigo *et al*[17] administered PUFA with an EPA:DHA ratio equal to 0.5.

Secondary prevention: Several studies have finally investigated the effect on n-3 PUFA on relapses of paroxysmal and persistent AF. Two studies[30,31], found fish oil administration (from 1 mo before, to 6 mo after cardioversion) helpful in AF prevention (Table 4). On the other hand, 4 further studies[32-35] failed to prove any effect.

A recent study[36] including 337 patients with symptomatic paroxysmal/persistent AF, randomized to receive fish oil (4 g/d) or placebo, showed no difference in time to first AF recurrence, as well as no significant decrease of inflammatory markers at 6 mo. Similarly, another RCT[37], proved no effect from n-3 PUFA on the time to AF relapses, as well as on concentrations of biomarkers of oxidative stress and inflammation and at follow-up. In particular, a large RCT[34] involving 586 patients with symptomatic paroxysmal or persistent AF, randomized to n-3 PUFA (1 g/d) *vs* placebo for 1 year, also proved no significant differences between the two arms, in terms of symptomatic recurrence of AF.

Contrasting outcomes between studies may be related to differences in PUFA somministration and populations characteristics. Generally, papers including subjects with more evident cardiac disease[30], more often co-administered with amiodarone[30] showed benefit. Of note, some unfavorable papers proved AF relapses to occur mostly within 3 wk, prior

Table 3 Recent metaanalises of studies of n-3 poly-unsaturated fatty acids in post-operative atrial fibrillation

Ref.	Clinical setting	NO. of studies and of patients	Results
Costanzo *et al*[26]	POAF	8 RCTs/2687 pts	AF reduction
Benedetto *et al*[27]	POAF	431 pts	No AF reduction; at meta-regression analysis: Trend toward a benefit from PUFA for administration of EPA/DHA ratio = 1:2
Zhang *et al*[28]	POAF	8 RCT/2687 pts	No AF reduction
Ali-Hassan-Sayegh *et al*[29]	POAF	23 RCTs/4278 pts	AF reduction

RCTs: Randomized controller trials; pts: Patients; PO: Post-operative; AF: Atrial fibrillation; PUFA: Poly-unsaturated fatty acids; EPA: Eicosapentaenoic acid; DHA: Docosahexaenoic acid.

Table 4 Clinical studies investigating the effect of n-3 poly-unsaturated fatty acids on secondary prevention for atrial fibrillation

Study design	Population	PUFA administration	PUFA quantification	AF diagnosis	Results
Double blind-RCT[30]	109 pts, age: 70 yr; Italy; heart structural abnormality: 90%; Amiodarone + ACE-i/ARBs: 100%	N-3 PUFA (EPA/DHA 1.2:1) 2 g/d, 1 mo before and 12 after ECV *vs* olive oil	No PUFA dosage	Weekly ECG for the first 3 wk after ECV and ECG + Holter ECG after 1, 3, 6, 12 mo and at symptoms occurrence	Less AF relapses with PUFA
Open-label randomized[31]	178 pts, Australia. Concomitant amiodarone, sotalol, ACE-i/ARBs	N-3 PUFA (EPA/DHA 1.3:1) 1.8 g/d for approximately 56 d before ECV and 1 year thereafter *vs* not	Serum dosage of EPA, DHA basally, before ECV	ECG at week 2 and 6 and every 3 mo. AF: ⩾ 1 wk	Less AF relapses at 90 d and 1 yr with PUFA, $P < 0.001$; higher serum EPA, DHA
Double blind-RCT[33]	663 pts; paroxysmal AF: 18%; age: 60.5 yr; United States. No heart abnormality. Amiodarone: 0%, antiarrhythmic drugs: 13%; ACE-i/ARBs: 39%	N-3 PUFA (EPA/DHA 4.6:3.7; load: 8 g/d for 1 wk) 4 g/d for 24 wk *vs* oil	Serum DHA, EPA dosage basally, after 4 and 24 wk	Biweekly transtelephonic monitoring	No lower symptomatic AF recurrence in the paroxysmal and persistent
Prospective[35]	50 pts; ⩾ 2 previous AF episodes; age: 54 yr, Japan. IC antiarrhythmic drugs: 100%	Observational period: no PUFA for 6 mo. Interventional period: EPA 1.8 g/d for 6 mo	Serum EPA, DHA dosage basally and at study end	Daily ECG monitoring and at symptoms occurrence	No lower AF burden and time to first relapse
Double blind-RCT[32]	204 pts, age: 69.3 yr; Italy. LAs 45 mm. First ECV: 59%; IC antiarrhythmic drugs: 29.5%, sotalol: 12.6%, amiodarone: 27.4%	N-3 PUFA (EPA/DHA 1.2:1) 3 g/d ⩾ 1 wk before and 2 g/d after ECV for 6 mo *vs* olive oil	N-3 PUFA serum dosage basally, 6 mo after ECV	Transtelephonic monitoring: 2/first week after ECV and 3/wk for 3 mo + clinical visits after 7 d, 1, 3, 6 mo	No difference in ECV success, AF incidence, time to first relapse. Increase of EPA and DHA
Double blind RCT[36]	337 pts; symptomatic paroxysmal or persistent AF within 6 mo of enrollment	Fish oil (4 g/d) or placebo	Followed, on average, for 271 ± 129 d	Trans-telephonic event recorder, 12-lead ECG or Holter	No lower AF with PUFA
Double blind-RCT[37]	190 pts with paroxysmal or persistent AF	N-3 PUFAs (4 g/d; n = 126) or placebo (n = 64) in a 2:1 ratio	No PUFA dosage	Not specified	No reduction of AF recurrence and inflammation markers
Double blind-RCT[34]	586 pts with symptomatic paroxysmal AF requiring ECV (n = 428), at least 2 episodes of AF in the 6 mo before (n = 55), or both (103)	N-3 PUFA (1 g/d) or placebo for 12 mo	No PUFA dosage	Not specified	No lower AF with PUFA

RCTs: Randomized controller trials; pts: Patients; PO: Post-operative; AF: Atrial fibrillation; PUFA: Poly-unsaturated fatty acids; EPA: Eicosapentaenoic acid; DHA: Docosahexaenoic acid; ACE-I: Angiotensin converting enzyme inhibitor; ARB: Angiotensin receptor blockers.

to an eventual effect from n-3 PUFA.

DISCUSSION

The effect of n-3 PUFA on AF primary and secondary prevention and after cardiac surgery, remains controversial. A major reason for this uncertainty, is to be found in differences between studies, in particular regarding study designs, patients characteristics, AF definition and types (lone, vagally/adrenergically induced, secondary to structural disease), fish oil-administration modes, formulations and time courses. Moreover, a great variability in n-3 PUFA serum concentrations between subjects, despite similar fish-oil administration, has been recently proved, likely secondary to genetic predisposition in PUFA metabolism.

Noteworthy, however, a recent RCT[38] examined the effects of high (6 g/d) or medium dose (3 g/d) fish oil supplementation, with or without multivitamin, on the inclusion of n-3 and n-6 PUFA within membranes of red blood cells after 16 wk. The authors found all treatments effective in increasing EPA composition of cell membranes

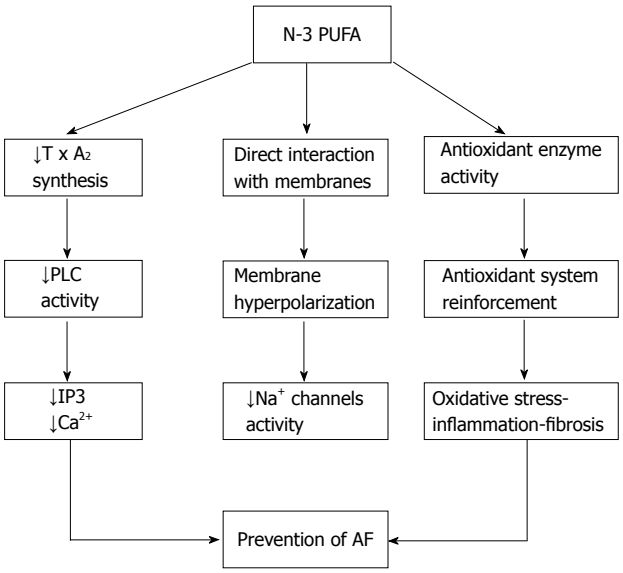

Figure 1 Antiarrhythmic effects of n-3 poly-unsaturated fatty acids. N-3 PUFA: N-3 poly-unsaturated fatty acids; TxA_2: Thromboxane A_2; PLC: Phospholipase C; IP_3: Inositol triphosphate; AF: Atrial fibrillation.

in females, but not in males, for whom the higher dose n-3 PUFA plus multivitamin combination was necessary. As a consequence, discrepancies between trials could be partially related to individual capability of n-3 PUFA incorporation, which in turn, could be influenced by sex, age, vitamin and/or drug administration. To counteract the variability in response to fish oil administration, inclusion of blood measures of n-3 PUFA status appears therefore to be essential in future studies.

The "Omega-3 Index" is the percentage of PUFA composed of EPA + DHA in red blood cell membranes[39] may represent a measurement of clinical utility to assess individual response to fish oil intake. Moreover, it may contribute to better understand the pharmacokinetics and pharmacodynamics of PUFA. Considering the results of recent studies showing an U-curve relationship between PUFA concentrations and AF[19,25], the greater protection from AF could be obtained from an individually-targeted approach for fish oil inclusion within membranes.

CONCLUSION

The complexity of the biological interactions of n-3 PUFA, their incorporation into cell membranes and the variability of clinical contexts, likely justify why PUFA administration does not automatically lead to AF reduction. RCTs focusing on clinical contexts of AF, and characterized by more accurate follow-ups and definitions of PUFA incorporation into red blood cells (or hopefully, in atrial tissue in the setting of cardiac surgery), are required. The RCT NCT00692718, will hopefully add information regarding fish oil effect on AF prevention in the context of HF and/or AMI.

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TOPIC HIGHLIGHT

2016 Nonalcoholic Fatty Liver Disease: Global view

Psoriasis, non-alcoholic fatty liver disease, and cardiovascular disease: Three different diseases on a unique background

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Abstract

Psoriasis is a chronic inflammatory immune-mediated skin disease, frequently associated with systemic comorbidities. According to recent data, patients with psoriasis show a greater prevalence of metabolic syndrome, which confers a higher cardiovascular risk. The link between these pathological conditions appears to be a chronic low-grade inflammatory status. The aim of this review is to focus on the multiple epidemiological and physio-pathogenetic aspects linking non-alcoholic fatty liver disease, psoriasis, and cardiovascular disease.

Key words: Psoriasis; Non-alcoholic fatty liver disease; Cardiovascular risk

Core tip: The review focuses on recent scientific data regarding the multiple physio-pathogenetic aspects of the possible link between psoriasis, non-alcoholic fatty liver disease, and cardiovascular disease. The multidisciplinary approach to psoriatic patients appears mandatory to treat concomitant psoriasis-related comorbidity, and the risk/benefit of both biologic and non-biologic therapies should be evaluated.

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INTRODUCTION

Psoriasis is a chronic inflammatory relapsing disease affecting 1%-4% of the general population[1].

Despite that psoriasis is a skin disorder clinically

characterized by red scaly plaques, it is no more limited to the skin surface and has been identified as a complex clinical entity with a systemic involvement. Many comorbidities have been associated with psoriatic disease, such as psoriatic arthritis (PsA), metabolic syndrome (MetS), cardiovascular disease (CVD), non-alcoholic fatty liver disease (NAFLD), inflammatory bowel disease, uveitis, depression and malignancy[2-5].

An higher prevalence of cardiovascular risk factors, such as dyslipidemia and obesity, has been reported in psoriatic patients[4,6].

NAFLD is one of the most frequent cause of chronic liver disease with a prevalence of 10%-25% in the general population[7].

NAFLD is now considered the hepatic manifestation of the MetS and a prospective cohort study has evidenced that MetS and its components may independently predict the risk of NAFLD[8,9].

NAFLD itself represents a further independent cardiovascular risk factor for atherosclerosis which is likely linked to arterial stiffness[10,11].

The aim of the present review is to focus on the association of psoriasis, NAFLD and CVD, focusing on epidemiologic data and the underlying common pathogenic process.

NAFLD AND PSORIASIS

The prevalence of the MetS has been estimated to be about 15%-25% in the general population, appearing significantly higher (an increase by about 3-fold) in psoriatic patients, as documented by many case-controls studies[12-16].

The association between psoriasis and MetS is directly correlated with the severity of psoriasis, independent from the presence of obesity in psoriatics[17-19].

NAFLD is defined as a spectrum of hepatic pathologies ranging from fatty liver disease (steatosis) to steatohepatitis (NASH) with the risk of evolution to cirrhosis and hepatocellular carcinoma[20].

NAFLD is more prevalent in psoriatic patients than in the general population. Roberts *et al*[21] enrolled a cohort of 103 psoriatic patients and found that NAFLD affected about 47% of patients and one of five of them showed NASH.

A large prospective population-based cohort study had been conducted by van der Voort *et al*[22] in patients older than 55 years. Among 2292 participants, 5.1% of the population were affected by psoriasis with a prevalence of NAFLD of about 46.2% in psoriatic patients *vs* 33.3% in subjects without psoriasis.

Furthermore, a recent meta-analysis has documented that patients with PsA and patients with moderate to severe psoriasis showed a significantly greater risk of NAFLD compared with those with mild psoriasis[23].

Aspartate transaminase (AST)/alanine aminotransferase (ALT) ratio is considered an independent predictive factor for liver fibrosis in patients with NAFLD; significantly higher AST/ALT ratio and higher non-invasive fibrosis scores have been detected in patients with both psoriasis and NAFLD compared to controls with only NAFLD[24].

CARDIOVASCULAR RISK FACTORS AND PSORIASIS

MetS confers an increased risk of cardiovascular events and mortality due to CVDs[25,26]. Psoriatic patients show a higher prevalence of cardiovascular risk factors, which are shared by NAFLD and CVD, thus representing the trade union between these pathologies. Obesity represents a great burden in global individual's health, significantly increasing morbidity and mortality[27].

Data from large cohort studies have shown that among 163517 enrolled individuals, 17% were obese (11465 men and 16612 women). Thus, obesity represents a great public health problem reaching worrying proportions both in pediatric and adult populations[27].

As demonstrated by recent observational studies, psoriatic population may have a higher risk of overweight and obesity with the consequent higher risk of components of MetS[28].

Danielsen *et al*[29] have conducted a recent population-based study confirming an increased prevalence of MetS in patients affected by psoriasis compared to controls. Interestingly, a different trend was emphasized between genders: A 3.8-times higher odds of MetS was found in young women (< 30 years) with an odds ratio reduction with increasing age. Conversely, men showed a 1.35-times higher odds ratio of MetS, independently from age.

Moreover, a direct correlation between severity of psoriasis and obesity has been evidenced in a recent meta-analysis: An odds ratio of 1.46 was found in mild psoriasis and an odds ratio of 2.23 in severe psoriasis[22,30].

Dyslipidemia is a further risk factor, which is shared by NAFLD, psoriasis and CVD. Observational studies have detected a lipid metabolism alteration in psoriatic patients contributing to a dyslipidemic profile and conferring a significant cardiovascular risk[31].

Psoriatic children present high plasma levels of total cholesterol, high content of total cholesterol and high cholesterol/protein ratio in LDL and in HDL[32].

Moreover, an increased odds of hypertriglyceridemia, significantly reduced levels of HDL cholesterol (< 40 mg/dL), hyperlipoproteinemia and hypercholesterolemia have been identified in psoriatic populations[31,33,34].

As for obesity, a positive correlation was found between dyslipidemia and severity of psoriasis with an increased odds of 1.10-3.38 in mild psoriasis and 1.36-5.55 in severe psoriasis[35,36].

The dyslipidemic profile appears extremely relevant; in fact, it is known that hypercholesterolemia can lead to atherosclerosis and coronary heart disease. In animal models, adipocyte differentiation and maturation can be altered by cholesterol accumulation in preadipocytes, leading to adipocyte hypertrophy and adipose tissue inflammation. In humans, it has been demonstrated that hypercholesterolemia leads to an imbalance in the

pro- and anti-inflammatory adipocytokine production by adipose tissue[37].

CVDS AND PSORIASIS

CVDs include atherosclerosis, hypertension, ischemic heart disease, myocardial infarction, stroke and arrhythmias[4].

An increased incidence of cardiovascular risk factors and major cardiovascular events has been found in psoriasis[4,5,15].

Gelfand *et al*[38] performed a cohort study on patients affected by severe psoriasis, evidencing a further 6.2% absolute risk of a 10-year rate of major cardiovascular events and suggesting the possible role of severity of the disease in the pathogenesis of CVD.

In particular, a 6-year reduction in life expectancy has been evidenced in patients with severe psoriasis[39].

Although the role of the extent of psoriasis-involved body sites has not been completely elucidated, studies showed that a wide skin involvement and the presence of inter-gluteal lesions may represent independent predictor factors of CVD in psoriatics[40].

A prospective, population-based cohort study had been conducted by Gelfand *et al*[41] in 2006, evaluating the risk of myocardial infarction (MI) in psoriatic patients. The authors found that psoriatics had a higher incidence of MI which was positively correlated with disease severity: 4.04 per 1000 person-years (95%CI: 3.88-4.21) in mild psoriasis and 5.13 per 1000 person-years (95%CI: 4.22-6.17) in severe psoriasis. Moreover, the risk of MI was higher in young 30-year-old psoriatic patients, and this risk persisted higher after adjustment for major risk factors for MI, suggesting that psoriasis itself confers an independent risk of MI.

This aspect was also confirmed by Brauchli *et al*[42], who found the highest incidence rate of MI in psoriatic patients aged 30-39 years with severe skin disease.

The concomitant presence of PsA seems to lead to an increased risk of non-fatal MI; a risk up to 10% of CVD disease within 10 years of PsA incidence has been identified in most of newly diagnosed PsA patients[43,44].

A retrospective study has shown that the concomitant presence of arterial hypertension (AH) and diabetes mellitus (DM) enhances the risk of CVD in PsA patients. The prevalence of AH and DM was significantly greater in PsA patients who have had CVD compared to those without CVD; the prevalence of AH was 95% *vs* 45% and the prevalence of DM was 60% *vs* 19%. These aspects have important repercussions on early recognition and targeted treatment of comorbidities in psoriatic patients in order to reduce morbidity and mortality[45].

An association between psoriasis and atherosclerotic disease has been recognized. A cross-sectional study conducted by Yiu *et al*[46] evaluated the prevalence and the extent of coronary and carotid atherosclerosis in 70 psoriatic patients compared to age- and gender-matched healthy controls. Psoriatic patients showed a 10-fold increased risk of subclinical coronary atherosclerosis and premature diffuse coronary and carotid atherosclerosis.

The subclinical vascular atherosclerosis in psoriasis has been also studied by Balci *et al*[47] on 43 psoriatic patients without cardiovascular risk factors and 43 healthy controls matched for sex and age. Significantly higher mean intima-media thickness values of the right, left and averaged common carotid arteries had been detected in psoriatics than in controls (0.607 ± 0.144 mm *vs* 0.532 ± 0.101 mm, 0.611 ± 0.157 mm *vs* 0.521 ± 0.117 mm, and 0.609 ± 0.146 mm *vs* 0.526 ± 0.104 mm, respectively). Conversely, the mean flow-mediated dilatation and nitroglycerin-induced dilatation values were significantly lower in patients with psoriasis than in controls (13.36 ± 6.39 mm *vs* 19.60 ± 11.23 mm and 21.08 ± 8.38 mm *vs* 26.85 ± 12.38 mm; $P = 0.002$ and $P = 0.013$, respectively).

It is well documented that calcium exerts an important role in atherosclerosis, and it is an important index of subclinical atherosclerosis and greatly impacts on the atherosclerotic plaque burden[48].

A recent case-control study was conducted on 40 patients with psoriasis and 42 controls matched for age, sex, and cardiovascular risk profile in order to examine the prevalence of coronary calcification. The same prevalence of calcified and non-calcified atherosclerotic coronary lesions was evidenced in both groups[49]. Conversely, emerging data show that patients with psoriasis have a higher coronary calcium score (CAC), which was directly correlated with psoriasis severity[50].

A cross-sectional study was conducted on Mediterranean population, aiming to determine the prevalence of ischemic CAD in patients with psoriasis establishing a significant independent association between psoriasis and CAD[51].

The coronary microvascular function has been evaluated in psoriatic patients by echocardiographic examination to emphasize the coronary flow reserve (CFR). A coronary impairment was shown with a reduction in CFR and with a positive inverse correlation between CFR and PASI score, disease duration and C-reactive protein[52].

Interestingly, it has been recently documented that psoriasis and coronary artery disease share similarities in coronary function and myocardial deformation with a subclinical left ventricular deformation. This aspect may contribute to vascular dysfunction in psoriatic patients, increasing the risk of coronary artery disease[53].

The early detection of specific inflammatory biomarkers implicated in CVDs and in subclinical atherosclerosis remains a fundamental item to promptly identify the cardiovascular risk in this population[54].

New data have emerged from studies on this topic. In particular, N-terminal pro B-type natriuretic peptide (NT-proBNP) is a molecule secreted by the ventricular myocardium in response to increased ventricular stretch and it plays an important role as a predictor of cardiovascular mortality, of negative outcome in stroke and of left ventricular systolic dysfunction[54].

Significantly higher serum levels of NT-proBNP were

found in 73 male psoriatic patients compared to controls with a direct correlation with disease duration[55].

These results appear relevant in the light of echocardiographic abnormalities found by Biyik *et al*[56], who showed left ventricle hypertrophy, diastolic dysfunction and wall motion alterations in patients affected by psoriasis. Moreover, a higher frequency of mitral and tricuspid valve prolapse had been diagnosed in psoriatics.

Another useful biomarker is homocysteine, which is considered an independent risk factor for CVD by promoting oxidative stress, lipoperoxidation and endothelial cell dysfunction. Moreover, hyperomocysteinemia is considered an independent risk factor for CVD, conferring an elevated risk of atherosclerosis, stroke and peripheral occlusive vascular diseases[57].

Homocysteine plasma levels have been evaluated in psoriasis, and significantly higher levels were found in psoriasis patients compared to healthy subjects, with a positive correlation with disease severity. No correlation was found between homocysteine serum levels and disease duration or the presence of arthritis[57,58].

Furthermore, high homocysteine plasma levels and reduced folic acid plasma levels in psoriatic patients seem to be implicated in a pro-thrombotic state[59].

A new interesting biomarker of vascular damage, YKL-40, has been recently studied in psoriatic patients. YKL-40 belongs to the chitinase family and it has been detected in atherosclerotic plaque, contributing to endothelial dysfunction (ED) and predicting early vascular damage in diseases with high cardiovascular risk. Increased levels of YKL-40 have been found in inflammatory conditions, such as rheumatoid arthritis, osteoarthritis, systemic lupus erythematosus and Crohn's disease[60,61].

A case-control study on 48 psoriatic patients has emphasized a statistically significant elevation of YKL-40 levels. These data had been confirmed by Erfan *et al*[60], who had also performed ultrasonography in order to identify ED. Psoriatic patients with ED showed higher YKL-40 serum levels than healthy controls without ED; moreover, psoriatic patients with concomitant cardiovascular risk factors, such as smoking, obesity and diabetes, showed higher YKL-40 levels than those without[62].

The higher cardiovascular risk in psoriasis appears also linked to the increased prevalence and incidence of hypertension. In fact, hypertension is a well-established risk factor for CVDs and cardiovascular mortality[63].

The association between psoriasis and hypertension has been evaluated in a recent meta-analysis conducted by Armstrong *et al*[63], who documented a higher odds of hypertension of 1.58 times in psoriatics compared to the general population. Moreover, hypertension and psoriasis severity were positively correlated with a hazard ratio (HR) of 1.17 in patients with severe psoriasis and HR of 1.07 in those with mild psoriasis. PsA patients showed a higher odds ratio of 2.07 compared to patients with only psoriasis.

The increased detection of hypertension in psoriatic patients could explain the increased risk of atrial fibrillation in this population. Atrial fibrillation is the most frequent cardiac arrhythmia, accounting for 0.4%-1% of the general population and strictly linking to cardiovascular morbidity and mortality[64].

Emerging data have focused on the potential association between psoriasis and atrial fibrillation and documented that psoriasis may be independently associated with a higher risk of new onset atrial fibrillation[64].

A Danish nationwide cohort study evaluated 36765 mild psoriasis patients and 2793 severe psoriasis patients *vs* 4478926 controls: An increased risk of atrial fibrillation was found in psoriatics with a direct correlation with skin disease severity. Furthermore, a strong association between atrial fibrillation and early onset psoriasis had emerged[65].

Conversely, Armstrong *et al*[66] had considered a cohort of 2078 psoriatic patients matched to 6234 healthy subjects and evidenced no statistically significant difference in a 5-year atrial fibrillation incidence between the two groups (2.5% *vs* 3.3%) and no association between incident atrial fibrillation and psoriasis severity.

PSORIASIS, NAFLD AND CVD: A COMMON INFLAMMATORY PROCESS

Psoriasis, NAFLD and CVD are considered multifactorial and multi-step diseases with not completely fully elucidated interactions between genetic, immunological and environmental factors[67,68].

Psoriasis is an immune-mediated disorder sustained and maintained by a Th1-Th17-Th22 cell immune response. The Th1-Th17-Th22 downstream pro-inflammatory cytokines contribute to creating a cytokine milieu participating in a systemic chronic inflammation process[69,70].

In fact, the low-grade chronic inflammatory process seems to represent the major component linking psoriasis to its comorbidities and leading to insulin resistance, to dysmetabolic profile and to ED and thus predisposing psoriatic patients to atherosclerosis and higher cardiovascular risk[2,4].

Both innate and adaptive immunity participates in physio-pathologic mechanism underlying psoriasis and atherosclerosis. Hansson *et al*[71] in 2012 have interestingly proposed the concept of "two plaques for one syndrome". In fact, the development of both psoriatic and atherosclerotic plaques is strictly dependent on T cells, monocytes, macrophages and pro-inflammatory cytokines. It is know that Th1 hyperactivity and the overexpression of Th1-related cytokines represent the basis for ED being associated with atherosclerotic plaque instability and with an increased risk of athero-thrombotic events[71-74].

Most of inflammatory cytokines are produced by the adipose tissue[75,76] (Table 1). It is known that the adipose tissue is a real endocrine organ able to synthetize adipocytokines, bioactive molecules deeply involved in the inflammation and in the development of MetS and its components, such as dyslipidemia and insulin resistance[75,76].

Table 1 Role of inflammatory biomarkers in psoriasis, non-alcoholic fatty liver disease and cardiovascular diseases

	Psoriasis	CVD	NAFLD
TNF-alpha	↑Keratinocyte proliferation ↑Pro-inflammatory cytokine production ↑Expression of vascular endothelial cell adhesion molecules ↑Angiogenesis	↑LDL transcytosis	↓IRS-1 phosphorylation ↑Insulin-resistance ↑Hepatic fibrogenesis
IL-1	↑Keratinocyte proliferation ↑Pro-inflammatory cytokine production ↑Expression of vascular endothelial cell adhesion molecules	↑Synthesis of IL-6, fibrinogen, RCP ↑Expression of adhesion molecules (ICAM, VCAM)	↑Activation of MAP and ERK pathways
IL-6	↑Pro-inflammatory cytokines (TNF-alpha, IL-1, IL-17) ↑Dermal and epidermal cell growth and differentiation ↑T cell migration into the epidermis	↑Pro-inflammatory cytokine production	↑Insulin-resistance ↓Hepatic cytokine signaling-3
Leptin	↑Keratinocyte proliferation ↑Promotes Th1 responses ↑Angiogenesis	↑Vascular smooth muscle cell migration and proliferation ↑Synthesis of TNF-alpha	↑Activation of JAK-2/IRS-2/PI3-K/Akt pathways ↑Leptin resistance ↑Hepatic fibrogenesis
Adiponectin	↑Anti-inflammatory cytokine production (Reduced levels in PsO)	↑Endothelial NO production ↑Endothelial dysfunction (Reduced levels in CVD)	↑Insulin sensitivity (Reduced levels in NAFLD)
Resistin	↑Pro-inflammatory cytokine production	↑Arterial inflammation ↑Vascular smooth muscle cell proliferation ↑Endothelial dysfunction	↑Insulin resistance (controversial data on NAFLD)
Visfatin	↑	↑	↑Protection against liver injury (not altered in the early stage)
IL-17	↑Pro-inflammatory cytokine production ↑Expression of vascular endothelial cell adhesion molecules	↑Atherosclerotic plaque vulnerability	↑Hepatic steatosis ↑Synthesis of pro-inflammatory cytokines
VEGF	↑Keratinocyte proliferation ↑Angiogenesis	↑	↑Microvascular changes implicated in the hepatic disease (fibrosis to cirrhosis)

CVD: Cardiovascular disease; NAFLD: Non-alcoholic fatty liver disease; LDL: Low-density lipoprotein; IRS-1: Insulin receptor substrate 1; MAPK: Mitogen-activated protein; ERK: Extracellular signal-regulated kinase; JAK: Janus kinase-signal transducers; VEGF: Vascular endothelial growth factor; IL: Interleukin; TNF: Tumor necrosis factor.

Among Th1 pro-inflammatory cytokines, tumor necrosis factor (TNF)-α is considered one of the most representative cytokines in psoriasis; elevated serum levels of TNF-α have been detected in psoriatics with a positive correlation with disease severity[77] (Table 1).

In psoriasis, TNF-α promotes keratinocyte proliferation, pro-inflammatory cytokine production, expression of vascular endothelial cell adhesion molecules and angiogenesis[78].

Although the role of TNF-α in the pathogenesis of atherosclerosis remains not completely elucidated, it seems to increase the LDL transcytosis across endothelial cells and to facilitate LDL retention in the vascular wall[79] (Table 1).

Furthermore, TNF-α interferes with insulin metabolism, thus reducing the auto-phosphorylation of tyrosine residues of insulin receptor and phosphorylation of insulin receptor substrate 1 (IRS-1) and contributing to the first hit of NAFLD[80] (Table 1).

Interleukin (IL)-1 is another important pro-inflammatory cytokine exerting both autocrine and paracrine effects on keratinocytes, lymphocytes and vascular endothelium. In particular, it stimulates the synthesis of inflammatory cardiovascular mediators such as IL-6, fibrinogen, C-reactive protein, and increases the expression of adhesion molecules ICAM and VCAM-1 by dermal endothelial cells, leading to the skin recruitment of immune cells[81] (Table 1).

Human atherosclerotic plaques show elevated levels of IL-1β mRNA. This element could suggest that the synthesis of growth factors and other cytokines leading to local inflammatory cascades may be activated by locally synthesized IL-1 protein[82] (Table 1).

IL-1 also participates in pancreatic β-cell activity by stimulating mitogen-activated protein kinases (MAPK) and extracellular signal-regulated kinase (ERK), by affecting the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) and by activating the inducible nitric oxide synthase (iNOS)[83].

IL-6 is an inflammatory cytokine, which amplifies inflammatory responses by synergizing with other pro-inflammatory cytokines, such as TNF-α, IL-1 and IL-17. IL-6 is responsible for dermal and epidermal cell growth and differentiation and for T cell migration into the epidermis[84] (Table 1).

Although the role of IL-6 is contradictory in NAFLD, recent data have evidenced that it may suppress hepatic cytokine signaling-3 leading to insulin resistance[85] (Table 1).

In addition to the above cytokines, adipose tissue produces leptin, adiponectin, resistin and visfatin, which are impaired in psoriasis and NAFLD and contribute to the ED[86].

ED is considered an early manifestation of vascular

alterations which precede the development of hypertension and atherosclerosis in obese people[86].

In psoriasis, increased serum levels of leptin, resistin and visfatin and reduced serum levels of adiponectin have been detected[7].

Leptin is a pro-inflammatory adipocytokine which interacts with its specific receptor on endothelial cells, leading to the activation of JAK-2/IRS-2/PI3-K/Akt pathways and nuclear translocation of STAT (signal transducer and activator of transcription) proteins[87].

Moreover, leptin is considered a pro-atherogenic factor by promoting vascular smooth muscle cell migration and proliferation and by stimulating the synthesis of TNF-α with the consequent amplification of inflammatory TNF-α related pathways. Recently, hyperleptinemia has been found as a possible risk factor for acute myocardial infarction[88,89] (Table 1).

Resistin seems to support atherosclerosis by favoring ED, vascular smooth muscle cell proliferation, arterial inflammation and foam cell formation. Serum levels of resistin were higher in patients with acute myocardial infarction compared to patients with stable angina. As another pro-inflammatory adipocytokine, resistin may be involved in the pathogenesis of MetS in psoriatic patients, despite its role in NAFLD remains uncertain[90,91] (Table 1).

Adiponectin is an anti-inflammatory adipocytokine that increases nitric oxide production in endothelial cells by the activation of phosphotidylinositol-3 (PI-3) kinase/Akt signalling pathway. Serum level of adiponectin appears reduced both in psoriasis and NAFLD and it may be associated to the decreased endothelial production of NO, which is in turn considered a marker of ED[87,91] (Table 1).

Visfatin is pro-inflammatory adipocytokine contributing to insulin resistance and to atherosclerotic plaque destabilization. Serum levels of visfatin had been found higher in patients with ischemic cerebrovascular disease and myocardial infarction[92,93] (Table 1).

Th17 is implied in the pathogenesis of psoriasis and of other immune-mediated inflammatory diseases by modulating immune cell trafficking and initiating inflammation and cytokine production[94].

Th17 had been found overexpressed both in psoriatics' serum and plaque with a positive correlation with disease severity; IL-17A levels were significantly higher in moderate to severe psoriasis than in mild psoriasis[95,96] (Table 1).

Although the precise role of Th17 in atherosclerosis remains controversial, recent data have hypothesized a putative role in the atherosclerotic plaque vulnerability, which represents the initial step of plaque rupture leading to vessel occlusion, myocardial infarction and stroke. In fact, increased expression of IL-17A has been observed in human carotid artery plaques of symptomatic patients with stroke or transient ischemic attack[97] (Table 1).

In mice, Th17 and IL-17 may be implicated in the progression from steatosis to steatohepatitis[98] (Table 1).

Angiogenesis is a physio-pathologic process characterized by the new blood vessel formation from the pre-existing vasculature and appears important in inflammatory, autoimmune and neoplastic diseases. Therefore, angiogenesis may represent a further link between psoriasis and psoriasis-related comorbidities[99].

Vascular endothelial growth factor (VEGF) is the pivotal angiogenic factor participating in the regulation of metabolism, gene expression, cell proliferation, migration, and survival[100] (Table 1).

VEGF participates in the pathogenesis of psoriasis either in an autocrine manner by directly stimulating keratinocyte proliferation and in a paracrine manner by inducing angiogenesis and by providing the fundamental elements to support epidermal proliferation. VEGF is upregulated in serum and lesional psoriatic skin with a correlation with disease severity[101] (Table 1).

Coulon *et al*[102] tested the TNF-α, IL-6 and VEGF serum concentrations in an obese population with NAFLD and found higher levels than those of controls, thus indicating the role of pro-inflammatory and pro-angiogenic factors in this pathology.

This aspect appears relevant; in fact, angiogenesis participates in the microvascular changes which are implicated in the hepatic disease progression from fibrosis to cirrhosis[103].

A further mechanism shared by psoriasis, NAFLD and CVD may be oxidative stress. Oxidative stress results from disequilibrium between the reduced anti-oxidant systems and abnormal excessive production of reactive oxygen species (ROS) or reactive nitrogen species. ROS are produced mainly by mitochondria and their production is regulated by the redox state of the respiratory chain[104,105].

The pathogenesis and progression of psoriasis are strictly linked to the redox sensitive cellular signaling pathways, such as mitogen-activated protein kinase/activator protein 1 (MAPK/AP1), NFκB, and Janus kinase-signal transducers (JAK) and transcription activators[106].

Many studies have been conducted to investigate the role of oxidative stress in psoriasis and have evidenced that psoriatics show an imbalance between biomarkers of oxidative stress and the antioxidant system. Ferretti *et al*[107] have shown an impairment of oxidant/antioxidant system; significantly higher serum levels of lipoprotein a [Lp(a)] and lipid hydroperoxides have been found in psoriatics compared to controls. Conversely, paraoxonase-1 (PON1), an anti-inflammatory and anti-oxidant enzyme, was lower than in healthy subjects. A positive correlation was found between serum levels of Lp(a), markers of lipid peroxidation and the severity of the disease, whereas PON1 activity and Lp(a) were negatively correlated[107,108].

Emre *et al*[109] have investigated the relation between oxidative status and smoking in psoriasis, demonstrating the increased serum levels of triglycerides and reduced levels of HDL cholesterol and arylesterase activity in smoker compared to non-smoker psoriatic patients. Therefore, smoking could be considered a risk factor for psoriasis severity by increasing oxidative stress and

thus predisposing psoriatic patients to a higher risk of cardiovascular comorbidities.

A reduction in total antioxidant capacity and in antioxidant vitamins A and E has been found by Rocha-Pereira *et al*[110], who had also confirmed a pro-atherogenic lipid profile in psoriatic patients with an increase of cholesterol, triglycerides, low density lipoprotein cholesterol (LDL), very low density lipoprotein cholesterol (VLDL), apolipoprotein B (apo B), Lp(a) and lipoperoxidation products. These data tend to underline an increased cardiovascular risk in psoriatic patients, particularly in those with severe disease.

It is known that oxidative stress participates in the second hit of the pathogenesis of NAFLD and it may be implicated in the NAFLD progression by interfering with normal cell division. In murine models, alterations of the polyploidization process were found in fatty liver with a large proportion of highly polyploid mononuclear cells, which were only rarely observed in normal hepatic parenchyma. Moreover, in humans, alterations in hepatocyte ploidy have been documented in liver biopsies from patients with NASH[111].

Oxidative stress participates in the mild chronic vascular inflammation in CVD. In fact, oxygen metabolites are able to interfere with LDL metabolism and promote the formation of oxidized low-density lipoprotein (Ox-LDL), which plays a representative role in atherosclerotic plaque development and in endothelial damage favoring inflammatory vascular cell infiltration[112,113] (Figure 1).

EFFECTS OF TNF-ALPHA INHIBITORS AND CONVENTIONAL PSORIATIC THERAPIES ON NAFLD AND ON CARDIOVASCULAR RISK FACTORS

As seen above, the inflammatory process represents the mainstay linking the pathogenesis of psoriasis, NAFLD and CVD. Therefore, anti-inflammatory drugs may represent important therapeutic options in the treatment and prevention of these pathologies. Data in the literature on the effect of both conventional and biological psoriatic therapies have shown discordant results on their possible action on NAFLD and cardiovascular risk factors[114].

Conventional treatments for moderate to severe psoriasis include cyclosporine A, methotrexate and retinoids. Although effective, their safety profile should be evaluated in their long-term use, with psoriasis-related comorbidities considered[115].

In fact, it is well known that methotrexate can mediate liver toxicity and patients with liver dysfunction, such as NAFLD/NASH patients, could present impaired drug metabolism with consequent liver accumulation and increased susceptibility to liver toxicity[116].

Methotrexate exerts opposite effects on cardiovascular risk in psoriatic patients. In 1989, Refsum *et al*[117] investigated the effect of methotrexate 25 mg weekly on plasma homocysteine levels and found a significant and transient increase within 48 h after administration.

Conversely, a lower risk of CVD has been found in psoriatic patient treated with MTX compared to patients without MTX[118].

Elevated serum levels of cholesterol and tryglicerides can occur during treatment with retinoids and cyclosporine, although no evidence of an increased cardiovascular risk has been stated with long-term use of etetrinate[118,119].

Moreover, as demonstrated in a prospective non-randomized study on patients affected by PsA, cyclosporine has been associated with a significant elevation of blood pressure values[119].

TNF-α inhibitors, IL12/23 inhibitors and IL-17 inhibitors represent three new classes of drugs used in moderate to severe psoriasis with a good efficacy and safety profile. Among biologics, metabolic effects of TNF-α blockers are most widely studied[120,121].

A cross-sectional study evaluated epicardial fat thickness (EAT), an emerging marker of cardiometabolic risk, in patients with rheumatoid arthritis (RA) treated with TNF-α inhibitors compared to RA patients treated with non-biological disease-modifying anti-rheumatic drugs (DMARDs). A significantly lower EAT thickness was detected in patients treated with TNF-α inhibitors than in those treated with DMARDs (8.56 ± 1.90 mm and 9.71 ± 1.45 mm, respectively)[122].

Jókai *et al*[123] evaluated the positive effect of TNF-α inhibitors on carotid and brachial intima-media thickness in patients with psoriasis.

Although data are few, TNF-α blockers seem to act on lipid and glucose metabolism by exerting a potential action on cardiovascular risk factors. An improvement of insulin-sensitivity in psoriatic patients treated with Etanercept and Infliximab has been evidenced[124,125].

Conversely, long-term use of TNF-α inhibitors in patients with rheumatoid arthritis seem not to influence insulin resistance parameters[126].

With regard to the lipid profile, although no statistically significant difference, raised values of total cholesterol, LDL-C and triglycerides were found after 24 wk of treatment with Etanercept in psoriatic patients[127].

Adipocytokine levels and fat distribution have been assessed in patients with RA and ankylosing spondilitis during long-term treatment with TNF-α blockers. A fat mass gain with a tendency to visceral fat accumulation, a reduction of resistin serum levels and no significant modification in leptin, total adiponectin or visfatin serum levels have been evidenced[128]. Another recent study focused on the influence of TNF-α inhibitors on serum levels of adipocytokines, showing a partial rebalancing between pro- and anti-inflammatory adipocytokines after 24 wk of anti-TNF-α treatment with a reduction of leptin, visfatin and resistin and a mild adiponectin increase[76].

A body weight increment has been identified after 6-mo treatment with Etanercept compared to psoriatic patients treated with methotrexate[129].

These data have been confirmed by Campanati *et al*[24] who showed an increase in waist-hip-ratio and

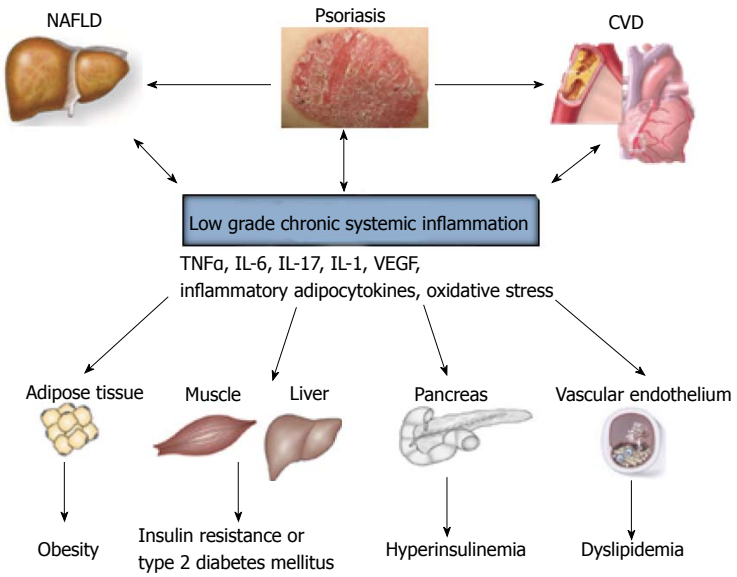

Figure 1 Psoriasis, non-alcoholic fatty liver disease, cardiovascular diseases and cardiovascular risk factors: A unique inflammatory background. CVD: Cardiovascular disease; NAFLD: Non-alcoholic fatty liver disease; VEGF: Vascular endothelial growth factor; IL: Interleukin; TNF: Tumor necrosis factor.

BMI during treatment with Etanercept. The authors documented a possible preventive effect of Etanercept on liver fibrosis, evidencing a significant reduction of AST/ALT ratio and an improvement of insulin-sensitivity parameters. These elements confirm the strong relation between the alteration of glucose metabolism and NAFLD[24].

Although further larger studies are needed to confirm these data, this hypothetic preventive role may be linked to anti-inflammatory properties of TNF-α inhibitors and their action on glucose homeostasis[24].

The favorable effect of TNF-α blockers on the risk of MI has been identified in a retrospective study monitoring patients affected by only psoriasis, by only PsA and by both psoriasis and PsA. Patients with only psoriasis had a significant MI risk reduction (HR = 0.26; 95%CI: 0.12-0.56), whereas a non-significant MI risk reduction was detected in those with only PsA (HR = 0.86; 95%CI: 0.28-2.70) and in those with both psoriasis and PsA. The duration of TNF-α inhibitor treatment did not seem to influence the risk of MI[130,131].

CONCLUSION

Psoriasis is a complex and already partially unknown disease whose skin manifestations represent only the edge of an iceberg, which is widely submerged and unknown. Psoriasis and psoriasis-related comorbidities significantly impact on patient's health and quality of life and negatively interfere in physical-psychic well-being with important repercussion in working daily life. As a multi-organ pathology, psoriasis needs a multidisciplinary approach and clinicians should evaluate this holistic vision in order to promptly identify and manage psoriasis-related comorbidities influencing patients' morbidity and mortality. The underlying inflammatory process is the leitmotiv shared by psoriasis, NAFLD and CVD and overlaps both the common genetic predisposition and modifiable risk factors, such as sedentary lifestyle, smoking and alcohol consumption.

Therefore, the therapeutic strategy for psoriasis should be multifaceted and should specifically tailor outcome tools and disease-related items by a patient-based evaluation and by selectively verifying the risk/benefit of each single therapeutic option.

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REVIEW

Impact of cardiac magnetic resonance imaging in non-ischemic cardiomyopathies

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Abstract

Non-ischemic cardiomyopathies include a wide spectrum of disease states afflicting the heart, whether a primary process or secondary to a systemic condition. Cardiac magnetic resonance imaging (CMR) has established itself as an important imaging modality in the evaluation of non-ischemic cardiomyopathies. CMR is useful in the diagnosis of cardiomyopathy, quantification of ventricular function, establishing etiology, determining prognosis and risk stratification. Technical advances and extensive research over the last decade have resulted in the accumulation of a tremendous amount of data with regards to the utility of CMR in these cardiomyopathies. In this article, we review CMR findings of various non-ischemic cardiomyopathies and focus on current literature investigating the clinical impact of CMR on risk stratification, treatment, and prognosis.

Key words: Cardiomyopathy; Magnetic resonance imaging; Heart; Cardiovascular imaging; Cardiology

Core tip: Cardiac magnetic resonance imaging (CMR) has established itself as a vital modality in the evaluation of numerous aspects of non-ischemic cardiomyopathies, ranging from establishing a diagnosis to detailed analysis of cardiac function. Lately, increasing data has become available regarding the clinical utility of CMR in the evaluation of these patients, although few articles have consolidated this these findings regarding CMR's impact in these pathologies. This review will summarize current literature investigating the clinical impact of CMR on risk stratification, treatment, and prognosis in the setting of non-ischemic cardiomyopathies.

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INTRODUCTION

Non-ischemic cardiomyopathies (NICM) include a wide spectrum of disease states afflicting the heart, whether a primary process or secondary to a systemic condition[1,2]. Several imaging modalities are used in the evaluation of NICM, particularly echocardiography, nuclear medicine, and cardiac catheterization. Cardiac magnetic resonance imaging (CMR) has established itself as an important modality in the evaluation of cardiomyopathies. The last decade has seen tremendous technological advances in CMR, both in software and hardware[3]. CMR offers a number of advantages that makes it an ideal imaging modality in a number of clinical settings. CMR allows for the non-operator dependent acquisition of high spatial and temporal resolution images in any desired imaging plane and regardless of patient-specific factors such size and body composition. With these high resolution images, accurate assessments of various chamber and vessels functional parameters can be made. Additionally, CMR is free of ionizing radiation, which makes it an ideal modality for evaluation of young patients, and those who may require frequent or regular follow-up assessments.

The increased use of CMR has resulted in accumulation of a tremendous amount of data on the utility of CMR in the clinical management of these patients. CMR is moving from simply an initial diagnostic tool to one whose findings can also have for significant clinical impact, including those on therapy response, risk stratification, and prognosis determination.

In this article, we review CMR findings of various non-ischemic cardiomyopathies and focus on current literature investigating the clinical impact of CMR on risk stratification, treatment, and prognosis.

MAGNETIC RESONANCE IMAGING OF NICM

In a patient with NICM, several dedicated CMR sequences are used as a part of the magnetic resonance imaging (MRI) protocol. Steady-state free precession (SSFP) is the most commonly used sequence, which helps in evaluating ventricular morphology and function. In addition, ventricular function can also be quantified by drawing endocardial and epicardial contours. Velocity-encoded phase contrast MR images enable flow and velocity quantification in vascular and valvular structures. Multi-echo gradient echo images are used for detecting and quantifying myocardial iron. T2-weighted images are useful in detection of myocardial edema, seen in acute myocardial infarction or myocarditis. T2-mapping is a more accurate technique of quantifying the myocardial fluid. Dynamic first-pass perfusion images are utilized for evaluation of perfusion defects or microvacular dysfunction. Delayed-enhancement images show scar and fibrosis, seen as different patterns of late gadolinium enhancement (LGE), which is useful in the characterization of cardiomyopathies. T1-mapping techniques can quantify the T1 values of myocardium, either before (native) or after administration of contrast and can measure extracellular volume (ECV), which is a biomarker of fibrosis. MR angiography is useful in evaluation of vascular anatomy. 3D-whole heart navigator gated SSFP sequence is useful for evaluation of coronary artery anatomy as well as vascular anatomy without administration of contrast.

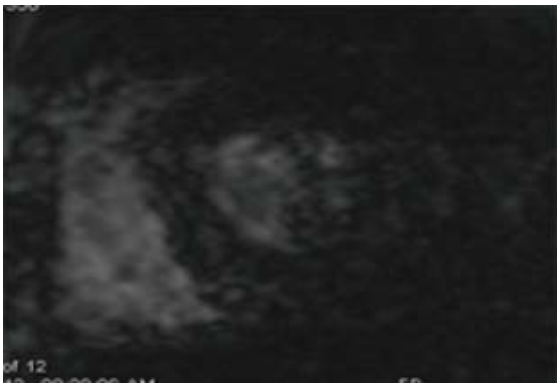

Figure 1 Iron overload cardiomyopathy. Short axis gradient echo image with long echo time (15 ms) shows dark signal in the left ventricular myocardium due to increased iron deposition.

A summary of main diagnostic CMR findings as well as the commonly evaluated CMR parameters and their clinical implications, discussed in greater in the following sections, are included in Table 1.

Iron overload cardiomyopathy

Myocardial iron deposition is shown on gradient-echo images, with lower signal at higher Echo time (TE) values (Figure 1). Utilizing gradient echo images at different TE levels (Multi-echo GRE), the absolute myocardial T2* can be measured and this has shown to be a more reliable indicator of true myocardial iron content as compared to serum ferritin levels or liver iron[4,5]. Myocardial T2* < 20 ms is considered to be significant iron deposition and < 10 ms is considered to be advanced iron deposition.

Myocardial T2* values have also been shown to detect myocardial changes of iron overload, significantly earlier than changes in left ventricular ejection fraction (LVEF)[4]. Myocardial T2* has been shown to be a strong independent predictor of adverse clinical outcomes such as development of heart failure, arrhythmias, and sudden cardiac death. A study by Anderson *et al*[4] showed that patients with a with T2* < 20 ms were at significantly increased risk for arrhythmias, and this risk was also shown to be increased further at lower T2*

Table 1 Summary of diagnostic findings and prognostic parameters at cardiac magnetic resonance

Cardiomyopathy	Key diagnostic CMR findings	Prognostic CMR parameters	Clinical outcomes evaluated
Iron overload cardiomyopathy	Myocardial T2* < 20 ms	Myocardial T2*	Adverse cardiac events, sudden cardiac death, treatment monitoring
Idiopathic dilated cardiomyopathy	LV dilatation, global systolic dysfunction, mid-myocardial septal LGE	LGE, longitudinal myocardial strain	Adverse cardiac events, transplant status, sudden cardiac death, treatment monitoring
Hypertrophic cardiomyopathy	Asymmetric septal hypertrophy, patchy LGE (RV insertion points), mitral valve systolic anterior motion	LGE	Adverse cardiac events, sudden cardiac death
Sarcoidosis	Mid-myocardial or sub-epicardial LGE with (acute) or without (chronic) edema	LGE	Adverse cardiac events, treatment monitoring
Myocarditis	Myocardial edema, high T2 in T2 mapping, early gadolinium enhancement, mid-myocardial or subepicardial distribution LGE	LGE	Adverse cardiac events, sudden cardiac death, cardiac function recovery
Amyloidosis	Diffuse subendocardial-transmural enhancement, early myocardial nulling on T1 mapping	LGE, ECV estimation, T2 ratio	Mortality, disease subtype differentiation
Left ventricular non-compaction	Non-compacted to compacted myocardium ratio (end diastole) > 2.3	Non-compacted to compacted thickness ratio, LGE	Functional status, adverse cardiac events, sudden cardiac death
Arrhythmogenic right ventricular dysplasia	Major wall motion abnormality, low ejection fraction, dilated RV (major criteria)	RV and LV abnormalities, LGE	Adverse cardiac events, sudden cardiac death, treatment planning
Takotsubo cardiomyopathy	Reduced global systolic function, abnormal apical wall motion with normal/hyperkinetic basal segments	Type of segmental involvement, LGE	Cardiac dysfunction severity and recovery
Fabry disease	Concentric LV thickening, basal inferolateral segment mid myocardial-subepicardial LGE	LGE, T1 mapping	Adverse cardiac events, sudden cardiac death, treatment monitoring
Muscular dystrophy	Ventricular dilation, systolic dysfunction, mid myocardial-subepicardial LGE	LGE, T1 mapping, ECV estimation, myocardial strain	Adverse cardiac events

CMR: Cardiac magnetic resonance; RV: Right ventricle; LV: Left ventricle; LGE: Late gadolinium enhancement; ECV: Extracellular volume.

levels. T2* value < 10 ms had a substantially higher risk of developing heart failure at the time of follow-up with risk increasing further for patients with T2* < 6 ms. As with the level of myocardial iron content, these outcomes predictors did not correlate with parameters such as serum ferritin or liver iron content. Similar findings were also seen in data from Patton *et al*[5], which also included sudden cardiac death as a part of their composite outcome. Data from this study also demonstrated worsening outcomes measured at lower T2* levels, leading them to propose a three-tiered risk stratification model based on T2* values - low risk: T2* > 20 ms; intermediate risk: T2* between 10 ms and 20 ms; and higher risk: T2* < 10 ms.

In addition to predicting outcomes, CMR has also shown to be an invaluable tool in the monitoring of treatment response to chelation therapies, which comprises a crucial element of the treatment of iron-overload cardiomyopathy. Multiple published studies have shown improvements in T2*[6-13] and LVEF[6-11] when evaluating treatment responses to several different chelating agents over variable treatment durations. The longest studied follow-up time was performed by Ambati *et al*[11], which demonstrated continued improvement in both T2* and LVEF extending to five years after treatment initiation. Although most studies evaluating cardiac response of chelation therapies have focused on objective parameters such as T2* and LVEF, Pennell *et al*[14] demonstrated that improvements in myocardial T2* and LVEF were also associated with significantly reduced risk of developing heart failure. It should be noted that this observed risk reduction was seen in the setting of only minimally improved LVEF, suggesting that, in the setting the chelation treatment of iron overload cardiomyopathy, conventional functional parameters such as LVEF may underestimate the clinical impact of therapies.

Given the evidence for the use of CMR in the diagnosis, risk stratification, and treatment monitoring in iron overload cardiomyopathy, CMR is recognized in the most current American Heart Association (AHA) Consensus Statement[15] as a critical tool in the diagnosis and clinical management of patients with iron overload cardiomyopathy. Additionally, the widespread adoption of CMR in management of these patients has correlated with the reduction in mortality from cardiac iron overload in patients in the United Kingdom[16,17], which has been largely attributed to clinical guidance by CMR findings in these patients. For example, Modell *et al*[16] showed that the death rate from iron overload between 2000 and 2003 was 2.3 per 1000 patients, significantly decreased from 7.9 per 1000 prior to the initiation of CMR screening in thalassemia patients, Additionally, Chouliaras *et al*[17] estimated that the risk of cardiac death before CMR screening of United Kingdom thalassemia patients was 82% higher compared to the risk observed after CMR screening.

Idiopathic dilated cardiomyopathy

Idiopathic dilated cardiomyopathy is characterized by dilation of the left ventricular left ventricle (LV) with global

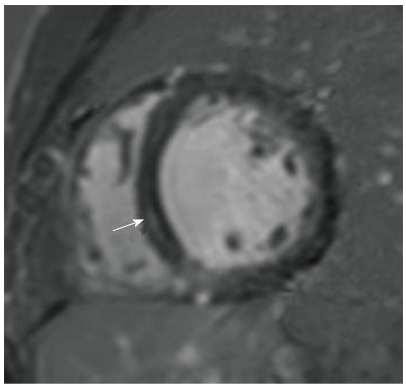

Figure 2 Idiopathic dilated cardiomyopathy. Short axis delayed-enhancement image shows linear mid myocardial enhancement (arrow) in the basal septum, and dilated left ventricle, which is indicative of idiopathic dilated cardiomyopathy.

systolic dysfunction. A linear mid-myocardial pattern of LGE in the septum (Figure 2) has been reported in these patients[18], due to presence of fibrosis. A study by McCrohon *et al*[19] showed that in a population with dilated cardiomyopathy, this linear mid-myocardial pattern was seen in 28% of patients, with no particular enhancement in 59% of patient. In 13% of these patients, a subendocardial pattern was seen in spite of normal coronary arteries in catheterization[19].

Buss *et al*[20] demonstrated the association of various strain parameters with cardiac outcomes including cardiac death and transplantation. In their analysis, longitudinal strain was shown to be a superior predictor of outcome compared to not only conventional parameters such as LVEF and New York Heart Association functional class, but the presence of LGE as well. Additionally, preserved longitudinal strain was associated with better outcomes, even in the presence of LGE or depressed LVEF[20].

Several published studies have shown the presence of LGE in these patients to be a significant risk factor for the development of arrhythmic events, including sudden cardiac death[18,21-24]. A pair of studies[18,24] have shown specifically the presence of mid-wall fibrosis to be associated with increased risk of adverse cardiac events and sudden death[18,24]. Furthermore, a study by Perazzolo Marra *et al*[21] demonstrated that the presence of LGE was a superior predictor to traditional parameters including depressed LVEF (less than 35%) in predicting arrhythmic events and sudden cardiac events. The presence of LGE has also been shown to be a useful predictor of adverse cardiac events in cohorts of asymptomatic and minimally symptomatic patients[25].

Prospective data is limited regarding the impact on screening dilated cardiomyopathy patients on management or treatment outcomes. However, in an analysis by Gulati *et al*[24], assuming a 15% threshold for sudden cardiac death risk for implantable cardioverter defibrillator (ICD) implantation, the addition of LGE to their risk assessment model would have resulted in nearly 19% of studied patients would have undergone ICD implantation, and 11% would have avoided ICD implantation. Although long-term clinical outcome data is lacking, this suggests that measurement of LGE at CMR may be an effective way to guide ICD therapies in these patients.

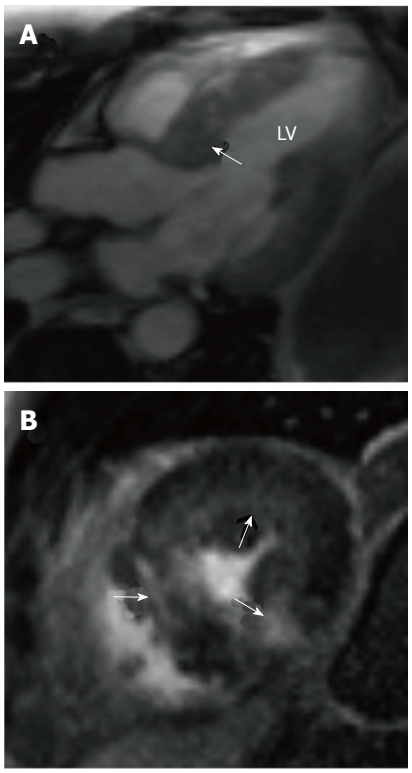

Figure 3 Hypertrophic cardiomyopathy. A: Three-chamber steady state free precession image shows severe hypertrophy of the basal anteroseptum (arrow), which causes LVOT obstruction; B: Short-axis delayed enhancement image shows patchy mid myocardial enhancement in hypertrophied segments, suggestive of interstitial fibrosis in a pattern specific for hypertrophic cardiomyopathy. LV: Left ventricular.

Hypertrophic cardiomyopathy

Hypertrophic cardiomyopathy (HCM) is a genetic disorder with a heterogeneous phenotypic expression. MRI can diagnose HCM and also characterize the morphology. The most common morphological type is asymmetric septal hypertrophy (ASH), and other forms include apical, mid-ventricular, concentric, spiral and mass-like forms. In ASH, there is hypertrophy of the basal septum (Figure 3A). MRI can detect and quantify LVOT flow obstruction and the flow velocity/gradient. Systolic anterior motion of the mitral valve and mitral regurgitation can also be detected and quantified. MRI is also useful in detection of papillary muscle abnormalities such as anomalous insertion, double bifid morphology, anteroapical displacement and hypermobile papillary muscles, which can cause obstruction without significant myocardial hypertrophy. Delayed enhancement is seen in 60% of patients[26] with HCM due to interstitial fibrosis, microfibrillar disarray or microvascular obstruction. This is typically seen in a mid-myocardial, patchy pattern at the RV insertion points, but is also seen in the rest of the hypertrophied (Figure 3B) and non-hypertrophied myocardium.

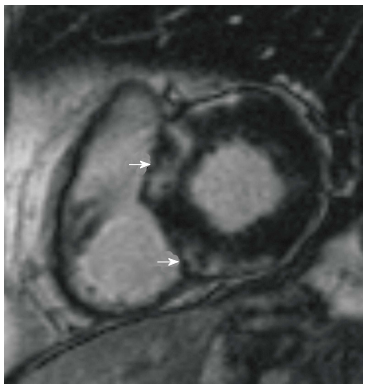

Figure 4 Sarcoidosis. Short axis delayed enhancement image shows patchy areas of mid myocardial enhancement in the basal septum and basal inferior segments.

The presence of LGE at CMR plays an important role in risk stratification and estimating prognosis in HCM. Several studies have demonstrated the independent predictive ability of the presence of LGE for cardiac outcomes including worsening heart failure symptoms, ventricular arrhythmias, ICD discharge, and sudden cardiac death[27-30]. Furthermore, the absence of LGE has shown to have useful negative predictive value in that the absence of LGE was associated with a lower, but not absent, risk for adverse cardiac outcomes[31]. However, unlike in dilated cardiomyopathy, several larger studies in HCM patients have noted that the extent of LGE, rather than its presence alone, is a significant predictor of adverse cardiac outcomes[31-34]. This observation may be in part due these larger studies being better powered to evaluate the full range of adverse outcomes. For example, a study by Ismail *et al*[35], the largest published to date evaluating CMR findings and clinical outcomes in over four hundred patients, demonstrated that only the extent of myocardial LGE was a strong predictor of cardiac events and mortality. However, contrary to other studies, LGE was not shown to be the strongest predictor (behind LVEF) of adverse events in this patient cohort.

To date, limited studies are available regarding the use of CMR in monitoring of treatment for hypertrophic HCM, whether pharmacologic, minimally invasive, or surgical. A study by Yuan *et al*[36] demonstrated the utility of CMR in characterizing the infarct size from septal ablations as well as decreased LV mass followed up to one year, although clinical outcome data was not included.

Although CMR remains an important modality in the diagnosis of hypertrophic cardiomyopathy, particularly in the setting of equivocal echocardiogram findings, it is yet to be formally recommended for all patients[37,38]. According to the most recent consensus AHA guidelines from 2011[37], the use of LGE with CMR for risk stratification received at a class Ⅱa recommendation and may be considered when risk stratification with conventional risk factors (*i.e.,* prior history of ventricular arrhythmias, family history of sudden cardiac death, and personal history of syncopal episode) are inconclusive.

Sarcoidosis

Cardiac sarcoidosis is characterized by the presence of nectrotizing granulomas in the myocardium. In the acute phase, myocardial thickening and edema may be seen. LGE is seen in a mid-myocardial (Figure 4) or sub-epicardial distribution. In chronic phase, wall thickening and LGE is seen, but edema is absent. In burnt out sarcoidosis, transmural enhancement may be seen[39].

The presence of LGE in sarcoidosis has been shown to be associated with adverse outcomes[40-42]. For example, Greulich *et al*[40] demonstrated that the presence of LGE as the strongest independent predictor death as well as other adverse events such as aborted sudden death, appropriate ICD discharge, and ventricular arrhythmias. The presence of LGE was also shown to be a stronger predictor of adverse outcomes relative to other functional and clinical parameters such as LVEF and clinical symptoms at presentation. Additionally, no included patients without LGE in this study died at the time of follow-up suggesting the potential high negative predictability of LGE in this patient population.

CMR has also been shown in several small studies to be effective in monitoring cardiac improvement in response to steroid therapy[42-44]. Overall, steroid therapy has been shown to be associated with not only improved functional parameters such as LVEF and LV end diastolic volume (EDV) index, but also decrease in LGE. However, data from Ise *et al*[42] suggest that CMR response to steroid therapy may depend on the extent of LGE upon treatment initiation. In the studied population, treated patients with a lower amount of LGE had significantly decreased LVEF and LV EDV after treatment. However, patients with more severe disease as indicated disease as evidenced by a larger extent of LGE were noted to not only have no significant change in LVEF or LV EDV, but also had worse clinical outcomes.

Similar to the assessment of dilated cardiomyopathy, current appropriate use guidelines from the AHA[3,45] still do not specifically recommend CMR exclusively for the purposes of risk stratification or prognostication with its use reserved for diagnosis and differentiation from other cardiomyopathies as well as functional assessment.

Myocarditis

Acute myocarditis seen in MRI as high signal in T2-weighted images and elevated values in T2 mapping due to myocardial edema, early gadolinium enhancement and LGE in a mid-myocardial or subepicardial distribution (Figure 5). Different patterns of enhancement have been described based on the etiological agent. Parvovirus B19 infection often involves the basal inferolateral segment, in a mid-myocardial/ subepicardial pattern and usually recovers without lasting damage, whereas human herpesvirus-6 more commonly involves the septum, in a linear mid-myocardial pattern and rapidly progresses to heart failure[46].

As in other cardiomyoapthies, the presence and per-

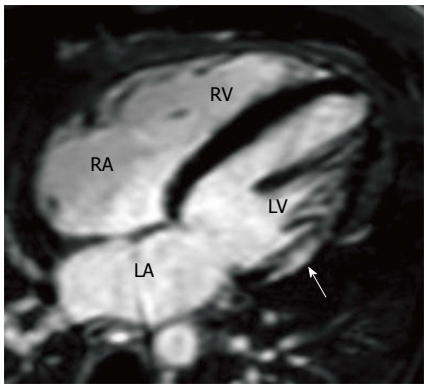

Figure 5 Myocarditis. Four-chamber delayed enhancement image shows mid myocardial enhancement in the basal lateral segment, consistent with acute myocarditis. RA: Right atrium; LA: Left atrium; RV: Right ventricular; LV: Left ventricular.

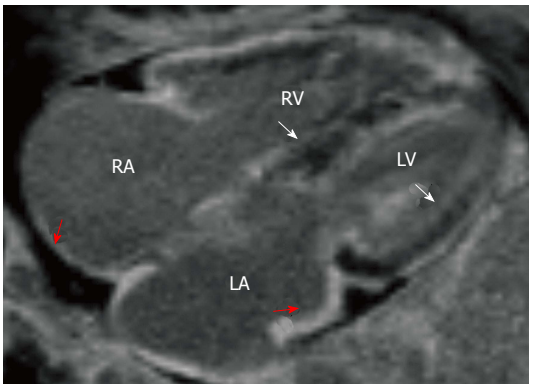

Figure 6 Amyloidosis. Four-chamber delayed enhancement image shows diffuse subendocardial enhancement of the ventricles (arrows) and atrial walls (red arrows). Note that the blood has lower signal than normal. RA: Right atrium; LA: Left atrium; RV: Right ventricular; LV: Left ventricular.

sistence of LGE in the setting the myocarditis reflects the presence of irreversible myocardial injury[47]. The presence, amount, and distribution of LGE at the time of diagnosis has shown to have important implication in cardiac functional parameters at follow-up after recovery from acute illness. For example, Mahrholdt *et al*[46] showed total amount of LGE (%LGE) was a significant independent predictor of impaired ventricular function and ventricular dilatation at follow-up. Additionally, the presence of LGE in the ventricular septum was shown to be the strongest CMR predictor for chronic ventricular dysfunction as well as ventricular dilatation.

CMR has shown promise in predicting clinical outcomes and adverse events in patients with myocarditis. Schumm *et al*[48] demonstrated that in the setting of suspected myocarditis, patients with abnormal CMR (defined at abnormalities in either LVEF, LV volume, or presence of LGE) had significantly more major adverse cardiac events including cardiac death, sudden cardiac death, ICD discharge, and aborted SCD. Additionally, no patients with a normal CMR suffered death or any major adverse cardiac events, suggesting a much more favorable recovery and long term course in patients with normal CMR findings. Similar to the other aforementioned non-ischemic cardiomyopathies, the presence of LGE on the diagnostic CMR was associated with increased of all-cause and cardiac mortality, independent of clinical presentation at diagnosis[49]. The absence of LGE was also associated with a more favorable clinical outcome with no sudden cardiac death events seen at a median follow-up of nearly five years in the study population.

Although typically regarded clinically as an acute, self-limiting illness[50], abnormal CMR findings may persist after the resolution of the acute phase of illness. Specifically, several studies have followed the presence of CMR abnormalities in various groups of myocarditis over their clinical course[46,51,52]. Specifically, LGE has been shown in anywhere between 24%-40% at the time of follow-up, with the relatively wide range of values likely reflective of heterogeneity of the studied patient populations[51].

Additionally, Wagner *et al*[53] showed in a small cohort of patients that the presence of CMR inflammatory markers at four weeks post-diagnosis was associated with poorer long-term LVEF and symptom score. Thus, given the impact of CMR findings at initial diagnosis on long-term cardiac functional parameters and clinical outcomes as well as potential prognostic implication of persistent abnormal CMR findings, a follow-up CMR exam at least 4 wk after the onset of disease can be considered to differentiate uncomplicated involvement of the myocardium in a systemic viral illness from a more complicated, persistent course[47].

Amyloidosis

Cardiac amyloidosis is characterized by diffuse subendocardial to transmural enhancement of not only the left ventricle, but also the right ventricle, interatrial septa and atrial walls (Figure 6). The T1 kinetics are altered, with the myocardium nulling before the blood pool (normal - the myocardium always nulls after the blood pull). The blood pool also appears darker on cardiac amyloidosis, due to high ECV and rapid redistribution of gadolinium from the blood pool. There is also concentric myocardial thickening, along with thickening of the interatrial septa and atrial walls.

Unlike many other non-ischemic cardiomyopathies, the use of LGE in risk stratification and evaluation of prognosis has seen mixed results. While several studies[54,55] have shown a significant association between the presence of LGE in cardiac amyloidosis patients after adjustment for other clinical parameters, data in other studies have not shown this trend. For example, Migrino *et al*[56] demonstrated a significantly higher one-year mortality rate for those patients with LGE, although LGE failed to remain predictive of mortality when observation carried out to five years. However, instead of presence or absence of LGE in amyloidosis patients, gadolinium kinetics may prove to be more useful in assessing prognosis. In a study by Maceira *et al*[57], presence of LGE in itself was not predictive of mortality; however, post-gadolinium intra-myocardial T1 difference between the subepicardial and subendocardial greater than 23 ms was instead shown to predict mortality

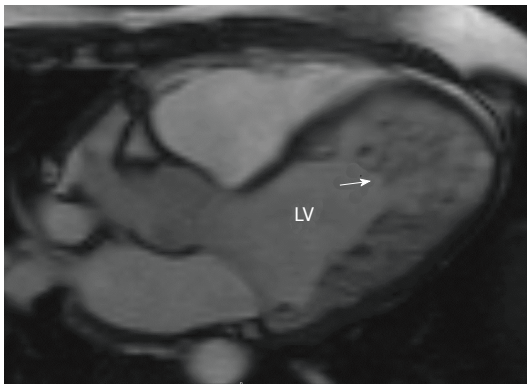

Figure 7 Left ventricular non compaction. Three-chamber steady state free precession image shows excessive trabeculations in the left ventricle, with the ratio of trabeculated to non trabeculated myocardium of 8, consistent with left ventricular non compaction. LV: Left ventricular.

with 85% accuracy. Lastly, as a modification of the more conventional CMR LGE analysis, White *et al*[58] showed that the presence of diffuse hyperenhancement by a visual T1 assessment is not only able to identify patients with cardiac involvement among patients with high clinical suspicion, but is also a strong predictor of mortality.

Additionally, the emerging techniques of T1 mapping and ECV estimation have shown promise in correlating with cardiac function and risk stratification[59,60]. For example, ECV measured at contrast equilibrium greater than 0.45 and pre-contrast T1 > 1044 ms have shown to be predictors of mortality. ECV was also shown to be predictive of mortality even when corrected for markers of ventricular function and serum proBNP values[59]. Furthermore, T2 weigted imaging has also shown prognostic implication in cardiac amyloidosis in that low T2 signal (*i.e.,* T2 ratio < 1.5) at triple-inverted fast spin echo imaging was associated with decreased survival[61].

In addition to its role in identifying cardiac involvement in amyloidosis, CMR has also shown promise in differentiating among subtypes of cardiac amyloidosis, namely between light chain amyloid (AL) and transthyretin-related amyloidosis (ATTR) based on parameters such as LV mass as well as location and extent of LGE. Distinguishing among cardiac amyloidosis subtypes is of critical importance given the marked difference of treatment strategies[62]. Additionally, cardiac amyloidosis subtype also impacts prognosis, with survival worse in AL as compared to ATTR subtype[62].

LV non-compaction

LV non-compaction is caused by persistence of embryonal sinusoids, resulting in an exaggerated presence of non-compacted myocardium compared to compacted myocardium. On MRI, a ratio of > 2.3 between non-compacted and compacted myocardium in end-diastole is considered diagnostic of non-compaction (Figure 7)[63]. Thrombosis, arrhythmia and LV dysfunction are complications.

The degree of LV non-compaction assessed at CMR has shown to correlate with not only cardiac function but risk assessment as well[64,65]. For example, Ashrith *et al*[64] showed that patients with a maximum non-compacted to compacted thickness ratio less than three were shown to have significantly greater improvement in NYHA functional class at follow up than those with ratio greater than three. Additionally, in patients with reduced LVEF, change in LVEF at follow up was also shown inversely correlated with non-compaction-compaction ratio. Furthermore, data from Stacey *et al*[65] suggest that measurement of non-compaction to compacted ratio measured at end-systole had a higher calculated higher odds ratio for combined cardiovascular events, including death than calculated at end-diastole.

Assessment of late gadolinium enhancement, both trabecular and myocardial, has also shown value in the clinical assessment of LV non-compaction[64,66-68]. The degree of trabecular LGE has shown to be an independent predictor of LVEF as well as correlate with severity of clinical stage of disease[66]. Additionally, both the presence and extent of myocardial LGE were shown to be significantly related to symptomatic status and electrocardiographic abnormalities as well as a significant predictor of LVEF, suggesting non-compaction as a marker of an underlying diffuse cardiomyopathy[67].

Arrhythmogenic right ventricular dysplasia/ cardiomyopathy

Arrhythmogenic right ventricular dysplasia/cardiomyopathy (ARVD/C) is characterized by fibrofatty replacement of the right ventricular myocardium. The diagnosis is based on Task Force criteria. On MRI, the presence of a major wall motion abnormality (aneurysm, akinesis, dyskinesis, asynchronous contraction) along with either low ejection fraction (EF) (< 40%) or dilated RV (EDVi > 110 mL/m^2 in men, > 100 mL/m^2 in women) is considered a major criteria (Figure 8). Major wall motion abnormality along with low EF (40%-45%) or dilated RV (EDVi 100-110 mL/m^2 in men, 90-100 mL/m^2 in women) is considered minor criteria. Other criteria include family history, tissue characterization, repolarization, depoloraization and arrhythmia. Two major or one major and two minor or four minor criteria are required for a diagnosis of ARVD. Fat may be seen in the RV myocardium, but this is not critical for diagnosis. LGE may be seen in the RV free wall. Furthermore, if myocardial biopsy is warranted to help confirm the diagnosis of ARVD, CMR findings can be used to help select an appropriate target for biopsy[69].

In the setting of clinically diagnosed ARVD, the presence of abnormalities at CMR has been shown to be associated with adverse cardiac outcomes[70-72]. Patients with right ventricular abnormalities at CMR experienced higher rates of cardiac death, ICD discharge, and ventricular arrhythmias. Furthermore, the presence of multiple abnormalities at CMR was shown to carry a higher clinical risk, while a normal CMR in patients meeting clinical criteria for ARVC was associated with a significantly better prognosis[70].

Although LGE assessment in the right ventricle can

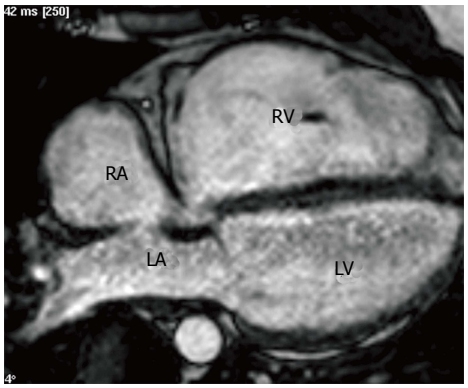

Figure 8 Arrhythmogenic right ventricular dysplasia. Four-chamber cine steady state free precession image shows wall shows aneurysmal dilation of the right ventricle. There was also low ejection fraction (ejection fraction-35%) and severe right ventricle dilation (end diastolic volume index-130 mL/m^2). These magnetic resonance imaging features satisfy one major criterion for arrhythmogenic right ventricular dysplasia. RA: Right atrium; LA: Left atrium; RV: Right ventricular; LV: Left ventricular.

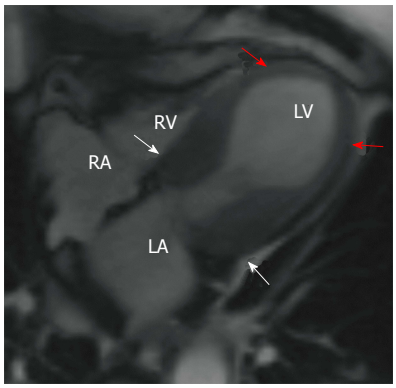

Figure 9 Takotsubo cardiomyopathy. Four-chamber cine steady state free precession image shows classical appearances of Takotsubo cardiomyopathy, with hyperkinesis of the basal segments (arrows) and akinesis of the apical segments (red arrows), which resembles a Japanese octopus pot. RA: Right atrium; LA: Left atrium; RV: Right ventricular; LV: Left ventricular.

be somewhat limited as compared to that within the left ventricle[73], LGE has shown to be useful in risk stratification in ARVD patients. In patients meeting diagnostic criteria for ARVD, up to 88% of patients demonstrated areas of LGE at CMR[74]. The presence of LGE has also shown to play a role in ARVD risk assessment with right ventricular LGE predicting the induction of ventricular tachycardia at electrophysiological testing[75].

Despite the emphasis placed on right ventricular findings, LV changes are also frequently seen in the setting of ARVD with CMR allowing assessment of LV changes not seen at other modalities[76]. Additionally, LV changes may also be more pronounced than those seen within the right ventricle ("left-dominant" disease). LV involvement at CMR was associated with a higher prevalence of ventricular arrhythmias, even in the setting of normal right ventricular size and function[76,77].

Lastly, CMR is an emerging as a tool in guiding ablation therapies in ARVD patients. For example, in a recent study by Wijnmaalen *et al*[78] CMR has been proposed as a useful adjunct in combination with voltage mapping in guidance of techniques in providing a potential roadmap for myocardial ablation. Specifically, CMR was shown to identify areas of non-transmural scar and infarct grey zones not detected by traditional voltage mapping.

Stress-induced (Takotsubo) cardiomyopathy

Stress-induced cardiomyopathy is classically seen on MRI as decreased global systolic function and abnormal wall motion of the apical segments with normal/hyperkinetic basal segments (Figure 9). There may be myocardial edema, but LGE is not typically seen. Variants include a reverse Takotsubo cardiomyopathy, with akinesis of the basal segments and hyperkinesis of the apical segments. These functional abnormalities are transient and recover with treatment of cardiac failure.

Takotsubo variants can readily be distinguished at CMR[79]. Accurate characterization of the particular segmental involvement is important as certain variants, namely typical and mid-ventricular types, have been associated worse worsened LV function[80]. Furthermore, CMR can readily detect associated valvular complications such as mitral regurgitation, which can complicate certain takotsubo subtypes[79]. Additionally, CMR can more easily detect right ventricular involvement, which can be seen in approximately one-third of cases[79]. Detection of right ventricular involvement, if present, has been associated with longer hospitalization and worse LV function[81].

While not a prominent feature in Takotsubo cardiomyopathy, LGE can be present to varying degrees, as shown in several small studies[82-85]. However, its implications for adverse events and recovery are mixed. For example, a pair of studies[82,83] showed that the presence of LGE on CMR performed in the acute or subacute phase (*i.e.,* within one week of presentation) was associated with increased risk of cardiogenic shock, longer duration for ECG normalization, and longer duration of wall motion abnormality recovery. Conversely, multiple studies[84,85] have shown no association with worsened LVEF or development of adverse outcomes as compared to patients without LGE.

Fabry disease

Fabry disease is seen on MRI as concentric LV thickening (Figure 10), which is not infrequently confused with HCM. There may be mid myocardial or subepicardial pattern of LGE, typically in the basal inferolateral segment[86].

The presence of LGE in Fabry's patients has shown to be associated with development of ventricular arrhythmias as well as sudden cardiac death[87]. However, a patient's annual increase in fibrosis as determined of LGE findings, rather than presence or absence of LGE, was the only independent predictor ventricular arrhythmias. Additionally, CMR findings of fibrosis were found to poorly correlate with blood serum markers of fibrosis[87]. T1 mapping techniques have also been applied to the characterization of Fabry's cardiomyopathy. Prior to the onset of LV hypertrophy, reduction in T1 values was associated with reduced longitudinal strain as well as early

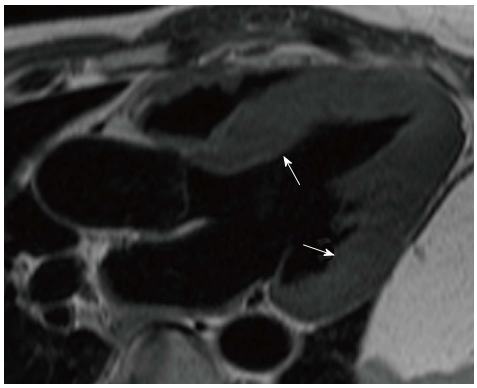

Figure 10 Fabry disease. Three-chamber black blood image shows moderate to severe concentric hypertrophy in a patient with Fabry's disease.

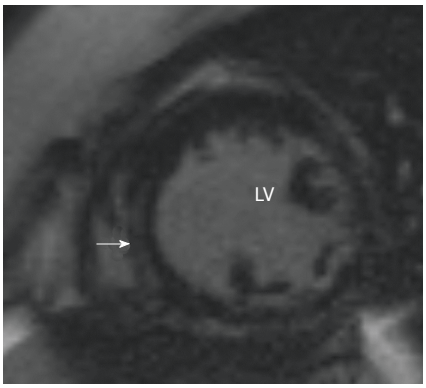

Figure 11 Duchenne muscular dystrophy. Short-axis delayed enhancement image shows dilated left ventricle, with mid myocardial septal enhancement (arrow) in a patient with Duchenne muscular dystrophy. LV: Left ventricular.

diastolic dysfunction, suggesting that T1 mapping may be useful in detecting early systolic and diastolic dysfunction before onset of cardiac structural abnormalities[88].

CMR has also been used in monitoring cardiac treatment response to enzyme replacement therapies[87,89-91]. While no significant changes in LVEF were seen at follow-up, reductions in LV mass at CMR with corresponding improvement in symptoms were noted[89-91]. Furthermore, a study by Krämer *et al*[87] showed that of a limited number of patients who underwent enzyme replacement therapy, LGE actually progressed despite therapy suggesting that patients undergoing treatment are still prone to developing worsening fibrosis. However, no clinical outcomes at follow-up were noted for these patients.

Muscular dystrophy

On MRI, muscular dystrophy may present with ventricular dilation, systolic dysfunction and mid myocardial/sub-epicardial pattern of LGE (Figure 11).

The significance of the presence of LGE with arrhythmic events has shown mixed results. While a pair of studies[92,93] have demonstrated significant association between LGE and the development of arrhythmias, Tandon *et al*[94] demonstrated no significant increased risk in arrhythmia seen in patients with at least one LGE-positive segments. Additionally, in the same study, greater number of LGE positive cardiac segments was predictive of decreases in LVEF, while decreases in LVEF were not seen at follow-up in patients without LGE. T1 mapping and ECV estimation have also been evaluated in muscular dystrophy. Calculated global ECV have been shown to correlate to LVEF and to the number of LGE-positive segments with global ECV significantly associated with occurrence of arrhythmic events[93]. Lastly, myocardial strain analysis has also been applied in this patient population with several studies[95,96] demonstrating that changes in myocardial strain precede changes in LVEF. However, data regarding association with clinical outcomes is lacking.

Limited data is available regarding CMR changes in response to steroid therapy. In a single study[94], longer steroid treatment durations were associated with lower age-related increases in LGE-positive segments, although its impact on clinical outcome is unknown.

Limitation of CMR

Although CMR has been shown to be a powerful tool in diagnosis and clinical assessment and offers a number of distinct advantages over other modalities, certain limitations and challenges are still present. Specific areas in which data is still lacking or contradictory for particular clinical outcomes was discussed in greater detail in the preceding sections. As a whole, although data on the utility of CMR has grown substantially, formal recommendations regarding the specific use of CMR in various clinical settings is lacking for most non-ischemic cardiomyopathies, which may limit its utilization. Furthermore, various technical and logistical aspects of CMR may also limit its usefulness. General contraindications to MRI such as the presence of metallic devices, particularly pacemakers and implantable defibrillators, may limit the usefulness in some cardiac patients. Furthermore, due to the risk of nephrogenic systemic fibrosis, the use gadolinium-based contrast agents, and therefore the assessment of LGE, is limited in patients with renal disease. Lastly, other factors such as the lack of widespread availability and intensive post-processing may further limit the use of CMR in some settings.

CONCLUSION

MRI is a valuable tool in the evaluation of non-ischemic cardiomyopathies, not only in the diagnosis, but also in risk stratification and prognostic determination. The results of several large scale studies show that there is a good correlation between MRI findings and clinical outcomes, which demonstrate the impact of cardiac MRI on the management of these patients.

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REVIEW

Mechanical dyssynchrony and deformation imaging in patients with functional mitral regurgitation

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Abstract

Chronic functional mitral regurgitation (FMR) is a frequent finding of ischemic heart disease and dilated cardiomyopathy (DCM), associated with unfavourable prognosis. Several pathophysiologic mechanisms are involved in FMR, such as annular dilatation and dysfunction, left ventricle (LV) remodeling, dysfunction and dyssynchrony, papillary muscles displacement and dyssynchrony. The best therapeutic choice for FMR is still debated. When optimal medical treatment has already been set, a further option for cardiac resynchronization therapy (CRT) and/or surgical correction should be considered. CRT is able to contrast most of the pathophysiologic determinants of FMR by minimizing LV dyssynchrony through different mechanisms: Increasing closing forces, reducing tethering forces, reshaping annular geometry and function, correcting diastolic MR. Deformation imaging in terms of two-dimensional speckle tracking has been validated for LV dyssynchrony assessment. Radial speckle tracking and three-dimensional strain analysis appear to be the best methods to quantify intraventricular delay and to predict CRT-responders. Speckle-tracking echocardiography in patients with mitral valve regurgitation has been usually proposed for the assessment of LV and left atrial function. However it has also revealed a fundamental role of intraventricular dyssynchrony in determining FMR especially in DCM, rather than in ischemic cardiomyopathy in which MR severity seems to be more related to mitral valve deformation indexes. Furthermore speckle tracking allows the assessment of papillary muscle dyssynchrony. Therefore this technique can help to identify optimal candidates to CRT that will probably demonstrate a reduction in FMR degree and thus will experience a better outcome.

Key words: Mitral regurgitation; Deformation imaging; 3D echocardiography; Mechanical dyssynchrony; Speckle tracking

Core tip: The epidemiologic and prognostic impact

of chronic functional mitral regurgitation (FMR) is fully acknowledged. Multiple factors are involved in the pathophysiology of FMR, such as mitral valve remodeling, left ventricle (LV) remodeling and mechanical dyssynchrony. Deformation imaging by 2 dimensional speckle tracking and 3 dimensional echocardiography are the echocardiographic techniques currently used to better characterize LV dyssynchrony. Pharmacologic and cardiac resynchronization therapy is the first line-therapeutic approach to treat FMR. In case of failure of this first therapeutic approach, surgery and percutaneous treatment in high risk patients represent an alternative option.

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INTRODUCTION

Chronic functional mitral regurgitation (FMR) is a frequent complication of ischemic heart disease or less frequently dilated cardiomyopathy (DCM), following left ventricular (LV) dysfunction and remodeling. Various degrees of severity of FMR are commonly described in patients with LV dysfunction despite a structurally normal valve. Indeed, according to Carpentier's functional classification, FMR can be due to dilated mitral annulus (type Ⅰ) or more often to a systolic restriction of leaflet motion (type Ⅲb).

The exact occurrence of FMR is difficult to assess because of different diagnostic approaches and timing of evaluation. The prevalence of FMR is nevertheless considerable, varying from 20% to 50% after myocardial infarction (MI) as assessed by echocardiographic studies[1]. This has been further confirmed by recent studies assessing long-term outcome of patients affected by heart failure associated with FMR treated with standard medical therapy[2].

Both ischemic and non-ischemic FMR are related to an unfavourable outcome in DCM[3,4], independently of the degree of ventricular dysfunction. Additionally the degree of FMR relates directly to the mortality and heart failure events. Actually, FMR is related to a decreased survival rate even if of mild degree, as MR severity positively correlates to increased mortality. An effective regurgitant orifice area > 20 mm^2 has been shown to double all-cause mortality and the risk of admission for acute decompensated heart failure. Furthermore, the presence of even moderate MR increased the risk of heart failure and death by more than 3-fold and 2-fold at 5 years respectively[5].

PATHOPHYSIOLOGY

Several pathophysiologic mechanisms are involved in determining FMR. Kaul *et al*[6] speculated that MR resulted from global LV dysfunction, rejecting the role of dysfunction of papillary muscles and the adjacent LV myocardium in determining FMR. Further studies failed to demonstrate that LV systolic dysfunction in the absence of LV dilatation and remodeling produced significant MR, whereas leaflets tethering was the only independent predictor of MR and LV sphericity was correlated to MR grade. Certainly an imbalance between closing and tethering forces is responsible for FMR due to LV dilatation and reduction of contractility, global LV dyssynchrony, papillary muscles displacement and dyssynchrony, altered systolic mitral annular contraction[7].

Tethering is the principal determinant of FMR, because of LV remodeling associated to apical and posterior papillary muscle displacement, that lead to a reduction in closing forces.

Depending on the type of global or local LV remodeling, two tethering patterns have been described[6]: The asymmetric and symmetric ones, depending on mitral leaflets position and their point of coaptation[8] (Figure 1).

The asymmetric pattern is caused by an an asymmetrical shift of the posterior papillary muscle, determining a greater tenting of the posterior leaflet compared to the anterior one. Papillary muscle tethers the body of the anterior leaflet generating a "hockey stick" or "bent knee" configuration (Figure 1A and B). MV coaptation point is moved posteriorly and the anterior leaflet coapts creating a "pseudo-prolapse" appearance. The associated MR jet is typically eccentric, directed posteriorly in the left atrium (LA). Conversely in the symmetric pattern MV leaflet coaptation point is displaced towards the apex and both leaflets are tethered, generating a typically central MR jet (Figure 1C and D). This usually occurs in the context of a large anterior myocardial infarction, multiple infarcted area or idiopathic DCM.

Chronic FMR cause progressive LV dilation and papillary muscles displacement, leading to a further increase of tethering forces acting on mitral leaflets and, therefore, to a worsening of MR in vicious cycle.

Also conduction abnormalities, caused either by right ventricular pacing or bundle branch block, predispose to FMR. In fact the presence of intraventricular conduction determines mechanical dyssynchrony and mitral valve deformation[9].

Cardiac mechanical dyssynchrony can be distinguished in atrioventricular, inter- and intraventricular. Prolongation of the atrioventricular conduction time delays systolic ventricular contraction, hampering early diastolic filling when atrial suddenly decrease. Accordingly LV diastolic pressure exceeds atrial pressure causing diastolic mitral regurgitation. The reduction in LV preload determines a decrease in its contractility, according to Starling law.

As for inter- and intraventricular dyssynchrony, the former refers to delayed activation of LV relative to the right one, whereas the latter indicates differences in the timing of contraction of distinct myocardial segments. Both types of conduction delays cause an asynchronous

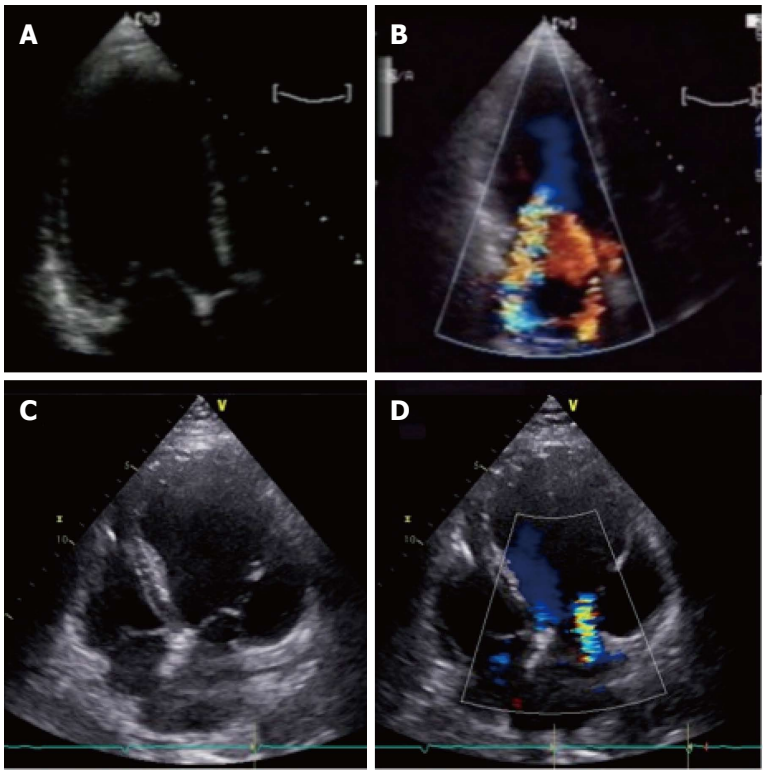

Figure 1 Asymmetric and symmetric tethering pattern. A, B:: Asymmetric tethering pattern. Typical "hockey stick" or "bent knee" configuration. MV coaptation point is moved posteriorly and the anterior leaflet coapts creating a "pseudo-prolapse" appearance with a large regurgitant jet oriented along the posterior wall of the left atrium; C: Symmetric tethering pattern. Both leaflets are apically dislocated and coapt at the same level into the ventricle; D: Color-Doppler shows large central jet.

contraction of LV wall (ventricular dyssynchrony), reducing stroke volume.

Mauer *et al*[10] first proved that significant differences in MR existed depending on the site of cardiac pacing. In particular they demonstrated in dogs that artificial stimulation through a right ventricular apical pacemaker generated a severe MR compared to a basal LV pacing within the coronary sinus.

Mechanical dyssynchrony may contribute to FMR as follows. First a decrease in MV closing forces can be determined by LV global dyssynchrony that may decrease the efficacy of LV systolic contraction[11,12]. Secondly, a geometric distortion of mitral valve apparatus may be induced by dyssynchronous contraction of the papillary muscle insertion sites[13]. Third, impaired leaflet coaptation can be enhanced by dyssynchronous contraction of LV basal segments, that may cause a papillary muscles asynchronous contraction[14] (Figure 2). The prolonged QRS duration correlates with both FMR severity and duration in patients with DCM[15,16]. Supporting this, several studies have shown that one of the positive effects of cardiac resynchronization therapy (CRT) is a decrease in FMR grade[17-20]. Soyama *et al*[21] analysed 32 patients affected by DCM with Tissue Doppler echocardiography showing that a dyssynchronous activation of myocardial segments adjacent to the papillary muscles could cause MR determining a non-synchronized closure of mitral leaflets. Donal *et al*[22] reported that MR in patients with DCM is a multifactorial and complex phenomenon, thus its accurate description should take into account LV contraction abnormalities and dyssynchrony, LV geometry and mitral orifice.

Considering LV reverse remodeling after CRT, certainly the changes in MV apparatus influence the improvement of FMR. Konstantinou *et al*[23] studied FMR secondary to ischemic (n = 55) and non-ischemic DCM (n = 48) and found that FMR severity is mainly determined by the degree of mitral apparatus distortion; furthermore the authors found that in these patients, a quick estimation of FMR severity could be obtained observing coaptation height. Finally, additional determinants of FMR included the presence of global LV dyssynchrony and reduced myocardial systolic velocities of the posteromedial papillary muscle insertion site.

FMR is a dynamic condition, changing dramatically with loading conditions, because of phasic fluctuations in the balance between tethering and closing forces. The increase in afterload (*i.e.*, hypertension, exercise) worsens MR, further deforming the infarcted papillary muscles bearing segments because they promptly deforms in response to increased intraventricular pressure. On the contrary diuretic therapy, afterload decrease by vasodilators or general anaesthesia reduce FMR severity. FMR is therefore a dynamic lesion, varying through the cardiac cycle, as the regurgitant volume is greater in the early and late systolic phases, lower in the mid systole, having a beat to beat variation[24]. In addition, Ennezat *et al*[25] showed that rest LV dyssynchrony is associated with worsening of FMR during exertion. In this study, 20% of patients with significant LV dyssynchrony developed an exercise-induced EROA increase, whereas the rest did not have a decrease in mitral EROA during exercise[25].

DEFORMATION IMAGING

Myocardial deformation imaging is a novel echocardiographic

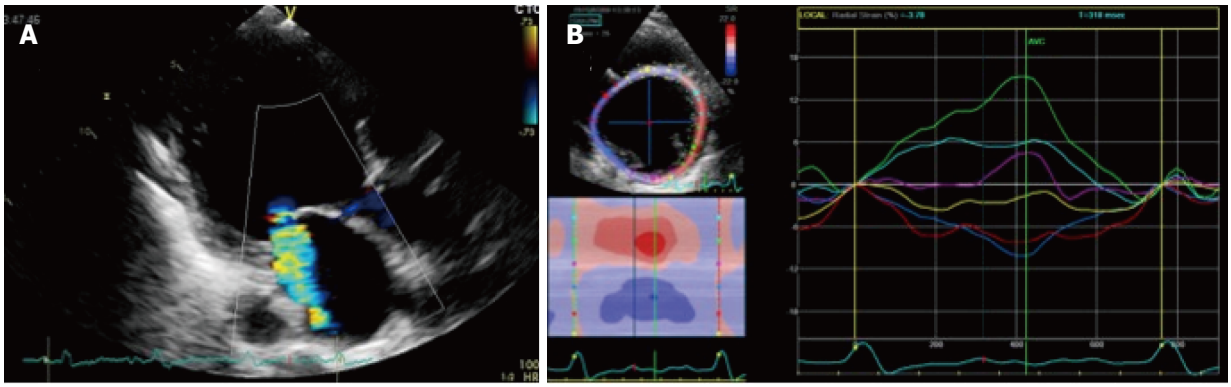

Figure 2 Impaired leaflet coaptation can be enhanced by dyssynchronous contraction of left ventricle basal segments, that may cause a papillary muscles asynchronous contraction. A: 2D radial strain of a papillary muscles short axis in a patient with functional MR; B: During systole, myocardial segments adjacent to postero-medial papillary muscles (red and blue segments) show negative radial strain values, whereas antero-lateral papillary muscles (light blue and green segments) show a positive strain values, resulting in a significant papillary dyssynchrony. 2D: 2 dimensional; MR: Magnetic resonance.

tool that can be used to evaluate global and regional myocardial function.

The evaluation of contractile function with echocardiography has traditionally been limited to volume-based assessment of global systolic function with ejection fraction (EF) and of segmental wall motion or visual estimation of regional thickening. These methods have suffered from lack of reproducibility and standardization and are generally considered to be extremely sensitive to loading conditions. These limitations have led to an interest in techniques that provide more objective and reproducible measures of contractile function.

During systolic phase, ventricular myocardium shortens in the longitudinal and circumferential planes, while getting thicker in the radial plane. Deformation imaging allows for a more direct evaluation of myocardial changes through the cardiac cycle by speckle tracking analysis.

Myocardial deformation imaging with echocardiography can be performed with the use of either tissue Doppler-based or 2-dimensional (2D) speckle tracking-based methods. Doppler methods suffer from limitations similar to those of traditional Doppler because it can only accurately assess deformation in the plane incident with the ultrasound beam and requires prospective acquisition of dedicated images at high frame rate.

Speckle tracking analysis is obtained assessing the spatial dislocation (tracking) of speckles (spots created by the interplay between ultrasounds and myocardial fibers) on bidimensional echo. This tool offers the advantage of an objective quantitative assessment of regional and global myocardial function, not affected by insonation angle, cardiac translational movements[26-28], with a good interobserver and intraobserver reproducibility, because of its semi-automated feature[29]. Furthermore, although initially proposed only for the LV functional assessment, many authors have showed its utility for the evaluation of other cardiac structures, in particular of the LA. A recent comparison between speckle tracking derived measures and jagged MRI showed feasibility and reproducibility of this echocardiographic tool[30].

Speckle tracking analysis evaluates strain, that can be described as the systolic change in length of a myocardial segment relatively to its length at rest, so expressed as a percentage. Strain rate is also calculated as the rate of this deformation[31].

This technique has some limitations, based on the need of a good definition of the endocardial borders, therefore being highly dependent on the quality of 2D images and frame rate.

Myocardial strain can be assessed in four principal planes of deformation: Radial strain (myocardial thickening) and circumferential strain (myocardial shortening) from short-axis views; transverse (myocardial thickening) and longitudinal strains (myocardial shortening) assessed from apical views. Furthermore, speckle tracking analysis allows a complete characterization of LV rotation (occurrence, direction and velocity) during cardiac cycle[32].

Longitudinal strain describes the systolic myocardial fibers shortening from the base to the apex. This deformation is expressed in negative trend curves, obtained analysing the myocardial shortening in apical 4-chamber, 2-chamber and long axis view (Figure 3). Both regional, so for each of the 17 LV myocardial segments, and global values are computed. Global longitudinal strain value has been shown to be a quantitative index of LV systolic performance[33]. Longitudinal strain can also be applied to LA[34] and right ventricle (RV) analysis strain[35], respectively assessing the peak atrial longitudinal strain and RV longitudinal strain values.

Radial strain describes myocardial deformation directed radially towards the centre of LV cavity, represented by systolic thickening and diastolic thinning (Figure 4). Therefore, during the systolic phase radial strain curve will have positive values. Radial strain can be obtained through the analysis of parasternal short axis view, both from the basal and the apical cut[36].

Circumferential strain is also obtained from speckle tracking analysis of the parasternal short axis view[37]. It represents the LV myocardial systolic shortening along its circumference and is expressed by systolic negative curves (Figure 5). A global circumferential strain value can also be calculated.

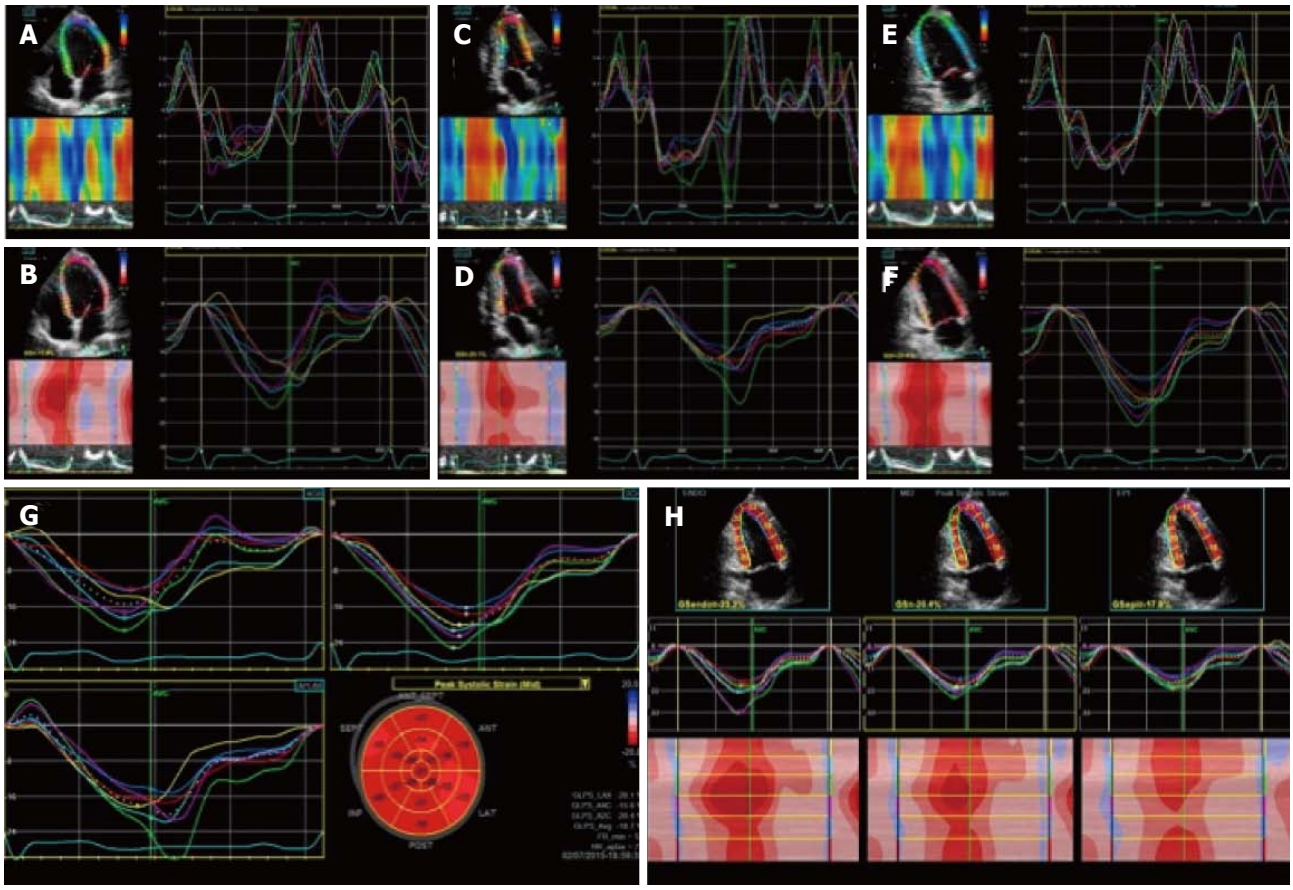

Figure 3 Two dimensional longitudinal strain. 2D longitudinal strain rate (A, C, E) and strain (B, D, F) analysis. Longitudinal strain is obtained from the 3 LV apical views (4C view, 2C view and 3C view). Strain values are then displayed in a bulls eye reconstruction (G). Longitudinal strain values for endocardium, mesocardium and epicardium can also be obtained (H). LV: Left ventricle; 2D: 2 dimensional.

Finally LV twisting[37], a fundamental component of LV systolic contraction, can be can be studied with speckle tracking analysis in terms of systolic reciprocal rotation of LV base and apex. LV twisting is computed as the difference between the mean rotation of the basal and the apical levels respectively, that can be the normalized for the apex-to-base distance, obtaining a "LV torsion" value[38].

Speckle tracking allows an early identification of global and segmental myocardial dysfunction, analysing the percentage of myocardial deformation that reflects the changes occurring in myocardial ultrastructure. Therefore lots of potential clinical application of this technique can be proposed, including the possibility to detect LV subclinical systolic impairment, if an alteration of longitudinal strain is discovered, for example in the setting of diabetes, coronary artery disease or valvulopathies. Several authors contributed to confirm this clinical application. Choi *et al*[39] studied asymptomatic patients without wall abnormalities and found that the presence of lower longitudinal strain values was a strong predictor of stable ischemic disease. Recently Voight *et al*[40] identified post systolic motion, after aortic valve closure, as a significant quantitative marker of the ischaemic myocardium. Further, it has been showed that with New York Heart Association (NYHA) functional class worsening from I to IV, progressively lower longitudinal strain values are observed in HF patients; in addition, in NYHA class Ⅲ and Ⅳ, a systolic impairment of LV circumferential and radial strain become evident[41,42]. Stanton *et al*[43] studied HF patients with low EF and found global circumferential strain to be a strong predictor of cardiovascular adverse events. Furthermore, global longitudinal strain was also found to be a stronger predictor of outcome than EF in Mele *et al*[44] study. In low EF patients with indication to CRT, strain parameters have recently been shown to identify CRT responders with good reproducibility and accuracy[45]. In particular, dyssynchrony analysis by radial strain has been shown to effectively predict CRT efficacy[46,47].

Three-dimensional speckle tracking echocardiography (3D-STE) is the newest tool among deformation imaging and dyssynchrony analysis[48,49]. Differently from 2D speckle tracking, that analyses only a single plane and may oversimplify the complexities of LV mechanics, 3D speckle tracking takes advantage of pyramidal and strain data that include the whole LV, acquired with a matrix arrays transducer, therefore tracking speckles moving through a 3D space (Figure 6).

Acquisition of a full-volume dataset requires smaller wedge-shaped sub-volumes from at least four consecutive heart beats (asking the patient to hold the breath),

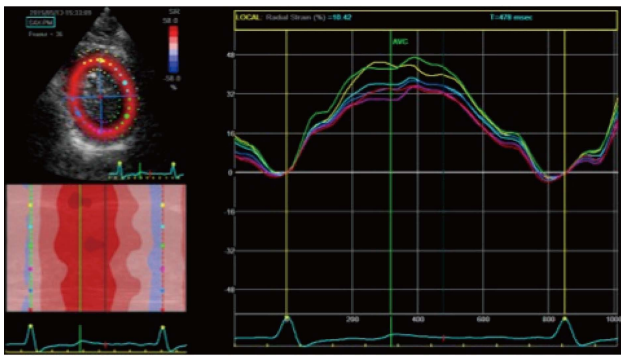

Figure 4 Radial strain analysis with 2 dimensional speckle tracking. Synchronous strain pattern in a normal patient. During systole, radial strain values are represented by positive curves.

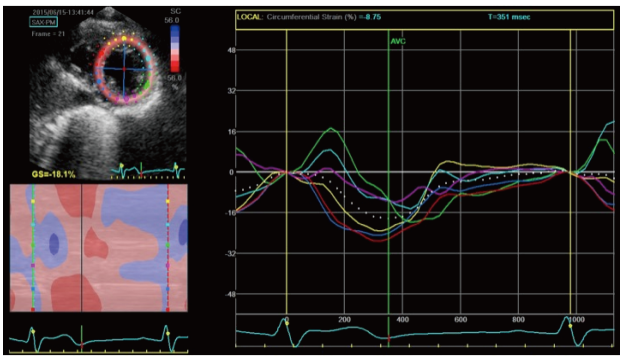

Figure 5 Two dimensional circumferential strain in a normal patient. It represents left ventricle myocardial fiber shortening along the circular perimeter on a short-axis view and during systole, it is represented by synchronous negative curves.

automatically combined in a single larger pyramidal volume. 3D datasets are displayed in different cross-sections including standard three short-axis views and apical four- and two-chamber views that could be modified interactively. Regions of interest are placed on the endocardium and epicardium from apical views, and the software automatically divides data into 16 standard segments to generate corresponding time-strain curves[50]. 3D-STE offers the advantage of simultaneously calculating radial, circumferential and longitudinal strain values in the whole LV myocardium. Furthermore, 3D-STE could help in selection of patients who may be CRT responders as it offers an accurate mechanical dyssynchrony map, and potentially it could guide the electrophysiologists during CRT implantation, precisely localizing the site of latest myocardial activation.

ROLE OF DEFORMATION IMAGING IN MITRAL VALVE DISEASE

STE in patients with mitral valve disease has been usually performed for LV and LA functional assessment. Asymptomatic patients with severe organic MR might develop latent LV systolic impairment even if EF appears to be normal. In asymptomatic patients affected by severe MR, preoperative evidence of LV dysfunction is associated with post-operative lower long term survival and worsening of systolic function. In fact, these patients usually have lower post-operative EF, higher incidence of heart failure and mortality, as compared to patients with severe MR without LV impairment before surgery[51]. Agricola *et al*[52] studied patients with MR and normal EF using TDI of the mitral annulus. They found out that longitudinal function can be altered despite normal EF and that systolic TDI value can predict post-operative LV impairment. Thus TDI has been proposed as a simple, available and immediate method to early recognize LV dysfunction due to volume overload in patients with significant MR. More recently, Lancellotti *et al*[53] underlined that limited exercise increase of global longitudinal strain in patients with degenerative MR, candidates to cardiac surgery, predicted post-operative LV dysfunction development.

Moonen *et al*[54] studied patients with MR and matched healthy controls using longitudinal strain analysis with 2D speckle tracking, both at rest and during exercise. At rest global longitudinal strain was significantly lower in MR patients. During exercise, a lower increase of this value was observed in MR patients compared to control group. In addition, up a small increase of global longitudinal strain at peak exercise was shown to be a predictor LV dysfunction during follow up[54].

MR generally progresses insidiously. Patients can be asymptomatic for a long time and, as the heart compensate to the regurgitant volume with LA enlargement, interpretation of LV EF can be challenging in presence of significant MR. Later, chronic volume overload will progressive LV dysfunction, subsequently worsening outcome.

Left atrial remodeling and dilation is associated with myocardiocyte hypertrophy and interstitial fibrosis, bringing with it the risk of atrial fibrillation (AF)[55]. Furthermore, the presence of LA remodeling predicts cardiovascular events, in particular stroke, death and heart failure. Transthoracic echocardiography permits only the evaluation of LA dimensions LA that has prognostic implication[56]. However the study of regional LA function may add information about atrial electromechanical remodeling, being useful for prognostic stratification, AF risk and management[55].

LA longitudinal deformation dynamics can be assessed by speckle tracking analysis. Peak atrial longitudinal strain allows the quantification of the reservoir phase of LA, that depends on atrial compliance. In fact, during this phase, LA longitudinal strain increases, reaching a peak at the end of LA filling, just before mitral valve opening (Figure 7). Cameli *et al*[57] demonstrated an inverse correlation between global peak longitudinal strain (PALS) and MR degree, as lower values of PALS were observed in patients with moderate and severe MR, compared to patients with mild MR. In this study, LA myocardial reservoir function impairment was associated with an higher incidence of

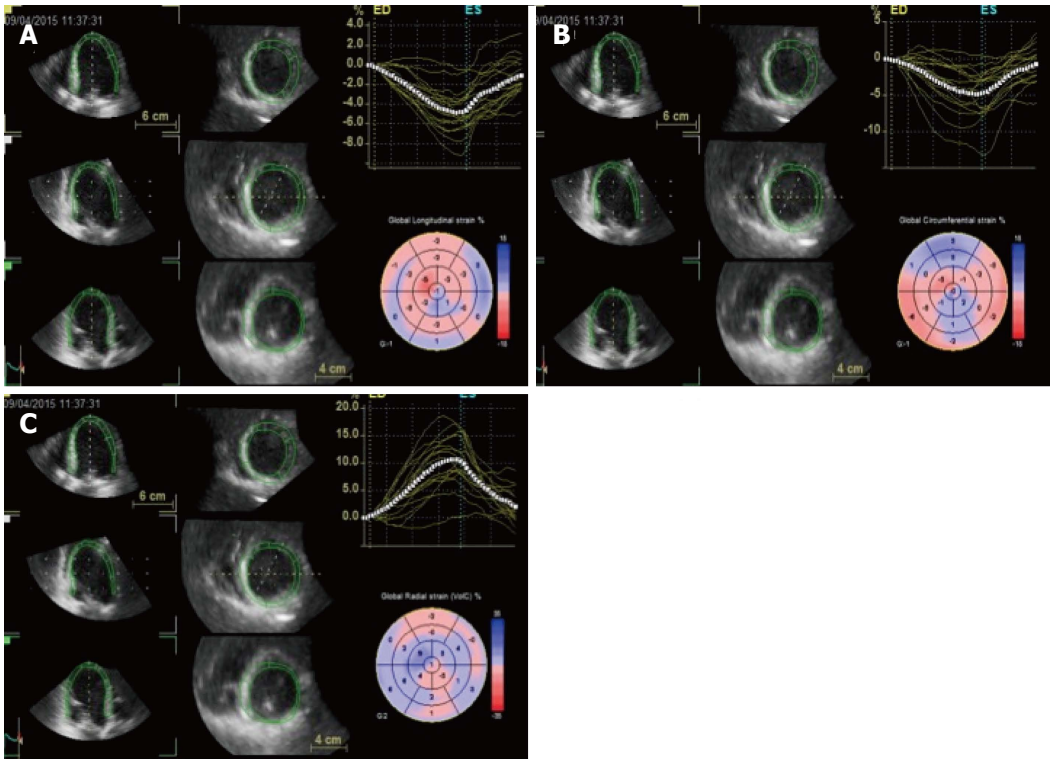

Figure 6 Three dimensional speckle tracking: data sets are displayed in different cross-sections including standard three short-axis views and apical four- and two-chamber views. The software automatically divides data into 16 standard segments to generate corresponding time–strain curves. Wall motion parameters are simultaneously displayed in particular, the 3 orthogonal strain values (longitudinal strain in A, circumferential strain in B and radial strain in C).

paroxysmal AF.

DEFORMATION IMAGING IN THE EVALUATION OF MECHANICAL DYSSYNCHRONY

Mechanical dyssynchrony can be assessed using different imaging modalities: Conventional M-Mode, Doppler echocardiography, tissue Doppler imaging (TDI) and newer modalities such as strain rate imaging (SRI) and 3D STE.

Echocardiographic evaluation of mechanical dyssynchrony has been of great interest for the identification of potential responders to CRT. Even though the largest body of publications on LV dyssynchrony and CRT response prediction is based on TDI[58,59]. However, in the PROSPECT (Predictors of Responders to Cardiac Resynchronization Therapy) trial time to peak time-to-peak dyssynchrony evaluation did not have enough predictive value to replace standard selection criteria for resynchronization therapy[60]. Also pulsed-Doppler evaluation of interventricular dyssynchrony may predict the response to CRT, but more solid evidence supports intraventricular dyssynchrony assessment by speckle tracking as a mean to identify CRT responder.

LV dyssynchrony study by speckle tracking was firstly proposed by Suffoletto *et al*[61]. In this study radial strain dyssynchrony analysis was performed in a cohort of 50 HF patients with standard indications to CRT. The authors found the presence of baseline significant radial dyssynchrony to be associated with a significant increase in EF at 5 to 8 mo after CRT. Furthermore a greater increase in EF was observed in patients with lead position concordant to the latest site of activation identified at the radial strain study, compared to patients with discordant lead position.

Gorcsan *et al*[62] studied 176 HF patients candidates to CRT with both 12-site TDI time to peak dyssynchrony analysis and radial strain. They found that 95% of patients with significant dyssynchrony both at TDI (> 60 msec) and radial strain (> 130 msec) studies showed an EF improvement, while only the 21% of patients without dyssynchrony at both tests had an EF response[62]. Based on several trials, actually a value of antero-septal to posterior wall peak delay > 130 msec is considered indicative of significant radial dyssynchrony (Figure 8). Bank *et al*[63] in the PROMISE-CRT trial studied HF patients with radial strain analysis and concluded that the presence of radial dyssynchrony predicted reverse remodeling after CRT. However the sample was small and so placebo effect could not be overcome. Gorcsan *et al*[64] then studied 197 candidates to CRT with radial strain, considering a delay > 130 msec significant for radial dyssynchrony. They found that patients with significant radial dyssynchrony before CRT had a lower incidence of adverse events [heart transplant, need for a LV assistance device (LVAD), death] at 4-year follow up, compared to patients without baseline dyssynchrony.

Most recently, in the STAR trial by Tanaka *et al*[65],

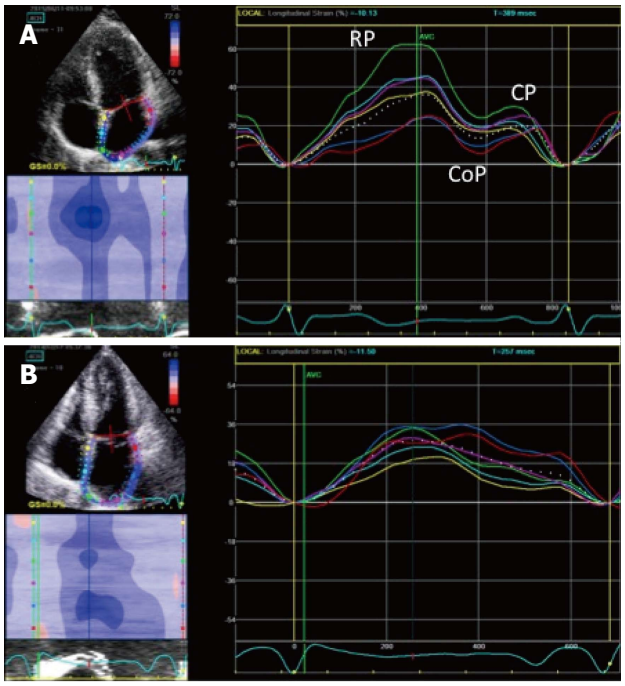

Figure 7 Two dimensional longitudinal atrial strain. A: PALS in a normal patient. Triphasic strain pattern is evident: Reservoire phase (RP), conduit (CoP) and contractile phase (CP); B: Reduced PALS in a patient with a large MV flail and severe MR, without triphasic strain pattern. PALS: Peak atrial longitudinal strain; MV: Mitral valve; MR: Mitral regurgitation.

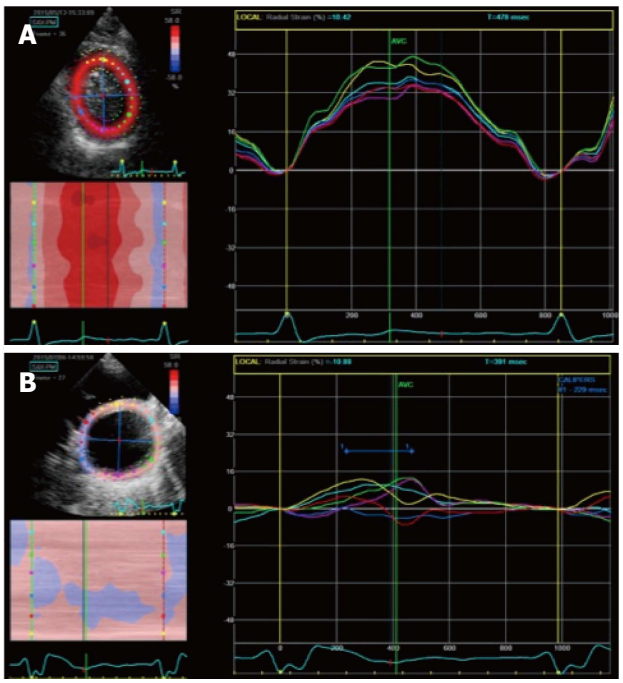

Figure 8 Radial strain analysis with 2 dimensional speckle tracking. A: Synchronous strain pattern in a normal patients; B: Significant intraventricular dyssynchrony in a patient with dilated cardiomyopathy. A significant delay (≥ 130 msec) between anteroseptal peak strain (yellow segment) and posterior peak strain (pink segment) is evident.

baseline dyssynchrony assessed with both radial and transverse strain was found to be a predictor of response to CRT, in terms of EF improvement and better long term survival, as only 11%-13% of these patients died or underwent heart transplant or LVAD implantation. Patients without either radial or transverse dyssynchrony prior to CRT had a worse prognosis, as in 50% of these cases an unfavourable event occurred. On the other hand, in one third of patients responders to CRT, both longitudinal and circumferential strain failed to detect significant dyssynchrony. Thus, the authors concluded that radial and transverse strain are the most reliable methods to assess dyssynchrony and predict response to CRT. Furthermore, radial strain dyssynchrony evaluation permitted the identification of the most delayed site of LV activation. Ypenburg *et al*[66] studied 244 patients before CRT with 2D radial strain analysis and found that the latest site of LV activation was most frequently represented by the posterior (36%) and the lateral segments (33%). They also evidenced that if the LV lead position was concordant to the identified latest site of activation, better echocardiographic response and long term outcome could be expected after CRT.

As for longitudinal dyssynchrony, Lim *et al*[67] studied 100 HF patients before CRT using longitudinal strain and derived a strain delay index, that resulted to be a marker of dyssynchrony and viability or scar. They reported a strain delay index > 25% to be consistently associated with LV reverse remodeling after CRT.

Shi *et al*[68] studied 53 HF patients with 2D speckle tracking obtaining standard deviation of time to PALS in 12 LV segments (Tstrain-SD) and standard deviation of time to the end of longitudinal systolic strain rate in six basal LV segments (Tsr-SD). No significant difference was observed in baseline Tsr-SD, and Tstrain-SD between non-responders and responders to CRT. However, the Tsr-SD was significantly higher in responders than non-responders. Ma *et al*[69] found that both global and regional longitudinal strain can be predictors of long-term response to CRT in patient with ischemic cardiomyopathy. Further, baseline longitudinal strain values in the site of LV leads were consistently higher in responder patients. Finally, also baseline global longitudinal strain was found to be higher in CRT responder patients than in non-responders, with a global longitudinal strain of -13% predicting response to CRT, thus suggesting that patients with better global LV function had less scar tissue and are likely to benefit more significantly from CRT. Becker *et al*[70] applied circumferential strain analysis to HF patients before CRT, showing that dyssynchrony assessed by circumferential strain did not differ between CRT responders and non-responders. Of note, this trial was more focused on the effect of LV lead position on CRT response than on the role of dyssynchrony. Delgado *et al*[71] compared circumferential, longitudinal and radial strain and found that only dyssynchrony assessed with radial strain was able to predict CRT responders in a study group of 161 patients, while circumferential and longitudinal strain were not. As a consequence of these several trials, we can assume that LV dyssynchrony analysed with radial strain is more informative than longitudinal or circumferential strain analysis and can predict CRT responders. Furthermore,

also magnetic resonance imaging studies confirmed that radial dynamics analysis can be more sensitive in identifying the presence of dyssynchrony, compared to longitudinal myocardial deformation study[72,73]. However higher global longitudinal strain and regional longitudinal strain at the site of LV lead positioning can also predict the response to CRT[74]. The dyssynchrony strain pattern evidenced by 2D speckle tracking echo is also very important to predict the response to CRT. In patients with heart failure, the presence of intraventricular dyssynchrony is usually evidenced by left bundle branch block (LBBB) at EKG. In presence of a true LBBB or right ventricular pacing, the contraction pattern is characterized by early contraction in early activated walls (septum) and pre-stretch followed by late contraction in late activated walls (lateral wall). The strain-pattern can reflect a complete LBBB in the so called "classical" pattern, that is defined by three components: (1) early activation of at least one basal or midventricular segment in the septal or anteroseptal wall and early stretching in at least one basal or midventricular segment in the opposite wall; (2) early peak contraction not exceeding 70% of the ejection phase; and (3) early stretching wall showing peak contraction after aortic valve closure. Patients who do not fulfil all these three criteria are considered having a heterogeneous strain-pattern. Risum *et al*[74] showed that contraction patterns reflective of a consistently delayed LV activation are predictive of response. The presence of a "classic" strain pattern strongly predicted the CRT efficacy, while other patients with wall motion patterns inconsistent with a LV activation delay were less likely to benefit. Importantly, the presence of a classical pattern significantly added to other predictors of response (etiology and QRS > 150 ms) further emphasizing a valuable role for pre-implantation assessment of mechanical dyssynchrony by speckle tracking approach.

Also apical transverse motion (ATM), to quantify "apical rocking", has been introduced as a new and integrative parameter for for LV dyssynchrony assessment and as a promising predictor of CRT efficacy[75]. ATM was proposed by Voigt *et al*[76], who suggested that ATM integrated information about temporal and regional inhomogeneities of LV function and exhibited a significant correlation with the difference between tissue Doppler-derived average strains of the septal and lateral wall. Gürel *et al*[77] showed that ATM is closely associated with radial dyssynchrony assessed by 2D speckle tracking analysis. Of note, a cut-off value of 2.5 mm for ATM loop could clearly differentiate between patients with and without radial dyssynchrony[77].

Previous studies showed that LV rotational mechanics are altered in patients with advanced HF and prolonged QRS[78]. In those with significant dyssynchrony, not only torsion is reduced but the basal and apical rotation sometimes follows the same direction of rotation[79]. Further, Sade *et al*[80] showed that LV altered rotational mechanics can be restored by resynchronization therapy. These authors then suggested the use of LV rotational parameters (LV torsion and twist)[80] for predicting CRT responders.

Potential important technical challenges encountered with 2D STE include interpretation of biphasic or multiple peaks in one segment at strain analysis. Seo *et al*[81] suggested to consider the earliest peak of the segmental strain curve, when more than one peak is evident, as it appears to be the most predictive of response to CRT. Another important limitation of strain analysis has to be faced in presence of akinetic or scar regions, as it could be difficult to get reliable strain curves of these segments. However, LV dyssynchrony is also a 3D phenomenon. Therefore 3D speckle tracking dyssynchrony analysis has been recently introduced and validated. Valuable studies in several studies, 3D-echocardiography has been used to study LV dyssynchrony, assessing volumetric changes in endocardial movement and regional blood displacement[82,83]. Tanaka *et al*[84] enrolled 54 candidates to CRT and used a 3D speckle tracking system to assess LV dyssynchrony. Radial dyssynchrony was analysed using a 16-segments scheme, expressed as maximal opposing wall delay in time-to-peak strain and standard deviation of time-to-peak strain. The authors found that both parameters significantly correlated with 2D radial strain antero-septal to posterior delay. Furthermore, 3D speckle tracking offers the advantage of identifying the most delayed myocardial region in 3D, in contrast to 2D speckle tracking and TDI analysis.

In fact radial strain 3D speckle tracking analysis offers a complete 3D mechanical activation map with the color-code 3D cine-loop map that provide an immediate visual assessment of the latest activation site among the 16 segments. In another study, Tanaka *et al*[85] used 3D speckle tracking to study 57 HF patients with prolonged QRS due to either LBBB (group 1) or RV pacing (group 2) with a need to undergo CRT upgrading. They found that the site of earliest mechanical activation was consistently different between the 2 groups (apex 6% in group 1 *vs* 28% in group 2 respectively), but the most delayed site of activation was similar in the both kind of LV conduction delay. These data supported the use of resynchronization therapy in patients with low EF and a need for pacing.

According to these data, we can conclude that deformation imaging can help to define the presence of intraventricular dyssynchrony better than TDI. Radial speckle tracking and 3D strain analysis appear to be the best method to quantify intraventricular delay and to predict CRT responders.

DEFORMATION IMAGING IN PATIENTS WITH MECHANICAL DYSSYNCHRONY AND FMR

LV dyssynchrony also plays a role in the pathophysiology of FMR. In fact it has been described that intraventricular mechanical dyssynchrony is an important contributor to functional MR[86,87].

Liang *et al*[11] enrolled patients with EF < 50% and at least mild MR, using TDI to assess global systolic

dyssynchrony (maximal difference in time to peak systolic velocity among the 12 LV segments) and regional dyssynchrony (delay between anterolateral and posteromedial papillary muscles insertion regions). These authors concluded that only global dyssynchrony could be considered a FMR determinant, with an incremental value to valve remodeling parameters (tenting area) that play the main role in FMR pathophysiology.

Soyama *et al*[21] analysed 32 patients with non-ischaemic DCM using TDI derived strain of the papillary muscles; they found FMR to be more frequent in patients with a significant delayed activation of the papillary muscles adjacent LV segments, and concluded that regional dyssynchrony and LV sphericity were independent predictors of FMR.

Agricola *et al*[88] evaluated 74 patients with chronic LV dysfunction (53% ischemic patients) with varying degrees of MR and suggested that systolic tenting was the main determinant of FMR, as a consequence of global and regional LV remodeling. The authors reported that regional dyssynchrony was independently associated with MR severity, with a minor influence, only in patients with DCM and not in those with ischaemic cardiomyopathy. They also found that the QRS duration had no effect on the severity of FMR. Of note, in this study intraventricular dyssynchrony was expressed as the SD of time-to-peak systolic velocity of 8 (not 12) LV segments. Donal *et al*[22], using regional strain analysis in 87 patients with DCM, demonstrated that the degree of FMR was determined by mitral orifice morphology, LV features, especially longitudinal contractility (strain of LV mid-lateral wall) and dyssynchrony defined as the delay between the septal and lateral mid-portion strain divided by RR squared root. In addition the authors found that MR was not correlated with interventricular mechanical delay. Also Sardari *et al*[89] demonstrated that the severity of MR was not correlated with the QRS duration nor with the echocardiographic interventricular dyssynchrony indices in the patients with ischemic or DCM. Moreover, in this study also intraventricular dyssynchrony was not correlated with MR severity. However in this study only Doppler imaging was applied to evaluate LV synchronicity, as neither strain nor time to peak systolic strain analysis were performed.

As for ischemic cardiomyopathy, inferior wall myocardial infarction is known to be associated with more severe MR degree, while anterior myocardial infarction should theoretically be characterized by a higher dyssynchrony index, due to larger infarct dimensions. Patients with anterior acute myocardial infarction (AMI), but not inferior AMI have worse prognosis, and either a larger dyssynchrony index or increased MR severity determine LV remodeling and outcome. Hung *et al*[90] found that both global and regional dyssynchrony in patients with anterior MI were independently associated with FMR degree. Dyssynchronized myocardial segments were assessed by 3D echo showing an independent impact on FMR grade in a narrow QRS population.

The dyssynchronous contraction of LV papillary muscles is a leading cause of FMR in HF patients, as inferior, posterior and lateral regions are usually identified as the most delayed sites and papillary muscles are regularly located adjacent to lateral and inferior walls. As the majority of the studies regarding papillary muscles dyssynchrony reported different cut off values, the optimal delay for cardia resynchronization has not been established yet. Thus, there is the need for defined cut off values in order to clearly identify the presence of papillary muscles dyssynchrony before CRT in patients with FMR. Tigen *et al*[91] reported that papillary muscle dyssynchrony with > 60 msec delay (assessed by TDI-derived longitudinal strain) was able to predict a regurgitant volume > 20 mL in DCM patients. Kjordybach *et al*[92] studied 31 patients with EF lower than 35% of both ischemic and non-ischaemic aetiology and evaluated papillary dyssynchrony by TDI derived time to peak strain. They showed that papillary muscles dyssynchrony was associated with the deformation of mitral apparatus (tenting area), but the haemodynamic consequences of MR (in particular left atrial area) could be better characterized by papillary dyssynchrony only in DCM. Ypenburg *et al*[13] and Goland *et al*[93] both assessed dyssynchrony at the papillary muscles insertion sites using radial strain analysis. They reported that MR improvement after CRT was significantly more frequent in patients with baseline dyssynchrony. In 2010, Tigen *et al*[94] firstly investigated both papillary muscles with 2D speckle tracking from the longitudinal axis in patients with DCM. They found that FMR was significantly correlated with intraventricular dyssynchrony and mitral valve remodeling parameters.

In addition, in this study significant papillary muscles dyssynchrony was found to be the only independent predictor of more than moderate MR. The proposed cut-off value for papillary muscles dyssynchrony (30 ms) predicted a mitral regurgitant volume > 20 mL or EROA > 0.20 cm^2 with high sensitivity and specificity.

STE has shown a fundamental role of intraventricular dyssynchrony in determining FMR especially in DCM, rather than in ischemic cardiomyopathy, in which MR severity seems to be more related to mitral valve deformation indexes. Finally the assessment of papillary muscle dyssynchrony can help to identify optimal candidates to CRT, especially among patients with DCM-associated FMR.

THERAPEUTIC CONSIDERATIONS

Medical therapy

The currently accepted optimal pharmacological therapy for HF embraces ACE-inhibitors, diuretics, aldosterone antagonists and beta-blockers[95], and its beneficial effects on HF symptoms in subjects with FMR and LV dysfunction may be remarkable. This combination therapy acts on both neurohormonal activation and the underlying maladaptive pathways, leading to a favourable myocardial remodeling. Several combinations of the above-mentioned drugs are commonly used aiming at reducing the severity of MR and reversing or at least delaying the LV remodeling

progression. Afterload-reducing drugs, *i.e.*, ACE-inhibitors, decrease MR regurgitant volume and increase forward output by reducing the pressure gradient between LV and LA. Vasodilators decrease MR regurgitant volume through a systolic unloading on the EROA. Likewise a reduction in MR might be achieved with preload reduction agents, *i.e.*, diuretics, through LV unloading and accordingly a decrease in leaflet tethering. The administration of ACE-inhibitors and beta-blockers is an independent predictor of better long-term survival in subjects with ischemic MR and LV dysfunction since they reduce the progression of LV remodeling and prevent sudden death. Beta-blocker therapy in HF patients reduces all cause mortality, cardiovascular mortality and mortality due to LV systolic dysfunction and sudden death by roughly 31%-39%[96]. In addition, it has been demonstrated that a combined therapy of carvedilol plus ACE-inhibitors decreases FMR by reducing LV dilation[97].

Indications for intervention

FMR surgery is indicated in patients with severe MR and LVEF > 30% undergoing coronary artery bypass grafting (CABG) (recommendation class I, level of evidence C)[98]. It should be considered in patients with moderate MR undergoing CABG (Ⅱa, C) and in symptomatic patients with severe MR, LVEF < 30%, option for revascularization and evidence of myocardial viability (Ⅱa, C). Furthermore FMR surgery may be considered in patients with severe MR and LVEF > 30% with persisting symptoms despite optimal medical management and with low comorbidity, when revascularization is not indicated (Ⅱb, C). In the other patients, optimal medical treatment and extended HF treatment is currently the best option.

Percutaneous mitral valve repair is feasible at low procedural risk in patients with secondary MR and may provide short-term improvement in functional condition and LV function. The percutaneous MitraClip procedure may be considered in patients with symptomatic severe secondary MR despite optimal medical therapy who fulfil the echocardiographic criteria of eligibility, are judged at high surgical risk by a team of cardiologists and cardiac surgeons, and who have a life expectancy greater than one year (Ⅱb, C). A recent metanalysis showed that MitraClip represents an efficacious strategy for patients with HF and severe MR, improving functional class and cardiac remodeling[99].

The management of moderate ischaemic MR in patients undergoing CABG is still unclear. In this circumstance, valve repair is preferable. In patients with low EF, mitral valve surgery should be considered if there is evidence of myocardial viability and if comorbidity is low. Exercise echocardiography should be considered in patients capable of exercising, since exercise-induced dyspnoea and a substantial increase in MR severity and systolic pulmonary artery pressure support mitral surgery in addition to myocardial revascularization.

CRT in patients with FMR

It has been widely demonstrated that CRT decreases mortality and hospitalization rate, improving cardiac function and structure in symptomatic chronic HF patients managed with optimal medical treatment[100], who present severely depressed LVEF (≤ 35%) and complete LBBB (class Ⅰ recommendation, level of evidence A). In these patients, CRT is superior either to optimal medical therapy or to ICD alone. Efficacy tends to be lower in patients with NYHA class Ⅰ and Ⅳ and in case of non-LBBB morphology with QRS duration < 150 ms. Therefore, in HF patients without LBBB and QRS ≥ 150 ms or LBBB and QRS duration 120-149 ms, CRT is still recommended but considered class Ⅱa or Ⅱb indication[101].

However the improvement in HF symptoms and survival profile after CRT is proportionate to the extent of improvement in LV systolic function. CRT reduces MR severity in patients with chronic HF and FMR. As showed by Upadhyay *et al*[102], reduction in MR after CRT is considerably related to lesser HF hospitalization and improved survival. In this study baseline MR degree and longer surface QRS to LV lead time were significant predictors of MR change. Furthermore mitral valve was less remodelled in patients with evidence of MR reduction after CRT. Indeed these patients exhibited a lower tenting area and coaptation height than those with stable or worsening MR, suggesting that ventricular geometry improvement could be a mechanism for MR change.

CRT is then responsible for immediate and late reduction in FMR contrasting its pathophysiologic determinants by reducing or virtually eliminating LV dyssynchrony through different mechanisms: (1) increasing "closing forces" (global synchronization); (2) reducing "tethering forces" (local synchronization); (3) reshaping annular geometry and function (local synchronization); and (4) correcting diastolic MR [atrio-ventricular (AV) synchronization].

As for global synchronization, CRT can restore AV and LV synchrony, increasing global LV contraction efficiency and therefore MV coaptation forces. In fact CRT generates a higher pressure-gradient through MV with a consequent rise in trans-mitral closing forces counteracting the tethering forces. Breithardt *et al*[17] studied 24 HF patients with LBBB and FMR after CRT implantation and confirmed that FMR reduction is directly related to the increased closing force (expressed as LV dP/dt max) that aid mitral valve closure. In addition CRT reduces FMR not only by increasing closing forces but also through "local" synchronization[36]. It was noticed that in CRT responders with FMR reduction, resynchronization was induced at the level of basal and mid-LV segments. At the multivariate analysis mid-LV segments synchrony was the most significant predictor of FMR reduction, suggesting that a more "local" synchronous contraction involving the segments adjacent to papillary muscles could determine FMR improvement. Kanzaki's *et al*[38] firstly correlated the immediate reduction in MR after CRT with a more synchronized mechanical activation of papillary muscle insertion points. Further, Goland *et al*[93], using through 2D Speckle Tracking Radial Strain (2D-RS), showed that a significant delay of time-to-peak 2D-RS in the mid-posterior and inferior segments prior to CRT, along

with preserved radial strain in the posterior and inferior segments, were strong predictors of FMR improvement after CRT. Most recently three echocardiographic aspects have been independently associated with FMR change after CRT[103]: Antero-septal to posterior wall radial strain dyssynchrony > 200 ms, non-severe LV dilatation (LV end-systolic diameter index < 29 mm/m^2), absence of scar at papillary muscle insertion sites. In the same study the importance of myocardial viability in predicting FMR response was stressed, because CRT can be effective only when responsive viable segments are present. Sénéchal *et al*[104] evaluated the presence of viability using dobutamine-stress echocardiography before CRT and confirmed that local viability was able to predict acute response to CRT with a proper sensitivity, making local viability an essential precondition for response to CRT. CRT is also thought to improve contraction of the posterior mitral annulus, coordinating the contraction of the segments at the base of the LV. However data are discordant as some studies demonstrate no immediate changes in mitral annular dimensions after CRT and other studies[14] show that annular contraction is correlated to FMR reduction after CRT, although as a minor determinant.

Interestingly all these described effects are pacing dependent as the interruption of CRT causes an immediate recurrence of MR.

According to the timing of response to CRT, there is clear distinction between two phases of MR reduction: (1) immediate MR reduction, occurring suddenly after CRT implantation; and (2) long-term MR reduction, occurring from weeks to months after CRT.

MR may show an immediate improvement after CRT, but the underlying mechanism is not completely clear. It is probably more likely to occur when LV dyssynchrony is mainly related to papillary muscles dyssynchrony. Ypenburg *et al*[105] showed that CRT may lead to an acute reduction in MR in LV dyssynchrony involving the posterior papillary muscle, as opposed to a late response when the lateral wall is involved. Long-term reduction is the consequence of LV reverse remodeling. In addition, CRT can be associated with acute decrease in resting MR but not in exercise-induced MR. In fact, after CRT only late reversed LV remodeling, restoring mitral apparatus geometry, is associated with a reduction in both resting and exercise-induced MR[106].

Between the two phases of FMR reduction, immediate MR reduction is the major determinant of favourable response to CRT, as it contributes to the acute reduction of volume overload, determining a rapid reverse remodeling. Therefore, immediate MR reduction is a major prognostic determinant after CRT[107].

Surgery

The ideal surgical strategy for the management of ischemic MR is still debated. Peri-operative mortality is higher compared to primary MR, and the long-term prognosis is worse mainly due to the more severe associated comorbidities. Moreover, there is a significant persistence and recurrence rate of MR after valve repair, as McGee demonstrated on a cohort of 585 patients with FMR[108], as well as the absence of prognostic evidences. Severe ischaemic MR is not usually improved by sole revascularization. At the same time the impact of valve surgery on survival remains uncertain because randomized trials are missing and the available observational studies do not draw definite conclusions because of study limitations[109]. With regard to prognosis, most studies failed to demonstrate improved long-term clinical outcome following surgical correction of secondary MR[110,111]. Fattouch *et al*[112] compared CABG *vs* CABG plus valve repair in patients with moderate ischemic MR, showing that the addition of MR repair improved functional class, EF, pulmonary artery pressure and LV diameter in the short-term. The study though was not designed to analyse the effect on survival of the addition of valve repair to CABG. When surgery is indicated, valve repair using undersized rigid ring annuloplasty is the first option, offering a low operative risk although it is associated with a significant rate of MR recurrence[113]. Preoperative predictors of recurrent secondary MR after undersized annuloplasty, associated with a worse prognosis, are left ventricular end diastolic diameter, posterior mitral leaflet angle, distal anterior mitral leaflet angle, systolic tenting area, coaptation distance, end-systolic inter-papillary muscle distance, and systolic sphericity index[114]. A meta-analysis of retrospective studies by Vassileva *et al*[115] suggested better short-term and long-term survival following valve repair compared to its replacement. A recent study on 251 patients with severe ischemic mitral regurgitation randomized to either mitral-valve repair or chordal-sparing replacement revealed no significant difference in LV reverse remodeling or survival at 12 mo; replacement provided a more durable correction of mitral regurgitation, but there was no significant difference in clinical outcomes between-group[116].

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REVIEW

Micromanaging cardiac regeneration: Targeted delivery of microRNAs for cardiac repair and regeneration

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Abstract

The loss of cardiomyocytes during injury and disease can result in heart failure and sudden death, while the adult heart has a limited capacity for endogenous regeneration and repair. Current stem cell-based regenerative medicine approaches modestly improve cardiomyocyte survival, but offer neglectable cardiomyogenesis. This has prompted the need for methodological developments that crease *de novo* cardiomyocytes. Current insights in cardiac development on the processes and regulatory mechanisms in embryonic cardiomyocyte differentiation provide a basis to therapeutically induce these pathways to generate new cardiomyocytes. Here, we discuss the current knowledge on embryonic cardiomyocyte differentiation and the implementation of this knowledge in state-of-the-art protocols to the direct reprogramming of cardiac fibroblasts into *de novo* cardiomyocytes *in vitro* and *in vivo* with an emphasis on microRNA-mediated reprogramming. Additionally, we discuss current advances on state-of-the-art targeted drug delivery systems that can be employed to deliver these microRNAs to the damaged cardiac tissue. Together, the advances in our understanding of cardiac development, recent advances in microRNA-based therapeutics, and innovative drug delivery systems, highlight exciting opportunities for effective therapies for myocardial infarction and heart failure.

Key words: Cardiac repair; Cellular plasticity; Targeted drug delivery; MicroRNA; Reprogramming

Core tip: Cardiac fibroblast reprogramming into cardiomyocytes holds great promise for future cardiac regenerative medicine therapies. Here, we discuss current advances in the state-of-the-art protocols for the direct reprogramming of cardiac fibroblasts into *de novo* cardiomyocytes *in vitro* and *in vivo* with an emphasis on

microRNA-mediated reprogramming. Additionally, we discuss current advances on the state-of-the-art targeted drug delivery systems that can be employed to deliver these microRNAs to the damaged cardiac tissue.

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INTRODUCTION

Ischemic cardiac disease is characterized by a chronic or acute reduction in myocardial perfusion and affects over 120 million people globally of which approximately 4% suffer from myocardial infarction (MI) annually[1,2]. MI is the process of cell death occurring after occlusion of a coronary vessel that supplies blood to a specific area of the heart and results in a massive loss (up to 11 billion cells) of viable muscle cells[3]. This loss of cardiac tissue may in turn lead to functional cardiac impairments and, if large enough, severe contractile dysfunction with an inability of the heart to maintain organ perfusion resulting in sudden death.

Although the recognition of MI and the success rates of primary angioplasty have greatly improved in the past decades, treatment of MI is commenced after the cardiac damage response has already started. Cell death, either by apoptosis or necrosis, is the initial response of cardiomyocytes to the decreased oxygen supply and commences already 4 h after MI[4,5]. Cardiomyocyte cell death is followed by the influx of inflammatory cells that phagocytize the dead cells, resulting in thinning of the ventricle wall. Cytokines secreted by these inflammatory cells recruit myofibroblasts that secrete collagens and replace the lost cardiomyocytes[6,7]. This remodeling process culminates in the formation of a scar tissue that preserves the ventricle integrity, but possesses little contractile function which hampers cardiac function. At this stage, chronic heart failure is likely to develop as the cardiac tissue is unable to regain its normal function[8,9]. Current treatment options consist of appropriate diet and lifestyle changes and medicinal in the use of diuretics, ACE inhibitors and AT receptor blockers, in an attempt to alleviate the heart from the waring strains it encounters. However, although these interventions have a pronounced effect on increasing the patients lifespan, the do not treat the underlying pathology, which is the loss of cardiomyocyte mass[10-12].

So, if the morbidity following MI is due to the massive loss of cardiomyocytes, would it not be logical to therapeutically induce cardiomyocyte proliferation to compensate for the lost myocytes?

Although most cardiomyocytes form terminally differentiated binucleated cells that withdraw from the cell cycle[13,14], limiting the myocardial regenerative capacity, some evidence exists for postnatal cardiomyocyte proliferation. Retrospective birth dating of human cardiomyocytes using carbon-14 in the DNA of cardiomyocytes demonstrated that human cardiomyocytes have a turnover rate of approximately 0.45%-1% per year[15]. During normal human wound healing, cell cycle activation occurs which compensates for the loss of tissue[16,17]. Indeed, a small number of cardiomyocytes enters the cell division cycle following myocardial infarction[18], however the level of proliferation is insufficient to regenerate the lost tissue.

The observation that the postnatal heart retains some proliferative capacity has inspired therapeutic approaches that aim to enhance the endogenous cardiomyocyte proliferation for regeneration. Indeed, forced expression of cell cycle activators such as Cyclin A2 and D2 promotes the proliferation of postnatal cardiomyocytes and limits damage following MI[19,20]. Additionally, regenerative medicine approaches using a wide variety of growth factors (*i.e.*, ERBB2[21], FGF1[22,23], HGF[24,25], IGF1[25], NRG1[22,26,27], MYDGF[28], and POSTN[29], reviewed in[30,31]) induce cardiomyocyte proliferation after MI, albeit relatively ineffectively.

The relative ineffectiveness of cardiomitogenic therapies using growth factors in restoring cardiomyocyte numbers following myocardial infarction warrants the need to increase cardiomyocyte numbers from exogenous sources. The effectiveness of adult stem and progenitor cells of various origins (*i.e.*, bone marrow-derived cells [Mesenchymal stem cells (MSC)[32] and endothelial progenitor cells (EPC/ECFC)[33]], adipose tissue-derived regenerative cells (ADRC)[34] and cardiac-derived progenitor cells (CPC)[35] to induce cardiac regeneration has been assessed in numerous clinical studies (reviewed in[36-39]). In general, intramyocardial transplantation of adult stem and progenitor cells in the post-infarct myocardium induces neoangiogenesis and promotes cardiomyocyte survival[40] and thereby reduces the infarct size and improves cardiac function long term[39]. Although these effects are beneficial to the survival of the myocardium, retention of therapeutic cells at the site of cardiomyocyte death is highly limited[41,42] and their cardiomyogenic effects are neglectable[43,44]. Hence, the regenerative effectiveness of transplantation of adult stem and progenitor cells is under debate[43,45].

Thus, MI results in a massive loss of cardiomyocytes that are replaced by scar tissue. Endogenous repair mechanisms, such as cardiomyocyte proliferation, are insufficient to efficiently regenerate the lost myocardial tissue and therapeutic approaches to induce cardiomyocyte proliferation using growth factors are ineffective. Current regenerative medicine therapies using stem and progenitor cells improve cardiomyocyte survival, but pose neglectable cardiomyogenesis. This warrants the development of new therapeutic strategies that focus on increasing the number of viable cardiomyocytes at the infarct site, reviewed below.

CELLULAR PLASTICITY AS THE NEW THERAPEUTIC OPPORTUNITY

Induced pluripotent stem cells and cardiomyogenesis

In 2006, Takahashi *et al*[46] challenged the dogma of terminal cell differentiation. Probing the effects of transcription factors that are pivotal to embryonic stem cell maintenance in terminally differentiated skin fibroblasts, four transcription factors (*i.e.,* Oct4, Sox2, Klf4 and c-Myc) were identified that could convert skin fibroblasts into a more primitive pluripotent stem cell resembling embryonic stem cells[46,47]. These data exemplify that cell fate is not fixed, but is determined by the available transcription factors and can be altered by the addition of alternative transcription factors. The obtained induced-pluripotent stem cells (iPSC) introduced a new era in regenerative medicine wherein cellular reprogramming is used to treat disease.

IPSC have been used in preclinical models of MI repair[48-51]. Transplantation of iPSC directly into the infarcted myocardium improves cardiac function [*e.g.*, left ventricle ejection fraction (LVEF), fractional shortening, and contractility] and reduces infarct size[48-50]. Although transplanted iPSC contribute to cardiac repair, a major impediment to their clinical use in human patients lies in the inefficiency of transplanted iPSC to form cardiomyocytes (0.5%-2%)[49], their tumorigenicity[52], and their limited retention in the infarcted tissue. Yet, proof-of-concept that iPSC can differentiate into functional cardiomyocytes has tantalized researchers in studying cardiac embryology as iPSC differentiation into functional cardiomyocytes is merely a reiteration of embryology.

Embryonic cardiogenesis (Figure 1A) begins from the mesoderm that arises from the primitive streak during gastrulation. Gene regulation and cell movement that control cardiogenesis are spatially and temporally stringently regulated (reviewed in[53]). Bone morphogenetic protein (BMP)-4, activin A and fibroblast growth factor (FGF)-2 induce mesoderm specification[54-56] from pluripotent progenitors in the primitive streak by inducing Wnt3a expression, whereas Notch signaling inhibits the transition from mesodermal precursors into cardiac mesoderm[57]. MESP1, the most early expressed marker of the cardiac lineage[58,59], is expressed by all cardiac precursors that arise from the cardiac mesoderm and drives further cardiac specification by the Dkk1-mediated repression of Wnt signaling[60], resulting in the formation of specialized cardiac progenitor cells. This pool of cardiac precursors gives rise to the endocardium, the first heart field (from which the atria, left ventricle and nodal conduction system are formed) and the second heart field (from which the right ventricle and outflow tract are formed)[61]. Specification of cardiac precursors into cells of the first and second heart field is regulated by the complex interplay of transcription factors downstream of MESP1[62,63]. Herein, GATA4, MEF2c, HAND2 and NKX2.5 represent common transcription factors to all cardiac precursors, whereas the expression of TBX5 is restricted to the first heart field[64] and ISL1 and TBX1 are restricted to the second heart field[65,66]. Once formed, cardiac cells of the first and second heart field proliferate in response to endocardial-derived Neuregulin (NRG1) and epicardial-derived retinoic acid and FGF2[67,68].

Indeed, reiteration of key steps in cardiogenesis by supplying iPSC with stage-specific pivotal signaling molecules efficiently differentiates iPSC into the cardiac lineage. Differentiation protocols rely on progressive sequential inductive signals using growth factors (Figure 1B). Monolayers of iPSC are stimulated with BMP4, Activin A and Wnt3a in the first 4 d of differentiation to induce cardiac mesoderm formation[69-72]. Inhibition of Wnt signaling using small molecule inhibitors after day 4 of differentiation advances mesodermal precursors to cardiac progenitors and reiterates the actions of Dkk1-mediated inhibition of Wnt signaling during embryology[69,70]. The addition of ascorbic acid[73] or G-CSF[74] at this stage enhances cardiomyocyte formation by stimulating proliferation of cardiac progenitor cells (Figure 1B). Culture of the obtained cardiac progenitor cells in the presence of NRG1 or IGF1 allows further maturation of cardiac progenitor cells into immature cardiac cells from the first and second heart field[75]. Modifications to this general protocol include embedding in extracellular matrix[76], mechanical[77] and electrical[78] stimulation of the immature cardiomyocytes. These modifications may influence the maturity of the iPSC-derived cardiomyocytes but do not increase the differentiation efficiency.

Direct reprogramming of cardiac fibroblasts into cardiomyocytes

In equivalence to the iPSC generation, where pluripotency-associated transcription factors are expressed in terminally differentiated cells, direct conversion of fibroblasts into the cardiac lineage has been attempted[79-83]. Although no single master regulator of cardiomyogenesis has been identified to date, in analogy to the pioneering iPSC work of Yamanaka, Ieda *et al*[79] used a reductionist approach to test fourteen different transcription factors to induce cardiomyogenic gene expression in fibroblasts, and found that the combination of cardiac-specific transcription factors GATA4, Mef2c and Tbx5 successfully reprograms murine cardiac fibroblasts directly into immature cardiomyocytes (Figure 1C)[79]. Although the efficiency of fibroblast reprogramming is rather low, with only about 30% of transduced cells display spontaneous contraction (about 6% of the total fibroblast population)[79,84], the proof-of-concept that cardiac fibroblasts can be converted into cardiomyocytes by retroviral expression of GATA4, Mef2c and Tbx5 paved the way for *in vivo* delivery of these transcription factors.

Cardiac fibroblasts account for the majority of cells in the heart[85] and are therefore considered a viable cell population for reprogramming and restoration of cardiac function. Lineage tracing models[86,87], wherein the cardiac fibroblasts are genetically tagged with a marker protein, were subjected to cardiac damage (either coronary ligation[86,87] or cryoinjury[84]) and treated with GATA4, Mef2c and TBX5 retroviruses. Up to three months

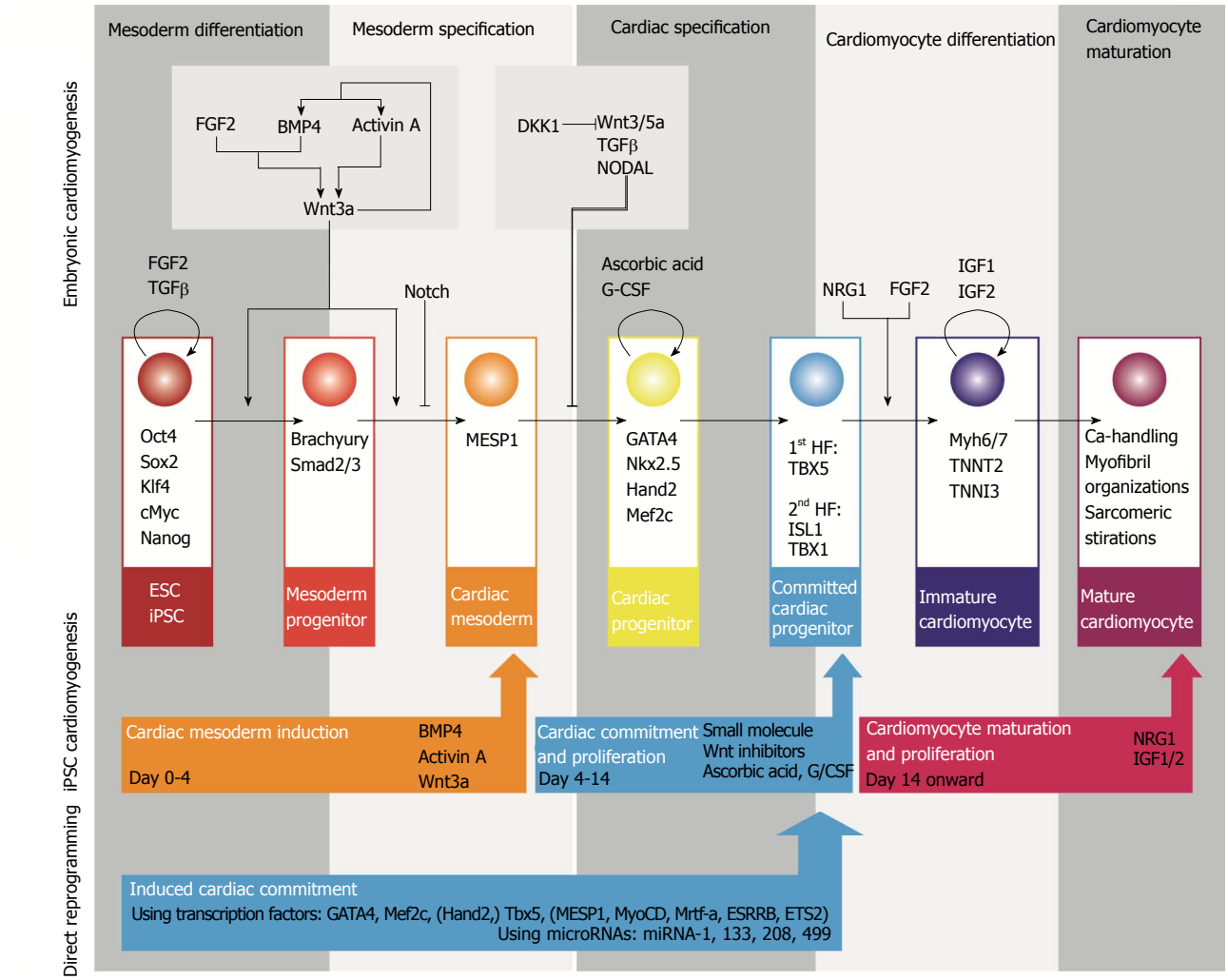

Figure 1 Schematic of factors involved in cardiomyocyte differentiation in embryology, embryonic stem cell/induced-pluripotent stem cells and cardiac fibroblast reprogramming. Factors that influence the progression through the five steps in cardiomyocyte differentiation and maturation: mesoderm differentiation, mesoderm specification, cardiac specification, cardiomyocyte differentiation and cardiomyocyte maturation in: A: Embryonic cardiomyocyte differentiation; B: Cardiomyocyte differentiation from ESC and iPSC using exogenous (growth) factors; C: In direct reprogramming of cardiac fibroblasts into cardiomyocytes. Transcription factors associated with each of the seven cell types during cardiomyocyte differentiation are presented in the boxes below. ESC: Embryonic stem cell; iPSC: Induced-pluripotent stem cells.

after treatment, cardiac transcription factor delivery to the heart reduces infarct sizes and attenuates cardiac dysfuntion[84,86,87], providing therapeutic proof-of-concept for *in vivo* cellular reprogramming, although efficiencies differ widely (1%-30%) between studies. Surprisingly, *in vivo* reprogrammed cardiomyocytes develop more characteristics (*e.g.*, binucleation, assembled sarcomeres) of native cardiomyocytes as compared to their *in vitro* counterparts[87]. This improvement in reprogramming may be derived from microenvironmental clues, exposure to native extracellular matrix or mechanical forces during reprogramming and could provide clues for further improvements to the reprogramming protocols.

Additionally, it must be noted that reprogramming of cardiac fibroblasts into cardiomyocytes is efficient in mice, however the conversion of human fibroblasts into the cardiac lineage proves more difficult[80-83]. The expression of GATA4, Mef2c and TBX5 in human cardiac fibroblasts is insufficient for cardiac induction. The addition of MESP1 and Myocardin (MyoCD)[80], MyoCD and MyoCD-related transcription factor-A (Mrtf-a)[81], MESP1 and estrogen-related receptor beta (ESRRB)[82], or MESP1 and ETS2 (Figure 1C)[83] all increase reprogramming efficiency of human cardiac myocytes and underscore the need for further research in this area before a definite transcription factor cocktail can be put to the test in human trials.

Moreover, additional major impediments need to be addressed prior to clinical translation. Although issues such as tumorigenicity and retention encountered with iPSC and stem cell therapeutics, may be minimalized by the direct conversion of cardiac fibroblasts into cardiomyocytes, heterogeneity in reprogramming efficacy, leading to the formation of immature cardiomyocytes that do not properly couple to adjacent cardiomyocytes, may cause fatal arrhythmias. Furthermore, current strategies rely on the use of viruses integrating randomly in the genome of cells that undergo reprogramming, which may elicit tumorigenic events. It is evident that *in vivo* reprogramming protocols without the use of viruses are essential before clinical translation can commence.

MicroRNAs in cardiomyocytes reprogramming

The use of microRNAs in reprogramming strategies may overcome some of the limitations encountered in reprogramming fibroblasts into cardiomyocytes using viruses, since chemically synthesized microRNA mimics are easily transfected into cells and exhibit low toxicity in animal models[88]. MicroRNAs are endogenous small (about 21-23 nucleotides in length) non-coding RNAs that function as repressors of gene translation[89,90]. Endogenously, microRNAs are encoded in the genome either in extronic regions that form microRNA gene clusters or intronically in both protein-coding and non-coding genes. Regardless of their genomic location, microRNA transcription is initiated by the RNA Polymerase Ⅱ, resulting in the generation of a pri-microRNA[91]. Pri-microRNAs are processed into pre-microRNAs by the RNA-processing complex formed by Drosha and DGCR8 and exported from the nucleus by Exportin 5[92-94]. In the cytosol, pre-microRNAs undergo a second processing step, performed by the cytoplasmic endonuclease Dicer, which forms of the mature microRNA duplex[95]. Next, one strand of the microRNA duplex is loaded in to the RNAi-induced silencing complex (RISC)[96] that utilizes the microRNA to identify and silence its target genes[97,98] (extensively reviewed in[90,99]). The effects of microRNAs on cardiomyogenesis might be powerful, as a single microRNA may target multiple signaling pathways simultaneously, a phenomenon known as multiplicity of microRNA targets[100]. Indeed, mice lacking the enzyme Dicer, which is essential to process microRNA precursors into their mature form[90], die at day E12.5 from cardiac failure[101].

Advances on iPSC and embryonic stem cell (ESC) differentiation into cardiomyocytes (described in sections "*Induced pluripotent stem cells and cardiomyogenesis*" and "*Direct reprogramming of cardiac fibroblasts into cardiomyocytes*") allowed Fu *et al*[102] and Wilson *et al*[103] to identify microRNAs essential to cardiomyogenesis. ESCs were differentiated using exogenous growth factors into beating cardiomyocytes and their "microRNA-ome" were analyzed on array platforms. Next, these microRNA signatures were compared to genuine fetal and adult cardiomyocytes and adult cardiac fibroblasts. MicroRNAs that are differentially expressed in ESC-derived cardiomyocytes and native ESC and that are not expressed by cardiac fibroblasts were identified as cardiomyogenic microRNAs or "cardiomiRs". Although the two "cardiomiR" screens show limited overlap (46%) when considering all differentially expressed microRNAs between native ESC and ESC-derived cardiomyocytes, the overlap is greatly increased when only microRNAs with increased abundance are compared (85%). This comparison allowed the identification of 7 "cardiomiRs" whose expression is increased during cardiomyogenesis (Table 1)[102,103].

MicroRNA-1 and microRNA-133 are pivotal regulators of muscle differentiation[104] and loss of microRNA-1 or microRNA-133 results in embryonic lethality due to several cardiac failures, including defective morphogenesis, electrical conduction and cardiomyocyte proliferation[101,105]. MicroRNA-1 and microRNA-133 are polycistronically transcribed from a duplicated locus in the human genome on chromosomes 18 and 20. MicroRNA-1 and microRNA-133 expression is under control of SRF and promotes cardiac mesoderm formation from naive ESCs[101,106].

MicroRNA-1 is highly conserved among mammals and its expression in ESC shifts their gene expression profile toward that of cardiomyocytes[107,108]. The induction of the cardiomyogenic phenotype is mediated through several cooperative actions of microRNA-1. Inhibition of Notch signaling by microRNA-1-mediated direct repression of Dll1[106] and its downstream effector Hes1[109], liberates the expression of the cardiac transcription factors GATA4, Nkx2.5 and Myogenin, whereas repression of the histone deacetylase HDAC4[104] liberates the cardiac transcription factor Mef2c (Figure 2). Additionally, repression of Hand2[110] and the smooth muscle transcription factor Myocardin[111] by microRNA-1 facilitate cardiomyocyte maturation through the repression of proliferation of mesenchymal progenitors and smooth muscle gene expression, respectively. Interestingly, the sole expression of microRNA-1 in cardiac fibroblasts is sufficient to induce cardiac reprogramming[112].

MicroRNA-133 aids in cardiomyogenesis, however, in contrast to microRNA-1, its sole expression is insufficient to differentiate ESC into spontaneously contracting cells[106]. MicroRNA-133 promotes the actions of microRNA-1 through the suppression of smooth muscle specific genes in the myogenic precursors, thereby facilitating cardiomyocyte maturation. The direct repression of SRF[104,105] and the mesenchymal transcription factor Snai1[113] during cardiac differentiation of ESC or reprogramming of cardiac fibroblasts into cardiomyocytes reduces smooth muscle and fibroblast associated genes, which allows for the maturation of cardiomyocytes (Figure 2).

The cardiac myosin genes, which facilitate cardiac contraction, house three additional cardiomiRs, namely microRNA-499 and the microRNAs-208a and b that are encoded by the Myh7b and Myh6/7, respectively[114]. MicroRNA-499 facilitates expression of the cardiogenic transcription factor Mef2c[103] through a Wnt/β-Catenin-mediated mechanism (Figure 2)[115], which remains to be elucidated but appears to involve repression of the transcription factor Sox6 and the transcription inhibitor Regulator of differentiation (Rod)-1[116].

MicroRNA-208a and microRNA-208b are involved in cardiomyocyte maturation and orchestrate the expression of myosin fibers in the heart. In the adult heart, the abundance of myosin fibers are alpha fibers (or fast fibers) whereas in the developing heart the majority of myosin fibers are beta fibers (or slow fibers). The gene encoding alpha-MHC encodes a cardiac-specific microRNA (microRNA-208a) that targets the repressors of beta-MHC Sox6, Purβ and SP3[114,117]. MicroRNA-208a-mediated repression of these inhibitors thus facilitates the expression

Table 1 MicroRNAs involved in cardiomyocytes differentiation

microRNA	Targets	Effect on cardiomyogenesis (mechanism)	Used in reprogramming	Ref.
Increased during cardiomyogenesis				
1	Dll1 (Notch)	↑ CM Differentiation (↑ Nkx2.5 and Myogenin)	+	[102-104,106,109-111]
	Hes1 (Notch)	↑ CM Differentiation (↑ Nkx2.5 and GATA4)		
	Hand2	↓ CM Proliferation		
	HDAC4	↑ CM Differentiation (↑ Mef2c)		
	Myocardin	↑ CM Maturation (↓ SMC phenotype)		
30a-e	Snai2	↑ CM Differentiation (↓ mesenchymal genes)	-	[102,103,120]
	Smarcd2	↑ CM Differentiation (↓ mesenchymal genes)		
	Tnrc6a	↑ CM Maturation (↓ miR-206: ↓ SMC Phenotype)		
133a-b	Snai1	↑ CM Differentiation (↓ mesenchymal genes)	+	[102-105,113]
	SRF	↓ CM Proliferation		
	Cyclin D2	↓ CM Proliferation		
181a-d	?	↑ CM Proliferation	-	[103,175]
195	Cyclin D1	↓ CM Proliferation	-	[102,103,119,176]
	HMGA	↓ CM Differentiation (↓ Nkx2.5)		
208b	Myostatin	↑ CM Proliferation	+	[103,114,117,118]
	Sox6, Purβ	↑ CM Maturation (↑ beta-Myosin Heavy Chain)		
	THRAP1	↑ CM Maturation (↑ beta-Myosin Heavy Chain)		
499-5p	? (↑ Wnt)	↑ CM Differentiation (↑ Nkx2.5, Mef2c and GATA4)	+	[102,103,115]
Decreased during cardiomyogenesis				
31	?	?	-	[103]
34c-3p	?	?	-	[103]
151-3p	ATP2a2	↓ CM Maturation (↓ beta-Myosin Heavy Chain)	-	[103,177]
221	?	?	-	[103]
222	?	?	-	[103]

ATP2a2: Sarcoplasmic reticulum Ca^{2+} ATPase 2; CM: Cardiomyocyte; Dll1: Delta-like 1; GATA4: GATA Binding Protein 4; Hand2: Heart and neural crest derivatives expressed 2; HDAC4: Histone deacetylase 4; Mef: Myocyte enhancer factor; miR: MicroRNA; Nkx2.5: NK2 homeobox 5; Purβ: Purine-rich element binding protein beta; Smarcd2: SWI/SNF related matrix associated actin dependent regulator of chromatin subfamily d member 2; SMC: Smooth muscle cell; Snai: Snail family zinc finger; Sox6: Sex determining region Y-box 6; SRF: Serum response factor; THRAP1: Thyroid hormone receptor associated protein 1; Tnrc6a: Trinucleotide repeat-containing gene 6A; Wnt: Wingless-type MMTV integration site family.

of beta-MHC by the developing cardiomyocyte. Moreover, the beta-MHC gene (encoded by Myh7) contains the related microRNA-208b. Expression of beta-MHC, induced by microRNA-208a, thus induces the expression of microRNA-208b that provides a feed forward mechanism that maintains the expression of beta-MHC[114,117]. Additionally, microRNA-208 targets myostatin[118], a known inhibitor of cardiac progenitor cell proliferation, which reduces the inhibitory effect of myostatin on cardiac progenitor cell propagation.

The other cardiomiRs, microRNA-30a-e, microRNA-181a and microRNA-195, are less well characterized. Overexpression of microRNA181a in ESC increased proliferation of differentiated cardiomyocytes through unidentified mechanisms[103], whereas the expression of microRNA-195 decreases cardiomyocyte proliferation through the inhibition of cell cycle regulator cyclin D1[119]. MicroRNA-30a-e regulate cardiomyogenesis by targeting Snai2 and Smarcd2[120], two known inducers of mesenchymal gene expression. Their inhibition by microRNA-30a-e thus favors maturation of the cardiac phenotype over the maintenance of the mesenchymal phenotype (Figure 2).

The non-cardiac restricted microRNAs let-7, microRNA-99, and the microRNA-17/92 cluster also facilitate cardiomyogenesis[121,122]. MicroRNA-99 facilitates the transition from mesenchymal precursor to cardiac progenitor cells by the Smarca5-mediated repression of TGFβ signaling[121]. Additionally, let-7 induces the expression of cardiogenic transcription factors GATA4, Mef2c, Nkx2.5 and Tbx5 by the repression of EZH2, a histone methyltransferase that epigenetically silences these genes in mesenchymal precursors[121]. The microRNA-17/92 cluster subsequently facilitates ventricular myocyte generation from the first heart field. The microRNA-17/92 cluster targets Tbx1 and ISL1, the master transcription factors for second heart field development, thereby favoring differentiation of the first heart field (Figure 2)[122].

Notably, Jayawardena *et al*[112] used the most abundantly expressed cardiomiRs, *i.e.*, microRNA-1, 133, 208 and 499, to reprogram cardiac fibroblasts directly into cardiomyocytes. Transient expression of these four microRNAs *in vitro* generated mature cardiomyocytes that spontaneous beat, albeit at low efficiency (1.5%-7.7% of all fibroblasts). The reprogramming efficiency could be increased to about 28% by the addition of a Janus Kinase inhibitor. Moreover, the four microRNAs reprogram cardiac fibroblasts *in vivo* in an mouse model of MI, providing therapeutic proof-of-concept for the microRNA-mediated reprogramming of fibroblasts to ameliorate damage following MI[112].

Thus, advances in iPSC biology and cardiac reprogramming have identified exogenous growth factors and endogenous transcription factors that drive cardio-

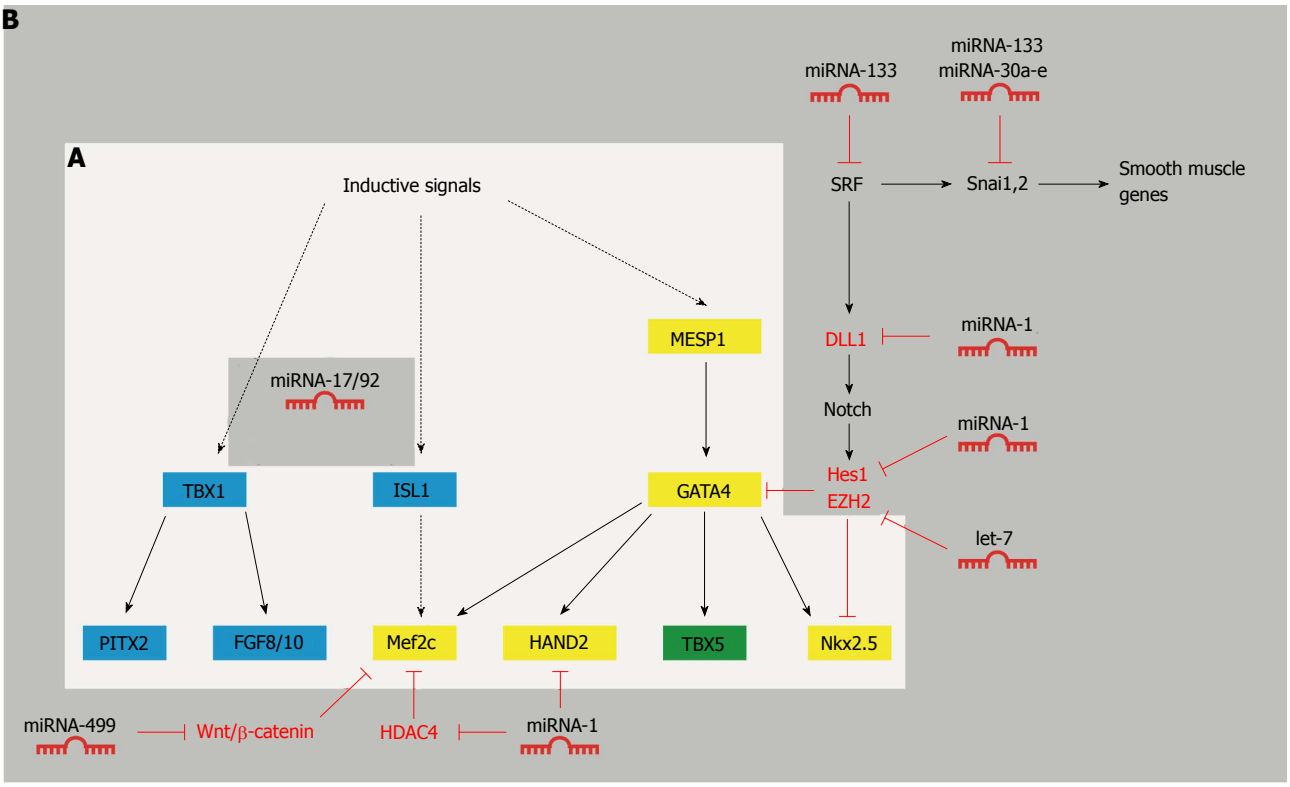

Figure 2 The complex web of transcription factors in cardiac specification and their regulation by microRNAs. A: Crosstalk between transcription factors involved in the formation of the first and second heart field (light grey box). MESP1, GATA4, Mef2c, HAND2 and Nkx2.5 are central transcription factors in the first and second heart field (yellow). TBX5 is only expressed in the first heart field (green). ISL1 and TBX1 are expressed in the second heart field (blue); B: MicroRNA-mediated regulation of cardiac transcription factors during cardiomyocyte differentiation (dark grey box).

myogenesis, and have provided novel therapeutic approaches for the amelioration of damage from MI by the therapeutic expression of cardiac transcription factors. Moreover, these recent advances have provided a platform to study cardiogenesis in more detail. MicroRNAs can similarly induce fibroblast reprogramming into cardiomyocytes and can be delivered to the cardiac tissue without the use of randomly integrating viruses, and may thus improve safety of reprogramming in a clinical context. The question that remains is how to deliver these microRNAs safely and efficiently to the site of damage and cell type of choice to perform their function. This question is addressed in the next section.

TARGETING MICRORNAS FOR CARDIAC REGENERATION

MicroRNA-mediated reprogramming of cardiac fibroblasts *in vivo* requires advanced delivery strategies. In the section below, we will describe general and targeted drug delivery strategies and discuss possibilities to specifically target microRNAs to cardiac fibroblasts.

A range of chemical modifications to enhance cellular uptake of microRNAs have been developed recently. Additionally, particulate drug delivery systems, including liposomes, polymeric micelles, polymeric vesicles, polymeric nanoparticles (NPs), and dendrimers have been investigated for targeted delivery of drugs[123] including microRNAs in a variety of disease models outside the cardiac field and with varying degrees of success. Current advances in targeted drug delivery from these fields provide a solid basis for the burgeoning field of cardiac drug delivery.

In general, the prime reasons for targeted drug delivery is the modulation of the drug's pharmacokinetics, the avoidance of toxicity of the drug in non-diseased tissue or cells and to alter the apparent physicochemical characteristics of a drug by making use of a carrier. An ideal drug delivery vehicle needs to be non-toxic, biocompatible, non-immunogenic and biodegradable[123]. Particle sizes of the drug delivery system have a preferred size between 10 and 200 nm. The lower limit is determined by the glomerular permselectivity in the kidney that captures particles below 10 nm and rapidly clears them through renal filtration[124], whereas the upper limit is set by clearance through the reticuloendothelial system and uptake by the spleen and liver[125]. Additionally, surface charge and chemistry are key parameters in the design of drug delivery systems. Systems with a positive surface charge may electrostatically interact with the cell membrane or its associated negatively-charged proteoglycans and subsequently internalized through endocytosis[126,127]. Negatively charged systems are preferentially recognized by monocytes/macrophages and internalized *via* the calveolar or clathrin endocytic

pathways[128-130].

Classes of drug targeting systems

Cardiac microRNA delivery poses huge challenges as unmodified microRNAs are rapidly degraded by systemic nucleases, secreted through renal filtration and phagocytosed by monocytes/macrophages, limiting their ability to reach their target cell[131,132]. A range of chemical modifications to enhance microRNA stability and cell permeability, including 2'-O-methyl modifications, locked nucleic acid chemistry, the conjunction of small molecules or cell penetrating peptides (Figure 3)[133] and peptide nucleic acids have been developed that increase therapeutic efficacy of microRNA therapies (reviewed in[131,132,134]), albeit they do not add cell or organ specificity. Hence, the development of targeted delivery systems for myocardial microRNA delivery is of the upmost importance.

As described above, various particulate drug delivery systems have been developed for cell and organ specific targeted delivery of drugs (Table 2). Liposomes[135], the related polymerosomes[136] and polymeric micelles[137] are a system of lipids or polymers that self-assemble into spherical structures with an aqueous core that can hold the microRNA payload[123,138,139]. Single or multiple types of lipids and polymers can be combined to generate liposomes, polymerosomes and polymeric micelles, which allows for additional flexibility in designing the physical and chemical properties of the drug delivery vehicle[140]. Liposomes and polymerosomes are internalized *via* endocytosis and destined for lysosomal degradation[141]. Endosomal escape from the liposomal content occurs through pH-sensitive fusion of the liposome and the endosomal membrane, resulting in drug release in the cytoplasm[142]. Although liposomes have a long history in drug delivery in basic and clinical medicine with FDA approval, some concerns regarding their clinical applicability are reported, such as the immunogenicity and toxicity of certain cationic lipid particles[143,144]. Regardless, liposomes and polymerosomes are highly promising for future clinical microRNA delivery.

Microbubbles (Table 2) are a second class of drug delivery systems that can be used for microRNA delivery *in vivo* and represent a specialized form of liposome that is sensitive to external clues, such as high powered ultrasound (described below). Microbubbles are gas-filled lipid spheres of various diameters (10-1000 nm)[145,146]. Cationic microbubbles can form complexes with anionic drugs, such as microRNAs, by electrostatic interaction[147,148]. The sensitivity of microbubbles to ultrasound, which destroys the microbubble, delivers the payload directly to its environment[145,147]. Hence, for efficient targeting of microRNAs into the tissue, additional modifications to the microRNA (described above) may be necessary to increase cellular uptake by the target cells[131,132].

Nanoparticles and nanospheres (Table 2) are a third class of drug delivery vehicles that consist of lipids or block co-polymers, respectively[149,150]. Nanoparticles and nanospheres are commonly produced using emulsion or precipitation techniques which form solid structures typically 10-100 nm in size[139,151]. Changing the composition of the block co-polymers that build up the nanoparticle allows tuning drug delivery rates[128], as drug delivery occurs through diffusion of the drug through the solid nanoparticle or *via* biodegradation of the particle[139,150,151]. The solid nature of nanoparticles confers great stability advantages *in vivo* and provides slow-release properties. Therefore, nanoparticles are more efficient in delivering proteinaceous and small molecule drugs than microRNAs, as cellular uptake and degradation properties are inferior to the delivery efficiency of liposomes and polymeric micelles.

Dendrimeres (Table 2), represent the last class of drug delivery systems are highly branched macromolecules with a controlled repeated branching around a central core that forms a small (1-10 nm), spherical and highly dense nanocarrier that holds many cavities that may contain drugs[152-155]. Targeting efficacy and extravasation of dendrimeres can be controlled by their size, molecular weight and the functional groups present on their surface[153,156].

Passive drug targeting

Targeting of drug delivery systems can be achieved *via* two general concepts, namely passive or active targeting. Passive targeting is based on the so-called enhanced permeability and retention effect (EPR)[157]. At sites of inflammation, the integrity of the endothelial lining is often compromised, resulting in a defective or leaky vasculature. Circulating drug delivery systems are able to pass these leaky vessels and can thus enter the inflamed tissue. Hence, colloidal drug delivery systems passively accumulate at sites of inflammation, such as the infarcted heart[158,159]. An important prerequisite for passive targeting is a relatively long (hours-days) circulation time of the drug delivery system since extravasation occurs only by chance. Additionally, if passive drug delivery is to be used to target cardiac fibroblasts, detection by monocytes/macrophages needs to be avoided in order to reduce rapid clearance of the drug carriers from the cardiac tissue by these phagocytic cells.

Active drug targeting

Active targeting drug delivery systems are equipped with specific targeting devices that recognize or have affinity for certain cells. Although the recent identification of biomarkers that are differentially expressed in the diseased cardiac tissue has advanced the development of experimental therapies that can be employed for the targeted delivery of microRNAs, there is a huge challenge for active-targeting strategies to find specific target molecules for a certain disease process and to test its effectiveness in drug delivery therapies.

Active drug targeting of microRNAs to cardiac fibroblasts may be achieved in two distinct manners, depending on the interaction of the targeting device and the cell. Either the drug delivery system can be internalized by the cell where it releases the microRNAs subsequently (epitope targeted drug delivery, Figure 3), or the drug delivery system can

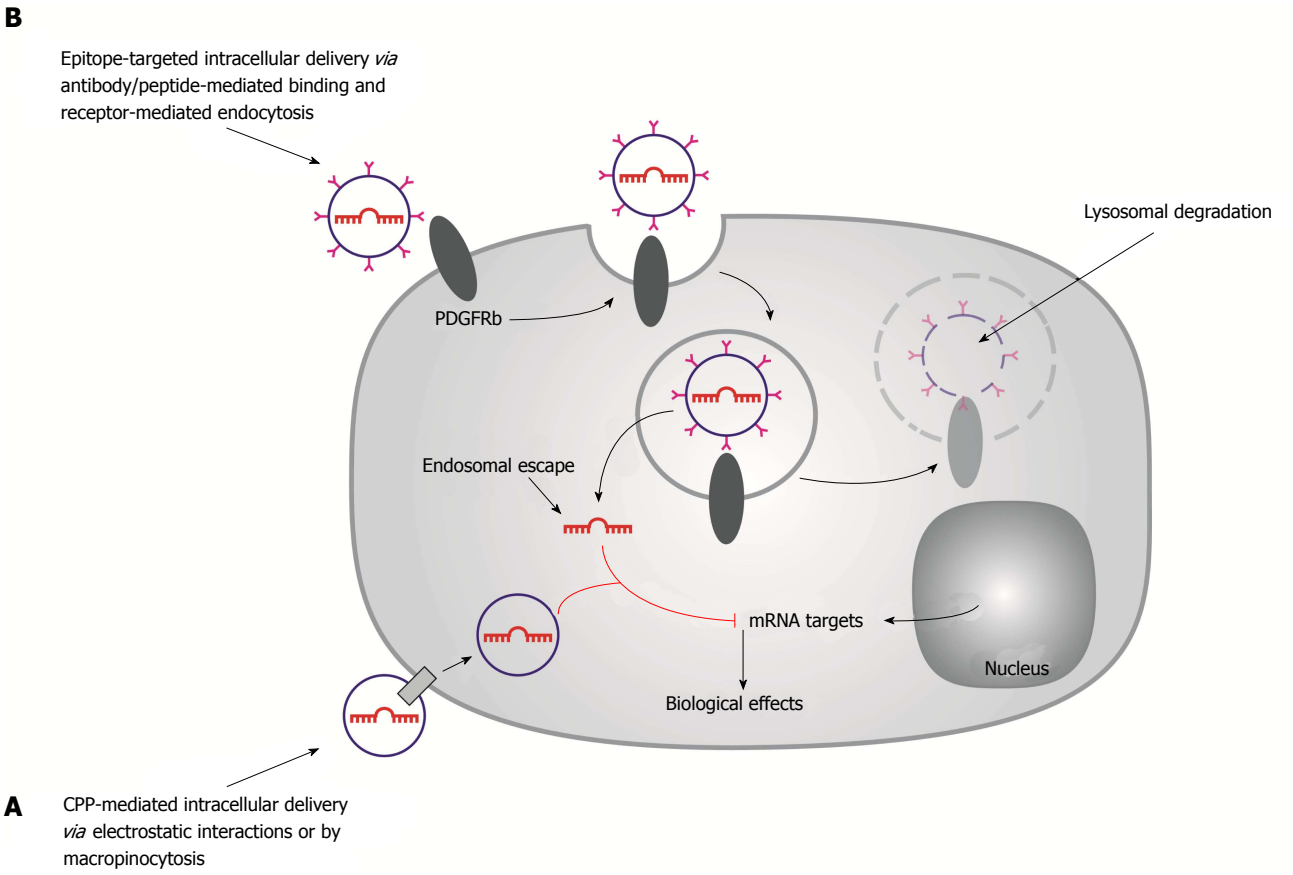

Figure 3 Schematic of passive and active targeted drug delivery systems for microRNA delivery. A: Passive targeting by cell-penetrating peptide-coated nanoparticles are internalized by receptor-mediated endocytosis; B: Active targeting by PDGFRb-targeted liposomes. Liposomes interact with cell surface receptors (PDGFRb) and internalized *via* receptor-mediated endocytosis. The endocytotic vesicles fuse to form early endosomes which ultimately become part of the lysosomes, where proteins and nucleic acids are degraded by acid hydrolases. To achieve target gene silencing, microRNAs need to be released from the liposome and escape from the endosomes into the cytoplasm, where the microRNA directs the cleavage of target mRNAs.

bind to the cell and act as a drug release depot that can be activated at the diseased site (inducible targeted drug delivery). Although targeted drug delivery approaches have been pursued cardiovascular disease, data on the delivery of microRNA to fibroblasts are scarce[160].

Epitope targeting of drug delivery systems is a rapidly evolving field in cardiac drug delivery and was shown by Dasa *et al*[161], who used *in vivo* phage display methods to identify peptide sequences specific for cardiac endothelial cells, cardiomyocytes and myofibroblasts[161]. These peptide sequences were conjugated to 1,2-distearoyl-sn-glycero-3-phosphoethanolamine (DSPE) liposomes using polyethylene glycol (PEG). The obtained peptide-PEG-DSPE was loaded with the small molecule inhibitor of PARP-1 activation AZ7379. Although the publication only shows proof-of-concept data in efficiently (> 90%) reducing PARP-1 activation in cardiomyocytes[161], it is tempting to assume that the targeted delivery of small molecule inhibitors or microRNAs to cardiac fibroblasts would be equally efficient as antibody-functionalized liposomes are highly efficient in delivering non-coding RNAs to vascular cells[162].

Inducible targeted drug delivery uses drug delivery systems that are sensitive to their environment, *e.g.*, heat[163], light[164], pH[165] or ultrasound[145], that will release their payload by the indicated external trigger if present at the disease site. Ultrasound-sensitive microbubbles (described in section "Classes of drug targeting systems") have been used for cardiac microRNA delivery with high efficiency, although reports on targeting of cardiac fibroblast remain scarce. Gill *et al*[166] used liposomal ultrasound-sensitive microbubbles to deliver microRNA-133 into HL1 cardiomyocytes *in vitro*. Both encapsulated (inside the microbubble) and complexed (on the outer shell of the microbubble) microRNA formulations efficiently delivered the microRNA-133 mimic, without affecting cardiomyocyte viability, indicating that, although encapsulation increases the microRNA-carrying capacity of microRNAs, complexation strategies do not affect the ability of microbubbles to deliver microRNAs[166]. Using a similar approach, Liu *et al*[167] delivered microRNA-21 mimics into the hearts of swine without inflicting cardiac damage. Myocardial microRNA-21 expression levels were efficiently elevated in hearts treated with the microRNA-microbubble complex that received ultrasound activation compared to control conditions. Interestingly, the transfection efficiency of microRNA-microbubble complexes that were administered by intracoronary

Table 2 Characteristics of particulate drug delivery systems

Carrier	Size range (nm)	Preparation method	Advantages for drug delivery	Disadvantages for drug delivery	Ref.
Liposomes and polymerosomes	10-2000	Self-assembly in aqueous solutions	High drug-carrying capacity Good for hydrophobic and hydrophilic drugs Surface functionalization possible Simple preparation	Batch-to-batch variability Difficulties in sterilization	[123,135,138,141,143,150,161,178]
Microbubbles	10-1000	Various depending on type	Surface functionalization possible	Not good for hydrophobic drugs Low drug-carrying capacity	[145-148,166,168,179]
Polymeric micelles	10-100	Direct organization or controlled aggregation in solvent	Long blood circulation time Surface functionalization possible Simple preparation	Not good for hydrophobic drugs Low drug-carrying capacity	[123,136,137,155,158]
Nanoparticles and nanospheres	10-100	Nanoparticles: Polymerization of monomers by emulsion Nanospheres: Interfacial polymerization and phase inversion with polymeric emulsions	Shape, size and mechanical properties tunable Possibility for controlled release	Toxicity of residual chemicals from preparation process Limited cellular uptake and degradation	[123,126,128,139,150,151,155,180]
Dendrimeres	1-10	Convergent or divergent synthesis	High functionalized surface	Difficult preparation process Toxicity	[123,154,156]

injection was higher compared to systemic administration. These results indicate that the application site may affect therapeutic outcome and should be considered in clinical translation[167]. Kwekkeboom *et al*[168] delivered microRNA mimics and antimiRs to the cardiac endothelium using a combination of microbubbles and ultrasound activation. Notably, delivery of antagomiRs (cholesterol-conjugates antimiRs[169]) had a higher transfection efficacy compared to control antimiRs implying that cellular uptake of delivered microRNAs is still highly dependent on their physicochemical properties[168].

The concept of cardiac fibroblast reprogramming into cardiomyocytes holds great therapeutic value for the treatment of MI and its associated cardiac failure. However, fibroblast reprogramming is a recent concept and although current studies have provided proof-of-concept, focus on its clinical translation is limited. A range of drug delivery systems are reported for the delivery of microRNAs outside the cardiac field (reviewed in[149,170]) that can easily be transposed onto the reprogramming paradigm. As this field evolves, clinically relevant delivery approaches and suitable targeting epitopes for fibroblast-specific drug delivery will be explored as will their clinical effectiveness.

SUMMARY AND FUTURE PERSPECTIVES

Deciphering the signaling pathways that underlie cardiac development has led to new therapeutic strategies that trigger cardiac regeneration. Vast progress is made in promoting cardiomyocyte proliferation and in direct reprogramming of cardiac fibroblasts into cardiomyocytes, which offer new perspectives on the possibility to advance from treating cardiac disease to curing cardiac disease. Additionally, advances in drug delivery have yielded a plethora of drug delivery systems that can selectively deliver therapeutic agents to relevant cell populations at the site of damage. However, many challenges remain to be addressed before clinical translation can commence.

During a MI, billions of cardiomyocytes are lost and although current reprogramming strategies using exogenous transcription factors or microRNAs have emerged as potential therapeutic strategies, they are vastly inefficient. Thus, to enhance cardiac regeneration it will be pivotal to develop procedures that increase the yield and efficiency of generating *de novo* cardiomyocytes. Advancing our mechanistic understanding of the reprogramming process, including the directed differentiation of subtypes of cardiomyocyte (*i.e.*, ventricular, atrial or nodal), is key to the success of this promising therapy, however when subtype specification occurs during development and how these processes are regulated remain elusive. Moreover, *in vivo* efficacy and safety in large animals needs to be addressed before clinical translation can commence.

Additionally, it has been reported that the delivery of immature or heterogeneous populations of cardiomyocyte derived from progenitor cells or iPSC can lead to arrhythmias[171,172]. Currently, reprogrammed cardiomyocytes are immature and phenotypical heterogeneous, which could contribute to arrhythmogenesis. Hence, it is crucial to promote maturation and integration of reprogrammed cardiomyocytes. Yet, our current understanding of these processes is limited and further research into these processes is highly warranted.

While an intense research focus has been on the

development of new drug delivery systems, efforts to identify epitopes that are differentially expressed in diseased cardiac tissue has received little attention, as the field of cardiac drug delivery is still in its infancy. The identification of target epitopes that discriminate between fibroblasts in the affected *vs* the healthy tissue is pivotal to clinical translation of targeted delivery of microRNAs using liposomes, polymeric micelles or microbubbles. In addition, the heart contains a large population of fibroblasts that are necessary for its normal function[173,174]. Therefore, it may be detrimental to the cardiac function to target all fibroblasts for reprogramming. Drug delivery systems may need to be comprised of multiple targeting mechanisms, *e.g.,* ultrasound sensitive and fibroblast targeted, if a sufficiently selective molecular targeting epitope cannot be identified that distinguishes fibroblasts in the scar tissue from those elsewhere in the heart.

In summary, MI results in a massive loss of cardiomyocytes that are replaced by scar tissue. Endogenous repair mechanisms are insufficient to efficiently regenerate the lost myocardial tissue and therapeutic approaches to induce cardiomyocyte proliferation using growth factors are relatively ineffective. Advances in our basic understanding of cardiomyogenesis obtained from embryology and iPSC biology has led to the identification of factors that drive cardiomyogenesis, and have provided a novel therapeutic approach for the amelioration of damage from MI through the therapeutic delivery of microRNAs that reprogram cardiac fibroblasts into cardiomyocytes. These microRNAs can be delivered to the cardiac fibroblasts using advanced drug delivery systems. Although there are many challenges ahead in advancing this emerging technology, the opportunities and potential clinical benefits are substantial and we are confident that the field will continue to push this technology further in the years to come.

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REVIEW

Genetic testing in congenital heart disease: A clinical approach

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Abstract

Congenital heart disease (CHD) is the most common type of birth defect. Traditionally, a polygenic model defined by the interaction of multiple genes and environmental factors was hypothesized to account for different forms of CHD. It is now understood that the contribution of genetics to CHD extends beyond a single unified paradigm. For example, monogenic models and chromosomal abnormalities have been associated with various syndromic and non-syndromic forms of CHD. In such instances, genetic investigation and testing may potentially play an important role in clinical care. A family tree with a detailed phenotypic description serves as the initial screening tool to identify potentially inherited defects and to guide further genetic investigation. The selection of a genetic test is contingent upon the particular diagnostic hypothesis generated by clinical examination. Genetic investigation in CHD may carry the potential to improve prognosis by yielding valuable information with regards to personalized medical care, confidence in the clinical diagnosis, and/or targeted patient follow-up. Moreover, genetic assessment may serve as a tool to predict recurrence risk, define the pattern of inheritance within a family, and evaluate the need for further family screening. In some circumstances, prenatal or preimplantation genetic screening could identify fetuses or embryos at high risk for CHD. Although genetics may appear to constitute a highly specialized sector of cardiology, basic knowledge regarding inheritance patterns, recurrence risks, and available screening and diagnostic tools, including their strengths and limitations, could assist the treating physician in providing sound counsel.

Key words: Congenital heart disease; Genetics; Genetic screening; Genetic testing

Core tip: Monogenic models and chromosomal abnormalities have been associated with syndromic and non-

syndromic forms of congenital heart disease (CHD), paving the way for genetic investigation and testing to shoulder an important role in patient management. Herein, we present an overview of the role of genetics in CHD, propose various clinical scenarios in which genetic testing may be appropriate, and discuss practical implications with regards to when and how to order genetic tests. Summary tables are provided regarding the various genes implicated in syndromic and non-syndromic forms of CHD and recurrence risks in siblings and offspring.

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INTRODUCTION

Congenital heart disease (CHD) afflicts 2 to 3 children per 100 live births[1,2]. It is the most common type of birth defect and encompasses a wide range of malformations. The spectrum of severity ranges from insignificant and even self-resolving lesions, such as ventricular septal defects that spontaneously close, to highly complex and multiorgan manifestations that are incompatible with natural survival. While much progress has been made regarding the management of children and adults with CHD, a greater understanding of underlying etiologies could potentially lead to further advances in preventive care and therapeutic strategies[3].

The complexity and heterogeneity of CHD has traditionally been attributed to multifactorial etiologies arising from interactions between multiple genes and environmental factors (so-called "polygenic model")[4]. Early investigations into environmental factors spawned recommendations for maternal multivitamin supplementation containing folic acid to reduce risks of developing CHD[5-7]. Other implicated maternal factors include pregestational diabetes, pollakiuria, febrile illnesses, rubeola, influenza, alcohol consummation, cigarette smoking, and teratogenic pharmacological agents such as thalidomide, warfarin, angiotensin converting enzyme inhibitors, and certain anticonvulsant and anti-inflammatory drugs[8].

Technological advances have permitted the confirmation of clinically suspected monogenetic subtypes of CHD, with dominant or recessive inheritance patterns. However, some forms of CHD could not be explained by a polygenic model[9], with much higher recurrence risks in first-degree relatives than predicted[3,10]. Chromosomal abnormalities have been associated with cardiac defects, particularly in the setting of syndromic phenotypes (*e.g.,* trisomy 21, DiGeorge, and Williams-Beuren syndromes). In so-called multiplex families with several affected members, identified candidate genes have been consistent with monogenetic models with Mendelian inheritance. Furthermore, the rate of CHD increases with consanguinity, as described in Arabic countries[11].

The fact that monogenic and chromosomal abnormality models account for a substantial proportion of CHD enhances the potential value of genetic investigation and testing[12]. Genetics carries the potential to unravel etiological mysteries that underpin CHD, provide pathophysiological insights, assist in risk assessment, inform clinical management, and counsel families regarding future offspring. The focus of this review is on the genetics of structural CHD, as opposed to other disease categories such as inherited channelopathies. Our review known implicated genes and chromosomal abnormalities, discussed when and how to perform genetic testing, and shared our perspective regarding clinical applications.

GENETICS IN STRUCTURAL CONGENITAL HEART DISEASES

Approximately 30% of patients diagnosed with CHD have syndromic phenotypes with extracardiac manifestations. The influence of genetics is well established for chromosomal aneuploidies such as Down, Turner, and DiGeorge syndromes. Other syndromes are linked to a mutation or deletion in one gene, such as Noonan, Alagille, and Holt-Oram syndromes[3]. For the 70% of CHD cases that are non-syndromic, new genes with Mendelian inheritance (dominant or recessive) have been identified, particularly in families with several affected members. Table 1 summarizes current knowledge regarding genetic etiology for several forms of CHD with syndromic or non-syndromic phenotypes.

Genes etiologically linked to CHD directly impact embryologic development. For example, defects in genes responsible for the embryonic formation of the atrial septum (*e.g.,* MYH6, TBX20) can result in atrial septal defects (ASD)[13,14]. In addition to their function in embryologic cardiac development, implicated genes may also play a role in heart regulation throughout life[15]. The critical purpose of these genes, which are primarily transcription factors, explains the possibility of dominant heritability. A mutation that modifies the protein function in one of these genes may have a major effect on cardiac development and regulation. Furthermore, interactions between transcription factors explain the diverse consequences associated with individual mutations. For example, NKX2.5 mutations may result in ASD, atrioventricular block, ventricular septal defect (VSD), Ebstein anomaly, and tetrology of fallot (TOF). GATA4, a transcription factor, has been associated with ASD, VSD, and pulmonary stenosis. TBX1 has been implicated in TOF, patent ductus arteriosus, and interrupted aortic arch; and TBX20 in ASD, VSD, valve defects, and impaired chamber growth. In addition to these transcription factors, other genes with varied roles have been implicated in CHD, such as MYH6, which codes for an alpha myosin heavy chain (ASD) and Notch 1, which is implicated in valve formation (bicuspid aortic valve and aortic stenosis)[15,16].

Table 1 Genes described in syndromic and non-syndromic forms of congenital heart disease

Syndromic: Syndrome name Non syndromic: Gene implicated	Phenotype associated with structural heart disease	Syndromic: Chromosomal aneuploidie, microdeletion or gene/locus/inheritance Non syndromic: Locus/inheritance	Ref.
Atrioventricular septal defect (AVSD)			
Down syndrome	MR, facial dysmorphia	Trisomy 21	[71-73]
Edward syndrome	IUGR, facial dysmorphia, clenched fingers	Trisomy 18	[74]
Patau syndrome	Cleft lip and palate, microphthalmia, polydactyly	Trisomy 13	[74]
Holt-Oram syndrome	Preaxial limb defects, absent or dysmorphic thumbs, cardiac conduction disease	TBX5/12q24.1/AD	[75]
Noonan syndrome	Hypertrophic cardiomyopathy, short stature, broad neck, unusual chest shape, facial dysmorphia, developmental delay	PTPN11/12q24/AD, *de novo*; SOS1/2p21/AD, *de novo*; KRAS /12p12.1/AD, *de novo*	[76]
Ellis-van Creveld syndrome	Common atrium, polydactyly, deformity of upper lip, dwarfism with narrow thorax, ASVD partial to complete	EVC and EVC2/4p16/AR	[77]
Locus 1p31-p21	AVSD partial to complete	Gene no yet found/AD	[78]
CRELD1	partial AVSD, heterotaxy syndrome	3p25/AD	[79-81]
GATA4	Family with ASD, VSD and one member with AVSD	8p23.1/AD, *de novo*	[82]
Atrial septal defect (ASD)			
Holt Oram syndrome	See AVSD above	See above AVSD	[83,84]
Noonan syndrome	See AVSD above	See above AVSD	[85,86]
Ellis-van Creveld syndrome	See AVSD above	See above AVSD	[77]
Cardiofaciocutaneous syndrome	Hypertrophic cardiomyopathy, facial dysmorphia, skin abnormalities: keratosis pilaris, nevi	MAP2K1/15q22.31/AD, *de novo*; MAP2K2 /19p13.3/AD, *de novo*; KRAS/7q34/AD, *de novo*; BRAF/12p12.1/AD, *de novo*	[87]
Cri du Chat	Sound of cry similar to cat's cry, facial dysmorphia, MR	CTNND2/5p15.2/*de novo*	[88]
NK2X-5	+/- Atrioventricular block	5q35.1/AD	[89]
GATA4	+/- Pulmonary stenosis	8p23.1/AD, *de novo*	[82,90]
MYH6		14q11.2/AD	[13]
TBX20		7p14.2/AD	[14,91]
Ventricular septal defect (VSD)			
Holt Oram syndrome	See AVSD above	See AVSD above	[92]
Ellis-van Creveld syndrome	See AVSD above	See AVSD above	[77]
Cri du chat	See AVSD above	See AVSD above	[88]
Down syndrome	See AVSD above	See AVSD above	[93,94]
Edward/patau syndrome	See AVSD above	See AVSD above	[95,96]
Digeorges syndrome	Facial dysmorphia, speech delay, learning delay, psychiatric disorder, cleft palate, immune deficiency, hypoplastic/aplastic thymus, hypocalcaemia.	Deletion 22q11.21/*de novo*, AD	[97]
NK2X-5	Atrioventricular block	5q35.1/AD	[89]
GATA4		8p23.1/AD, *de novo*	[82,98]
Ebstein anomaly			
Down syndrome	See AVSD above	See AVSD above	[99]
NKX2-5		5q35.1/AD	[100]
Pulmonary stenosis			
Noonan syndrome	See ASVD above	See AVSD above	[101, 102]
Costello syndrome	Hypertrophic cardiomyopathy, MR, loose skin, facial dysmorphia large mouth	HRAS/11p15.5/AD	[103]
Leopard syndrome	Lentigines, short stature, hearing loss, closed to Noonan syndrome	PTPN11/12q24/ D, *de novo*; RAF1/3p25.2 /AD, *de novo*; BRAF/7q34/AD, *de novo*	[104]
Alagille syndrome	Pulmonary branch stenosis, bile duct paucity, cholestasis, facial dysmorphia, deep-set eyes, butterfly vertebrae	JAG1/20p12/AD NOTCH2/1p12/AD Deletion/20p12/AD	[105, 106]
Cardiofaciocutaneous syndrome	See ASD above	See ASD above	[107]
GATA4	+/- Atrial septal defect	8p23.1/AD, *de novo*	[90, 108]
Aortic valve stenosis			
Turner syndrome	Female, webbed neck, widely spaced nipples, short stature, streaked ovaries	Monosomy X or mosaics (45,X/46,XX)	[109]
Noonan syndrome	See above AVSD	See above AVSD	[76]
NOTCH1		9q34.3/AD	[16, 110]
SMAD6		15q22.31/?	[111]
Supravalvular aortic stenosis			
Williams-Beuren syndrome	Elfin facies, cocktail personality, hypercalcaemia, developmental delay, thyroid disorder, renal and connective tissue abnormalities.	Deletion/7q11.23/*de novo*, AD	[112]
Aortic coarctation			
Turner syndrome	See aortic valve stenosis above	See aortic valve stenosis above	[109]

Down/Edward/Patau syndrome	See AVSD above	See AVSD above	[113]
NOTCH1		9q34.3/AD	[110]
Bicuspid aortic valve			
Turner syndrome	See aortic valve stenosis above	See aortic valve stenosis above	[109]
Anderson syndrome	Long QT syndrome, ventricular arrhythmias, sudden cardiac death, facial dysmorphia, short stature	KCNJ2/17q24.3/AD	[114]
NOTCH1		9q34.3/AD	[16,110]
SMAD6		15q22.31/?	[111]
Tetralogy of fallot			
DiGeorges syndrome	See VSD above	See VSD above	[97]
Alagille syndrome			
	See pulmonary stenosis above	See pulmonary stenosis above	[105,106]
Cat-Eye syndrome	Dysmorphic ears, microphthalmia, anal atresia, renal abnormalities, coloboma, cleft palate	Duplication/22q11/*de novo*	[115]
NKX2.5		5q35.1/AD	[100]
GATA4		8p23.1/AD, *de novo*	[116]
NOTCH1		9q34.3/AD	[16]
FOG2		8q23.1/?	[117,118]
Truncus arteriosus			
Digeorges syndrome	See VSD above	See VSD above	[97]
Hypoplastic left heart syndrome			
NKX2.5		5q35.1/AD	[119]
NOTCH1		9q34.3/AD	[16,110]

The phenotype syndrome most commonly associated with the particular CHD is indicated in bold. AVSD: Atrioventricular septal defect; ASD: Atrial septal defect; VSD: Ventricular septal defect; MR: Mental retardation; IUGR: Intrauterine growth retardation; AD: Autosomal dominant; AR: Autosomic recessive; CHD: Congenital heart disease.

WHEN AND HOW TO PERFORM A GENETIC INVESTIGATION?

When to consider genetic testing

The first clinical situation to consider genetic testing in CHD is the presence of a syndromic phenotype. A comprehensive clinical examination is paramount in recognzing extracardiac involvement. Common physical findings include facial dysmorphia (eye, ear, mouth, nose abnormalities), limb dysmorphia (atrophy, length reduction), hand and feet dysmorphia (polydactyly, short fingers, clinodactyly), and other skeletal abnormalities such as scoliosis[17]. Growth delays may be identified by monitoring height and weight and neurological status must be assessed to diagnose mental impairment and learning disabilities. Other organs must be screened to exclude associated gastrointestinal, urologic, and genital defects. Thus, a thorough investigation often involves a multidisciplinary approach including a neurologist, ophthalmologist, otolaryngologist, gastrointestinal specialist, and orthopedic surgeon. Additional paraclinical testing may be guided by the clinical examination: radiography, abdominal ultrasound, cerebral imaging, and laboratory testing (liver and renal function, and others depending on the clinical examination). While investigating newborns in the intensive care unit can be particularly difficult, it is important to identify defects that may benefit from early surgical intervention. Variable expressivity adds a further layer of complexity justifying a broader screening approach. For example, it has been recommended to screen all children with supra-valvular aortic stenosis or pulmonary stenosis for Williams-Beuren syndrome and those with an interrupted aortic arch, truncus arteriosus, TOF, VSD with aortic arch anomaly, isolated aortic arch anomaly, or discontinuous branch pulmonary arteries for DiGeorge syndrome[17]. In general, genetic consultation is recommended when a probable syndromic phenotype is identified.

The second clinical situation to consider genetic testing is in the context of a multiplex family, *i.e.,* a family in which a person diagnosed with CHD has an afflicted first- or second-degree relative. A comprehensive clinical investigation includes a detailed assesment of past medical, surgical, and family histories. A family history can point to a genetically transmitted disease and is important in understanding inheritance patterns (autosomal recessive, dominant, X-linked, and mitochondrial), penetrance, and expressivity of genetic variations. While some have advocated exhaustive family history questionnaires[18], basic themes include screening for cardiac diseases within families, particular phenotypes such as dysmorphias, aborted pregnancies, other birth defects, infertility, and early deaths. Importantly, in some families with CHD, different phenotypes may be expressed such as a bicuspid aortic valve in one family member and hypoplastic left heart syndrome in another. The origin of all four grandparents may provide relevant information, such as the potential for consanguinity. If positive elements are detected, a detailed family tree should be performed that includes each proband's first- and second-degree relatives. The family tree may be further expanded, depending of which side of the family has diseased members. Supportive documents, such as surgical and autopsy reports, should be sought. It is also important to update family pedigrees to include new events over time.

In summary, the phenotypic description associated with the family tree is an essential tool in guiding further genetic investigation. Identification of a clinical feature related to an established syndrome associated with CHD should prompt syndrome-specific investigation. Wider scale screening is recommended on the basis of variable expressivity

for syndromes such as Williams-Beuren and DiGeorge. For non-syndromic CHD, the family tree may orient the clinician towards a genetic etiology and a specific pattern of inheritance. Nevertheless, in the majority of cases, there are no known karyotype abnormalities to investigate. Currently, genetic testing of known cardiac candidate genes is not routinely recommended in the clinical setting. However, genetic testing of multiplex families in the context of research studies may identify novel mutations in known genes or entirely new causal genes.

Choosing a genetic test

An individualized approach to genetic testing begins with the diagnostic hypotheses elicited by a thorough clinical assessment. In general, chromosomal abnormalities represent changes in the structure or number of chromosomes and are diagnosed by cytogenetic methods. The standard metaphase karyotype analysis detects numerical and structural chromosomal aberrations with a resolution of 5 megabases. It is indicated to search for such anomalies as trisomy 21, 18, 13, or monosomy X. Fluorescence in situ hybridization (FISH) is a method to detect deletion or duplication of specific regions of DNA using targeted probes. It provides a higher resolution than karyotype and is the predominant technique used to identify Williams-Beuren, DiGeorge, and Alagille syndromes. Subtelomere FISH analyses, while less commonly used today, provide a high resolution to detect abnormalities in subtelomere (*i.e.,* DNA segments between telomeric caps and chromatin) and telomere (*i.e.,* regions of repetive nucleotide sequences at each end of a chromatid) DNA regions[17]. Subtelomeric anomalies have been reported in patients with a syndromic phenotype associated with facial dysmorphia and mental retardation combined with CHD such as VSD, ASD, pulmonary stenosis, and right sided aortic arch[19,20].

Array-based comparative genomic hybridization (aCGH) is used to detect unbalanced structural and numerical chromosomal abnormalities with a resolution inferior to 5 megabases, such as copy number variants (CNV), *i.e.,* number of copies of a particular gene that deviate from normal (two for autosomes, one X chromosome for males (XY), and two X chromosomes for females (XX). This molecular karyotype provides rapid identification of duplications/deletions, unbalanced translocations, and aneuploidies. This method analyzes the entire genome and compares it to controls, in contrast to FISH techniques that target specific DNA regions. It may be particularly useful when a probable chromosomal syndrome is identified but the karyotype is normal and there is no known specific region to test[21]. Furthermore, this method is of additional value in detecting CNVs such as in screening for DiGeorge syndrome when the karyotype and 22q11 microdeletion analyses by FISH are unrevealing[20]. Cytogenetic testing has been recommended for all children with CHD associated with mental retardation, developmental delay, dysmorphic features, or other organ involvement and for establishing a prenatal diagnosis when CHD is identified by fetal echocardiography[17]. Most CNV studies in CHD report 10%-25% of abnormal findings across the disease spectrum.

Gene mutations represent a second category of genetic abnormalities. Mutations can affect the coding portion of a gene, a case in which interpretation is usually straightforward. They can also affect the non-coding portion of the genome, in which case they are more difficult to interpret. With the advent of NextGeneration sequencing technologies, large gene panels, which specifically target genes that are known or suspected to play a role in cardiac biology, can be more readily screened than previously possible by Sanger sequencing[22,23]. This approach affords a high quality diagnosis. Gene sequencing can be helpful in conditions such Noonan syndrome, Alagille syndrome with a normal FISH analysis, Holt-Oram syndrome, and several other diseases.

Interpretation of a genetic test

When a genetic variation is diagnosed, the clinician must determine its relation to the phenotype. Although genetic variants are identified with increasing frequency by high throughput sequencing, not all variants are pathogenic[22,23]. Determination of pathogenic potential is based on the following three questions: (1) Has this genetic variant already been described in association with the particular phenotype? (2) Is the genetic variant predicted to alter gene function or regulation, gene coding, or the gene splice site, and does it occur in an evolutionarily conserved nucleotide? and (3) Does the genetic variant segregate with the affected family members and not unaffected members or controls? This assessment is not foolproof. For example, genetic variants may be identified in unaffected family members because of variable penetrance and expressivity. Each genetic result must, therefore, be placed in context of the clinical and family evaluation.

Genetic counseling

Genetic counseling is important before and after genetic testing[24]. Prior to testing, the patient or guarantor should be informed of the risks of a negative result arising from the fact that all genes implicated in a given phenotype have not been identified. Second, the pathogenic potential of a genetic variant may be difficult to determine. Third, if a genetic familial disorder is identified, the patient is responsible for informing the family. After genetic testing, counseling is important to review the results, explain the genetic variant, and discuss implications with the patient and family[25].

OBJECTIVES OF GENETIC TESTING IN CLINICAL PRACTICE

Confidence in the diagnosis

Objectives of genetic testing may vary according to the clinical scenario. One objective is to establish confidence in the diagnosis. An accurate diagnosis could allow the clinician to explain causes and mechanisms of disease, provide more precise prognostic information, and elucidate implications for future offspring. Genetic counseling is of

paramount importance in relaying such information[26].

Appropriate management

Non-cardiac organ involvement: An accurate diagnosis could alert the clinician to the possibility of associated non-cardiac organ involvement. Down, Patau, Edward, DiGeorge, Turner, Williams-Beuren, Noonan, and Alagille syndromes all involve extracardiac abnormalities[27].

Craniofacial anomalies have been associated with endocardial cushion defect, truncus arteriosus, and aortic arch anomalies; respiratory disease with endocardial cushion defect and pulmonary valve disease; genitourinary malformations with septal defects, pulmonary valve disease, aortic valve disease, and truncus arteriosus; and situs inversus with heterotaxy and endocardial cushion defect[27].

Establishing a genetic diagnosis could help orient clinical and paraclinical investigations and subspecialty referral for all potential organs involved. Unrecognized and untreated interactions between various organ pathologies could worsen the cardiac prognosis. Identification of a genetic syndrome may also prove useful in the event of an emergency, when a frequent complication associated with a given syndrome occurs. Moreover, recognition of a syndrome provides a more defined guide for follow-up, including surveillance and screening for reported complications.

Other associated cardiac complications: In addition to the genetic origins of CHD, genetic variations can modulate the propensity to develop associated cardiac complications, such as arrhythmias[28] and heart failure[29,30]. Transcription factors play a key role in the formation of cardiac structures and maintenance of cardiac function and, conversely, their dysregulation can have multifaceted manifestations. For example, in the setting of an ASD, those with an NKX2.5 syndrome are more likely to develop atrioventricular block and progressive ventricular dysfunction[28]. Interestingly, patients with NKX2.5 mutations can also develop dilated cardiomyopathy[31]. *TBX5*, a gene implicated in Holt-Oram syndrome (septation defects, atrioventricular node disease, and upper limb defects) also modulates diastolic function[32]. Genes implicated in RASopathy syndromes responsible for Noonan, Leopard, cardiofaciocutaneous, and Costello syndromes are also responsible for cardiac hypertrophy in later development[33]. Thus, the genetic environment could modulate the prognosis of various forms of CHD, help to elucidate risks of developing conduction defects and systolic and diastolic dysfunction, and a provide a basis to adapt follow-up accordingly.

Overlap of CHD with muscular heart disease: Structural CHD and cardiomyopathy may be modulated by the same mutations that give rise to varied phenotypes within the same family. For example, some family members with a TBX20 mutation may have an underlying ASD, VSD, or mitral valve disease or may present exclusively with pulmonary hypertension or cardiomyopathy[14]. Mutations in MYH6 (alpha-cardiac myosin heavy chain) are associated with various forms of CHD but also dilated and hypertrophic cardiomyopathy[34]. Moreover, mutations in MYH7 have been reported in patients with Ebstein anomaly and left ventricular noncompaction[35,36]. Some family members may have CHD whereas others could develop progressive cardiomyopathy or electrophysiologic disorders. Thus, if a mutation is discovered in a family with a discordant phenotype, clinical screening and genetic testing can identify seemingly phenotypically normal individuals who are at risk of developing cardiomyopathy or electrophysiologic manifestations.

Prognosis: In addition to the prognostic implications of genetic factors discussed above, certain gene defects have been associated with post-operative survival and long-term outcomes. For example, endothelin-1 G5665T has been associated with transplant-free survival in patients with single ventricles, primarily hypoplastic left heart syndrome[37]. This variant is linked to increased vascular reactivity and hypertension. Similarly, in a study of genetic variants involved in vascular response and oxidative stress, two major alleles of two single nucleotide polymorphisms (SNPs; *i.e.,* VEGFA rs833069 and SOD2 rs2758331) were associated with worse transplant-free survival in patients with non-syndromic CHD[38]. The higher number of copies of deleterious alleles, the worse the prognosis[38]. Genotype has also been associated with early postoperative outcomes. For example, in patients with TOF, 22q11.2 deletion (DiGeorge syndrome) predicts a longer cardiopulmonary bypass time and a greater length of stay in intensive care[39]. While several explanations have been proposed, potential factors include a higher prevalence of aortopulmonary shunts and respiratory problems prior to surgical repair in patients with 22q11.2 deletion, resulting in longer mechanical ventilatory support. Conceivably, a SNP profile may one day prove to be of value in pre-operative risk assessment.

Therapeutic potential: Ultimately, the holy grail of genetically diagnosing CHD is to provide targeted curative therapy. While such interventions are currently beyond our reach, provocative studies support its potential. For example, a knock-out model of Wnt2 in null mutants results in a phenotype resembling complete atrioventricular septal defect[40,41]. The phenotype could be rescued *in vivo* by pharmacological activation of Wnt signalling.

Genetics and recurrence risk

With a Mendelian pattern of inheritance, recurrence risks are 50% and 25% for autosomally dominant and recessive genes, respectively. However, variable penetrance complicates these predictions, even for syndromic CHD. In the majority of cases with CHD, difficulties in estimating recurrence risks are compounded by the absence of a clear genetic diagnosis[42,43]. Estimates are, therefore, largely based on a detailed family tree and the published literature[18].

In patients with atrial septal defects, the recurrence

Table 2 Recurrence risks for non-syndromic congenital heart disease in first-degree relatives

Type of non-syndromic CHD	Recurrence risk of same CHD in first-degree relatives (%)	Recurrence risk of discordant CHD in first-degree relatives (%)	Recurrence risk of any CHD in first-degree relatives (%)
ASVD	1.10	2.2	3.30
ASD	0.88	2.4	3.28
VSD	0.67	1.9	2.57
ASD and VSD	0.24	2.2	2.44
Conotruncal defect[1]	1.30	2.4	3.70
Right ventricular outflow tract obstruction[2]	1.70	3.0	4.70
Left sided obstructions[3]	0.79	2.4	3.19

The recurrence risks for non-syndromic CHD in first-degree relatives are derived from a Danish cohort study[10,56]. [1]Tetralogy of fallot, truncus arteriosus, interrupted aortic arch, double outlet ventricle, transposition of the arteries; [2]Pulmonary valve stenosis, infundibular or subvalvular stenosis, double chambered right ventricle; [3]Bicuspid aortic valve, aortic coartaction, aortic stenosis, hypoplastic left heart, shone complex. First-degree relatives include parents, siblings and twins; CHD: Congenital heart disease; ASVD: Atrioventricular septal defect; ASD: Atrial septal defect; VSD: Ventricular septal defect.

risk has been estimated to be 3% in first-degree relatives, although a dominant inheritance pattern has been described in some families. A CHD recurrence risk of 1.2% was reported for first-degree relatives with an isolated septal defect[10]. For probands with atrioventricular septal defects, the prevalence of any CHD in a family member appears to be in the order of 12%-15% overall, 1%-2% of parents, 2%-4% of siblings, and 10%-14% of offspring[44-46]. Risk of recurrence is greater if the mother rather than the father has the atrioventricular septal defect (*i.e.,* 14% *vs* 10%). Nevertheless, exact figures remain debated with some studies reporting considerably lower risks[10]. In TOF, the recurrence risk has been estimated to be 2.5%-3% overall, with a phenotype that is often concordant[44,47]. However, the recurrence risk in offspring is higher when the mother is affected[9]. Moreover, some families without a 22q11 deletion syndrome have been suspected of having a recessive inheritance pattern[48]. In complete transposition of the great arteries, a very low recurrence risk has been described with no offspring affected in a British collaborative study, suggesting a sporadic model[9]. Other studies have reported a recurrence risk of 1.8% in siblings[49] and 2.7% in first-degree relatives (siblings and parents)[50], which includes varied forms of CHD such as aortic valve stenosis and double outlet right ventricle[50]. In patients with congenitally corrected transposition of the great arteries, a 5.2% recurrence risk was reported in siblings, with concordant and discordant phenotypes, including complete transposition of the great arteries, suggesting that some genes may be common to both types of transposition[51].

Left-sided obstructive lesions (*e.g.,* aortic coarctation, hypoplastic left heart syndrome, aortic stenosis, bicuspid aortic valve, and hypoplastic aortic arch) may segregate within families, suggesting a common genetic basis[52,53]. Overall recurrence risks have ranged from 1.8% to 3.2% of siblings, 3% of offspring of affected fathers, and 8% to 13% of offspring of affected mothers[52]. However, much higher recurrence risks have been described in certain geographic locations, such as 37% of first-degree relatives in Texas[52]. Moreover, some defects appear to have higher recurrence risks, such as aortic coarctation (13% of siblings)[50], hypoplastic left heart syndrome (31% of siblings)[50], and bicuspid aortic valves (> 10% of siblings)[54,55]. However, considerably lower recurrence risks for left-sided obstructive lesions in first degree relatives have also been reported (*e.g.,* 0.79% with a relative risk of 12.9)[10].

As noted by the examples above, estimating recurrence risks is an imperfect science. Empiric estimates consider the mathematical prediction of recurrence in a polygenic model of inheritance combined with the type of CHD, current knowledge base, and relationship to proband. As a general rule of thumb, recurrence risks are in the order of 1% to 6% for siblings of affected probands with unaffected parents and increase to approximately 10% when two siblings are affected. Recurrence risks in offspring are greater than siblings, higher if the proband is the mother[3], and generally higher for left-sided obstructive lesions (8%-10%). A recent population-based study from Denmark challenges these statistics and provides far lower estimates for first-degree relatives than previously reported, as summarized in Table 2[10]. These disparate results could be explained, in part, by differences in the study designs and methodologies employed, and underscore the difficulties in accurately quantifying recurrence risks. Estimating recurrence risks must consider an in depth analysis of the family history to identify specific patterns of inheritance. If the pedigree is not informative and estimates are based on a polygenic model of inheritance, limitations of empiric estimates should be discussed with the patients, including the possibility of under- or overestimation. The notion of concordant or discordant recurrent phenotypes should also be conveyed. Overall, exact concordance is low for left-sided obstructive defects (26%), intermediate for outflow tract defects (37%), and higher for septal defects (48%)[43]. Conceptually, CHD may be grouped into constellations of malformations such as septal defects, conotroncal anomalies, and left-sided obstructive lesions that share implicated genes, although such a concept is not universally supported[56].

Assessing family members

A strong case has been made for screening first-degree relatives of patients with left-sided obstructive lesions and bicuspid aortic valves. As previously noted, recurrent phenotypes in first-degree relatives are relatively common and frequently discordant such that a bicuspid aortic valve, aortic coarctation, and/or aortic dilation may be identified in asymptomatic family members. Echocardiographic screening has been recommended for first-degree relatives of patients with bicuspid aortic valve or supra-aortic stenosis, since a physical examination alone lacks sensitivity[57]. The rationale for family screening is that early

detection may help avert complications related to aortic dilatation (*e.g.,* 6-fold higher risk of aortic dissection), aortic stenosis, aortic insufficiency, endocarditis, and aortic coarctation (*e.g.,* arterial hypertension). Early detection may lead to lifestyle recommendations (*e.g.,* limit isometric exercises), enhanced monitoring (*e.g.,* for progressive aortic dilatation), or preventive surgery (*e.g.,* prior to aortic dissection). Age at screening remains controversial. It should generally be proposed to adults if not previously performed during childhood.

At present, systematic screening of first-degree relatives is not recommended for other forms of non-syndromic CHD. However, fetal echocardiographic screening is indicated if either parent is afflicted with any form of CHD. It should be performed in a specialized center at 18-20 wk of gestation[58]. Early detection of complex CHD can drastically improve outcomes by planning delivery in a specialized (level 3) tertiary care center with appropriate monitoring and early catheter-based or surgical interventions when indicated[58-60]. Furthermore, prenatal diagnosis may lead to a parental decision to terminate the pregnancy.

Finally, identification of a specific mutation in a multiplex family with CHD may allow for targeted screening of additional family members. While there is no clear-cut indication for genetic screening to identify CHD in family members with structurally normal hearts, there may be a rationale to screen seemingly normal family members for entities that include CHD as one aspect of a multiple constellation phenotype.

Prenatal diagnosis

The impact of a prenatal diagnosis of CHD on the pregnancy termination rate varies by region. For example, reported pregnancy termination rates for severe CHD identified by prenatal screening were 45% in the Netherlands[58], 49% in Boston, MA[61], and 86% in Switzerland[62]. In a study from France, factors associated with pregnancy termination included severity of CHD, gestational age at diagnosis, presence of chromosomal abnormalities, and parental ethnicity[63].

Fetal genetic screening for CHD is also possible, including genome-wide high-resolution SNP arrays to identify CNVs[64] and competitive genomic hybridization to detect submicroscopic chromosomal aberrations[65]. A prenatal diagnostic test can be performed after chorionic villus sampling before 14 wk of gestation. Thus far, such testing has been limited to specific disease entities such as trisomy 21, 18, and 13, cystic fibrosis, and microdeletion syndromes (*e.g.,* DiGeorge). It could also be performed for any severe monogenetic disease if the result could influence the decision to terminate pregnancy[66]. Preimplantation diagnostic testing could be proposed in selected cases, particularly for women with a history of multiple therapeutic abortions. It has already been used for Holt Oram and Marfan syndromes[67]. Beyond syndromes such as trisomy 21, 18 or 13, prenatal or preimplantation genetic screening remains controversial. Ethical dilemmas may arise as a result of uncertainties in interpreting tests, potential for false positives, and the inability to predict disease severity, penetrance and expressivity of a mutation, and concordant or discordant phenotypes.

Limitation of genetics in CHD

Despite the fact that CHD is the most common birth defect, the genetic etiology remains unknown in the majority of cases, with slower progress than for other forms of heart disease such as inherited arrhythmia syndromes and hypertrophic and dilated cardiomyopathy. Genetic studies in CHD were traditionally restricted to multiplex families with strong phenotypic penetrance, which represent the minority of cases[40]. The relatively low familial recurrence risk is not fully understood but may be due, in part, to *de novo* mutations, incomplete penetrance, and other etiological factors such as environmental influences. Patterns of inheritance may be difficult to sort out in the presence of environmental interactions, age-dependent or incomplete penetrance, and variable expressivity. In addition, genetic analysis based on individual families requires a large number of members or consanguinity[11]. Moreover, mutations may involve non-exonic DNA, such as regulatory regions, the functional validation of which is more difficult and resource consuming. Establishing genotype-phenotype correlations may be further complicated by mutations that are rare and unique to individual families[2]. In fact, most CHD mutations identified to date appear to be private or do not recur. Despite these numerous limitations, genetics has and will hopefully continue to provide insights into the etiology of CHD, embryonic heart development, potential therapeutic targets, risk assessment, and patterns of inheritance.

Future perspective

Objetives of genetic testing for clinical reasons differ from research goals. From a clinical perspective, a genetic test should be directly relevant to a patient by serving the purpose of establishing or confirming a diagnosis, providing prognostic information, informing therapeutic decisions, and/or assisting with family planning. In contrast, genetic testing for research purposes may provide pathophysiological insights into a disease entity and identify potential therapeutic targets, thereby carrying the potential to impact care at a longer-term horizon. Nevertheless, genetic results derived from research studies are generally communicated to the clinical team and may directly contribute to the care of a given family[68]. It is important, therefore, for the clinical team to be well versed in the domain in order to effectively communicate with the patient, explain results, and establish an appropriate surveillance plan. In parallel, genetic testing within clinical laboratories may discover new mutations in known genes and novel implicated genes, particulary when modern technologies that sequence a broad array of genes are applied. In the future, therefore, enhanced partnerships between clinical and research teams could maximize the potential for progress. Resources available for research, including highly qualified personnel, informatics infrastructures, laboratory equipment, novel platforms, and more rapid time to analyses could complement the

clinical laboratory setting in enhancing clinical care. Greater integration between clinical and research teams could also contribute to ensuring that discoveries are progressive and clinically meaningful, with direct applications to patient care. Along these lines, the multicenter prospective "CHD GENES" study was initiated in December 2010 to explore relationships between genetic factors, clinical features, and outcomes in patients with CHD[2].

CONCLUSION

Despite major inroads over the past few decades in genetics related to CHD, the majority of patients with CHD are without a genetic diagnosis such that the etiology of their CHD remains incompletely understood. In this article, we discussed the multifaceted implications of genetics in CHD including the potential for personalized care, confidence in the clinical diagnosis, prognostic implications, early identification of non-cardiac organ involvement and associated complications, and tailoring clinical follow-up. Genetic testing could also provide valuable information in predicting recurrence risk, defining the pattern of inheritance, screening family members, and family planning. Various methodologies are available to diagnose chromosomal abnormalities and gene mutations. The challenge lies in first identifying potential genetic etiologies, selecting the appropriate test, and interpreting the test within the context of available knowledge. Collaboration between clinicians and genetics researchers offers the best opportunity for progress in clinical care and innovative breakthroughs[69,70]. Much remains to be discovered in tapping the potential of genetics in CHD.

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MINIREVIEWS

Diagnosis and management of patients with asymptomatic severe aortic stenosis

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Abstract

Aortic stenosis (AS) is a disease that progresses slowly for years without symptoms, so patients need to be carefully managed with appropriate follow up and referred for aortic valve replacement in a timely manner. Development of symptoms is a clear indication for aortic valve intervention in patients with severe AS. The decision for early surgery in patients with asymptomatic severe AS is more complex. In this review, we discuss how to identify high-risk patients with asymptomatic severe AS who may benefit from early surgery.

Key words: Aortic stenosis; Asymptomatic; Diagnosis; Management; Treatment

Core tip: We focused on how to identify high-risk patients in asymptomatic aortic stenosis. Revised American Heart Association/American College of Cardiology guidelines and diagnostic testing for appropriate clinical decision making are discussed in this article.

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INTRODUCTION

As a result of the aging population, aortic stenosis (AS) is currently one of the most common valvular heart diseases to need surgical intervention. AS is a slowly progressive chronic condition, but once a patient becomes symptomatic, the prognosis is dismal. Although percutaneous valve technology is now approved for high-risk patients with symptomatic AS, clinical management of asymptomatic patients with severe AS is still difficult. Assessment of symptoms in sedentary elderly patients with severe AS is often challenging. It is common for patients to have nonspecific symptoms such as shortness of breath or general feelings of weakness that can be

explained by many reasons other than cardiac diseases. Advances in multiple modality imaging provide additional objective information about subtle functional deterioration of the left ventricle (LV), myocardial tissue damage, and the amount of the valve calcification. Existing and new parameters are investigated to improve the clinical decision-making process.

In this review, we focus on recent advances in diagnostic methods for assessment of AS and discuss how to implement these methods in current clinical practice as it relates to the management of patients with asymptomatic severe AS.

PATHOPHYSIOLOGY AND HEMODYNAMICS OF AS

A normal aortic valve is tricuspid and a normal valve opening area is 3 to 4 cm^2. Progression from aortic valve sclerosis to AS is reported to be 9% per 5 years[1]. There is some evidence to suggest that NOTCH 1 genetic mutations and specific lipoprotein polymorphism is associated with congenital AS and valve calcification[2]. In AS, it has been reported that an average rate of increase in mean gradient is 7 to 8 mmHg/year; in maximum velocity, 0.2 to 0.4 m/s per year; and in a decrease in valve area, 0.1 to 0.15 cm^2/year[3-6]. Hemodynamic progression of AS is gradual and linear, though there is variability and some patients present with rapid progression. Presence of aortic valve calcification, coronary artery disease, advanced age, renal impairment, and baseline AS severity are risk factors for rapid progression[4,7-9].

The hemodynamic progression of AS lead to LV hypertrophy (LVH) as a compensation mechanism of the heart. Morphological changes such as increasing muscle fiber thickness, collagen volume, and interstitial fibrosis occur in AS patients[10]. These changes result in LV diastolic and systolic dysfunction[11]. LV mass regression starts soon after aortic valve replacement (AVR) and may continue through another 8 years postoperatively, while diastolic dysfunction persists up to 2 years due to the relatively increased amount of fibrotic tissue in the myocardium[12-14]. These results may encourage AVR before the fibrotic change becomes too substantial or irreversible to advance postoperative recovery. Thus, the amount of myocardial structural change in AS can be a good parameter to define the severity of AS, and the new imaging technique gains greater prominence to determine the timing of surgical intervention in asymptomatic severe AS[15].

When the valve area is decreased to one-fourth of the normal valve area (0.75-1.00 cm^2), in general, patients develop symptoms, although there is high inter-individual variability. A fundamental principle of fluid dynamics is that flow velocity within the conduit depends on volumetric flow rate. Patients with normal LVEF (LV ejection fraction) and normal flow will generally have a mean gradient > 40 mmHg in the setting of severe AS. However, recent studies have identified a new entity, termed "paradoxical low-gradient severe AS", where the stroke volume is reduced in the setting of increased afterload and concentric LVH, resulting in a low gradient despite severe AS in the setting of normal LVEF. Recent American College of Cardiology/American Heart Association (ACC/AHA) guidelines have recognized this entity and have developed guidelines for management of this new group of AS patients.

DEFINITION OF AS

AHA/ACC guidelines for the management of patients with valvular heart disease, which was revised in 2014, has a major change for the staging of AS (Table 1)[16].

It should be noted that the stage D3 definition is based on a relatively new concept related to the progression of AS. Specifically, low-flow/low-gradient AS with preserved EF represents a more advanced stage of AS with severe concentric hypertrophy, high peripheral arterial pressure, and low systemic arterial compliance[17-19]. Valvulo-arterial impedance (Zva) calculated as shown below was introduced as a global hemodynamic load on the LV in AS[17,20,21]. Zva = (systolic blood pressure + mean gradient of aortic valve)/stroke volume index.

More importantly, low-flow/low-gradient severe AS is reported to have a poorer prognosis without surgical intervention in some studies[17,22,23], while other studies report a better prognosis-similar to the prognosis of patients with moderate AS[24-26]. Nevertheless, the majority of evidence is in favor of the new entity termed "paradoxical low-gradient AS", in which LVEF is preserved yet the mean aortic valve gradient is low due to low stroke volume.

This condition must be diagnosed with utmost caution, avoiding measurement errors and, in some cases, establishing additional diagnostic methods such as cardiac catheterization or other imaging studies, including magnetic resonance imaging (MRI) and computed tomographic (CT) scans.

Current ACC/AHA guidelines put much more focus on velocity/pressure gradient findings than on aortic valve area (AVA) given that prior natural history studies show their prognostic importance. Namely, aortic velocity (> 4 m/s) is reported to be one of the most important factors associated with a higher event rate in AS[4,5,27]. Asymptomatic patients with very severe AS with a V_{max} $\geqslant$ 5 m/s or mean gradient $\geqslant$ 60 mmHg have an even worse event-free survival[28].

DIAGNOSTIC TESTING

Echocardiography for diagnosis of severe AS

Two-dimensional/Doppler echocardiography plays a fundamental role in the diagnosis of AS. It is important to examine the etiology of AS, visual severity of valve calcification, position of the coronary artery orifice, concomitant myocardial disease, wall motion asynergy, and other valvular heart diseases with echocardiography.

Table 1 Stages of aortic stenosis on the basis of American College of Cardiology/American Heart Association recommendations

		Hemodynamics	LV Function	AVA	Aortic valve
A	At risk of AS	V_{max} < 2 m/s	Normal EF	-	Bicuspid, sclerosis
B	Progressive AS	Mild AS: V_{max} < 2.0-2.9 m/s or mean ΔP < 20 mmHg Moderate AS: V_{max} > 3.0-3.9 m/s or mean ΔP > 20-39 mmHg	Normal EF Early diastolic dysfunction	-	Mild to moderate calcification Reduction in motion Commissural fusion
C1	Asymptomatic severe AS	V_{max} ≥ 4 m/s or mean ΔP ≥ 40 mmHg	Normal EF Diastolic dysfunction	≤ 1.0 cm^2 or ≤ 0.6 cm^2/m^2	Severe calcification Severely reduced opening
C2	Asymptomatic severe AS with LV dysfunction	V_{max} ≥ 4 m/s or mean ΔP ≥ 40 mmHg	EF < 50%	≤ 1.0 cm^2 or ≤ 0.6 cm^2/m^2	Severe calcification Severely reduced opening
D1	Symptomatic severe high-gradient AS	V_{max} ≥ 4 m/s or mean ΔP ≥ 40 mmHg	EF normal or decreased diastolic dysfunction	≤ 1.0 cm^2 or ≤ 0.6 cm^2/m^2 Larger with AR/MR	Severe calcification Severely reduced opening
D2	Symptomatic severe low-flow/low-gradient AS with reduced LVEF	V_{max} < 4 m/s or mean ΔP < 40 mmHg DOB stress shows V_{max} > 4 m/s and AVA ≤ 1.0 cm^2	EF < 50% diastolic dysfunction	≤ 1.0 cm^2	Severe calcification Severely reduced opening
D3	Symptomatic severe low-gradient AS with normal LVEF or paradoxical low-flow severe AS	V_{max} < 4 m/s or mean ΔP < 40 mmHg Stroke volume index < 35 mL/m^2	EF ≥ 50% Small LV chamber Restrictive diastolic filling	≤ 1.0 cm^2 or ≤ 0.6 cm^2/m^2	Severe calcification Severely reduced opening

Modified from Nishimura *et al*[16] with permission. ACC/AHA: American College of Cardiology/American Heart Association; AR: Aortic regurgitation; AS: Aortic stenosis; AVA: Aortic valve area; EF: Ejection fraction; LV: Left ventricular; MR: Mitral regurgitation; ΔP: Pressure gradient; V_{max}: Maximum aortic velocity.

Echocardiography can provide systolic and diastolic functions. All parameters referred to in guidelines are available by echocardiography, which sometimes needs careful data interpretation while recognizing limitations.

An important consideration in echocardiography is to detect the highest peak aortic flow velocity using multiple transducer positions (the suprasternal window and right parasternal window with right decubitus position should be used in addition to the apical window). The Pedoff probe, which has a high signal to noise ratio, is ideal to detect the highest velocity. This requires advanced operator skill and, therefore, missing the highest velocity in AS is one of the causes of underestimation of the gradient.

The pressure gradient is calculated according to the modified Bernoulli equation; the pressure gradient = 4 × v^2. However, if there is an increased velocity (> 1.5 m/s) at the LV outflow tract (LVOT) by septal thickening or by systolic anterior motion of the mitral valve, this simplified equation is less reliable. In those cases, it is recommended that the corrected peak to peak gradient should be used[29].

AVA is calculated by a continuity equation. Measurement of the LVOT size for stroke volume calculation is the second possible error for diagnostic severity. American Society of Echocardiography guidelines recommend the measurement at the same position of the pulse wave sample volume, specifically 0.5 to 1 cm below the aortic annulus[29]. Accurate measurement of LVOT diameter is critical, as the continuity method requires squaring of this measurement. Even an error of a few millimeters in this measurement can lead to large differences in the calculated valve area.

Additionally, appropriate position of the pulse-wave Doppler signal to avoid flow acceleration by calcified valve or outflow obstruction is important. Overestimation or underestimation of stroke volume can lead to an unreliable calculation of AVA. In some patients, one may also encounter dynamic LVOT obstruction with flow acceleration in the LVOT. In these patients, one must calculate stroke volume either by two-dimensional or three-dimensional volumetric methods. One can also use RVOT diameter and Doppler signals at the right ventricular outflow tract to calculate stroke volume.

AVA can also be measured by planimetry, both by transthoracic echocardiography and transesophageal echocardiography[30]. The planimetry method has its own limitations. Shadowing by calcification interferes with the visualization of the valve edge. The anatomical orifice area can be measured larger than the effective orifice area. Nonplanar structures of the valve may cause difficulty in reliable measurement, which is improved by real-time three-dimensional echocardiography[31]. With careful attention to these limitations, planimetry can be considered an alternative/complimentary measure when Doppler measurements are not appropriate.

A low-dose dobutamine stress echocardiography is performed to diagnose true or pseudo AS in low-gradient, reduced EF patients (though usually symptomatic, patients rarely present with low LVEF and gradient without any symptom). In addition, low-dose dobutamine echocardiography can identify high-risk patients who do not have contractile reserve, *i.e.*, an increase in stroke volume ≥ 20%. Loss of contractile reserve suggests a

patient may have other myocardial disease or advanced stages of severe AS. A maximum velocity ⩾ 4.0 m/s with AVA ⩽ 1.0 cm^2 at any flow rate during dobutamine stress echocardiography is diagnosed as true severe AS[16,29]. Pseudo AS would show an increase of valve area to > 1.0 cm^2. Although suggested, evidence for the use of dobutamine stress evaluation of low-flow/low-gradient AS with preserved EF ("paradoxical low-gradient severe AS") to diagnose true/pseudo AS is limited.

Diastolic dysfunction is an important parameter in the evaluation of AS. Worsening of diastolic function is related to age and other comorbidities, such as hypertension, that are not uncommon in the elderly. It has been reported by Park *et al*[32] that echocardiographic markers of diastolic dysfunction, such as increased E/e' and left atrial volume index, are associated with dyspnea in severe AS patients. Increased E/e' (> 15) has been shown to predict survival in both asymptomatic and symptomatic patients with AS (adjusted mortality risk = 2.34; 95%CI: 1.27-4.33)[33]. Although echocardiographic measures of diastolic dysfunction are markers of worse AS, current guidelines do not support its use in surgical decision making in patients with either symptomatic or asymptomatic AS.

Recent advances in echocardiography led to the development of newer methods to detect subtle changes in LV function beyond EF. Specifically, two-dimensional speckle-tracking echocardiography has been used in numerous research studies to detect early systolic functional deterioration in cardiomyopathies, including amyloidosis and hypertrophic cardiomyopathy. Global longitudinal strain (GLS) by two-dimensional speckle-tracking echocardiography is decreased in severe AS and can be used as a prognostic measure. Kearney *et al*[34] reported that decreased GLS (> -15%) in asymptomatic severe AS with preserved EF had poor survival when compared to patients with GLS ⩽ -15%, and GLS was a predictor of all-cause mortality (HR = 1.42; 95%CI: 1.27-1.59). Using echocardiography, van Dalen *et al*[35] and Staron *et al*[36] reported that increased apical rotation is more common in AS patients than control patients. In general, worsening systolic longitudinal motion, apical rotation, and diastolic untwisting working in concert are manifestations of progressive AS. Further research studies and standardization of analyzing software are necessary to incorporate these measurements into current clinical practice, specifically their role in surgical decision making for patients with asymptomatic severe AS.

CT calcification score

Aortic valve calcification (AVC) is a prognostic factor in asymptomatic AS. Rosenhek *et al*[27] evaluated the degree of AVC using echocardiography and showed moderate and severe AVC related to future death or development of symptoms (RR = 5.2; 95%CI: 2.4-13.5). However, the definition of the degree of AVC by echocardiography has not been established. Therefore, evaluation of AVC by echocardiography is still a qualitative and subjective measure that is dependent on the echocardiographer's experience. A cardiac CT scan can provide quantitative measure of AVC, and > 1000 Agaston units can be considered severe calcification[16,37]. Currently, a cardiac CT scan can be used as a complementary method for the diagnosis and management of AS[16]. When it is difficult to judge the severity of AS due to discordant measurements in echocardiography or a possible paradoxical low-flow/low-gradient AS, CT imaging can help to provide the calcium score, which relates to stenosis severity and prognosis[38,39]. Due to the recent rapid development of transcatheter aortic valve replacement (TAVR) procedures, the cardiac CT scan has emerged as a key imaging modality not only to assess aortic valve and root calcification, but also for precise measurement of the aortic annulus and peripheral arteries[40-42]. Whether or not three-dimensional LVOT measurements by CT imaging should replace echocardiography in order to resolve the measurement error issue is still uncertain, and warrants further research[43,44].

Magnetic resonance imaging

Magnetic resonance imaging (MRI) has the advantage of providing more accurate anatomical and hemodynamic information, LV mass, and stroke volume than echocardiography. In addition, cardiac MRI with gadolinium contrast can provide information about fibrosis or collagen deposition of the myocardium, which is a consequence of long-term exposure to substantial afterload. The presence or absence of myocardial fibrosis in any cardiac disease is an important prognostic factor[45-48]. Dweck *et al*[49] performed contrast-enhanced cardiac MRI in 143 AS patients, and the reported late gadolinium enhancement in the mid wall was a predictor of all-cause mortality (HR = 8.59; 95%CI: 1.97-37.38). Further research using more sensitive methods, *i.e.*, T1 mapping, to detect myocardial fibrosis in AS patients, as well as prognostic studies linking fibrosis to better outcomes, are warranted before MRI can be used in routine clinical practice for the management of patients with AS[50].

Biomarkers in AS

Brain natriuretic peptide (BNP) is thought to be a good marker of increased wall stress in the myocardium, thus BNP increases with age, the presence of hypertension, valvular heart disease, and other myocardial diseases. It has been reported that BNP increases along with the severity of AS, but considerable overlap between the groups has also been observed. Bergler-Klein *et al*[51] reported that asymptomatic severe AS patients whose plasma BNP was < 130 pg/mL rarely developed symptoms for 6 to 9 mo. Another study showed that a BNP ⩾ 300 pg/mL was a poor prognostic factor in medically followed severe AS patients who were both symptomatic and asymptomatic[33]. More recently, Clavel *et al*[52] reported that moderate/severe asymptomatic AS patients with BNP clinical activation and an elevated BNP greater than the upper normal range of the same age/sex have a higher rate of mortality (HR = 2.35; 95%CI: 1.57-3.56). Recently published research is summarized in Table 2. Disadvantages of BNP include

Table 2 High-risk patients predicted from brain natriuretic peptide level

Source	BNP cut-off value	Results	Enrolled patients
Bergler-Klein *et al*[51]	BNP 130 pg/mL	BNP < 130 pg/mL (n = 25) had better symptom-free survival (P < 0.001)	Asymptomatic severe AS, EF ⩾ 50% (n = 43)
Biner *et al*[33]	BNP 300 pg/mL	Combined use of BNP > 300 pg/mL and E/e' > 15 predicted 1-yr mortality (hazard ratio = 2.59; 95%CI: 1.21-5.55, P = 0.014)	Severe AS, symptomatic and asymptomatic, any EF included (n = 79)
Berger-Klein *et al*[54]	BNP 550 pg/mL	BNP ⩾ 550 pg/mL showed poorer survival both in medically and surgically treated groups	Indexed effective orifice area ⩽ 0.6 cm^2/m^2 with low-flow/low-gradient AS; symptomatic and asymptomatic, with EF ⩽ 40% (n = 69)
Clavel *et al*[52]	BNP ratio: Measured BNP/maximal-normal-BNP for age and sex	Higher BNP ratio showed worse mortality in asymptomatic patients with preserved EF (hazard ratio = 2.35; 95%CI: 1.57-3.56, P < 0.0001)	Total, moderate or severe AS, any EF (n = 1953) Asymptomatic, with EF > 50% (n = 565)

AS: Aortic stenosis; BNP: Brain natriuretic peptide; EF: Ejection fraction.

that fact that it is not disease-specific, and BNP levels vary even in the same patient according to physical activities and loading conditions. Therefore, a single value of BNP may not be helpful in surgical decision making in asymptomatic severe AS patients. However, serial measures and rising levels of BNP can be used for surgical decision making in asymptomatic severe AS patients, as proposed by European Society of Cardiology (ESC) guidelines[53].

Stress testing in AS

Symptom onset is the key to referring severe AS patients for AVR because of a poor prognosis without AVR. However, it is challenging in some patients who claim to be asymptomatic yet have severe AS. In order to risk-stratify high-risk asymptomatic patients, an exercise test, such as the standard treadmill test, without imaging is reasonable according to recently published guidelines[16,55-57]. Development of symptoms early on in exercise treadmill testing or an abnormal blood pressure response (below baseline or an inadequate increase of blood pressure < 20 mmHg) are considered indications for surgery in patients with severe AS; however, exercise testing is contraindicated in patients with symptomatic severe AS (Class Ⅲ)[16]. Although ESC guidelines[53] have suggested the use of an increased mean gradient during exercise testing (> 20 mmHg) as an indication for surgery in asymptomatic patients (Class Ⅱb), it was not supported in the more recent ACC/AHA guidelines[16].

Cardiac catheterization

Catheterization has the risk of a small cerebral emboli when the wire crosses the valve[58]; thus, catheterization is recommended only when there is discrepancy between noninvasive testing, clinical examination, and clinical presentation.

MANAGEMENT

Indications for AVR

It is clear that AVR is recommended in symptomatic patients with severe AS; however, the decision to recommend early surgery in asymptomatic severe AS patients is still challenging. Indications for AVR in asymptomatic patients are shown in Figure 1, which is based on 2014 AHA/ACC guidelines. Indications for AVR have been consistent between AHA/ACC guidelines and ESC guidelines, though there are slight differences. Asymptomatic patients with severe calcification and a rapid increase in aortic peak transvalvular velocity should be considered for AVR in ESC guidelines with a Class Ⅱa indication, but that is a Class Ⅱb indication according to AHA/ACC guidelines. Patients with elevated BNP levels, an increase in the Doppler mean pressure gradient with exercise, and excessive LVH may be considered for AVR by ESC guidelines (Class Ⅱb), but these are not employed in AHA/ACC guidelines.

Based on the current evidence and guidelines, it is reasonable to consider AVR in severe AS patients when (1) systolic function is decreased (EF < 50%); (2) it is very severe AS (V_{max} ⩾ 5 m/s, ΔP ⩾ 60 mmHg); (3) results of the exercise test are abnormal; or (4) there is rapid progression in AS severity (ΔV_{max} > 0.3 m/s per year) (Figure 1). One must follow patients more closely despite asymptomatic severe AS when there is (1) severe aortic valve calcification; (2) end-stage renal disease; (3) worsening diastolic dysfunction; (4) increased left atrial volume; (5) high brain natriuretic peptide, especially during serial measurements; and (6) new onset of atrial fibrillation or frequent episodes of paroxysmal atrial fibrillation.

Possible beneficial medications

Coronary artery disease and AS have similar risk factors. Additionally, AS has an active inflammation that causes valve calcification. Positive results in experimental and clinical studies on the effectiveness of statins to decrease hemodynamic progression have been published[59,60], while randomized clinical trials were performed to validate the effect of statins on AS progression[61]. Although there was the benefit of fewer ischemic cardiovascular events in the treatment groups, no considerable difference in

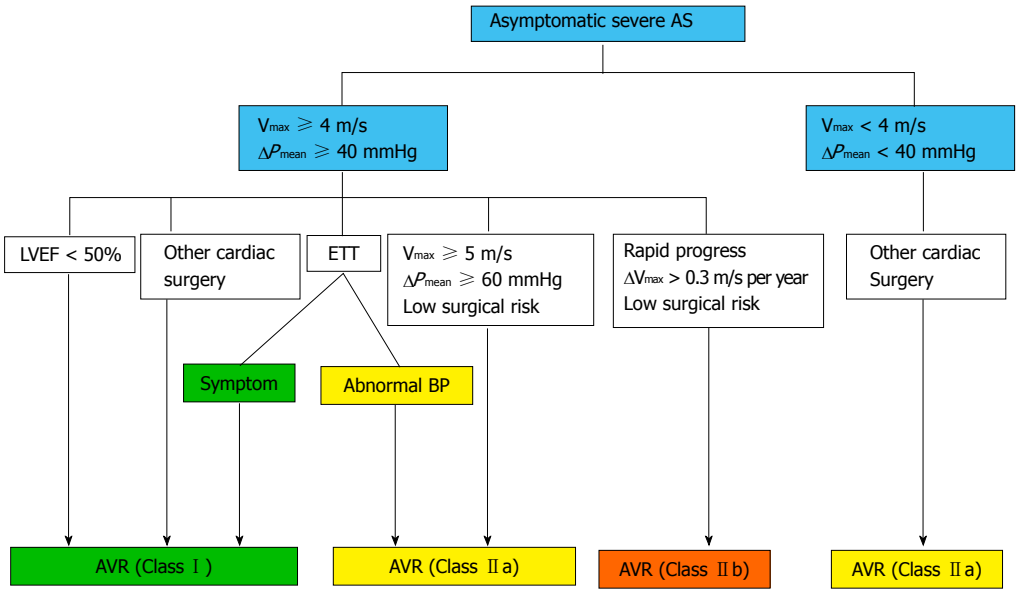

Figure 1 Indications for aortic valve replacement in patients with asymptomatic severe aortic stenosis on the basis of American College of Cardiology/American Heart Association recommendations. Modified from Nishimura *et al*[16] with permission. ACC/AHA: American College of Cardiology/American Heart Association; AS: Aortic stenosis; AVR: Aortic valve replacement; ETT: Exercise treadmill test; LVEF: Left ventricular ejection fraction.

hemodynamic progression was observed between the treatment and placebo groups[6]. However, many patients with AS have known concomitant coronary artery disease or risk factors and hyperlipidemia. Guideline-based statin therapy should be considered in these patients regardless of presence of AS.

For AS, the only effective treatment is valve replacement, but it is important to properly manage comorbidities, especially hypertension. Calcific AS is commonly found in the elderly, thus many patients have already been on antihypertensive medication at the time of diagnosis, including diuretics and vasodilators, though diuretics and vasodilators have been thought to be avoided. The current guidelines recommend following guideline-directed medical therapy for hypertension, starting at a low dose and gradually increasing to achieve appropriate blood pressure control. Effectiveness of angiotensin-converting enzyme inhibitors has been investigated on AS in terms of potential benefit on reducing LV fibrosis[62-64]. Patients with LVOT obstruction caused by discrete upper septal thickening or mid-ventricular obstruction by severely concentric hypertrophy in the setting of AS and hypertension pose a clinical challenge. A β-blocker and appropriate hydration is recommended, and diuretics/vasodilators should be avoided in these patients.

CONCLUSION

Currently, due to an aging population, AS is one of the most common valvular heart diseases. Recent ACC/AHA guidelines provide a new classification system of categorizing valve diseases in patients, including those with AS, that is similar to the classification used in patients with heart failure. In addition, diagnostic strategies and treatment options for the new entity termed "paradoxical low-gradient severe AS", despite preserved EF, are given.

Decisions for AVR are based on the presence or absence of symptoms, but proactive investigation with multimodality testing for risk assessment is recommended in patients who are asymptomatic or who have indeterminate symptoms. Exercise stress testing is recommended for asymptomatic severe AS patients in addition to two-dimensional/Doppler echocardiographic testing at rest for risk stratification. If a patient is not physically appropriate for exercise testing, use of a biomarker and multiple imaging modalities, such as CT and MRI with contrast, can complement the risk stratification of asymptomatic severe AS.

Based on the available evidence, it is now reasonable to consider AVR in asymptomatic severe AS patients with (1) decreased EF (< 50%); (2) very severe AS (V_{max} > 5 m/s or ΔP ≥ 60 mmHg); (3) an abnormal exercise test; (4) rapid progression of AS (ΔV_{max} >0.3 m/s per year); and (5) progressively rising BNP.

Careful attention with frequent follow up is necessary in patients with (1) heavy calcification of the aortic valve (especially end-stage renal disease patients); (2) advanced stage of diastolic dysfunction (≥ stage 2); (3) elevated BNP compared to same age/sex; and (4) new onset of atrial fibrillation.

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MINIREVIEWS

Dyslipidemia management in primary prevention of cardiovascular disease: Current guidelines and strategies

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Abstract

Cardiovascular disease is the leading cause of death in the United States. In 2010, the Centers for Disease Control and Prevention estimated that $444 billion was spent on cardiovascular diseases alone, about $1 of every $6 spent on health care. As life expectancy continues to increase, this annual cost will also increase, making cost-effective primary prevention of cardiovascular disease highly desirable. Because of its role in development of atherosclerosis and clinical events, dyslipidemia management is a high priority in cardiovascular prevention. Multiple major dyslipidemia guidelines have been published around the world recently, four of them by independent organizations in the United States alone. They share the goal of providing clinical guidance on optimal dyslipidemia management, but guidelines differ in their emphasis on pharmacotherapy, stratification of groups, emphasis on lifestyle modification, and use of a fixed target or percentage reduction in low density lipoprotein cholesterol. This review summarizes eight major guidelines for dyslipidemia management and considers the basis for their recommendations. Our primary aim is to enhance understanding of dyslipidemia management guidelines in patient care for primary prevention of future cardiovascular risk.

Key words: Dyslipidemia; Guidelines; Cardiovascular diseases

Core tip: Guidelines for dyslipidemia management have been developed by independent organizations internationally for the purpose of improving patient care and reducing costs related to cardiovascular disease. In

this review article, we briefly summarize the key strategies suggested by each of eight major dyslipidemia guidelines, and the evidence that forms the foundation of the recommendations. We attempt to present a balanced view, commenting on potential strengths and weaknesses of each approach. Overall, we aim to enhance understanding of dyslipidemia management guidelines for primary prevention of future cardiovascular events.

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CLINICAL CASE

A 59-year-old African American man with a history of chronic kidney disease, type 2 diabetes mellitus, and long-standing hypertension presents for a follow-up visit. His blood pressure is 135/80 mmHg, and hemoglobin A1c (HbA1c) is 7.2%. He denies any chest pain or shortness of breath and has no exercise intolerance. His recent fasting lipid panel shows: Total cholesterol 159 mg/dL, triglycerides 190 mg/dL, high density lipoprotein cholesterol (HDL-C) 45 mg/dL, and low density lipoprotein cholesterol (LDL-C) 76 mg/dL. He is currently on atorvastatin 10 mg daily, carvedilol 25 mg twice a day, lisinopril 40 mg daily, and aspirin 81 mg daily. Should he receive a higher dose of atorvastatin?

INTRODUCTION

Cardiovascular disease (CVD) has been recognized as the number one killer in the United States and in the world for decades. Even though there was a 31% decline in CVD deaths from 2001 to 2011 in the United States, CVD still accounted for 1 of every 3 deaths in 2011[1]. With the decline of cigarette smoking, dyslipidemia has become the number one modifiable risk factor for vascular disease. In the INTERHEART case-control study with 27098 participants in 52 countries, dyslipidemia [elevated apolipoprotein (Apo) ApoB/ApoA1) had the highest mortality odds ratio (3.25), followed by smoking (2.87), psychosocial factors (2.67), and history of diabetes (2.37), and hypertension (1.91)[2]. In a prospective study of 27673 women, in addition to Apos, CVD risk was also strongly related to nuclear magnetic resonance measures of dyslipidemia and standard lipids (TC/HDL-C)[3].

Multiple lines of evidence have shown the central role of dyslipidemia in development of atherosclerosis and major CVD events. Traditional management of dyslipidemia includes lifestyle modification and pharmacotherapy based on identification of groups considered at high, medium, or low risk of major cardiovascular events. Guidelines for dyslipidemia management have been developed by independent organizations internationally for the purpose of improving patient care and reducing costs related to cardiovascular disease. However, many busy clinicians may have difficulty finding the time to read them. Moreover, the existence of multiple different guideline recommendations from different societies can present an added challenge.

In this review article, we briefly summarize the key strategies suggested by each of eight major dyslipidemia guidelines, and the evidence that forms the foundation of the recommendations. We attempt to present a balanced view, commenting on potential strengths and weaknesses of each approach. Overall, we aim to enhance understanding of dyslipidemia management guidelines for primary prevention of future cardiovascular events.

GUIDELINES

American College of Cardiology/American Heart Association 2013

The American College of Cardiology/American Heart Association (ACC/AHA) 2013 guideline recognizes four "statin benefit groups" in whom the risk reduction benefits clearly outweigh the risk of adverse events[4] (Table 1). Follow-up monitoring includes assessment for the anticipated LDL-C reduction (30%-49% and $\geqslant$ 50% with moderate- and high-intensity statin therapy, respectively) from baseline after starting the maximal tolerable dose of statin therapy. When such a percentage reduction is not seen, adherence to lifestyle modification and medication should be reinforced, along with evaluation for a secondary cause of dyslipidemia. Non-statin therapy can be considered in high-risk groups if the response to statin therapy is not acceptable. The ACC/AHA guidelines removed fixed target LDL-C levels, although when the baseline LDL-C is not known, the guideline notes that "an LDL-C < 100 mg/dL was observed in most individuals receiving high-intensity statin therapy in RCTs".

The new Pooled Cohort Equations (PCE) are used to calculate 10-year risk of atherosclerotic cardiovascular disease (ASCVD) in this guideline. In contrast to the Framingham Risk Score (FRS) used in adult treatment panel Ⅲ (ATP Ⅲ), the PCE use separate equations based on sex and race. Stroke is now included with coronary events in an ASCVD endpoint, whereas the ATP Ⅲ FRS only predicted coronary events. Along with the ASCVD endpoint, a new cut-point of 7.5% is featured to guide statin decision making. The use of this cut-point is not intended to lead to automatic prescription of a statin, but instead, to serve as the starting point for a clinician-patient risk/benefit discussion and consideration of statin therapy as one management option[5].

The 7.5% cut-point is derived from three exclusively primary prevention clinical trials: Air Force Coronary Atherosclerosis Prevention Study, Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese, and Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin trials. It is felt that this new cut-point

Table 1 Fixed-dose strategies

Strategy	ACC/AHA 2013	NICE 2014	VA/DoD 2014
Risk score	PCE to determine 10-yr risk of non-fatal and fatal hard ASCVD events (CHD and CVA)	QRISK2 to determine 10-yr risk of non-fatal and fatal CVD events (CHD, CVA, PAD)	FRS or PCE to determine 10-yr risk of non-fatal and fatal CVD events
Step 1: Identify statin-benefit group	Statin benefit groups: (moderate to high-intensity statin) History of ASCVD; LDL-C ⩾ 190, age ⩾ 21; DM at age 40-75 with LDL-C ⩾ 70; ⩾ 7.5% of ASCVD risk at age 40-75 with LDL-C; ⩾ 70 (in some individuals, not all; discussion required) Consider moderate intensity statin as initial dose for: DM with ⩽ 7.5% ASCVD risk; ⩾ 7.5% of ASCVD risk without DM Inadequate data to make recommendation (weigh risk, benefit and patient preference) DM at age < 40 or > 75 with LDL-C > 70; Age < 40 or > 75 with LDL-C > 70; 5%-7.4% of ASCVD risk at age 40-75 with LDL-C > 70; < 5% of ASCVD risk at age 40-75 with LDL-C > 70; Age < 40 with low 10 yr ASCVD risk but high lifetime risk based on 1 strong or multiple risk factors; Those with serious co-morbidities and increased ASCVD risk (*e.g.*, HIV, rheumatologic or inflammatory diseases, or solid organ transplantation) Other factors for consideration: family history of premature CVD, hsCRP ⩾ 2, elevated CAC, ABI < 0.9, LDL-C ⩾ 160	Statin benefit groups: (initial dose: Atorvastatin 20 mg/d) Type 1 DM; CKD st. Ⅲ; Risk score > 10%; Age > 85; Familial hypercholesterolemia Elevated risk groups that are underestimated by or not included in QRISK2: Possible benefit with statin HIV; Serious mental problem; On medication that cause dyslipidemia (antipsychotic, corticosteroid, immunosuppressant); Autoimmune disorder and systemic inflammatory disorder; TG > 175; On anti-hypertension or lipid modification therapy; Recently stopped smoking	Statin benefit group: (initial dose: Atorvastatin 10-20 mg/d) Risk score > 12% Moderate dose statin initiation can be considered in patient with 6%-12% risk score after discussion of benefit, risk, and patients' preference
Step 2: Determine adequacy of treatment effect	For group treated with high intensity statin: > 50% ↓ of LDL-C For group treated with moderate intensity statin: 30%-50% ↓ of LDL-C If patients are already on statin and baseline LDL-C is unknown, an LDL-C < 100 was observed in most individuals receiving high-intensity statin therapy in RCTs	> 40% ↓ of non-HDL-C	No objective parameters recommended
Step 3: Follow-up lipids	1-3 mo after initiation therapy Every 3-12 mo as clinically indicated thereafter	3 mo after initiation of therapy Annually when target achieved	Not recommended Lipid measurement can be utilized for compliance monitoring
Step 4: Options if treatment effect judged not adequate	Reinforce lifestyle change and adherence to medication Exclude secondary cause of dyslipidemia Add non-statin agent in those with LDL-C ≥ 190 or DM at age 40-75 with LDL-C ⩾ 70	Discuss adherence to lifestyle and medication Up-titrate statin dose; may go up to a torvastatin 80 mg/d	No recommendation

ACC/AHA: American College of Cardiology/American Heart Association; NICE: National Institute for Health and Care Excellence; PCE: Pooled Cohort Equations; ASCVD: Atherosclerotic cardiovascular disease; CHD: Coronary heart disease; CVA: Cerebrovascular accident; CVD: Cardiovascular disease; PAD: Peripheral artery disease; FRS: Framingham Risk Score; LDL-C: Low density lipoprotein cholesterol; HDL-C: High density lipoprotein cholesterol; DM: Diabetes mellitus; CKD: Chronic kidney disease; HIV: Human immunodeficiency virus; TG: Triglyceride; hsCRP: High sensitivity C-reactive protein; ABI: Ankle-brachial index; RCT: Randomized controlled trials.

builds in some room for potential overestimation of risk[6]. A recent study showed that these new guidelines significantly increase the number of potentially eligible adults for statin therapy (12.8 million people), especially in older age groups[7].

A 2013 Cochrane review on use of statins in primary prevention of ASCVD reported that, for patients with estimated 5% to 10% 5-year ASCVD risk, 15 major vascular events would be avoided per 1000 people treated for five years, which correlates with a number needed to treat (NNT) of 67[8]. In comparison, a study based on 5 trials with a total of 18564 participants (mean age 46 years)[9] showed an estimated 5-year NNT of 120 for CVD events when treating patients with mild hypertension (BP 140-160/90-100 mmHg) with anti-hypertensive medications for primary prevention.

The ACC/AHA guidelines rely on the highest quality randomized control trials (RCTs) and meta-analyses to date to form the foundation of evidence-based guidelines. The fixed-dose strategy promotes the appropriate use of high-intensity statin therapy and avoids overutilization of non-statin drugs, for which evidence is weaker and net benefit is less clear than evidence for statins. Under the "traditional" fixed target level strategy of combining statin and non-statin medications, a patient might receive a lower statin dose because of potential drug interaction with a second agent[10]. However, on-treatment lipid levels can still be used to motivate additional lifestyle change when statin therapy has been appropriately maximized, and can guide the selective addition of non-

statin therapy. Observational studies have consistently shown a log-linear association of LDL-C level and CVD morbidity[11].

European Society of Cardiology/European Atherosclerosis Society 2011

The European Society of Cardiology/European Atherosclerosis Society (ESC/EAS) 2011 guideline uses a target level strategy[12] combined with risk stratification based on estimated 10-year risk of a fatal CVD event by the Systemic Coronary Risk Evaluation (SCORE)[13]. After stratification, ESC/EAS advises group-specific intervention. The initial statin dose is determined by calculating the percentage reduction needed to achieve the target level, and then choosing the intensity of statin accordingly. ApoB and non-high-density lipoprotein cholesterol (non-HDL-C) are alternatives to LDL-C as targets. Up-titration of the statin dose or addition of a non-statin agent may be considered if the target is not attained with the initial statin regimen.

SCORE is based on large European cohorts and can be calibrated to each European country. The rationale for focusing on fatal CVD events is that variation in the definition of non-fatal events makes that parameter less reliable. A 5% risk of fatal CVD events is approximately equal to 15% risk of total (fatal and non-fatal) CVD events[13]. Recognizing that risk must be interpreted in light of clinical judgment and the pretest probability of CVD, the guideline lists some conditions that are often associated with risk score underestimation, such as elevated high sensitivity C-reactive protein (hsCRP), elevated homocysteine, low HDL-C, family history of premature coronary artery disease, and asymptomatic atherosclerotic disease. High HDL-C and family history of longevity are associated with overestimation of risk.

Overall, the guideline uses an individualized strategy for management, accounting for specific conditions, such as heart failure, diabetes, autoimmune diseases, metabolic syndrome, and HIV. An extensive section of the guideline focuses on management of hypertriglyceridemia and low HDL-C, although the panelists acknowledge that the evidence for these variables impacting future CVD incidence is still weak.

Canadian Cardiovascular Society 2009 Guideline and 2012 Updates

The Canadian Cardiovascular Society (CCS) guideline adopts the traditional approach of risk stratification and group-specific target treatment using LDL-C[14] (Table 2). Patients are stratified into low, intermediate, or high risk categories using comorbidities in addition to a modified FRS, which includes an additional rule of multiplying the calculated risk by 2 if there is a family history of premature coronary heart disease (CHD)[15]. The LDL-C level and percentage reduction in LDL-C are the recommended primary targets.

The high-risk and low-risk groups receive interventions according to their respective risk. The intermediate risk group is further refined using LDL-C and, if indicated, ApoB and/or non-HDL-C to identify candidates for more aggressive intervention. Secondary tests, such as a coronary calcium scan and high-sensitivity C-reactive protein (hsCRP), are optional secondary tests to refine risk assessment in the low- and intermediate-risk groups.

When communicating risk to a patient, a unique aspect of this guideline is the suggestion to use "cardiovascular age" as an easier-to-understand explanation of a patient's ASCVD risk, with the potential to improve awareness and adherence. Cardiovascular age is calculated by age minus the difference between estimated life expectancy and average life expectancy, based on age and sex.

International Atherosclerosis Society 2013

International Atherosclerosis Society (IAS) 2013 makes evidence-based recommendations based on numerous studies from the 1970s to 2013[16] (Table 2). The risk estimator used is the Lifetime Framingham risk score[17], which may help call attention to risk in young people and motivate them to improve their lifestyle habits. This score can be recalibrated by nationality.

For those in high and moderately-high risk groups, it is suggested to aim for "optimal" lipid levels (LDL-C < 100 mg/dL or non-HDL-C < 130 mg/dL). "Near optimal" levels (LDL-C < 130 mg/dL or non HDL-C < 160 mg/dL) are considered acceptable for the lower risk group. Statins are the first-line drug when pharmacotherapy is indicated. The initial dose is tailored according to the group-specific lipid target.

National Lipid Association 2014

The National Lipid Association (NLA) guideline uses a multilevel stratification approach to identify patients with a higher CVD risk factor who require more intensive management[18] (Table 2). First, "very-high" and "high risk" groups are identified based on specified parameters. The remaining patients are then further risk-stratified based on the number of major ASCVD risk factors. People with two major risk factors are deemed to be intermediate risk, but the presence of any secondary risk indicator or a high-risk score places them in the higher risk group. Similar to other guidelines, the goal of treatment in this guideline is group-specific. Non-HDL-C is favored over LDL-C as the therapeutic target, but both are viewed as reasonable.

The NLA guideline is thorough in categorizing groups for whom aggressive intervention is either necessary or optional. The guideline emphasizes the potential for risk score estimation to overestimate or underestimate the risk in certain settings. A general LDL-C goal of < 100 mg/dL or non-HDL-C goal of < 130 mg/dL is recommended for low to high risk groups. LDL-C targets are used to motivate lifestyle change in addition to drug therapy.

National Institute for Health and Care Excellence 2014

The National Institute for Health and Care Excellence (NICE) guideline uses a fixed dose approach similar to ACC/AHA. All people aged ⩾ 40 years are screened formally with the QRISK2 score[19] (Table 1). This

Table 2 Target-level strategies

Strategy	EAS/ESC 2011	CCS 2012	IAS 2013	NLA 2014	AACE 2012
Risk score	SCORE chart to estimate 10-yr risk of fatal CVD	Modified FRS to estimate 10-yr risk of non-fatal and fatal CVD	Lifetime FRS to estimate lifetime risk of non-fatal and fatal CVD	PCE or FRS or lifetime FRS	FRS to determine 10-yr risk of non-fatal and fatal CVD
Step 1: Stratify CVD risk	Very-high: ⩾ 10% of fatal CVD risk; CHD equivalent risk; DM with microalbuminuria; CKD st. Ⅲ High: 5%-9% of fatal CVD risk; DM; 1 markedly abnormal risk factor Moderate: 1%-4% of fatal CVD risk Low: < 1% of fatal CVD risk	High: ⩾ 20% risk of CVD; CHD risk equivalent; DM, age > 40 or > 30 with 15 yr DM history; CKD st. Ⅲb or Ⅲa with microalbuminuria; HTN with ⩾ 3 CVD risk factors Intermediate: 10%-19% risk of CVD Low: < 10% risk of CVD (CVD risk factor: age > 55, smoker, TC/HDL-C > 6, LVH, abnormal ECG, microalbuminuria)	High: ⩾ 45% lifetime risk of CVD; DM with major risk factor; Familial hyperlipidemia; CKD Moderately-high: 30%-44% lifetime risk of CVD; DM alone; Metabolic syndrome; CKD Moderate: 15%-29% lifetime risk of CVD Low: < 15% lifetime risk of CVD [Major risk factor: high LDL-C, HDL-C < 40, HTN, smoker, family history of premature CAD, age (men > 55, women > 65)]	Very-high: CHD risk equivalent; DM with ⩾ 2 major risk factors or evidence of end organ damage High: DM with 0-1 major risk factor; CKD st. Ⅲb; LDL-C ⩾ 190; ⩾ 3 major risk factors; ⩾ 1 secondary risk (marked major CVD risk, LDL-C > 160 or non-HDL-C > 190, CAC > 300, hsCRP > 2, Lp(a) > 50, microalbuminuria); High risk score (PCE > 15%, FRS > 10%, lifetime FRS > 45%) Intermediate: 2 major risk factors Low: 0-1 risk factor	Very-high: CHD risk equivalent + ⩾ 1 major risk factor High: CAD risk equivalent; ⩾ 2 major risk factor + ⩾ 20% risk of CVD Moderately-high: ⩾ 2 major risk factor + 10%-19% risk of CVD Moderate: ⩾ 2 major risk factor + < 10% risk of CVD Low: ⩾ 1 major risk factor
Step 2: Determine target	Very-high: LDL-C < 70; Alt: ApoB < 80, non-HDL-C < 100 High: LDL-C < 100; Alt: ApoB < 80, non-HDL-C < 130 Moderate-Low: LDL-C < 100-115	High: LDL-C < 77 or ⩾ 50% ↓; Alt: ApoB < 80, Non-HDL-C < 100 Intermediate: LDL-C < 77 or ⩾ 50% ↓ Alt: ApoB < 80, Non-HDL-C < 100 Low : ⩾ 50% ↓ of LDL-C	High to moderately-high: LDL-C < 100 or non-HDL-C < 130 (goal may be lower for very-high risk) Moderate to low: LDL-C < 130 or non-HDL-C < 160	Very-high: LDL-C < 70, non-HDL-C < 100 Alt: ApoB < 80 High-Moderate-Low: LDL-C < 100, non-HDL-C < 130	Very-high: LDL-C < 70, ApoB < 80 High: LDL-C < 100, ApoB < 90 Moderately-high: LDL-C < 130 Moderate: LDL-C < 130; Low: LDL-C < 160; All category: HDL-C > 40, TG < 150
Step 3: Treat according to risk	Very-high or High: Lifestyle intervention + drug intervention Moderate: Lifestyle inter-vention; consider drug if uncontrolled with lifestyle Low: Life style intervention only	High: Statin and lifestyle change Intermediate: LDL-C > 135: Statin if lifestyle change insufficient; LDL-C < 135: Get ApoB or non-HDL-C: # Apo B > 120 or Non-HDL-C > 165: Start statin if lifestyle change insufficient # Apo B< 120 or Non-HDL-C < 165: Lifestyle change Optional use of secondary test for further stratification Low: LDL-C > 190: Lifestyle change and statin; 5%-9% risk of CVD: Lifestyle change only optional use of secondary test for further stratification; < 5% risk of CVD: Lifestyle change only	High: Statin and lifestyle change Moderately-high: Lifestyle change; Initiation of statin may be considered Moderate: Lifestyle change; initiation of statin may be considered if LDL-C > 160 Low: Lifestyle change only	Very-high: Statin and lifestyle change; statin optional if baseline LDL-C, non-HDL-C and ApoB below target High: Concurrent statin and lifestyle change or statin after insufficient lifestyle change Moderate: Lifestyle change only; statin may be considered after 3 mo of optimal lifestyle change and LDL-C > 130 Low: Lifestyle change only; statin may be considered after 3 mo of optimal lifestyle change and LDL-C > 160	Exclude secondary cause of hyperlipidemia; Lifestyle change; Lipid lowering agent; Combination lipid lowering agent
Step 4: Follow-up lipids	1-12 wk after initiation; 1-3 mo after every change of dose or change of medication; Annually when target is achieved			Every 3 mo until target is achieved; Every 4-12 mo when target is achieved	6 wk after initiation; Every 6-12 mo when target is achieved
Step 5: Options if target not reached	Up-titration of statin dose; Add non-statin agent			Add non-statin agent; Referral to lipid specialist	

ESC: European Society of Cardiology; EAS: European Atherosclerosis Society; CCS: Canadian Cardiovascular Society; IAS: International Atherosclerosis Society; NLA: National Lipid Association; AACE: American Association of Clinical Endocrinologists; FRS: Framingham risk score; PCE: Pooled Cohort Equations; CVD: Cardiovascular disease; CHD: Coronary heart disease; CKD: Chronic kidney disease; DM: Diabetes mellitus; CAD: Coronary artery disease; LDL-C: Low density lipoprotein cholesterol; HDL-C: High density lipoprotein cholesterol; hsCRP: High sensitivity C-reactive protein; TG: Triglyceride; ApoB: Apolipoprotein B.

estimates 10-year risk of CVD using validated population data in England, taking into account ethnicity and geographical location[20]. QRISK2 used the same main outcomes as PCE with addition of transient ischemic attack and angina; hence, a 10% risk estimation by the QRISK2 score is approximately equivalent to a 7.5% ASCVD risk estimation by PCE. Both scores are best used in the populations for which they were intended to be implemented. People with a QRISK2 score of ⩾ 10% along with those who have other selected risk factors are categorized into a "statin-benefit group" wherein atorvastatin 20 mg is recommended.

The guideline lists conditions that are known to increase risk of cardiovascular disease which are not included in QRISK2, suggesting that risk may be underestimated in people with these conditions. Reducing non-HDL-C > 40% is used as the target for people who initiate statin therapy. For people who do not attain the target with atorvastatin 20 mg/d, up-titration of atorvastatin to 80 mg/d and/or reinforcement of lifestyle and medication adherence are recommended.

NICE is the first guideline to endorse non-HDL-C as the sole target. The justification is based on epidemiologic evidence supporting non-HDL-C as a cardiovascular risk predictor and the greater practicality for testing because both fasting and non-fasting results are considered reasonable. In targeting non-HDL-C initially, the NICE guideline recommends 20 mg/d of atorvastatin rather than a higher dose for several reasons, including considerations of cost and net clinical benefits[21].

American Association of Clinical Endocrinologists 2012

The American Association of Clinical Endocrinologists (AACE) guideline uses conventional risk stratification and a group-specific target level strategy[22] (Table 2). Using a combination of the FRS and presence of major ASCVD risk, the guideline stratifies patients into 5 groups. The entire standard lipid panel is used as the target and for the highest risk population, ApoB can be used as an alternative. AACE 2012 endorses a comprehensive approach to managing dyslipidemia without giving specific criteria for when to initiate pharmacotherapy.

The guideline also does not specify an initial dose for statin therapy. For patients who fail to meet their target after initial management, a non-statin lipid lowering agent can be added. Ezetimibe is recommended as the non-statin agent of choice based on the SHARP (*Study* of Heart and Renal Protection) trial[23]. The guideline also endorses possible combination therapy with a fibrate, specifically when triglyceride levels are >200 mg/dL and the HDL-C is < 40 mg/dL, due to evidence of non-fatal CVD event reduction in the FIELD (Fenofibrate Intervention and Event Lowering in Diabetes) and ACCORD (Action to Control Cardiovascular Risk in Diabetes) trials[24].

United States Department of Veteran Affairs and United States Department of Defense 2014

Using similar rationale to 2013 ACC/AHA guideline, the recent United States Department of Veteran Affairs and United States Department of Defense (VA/DoD) guideline advocates the use of a fixed-dose strategy[25] (Table 1). Men older than 35 years, and women older than 45 years are screened using a 10-year CVD risk calculator (either Framingham or PCE). Patients who have > 12% estimated 10-year CVD risk are recommended to be started on a moderate dose of statin therapy based on evidence supporting that benefit clearly outweighs risk in this group. For people with intermediate risk (6%-12%), the recommendation for statin initiation is less clear. The guideline's distinct feature is its recommendation against the routine measurement of lipid panel after statin initiation. Thus, neither a target level nor a percentage change from baseline is utilized as a parameter of treatment adequacy. Combination with a non-statin agent is avoided, but a non-statin agent (gemfibrozil or bile acid sequestrant) may be used in patients who cannot tolerate statin.

DISCUSSION

These guidelines approach primary prevention with similar overarching aims. Several adopt traditional risk stratification with group-specific management. ACC/AHA, NICE, and NLA (partially) recommend identifying groups in which benefits of statin therapy clearly outweigh adverse effects. Risk estimation using traditional risk factors to estimate an absolute risk score, secondary testing (including hsCRP, CAC, and ApoB), and secondary risk factors (such as HIV, autoimmune diseases, and medications) are tools that are commonly used to further stratify those in the intermediate risk group to guide management.

Critical role of risk scores

In primary prevention, risk estimators/calculators may have a major impact in determining how many people will be treated with pharmacotherapy. The decision to use one over another could affect treatment of millions of people, and it is worth noting that when a calculator is applied to a given individual, the population from which the calculator was derived may not be representative of that specific individual. For example, a calculator developed from and valid for Asian Americans might not be as well suited to Asian people in general. When using PCE, it is specifically noted that underestimation of ASCVD risk is expected in American Indians, some Asian Americans (*e.g.*, of South Asian ancestry), and some Hispanics (*e.g.*, Puerto Ricans). On the other hand, the overestimation tends to occur in Asian Americans (*e.g.*, of East Asian ancestry) and some Hispanics (*e.g.*, Mexican Americans)[25].

Ideally, every distinct population would have its own risk calculator; however, this is not practical at this time because of the lack of national representative cohorts in most countries. It is important to realize that the accuracy of a risk calculator in estimating "true" future risk is difficult to ascertain. A risk score is an estimate based

on a population average and the information needs to be contextualized through discussion with a patient and consideration of unique aspects of their case. Concerns with the potential inaccuracies of risk calculators support, in our view, a less calculator-reliant approach[5].

Pharmacotherapy threshold

Choosing a cut-point of ASCVD risk for stratification can be challenging, and while it can be data driven, it also requires panelist consensus to some extent. In the ACC/AHA guidelines, the cut-point of 7.5% was selected based on a balancing of the estimated NNT and number needed to harm (NNH). By extrapolation from trial data showing the NNT to avoid an ASCVD event with statin therapy *vs* the NNH for diabetes[4], comparisons were made for moderate- and high-intensity statin therapy. Again, the cut-point is not intended to automatically trigger a statin prescription, but rather to start a clinician-patient risk discussion.

RCTs are attractive because they allow an unbiased comparison of the NNT and NNH in defined populations. Since there have been over 25 statin trials embracing various populations, guidelines based on high-quality RCTs have merit. But the NNT and NNH have potential shortcomings as the NNT is dependent on the time frame of the trials. In WOSCOPS, there was a significant difference in the NNT at 5 years *vs* 20 years of follow–up[26]. The NNH obtained from RCTs may also not reflect the true incidence of adverse effects in a particular case of interest. For example, statin-related diabetes appears to occur in persons with risk factors for diabetes (components of the metabolic syndrome) and, therefore, the NNT *vs* NNH assessment may not be as relevant to someone without these diabetes risk factors.

Moreover, many patients seen in routine clinical practice may differ from the patients who participated in RCTs. In a recent retrospective cohort study of 107835 statin-treated participants[27], 17% of patients (18778) reported having a statin-related adverse effect, 40% of which were musculoskeletal. Of these individuals, 6579 subjects were re-challenged with statin. Eventually, over 90% of those previously intolerant patients continued on statin therapy suggesting that many adverse effects were incorrectly attributed to statins. In contrast, in RCTs, people with a history of statin intolerance and those who develop muscle symptoms or elevated CK during run-in phases may be excluded from trials. This selection process limits the ability to generalize such studies to the general population[28].

Target treatment

Arguments can be made to support a focus on the percentage LDL-C reduction (as in ACC/AHA, NICE) or target LDL-C level (as in EAS/ESC, CCS, IAS, NLA, and AACE). Both approaches inherently acknowledge that the benefit is through LDL-C lowering. Focus on the anticipated response to statin therapy, as reflected by the percentage LDL-C reduction, is felt to be more aligned with evidence from RCTs and high quality meta-analyses. On the other hand, lack of RCT evidence for efficacy is not the same as RCT evidence for lack of efficacy[29].

The fixed target LDL-C level could be easier for patients to understand, which theoretically could help maximize adherence to treatment and motivate lifestyle change. Having a target LDL-C level could also be helpful in assessing the success of treatment, particularly when baseline LDL-C is unknown, such as in patients already on a statin. Moreover, some high risk patients with high baseline LDL-C levels may not achieve what would be considered an optimal LDL-C level even with a large percentage change, and without a fixed target LDL-C, the role or timing of the addition of non-statin medications such as ezetimibe becomes less clear. Importantly, patient counseling about the primary goal of LDL-C reduction, which is prevention of future heart attacks and strokes, is critical.

As noted in three guidelines, on-treatment non-HDL-C levels can be a stronger predictor of future cardiovascular events than LDL-C[30,31]. One contributing factor is that non-HDL-C captures information on triglyceride-rich remnant lipoprotein cholesterol that LDL-C does not. In addition, calculated LDL-C can be inaccurate in the setting of elevated triglyceride levels or low LDL-C levels (particularly levels < 70 mg/dL) as it is derived from Friedewald estimation[32,33]. Avoiding the issues with such estimation, non-HDL-C is simply a subtraction of total and HDL cholesterol.

Follow-up

Most guidelines advise follow-up at 6 to 12 wk after initiation of treatment and/or dose change and thereafter every 6 to 12 mo when the target is achieved. Reinforcement of lifestyle modification and medical adherence can be done at each follow-up visit. If inadequate time is given to observe the effect of lifestyle changes, this may lead to premature conclusions about the ineffectiveness of lifestyle modification and unnecessary medication changes.

Options for management after maximum statin therapy

In addition to reinforcing intensive lifestyle modification, drug adherence and the possible role of adding a non-statin agent are relevant considerations. Effort to determine a possible secondary cause of dyslipidemia is reasonable when the expected response or target is not achieved (as in ACC/AHA and AACE). This management step may often be overlooked but can be important for treatment. Secondary causes of dyslipidemia include drugs, such as diuretics, steroid, amiodarone, cyclosporine, and protease inhibitors; and diseases, such as nephrotic syndrome, hypothyroidism, biliary obstruction, and anorexia.

Regarding combination therapy, recent evidence showing no overall benefit from the addition of niacin in AIM-HIGH and HPS2-THRIVE to patients with well-controlled LDL-C and fenofibrate in ACCORD[34-36] has led to less emphasis on routine non-statin therapy. This approach is articulated clearly by ACC/AHA and

NICE. The other guidelines also note the shortage of evidence for the additional use of non-statin agents to background statin therapy, although use of these agents appears to be more of a routine option in their recommendations.

However, the above trials did not test use of a second agent in people who were not at target despite statin therapy. The participants had generally well-controlled LDL-C levels on background therapy. Moreover, pre-specified subgroups with high triglycerides and low HDL-C showed benefit of added therapy. Thus, it may be an overgeneralized conclusion to say that combination therapy has no role in management of adults with mixed hyperlipidemia. Rather, it may be that selective use is reasonable, and indeed the guidelines would generally tend to support such a strategy.

For additional LDL-C lowering, the preferred agent at this time is likely ezetimibe, which showed additional benefit in combination with statin therapy in preliminary reporting of the secondary prevention IMPROVE-IT trial[37]. Of note, the relative risk reduction was fairly modest, consistent with the fairly modest 20% LDL-C lowering from ezetimibe. Therefore, the additional benefit is most justified in those with high enough absolute risk where such a reduction would be clinically significant.

CASE DISCUSSION

Going back to our case, the patient has three important cardiovascular risk factors: Type 2 diabetes mellitus, chronic kidney disease, and hypertension. By all guidelines, he will be categorized as either high risk or in a statin-benefit group. He has been on chronic statin therapy, and determining a percentage reduction is not possible because baseline LDL-C and non-HDL-C are not known. Per the five guidelines that use a fixed target LDL-C goal (EAS/ESC, CCS, IAS, NLA, and AACE), the most aggressive LDL-C goal is < 70 mg/dL and non-HDL-C goal is < 100 mg/dL. With an LDL-C of 76 mg/dL and non-HDL of 119 mg/dL, the patient' s on-treatment lipids are probably not optimal and this should be discussed with the patient. In addition, the on-treatment triglycerides level is elevated and LDL-C may be underestimated by the Friedewald equation. Options include improving medication adherence if there is a need, consideration of up-titrating drug therapy, further addressing lifestyle modification, and addressing a possible secondary cause of dyslipidemia. In this case, after clinician-patient discussion, the patient elected to work even harder on lifestyle modification and increase atorvastatin to 40 mg/d.

CONCLUSION

There is no perfect guideline. Each guideline has advantages and limitations. We hope that, by gathering and elaborating upon current guidelines, important concepts were highlighted about dyslipidemia management to prevent ASCVD. We anticipate that, in the future, having more congruent guidelines will help avoid confusion among clinicians throughout the world.

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MINIREVIEWS

Novel epigenetic-based therapies useful in cardiovascular medicine

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Abstract

Epigenetic modifications include DNA methylation, histone modifications, and microRNA. Gene alterations have been found to be associated with cardiovascular diseases, and epigenetic mechanisms are continuously being studied to find new useful strategies for the clinical management of afflicted patients. Numerous cardiovascular disorders are characterized by the abnormal methylation of CpG islands and so specific drugs that could inhibit DNA methyltransferase directly or by reducing its gene expression (*e.g.*, hydralazine and procainamide) are currently under investigation. The anti-proliferative and anti-inflammatory properties of histone deacetylase inhibitors and their cardioprotective effects have been confirmed in preclinical studies. Furthermore, the regulation of the expression of microRNA targets through pharmacological tools is still under development. Indeed, large controlled trials are required to establish whether current possible candidate antisense microRNAs could offer better therapeutic benefits in clinical practice. Here, we updated therapeutic properties, side effects, and feasibility of emerging epigenetic-based strategies in cardiovascular diseases by highlighting specific problematic issues that still affect the development of large scale novel therapeutic protocols.

Key words: Epigenetics; Cardiovascular diseases; Heart failure; Inhibitors of histone deacetylases; Antisense microRNAs

Core tip: Recent evidence suggests that specific epigenetic regulatory mechanisms play key roles in cardiac differentiation, homeostasis, injury response, and disease development. Drug therapies that work *via* epigenetic mechanisms are currently limited to antineoplastic agents; large controlled trials are required to establish whether

current possible candidate antisense microRNAs or histone deacetylase inhibitors could offer better therapeutic benefits in cardiovascular disease. We review recent findings on the epigenetic control of several cardiovascular diseases and the new challenges for therapeutic strategies in cardiovascular diseases.

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INTRODUCTION

Cardiovascular diseases (CVDs) are the primary cause of death worldwide, with 17.5 million deaths from CVD in 2012 representing 31% of all global deaths that year. CVDs include a number of alterations affecting heart and vascular structures, such as heart valves, heart muscle (*e.g.*, cardiomyopathy), and pericardial and coronary artery diseases. All these conditions may result in cardiomyocyte loss, cardiac-remodeling with consequent heart failure (HF), and an increased risk of arrhythmias and death. Cardiac fibroblasts also have a pivotal role in HF[1]. Indeed, endothelial cell activation and inflammation promotes the transdifferentiation of fibroblasts to myofibroblasts which, after extensive collagen production, results in the release of chemokines and the activation of inflammatory cells, which in turn causes cardiomyocyte stiffness by contributing to HF pathogenesis[1]. Increasing evidence has shown that epigenetic mechanisms control and influence the expression of cell cycle central genes involved in human disease progression[2]. Toward this context, significant epigenetic and epigenomic findings have opened a new area of research by exploring the role of genetic heritability and environmental interaction in CVDs[3]. Some deregulated epigenetic steps are involved in the pathophysiology of CVDs[4]. Specific epigenetic regulatory mechanisms could impact on the endothelium, cardiac muscle, smooth muscle, and fibroblasts[5]. Thus, the pharmacological setting of these pathways might represent a specific target for CVDs. Due to the reversible nature of these modifications, researchers are continuously engaged in the development of novel epigenetic-based drugs (epidrugs) for CVD treatment[6,7]. The primary goal of future studies will be to allow for the identification of selective therapeutic molecules that have been conceived in order to act on specific epigenetic-related pathogenic events.

Here, we summarize the current knowledge concerning epigenetic-based strategies in CVDs by outlining novel therapeutic steps in clinical practice.

EPIGENETICS INVOLVEMENT IN CVDs

DNA methylation as therapeutic target

DNA methylation is the most studied epigenetic modification and mainly involves methylation of CpG islands in the promoter genes. It has good long-term stability and is the most common modification involving the regulation of gene expression in the mammalian genome. All changes in methylation are modulated by specific catalytically-active enzymes, including "maintenance" methyltransferase (DNMT1) and "*de novo*" methyltransferase (DNMT3a and DNMT3b). DNMTs act by adding methyl groups to CpG residues, thereby modifying the accessibility of DNA to the transcriptional machinery. Altered regulation of cytosine methylation has been linked to CVD development and progression[8], as well as to cancer cell development[9]. In addition, DNA methylation has been shown to regulate biological processes underlying CVDs, such as atherosclerosis, inflammation, hypertension, and diabetes[10,11]. DNA methylation is also involved in essential arterial hypertension[12,13]. To date, DNA methylation remains an attractive target for CVD interventions, owing to its reversible nature. Dietary compounds, including polyphenols and catechins, act on DNA methylation processes[14,15]. In particular, some interesting clinical studies have shown that elevated consumption of polyphenols decreases global DNA methylation of peripheral leukocytes in humans with cardiovascular risk factors (NCT00511420 and NCT00502047)[16]. However, the role of nutrients in the evolvement of CVDs through the epigenetic link remains as yet studied. Conversely, the cardiovascular implication of pharmacological epigenetic compounds appears to be more direct and far-reaching. Indeed, some drugs are known to affect DNA methylation. Hydralazine, a vasodilator used to treat hypertension[17], is an example of compound that has been shown to inhibit DNA methyltransferase directly or by reducing its gene expression[18]. There are several clinical trials focusing on the use of hydralazine to combat hypertensive conditions (Table 1). Many of these completed trials have highlighted the beneficial effect of hydralazine on both hypertension and other cardiovascular conditions compared to other compounds. Several studies have shown that hydralazine might function by modulating the effect of purine-like compounds released from sympathetic nerve endings and/or by inducing an altered Ca^{2+} balance in vascular smooth muscle cells[19,20]; unfortunately, there are fundamental as-yet unresolved issues concerning this area of research that remain unclarified.

Procainamide is another drug that inhibits DNA methyltransferase I. It is a sodium channel blocker that belongs to the class of benzamides used against arrhythmias[21]. Clinical trials have evaluated this anti-arrhythmic drug in the acute treatment of monomorphous ventricular tachycardia with positive effects (Table 1). Nevertheless, recent evidence has shown toxic effects of procainamide on the lung after orthotopic cardiac transplantation[22].

Despite the use of the aforementioned drugs in cancer treatment appearing to have promising results[23], the implication of their epigenetic effects in CVDs requires further investigation in future studies.

Table 1 Interventional and randomized ongoing clinical trials on the use of hydralazine and procainamide in cardiovascular diseases

No.	Status	Condition	No. of enrolled patients	Intervention
NCT00684489	Completed	Hypertension	52	Hydralazine and other drugs
NCT02305095	Not open for participant recruitment	Heart failure	500 (estimated enrollment)	Hydralazine in combination with isosorbide dinitrate
NCT00661895	Completed	Hypertension	99	Hydralazine and other drugs
NCT00599235	Completed	Hypertension	30	Hydralazine, sildenafil, and placebo
NCT00223717	Recruiting participants	Hypertension	160 (estimated enrollment)	Hydralazine and other drugs
NCT01255475	Completed	Heart failure, cardiac failure, and congestive heart failure	21	Hydralazine/amlodipine and placebo
NCT01516346	Recruiting participants	Heart failure and congestive heart failure	54 (estimated enrollment)	Hydralazine, isosorbide dinitrate, and placebo
NCT01822808	Recruiting participants	Acute heart failure and left ventricular dysfunction	500 (estimated enrollment)	Hydralazine, isosorbide dinitrate, and placebo
NCT00000499	Completed	Cardiovascular diseases, heart diseases, hypertension, and vascular diseases	Not provided	Hydralazine, reserpine, chlorthalidone, and metoprolol
NCT02050529	Recruiting participants	Hypertension, Pregnancy induced	180 (estimated enrollment)	Hydralazine, labetalol
NCT01538875	Completed	Hypertension, Pregnancy induced	261	Hydralazine, labetalol
NCT00383799	Unknown	Ventricular tachycardia	302 (estimated enrollment)	Procainamide, amiodarone
NCT00000464	Completed	Arrhythmia, Cardiovascular diseases	115	Procainamide, quinidine, disopyramide, and other drugs
NCT00702117	Completed	Atrial fibrillation, tachycardia	123	Procainamide, ajmaline, flecainide
NCT00589303	Terminated	Atrial fibrillation, heart failure	27	Rhythm control drugs: Procainamide and other drugs
NCT00000556	Completed	Arrhythmia, atrial fibrillation, cardiovascular diseases	4060	Procainamide and other drugs
NCT01205529	Recruiting	Atrial fibrillation	750 (estimated enrollment)	Procainamide

Histone modifications as therapeutic target

Epigenetic alterations occur in the histone code, and so can modulate histone-DNA interactions and significantly influence chromatin structure by modifying the accessibility of transcriptional regulators to DNA-binding elements[24]. The most common modifications are lysine acetylation and methylation, arginine methylation, and serine phosphorylation. Histone acetylation is catalyzed by histone acetyltransferases (HATs), while histone deacetylation is carried out by histone deacetylases (HDACs)[25].

Inhibitors of histone deacetylases (HDACi) represent a significant group of epidrugs that could be highly relevant to the treatment of CVDs. Indeed, HDACi exert anti-proliferative and anti-inflammatory effects, and their cardio-protective therapeutic use has been recently confirmed in preclinical studies[26,27].

According to their chemistry, HDACi can be divided into four main groups: Hydroxamates, aliphatic acids, benzamides, and cyclic peptides. Hydroxamates like trichostatin A (TSA) and vorinostat (suberoylanilide hydroxamic acid, SAHA) serve as pan-HDACi and are generally most often used for preclinical studies[28-30].

Principal histone modifications and therapeutic targets involved in CVDs are reported in Table 2. Animal studies *in vivo* showed that TSA treatment improved functional myocardial recovery after myocardial infarction (MI) *via* a reduction in myocardial and serum tumor necrosis factor-α. Neo-angiogenesis was demonstrated in MI animals after receiving TSA treatment[31]. Taken together, these results indicate that HDACi could preserve cardiac performance and mitigate myocardial remodeling by stimulating endogenous cardiac regeneration[31]. HDAC inhibition was also shown to attenuate ischemic injury in the heart and other tissues. Pre-treatment with TSA resulted in improvements in post-ischemic ventricular function, with a reduction in infarct size in both early and delayed preconditioning models[32]. Despite the high activity of TSA, it was disqualified as a clinical drug due to its many side effects, such as non-transformed cell apoptosis and increased DNA damage[33].

Vorinostat was approved by the Unites States Food and Drug Administration (FDA) for the treatment of advanced cutaneous T cell lymphoma[34]. Suberoylanilide hydroxamic acid (SAHA/vorinostat) reduced myocardial infarct size in a large animal model, even when delivered in the clinically relevant context of reperfusion[35,36].

Aliphatic acids like valproic acid (VPA, 2-propylpentanoic acid) inhibits class I HDACs, causing accumulation of hyperacetylated histone tails (H3 and H4 histones) and other protein targets such as p53. VPA has anti-proliferative and pro-apoptotic activities. Lee *et al*[37] demonstrated the

Table 2 Histone modifications and therapeutic targets involved in cardiovascular diseases

Target	Epigenetic mechanisms	Condition	Organism/*in vitro*, *in vivo*	Effects	Ref.
TSA	Inhibition of HDAC4	Ischemic injury	Mouse, *in vitro* and *in vivo*	HDACi would be predicted to have a beneficial effect in the context of active ischemia	Granger *et al*[28] (2008)
TSA/VPA	Class I HDACs	Cardiac hypertrophy	Mouse, *in vitro* and *in vivo*	Therapeutic target for preventing or reversing cardiac hypertrophy and subsequent heart failure	Kee *et al*[29] (2006)
TSA	Inhibition of HDACs	Atrial fibrosis and arrhythmias	Mouse, *in vitro* and *in vivo*	Reversed myocardial fibrosis	Liu *et al*[30] (2008)
TSA	Inhibition of HDACs	Acute myocardial ischemia and reperfusion injury	Mouse, *in vitro* and *in vivo*	Improved cardiac functional recovery and antagonized myocardial remodeling in chronic myocardial infarction	Zhang *et al*[31] (2012)
TSA/SAHA	HDAC inhibitor	Myocardial infarct	Mouse, rabbit, *in vivo*	Reduced infarct size in a large animal model	Xie *et al*[35] (2014)
SAHA/sodium valproate	Inhibition of HDACs	Ischemic injury	Mouse, *in vitro* and *in vivo*	Potential therapeutic strategy for restoring compromised cardiac proteostasis	Wang *et al*[36] (2011)
VPA or tributyrin	Inhibition of HDACs	Infarct	Rat, *in vitro*	Attenuated ventricular remodeling after infarction	Lee *et al*[37] (2007)
MS-275A	Inhibition of class I/II HDACs	Infarct	Rat, *in vivo*	Significant reduction of infarct area observed	Aune *et al*[39] (2014)
Apicidin	Inhibition of class I HDACs	Cardiac hypertrophy and heart failure	Rat pups, *in vitro* Mouse, *in vivo*	Preserved cardiac function in the long-term	Gallo *et al*[42] (2008)
Curcumin	p300 HAT inhibitor	Heart failure	Rat, *in vitro*	Prevented deterioration of systolic function and heart failure	Morimoto *et al*[45] (2008)

TSA: Trichostatin A; HDAC: Histone deacetylases; HDACi: Inhibitors of histone deacetylases; SAHA: Suberoylanilide hydroxamic acid; VPA: Valproic acid.

attenuation of ventricular remodeling following MI *in vivo* when VPA or tributyrin was administered to rats 24 h after ligation of the left anterior descending artery. However, these short chain fatty acids are known to weakly inhibit HDAC activity with a number of off-target effects[38].

Benzamides are small molecules that are mostly active against class Ⅰ HDACs. Class Ⅰ HDACi is entinostat (MS-275A) and prompts protective effects against ischemia reperfusion injury in isolated rat heart. MS-275A is not effective against class Ⅱb HDAC6[39]. Entinostat might be more advantageous than first-generation examples such as TSA, vorinostat, romidepsin, and VPA, as less profound side effects are observed[40]. Some studies have suggested that tranilast also has cardiovascular-protective effects[41]. Depsipeptide is a natural cyclic peptide that inhibits HDAC 1 and 2, and selectively modulates the expression levels of different genes such as c-myc, Hsp90, and p53. The cyclic peptide family includes other HDACi, such as apicidin. The apicidin derivative API-D is capable of reducing hypertrophy and, consequently, the transition to HF in mice subjected to thoracic aortic constriction. Treatment with this substance therefore establishes a relevant therapeutic approach for HF[42].

The cardiovascular protective effects of p300 HAT inhibitor curcumin have been demonstrated[43,44]. In a rat model of HF and primary cultured rat cardiac myocytes and fibroblasts, curcumin prevented ventricular hypertrophy and preserved systolic function[45].

RNA-based mechanisms as novel biomarkers

MicroRNAs are key regulators of gene expression acting at the post-transcriptional level. MiRNAs are implicated in the pathogenesis of several CVDs[46]. The modulation of miRNA expression could represent an innovative therapeutic approach to the treatment of cardiovascular conditions by targeting a single cell type or specific pathways, as demonstrated in an animal model[47,48]. Recently, several study population have investigated the involvement of transcriptionally regulated miRNAs as an attractive target for the treatment of several cardiovascular conditions (Table 3). Preclinical studies using antisense oligonucleotide (antagomir) -mediated knockdown have demonstrated the role of specific miRNAs in HF[47,49,50]. Indeed, it was shown that a single treatment with the infusion of a miR133 antagomir induced cardiac hypertrophy in mice[49]. Recently, Wahlquist *et al*[47] demonstrated that high levels of miR25 can depress cardiac function, although the inhibition of this miRNA by anti-miR25 effectively restores cardiac function in an HF mouse model. Interestingly, it was demonstrated that miRNAs secreted by cardiac fibroblasts may also act as mediators of cardiomyocyte hypertrophy *via* a paracrine mechanism[50]. During hypertension or pathological cardiac hypertrophy, reactivation of fetal cardiac genes such as atrial natriuretic peptide, (ANP)/B-type natriuretic peptide (BNP), and beta-myosin heavy chain (β-MHC) can occur. In a hypertensive mouse model, aldosterone-dependent inhibition of miR-208a can occur, resulting in β-MHC inhibition and an increase of cardiac hypertrophy[51]. It was also shown that therapeutic inhibition of miR-208a led to a reduction in cardiac remodeling, which coincided with a significant improvement in survival and cardiac function during heart disease[48]. Additionally, in hypertensive rat models, changes in β-MHC expression were observed

Table 3 Recent evidence investigating the role of circulating miRNAs as biomarkers in several cardiovascular diseases

miRNAs	Sources	Conditions	Ref.
↑miR-339-5p, miR-483-3p ↓miR-139-5b	Plasma	LVI	Saddic *et al*[64] (2015)
↓miR-145	Plasma	AMI	Gao *et al*[65] (2015)
↑miR-122, miR-140-3p, miR-720, miR-2861, miR-3149	Plasma	ACS, AMI	Li *et al*[66] (2015)
↑Let-7e, miR-15a, miR-196b ↓miR-411	Plasma	AAA, Atherosclerosis	Stather *et al*[67] (2015)
↓ miR-125b, miR-320b	Plasma	AMI, CAD	Huang *et al*[68] (2014)
↓miR-21	Serum	CAD	Fan *et al*[69] (2014)
↓miR-31	Plasma	CAD	Wang *et al*[70] (2014)
↑miR-146a, miR-186, miR-208b, miR-499	Serum	ACS, Stable CAD, CV risk	Wu *et al*[71] (2014)
↑miR-210	PBMC	HF	Endo *et al*[72] (2013)
↑miR-21, miR-25, miR-92a, miR-106b, miR-126, miR-451, miR-590-5p	Plasma	AP, UA	Ren *et al*[73] (2013)
↔ miR-1, miR-208a, miR-423-5p	Plasma	AMI, CAD	Nabialek *et al*[74] (2013)
↑miR-30a, miR-210	Serum	HF	Zhao *et al*[75] (2013)
↑miR-337-5p, miR-433, miR-485-3p, miR-1, miR-122, miR-126, miR-133a/b, miR-199a ↔miR-17-5p, miR-92a, miR-145, miR-155, miR-208a, miR-375, miR-799-5p	Plasma	AP, UA	D'Alessandra *et al*[76] (2013)
↓miR-103, miR-142-3p, miR-30b, miR-342-3p	Plasma	HF	Ellis *et al*[77] (2013)
↑miR-122, miR-200b, miR-520d-5p, miR-622 ↓miR-558	WB and serum	HF	Vogel *et al*[78] (2013)
↑miR-21, miR-133a, miR-423-5p, miR-499-5p ↔miR-1, miR-208a	Plasma	HF, NSTEMI	Olivieri *et al*[79] (2013)
↑miR-133a	Plasma	AMI, AP	Wang *et al*[80] (2013)
↓miR-214	Plasma	AMI, AP, UA	Lu *et al*[81] (2013)

AAA: Abdominal aortic aneurysm; ACS: Acute coronary syndrome; AMI: Acute myocardial infarction; AP: Angina pectoris; CAD: Coronary artery disease; CV: Cardiovascular; HF: Heart failure; LVI: Left ventricular ischemia; NSTEMI: Non-ST-elevation myocardial infarction; PBMC: Peripheral blood mononuclear cells; UA: Unstable angina; WB: Whole blood.

after treatment with anti-miR-208a that acted by reverting the levels of several miRNAs, including miR-16, -19b, and -20b[52]. Recently, the regulation of miR-208a and endoglin in AMI were investigated, with the authors demonstrating that the overexpression of antagomir-208a significantly inhibited the increase of myocardial endoglin and β-MHC protein expression induced by infarction[53]. In addition, pre-treatment with atorvastatin and valsartan, members of a drug class known as statins that are primarily used for the prevention of events associated with cardiovascular disease, can decrease myocardial fibrosis induced by AMI by attenuating miR-208a and endoglin expression[53]. Clinical evidence supports the different levels of miR-143, miR-145, miR-21, miR-133, and miR-1 expression in patients with essential hypertension, suggesting that these miRNAs can act in vascular smooth muscle cell phenotypic modulation and could represent potential therapeutic targets in essential hypertension[54]. It was found that the chronic restoration of miR-1 gene expression in an animal model reverted pressure-induced cardiac hypertrophy and prevented the adverse cardiac remodeling induced by pressure overload[55]. Recently, Han *et al*[56] found higher levels of miR-29a in patients with hypertension and left ventricular (LV) hypertrophy compared to patients with hypertension alone. MiR-29a levels were significantly associated with collagen type Ⅰ and Ⅲ and MMP-9 expression. The same authors, employing a mouse model of pressure overload, have shown that antagomir-29a significantly suppressed the hypertrophy of cardiomyocytes and reduced the expression of ANP and β-MHC, suggesting a possible role of miR-29a as a therapeutic target[56]. Several preclinical studies showed the beneficial effects of antagomir-92a administration on small and large animal models before MI[57-59]. Inhibition of miR-92a by repeated intravenous injections of antagomir-92a induced angiogenesis and improved recovery of ventricular function in MI mouse model[57]. In MI large animal models, antagomir-92a treatment revealed cardio-protection against ischemia/reperfusion[58]. Recent evidence has demonstrated favorable post-ischemic myocardial repair after intravenous administration of antagomir-92a in adult large animal models[59]. Indeed, neovasculogenesis and the prevention of adverse ventricular remodeling, the major cause of contractile dysfunction and HF after MI, were observed after intravenous administration of antagomir-92a[59]. These results reveal a promising therapeutic approach for patients affected by MI. Progression of post-infarction LV remodeling in mice was studied by Tolonen *et al*[60], who observed that the inhibition of Let-7c was associated with decreased apoptosis, reduced fibrosis, and a reduction in the number of discoidin domain receptor 2-positive fibroblasts, while the number of c-kit$^+$ cardiac stem cells and Ki-67$^+$ proliferating cells remained unaltered[60]. Although Let-7c inhibitor injection improved cardiac function after MI, the safety of Let-7c inhibition has yet to be clarified due to its dualistic function that appears to have a causative role in various cancer diseases.

Circulating miRNA patterns are analyzed as potential disease specific biomarkers in CVDs in two observational

prospective studies on aortic aneurism in hereditary aortopathy syndromes (NCT02213484), coronary artery diseases, and myocardial infarction (NCT02076153). Three interventional randomized studies are focusing on the association between miRNA profile modifications and the administration of specific molecules like anti-platelet agents (NCT02071966) (NCT02447809) in coronary syndromes and anti-diabetics drugs in diabetic stable and unstable angina (NCT01331967).

CONCLUSION

To date, several epidrugs (such as vorinostat and panobinostat) have been approved for the treatment of cancer and myelodysplastic syndromes, and are therefore commercially available. However, no epigenetic drugs for CVDs have yet been actually approved by the FDA. Nevertheless, the opportunity to control genetic and epigenetic processes could be considered a promising and attractive tool in cardiovascular medicine. For this reason, the investigation of epigenetic-related mechanisms might help to explain how environmental and lifestyle factors can influence aberrant gene expression patterns over a lifetime that can result in increased cardiovascular risk. Preclinical experiments have identified some HDACi that could have future implications in the treatment of several cardiovascular conditions, including atrial fibrillation, cardiac hypertrophy, and HF. Ongoing human clinical controlled studies are emphasizing the ability of some drugs such as hydralazine and procainamide to act on DNA methylation in CVDs. However, the clinical experience with HDACi in CVDs is limited due to the observed toxic cardiac side effects in oncologic patients.

The study of the human genome will find biomarkers that might affect CVDs. It is likely that only epigenetic profiles obtained from large cohorts of patients with the same genetic mutations will be able to promote the development of surveillance programs and novel effective drugs for the transition of *in vitro* to *in vivo* treatments for the early stage of CVDs[61-63].

To date, few clinical trials have investigated the link between drugs and specific miRNA profiles, which might be considered as biomarkers for the classification of CVDs with scarce compliance to standard therapy and affected by the incidence of more aggressive clinical phenotypes. Unfortunately, antagomir in the area of cardiovascular disease has not yet been tested in clinical trials. However, the promising studies covered here reflect the open debate for possible future applications of miRNA therapeutics in CVDs.

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ORIGINAL ARTICLE

Retrospective Study

Red cell distribution width in anemic patients undergoing transcatheter aortic valve implantation

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Author contributions: Hellhammer K and Zeus T performed the research and wrote the paper; Verde PE designed the research and contributed to the analysis; Veulemanns V and Kahlstadt L designed the research and supervised the report; Wolff G, Erkens R, Westenfeld R, Navarese EP and Merx MW provided clinical advice; Rassaf T and Kelm M supervised the report.

Institutional review board statement: This study was reviewed and approved by the Ethics Committee of the University Hospital Düsseldorf.

Informed consent statement: Patients were not required to give informed. To the study because the analysis used anonymous clinical data that was obtained after each patient agreed to treatment by written consent.

Conflict-of-interest statement: None of the authors has conflicts of interest to declare. There is no existing relation with the industry.

Data sharing statement: No additional data are available.

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Abstract

AIM: To determine the impact of red blood cell distribution width on outcome in anemic patients undergoing transcatheter aortic valve implantation (TAVI).

METHODS: In a retrospective single center cohort study we determined the impact of baseline red cell distribution width (RDW) and anemia on outcome in 376 patients with aortic stenosis undergoing TAVI. All patients were discussed in the institutional heart team and declined for surgical aortic valve replacement due to high operative risk. Collected data included patient characteristics, imaging findings, periprocedural in hospital data, laboratory results and follow up data. Blood samples for hematology and biochemistry analysis were taken from every patient before and at fixed intervals up to 72 h after TAVI including blood count and creatinine. Descriptive statistics were used for patient's characteristics. Kaplan-Meier survival curves were used for time to event outcomes. A recursive partitioning regression and classification was used to investigate the association between potential risk factors and outcome variables.

RESULTS: Mean age in our study population was 81 ± 6.1

years. Anemia was prevalent in 63.6% (n = 239) of our patients. Age and creatinine were identified as risk factors for anemia. In our study population, anemia per se did influence 30-d mortality but did not predict longterm mortality. In contrast, a RDW > 14% showed to be highly predictable for a reduced short- and longterm survival in patients with aortic valve disease after TAVI procedure.

CONCLUSION: Age and kidney function determine the degree of anemia. The anisocytosis of red blood cells in anemic patients supplements prognostic information in addition to that derived from the WHO-based definition of anemia.

Key words: Anemia; Red cell distribution width; Red blood cells; Transcatheter aortic valve implantation; Aortic stenosis

Core tip: This is a retrospective study to evaluate the impact of prevalent anemia and the importance of red cell distribution width (RDW) on the outcome in patients undergoing transcatheter aortic valve replacement. Anemia was prevalent 63.6% of the patients and did influence 30-d mortality but did not predict longterm mortality. In contrast, a RDW > 14% showed to be highly predictable for a reduced short- and long-term survival in patients with aortic valve disease after transcatheter aortic valve implantation procedure. Age and creatinine were identified as risk factors for anemia.

Hellhammer K, Zeus T, Verde PE, Veulemanns V, Kahlstadt L, Wolff G, Erkens R, Westenfeld R, Navarese EP, Merx MW, Rassaf T, Kelm M. Red cell distribution width in anemic patients undergoing transcatheter aortic valve implantation. *World J Cardiol* 2016; 8(2): 220-230 Available from: URL: http://www.wjgnet.com/1949-8462/full/v8/i2/220.htm DOI: http://dx.doi.org/10.4330/wjc.v8.i2.220

INTRODUCTION

Anemia is common in elderly patients with cardiovascular disease. An association of increased mortality with decreasing levels of hemoglobin has been shown in patients with coronary artery disease (CAD), acute myocardial infarction, cardiac heart failure (CHF) and structural heart disease[1-4]. Anemia also affects outcome after percutaneous coronary artery intervention (PCI), coronary artery bypass graft (CABG), and transcatheter aortic valve replacement (TAVI)[5-7]. In patients with aortic valve disease anemia often occurs in combination with occult bleeding within the gastro-intestinal tract.

According to the WHO, anemia is defined by a level of hemoglobin < 13 g/dL in men and < 12 g/dL in women[8]. Studies correcting anemia by either erythropoiesis stimulating agents (ESA) or by transfusion of packed red blood cells (RBC) yielded conflicting results[9]. ESA failed to improve outcome in acute myocardial infarction[10], chronic kidney disease[11], and heart failure[12]. RBC transfusions to patients undergoing primary PCI[13,14], CABG[15], and TAVI[7], respectively, may be even harmful and were associated with increased mortality. The storage lesion and subsequent scavenging of nitric oxide (NO) through occult hemolysis after transfusion may at least in part account for these detrimental effects[15-17]. These data raise the question whether or not the mere determination of the hemoglobin levels is appropriate for risk stratification and guidance of anemia treatment in mostly elderly patients at high cardiovascular risk.

Red blood cell distribution width (RDW) is a quantitative measure of anisocytosis, the variability in size of circulating RBC. It is routinely measured in automated hematology analyzers and is reported together with hemoglobin, RBC number, and hematocrit as a component of complete blood count. RDW is typically elevated in conditions of ineffective RBC production, *e.g.*, iron or vitamin B12 deficiency, increased RBC destruction such as in hemolysis, after blood transfusion or during severe inflammation. Conceivably, RDW may represent an integrative measure of multiple pathologic processes in the elderly patient with structural heart disease, explaining its strong association with clinical short and long term outcomes[18-24]. Relevant comorbidities affecting RDW in those patients may include renal dysfunction, inflammatory stress, and nutritional deficiencies. Thus, the measurement of RDW as compared to hemoglobin may add or provide even superior information to stratification of those high risk patients with advanced aortic valve stenosis undergoing TAVI procedures.

Recent studies indicate that the detrimental effects of anemia is not only mediated by the absolute hemoglobin levels, but also by the quality of the endogenous and the substituted RBCs. Different subtypes of anemia affect the outcome after stenting in stable coronary artery disease distinctly[25]. Red cell distribution width (RDW) has emerged as a novel marker not only of the size of erythrocytes, but also as an index of quality and function of RBC[19,26]. RDW is a powerful and independent predictor of mortality in cardiac heart failure[18,20,21]. The role of RDW in anemic patients undergoing TAVI is not clear. We therefore investigated whether RDW may have the potential to act as a novel prognostic parameter for risk stratification in addition to anemia, as defined by WHO criteria.

MATERIALS AND METHODS

Patient selection and study design

The study population consisted of 376 patients with severe symptomatic aortic stenosis who underwent TAVI with either the Medtronic CoreValve system (Medtronic Inc, Minneapolis, MN) or the Edwards SAPIEN Valve (Edwards Lifesciences, Irvine, CA) from August 2009 to August 2013 at the Heart Center Duesseldorf. All patients were discussed in the institutional heart team and

declined for surgical aortic valve replacement due to high operative risk. All patients gave their written informed consent for TAVI and the use of clinical, procedural and follow up data for research. Study procedures were in accordance with the Declaration of Helsinki and the institutional Ethics Committee of the Heinrich-Heine University approved the study protocol. The study is registered at clinical trials (NCT01805739).

Data collection and definitions

Collected data included patient characteristics, imaging findings, periprocedural in hospital data, laboratory results and follow up data. Blood samples for hematology and biochemistry analysis were taken from every patient before and at fixed intervals up to 72 h after TAVI including blood count and creatinine. As reported by the World Health Organisation (WHO) baseline anemia was defined as a hemoglobin (Hb) level of < 13 g/dL for men and < 12 g/dL for women. Preoperative serum creatinine values were used to calculate the baseline serum creatinine clearance using the Cockcroft and Gault equation[27]. Chronic kidney disease (CKD) was defined as a calculated serum clearance < 60 mL/min[28]. Clinical endpoints were reported according to The Valve Academic Research Consortium (VARC) consensus statement[29]. Follow up data for mortality were collected by contacting the attending physician and the civil registries. Technical appendix, statistical code, and dataset are available from the corresponding author. Participants gave informed consent for data sharing.

TAVI procedure

TAVI procedures were performed according to current guidelines[30]. A single antibiotic shot was given shortly before TAVI procedure. All patients were referred to intensive care after the procedure. For antiplatelet therapy, patients received a combination therapy of aspirin 100 mg/d and clopidogrel 75 mg/d for three months after TAVI followed by permanent aspirin mono therapy. Patients on oral anticoagulation received clopidogrel 75 mg/d and oral anticoagulation for three months followed by oral anticoagulation.

Statistical analysis

The statistical methods of this study were reviewed by Pablo E Verde from the Coordination Center for Clinical Trials Düsseldorf. Descriptive statistics are based on frequency tables for categorical data, means and standard deviations for continuous variables and Kaplan-Meier survival curves for time to event outcomes. Association between continues variables are analyzed with Person's correlation coefficient and displayed graphically with scatter plots.

A recursive partitioning regression and classification was used to investigate the association between potential risk factors and outcome variables. This approach is based on the method describe by Horhorn *et al*[31]. This technique combines an algorithm for recursive partitioning together with a well defined theory of permutation tests. Multiple test procedures are applied to determine whether a significant association between any of the covariables and the response variable can be stated. The resulting partitioning regression analysis is graphically displayed as a classification tree. The partitioning nodes are displayed by an optimal cut-off point for continues covariables and with a classification split for categorical covariables. Each node-split is assessed with a *P*-value calculated by a permutation test. In addition, regression analysis for binary outcomes was performed using the classical logistic regression and for time to event outcomes the proportional hazard Cox's regression. In each case we report results for all covariables included in the model and with covariables selected by using a step-wise variable selection based on taking the minimum value of AIC (Akaike Information Criteria). As graphical outputs for regression analysis a forest plot is used, in this figure the odds ratio and the 95% confidence interval is displayed for each variable in the model. Data analysis was performed using the statistical software R version 3.1.0[32], SPSS Statistics 22 (IBM®) and GraphPad (Prism®).

RESULTS

Baseline characteristics

Anemia was prevalent in 63.6% (n = 239) of our study population (Table 1). Groups with and without anemia did not differ except for chronic kidney disease (P = 0.001), history of myocardial infarction (P = 0.029), and the need for dialysis due to end-stage chronic kidney disease (P = 0.009).

Serum levels for baseline serum creatinine (anemia: 1.5 mg/dL ± 1.2 mg/dL *vs* no anemia: 1.0 mg/dL ± 0.5 mg/dL; P < 0.001) and C-reactive Protein (anemia: 1.4 mg/dL ± 2.0 mg/dL *vs* no anemia: 0.8 mg/dL ± 1.1 mg/dL; P < 0.001) were higher in patients with anemia whereas baseline creatinine clearance was lower in anemic patients (54.5 mL/min ± 23.6 mL/min *vs* 65.9 mL/min ± 22.2 mL/min; P < 0.001). As a marker for the variability in size of the circulating erythrocytes the RDW was higher in patients with anemia (15.4% ± 1.8% *vs* 14.4% ± 1.6%; P < 0.001).

Procedural outcome and 30-d mortality

Clinical outcome was reported according to VARC criteria[29]. The findings are summarized in Table 2. There was no difference with regard to vascular or bleeding complications in between both groups. Overall incidence of acute kidney injury (AKI) after TAVI was higher in patients with anemia (25.1% *vs* 10.9%; P = 0.001). Further clinical endpoints as stroke (anemia: 2.9% *vs* no anemia: 2.2%; P = 0.668), myocardial infarction (anemia: 0.4% *vs* no anemia: 0.0%; P = 0.448), endocarditis (anemia: 0.0% *vs* no anemia: 0.0%) and need for permanent pacemaker after TAVI (anemia: 21.3% *vs* no anemia: 19.0%; P = 0.585) did not differ

Table 1 Baseline characteristics of patients undergoing transcatheter aortic valve replacement according to the presence of baseline anemia *n* (%)

	Entire cohort (*n* = 376)	Anemia (*n* = 239)	No anemia (*n* = 137)	*P*-value
Age, years ± SD	81 ± 6.1	82 ± 6.2	81 ± 5.9	0.101
Male	167 (44.4)	112 (46.9)	55 (40.1)	0.207
Weight, kg ± SD	74 ± 14.4	73 ± 14.2	75 ± 15.0	0.351
Height, cm ± SD	168 ± 8.8	168 ± 8.7	168 ± 9.1	0.685
NYHA Ⅲ and Ⅳ	288 (76.6)	187 (78.6)	101 (73.7)	0.284
CAD	263 (69.9)	170 (71.1)	93 (67.9)	0.209
Previous myocardial infarction	39 (10.4)	31 (13.0)	8 (5.8)	0.029
Previous percutaneous intervention	168 (44.7)	113 (47.3)	55 (40.1)	0.181
Previous CABG	89 (23.7)	55 (23.1)	34 (24.8)	0.708
Previous valve	8 (2.1)	5 (2.1)	3 (2.2)	0.954
Previous stroke	34 (9.0)	23 (9.6)	11 (8.0)	0.604
Diabetes mellitus	93 (24.7)	59 (24.7)	34 (28.4)	0.977
Hypertension	355 (94.4)	224 (93.7)	131 (95.6)	0.441
Peripheral vascular disease	115 (30.6)	75 (31.4)	40 (29.2)	0.658
Cerebroarterial vascular disease	81 (21.5)	56 (23.4)	25 (18.2)	0.239
COPD	72 (19.1)	46 (19.2)	26 (19.0)	0.949
Atrial fibrillation	87 (23.1)	52 (21.8)	35 (25.5)	0.414
Permanent pacemaker	64 (17.0)	43 (18.1)	21 (15.3)	0.497
Chronic kidney disease	203 (54.0)	144 (60.3)	59 (43.1)	0.001
Dialysis	21 (5.6)	19 (7.9)	2 (1.5)	0.009
Aortic valve area, cm^2 ± SD	0.73 ± 0.2	0.71 ± 0.19	0.75 ± 0.22	0.094
Mitral regurgitation ≥ grade Ⅱ	114 (30.3)	73 (32.2)	41 (31.5)	0.904
LVEF < 30%	20 (5.3)	16 (6.7)	4 (2.9)	0.253
LVEF 30%-44%	68 (18.1)	47 (19.7)	21 (15.3)	0.292
LVEF 45%-55%	49 (13.0)	29 (12.1)	20 (14.6)	0.493
LVEF > 55%	239 (63.6)	147 (61.5)	92 (67.2)	0.273
Logistic EuroSCORE, % ± SD	19.7 ± 12.9	20.5 ± 13.1	18.4 ± 12.5	0.133
Baseline hemoglobin, g/dL ± SD	11.9 ± 1.7	11.0 ± 1.1	13.6 ± 1.1	< 0.001
Baseline RDW, % ± SD	15.0 ± 1.8	15.4 ± 1.8	14.4 ± 1.6	< 0.001
Baseline serum creatinine, mg/dL ± SD	1.3 ± 1.1	1.5 ± 1.2	1.0 ± 0.5	< 0.001
Baseline GFR, mL/min ± SD	58.7 ± 23.7	54.5 ± 23.6	65.9 ± 22.2	< 0.001
Baseline CRP, mg/dL ± SD	1.2 ± 1.8	1.4 ± 2.0	0.8 ± 1.1	< 0.001
TF access	270 (71.8)	172 (72.0)	98 (71.5)	0.742
TA access	105 (27.9)	66 (27.6)	39 (28.5)	0.862
TS access	1 (0.3)	1 (0.4)	0 (0.0)	0.637

CABG: Coronary artery bypass grafting; CAD: Coronary artery disease; COPD: Chronic obstructive pulmonary disease; CRP: C-reactive protein; GFR: Glomerular filtration rate; LVEF: Left ventricular ejection fraction; NYHA: New York Heart Association; RDW: Red cell distribution width; TA: Transapical; TF: Transfemoral; TS: Transsubclavian.

between the groups. The incidence of a septical event was higher in patients with anemia (8.4% *vs* 2.2%; *P* = 0.016). Overall 30-d mortality was 7.2% (*n* = 27). In patients with anemia 30-d mortality was 9.2% (*n* = 22) whereas 3.6% (*n* = 5) of the patients without anemia died within 30 d (*P* = 0.045). The partitioning regression analysis, displayed as a classification tree, showed that life-threatening bleeding (*P* < 0.001) after TAVI and occurrence of AKI (*P* = 0.002) were statistically relevant risk factors for 30-d mortality (Figure 1A). Stepwise multiple logistic regression analysis with all covariables and the best selected covariables (Figure 1B and C) confirmed these findings and showed that RDW was a statistically significant risk factor as well (*P* = 0.044).

Factors associated with anemia

The partitioning regression analysis using anemia as outcome parameter showed that a creatinine level > 1.1 mg/dL (*P* < 0.001) and age > 83 years (*P* = 0.027) were statistically relevant risk factors for anemia (Figure 2A). Stepwise multiple logistic regression analysis with all covariables and the best selected covariables confirmed these findings (Figure 2B and C). Mean Hb concentration in our study population was 11.9 g/dL ± 1.7 g/dL. In Figure 3A the distribution of Hb levels in our study population and marking lines for cut-off points defining anemia based on the WHO definition is shown. The distribution of RDW as a marker for the variability and function of circulating erythrocytes is shown in Figure 3B.

Hemoglobin level and 1-year survival

One-year follow up was completed in 100% (*n* = 376) of patients. The Kaplan-Meier survival curves for one-year mortality in patients with and without anemia are shown in Figure 4A. As the mean Hb concentration in our study population was 11.9 g/dL, the 1-year survival of patients grouped according to their Hb below or above this value is shown in Figure 4B. To find the best hemoglobin cut-off point to predict One-year mortality we performed a partitioning regression analysis which found a hemoglobin of 9.7 g/dL to be the optimal cut-

Table 2 Clinical outcome of patients undergoing transcatheter aortic valve replacement according to the presence of baseline anemia *n* (%)

	Entire cohort (*n* = 376)	Anemia (*n* = 239)	No anemia (*n* = 137)	*P*-value
Vascular complications				
Any vascular complications	34 (9.0)	24 (10.0)	10 (7.3)	0.372
Minor vascular complications	20 (5.3)	14 (5.9)	6 (4.4)	0.639
Major vascular complications	4 (1.1)	3 (1.3)	1 (0.7)	0.633
Bleeding complications				
Any bleeding complications	45 (12.0)	27 (11.3)	18 (13.1)	0.596
Life-threatening bleeding	20 (5.3)	12 (5.0)	8 (5.8)	0.732
Minor bleeding	21 (5.6)	12 (5.0)	9 (6.6)	0.529
Major bleeding	4 (1.1)	3 (1.3)	1 (0.7)	0.633
Percutaneous closure device failure	10 (2.7)	7 (2.9)	3 (2.2)	0.668
Acute kidney injury	75 (31.4)	60 (25.1)	15 (10.9)	0.001
Acute kidney injury stage Ⅰ	44 (11.7)	33 (13.8)	11 (8.0)	0.093
Acute kidney injury stage Ⅱ	1 (0.3)	1 (0.4)	0 (0.0)	0.636
Acute kidney injury stage Ⅲ	30 (8.0)	26 (10.9)	4 (2.9)	0.007
Need for dialysis	22 (5.9)	18 (7.5)	4 (2.9)	0.069
Myocardial infaction	1 (0.3)	1 (0.4)	0 (0.0)	0.448
Stroke	10 (2.7)	7 (2.9)	3 (2.2)	0.668
Conversion to open surgery	8 (2.1)	6 (2.5)	2 (1.5)	0.497
Sepsis	23 (6.1)	20 (8.4)	3 (2.2)	0.016
Endocarditis	0 (0.0)	0 (0.0)	0 (0.0)	
Need for pacemaker	77 (20.5)	51 (21.3)	26 (19.0)	0.585
Length of stay > 14 d	235 (62.5)	152 (63.6)	83 (60.6)	0.561
30-d mortality, *n* (%)	27 (7.2)	22 (9.2)	5 (3.6)	0.045

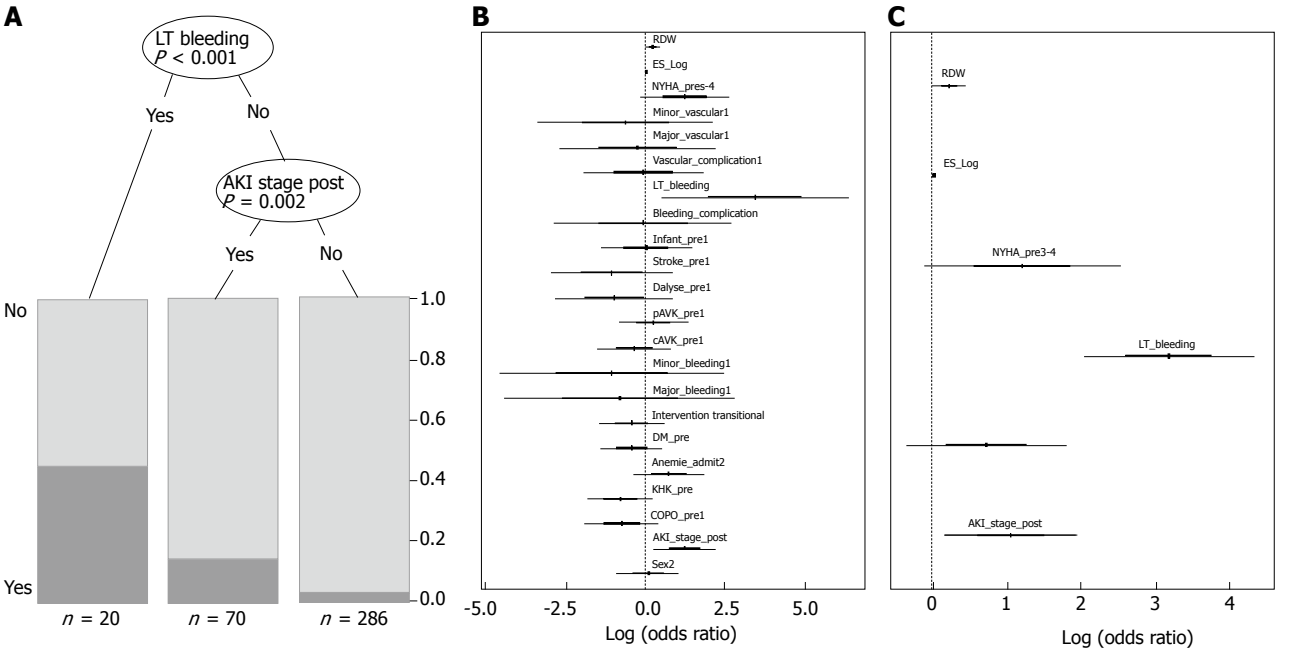

Figure 1 Regression analysis for risk factors associated with 30-d mortality. A: Results from the classification tree with significant node-splits and distribution of patients. Life-threatening bleeding ($P < 0.001$) and acute kidney injury ($P = 0.002$) were found to be statistically relevant risk factors for 30-d mortality; B: Logistic regression with all covariables which were supposed to be associated with 30-d mortality. Forest plot with odds ratios and 95%CI (logarithmic scale); C: Logistic regression with the best selected covariables using AIC. Life-threatening bleeding ($P < 0.001$), acute kidney injury post procedure ($P = 0.018$) and RDW ($P = 0.044$) were found to be statistically relevant risk factors for 30-dmortality. AIC: Akaike information criterion; AKI stage post: Acute kidney injury stage I-III post; CAD: Coronary artery disease; Cavk: Cerebroarterial vascular disease; COPD: Chronic obstructive pulmonary disease; DM: Diabetes mellitus; ES log: Logistic EuroSCORE; LT bleeding: Life-threatening bleeding; NYHA: New York Heart Association; pAVK: Peripheral vascular disease; RDW: Red cell distribution width.

off point ($P = 0.012$). The Kaplan-Meier survival curves of patients grouped according to their hemoglobin level above or below this cut-off point is shown in Figure 4C.

RDW and mortality

As already described, RDW was found to be a risk factor for 30-d mortality in our study population. The partitioning regression analysis using 30-d mortality as an outcome parameter showed a RDW cut-off point of 14% to predict 30-d mortality with the highest sensitivity and specificity (Figure 5A). In patients with RDW > 14% 30-d mortality and one-year mortality was

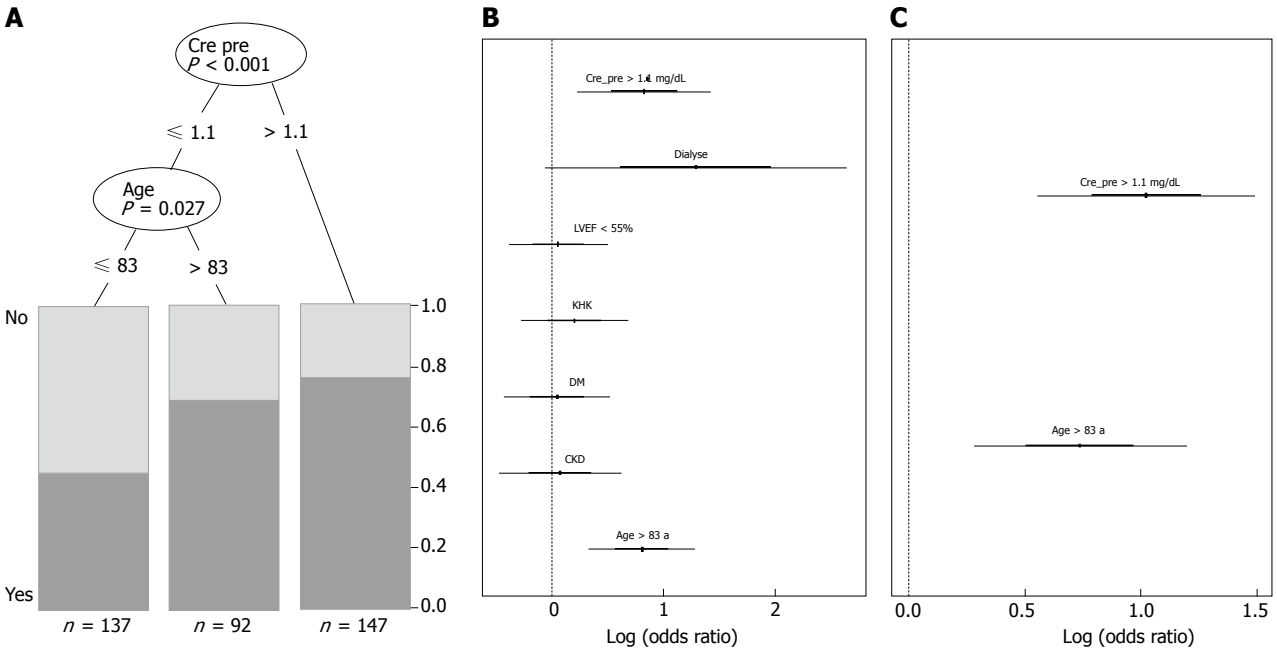

Figure 2 Regression analysis for risk factors associated with anemia. A: Classification tree with significant node-splits and distribution of patients with anemia. A creatinine > 1.1 mg/dL (P < 0.001) and age > 83 (P = 0.027) were found to be statistically relevant risk factors for anemia; B: Logistic regression with all covariables which were supposed to be associated with anemia. Forest plot with odds ratios and 95% confidence intervals (logarithmic scale); C: Logistic regression with the best selected covariables using AIC. A creatinine > 1.1 mg/dL (P < 0.001) and age > 83 (P = 0.001) were found to be statistically relevant risk factors for anemia. a: Years; AIC: Akaike information criterion; CAD: Coronary artery disease; CKD: Chronic kidney disease; Crea pre: Creatinine (mg/dL) preoperative; DM: Diabetes mellitus; LVEF: Left ventricular ejection fraction (%).

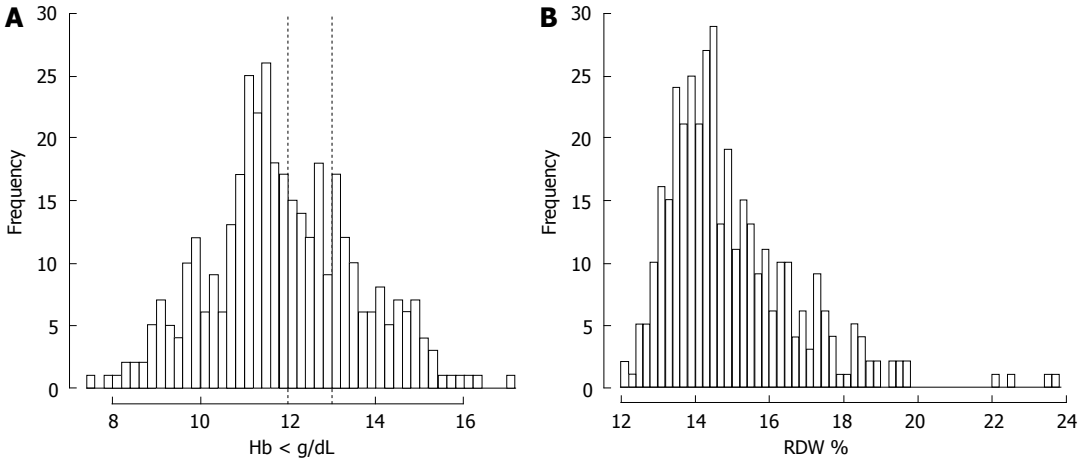

Figure 3 Histogram of the distribution of hemoglobin and red cell distribution width levels. A: Histogram of the distribution of hemoglobin levels. Vertical lines at 12 g/dL and 13 g/dL for population based cut-off points for women and men according to WHO definition of anemia; B: Histogram of RDW levels. Hb: Hemoglobin; RDW: Red cell distribution width.

significantly higher than in patients with a RDW < 14% (Figure 5B).

To assess the association between hemoglobin and RDW we performed a correlation analysis (Figure 6) which revealed a significant negative correlation between hemoglobin and RDW (-0.36; 95%CI: -0.45, -0.27; P < 0.001) reflecting that an increasing severity of anemia is associated with an increased heterogeneity of red blood cell size.

Anemia and RDW

RDW has been shown to be elevated in conditions of ineffective RBC production[19]. In our study population, anemic patients presented with a higher RDW than patients without anemia (P < 0.001). The distribution of RDW levels in patients with and without anemia is shown in Figure 7A and B. The Kaplan-Meier survival curves of anemic patients grouped according to the presence of a RDW below or above 14% are shown in Figure 7C (P = 0.013).

DISCUSSION

The major findings of the present study are: (1) two

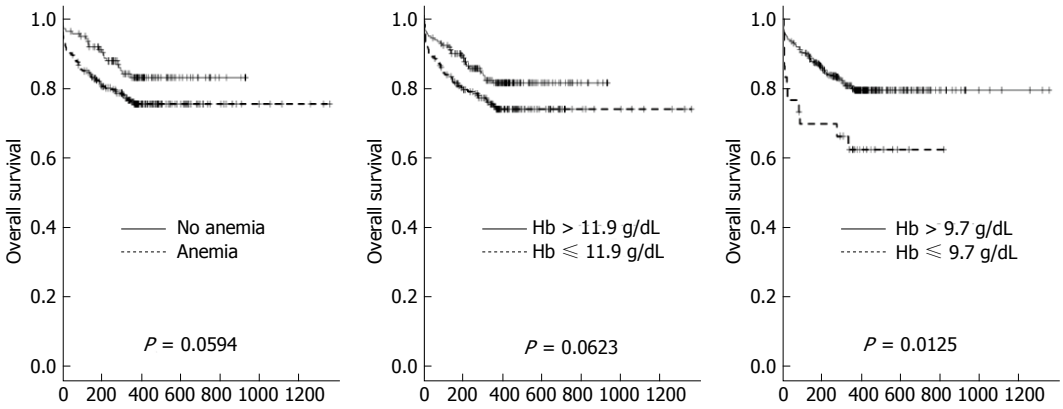

Figure 4 Anemia and one-year mortality. A: One-year survival curves of patients with and without anemia (P = 0.0594); B: One-year survival curves of patients grouped according to their hemoglobin level above or below mean Hb level of 11.9 g/dL; C: One-year survival curves of patients grouped according to their hemoglobin level above or below cut-off point of 9.7 g/dL.

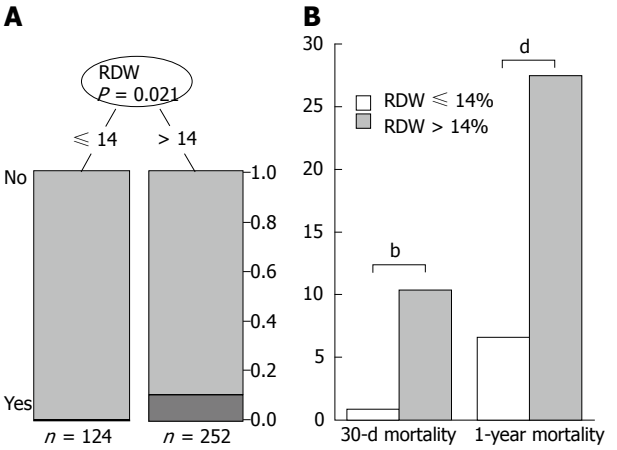

Figure 5 Red cell distribution width and mortality. A: Classification tree for 30-d mortality with significant node split at RDW 14% (P = 0.021); B: Thirty-day (P < 0.01) and one-year mortality (P < 0.001) of patients grouped according to the presence of RDW ⩽ 14% or > 14%. RDW: Red cell distribution width.

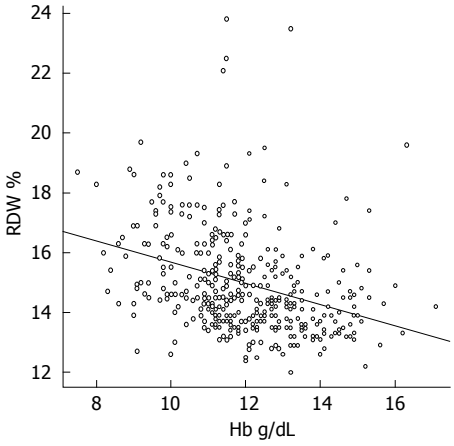

Figure 6 Correlation of hemoglobin with red cell distribution width. RDW and hemoglobin showed a significantly negative correlation (-0.36; 95%CI: -0.45, -0.27; P < 0.001). Hb: Hemoglobin; RDW: Red cell distribution width.

thirds of TAVI patients are anemic according to the WHO definition; (2) age and level of creatinine determine independently the incidence of anemia in this population; (3) anemia affects incidence of TAVI related kidney injury and 30 d mortality according to VARC criteria for short term outcome; (4) a lower threshold of Hb (9.7 mg/dL) predicts 1 year mortality more precisely than the classical WHO definition of anemia in this patient cohort in our study; (5) absolute levels of hemoglobin are related only loosely to size, distribution and presumably function of red blood cells; and (6) a red blood cell distribution width of > 14% is highly predictable for a reduced rate of survival in patients with aortic valve disease one year after TAVI procedure, particularly in those patients with already preexisting anemia. These findings raise the question whether or not the RDW should be integrated in the risk stratification in elderly anemic patients undergoing TAVI procedure.

Definition and incidence of anemia

In elderly patients with aortic valve disease the age and the kidney function are the major predictors on the prevalence of anemia, which is similar to reports in patients with CAD and CHF[1,3]. Kidney function deteriorates with increasing age and the number of circulating RBC is critically dependent on the axis of renal stimulation of bone marrow synthesis of erythrocytes. According to the definition of the WHO, anemia was common in elderly patients with aortic valve stenosis and the mean value of hemoglobin level in the entire cohort was only 11.9 g/dL. Both the threshold levels suggested by the WHO and the mean value of Hb failed to precisely discriminate those patients at increased or reduced mortality rate in our study cohort. Only a level of < 9.7 g/dL hemoglobin identified patients with a reduced survival at one year after TAVI. This finding is in line with previous reports on an increased mortality one year after TAVI with decreasing levels of hemoglobin[7]. These data imply that categorizing patients as anemic or non-anemic according to the WHO criteria might be helpful to stratify patients undergoing TAVI for their periprocedural risk and short term survival, whereas long term mortality and overall risk is better achieved with a threshold of < 10 g/dL of hemoglobin.

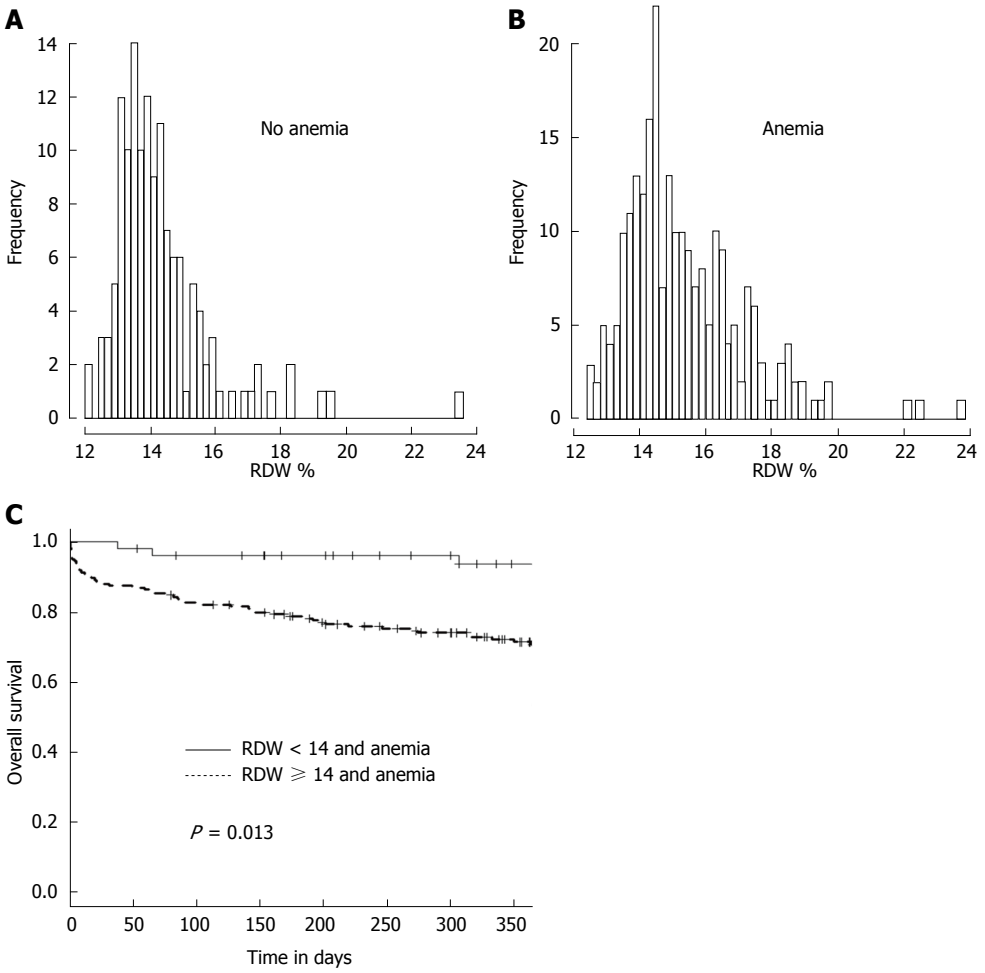

Figure 7 Distribution of red cell distribution width and survival of anemic patients according to their red cell distribution width. A: Distribution of RDW in patients without anemia; B: Distribution of RDW in patients with anemia; C: Survival curves of patients with anemia grouped to their RDW above or below cut off point of 14% (P = 0.013). RDW: Red cell distribution width.

Assessment of red blood cell function

The major task of erythrocytes is to deliver oxygen required to meet metabolic demands to tissues. Apart from the hemoglobin-dependent transport of oxygen, RBC serve many other functions. Number and distribution of RBC in the circulation are determined by their membrane and erythrocrine function[33-35]. Alterations of the redox status and the conformation of membrane regulate their shape, their distribution, passage through the microcirculation and their removal from the circulation by the reticulo-endothelial. RBC release ATP, NO, nitrite, prostanoids, chemo kinins and sulfide[36]. More recently we and others have shown that RBCs modulate their deformability, vascular tone, infarct size and thrombus formation at the endothelium through NOS/sGC signaling[37-40]. The RBC deformability and the rapid shape change are of paramount importance for the passage through the microcirculation and effective tissue perfusion. An increased RDW is associated with an impairment of RBC deformability[19]. These data may raise concerns with the view that sole measurements of hemoglobin levels reflect appropriately consequences of anemia and their impact on outcome in cardiovascular diseases and interventions.

The distribution and width of RBC as a novel marker for adverse outcome in CHF has been described in the cohort of the CHARM trial only recently[20]. Among 36 routine laboratory values including hematocrit and hemoglobin, higher RDW showed the greatest association with morbidity and mortality. Given the association of hemoglobin with adverse outcome in CHF and CAD we evaluated the relationship of RDW and level of hemoglobin (Figure 6). We observed a moderate negative correlation as was also reported for CHF[20]. In all final multivariate models RDW was a significant predictor of short term outcome after TAVI.

Conclusion

Age and kidney function determine the degree of anemia. The anios cytosis of red blood cells in anemic patients is emerging as an important parameter to assess short and long term mortality in patients undergoing TAVI. These findings demonstrate that RDW supplements prognostic information in addition to that derived from the WHO-

based definition of anemia.

Study limitations

Our results have to be confirmed in larger cohorts with a longer follow up period to establish RDW as an independent and powerful prognostic marker in elderly patients with structural heart disease. In our retrospective single center cohort study we did not systematically substitute anemia with packed red blood cells and left this decision at the discretion of the interventionalists and the colleagues supervising the patients after the TAVI procedure on the ICU and the regular ward. However, we did focus on the Hb levels and RDW at the time of admittance prior to the TAVI procedure and the percentage of patients that received transfusion within the hospital was comparable in the anemic and the non-anemic group. Therefore, we believe that this did not affect outcome differences with respect to RDW (prior to TAVI) between both groups. Further, we did not investigate the treatment of anemic patients and patients with chronic kidney disease which may have been an interesting aspect.

In addition mechanistic studies focusing on RBC signaling cascades that might be altered in these elderly patients appear highly mandatory to identify potential novel therapeutic targets to improve RBC function and to determine how treatment of anemia should be guided and monitored in this elderly population with aortic valve disease.

COMMENTS

Background

Anemia is common in elderly patients with cardiovascular disease. An association of increased mortality with decreasing levels of hemoglobin has been shown in patients with coronary artery disease, acute myocardial infarction, cardiac heart failure and structural heart disease. Red blood cell (RBC) distribution width (RDW) is a quantitative measure of anisocytosis, the variability in size of circulating RBC. It may represent an integrative measure of multiple pathologic processes in the elderly patient with structural heart disease, explaining its strong association with clinical short and long term outcomes. Recent studies indicate that the detrimental effects of anemia are not only mediated by the absolute hemoglobin levels, but also by the quality of the endogenous and the substituted RBCs. The role of RDW in anemic patients undergoing TAVI is not clear. The authors therefore investigated whether RDW may have the potential to act as a novel prognostic parameter for risk stratification in addition to anemia, as defined by WHO criteria.

Research frontiers

Red cell distribution width has been shown to be a novel marker not only of the size of erythrocytes, but also as an index of quality and function of RBC. It has been shown to be a powerful and independent predictor of mortality in cardiac heart failure. The results of this study contributes to evaluate the impact of prevalent anemia on outcome and to clarify the prognostic value of RDW in anemic TAVI patients.

Innovations and breakthroughs

In this study, anemia was prevalent 63.6% of the patients and did influence 30-d mortality but did not predict longterm mortality. In contrast, a RDW > 14% showed to be highly predictable for a reduced short- and long-term survival in patients with aortic valve disease after TAVI procedure. Age and creatinine were identified as risk factors for anemia.

Applications

This study suggests that RDW is a useful additional parameter which gives prognostic information concerning the outcome of anemic patients undergoing transcatheter aortic valve implantation.

Terminology

Red cell distribution width (RDW): RDW is a quantitative measure of anisocytosis, the variability in size of circulating RBC. It has been shown to be a novel marker not only of the size of erythrocytes, but also as an index of quality and function of RBC.

Peer-review

The paper is well structured, the presentation is clear and the discussion is in accordance with the results presented. The paper brings some novelty in the field.

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ORIGINAL ARTICLE

Observational Study

Association of arterial stiffness with coronary flow reserve in revascularized coronary artery disease patients

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Data sharing statement: Technical appendix, statistical code, and dataset available from the corresponding author at ignoik@otenet.gr. Participants gave informed consent for data sharing.

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Abstract

AIM: To investigate the association of arterial wave reflection with coronary flow reserve (CFR) in coronary artery disease (CAD) patients after successful revascularization.

METHODS: We assessed 70 patients with angiographically documented CAD who had undergone recent successful revascularization. We measured (1) reactive hyperemia index (RHI) using fingertip peripheral arterial tonometry (RH-PAT Endo-PAT); (2) carotid to femoral pulse wave velocity (PWVc-Complior); (3) augmentation index (AIx), the diastolic area (DAI%) and diastolic reflection area (DRA) of the central aortic pulse wave (Arteriograph); (4) CFR using Doppler echocardiography; and (5) blood levels of lipoprotein-phospholipase A_2 (Lp-PLA_2).

RESULTS: After adjustment for age, sex, blood pressure parameter, lipidemic, diabetic and smoking status, we found that coronary flow reserve was independently related to AIx (b = -0.38, r = 0.009), DAI (b = 0.36, P = 0.014), DRA (b = 0.39, P = 0.005) and RT (b = -0.29,

P = 0.026). Additionally, patients with CFR < 2.5 had higher PWVc (11.6 ± 2.3 *vs* 10.2 ± 1.4 m/s, *P* = 0.019), SBPc (139.1 ± 17.8 *vs* 125.2 ± 19.1 mmHg, *P* = 0.026), AIx (38.2% ± 14.8% *vs* 29.4% ± 15.1%, *P* = 0.011) and lower RHI (1.26 ± 0.28 *vs* 1.50 ± 0.46, *P* = 0.012), DAI (44.3% ± 7.9% *vs* 53.9% ± 6.7%, *P* = 0.008), DRA (42.2 ± 9.6 *vs* 51.6 ± 11.4, *P* = 0.012) and LpPLA2 (268.1 ± 91.9 *vs* 199.5 ± 78.4 ng/mL, *P* = 0.002) compared with those with CFR ⩾ 2.5. Elevated LpPLA2 was related with reduced CFR (*r* = -0.33, *P* = 0.001), RHI (*r* = -0.37, *P* < 0.001) and DRA (*r* = -0.35, *P* = 0.001) as well as increased PWVc (*r* = 0.34, *P* = 0.012) and AIx (*r* = 0.34, *P* = 0.001).

CONCLUSION: Abnormal arterial wave reflections are related with impaired coronary flow reserve despite successful revascularization in CAD patients. There is a common inflammatory link between impaired aortic wall properties, endothelial dysfunction and coronary flow impairment in CAD.

Key words: LpPLA2; Coronary artery disease; Arterial stiffness; Coronary flow reserve; Reactive hyperemia index

Core tip: The present study is a contribution to investigate the association between the abnormalities in arterial wave reflections and coronary flow reserve. We demonstrated that augmentation of the systolic component of the central aortic pulse wave instead of diastolic is related with impaired coronary flow reserve after adjustment for several other factors potentially influencing coronary microcirculatory function. Furthermore, endothelial dysfunction as assessed by reactive hyperemia index and an inflammatory process as assessed by increased levels of lipoprotein-associated Phospholipase A_2 are related with increased arterial stiffness and abnormal wave reflections in coronary artery disease patients.

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INTRODUCTION

Atherosclerosis is a complex process with many faces which include impaired coronary microcirculatory function, endothelial dysfunction, increased arterial stiffness and discrete plaque formation within epicardial coronary tree.

The measurement of peripheral vasodilator response using fingertip peripheral arterial tonometry (PAT) provides a useful method for assessing arterial endothelial function[1-3]. Previous studies have shown an independent association of reactive hyperemia (RH-PAT) index with coronary endothelial function[3] and cardiovascular risk in patients with coronary artery disease (CAD)[4].

Coronary flow reserve assessed by Doppler echocardiography (CFR) is a reliable, non-invasive method to identify epicardial coronary patency as well as coronary microcirculatory integrity[5-8]. The scaling values of decreasing CFR constitute a comprehensive indicator of cardiovascular risk even in the presence of critical epicardial coronary stenosis[6].

Pulse wave velocity (PWV)[9] a valid marker of arterial stiffness, is independently related with the impairment of coronary microcirculation as assessed by CFR in patients with CAD[10,11]. Increased arterial stiffness causes an early arrival of wave reflection in systole instead of diastole and thus reduces coronary perfusion. Augmentation index (AIx), aortic diastolic reflection area (DRA) and index (DAI), derived by pulse wave analysis, are non-invasive markers of wave reflections[9,11-13]. However, the association between the abnormalities in wave reflections and coronary flow reserve in CAD patients after successful revascularization has not been fully investigated.

Lipoprotein-associated Phospholipase A_2 (Lp-PLA_2) is an inflammatory biomarker related with endothelial dysfunction, carotid atherosclerosis, impaired coronary flow reserve and increased arterial stiffness in CAD patients[14]. However its association with abnormal wave reflections has not been clarified.

In the present study we hypothesized that abnormal arterial wave reflections may determine coronary flow reserve. Thus, we examined the association of abnormal wave reflections, as assessed by AIx, DRA and DAI with coronary flow reserve using Doppler echocardiography after successful revascularization in CAD patients. Finally we examined the association of wave reflection with endothelial dysfunction as assessed by RHI and with inflammatory process assessed by circulating levels of LpPLA2.

MATERIALS AND METHODS

Study population

We enrolled 70 patients (84.3% men, mean age 60.2 ± 9.8 years) with (1) exercise- and/or stress-related angina (2) evidence of reversible ischemia during stress echocardiography or thallium scintigraphy (3) stenosis of ⩾ 50% in the left main coronary artery and or ⩾ 70% in one or several of the major coronary arteries before inclusion in the study as defined in the ESC guidelines[15] (Table 1). All the patients had undergone successful revascularization (PCI, *n* = 64 or CABG, *n* = 6) into their LAD within a year before inclusion in the study. PCI was considered successful when there was remained reduction in the caliber of the stenotic artery to < 20%

Table 1 Clinical, biochemical and vascular markers of the study population

Variables	Values (n = 70)
Clinical	
Age (yr)	60.2 ± 9.8
Gender (males), *n* (%)	59 (84.3)
Hypertension, *n* (%)	38 (54.2)
DM, *n* (%)	23 (32.8)
Dyslipidemia, *n* (%)	57 (81.4)
Smoking, *n* (%)	43 (61.5)
FH of CAD, *n* (%)	25 (35.7)
SBP (mmHg)	128 ± 18
DBP (mmHg)	77 ± 10
Medications	
ASA *n* (%)	70 (100)
Nitrates *n* (%)	38 (54.3)
ACEIs/ARBS *n* (%)	59 (84.2)
CCBs *n* (%)	12 (17.1)
Statins *n* (%)	65 (92.8)
β-blockers *n* (%)	60 (85.5)
Biochemical	
Chol (mg/dL)	198.8 ± 40.8
TG (mg/dL)	148.2 ± 79.9
HDL (mg/dL)	40.9 ± 11.4
LDL (mg/dL)	134.5 ± 35.9
Glu (mg/dL)	106.5 ± 32.5
CRP (mg/L)	2.44 ± 1.66
Lp-PLA$_2$ (ng/mL)	231.9 ± 90.9
Vascular markers	
CFR	2.65 ± 0.94
RHI-PAT	1.37 ± 0.43
PWVc (m/s)	10.32 ± 2.39
AIx (%)	35.8 ± 15.4
SAI (%)	50.6 ± 8.7
DAI (%)	49.4 ± 8.7
DRA	45.4 ± 12.6
RT (ms)	115.1 ± 22.5
SBPc (mm Hg)	133.2 ± 19.6
DBPc (mmHg)	83.3 ± 12.4

FH: Family history; CAD: Coronary artery disease; DM: Diabetes mellitus; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; ASA: Acetylsalycilic acid; ACEIs: Angiotensin converting enzyme inhibitors; ARBs: Angiotensin receptors blockers; CCBs: Calcium channel blockers; Chol: Total cholesterol; TG: Triglycerides; LDL: Low density; HDL: High density lipoprotein; FPG: Fasting plasma glucose; CRP: C-reactive protein; Lp-PLA$_2$: Lipoprotein-phospholipase A$_2$ patients with multivessel coronary artery disease before revascularisation; CFR: Coronary flow reserve; PWVc: Pulse wave velocity as measured with complior apparatus; AIx: Augmentation index; SAI: Systolic area index; DAI: Diastolic area index; DRA: Diastolic reflection area; RT: Return time; SBPc: Central systolic blood pressure.

with a final TIMI flow grade 3 without side branch loss, flow-limiting dissection, or angiographic thrombus (as visually assessed by angiography[16]). All participants attended our preventive medicine laboratory. Using valid questionnaire, we recorded pharmaceutical regimens and other cardiovascular risk factors (smoking, hypertension, diabetes mellitus, dyslipidemia, family history of CAD).

Exclusion criteria were: The presence of acute infection, malignancy, chronic heart failure (class NYHA Ⅲ and Ⅳ), chronic obstructive pulmonary disease, recent major surgery, and severe chronic auto-immune diseases, liver and renal impairment. We also excluded patients with recent (within 6 mo) acute cardiovascular events.

Blood sampling for measurement of Lp-PLA$_2$ was performed on the morning before we performed echocardiography and vascular tests in all patients.

The study protocol was approved by the Local Ethics Committee, conducted in compliance with the Declaration of Helsinki and written informed consent was obtained from all patients before study entrance.

Peripheral arterial tonometry

Measurement of peripheral vasodilator response with fingertip peripheral arterial tonometry (PAT) technology (EndoPAT; Itamar Medical Ltd, Caesarea, Israel) is increasingly being used as an alternative measure of endothelium-dependent dilation in response to reactive hyperemia[3]. The EndoPAT device records digital pulse wave amplitude (PWA) using fingertip plethysmography and consists of two finger-mounted probes, which include a system of inflatable latex air-cushions within a rigid external case. A blood pressure cuff is placed on one upper arm (study arm), while the contralateral arm serves as a control (control arm)[2]. PWA is measured continuously during three phases: A quiet baseline period, 5-min forearm occlusion (with inflation of the arterial pressure cuff to supra-systemic pressure), and reactive hyperemia following cuff release.

The reactive hyperaemia index (RHI) is calculated as follows: The ratio of the average amplitude of the PAT signal over a 1-min time interval starting 1 min after cuff deflation divided by the average amplitude of the PAT signal of a 3.5 min time period before cuff inflation (baseline)[3]. The result is further divided by the same ratio from the control arm, which allows the device to account for potential effects of systemic changes in vascular tone during testing. The final ratio is then multiplied by a proprietary baseline correction factor.

The reactive hyperemia index (RHI) measures nitric-oxide dependent changes in vascular tone[17]. An RHI < 1.35 has been related with impaired coronary endothelial function[3]. All studies were stored digitally and were analyzed by personnel blinded to clinical and laboratory data, using a computerized station.

Pulse waveform analysis

Assessment of arterial wave reflections was performed non-invasively with the commercially available Arteriograph apparatus (TensioMed Budapest Hungary, Ltd) by analysis of the oscillometric pressure curves registered on the upper arm with a single pressure cuff. The principle of the oscillometric method is based on plethysmography and registers oscillometric pulsatile pressure changes in the brachial artery[18]. An upper arm cuff was applied to the patient and after a first simple BP measurement, the cuff was over-inflated with 35-40 mmHg beyond the systolic BP. During systole, the blood volume having been ejected into the aorta generates pulse wave (early systolic peak, P1). This pulse wave runs down and reflects from the bifurcation of aorta, creating a second wave (late systolic peak, P2). Both early and late systolic peak were

obtained and recorded on the computer as pulse waves. The software of Arteriograph decomposes the early, late systolic and diastolic waves and also determines the onset and peaks of the waves, measuring noninvasively and other hemodynamic parameters as central systolic and diastolic blood pressure (SBPc, DBPc mmHg), augmentation index (AIx%), return time (RT in sec.) of the wave reflection, systolic area index (SAI%), diastolic area index (DAI %) and diastolic reflection area (DRA)[18].

The AIx is defined as the ratio of the difference between the second (P_2, appearing because of the reflection of the first pulse wave) and first systolic peaks (P_1 induced by the heart systole) to pulse pressure (PP), and it is expressed as a percentage of the ratio [Aix = 100 × (P_2-P_1)/PP]. DRA is derived by duration of the diastole and the area between the expected (theoretical) diastolic pressure curve without reflection and the truly measured diastolic curve with reflection and reflects the quality of the coronary arterial diastolic filling. SAI and DAI are the areas of systolic and diastolic portions under the pulse wave curve of a complete cardiac cycle, respectively. Thus, the higher the DAI and DRA are, the better the coronary perfusion is. Furthermore, RT is the time of the pulse wave travelling from the aortic root to the bifurcation and back, so this value is smaller as the aortic wall is stiffer[18].

All studies were stored digitally and were analyzed by personnel blinded to clinical and laboratory data, using a computerized station.

Echocardiography

Studies were conducted using a Vivid 7 (GE Medical Systems, Horten Norway) phased array ultrasound system using second harmonic imaging. Dr Ignatios Ikonomidis, counting more than 5500 CFR echo studies the last 10 years, has performed the echocardiographic examinations and the CFR measurements for this study[5,8,14]. All studies were stored digitally and were analyzed by two observers blinded to clinical and laboratory data, using a computerized station (Echopac GE, Horten Norway). All patients had adequate quality of images for analysis.

Coronary flow reserve

We assessed transthoracic Doppler Echocardiographic-derived coronary flow reserve by obtaining the color-guided pulse-wave Doppler signals. In the long axis apical projections using a 7 MHz transducer, we recorded the maximal velocity and velocity-time integral in the distal LAD at baseline and during hyperaemic conditions after the intravenous administration of adenosine (0.14 mg/kg per minute)[5-8] for 3 min. Measurements of three cardiac cycles were averaged. CFR was calculated as the ratio of hyperemic to resting maximal diastolic velocity. The feasibility of the method was greater than 98% for all indices in our study cohort (initially 71 patients were recruited, but one patient was excluded due to unfeasible CFR study).

The mean CFR value of our cohort (< 2.5) was used for subgroup analysis after previously published cutoff values for impaired CFR in CAD patients[6,19].

PWV measurement

The carotid-femoral PWV (PWVc) was assessed by measuring the pulse transit time and the distance travelled between the two recording sites. For pulse wave recording we used a validated noninvasive device (Complior SP®, Alam Medical, France) with capability of online wave recording. A simultaneous recording was performed by two pressure-sensitive transducers of two different pulse waves based over the right common carotid artery and the right femoral artery, respectively. Measurement of the distance between the transducers over the body surface allowed obtaining PWVc. Measurements were performed by a single observer, blinded to clinical and laboratory data, and the whole procedure has been internally validated in our laboratory[8,20].

Lp-PLA$_2$ levels

Serum levels of Lp-PLA$_2$ were measured in our biochemistry laboratory with a commercially available enzyme-linked immunoassay (ELISA) (PLAC test, diaDexus, Inc, San Francisco, CA) with minimum detection limit of 0.34 ng/mL[14]. The inter- and intra assay variations were < 5% and 8%. An Lp-PLA$_2$ concentration of 235 ng/mL has been suggested to use as a clinical decision threshold[21]. Analyses were performed by personnel blinded to clinical and laboratory data.

Statistical analysis

All variables are expressed as mean ± SD. Statistical analysis was performed using SPSS 21.0 statistical software package (SPSS Inc, Illinois, United States). Categorical data were analysed using the standard chi-square test. Variables were tested by the Kolmogorov-Smirnov test to assess the normality of distribution. Parameters without normal distribution were transformed into ranks for further analysis. Patients were categorised into equal subgroups, according to the median value of CFR in our study cohort. Mean values of continuous variables were compared between groups using unpaired Student's *t*-test or the Mann-Whitney *U*-test, where applicable.

Simple linear regression was used to investigate relations between variables. Multiple linear relations were checked by multiple linear regression analysis using forward or backward procedure. Associations are presented by means of standardized regression coefficient (b). All covariates included in the final models were tested for interactions. Tolerance values for each covariate was > 0.5 in the multivariate models.

RESULTS

Study population characteristics

Clinical and biochemical characteristics of our study

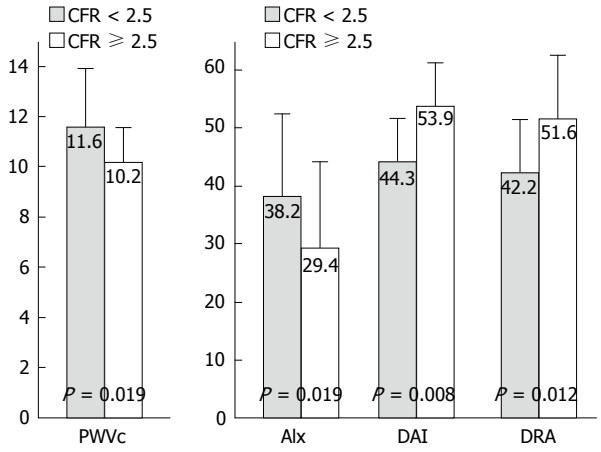

Figure 1 Graphic representation of the differences in pulse wave velocity (m/s), augmentation index (%), diastolic area (%) and diastolic reflection area (%) between patients with reduced coronary flow reserve (< 2.5) and patients with preserved coronary flow reserve (⩾ 2.5). CFR: Coronary flow reserve; PWV: Pulse wave velocity; Aix: Augmentation index; DRA: Diastolic reflection area; DAI: Diastolic area.

population are presented in Table 1. The mean values of the vascular parameters and the pharmaceutical regimen of the study cohort are shown in Table 1.

Determinants of coronary flow reserve.

In univariate analysis, a decreasing CFR was related with increasing PWVc (r = -0.38, P = 0.015), SBPc (r = -0.34, P = 0.022), AIx (r = -0.50, P = 0.003), SAI (r = -0.49, P = 0.006) as well as decreasing RT (r = 0.45, P = 0.009), DAI (r = 0.49, P = 0.006) DRA (r = 0.55, P < 0.001) and RHI (r = 0.47, P = 0.002). Furthermore, RHI was related to AIx (r = 0.48, P < 0.001), RT (r = -0.29, P = 0.024) and SBPc (r = 0.40, P = 0.001).

In multivariate analysis, after adjustment of age, sex, blood pressure parameter, lipidemic, diabetic and smoking status, we found that coronary flow reserve was independently related to AIx (b = -0.38, r = 0.009), DAI (b = 0.36, P = 0.014), DRA (b = 0.39, P = 0.005) and RT (b = -0.29, P = 0.026).

Patients with high vs patients with low coronary flow reserve

Patients were categorised in high and low CFR according to the median value of CFR. Patients with CFR < 2.5 had similar clinical characteristics with those with CFR ⩾ 2.5 with the exception of higher cholesterol level, (Table 2, P < 0.05). However, patients with CFR < 2.5 had higher PWVc, SBPc, AIx, SAI and lower RT, DAI and DRA compared with those with CFR ⩾ 2.5 after adjustment for cholesterol levels (Table 2, P < 0.05 and Figure 1).

Furthermore, these patients with CFR < 2.5 had higher $LpPLA_2$ compared with those with CFR ⩾ 2.5 (Table 2, P = 0.002).

Relation of vascular markers with Lp-PLA$_2$

Elevated $LpPLA_2$ was related with reduced CFR (r = -0.331, P = 0.001), RHI (r = -0.371, P < 0.001) and DRA (r = -0.35, P = 0.001) as well as increased PWVc (r = 0.34, P = 0.012) and AIx (r = 0.34, P = 0.001).

DISCUSSION

In the present study, we found a close association between arterial wave reflection markers, as assessed by AIx, DRA and DAI, and decreasing CFR in CAD patients after successful revascularization. Furthermore, we demonstrated that diastolic component of central aortic pulse wave as expressed with DRA and DAI is an independent determinant of impaired coronary flow reserve after adjustment for several other factors potentially influencing coronary microcirculatory function. Finally we have shown that endothelial dysfunction as assessed by RHI and the inflammatory process as assessed by $LpPLA_2$ are associated with abnormal wave reflection and increased arterial stiffness.

Association between aortic stiffness and coronary flow reserve

Coronary flow reserve (CFR) represents the capacity of the coronary circulation to dilate following an increase in myocardial metabolic demands and can be expressed by the difference between the hyperemic flow and the resting flow curve. Impaired CFR constitutes a marker of coronary microcirculatory dysfunction and reflects the impairment of the epicardial coronary artery flow in the presence of significant coronary stenosis[6], as well as coronary microcirculatory dysfunction[11,14]. CFR entails strong prognostic significance in stable patients with known or suspected ischemic heart disease, independently of other risk factors[22-26]. Thus, the scaling values of decreasing CFR constitute a comprehensive indicator of cardiovascular risk even in the presence of critical epicardial coronary stenosis[6].

The association of increased PWV with the presence and prognosis of angiographic CAD has been extensively demonstrated[11,27,28]. Experimental studies have shown that low aortic compliance is associated with a reduction in coronary blood flow[29], particularly subendocardial flow[30,31]. In a human study, Leung *et al*[32] have shown that a compliant aorta, as measured by PWV, is associated with a greater improvement in hyperemic coronary blood flow from successful PCI than a stiff aorta and this relationship persisted for PWV even after accounting for stenosis severity. Furthermore, exercise-induced rise in coronary blood flow, related to ischemic threshold, could be determined by aortic stiffness. This is supported by the findings of Kingwell *et al*[33] who found indexes of arterial stiffness were stronger independent predictors of the exercise-induced ischemic threshold than maximum coronary stenosis assessed angiographically.

In the present study, we confirm the above mentioned close relation of PWV with CFR. PWV is a marker of aortic stiffness, whereas AIx, which is largely determined by wave reflections, represents much more the vasomotor

Table 2 Clinical and biochemical parameters of the study population divided by the median value of coronary flow reserve

	CFR < 2.5 (*n* = 34)	CFR ⩾ 2.5 (*n* = 36)	*P*
Clinical			
Age (yr)	62.1 ± 9.2	58.4 ± 10.5	0.265
Males, *n* (%)	29 (85.2)	30 (83.3)	0.869
Hypertension, *n* (%)	20 (58.8)	18 (50)	0.368
Diabetes, *n* (%)	13 (38.2)	10 (27.7)	0.631
Dyslipidemia, *n* (%)	28 (82.3)	29 (80.5)	0.307
Smoking, *n* (%)	23 (67.6)	20 (55.5)	0.449
FH of CAD	14 (41.1)	11 (30.5)	0.334
SBP (mmHg)	130.9 ± 20.3	120.4 ± 14.8	0.011
DBP (mmHg)	77.4 ± 10.4	74.8 ± 8.8	0.058
Medications			
ASA, *n* (%)	33 (97)	34 (94.4)	0.942
Nitrates, *n* (%)	23 (67.6)	27 (75)	0.131
ACEIs/ARBS, *n* (%)	33 (97)	34 (94.4)	0.956
CCBs, *n* (%)	5 (14.7)	7 (19.4)	0.597
Statins, *n* (%)	32 (94.1)	33 (91.6)	0.547
β-blockers, *n* (%)	29 (85.2)	31 (86.1)	0.765
Biochemical			
Chol (mg/dL)	206.7 ± 44.1	190.6 ± 38.9	0.078
TG (mg/dL)	147.0 ± 57.1	143.9 ± 69.7	0.824
HDL (mg/dL)	39.6 ± 8.6	40.9 ± 12.8	0.567
LDL (mg/dL)	141.6 ± 37.8	126.6 ± 32.9	0.055
Glu (mg/dL)	100.9 ± 2 2.7	112.4 ± 39.9	0.126
CRP (mg/L)	2.5 ± 1.8	2.4 ± 1.5	0.279
Lp-PLA2 (ng/mL)	268.1 ± 91.9	199.5 ± 78.4	0.002
Vascular markers			
RHI-PAT	1.26 ± 0.28	1.50 ± 0.46	0.012
PWVc (m/s)	11.6 ± 2.3	10.2 ± 1.4	0.019
AIx (%)	38.2 ± 14.8	29.4 ± 15.1	0.011
SAI (%)	55.7 ± 7.9	46.1 ± 6.7	0.008
DAI (%)	44.3 ± 7.9	53.9 ± 6.7	0.008
DRA	42.2 ± 9.6	51.6 ± 11.4	0.012
RT (ms)	106.1 ± 20.8	123.0 ± 22.1	0.015
SBPc (mm Hg)	139.1 ± 17.8	125.2 ± 19.1	0.026
DBPc (mmHg)	84.7 ± 12.1	80.0 ± 11.0	0.118

FH: Family history; CAD: Coronary artery disease; DM: Diabetes mellitus; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; ASA: Acetylsalycilic acid; ACEIs: Angiotensin converting enzyme inhibitors; ARBs: Angiotensin receptors blockers; CCBs: Calcium channel blockers; Chol: Total cholesterol; TG: Triglycerides; LDL: Low density; HDL: High density lipoprotein; FPG: Fasting plasma glucose; CRP: C-reactive protein; Lp-PLA2: Lipoprotein-phospholipase A2 patients with multivessel coronary artery disease before revascularisation; CFR: Coronary flow reserve; PWVc: Pulse wave velocity as measured with complior apparatus; AIx: Augmentation index; SAI: Systolic area index; DAI: Diastolic area index; DRA: Diastolic reflection area; RT: Return time; SBPc: Central systolic blood pressure; DBPc: Central diastolic blood pressure.

tone in the small medium-sized muscular vessels downstream in the circulation[9,12]. In our study, we demonstrated for the first time that AIx is related to CFR, indicating that not only stiffness of the large elastic arteries impairs CFR, but stiffening of the smaller muscular arteries contributes as well. However, the net effect of increased systemic arterial stiffness on coronary vasodilatory reserve is thought to be mediated by reduced coronary perfusion during diastole.

Increased arterial stiffness increases the velocity of both forward and reflected pulse wave[9]. This increase in velocity of wave of pulse causes arrival of reflected waves at the aorta during systole and not during diastole as it occurs under conditions of normal aortic elastic properties. The early arrival of the reflected waves (1) augments the systolic aortic pressure and thus increase of LV afterload, wall stress and cardiac workload leading to increased myocardial oxygen demands; (2) reduces the diastolic aortic pressure resulting in reduced myocardial perfusion[9,34]. Thus, arterial stiffness causes a mismatch between myocardial oxygen demands and myocardial perfusion resulting in reduction of coronary flow reserve after hyperemia[10,19,22]. Additionally, stiffening of the large arteries, results in reduction of their capacity to function as an elastic reservoir resulting in a greater peripheral runoff of stroke volume during systole[13,29,31]. Together with the reduced elastic recoil, the diastolic blood pressure and hence coronary blood flow is decreased.

Indeed, in our study, we found that DAI and DRA, two markers that reflect the contribution of reflected waves to perfusion of the coronary circulation, were closely associated with CFR, even after adjustment for other factors influencing CFR. This finding supports the above mentioned pathophysiological mechanism.

Role of endothelial dysfunction for the relationship between coronary flow reserve and arterial stiffness

Besides the above mentioned arterio-coronary coupling that may explain the lower coronary flow reserve associated with a stiff arterial tree, arterial stiffness may be a marker of a more generalized vascular disease process which among others, includes endothelial dysfunction. Previous studies have shown that large artery stiffness itself is influenced by endothelial function via basal release of nitric oxide[35] as well as that aortic stiffness is associated with brachial artery endothelial dysfunction[36]. On the other side, adenosine-induced CFR is also thought to be at least partly endothelium dependent[8]. Thus, endothelial function through NO production is an important determinant of coronary flow response to physiological or pharmacological stimuli[10,19].

Reactive hyperaemia peripheral arterial tonometry (RHI-PAT) is a method to assess peripheral microvascular endothelial function and is linked to coronary microvascular endothelial dysfunction[3], as this parameter is predominantly determined by the bioavailability of NO[16]. Both impaired CFR and reduced RHI-PAT have proven prognostic value in CAD patients[4,6,7]. In the present study we document an independent association of peripheral endothelial dysfunction, assessed by RH-PAT, with coronary endothelial dysfunction, assessed by CFR after successful revascularization in patients with CAD. It is possible that coronary endothelial dysfunction may coexist with aortic stiffness and may contribute to abnormal coronary microcirculatory response to hyperemia, as well as impaired aortic wall properties. Furthermore, the association of RHI-PAT with AIx and RT indicates that peripheral endothelial dysfunction contribute to impaired aortic wall properties, as well as that determines at least partly, stiffening of both large

elastic arteries and smaller muscular arteries.

Role of vascular inflammation

On the other hand increased PWV is associated with enhanced vascular inflammation and injury[20,27]. Indeed, in our study we measured LpPLA$_2$ as a marker of vascular inflammation and we found that patients with high LpPLA$_2$ levels had higher PWVc, AIx, and reduced DRA, DAI, CFR and RHI. These findings indicate a common effect of LpPLA$_2$ in all vascular territories, indicating a generalized vascular disease process which causes reduced CFR directly and/or indirectly through arterial stiffness and impaired endothelial function as we mentioned above.

Study limitations

Our results establish a close relation between increasing PWVc, AIx, DAI, DRA, RHI-PAT and CFR in CAD patients. However, this study was not designed to verify whether this relation is causative or secondary to endothelial dysfunction and interstitial fibrosis within aortic and coronary wall in CAD patients. It is possible that the generalized vascular damage was the link between PWVc, AIx and CFR in our study.

In summary, in the present study, we demonstrated that augmentation of the systolic component of the central aortic pulse wave, as expressed by augmentation index and reduced diastolic component of central aortic pulse wave as expressed by diastolic reflection area and index are related with impaired coronary flow reserve after adjustment for several other factors potentially influencing coronary microcirculatory function. Furthermore, endothelial dysfunction as assessed by RHI and an inflammatory process as assessed by increased levels of Lp-PLA$_2$ are related with increased arterial stiffness and abnormal wave reflections in CAD patients. These findings underscore the need to assess arterial wall properties in CAD patients to better stratify the risk of future events after successful revascularization.

COMMENTS

Background

Atherosclerosis is a complex process with many faces which include impaired coronary microcirculatory function, endothelial dysfunction, increased arterial stiffness and discrete plaque formation within epicardial coronary tree.

Research frontiers

Pulse wave velocity (PWV) a valid marker of arterial stiffness, is independently related with the impairment of coronary microcirculation as assessed by coronary flow reserve in patients with coronary artery disease (CAD).

Innovations and breakthroughs

The authors demonstrated that augmentation of the systolic component of the central aortic pulse wave, as expressed by augmentation index and reduced diastolic component of central aortic pulse wave as expressed by diastolic reflection area and index are related with impaired coronary flow reserve after adjustment for several other factors potentially influencing coronary microcirculatory function.

Applications

These findings underscore the need to assess arterial wall properties in CAD patients to better stratify the risk of future events after successful revascularization.

Terminology

The authors measured (1) reactive hyperemia index (RHI) using fingertip peripheral arterial tonometry (RH-PAT Endo-PAT); (2) carotid to femoral pulse wave velocity (PWVc-Complior); (3) augmentation index (AIx), the diastolic area (DAI%) and diastolic reflection area (DRA) of the central aortic pulse wave (Arteriograph); (4) CFR using Doppler echocardiography and 5) blood levels of Lipoprotein-phospholipase A$_2$ (Lp-PLA$_2$).

Peer-review

The authors studied a group of 70 patients with CAD by means of coronary flow reserve and several indexes related to arteriosclerosis (peripheral arterial tonometry, pulse waveform analysis, carotid to femoral pulse wave velocity) and to inflamation (Lp-PLA$_2$). As expected these indexes were impaired in patients with lower coronary flow reserve.

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META-ANALYSIS

Biodegradable polymer stents *vs* second generation drug eluting stents: A meta-analysis and systematic review of randomized controlled trials

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Abstract

AIM: To evaluate the premise, that biodegradable polymer drug eluting stents (BD-DES) could improve clinical outcomes compared to second generation permanent polymer drug eluting stents (PP-DES), we pooled the data from all the available randomized control trials (RCT) comparing the clinical performance of both these stents.

METHODS: A systematic literature search of PubMed, Cochrane, Google scholar databases, EMBASE, MEDLINE and SCOPUS was performed during time period of January 2001 to April 2015 for RCT and comparing safety and efficacy of BD-DES *vs* second generation PP-DES. The primary outcomes of interest were definite stent thrombosis, target lesion revascularization, myocardial infarction, cardiac deaths and total deaths during the study period.

RESULTS: A total of 11 RCT's with a total of 12644 patients were included in the meta-analysis, with 6598 patients in BD-DES *vs* 6046 patients in second generation PP-DES. The mean follow up period was 16 mo. Pooled analysis showed non-inferiority of BD-DES, comparing events of stent thrombosis (OR = 1.42, 95%CI: 0.79-2.52, P = 0.24), target lesion revascularization (OR = 0.99, 95%CI: 0.84-1.17, P = 0.92), myocardial infarction (OR = 1.06, 95%CI: 0.86-1.29, P = 0.92), cardiac deaths (OR = 1.07, 95%CI 0.82-1.41, P = 0.94) and total deaths (OR = 0.96, 95%CI: 0.80-1.17, P = 0.71).

CONCLUSION: BD-DES, when compared to second generation PP-DES, showed no significant advantage

and the outcomes were comparable between both the groups.

Key words: Stent design; Drug eluting stent; Zotarolimus eluting stent; Cobalt-chromium stent; Biodegradable drug eluting stent

Core tip: No direct comparison has been done so far with biodegradable polymers in drug eluting stent compared to permanent alloy in second-generation drug eluting stent. We explored the efficacy of these two stents via meta-analysis of randomized control trials in terms of definite stent thrombosis, target lesion revascularization, myocardial infarction, cardiac deaths and total deaths.

Pandya B, Gaddam S, Raza M, Asti D, Nalluri N, Vazzana T, Kandov R, Lafferty J. Biodegradable polymer stents *vs* second generation drug eluting stents: A meta-analysis and systematic review of randomized controlled trials. *World J Cardiol* 2016; 8(2): 240-246 Available from: URL: http://www.wjgnet.com/1949-8462/full/v8/i2/240.htm DOI: http://dx.doi.org/10.4330/wjc.v8.i2.240

INTRODUCTION

It's been more than two decades since the introduction of coronary stents and during this period the stent designs have been modified to improve patient safety. Bare metal stents (BMS) were trailed by first generation permanent polymer drug eluting stents (PP-DES) (Paclitaxel and Sirolimus) then followed by second generation PP-DES (Everolimus and Zotarolimus) and now biodegradable polymer DES (BD-DES) are envisaging potentially improved patient outcomes.

Stent designing is the crux of interventional cardiology research and the changes have been dynamic. Initial BMS used a simple expandable metal alloy frame work, while PP-DES use an anti-proliferative drug coating on the metal platform, glued by a binding durable polymer to hold and elute the drug over time. Beyond any uncertainty, PP-DES are superior to BMS in decreasing restenosis, however PP-DES require longer duration of dual-antiplatelet therapy to avert the risk of stent thrombosis[1]. It is now understood, the metal alloy and the permanent polymer are among the culprits for prolonged inflammation leading to very late stent thrombosis and late restenosis (termed late catch-up phenomena) and henceforth the unremitting search for safer stents[2]. The second generation PP-DES introduced few years ago, have superior metal frame work (cobalt-chromium and platinum-chromium) with thinner metal struts, enhanced biocompatible binding polymer and these stents have proven improved patient outcomes compared to its predecessors[3]. Nevertheless, the potential need for dual-antiplatelet therapy beyond one year is still an apprehension among cardiologists and patients with second generation PP-DES. The BD-DES, unlike second generation PP-DES, will elute the anti-proliferative drug and the biodegradable polymer subsequently dissolves leaving behind a bare metal stent[4]. BD-DES is introduced with an anticipation to decrease the stent thrombosis events (especially very late events) and evading the need for prolonged dual-antiplatelet therapy.

Several randomized control trials and registries have been published in last few years, with most trials comparing first generation PP-DES to BD-DES. As anticipated, long term follow up data has shown superiority of BD-DES in decreasing very late stent thrombosis events when compared with Sirolimus (first generation) PP-DES[5]. However, there are only fewer studies comparing second generation PP-DES to BD-DES. Since second generation PP-DES is current standard of care in United States, it is of immense importance to study if the newer BD-DES offer any better outcomes. We performed a meta-analysis and systematic review of randomized control trials comparing efficacy and safety of BD-DES to second generation PP-DES (Everolimus and Zotarolimus).

MATEIRALS AND METHODS

Literature search

Two independent investigators systematically searched PubMed, Cochrane and Google scholar database from January 2001 to April 2015. We used following keywords: "biodegradable stent", "biodegradable polymer", "biodegradable polymer drug eluting", and "biodegradable stent coronary". Reference lists from selected studies were manually searched for potentially relevant studies. Whenever available, the most recent follow up data on a study was included. The PRISMA statement was used as guidance for selection of studies to be included in the meta-analysis and is depicted in Figure 1. Randomized control trials comparing BD-DES *vs* second generation DES with a primary end point of definite stent thrombosis, target lesion revascularization, myocardial infarction, cardiac deaths and total death were included in the study. We found 11 trials comparing BD-DES to second generation (Everolimus or Zotarolimus) PP-DES. In ISAR-TEST 4 trial, both first generation Sirolimus and second generation Everolimus DES were used, but in our meta-analysis we only used data pertinent to second generation Everolimus DES. Given the low incidence of stent thrombosis and other outcomes, a meta-analysis was performed to prove treatment differences between these two stents.

Study selection

Two authors screened all relevant literature by their abstract and title found by electronic search. Only trails published in English were taken into consideration. Inclusion criteria were (1) randomized control trials; (2) comparing biodegradable polymers to second generation drug eluting stents; and (3) reporting outcomes as

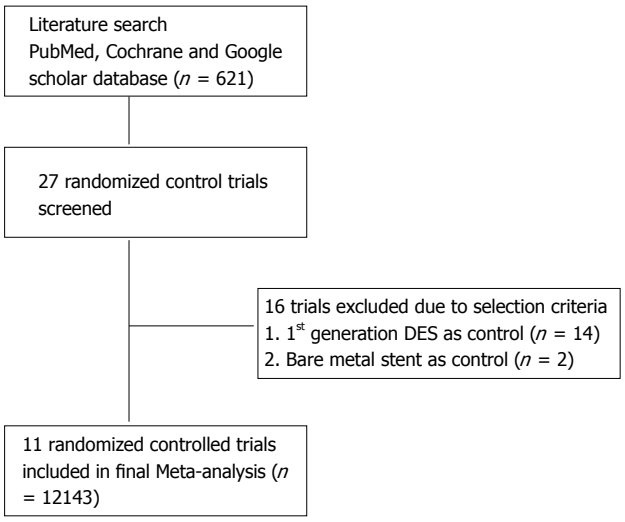

Figure 1 Study selection. DES: drug eluting stents.

a target lesion revascularization [target lesion revascularization (TLR)], definite stent thrombosis (DST), myocardial infarction (MI), cardiac deaths and total deaths. We excluded studies with first generation drug eluting stents and bare metal stents as controls and also studies performed on select population, like complex lesions or on bifurcating lesions. Randomized control trials comparing BD-DES to second generation PP-DES were only included in this study.

Data extraction

Data from all 11 trials were extracted by same two authors in regards to first author, year of publication, total No. of patients and No. of patients in each group (Table 1). Authors also extracted mean age group of patients, patients with DM and HTN, follow up duration and duration of use of dual antiplatelet therapy (Table 2).

Outcome measures

Clinical end points compared were definite stent thrombosis (DST), target lesion revascularization (TLR), myocardial infarction (MI), cardiac deaths and total deaths during the study period.

Statistical analysis

The results for each trial were obtained on an intention-to-treat analysis. The dichotomous and continuous endpoints from individual trials were analyzed using the odds ratio (OR) and the standard difference in mean (SDM) respectively as a parameter of efficacy with its 95%CI. We assessed heterogeneity with I^2 that describes the percentage of total variation across trials due to heterogeneity rather than chance. I^2 can be calculated as $I^2 = 100\% \times (Q\text{v} - \text{df})/Q$, where Q is Cochran's heterogeneity statistics and df the degrees of freedom. Negative values of I^2 are put equal to 0, so I^2 lies between 0% (no heterogeneity) and 100% (maximal heterogeneity). The continuous outcomes were analyzed using the standard difference in mean. Binary outcomes from individual studies were combined and the summary estimators of treatment effect were calculated using fixed-effect method. Weighting of trial data in the models was based on the inverse variance weight computed as the inverse of the squared standard error value of the effect size. A P value of $\leqslant 0.05$ was regarded as significant. All analyses were performed using Review Manager (RevMan) Version 5.3 for Windows Oxford, England.

RESULTS

Study selection

A total of 11 RCT's with a total of 12644 patients were included in the meta-analysis, with 6598 patients in BD-DES *vs* 6046 patients in second generation PP-DES. The mean follow up period was 16 mo. Table 1 shows the main characteristics of the included studies. Table 2 shows the main characteristics of the BD-DES patients included in the studies. The final summary of clinical end points is depicted in Table 3.

DST

The forest plot for summary effect is shown in Figure 2. There were a total of 34 (0.6%) stent thrombosis events in BD-DES group and 24 (0.46%) stent thrombosis in PP-DES group. The forest plot is shown in the Figure 2, with pooled OR of 1.42 (95%CI: 0.79-2.52), $P = 0.24$, and I^2 for heterogeneity 0%.

TRL

The forest plot for summary effect is shown in Figure 3. There were a total of 294 (4.77%) TLR in BD-DES group *vs* 350 (6.05%) TLR in PP-DES group. The forest plot is shown in the figure, with pooled OR of 0.99 (95%CI: 0.84-1.17), $P = 0.92$, and I^2 for heterogeneity 0%.

MI

The forest plot for summary effect is shown in Figure 4. There were a total of 202 (3.27%) myocardial infarctions in BD-DES group *vs* 238 (4.11%) myocardial infarctions in PP-DES group. The forest plot is shown in the Figure 4, with pooled OR of 1.06 (95%CI: 0.86-1.29), $P = 0.59$, and I^2 for heterogeneity 0%.

Cardiac deaths

The forest plot for summary effect is shown in Figure 4. There were a total of 108 (1.78%) cardiac deaths in BD-DES group *vs* 124 (2.18%) cardiac deaths in PP-DES group. The forest plot is shown in the figure, with pooled OR of 1.07 (95%CI: 0.82-1.41, $P = 0.60$), and I^2 for heterogeneity 0%.

Total deaths

The forest plot for summary effect is shown in Figure 5. There were a total of 229 (3.65%) deaths in BD-DES group *vs* 236 (4.01%) deaths in PP-DES group. The

Table 1 Summary of included trials

Ref.	Trial acronym	Yr	BD-DES type	PP-DES type	Total patients	BD-DES patients	PP-DES patients
Natsuaki *et al*[8]	NEXT	2013	Biolimus	Everolimus	3235	1617	1618
Smits *et al*[9]	COMPARE 2	2013	Biolimus	Everolimus	2707	1795	912
Gao *et al*[10]	TARGET 1	2013	Sirolmus	Everolimus	458	227	231
Byrne *et al*[11]	ISAR-TEST 4	2011	Sirolimus	Everolimus	2603	652	1304
Xu *et al*[12]		2011	Sirolimus	Zotarolimus	324	168	156
Separham *et al*[13]		2011	Biolimus	Everolimus	200	100	100
Meredith *et al*[14]	EVOLVE	2012	Biolimus	Everolimus	192	98	94
Pilgrim *et al*[15]	BIOSCIENCE	2014	Sirolimus	Everolimus	2119	1063	1056
Serruys *et al*[7]	ABSORB 2	2014	Everolimus	Everolimus	501	335	166
Lee *et al*[16]		2014	Biolimus	Everolimus	500	245	255
Windecker *et al*[17]	BIOFLOW 2	2014	Sirolimus	Everolimus	452	298	154

BMS: Bare metal stents; PP-DES: Permanent polymer drug eluting stents; BD-DES: Biodegradable polymer drug eluting stents.

Table 2 Main characteristics of biodegradable polymer drug eluting stents patients in the study

Ref.	Mean age	Male %	Diabetes %	Inclusion criteria	Exclusion criteria	DAPT mo	Follow up mo
Natsuaki *et al*[8]	69	77	46	SA[1]/ACS[2]	Major surgery in 30 d, cardiogenic shock	3	12
Smits *et al*[9]	63	74	22	SA/ACS	Major surgery in 30 d, cardiogenic chock	12	12
Gao *et al*[10]	59	69	14	SA/UA[3]	AMI[4] < 1 wk, CT[5], LM[6] bifurcation, ISR[7]	12	12
Byrne *et al*[11]	67	75	29	SA/ACS	LM. shock, malignancy, life expectancy < 1 yr	6	36
Xu *et al*[12]	57	70	26	SA/UA	AMI < 1 wk, LM, CTO	6	24
Separham *et al*[13]	61	66	28	SA/ACS	Allergy to aspirin, plavix, heparin, stainless steel, everolimus, biolimus or contrast and pregnancy	12	12
Meredith *et al*[14]	62	80	22	Symp CAD[8], Silent Ischemia	AMI, LM CAD, ISR, thrombus in target vessel	6	6
Pilgrim *et al*[15]	66	77	24	Stable CAD/ACS	Pregnancy, intolerance to aspirin, plavix, planned surgery in 6 mo	12	12
Serruys *et al*[7]	61	76	24	Evidence of myocardial Ischemia	AMI, unstable arrhythmias, LVEF[9] < 30	NA	12
Lee *et al*[16]	63	68	32	SA/UA/ NSTEMI[10]	STEM[11], cardiogenic shock, allergy to aspirin/ plavix/heparin/stainless steel/biolimus/ everolimus, HD pts, LM CAD	⩾ 12	12
Windecker *et al*[17]	63	78	28	SA/UA/Clinical evidence of myocardial Ischemia	MI within 72 h, LM CAD, triple vessel CAD, LVEF < 30%	⩾ 6	9

[1]Stable angina; [2]Acute coronary syndrome; [3]Unstable angina; [4]Acute myocardial infarction; [5]Complete total occlusion; [6]Left main; [7]In stent restenosis; [8]Coronary artery disease Left ventricular ejection fraction; [9]Left ventricular ejection fraction; [10]Non ST elevation myocardial infarction; [11]ST elevation myocardial infarction; BMS: Bare metal stents; PP-DES: Permanent polymer drug eluting stents; BD-DES: Biodegradable polymer drug eluting stents; NA: Not available.

Table 3 Summary of clinical end points

Events	BD-DES (n = 4459)	PP-DES (n = 4221)	ODD S RATIO (95%CI)	P-value
Definite stent thrombosis	34	24	1.42 (0.79-2.52)	0.24
Target lesion revascularization	294	350	0.99 (0.84-1.17)	0.92
Myocardial infarction	202	238	1.06 (0.86-1.29)	0.59
Cardiac deaths	108	124	1.07 (0.82-1.41)	0.6
Total deaths	229	236	0.96 (0.80-1.17)	0.71

PP-DES: Permanent polymer drug eluting stents; BD-DES: Biodegradable polymer drug eluting stents.

forest plot is shown in the figure, with pooled OR of 0.96 (95%CI: 0.80-1.17, P = 0.71), and I^2 for heterogeneity 0%.

DISCUSSION

From our study, at a mean follow up of 16 mo, BD-DES use did not significantly decrease mortality (OR = 0.96, P = 0.71) or myocardial infarction events (OR = 1.06, P = 0.59). Rates of stent thrombosis (OR = 1.42, P = 0.24) and target lesion revascularization (OR = 0.99, P = 0.92) were comparable between both the stents. In this study the results for BD-DES, against contrary belief, failed to show any significant

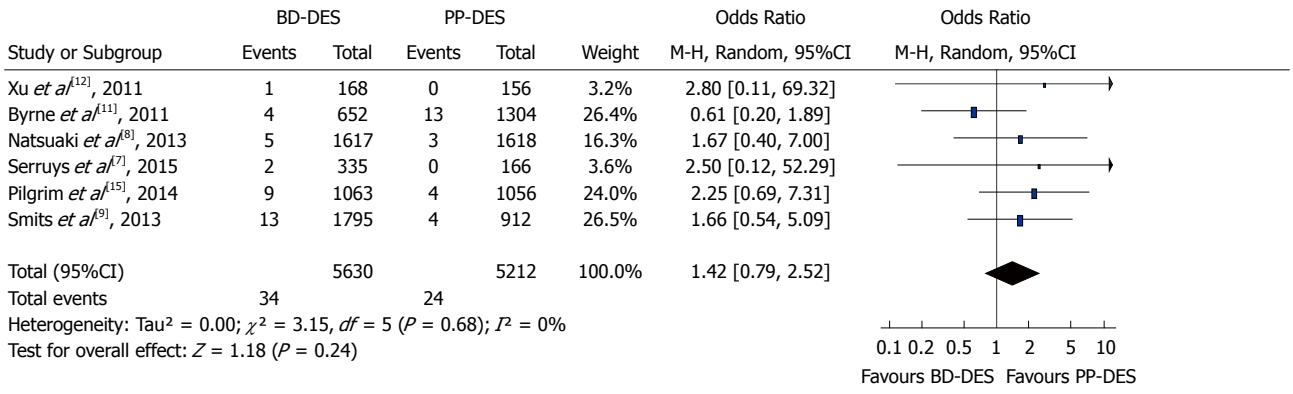

Figure 2 Definite stent thrombosis. BMS: Bare metal stents; PP-DES: Permanent polymer drug eluting stents; BD-DES: Biodegradable polymer drug eluting stents.

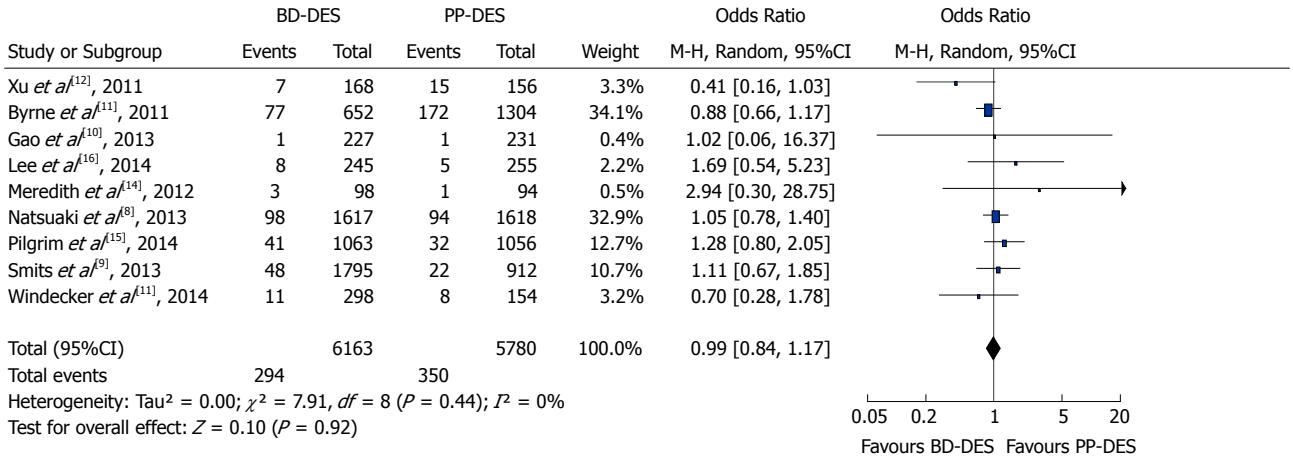

Figure 3 Target lesion revascularization. BMS: Bare metal stents; PP-DES: Permanent polymer drug eluting stents; BD-DES: Biodegradable polymer drug eluting stents.

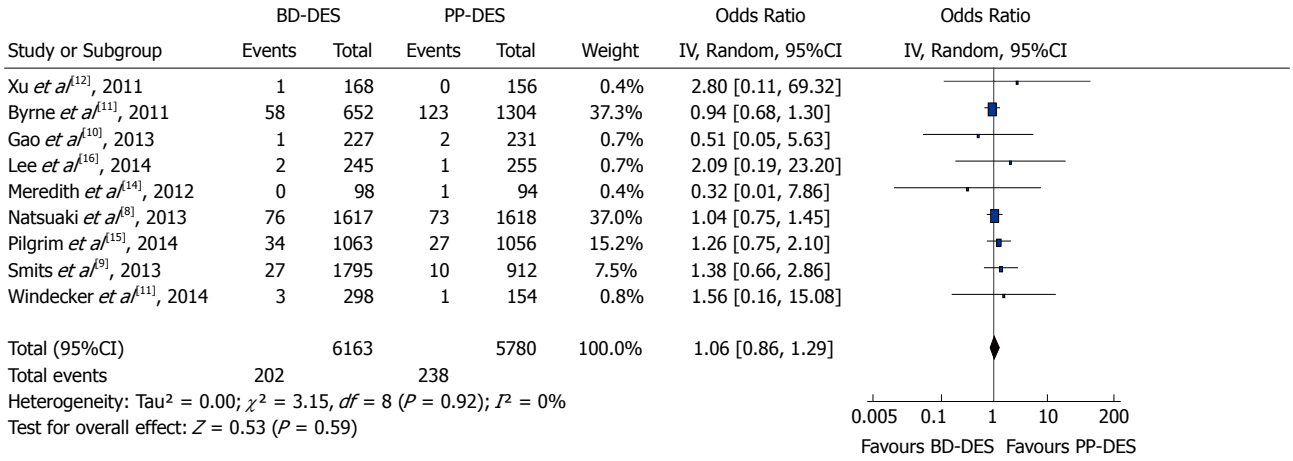

Figure 4 Myocardial infarction. BMS: Bare metal stents; PP-DES: Permanent polymer drug eluting stents; BD-DES: Biodegradable polymer drug eluting stents.

decrease in stent thrombosis. Looking at individual study results, except for ISAR-TEST 4, all trials showed non-significant increase in odds of stent thrombosis compared to second generation PP-DES. However it should be remembered, BD-DES are anticipated to have decreased stent thrombosis events at long term follow up, especially after the biodegradable polymer dissolves and leaves behind a bare metal stent. It is important to wait for long term follow up data on these trials, to observe if the very late stent thrombosis rates are lower, as seen in long term follow up data of ISAR-TEST 4. It is also crucial and remains to be observed, if the stent thrombosis events would be lower even after discontinuing dual anti-platelet therapy and the when

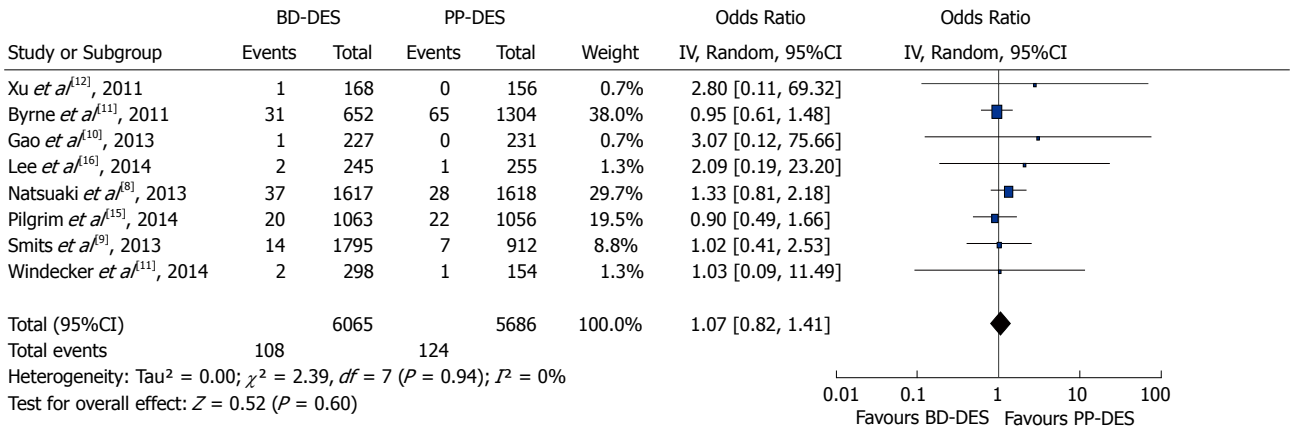

Figure 5 Cardiac deaths. BMS: Bare metal stents; PP-DES: Permanent polymer drug eluting stents; BD-DES: Biodegradable polymer drug eluting stents.

event rates are adjusted for dual-antiplatelet therapy use between both the groups. Henceforth, it is too early to come to any firm conclusions in regards to superiority of BD-DES to currently used second generation PP-DES. A recent network meta-analysis comparing BD-DES, first and second generation PP-DES and bare metal stents, concluded BD-DES are not superior to second generation BD-DES[6]. In our study, we systematically reviewed all the studies and believe long term follow up of the trials are needed before we can make any such firm conclusions.

A pooled analyses comparing ISAR-TEST3, ISAR-TEST-4 and LEADERS trial showed decreased risk of stent thrombosis with BD-DES at 4 year follow up[5]. It is likely because those trials used first generation Sirolimus DES, and the first generation stents are known to have increased late restenosis and stent thrombosis events. However, the second generation DES, use different metal alloy framework with thin struts and the binding polymer is biocompatible and hence the results of such studies cannot be extrapolated to second generation PP-DES. The time for dual anti-platelet therapy with the biodegradable stent is shorter. In fact, in some trials (Table 2), the time for DAPT is reduced to 3-6 mo, while for the drug-eluted stents can be longer. This can be an advantage in any case, since patients on DAPT may have an increased risk of bleeding, especially if unplanned surgery is needed or in case oral anticoagulation is needed for concomitant disease (atrial fibrillation or deep venous thrombosis).

Interventional cardiologists have always been welcoming to newer technology and novel stent designs. The early enthusiasm of most stents, introduced in the past, could not meet the expectations during long-term follow up. With new BD-DES being studied across the globe, we need to analyze the data more closely before drawing conclusions on their superiority to currently used second generation PP-DES.

Limitation

The major limitation of this study is the wide variation of follow-up period. In articular, the ISAR-TEST 4 study had the longest mean follow-up period (36 mo), and the odds ratio was completely opposite to all other included studies as pointed out. The results may change with long-term follow-up. Second, Serruys *et al*[7] included a study investigating a bioresorbable scaffold into the analysis because you aimed to compare BD-DES and PP-DES. Other minor issues are described below. BD-DES used in the RCT was of various types (Biolimus and Sirolimus) and the results should be interpreted with caution in generalizing our results to all types of BD-DES. The patient population in all these studies did vary to some degree (as described in Table 2). Also, the lesions treated and characteristics of stents used- like length and diameter along with lesion complexity could have affected the outcomes.

BD-DES when compared to second generation PP-DES, showed no significant advantage and the outcomes were comparable between both the groups. Long term follow up data is needed, to demonstrate any decrease in very late stent thrombosis events with BD-DES compared to second generation PP-DES.

COMMENTS

Background

Biodegradable polymer stent are currently used in Europe for PCI. Despite that there is no clear-cut evidence in literature comparing the efficacy of these two types of stent.

Research frontiers

Now a day every effort is made to find the new design of stents, which will minimize the need for longer duration of dual antiplatelet therapy, which can be responsible for their notorious side effect in some situations.

Innovation and breakthrough

In present study, the authors compared the efficacy of novel biodegradable dug eluting stent with the standard of care second-generation drug eluting stents in the form of meta-analysis of current randomized control trials.

Application

The present results allow authors to think the role of biodegradable drug eluting stent in stent thrombosis, interests them in further investigating the long term outcomes in form of late stent thrombosis and duration of dual antiplatelet therapy.

Peer-review

The present meta-analysis provides more insight into clinical practice in regards to usage of different stent designs.

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REVIEW

Lipoprotein abnormalities in South Asians and its association with cardiovascular disease: Current state and future directions

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Abstract

South Asians have a high prevalence of coronary heart disease (CHD) and suffer from early-onset CHD compared to other ethnic groups. Conventional risk factors may not fully explain this increased CHD risk in this population. Indeed, South Asians have a unique lipid profile which may predispose them to premature CHD. Dyslipidemia in this patient population seems to be an important contributor to the high incidence of coronary atherosclerosis. The dyslipidemia in South Asians is characterized by elevated levels of triglycerides, low levels of high-density lipoprotein (HDL) cholesterol, elevated lipoprotein(a) levels, and a higher atherogenic particle burden despite comparable low-density lipoprotein cholesterol levels compared with other ethnic subgroups. HDL particles also appear to be smaller, dysfunctional, and proatherogenic in South Asians. Despite the rapid expansion of the current literature with better understanding of the specific lipid abnormalities in this patient population, studies with adequate sample sizes are needed to assess the significance and contribution of a given lipid parameter on overall cardiovascular risk in this population. Specific management goals and treatment thresholds do not exist for South Asians because of paucity of data. Current treatment recommendations are mostly extrapolated from Western guidelines. Lastly, large, prospective studies with outcomes data are needed to assess cardiovascular benefit associated with various lipid-lowering therapies (including combination therapy) in this patient population.

Key words: Dyslipidemia; South Asians; Asian Indians; Cardiovascular disease

Core tip: South Asians have a high prevalence of coronary heart disease (CHD) and suffer from early-onset CHD. Indeed, an important contributor is their unique lipid profile which is characterized by elevated levels of triglycerides, low levels of high-density lipoprotein (HDL) cholesterol, elevated lipoprotein(a) levels, a higher atherogenic particle burden despite comparable low-density lipoprotein cholesterol levels compared with other ethnic subgroups. HDL particles also appear to be smaller, dysfunctional, and proatherogenic. Despite the rapid expansion of the current literature with better understanding of the specific lipid abnormalities in this patient population, specific management goals and treatment thresholds do not exist for South Asians because of paucity of data. Current treatment recommendations are mostly extrapolated from Western guidelines. Lastly, large, prospective studies with outcomes data are needed to assess cardiovascular benefit associated with various lipid-lowering therapies (including combination therapy) in this patient population.

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INTRODUCTION

The term "South Asian" refers to people who have ancestral origins in the Indian subcontinent (the countries of India, Pakistan, Bangladesh, Sri Lanka, and Nepal), where 1.6 billion people live. This region constitutes about 1/5 of the world's population. Nearly 3.6 million South Asians live in the United States, and the South Asian population has the highest rates of coronary heart disease (CHD) among all ethnic groups[1]. CHD in this population is usually premature and severe with 3- to 5-fold higher risk of morbidity and mortality[1-4]. The prevalence of CHD is higher in South Asian immigrants compared with the overall United States population, with similar rates among vegetarians and non-vegetarians[4-6]. Interheart, a global case-control study, was performed in 15152 cases with acute myocardial infarction (AMI) and 14820 controls in 52 countries. Of these, 1732 cases and 2204 controls were South Asian. Median age at first AMI was 53 years in South Asia compared with 63 years in both China and Western Europe. The highest proportions of cases with first AMI at age 40 years or younger were in men from the Middle East (12.6%), Africa (10.9%), and South Asia (9.7%), and the lowest proportions were in women from China and Hong Kong (1.2%), South America (1.0%), and central and eastern Europe (0.9%)[7]. These results indicate the magnitude of premature CHD risk in South Asians.

Although CHD rates in the general United States population have declined over the last few decades because of aggressive modification of risk factors and population-based interventions[8], the rates have conversely doubled in South Asian immigrants[3] and remain higher than their counterparts in their country of origin[9-11].

Given the consistent findings of increased prevalence, premature onset, and increased mortality from CHD in South Asians, there has been much interest in determining the underlying causes. Conventional risk factors such as hypertension, hypercholesterolemia, diabetes mellitus, abdominal obesity, metabolic syndrome, and tobacco use have been clearly associated with CHD risk among South Asian populations[7,12].

Other factors such as sedentary life style and dietary influences also play a role. Although a considerable percentage of South Asians are vegetarians, excess sugars and refined carbohydrates remain problematic for this population. Indeed India is among the largest consumers of sugar in the world. Diet rich in sugar and processed carbohydrates may be a considerable threat to the future health and wellness of the increasingly sedentary South Asian people with their innate genetic predisposition to CHD.

Although South Asians represent an heterogeneous population, with varied practices in terms of diet and exercise, they have a much higher prevalence of diabetes, insulin resistance, central obesity, increased thrombotic tendency, and physical inactivity than other populations[1,7,9,13-16]. Conversely, the prevalence of hypertension, smoking, and obesity (using traditional body mass index cut-offs) is lower in South Asians compared with the Western World[5]. Studies comparing South Asians with other ethnic groups have consistently shown that differences in these risk factors do not fully account for the excess incidence of CHD noted in South Asians[1,3,7,17-21]. The Study of Health Assessment and Risk in Ethnic Groups assessed conventional and novel cardiovascular risk factors among 985 participants of South Asian, Chinese, and European descent living in Canada. South Asians had an increased prevalence of glucose intolerance, higher total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), and triglyceride levels, and lower high-density lipoprotein cholesterol (HDL-C) levels compared with Caucasians. These abnormalities only partially explained the high atherosclerosis burden (defined by carotid atherosclerosis measured with B-mode ultrasonography) in this population[14]. Thus, other factors may apply to the increased CHD risk in South Asians. Despite these findings, the INTERHEART study reported the association of smoking, history of hypertension or diabetes, waist/hip ratio, dietary patterns, physical activity, consumption of alcohol, blood apolipoproteins, and psychosocial factors with myocardial infarction in 9 ethnic populations including South Asians. Dyslipidemia appeared to be the strongest contributor of AMI in South Asians, with a population-

attributable risk of 49.2%[22]. Therefore, dyslipidemia appears to be an important determinant of increased CHD burden in South Asians.

In this article, we review the lipid and lipoprotein abnormalities in South Asian population as a potential cause of increased CHD risk. We also provide a succinct discussion on the efficacy of lipid-lowering therapy in South Asians. In Table 1, we provide references and a brief overview of studies discussed in this review. In Table 2, we summarize major lipid abnormalities in South Asians.

SEARCH STRATEGY

A PubMed/Medline search using key words "South Asian, Asian, Indian, lipids, cholesterol, cardiovascular disease, metabolic syndrome" was conducted. Studies since 1990 were included. Individual studies were initially screened using their titles and abstract content. An initial pool of studies was identified with this methodology. We subsequently reviewed references listed in the selected studies and included them in this review when relevant to the topic. Individual study references known to the authors of this review were also included.

DYSLIPIDEMIA IN SOUTH ASIANS

Total cholesterol, LDL-C and small dense LDL

Hypercholesterolemia (TC > 200 mg/dL) has been reported to have a prevalence of up to 35% in men and 36% in women from South Asian countries[23-25]. LDL-C is a well-established marker for the occurrence, recurrence, and severity of CHD. It is the co-primary target for lipid-lowering therapy as per the National Lipid Association recommendations for cholesterol management[26].

Elevated LDL-C levels clearly predict CHD risk in the South Asian population[17,22,27,28]. In various reports, LDL-C levels have been found to be either similar[5,29-32] or lower[33] among South Asians compared with Caucasians. Compared with Caucasian participants in the Framingham Offspring Study, LDL-C level and LDL particle size were similar in South Asians (LDL-C level: 139 ± 33 mg/dL *vs* 135 ± 31 mg/dL, respectively, $P < 0.10$; and LDL particle size: 20.6 nmol ± 0.7 *vs* 20.7 nmol ± 0.6, respectively, $P < 0.08$)[31]. LDL-C levels did not discriminate between Asian Indian and non-Asian Indian males[30]. On the other hand, studies have shown that CHD may appear at relatively lower LDL-C levels in South Asians. As shown in the INTERHEART study, although the overall associations between LDL-C and risk for AMI were similar among South Asians and others, South Asians had LDL-C levels that were on average 10 mg/dL lower than other groups. Interestingly, the proportion of cases and control subjects from Asia who had LDL-C levels < 100 mg/dL was 25.5% and 32.3% respectively, compared with 19.4% and 25.3% in non-Asians, with consistent results in both sexes[22]. These results indicate that although LDL-C is associated with AMI risk in South Asians, the risk is elevated even at a much lower LDL-C level compared with other ethnic groups.

Another study analyzed metabolic profile in 1066 Indian patients of whom 877 had CHD and 189 did not have CHD. The 50th percentile for TC was 205 mg/dL for the cases and 186 mg/dL for controls, while for triglycerides, the 50th percentile was 158 mg/dL for cases and 140 mg/dL for controls, thus suggesting the occurrence of CHD in this patient population at relatively lower levels of cholesterol[34].

Why South Asians carry a higher CHD risk at a given LDL-C level remains a question. One of the postulated mechanisms is that South Asians carry a higher LDL particle burden at a given LDL-C level. Smaller LDL particles are denser and may be more atherogenic[35]. A small study showed that the prevalence of small dense LDL, (defined as LDL subclasses 5 and 6 as measured by the Vertical Auto Profile test) was significantly higher in Asian Indians ($n = 39$) compared with white subjects ($n = 39$) (44% *vs* 21%, $P < 0.05$)[36]. A nonsignificant trend towards lower LDL particle size as measured by gel electrophoresis was also shown in South Asian adolescent boys compared with age-matched Caucasian adolescent boys[37]. Importantly, the INTERHEART study showed that for any LDL-C level, South Asians had higher apolipoprotein (apo) B concentration compared with other ethnic groups, indicating that for any LDL-C level, South Asians carry a higher number of atherogenic lipoproteins[22].

Therefore, although elevated LDL-C levels predict CHD risk in South Asians as in other ethnicities, the LDL-C levels in general are similar or lower in South Asians compared with other ethnicities. As shown in INTERHEART, a higher LDL-C level, although less frequent in South Asians, carries a similar risk for myocardial infarction as in other ethnic groups. In addition, at any given LDL-C level, South Asians tend to carry a higher total atherogenic burden as noted by higher levels of LDL particles and apo B in some studies as described above.

Triglycerides and HDL-C

HDL-C levels have been associated with a lower risk of CHD, and increasing HDL-C levels and augmenting HDL function have been associated with vascular protective effects[38-41]. Low HDL-C level (< 40 mg/dL) was defined as a CHD risk factor by the National Cholesterol Education Program Adult Treatment Panel Ⅲ guidelines[42]. Conversely, elevated triglycerides (> 150 mg/dL) are associated with increased CHD risk and are commonly associated with other lipid abnormalities (elevated non-HDL-C levels and increased LDL particle number) and nonlipid risk factors (diabetes mellitus and metabolic syndrome)[43].

One of the most common dyslipidemia in South Asians is low HDL-C and high triglycerides[14,23-25,44]. The rate of hypertriglyceridemia has shown to be higher in South Asians compared to Caucasians in several studies[45]. Hypertriglyceridemia (> 150 mg/dL) was observed in up to 70% of South Asian populations in studies with large

Table 1 Articles related to dyslipidemias in South Asians

Ref.	Methodology	Primary end point
Enas *et al*[5]	Cross-sectional, case-control study in Asian Indians and Caucasians (*n* = 1688)	CV risk factors
Anand *et al*[14]	Comparative population-based study in South Asians, Chinese, and Europeans (*n* = 985)	CV risk factors
Tillin *et al*[17]	Retrospective chart review (*n* = 2049 Europeans, 1517 South Asians, and 630 African Caribbeans)	CV risk factors
Karthikeyan *et al*[22]	Cross-sectional, population-based case-control study in 65 centers in Asia (*n* = 5731 cases of a first AMI *vs* 6459 controls)	CV risk factors
Gupta *et al*[23]	Cross-sectional study in South Asians (*n* = 1800)	CV risk factors
Sekhri *et al*[25]	Cross-sectional study in Indians (*n* = 10642 men and *n* = 1966 women)	CV risk factors
Hoogeveen *et al*[27]	Cross-sectional comparative study in Indians living in India (*n* = 103) *vs* those living in United States (*n* = 206)	Lipid profile
Sewdarsen *et al*[28]	Cross-sectional, case-control study in Indian men with CAD (*n* = 50) *vs* controls (*n* = 122)	Lipid profile
Lyratzopoulos *et al*[29]	Comparative study between South Asians and Caucasians (*n* = 34122 men and 37294 women)	CV risk factors
Superko *et al*[30]	Comparative study between Asian Indian men (*n* = 224) and non-Asian Indian men (*n* = 239)	Lipid profile
Bhalodkar *et al*[31]	Comparative study between Asian Indian men (*n* = 211) and Caucasian men (*n* = 1684)	Lipid profile
Joseph *et al*[32]	Descriptive study in Asian Indians (*n* = 206)	Lipid profile
Cappuccio *et al*[33]	Population-based survey in 505 South Asians, 524 Caucasians, and 549 Africans	CV risk factors
Krishnaswami *et al*[34]	Cross-sectional study in 1066 Indian male patients	Lipid profile
Kulkarni *et al*[36]	Cross-sectional study in 39 Asian Indians and 39 Caucasians	Lipid profile
Rashid *et al*[53]	Comparative study in 135 adolescent Indian and Caucasian boys	Lipid profile
Misra *et al*[45]	Comparative study in Asian Indians and Caucasians	CV risk factors
Bhardwaj *et al*[46]	Cross-sectional epidemiological descriptive study in 459 Indian subjects	CV risk factors
Gopinath *et al*[47]	Community-based epidemiological survey in 13414 Indian adults	CV risk factors
Misra *et al*[48]	Cross-sectional epidemiological descriptive study in 532 Indian subjects	CV risk factors
Ehtisham *et al*[50]	Cross-sectional community-based cohort study of 129 Caucasian European and Asian Indian boys	CV risk factors
Patel *et al*[51]	Cross-sectional comparative study in Indians (*n* = 294) and their immigrant counterparts in UK (*n* = 242)	Lipid profile
Sharobeem *et al*[52]	Cross-sectional study in South Asians with stroke (*n* = 55) and healthy controls (*n* = 85)	Lipid profile
Chow *et al*[54]	Cross-sectional comparative study in Indian (*n* = 303) and Caucasian (*n* = 1111) subjects	Association of CIMT with lipid profile
Dodani *et al*[55]	Cross-sectional study in South Asian immigrants in United States	Association of CIMT with lipid profile
Dodani *et al*[56]	Cross-sectional community-based study in 130 South Asian immigrants in United States	Association of CIMT with lipid profile
Isser *et al*[74]	Descriptive study in 50 Indian patients with premature CAD and their first-degree relatives	Lp(a) levels
Palaniappan *et al*[75]	Cross-sectional community-based study in Asian Indian American, African American, and Caucasian women (*n* = 70 each)	Lipid profile
Kamath *et al*[76]	Cross-sectional community-based study in 47 South Asian and 47 American women	CV risk factors
Anand *et al*[77]	Comparative cross-sectional study in South Asians and Americans	Lipid profile
Chopra *et al*[78]	Comparative study in 74 Indians with CAD and 53 controls	Lp(a) levels
Gambhir *et al*[79]	Comparative study in 50 Indians with CAD and 50 controls	Lp(a) levels
Gupta *et al*[80]	Descriptive study in 101 Indian subjects	Lp(a) levels
Articles related to treatment of dyslipidemias in South Asians		
Lee *et al*[89]	Rosuvastatin pharmacokinetics in White, Chinese, Malay, and Asian Indian subjects (*n* = 35 each)	
Patel *et al*[83]	Efficacy and safety of atorvastatin in 33 hyperlipidemic South Asians	
Gupta *et al*[85]	Lipid-modifying effects of atorvastatin and simvastatin in 86 South Asians and 137 Caucasians	
Gupta *et al*[84]	ACTFAST: 12 wk prospective, open-label study of atorvastatin in 1978	

AMI: Acute myocardial infarction; CAD: Coronary artery disease; ACTFAST: Achieve Cholesterol Targets Fast with Atorvastatin Stratified Titration; CIMT: Carotid intima-media thickness; Lp(a): Lipoprotein(a); CV: Cardiovascular.

sample sizes[46-48]. compared with 34% in Caucasians[49]. Low levels of HDL-C (< 40 mg/dL) were seen in up to a third of South Asians. In a cross-sectional epidemiological descriptive study with 459 Indian subjects in New Delhi, HDL-C levels < 40 mg/dL were seen in 37% of subjects[45].

Enas *et al*[5] compared HDL-C levels in 580 Asian Indian immigrants in the United States with those of native Caucasians in the Framingham Offspring Study. The mean levels of HDL-C were 38 mg/dL in Asian Indian men compared with 46 mg/dL in Caucasian men ($P < 0.001$). Similar results were seen in women, with mean HDL-C levels of 48 mg/dL in Asian Indian women compared with 56 mg/dL in Caucasian women ($P < 0.001$). Ehtisham *et al*[50] compared 64 white European with 65 South Asian healthy adolescents. Mean HDL-C levels were 65 mg/dL in European women compared with 58 mg/dL in South Asian women ($P = 0.001$), whereas they were 54 mg/dL in European men compared with 50 mg/dL in South Asian men ($P = 0.001$). Similarly, in the INTERHEART study, HDL-C levels were the lowest in the South Asian population, at 32.5 mg/dL in cases and

Table 2 Summary of lipoprotein abnormalities in South Asians

CAD occurs with relatively lower levels of LDL-C among South Asians
At any given LDL-C level, South Asians tend to carry a higher total atherogenic burden (*i.e.*, higher levels of apo B and a higher LDL particle concentration)
South Asians tend to suffer from atherogenic dyslipidemia (*i.e.*, high triglyceride and low HDL-C levels) more frequently compared with other ethnic groups
In South Asians, higher HDL-C levels may not be as protective against CAD as in other ethnic groups
In South Asians, HDL particles tend to be smaller and dysfunctional
South Asians have a genetic tendency for elevated atherogenic Lp(a) levels

Apo B: Apolipoprotein B; CAD: Coronary artery disease; HDL-C: High-density lipoprotein cholesterol; LDL-C: Low-density lipoprotein cholesterol; Lp(a): Lipoprotein(a).

33.5 mg/dL in controls, compared with other Asian and non-Asian groups. More than 80% of both cases and control subjects in South Asia had low HDL-C levels [HDL-C < 40 mg/dL (men) and < 50 mg/dL (women)][22]. These results indicate that the prevalence of low HDL-C levels is much higher in South Asians compared with other ethnic groups.

High triglyceride and low HDL-C levels are metabolically interlinked. This metabolic phenotype is also associated with increased levels of small LDL particles despite relatively normal levels of LDL-C among South Asians. This clinical syndrome is accompanied by insulin resistance, a condition frequently referred to as atherogenic dyslipidemia, which is a common metabolic derangement among Asian Indians[5,31,36,45,50-52]. Rashid *et al*[53] compared lipid levels among South Asians and Europeans (n = 244 and 238, respectively) and all elements of atherogenic dyslipidemia were more severe in South Asians compared to Europeans. Mean triglyceride level was 174 mg/dL *vs* 136 mg/dL (P < 0.0001), LDL-C level was 129 mg/dL *vs* 122 mg/dL (P < 0.02), and HDL-C level was 39 mg/dL *vs* 46 mg/dL among South Asians and Europeans, respectively (P < 0.0001).

These studies indicate that atherogenic dyslipidemia is more prevalent and severe among South Asians and may partially explain the increased CHD risk in this population despite relatively normal levels of LDL-C compared with other ethnic groups.

HDL PARADOX IN SOUTH ASIANS

Higher HDL-C levels have been shown to be associated with a lower risk of CHD[22,27,28,44]. In the INTERHEART study, higher HDL-C levels were associated with a decreased risk of AMI in South Asians. However, the protective effect of higher HDL-C levels seemed to be weaker for South Asians (with OR crossing unity) compared with other Asians in the INTERHEART study (OR for risk of first AMI per 1-SD increase in HDL-C in South Asians: 0.87, 95%CI: 0.72-1.06; OR for rest of Asia: 0.77, 95%CI: 0.70-0.85)[22]. Other investigators have also shown a similar lack of protective effect of HDL-C among South Asians. In a community-based cross-sectional study assessing the correlation of risk factors with carotid intima-media thickness (CIMT) among South Asians from India (n = 303) and Caucasians from Australia (n = 1111), increasing HDL-C levels were associated with decreasing CIMT in the Australian population, but the reverse was true for the Indian population (P < 0.001)[54]. Therefore, South Asians not only have low levels of HDL-C but also appear to have much less cardiovascular protection from HDL-C compared to other ethnic groups.

Why HDL loses its cardioprotective properties in South Asians is unclear. One proposed mechanism is presence of dysfunctional HDL particles. In a small study, Dodani *et al*[55] examined 30 South Asian immigrants and found that 50% had dysfunctional HDL (as determined by using HDL inflammatory index). Presence of dysfunctional HDL correlated with subclinical atherosclerosis measured by CIMT (P = 0.03)[55]. This finding was supported by recently published data from the same authors on 130 South Asian immigrants who underwent HDL function assessment and CIMT measurements; 26% had dysfunctional HDL defined as HDL inflammatory index value of 1 or greater. Presence of dysfunctional HDL correlated with CIMT measurement (P < 0.0024)[56].

It is postulated that metabolic syndrome may render HDL pro-inflammatory[57]. The association between dysfunctional HDL particles and atherosclerosis in South Asians could be potentially explained by a high prevalence of metabolic syndrome in South Asians[19]. However, this might be a noncausal association, and HDL dysfunction indeed may be the result of a diffuse atherosclerotic process[58-62]. What causes HDL to become dysfunctional in South Asians and whether dysfunctional HDL is a true risk factor for increased cardiovascular risk in South Asians is not known. In addition, how much the higher prevalence of metabolic syndrome in South Asians contributes to this effect is not entirely clear. Studies with large sample size are needed to further address this important question.

HDL SUBFRACTIONS IN SOUTH ASIANS

Another potential explanation for the apparent blunted cardioprotection of HDL in South Asians might be related to HDL particle size. Similar to LDL, HDL is composed of heterogeneous particles, with large particles performing highly efficient reverse cholesterol transport, whereas small particles might be less efficient in reverse cholesterol transport. In general, HDL particle size tends to be lower in patients with CHD and those with low HDL-C levels[55].

The role of HDL and other proteins in reverse cholesterol transport is of crucial importance for cholesterol clearance. Cholesterol is removed from vascular endothelial cells and tissue macrophages through a reverse transport process, in which receptors on the HDL surface, such as apo A-I, bind free cholesterol, which is then

carried to the liver and secreted into the bile[63-65]. HDL2b is a major HDL subfraction that is larger in size and may be more efficient in reverse cholesterol transport[30]. Superko *et al*[30] investigated the prevalence of metabolic disorders among Asian Indian and non-Asian Indian males. The standard lipid measurements did not discriminate between groups. However, the levels of HDL2b were significantly lower (12 mg/dL *vs* 14 mg/dL, respectively, $P = 0.0002$) and the prevalence of low HDL2b subfraction (< 20% of total HDL) was higher among Asian Indians compared with non-Asian Indians (92% *vs* 76%, respectively, $P < 0.0002$), suggesting impaired reverse cholesterol transport in South Asians. Bhalodkar *et al*[31] compared various lipoprotein concentrations and sizes between 211 healthy Asian Indian men and 1684 Caucasian men from the Framingham Offspring Study. Asian Indians had significantly lower concentrations of large HDL particles (21 mg/dL *vs* 24 mg/dL, respectively, $P < 0.005$), higher concentrations of small HDL particles (20 mg/dL *vs* 17 mg/dL, respectively, $P < 0.0001$), and smaller HDL particle size (8.5 nm *vs* 8.9 nm, respectively, $P < 0.0001$) compared with Caucasian men.

Therefore, small HDL particle size potentially resulting in inefficient reverse cholesterol transport may be more common in South Asians than in other populations and could partially explain the observed weaker association between HDL-C and cardiovascular events in South Asians compared with other ethnicities. As discussed previously, prospective studies with large sample size are needed to assess further the association between HDL particle size and future risk for cardiovascular disease in South Asians. It is important to note that in the studies described above, HDL particle size was used a surrogate for HDL's reverse cholesterol transport function and no direct measurement of reverse cholesterol transport (*e.g.,* HDL's efflux capacity) was performed.

Lipoprotein(a)

Lipoprotein(a) [Lp(a)] is a highly atherogenic and has been associated with premature atherosclerosis in coronary, cerebral, and peripheral arteries[66-73]. Lp(a) levels are primarily genetically determined, and South Asian immigrants have Lp(a) levels that are similar to those in their counterparts in their home country[71-74] and higher than those in Caucasians. Bhatnagar *et al*[9] compared Lp(a) levels of Indian immigrants in West London with their siblings in Punjab and found that Lp(a) concentrations were similar in both the West London Indian and Punjab populations, but were significantly higher ($P = 0.01$) than those of a white European population in London.

A comparative study of African American, Asian Indian American, and Caucasian American women ($n = 70$ for each) was performed by Palaniappan *et al*[75]. In this study, African Americans had the highest Lp(a) levels, followed by Asian Indian Americans and Caucasian Americans [(Lp(a) 0.5 g/L, 0.3 g/L, and 0.2 g/L, respectively, $P = 0.0001$]. Kamath *et al*[76] also compared Lp(a) levels in 47 South Asian women with those in 47 American women. Lp(a) levels were higher in South Asian women compared with American women [median level (range): 50.7 (2.9-323) nmol/L *vs* 18.3 (2.9-196) nmol/L, respectively, $P < 0.012$]. Anand *et al*[77] performed 3 separate studies comparing Lp(a) levels in South Asians and Caucasians living in North America. The first study included a group of South Asian physicians aged 40-57 years who attended an annual meeting in North America, whose Lp(a) levels were compared with those of their North American counterparts ($n = 141$ and 138, respectively). The mean Lp(a) concentration for South Asian physicians was 19.6 mg/dL compared with 17.5 mg/dL for Caucasian North American physicians ($P = 0.55$). The second study compared 255 South Asian churchgoers aged 22-70 years with 246 Caucasian Americans. The mean Lp(a) concentration was significantly elevated in South Asians (20.2 mg/dL) compared with Caucasian Americans (16.3 mg/dL, $P < 0.002$). In the third study, 30 South Asians and 21 Caucasians who were randomly sampled from the community in Canada were compared. South Asian Canadians had significantly higher mean Lp(a) concentrations compared with Caucasian Canadians (34.1 *vs* 17.3 mg/dL, $P < 0.013$). Therefore, Lp(a) levels in South Asian North Americans are higher than those in Caucasian North Americans but lower than in African Americans.

In an attempt to evaluate the association between Lp(a) levels and CHD risk, Lp(a) levels were compared in 74 Indian patients with CHD and 53 healthy Indian controls. Patients with CHD had almost 5-fold higher Lp(a) levels compared with controls (105 ± 565 mg/dL *vs* 23 ± 76 mg/dL, $P < 0.01$)[78]. In another study, Lp(a) levels were measured in 50 South Asian patients (< 40 years old) with angiographically documented CHD and an equal number of age-matched healthy South Asian controls. In patients with angiographically confirmed CHD, mean Lp(a) levels were significantly higher than in controls (35 mg/dL *vs* 20 mg/dL respectively, $P < 0.002$). Multiple regression analysis showed that elevated Lp(a) level was independently associated with presence of CHD among South Asians (OR = 3.06, 95%CI: 1.24-7.55; $P < 0.001$)[79]. Similarly, Gupta *et al*[80] compared Indian patients with angiographically confirmed CHD with age- and sex-matched Indian controls. Lp(a) concentration was higher in the CHD group ($n = 77$) compared to the control group ($n = 24$) (27 mg/dL *vs* 15 mg/dL, $P < 0.05$). Furthermore, Lp(a) values had a graded association with CHD. The prevalence of CHD in the first (< 5 mg/dL), second (5-25 mg/dL), third (26-75 mg/dL), and highest quartile (≥ 76 mg/dL) of Lp(a) levels was 66.7%, 69.0%, 87.5%, and 100%, respectively[80].

Overall, these studies point towards a genetic tendency for elevated Lp(a) levels in South Asians. These elevated Lp(a) levels correlate with presence of CHD and might partially explain the population-attributable risk for excessive CHD in this group.

TREATMENT OF DYSLIPIDEMIA IN SOUTH ASIANS

Data on the management of dyslipidemia in South Asian subjects are sparse despite the critical importance of dyslipidemia as a cardiovascular risk factor in this population. In the United States, the lipid management guideline developed by the American College of Cardiology/American Heart Association in 2013 is used for management of dyslipidemia[81]. Chandra *et al*[82] recently published a consensus statement regarding dyslipidemia management in Indian subjects. The vast majority of recommendations are extrapolated from the current Western guidelines, because of the paucity of primary data in South Asian populations.

Statin therapy

LDL-C-lowering therapy with statins is the mainstay in the pharmacological treatment of hypercholesterolemia in South Asians, with a suggested LDL-C goal of < 100 mg/dL in high-risk patients and < 70 mg/dL for very-high-risk patients as per a recent consensus statement[82]. There are no South Asian-specific treatment goals or thresholds, given the absence of prospective outcomes data, and thus, these goals were derived from studies mostly performed in Caucasian populations.

In a study in 33 South Asians with hyperlipidemia, a target LDL-C goal of < 77 mg/dL was achieved in 81% of patients after 4 wk treatment with 10 mg/d atorvastatin, without statin-related adverse effects being noted[83]. Similarly, a study in patients with established CHD on statins compared the efficacy and safety of atorvastatin and simvastatin in South Asians and Caucasians. Atorvastatin (median dose = 20 mg/d in both groups) produced similar decreases in LDL-C in South Asian (43%) and Caucasian (41%) patients and increased in HDL-C by 19% in South Asians and by 12% in Caucasians (P = NS). Simvastatin (median dose = 20 mg/d in both groups) reduced LDL-C by 35% in South Asians and by 37% in Caucasians while raising HDL-C by 12% in both groups (P = NS). Both medications were well tolerated[84].

The Achieve Cholesterol Targets Fast with Atorvastatin Stratified Titration study was a 12 wk prospective, open-label study in patients at high risk for atherosclerosis (European origin: n = 1978; South Asian origin: n = 64). After propensity matching, atorvastatin lowered LDL-C to a similar degree in both groups (reduction in LDL-C from baseline was 34% in South Asians compared with 38% in Europeans, P = 0.22), with no differences in safety observed[85]. Furthermore, postmarketing data for statins have not identified any particular safety issues with statins in South Asians[86].

Other studies performed head-to-head comparisons among different statins in South Asians. Jayaram *et al*[87] compared the use of rosuvastatin 10 mg/d with atorvastatin 10 mg/d in adult Indian patients with dyslipidemia (mean LDL-C > 160 mg/dL and triglyceride > 400 mg/dL). The fall in the mean LDL-C levels after 6 wk of treatment in the rosuvastatin group was 40%, compared with 30% in the atorvastatin group. This higher efficacy of rosuvastatin in terms of LDL-C lowering was further tested in the Investigation of Rosuvastatin in South Asians study. In this randomized trial, 740 patients of South Asian origin living in United States and Canada received 6 wk of treatment with either rosuvastatin (10 or 20 mg/d) or atorvastatin (10 or 20 mg/d). A total of 485 patients (66%) were categorized as being at high risk for CHD, with a National Cholesterol Education Program Adult Treatment Panel Ⅲ treatment goal of LDL-C < 100 mg/dL. LDL-C levels decreased by 45% with rosuvastatin 10 mg *vs* 40% with atorvastatin 10 mg (P = 0.002) and by 50% with rosuvastatin 20 mg *vs* 47% with atorvastatin 20 mg (P = NS). National Cholesterol Education Program Adult Treatment Panel Ⅲ LDL-C goal attainment rates in high-risk patients were 76% (79%) and 88% (89%) with rosuvastatin 10 (20 mg), respectively, compared with 70% (76%) and 81% (85%) with atorvastatin 10 (20 mg), respectively. Rosuvastatin and atorvastatin were both well tolerated[88].

In a pharmacokinetic study of rosuvastatin, both lasting time in serum and peak plasma concentrations were higher in Asian Indians compared with non-Asian-Indians living in Singapore (P < 0.0001)[89]. This lower statin metabolism has raised a concern about increased side effects of statins in South Asians, especially with higher doses. The United States Food and Drug Association-approved highest doses of statin are, therefore, lower for Asians compared with other groups[90], and it might be prudent to start a lower dose of a statin in Asian patients.

Overall, these results point to similar efficacy with statin therapy in South Asians compared with Caucasians, although, based on pharmacokinetic data, the maximum approved dose for rosuvastatin is lower for Asians (including South Asians) compared with other ethnicities. The recommended initiation dose for rosuvastatin is 5 mg once daily, with maximum recommended dose of 20 mg daily, for Asians.

Combination drug therapy

Given the plethora of lipoprotein abnormalities in South Asians, targeting non-LDL lipid fractions may be relevant. Sharma *et al*[91] studied combination therapy of lovastatin and niacin in a prospective multicenter study that included 131 Asian Indians with LDL-C levels ≥ 130 mg/dL. A significant trend was observed in LDL-C lowering (levels at baseline and weeks 4, 12, and 24, respectively: 153, 127, 109 and 95 mg/dL; P < 0.05). The percentage decrease in LDL-C from baseline was 38% at 24 wk. Similarly, HDL-C was increased by 18%, triglycerides were decreased by 21%, and Lp(a) was decreased by 44.5% (P < 0.05) at 24 wk compared with baseline. No significant changes were observed in systolic or diastolic blood pressure, blood creatinine, transaminases, or creatinine kinase, suggesting an acceptable safety profile.

Ezetimibe is a nonstatin medication that lowers plasma levels of LDL-C by inhibiting the activity of the

Niemann- Pick C1-like 1 (NPC1L1) protein. Stitziel *et al*[92] sequenced the exons of NPC1L1 in 7364 patients (844 South Asians) with CHD and in 14728 controls (1107 South Asians). Naturally occurring mutations that disrupt NPC1L1 function were found to be associated with reduced plasma LDL-C levels and a reduced risk for CHD in individuals with various ethnic backgrounds, including South Asians. This finding suggested that inhibitory drugs such as ezetimibe could reduce LDL-C level and CHD risk reduction in South Asians similar to in other populations. In another study, ezetimibe and statin combination therapy was examined in 64 South Asian Canadians with CHD or diabetes and persistent hypercholesterolemia on statin therapy. Patients were randomized to receive ezetimibe 10 mg/d coadministered with statin therapy or a doubling of their current statin dose. At 6 wk, the proportion of patients achieving target LDL-C (< 77 mg/dL) was significantly higher among the ezetimibe + statin-treated patients compared with the statin-doubling group (68% *vs* 36%, respectively; P = 0.031) with an OR (95%CI) of 3.97 (1.19-13.18), accounting for baseline LDL-C levels and adjusting for age. At 12 wk, 76% of ezetimibe + statin patients achieved target LDL-C compared with 48% of the patients in whom statin dose was doubled (adjusted OR = 3.31, 95%CI: 1.01-10.89; P = 0.047). No serious adverse effects were recorded[93]. Despite these findings, it is important to note that the current cholesterol treatment guidelines recommend the use of maximum tolerated statin dose before adding a second LDL-C-lowering agent.

Combination therapy targeting various dyslipidemias in South Asians appears to be promising. Prospective studies with large sample size and longer follow-up period are needed to assess accurately the efficacy and safety profile of these agents in South Asian populations. Importantly, data are needed to assess whether the use of combination therapy improves cardiovascular outcomes in this patient population with a specific need for combination therapy, given the high prevalence of atherogenic dyslipidemia as discussed above.

CONCLUSION

South Asians have a high CHD prevalence and suffer from early-onset CHD compared with other ethnic groups. Conventional risk factors may not fully explain the increased CHD risk in this population. Indeed, South Asians have a unique lipid profile which may predispose them to premature CHD. The dyslipidemia in South Asians is most importantly characterized by elevated levels of triglycerides, low levels of HDL-C, elevated Lp(a) levels, and a higher atherogenic particle burden despite relatively normal LDL-C levels. HDL particles appear to be smaller, dysfunctional, and proatherogenic in South Asians. Despite the rapid expansion of the current literature with better understanding of the specific lipid abnormalities in this patient population, studies with adequate sample sizes are needed to assess the significance and contribution of a given lipid parameter on overall cardiovascular outcomes in this patient population. Specific lipid management goals and treatment thresholds do not exist for South Asians due to the paucity of data. Current treatment recommendations are mostly extrapolated from Western guidelines. Lastly, large, prospective studies with outcomes data are needed to assess cardiovascular benefit associated with various combination therapies in this patient population.

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REVIEW

Exercise oscillatory ventilation: Mechanisms and prognostic significance

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Abstract

Alteration in breathing patterns characterized by cyclic variation of ventilation during rest and during exercise has been recognized in patients with advanced heart failure (HF) for nearly two centuries. Periodic breathing (PB) during exercise is known as exercise oscillatory ventilation (EOV) and is characterized by the periods of hyperpnea and hypopnea without interposed apnea. EOV is a non-invasive parameter detected during submaximal cardiopulmonary exercise testing. Presence of EOV during exercise in HF patients indicates significant impairment in resting and exercise hemodynamic parameters. EOV is also an independent risk factor for poor prognosis in HF patients both with reduced and preserved ejection fraction irrespective of other gas exchange variables. Circulatory delay, increased chemosensitivity, pulmonary congestion and increased ergoreflex signaling have been proposed as the mechanisms underlying the generation of EOV in HF patients. There is no proven treatment of EOV but its reversal has been noted with phosphodiesterase inhibitors, exercise training and acetazolamide in relatively small studies. In this review, we discuss the mechanistic basis of PB during exercise and the clinical implications of recognizing PB patterns in patients with HF.

Key words: Exercise; Oscillatory ventilation; Heart failure

Core tip: Alteration in breathing patterns in patients with advanced heart failure (HF) characterized by cyclic variation of ventilation with a period of approximately one minute is known as periodic breathing. Periodic breathing during exercise, known as exercise oscillatory ventilation (EOV), is an oscillatory ventilatory pattern during

exercise that persists for at least 60% of the exercise test with an amplitude ≥ 15% of the average resting value. Circulatory delay, pulmonary congestion and chemoreceptor sensitivity has been proposed to cause generation of EOV. EOV is found to be an independent predictor of worse outcome irrespective of other gas exchange variables in HF patients.

Dhakal BP, Lewis GD. Exercise oscillatory ventilation: Mechanisms and prognostic significance. *World J Cardiol* 2016; 8(3): 258-266 Available from: URL: http://www.wjgnet.com/1949-8462/full/v8/i3/258.htm DOI: http://dx.doi.org/10.4330/wjc.v8.i3.258

INTRODUCTION

Impaired cardiac filling or ejection of the blood are the cardinal features of heart failure (HF) which leads to multiple organ systems dysfunctions[1] with dyspnea on exertion and exercise intolerance being the most common. Alteration in breathing patterns with cyclic variation of breathing secondary to instability in respiratory control has been a recognized feature of HF for almost two centuries[2,3]. Cheyne[2] (1818) first described a severe form of disordered breathing during rest characterized by alternating hyperpnea and hypopnea with intervals of apnea lasting almost a minute in a patient with HF and similar case was described by Stokes[3] nearly three decades later (1854) after which the condition was named Cheyne-Stokes breathing.

Periodic breathing (PB) characterized by cyclic variation of ventilation with or without interposed apnea have been observed at rest[4], during sleep[4-7] and during exercise[8-10] (Figure 1) in HF patients. Sleep disordered breathing such as obstructive sleep apnea (OSA) and central sleep apnea (CSA) has been observed in nearly 50% of stable HF patients[6] with CSA being significantly more prevalent (40%) than OSA. In one study, the presence of sleep disordered breathing at night was accurately predicted by concomitant daytime PB (AUC 0.821, $P < 0.01$ at receiver operating characteristic analysis, sensitivity 75%, specificity 75%)[4].

An unusual crescendo-decrescendo ventilatory response to exercise in patients with heart disease without resting Cheyne-Stokes breathing was initially reported by Weber[11] and further described by Kremser *et al*[12] in 1987. This phenomenon of periodic oscillatory breathing during exertion without interposed apnea is now known as exercise PB or exercise oscillatory ventilation (EOV) (Figure 2). EOV has recently been recognized in significant percentage of symptomatic HF patients, both with reduced[4,9,10,12-17] and preserved[18] left ventricular ejection fraction (LVEF). Despite the frequent occurrence of PB in patients with HF, pathophysiologic mechanisms that induce irregular breathing as well as the therapeutic modalities to reverse this condition in HF still remain incompletely understood. In this review, we focus specifically on EOV discerned in the context of measuring expired gas exchange variables during exercise through cardiopulmonary exercise testing.

CARDIOPULMONARY EXERCISE TESTING AND EOV

Cardiopulmonary exercise testing (CPET) provides a unique opportunity to evaluate patient's aerobic capacity with breath-by-breath expired gas parameters[19]. Besides providing information about patient's functional capacity with peak oxygen uptake (VO_2)[20], CPET is also helpful in delineating pulmonary vascular abnormalities in HF patients. Studies have shown that ventilatory efficiency (V_E/VCO_2 slope)[21,22] is even better predictor of HF outcomes than peak VO_2. EOV on the other hand is discerned in HF patients during submaximal exercise which makes it a very attractive CPET parameter in those patients who are not able to complete maximal effort exercise testing.

EOV

Definitions

Presence of EOV during CPET is identified by ventilatory oscillations with a typical cycle length and amplitude but there are a lot of variations on its definition[23]. Cycle length of an oscillation in V_E is the time between nadirs of two ventilatory oscillations and the amplitude of oscillation is the difference between the peak V_E during an oscillation and the nadirs in V_E (Figure 2)[24]. Some of the definitions used for EOV are: (1) Kremser *et al*[12] and Corrà *et al*[10,13]: Oscillations in V_E with a cycle length of approximately 1 min, amplitude > 15% of resting V_E, and duration > 60% (> 66%[12]) of exercise duration; (2) Ben-Dov *et al*[25]: 3 or more consecutive regular oscillations in V_E with oscillation amplitude > 25% of average V_E and cycle length 30-60 s; (3) Leite *et al*[15]: Three or more cycles of regular oscillation in V_E with standard deviation of 3 consecutive cycle lengths within 20% of the average and minimal average amplitude of oscillation > 5 L/min; and (4) Sun *et al*[24]: Three or more consecutive cyclic fluctuations in V_E, amplitude > 30% of concurrent mean V_E, oscillation of ≥ 3 gas exchange variables, cycle length of 40-140 s.

The American Heart Association consensus statement has defined EOV as an oscillatory ventilatory pattern that persists for at least 60% of the exercise test at amplitude 15% or more of the average resting value[19]. Due to the lack of automated measurement methods, presence of EOV during CPET is usually analyzed manually which may have lead to variations in its definitions and appropriate identification. More recently custom software has been used to identify EOV during exercise[26,27].

Prevalence of EOV

The prevalence of EOV has been different based on

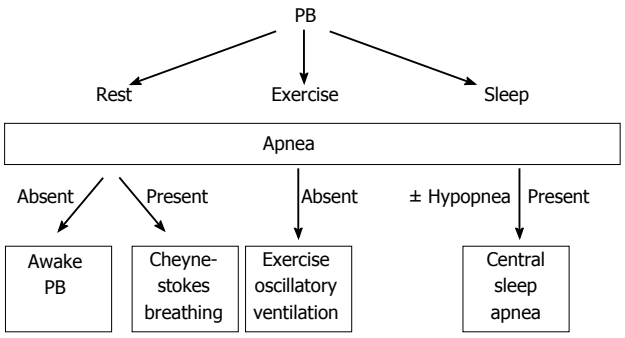

Figure 1 Types of periodic breathing in heart failure patients. PB: Periodic breathing.

the severity and type of HF patient population studied. Patients with HF with reduced ejection fraction (HFrEF) has been found to have EOV prevalence of 12%-58% [8-10,12,13,15,16,18,24,28]. We found EOV prevalence of 45% in a subset of patients with HFrEF (n = 56, mean ± SD: LVEF = 30% ± 6%, peak VO_2 = 12.4 ± 0.5 mL/kg per minute)[8]. EOV is similarly common in patients with HF and preserved ejection fraction (HFpEF)[18,29-31] with one previous study reported prevalence of 31%[18]. Olson *et al*[29] found that 41% of HF patients with EOV had LVEF ≥ 40%, and in the study by Matsuki *et al*[30] the mean LVEF in HF patients with EOV was 41.3 ± 16.3.

Mechanisms of generation of EOV

There is limited data regarding the mechanistic basis for EOV despite its significant association with poor outcomes in HF patients[32]. The control of the normal ventilation is through the feedback loop between pulmonary gas exchanging capillaries and peripheral chemoreceptors located in the carotid bodies and the central chemoreceptors located in the medulla (Figure 3)[33-37]. Any instability of this ventilatory regulation can lead to generation of oscillatory respiratory pattern. The generation of crescendo and decrescendo respiratory pattern can be caused by: (1) Circulatory delay (*i.e.,* increased circulation time from the lung to the brain and chemoreceptors due to reduced cardiac index leading to delay in information transfer)[15,36,37]; (2) increase in controller gain (*i.e.,* increased central and peripheral chemoreceptor sensitivity to $PaCO_2$ and PaO_2)[14,35,38]; or (3) reduction in system damping (*i.e.,* baroreflex impairment) (Figure 3). The possible mechanisms responsible for generation of PB during exercise (*i.e.,* EOV) have largely been extrapolated from studies of PB at rest[39] and during sleep[15,40] even though there has been limited overlap between PB during exercise and during sleep[13].

Circulatory delay: Reduced cardiac output in patients with HF increases the circulation time from lungs to chemoreceptors and respiratory centers. This delayed transfer of information has been postulated to generate late feedback signals leading to oscillations in ventilation[41]. Hypotension and circulatory delay has been shown to induce cardiorespiratory oscillations in experimental rat models[42]. Similarly reduced resting CI and prolonged lung-to ear circulation time (LECT) were the major determinants of PB at rest in HF patients in one previous study[43]. LVEF has also been noted to be significantly lower in HF with PB compared to those without PB[44]. Delayed generation of respiratory and pulmonary blood flow oscillations during exercise compared to LVEF fluctuations in HF patients also supports delayed circulation causing alterations in respiratory feedback mechanisms[45].

In a study of 56 HFrEF patients, those with EOV demonstrated a greater degree of hemodynamic impairment both at rest and during exercise and had 25% lower cumulative CI compared to HF patients without EOV[8]. The amplitude and duration of oscillations were inversely related to exercise CI, and the changes in cycle length and amplitude of EOV after 12 wk of treatment with sildenafil were inversely related to changes in CI[8]. In another small study (n = 17, age 68 ± 12 years), patients with advanced HF, as reflected by a lower peak VO_2 and higher V_E/VCO_2 slope, had a longer cycle length of ventilatory oscillations and a longer phase difference between oscillating VO_2 and V_E[46]. Attenuation of EOV during high-intensity exercise could be due to increased CI during exercise leading to reduced circulation time which supports circulatory delay as an important determining factor for the generation of EOV. However, some investigators have argued against contribution of circulatory delay to EOV but did not directly measure cardiac output or circulation time[45].

Increased chemosensitivity: Increased carotid and aortic chemoreceptor sensitivity to minimal changes in arterial O_2 and CO_2 may contribute to sympathetic overactivity which leads to excessive and irregular ventilation during exercise[47]. Enhanced hypoxic and central hypercapneic chemosensitivity may cause increased ventilatory response (V_E/VCO_2) to exercise in HF patients[48]. Such chronically increased ventilation causes reduction in arterial concentration of both CO_2 and bicarbonate[49] which weakens the blood's ability to buffer against changes in CO_2 levels leading to overly sensitive ventilatory control system. Pitt *et al*[50] in 1907 observed that a modest increase in partial pressure of CO_2 triggers a cycle of hyperventilation-induced reduction in $PaCO_2$ until the apnea threshold is reached leading to Cheyne-Stokes breathing. In a quantitative algebraic analysis of the dynamic cardiorespiratory physiology, circulatory delay and increased chemoreflex gain were found to be the primary factors causing EOV[47]. In both experimental cat models and stable HF patients, inhalation of 100% O_2 decreased the peripheral chemoreceptor discharge and thus oscillatory ventilation[34,42]. Steens *et al*[51] noticed that inhalation of 3% CO_2 virtually eradicated Cheyne Stokes Respiration in HFrEF patients with stable NYHA class Ⅲ-Ⅳ symptoms. Similarly dihydrocodeine attenuated PB by reducing chemosensitivity in 42% of HF patients[34].

Despite the proposed mechanism of increased peripheral chemoreceptor sensitivity causing EOV, there may be other non-peripheral chemoreceptor mediated

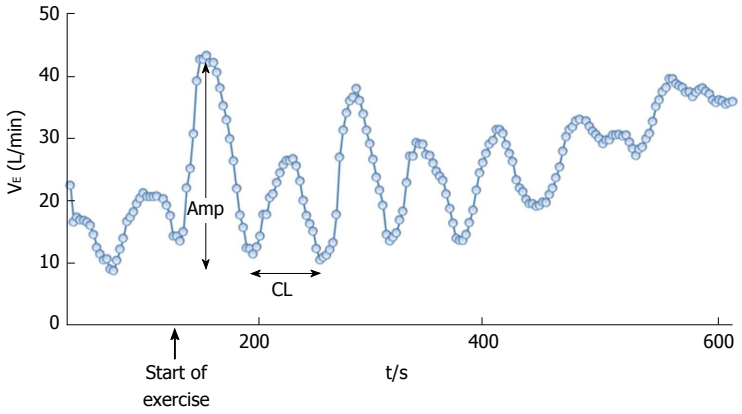

Figure 2 Oscillatory ventilation during exercise. CL: Cycle length; Amp: Amplitude of oscillation; V_E: Ventilation.

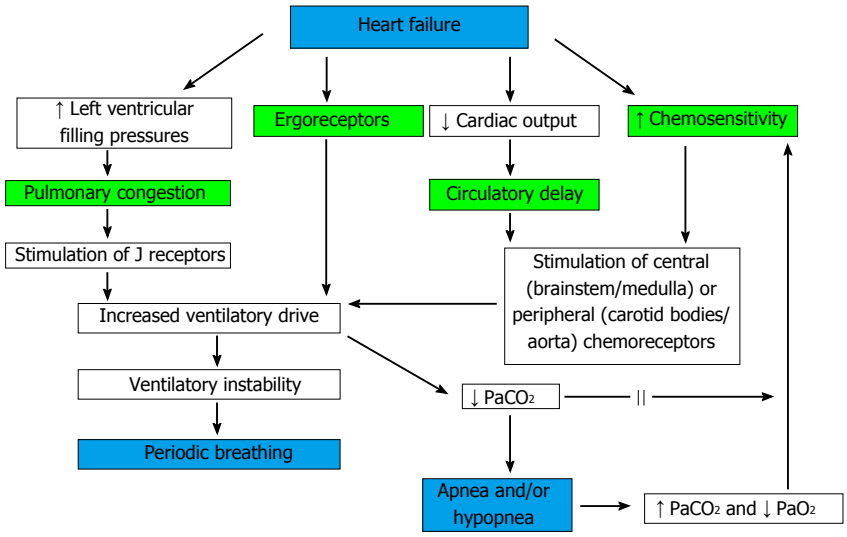

Figure 3 Mechanisms of generation of periodic breathing in heart failure patients.

mechanisms involved in mediating increased ventilatory response to exercise[52]. In one study of HFrEF patients, arterial blood gases ($PaCO_2$ and PaO_2) at rest and average values across the first 6 min of exercise in HF patients had no relationship with EOV[8]. The amplitude and duration of EOV was also not related to mean $PaCO_2$ which argues against a $PaCO_2$ set point close to the apnea threshold, serving as a major determinant of the presence of EOV in HF patients[8].

Pulmonary congestion: Pulmonary congestion[53] and decreased lung compliance[54] has been postulated to cause overstimulation of the ventilatory control center which leads to hyperventilation and decrease in PCO_2[55] and thus generating PB. Elevated pulmonary capillary wedge pressure, a surrogate marker for pulmonary congestion, stretches pulmonary C fibers (J receptors)[56] which in turn stimulates the medullary respiratory center *via* vagal afferents[57], leading to rapid shallow breathing, hypocapnia, and initiation of PB at rest. The damping effects of O_2 and CO_2 stores which prevent oscillations are also reduced by pulmonary congestion and a small fluctuation in CO_2 level makes the respiratory control unstable in HF patients with pulmonary congestion[37]. In 1943, Christie *et al*[58] were able to induce PB due to pulmonary congestion by occluding a pulmonary vein. Recent findings of increased resting and exercise cardiac filling pressures[8,30] and higher NT-proBNP[30] levels in HF patients with EOV compared to those without EOV extends their findings. Despite these findings suggestive of role of pulmonary congestion as the etiology for EOV, this mechanism has been questioned by some investigators[45] which noticed disappearance of EOV during later exercise in HF patients despite an increase in PCWP.

Ergoreflex signaling: HF causes metabolic and structural abnormalities in the skeletal muscles which may also lead to enhanced ergoreflex signaling during exercise which has been postulated as an etiologic factor for generation of PB. Increased ergoreflex may be associated with worse NYHA class, decreased exercise tolerance, and hyperventilation during exercise in HF patients[59-61]. In a study by Pardaens *et al*[62], ergoreflex

activity contributed to hyperventilation in HF patients with a history of recent decompensation or persistent symptoms. Oscillations in output of neurologic stimuli from the medullary vasomotor center may explain disappearance of respiratory oscillations found at rest or at low levels of exercise during more intense exercise[43]. Decreased activation of both CO_2 chemoreflex and the ergoreflex has recently been shown to decrease ventilatory drive after cardiac resynchronization therapy[63]. Despite the proposed contribution of ergoreceptors to the autonomic, hemodynamic, and respiratory responses to exercise in HF patients, further investigation is needed to establish its relationship to hyperventilation and EOV in HF patients.

Prognostic Significance of EOV

It has been well known that the prevalence of EOV tracks with the metrics of HF severity such as higher NYHA class, lower peak VO_2, higher V_E/VCO_2 slopes and lower $PETCO_2$[8,12,13,15,16,24,28-30,64-69] (Table 1). EOV actually provides strong independent prognostic information regarding the severity of HF even after adjustment for these variables. The initial study describing the prognostic significance of PB by Ponikowski *et al*[34] predicted poor 2-year survival in HF patients with abnormal breathing patterns which was independent of peak VO_2 and NYHA class. Similarly Bard *et al*[17] also observed resting ventilatory variation to be the best predictor of mortality in 44 matched HFrEF patients. Leite *et al*[15] and Corrà *et al*[10,13] both found that HF patients with EOV had 3-fold higher mortality compared to those without EOV (Table 1). When EOV is present along with other abnormal ventilatory patterns either during sleep or during exercise, the risk of mortality increases even further as those observed by Corrà *et al*[13] in a group of HF patients who had abnormal breathing patterns during sleep and EOV during exercise (54% adverse events in patients with EOV and apnea hypopnea index > 30/h *vs* 17% with EOV alone, OR = 6.65, 95%CI: 2.6-17.1, $P < 0.01$). Similarly the odds of dying in 6 mo increased by 4-fold (9.4 to 38.9) when EOV was present along with elevated V_E/VCO_2 slope in another group of HF patients[24]. EOV is not only known to be the independent predictor of overall mortality and sudden cardiac death in HFrEF patients but also the strongest predictor of mortality in HFpEF patients in multivariate models[9]. Ingle *et al*[28] observed EOV to be the predictor of mortality independent of peak VO_2, V_E/VCO_2 slope, LVEF, age, and 6-min walking distance. EOV has recently been recognized as a potent prognostic indicator in patients with congenital heart disease as EOV along with the percentage of maximum predicted HR were independent predictors of the combined outcome of death, transplantation or cardiovascular hospitalization in patients who underwent Fontan procedure[27].

The superior prognostic value of EOV and V_E/VCO_2 slope compared to peak VO_2 has been observed in multiple studies examining the relative predictive values of various CPET variables (Table 1). EOV along with other CPET derived variables (V_E/VCO_2 slope, oxygen uptake efficiency slope and ventilatory equivalent for CO_2 nadir) has been shown to outperform the traditional Heart Failure Survival Score in predicting outcomes in patients with mild-to-moderate HF[70]. Guazzi *et al*[71] recently characterized EOV in patients with broader cardiovascular risk factors and found the EOV to be an indicator of worse CV risk factor profile in patients even without clinical manifestations of HF. The feasibility of EOV measurements during submaximal exercise during CPET makes it particularly attractive in HF population who are unable to do maximum effort exercise testing.

EOV reversibility

Various pharmacological or surgical interventions has been performed in HF patients to identify the potential reversibility of EOV but there has not been any large scale clinical trial with EOV as the primary endpoint. In a small randomized double-blind placebo controlled trial of HFrEF patients, serial assessment of EOV before and after 12 wk of sildenafil treatment showed reduction in EOV cycle length and oscillatory amplitude and increase in exercise CI in the sildenafil group compared to placebo[8]. The changes in oscillatory cycle length and amplitude after sildenafil treatment were inversely related to changes in exercise CI[8]. This finding was further supported by another study from Guazzi *et al*[18] who noted resolution of EOV in the majority of patients treated with sildenafil, although EOV was not a pre-specified endpoint in these trials with small number of study subjects ($n < 40$).

Attenuation of PB has been observed with valvular[72] and open heart surgeries, and cardiac transplantation[73]. There are few other studies involving small number of patients that showed resolution of EOV with different therapeutic interventions. For example, Ribeiro *et al*[74] noticed reduction in EOV with phosphodiesterase-3 inhibitor milrinone in three patients and Castro *et al*[75] reported reversal of EOV and improvement in NYHA class with exercise training in one HF patient despite no change in LVEF. Reversal of EOV in 71% of stable HFrEF patients has also been observed after 3 mo of outpatient exercise training program[76]. This highlights the importance of exercise therapy in both HFrEF and HFpEF patients. Recent studies have shown that inhalation of CO_2[77] and acetazolamide[77,78] treatment significantly reduced PB during exercise in HF patients. Kazimierczak *et al*[67] noticed reversal of EOV in more than 85% of the HF patients after three months of nocturnal adaptive servoventilation even though it was a very small study ($n = 8$). Finally, in an experimental study of pacing induced-CHF rabbit models, carotid body chemoreceptor denervation reduced disordered breathing patterns[79].

CLINICAL IMPLICATIONS

EOV is a significant prognostic indicator of adverse outcomes in HF patients. EOV identification at submaximal levels of exercise during CPET and the possibility of EOV reversal with HF interventions makes it a potential

Table 1 Prevalence and clinical significance of exercise oscillatory ventilation in heart failure patients

Ref.	No. of patients	NYHA class, LVEF	Prevalence of PB	Clinical and prognostic significance of EOV	Significant mortality predictors
Corrà *et al*[10], (2002)	323	NYHA 2.2 ± 0.9 LVEF 24 ± 8	12%	EOV present in 28% of nonsurvivors *vs* 9% survivors, follow-up period 22 ± 11 mo	NYHA class, LVEF, peak VO_2
Leite *et al*[15], (2003)	84	NYHA 2-4 LVEF 35 ± 7	30%	EOV independently increased the risk of death by 2.97 fold, median follow-up period of 11.3 mo	Peak VO_2, NYHA class, V_E/VCO_2 slope
Corrà *et al*[13], (2006)	133	NYHA 2.3 ± 0.7 LVEF 23 ± 7	21%	42% mortality in EOV patients *vs* 15% in non EOV, follow-up period 39 ± 11 mo	NYHA class, peak VO_2, V_E/VCO_2 slope, AHI, LVEF, lower rate of beta blocker use, peak HR
Guazzi *et al*[9], (2007)	156	NYHA 1-4 LVEF 35 ± 11	33%	EOV was the strongest predictor of overall and SCD mortality. EOV present in 100% arrhythmic and 47% nonarrhythmic deaths, follow-up period 28 ± 25 mo	LV mass, LVESV. V_E/VCO_2 slope maintained a predictive value as to overall cardiac mortality and pump failure death outperforming EOV as predictor of pump failure mortality
Guazzi *et al*[18], (2008)	556 (405 HFrEF, 151 HFpEF)	NYHA 2.4 ± 0.8 in HFrEF, 2.0 ± 0.9 in HFpEF	35% in HFrEF, 31% in HFpEF	EOV was strongest predictor of mortality in HFpEF compared to HFrEF in multivariate models; EOV was similar predictor of mortality in both HFrEF and HFpEF without LVAD or transplant	V_E/VCO_2 slope in multivariate model, peak VO_2 in univariate model
Arena *et al*[16], (2008)	154	NYHA 2.2 LVEF 30 ± 14	36%	Event (death, transplant or LVAD) free survival 55% in EOV *vs* 82% in non EOV patients, follow-up period 3 yr	V_E/VCO_2 slope, LVEF
Bard *et al*[17], (2008)	44	LVEF 19 ± 7	13%	Death or transplant rate 68% in patients with PB *vs* 52% without PB	Resting ventilatory variation more powerful predictor of mortality than peak VO_2 and V_E/VCO_2 slope
Olson *et al*[29], (2008)	47	NYHA 2.6 ± 0.8 LVEF 37 ± 17	7%	EOV associated with higher V_E/VCO_2 slope, V_D/V_T, lower $PETCO_2$, higher NYHA class	
Ingle *et al*[28], (2009)	240	LVEF 34 ± 6	31% by Leite and 25% by Corrá Criteria	50% of patients diagnosed with EOV by Corrá criteria and 58% diagnosed by Leite criteria died within 1 yr	
Sun *et al*[24], (2010)	580	NYHA 2-4 LVEF 26 ± 7	51%	EOV combined with elevated V_E/VCO_2 (≥ 155% predicted) resulted in an OR of 39 for 6 mo mortality	Peak VO_2, AT, peak oxygen pulse significantly worse in nonsurvivors
Ueshima *et al*[68], (2010)	50	NYHA 1-3	28%	EOV associated with lower peak VO_2 and higher V_D/V_T	
Murphy *et al*[8], (2011)	56	NYHA 2-4 LVEF 30 ± 6	45%	EOV related to ↓exercise cardiac output and ↑cardiac filling pressures	
Scardovi *et al*[31], (2012)	370	NYHA 1-3 LVEF 41% (range 34%-50%)	58%	EOV, V_E/VCO_2 slope and its ratio to peak VO_2 predicted all-cause mortality independent of LVEF	Hemoglobin level, creatinine, BMI, HF admissions in the previous year
Matsuki *et al*[30], 2013	46	NYHA 3 LVEF 41 ± 16	44%	EOV patients had ↑cardiac filling pressures, higher NT-proBNP value, ↑V_E/VCO_2 slope, low $PETCO_2$ and greater Borg dyspnea score	
Nathan *et al*[27], (2015)	253	NYHA 1-3	38%	5 yr rate of death or transplant 14.1% in Fontan patients with EOV *vs* 4.1% of those without EOV	NYHA class, peak HR

LVEF and follow-up periods are in mean ± SD. NYHA: New York Heart Association; VO_2: Oxygen uptake; V_E: Ventilator efficiency; AHI: Apnea-hyponea index; AT: Anaerobic threshold; HR: Heart rate; LVEF: Left ventricular ejection fraction; HFrEF: HF and reduced ejection fraction; HFpEF: HF and preserved ejection fraction; HF: Heart failure; OR: Odds ratio; SCD: Sudden cardiac death; LVAD: Left ventricular assist device; LVESV: Left ventricular end systolic volume; $PETCO_2$: End tidal partial pressure of carbon dioxide; V_D/V_T: Ratio of physiologic dead space over tidal volume; BMI: Body mass index; NT-proBNP: N terminal pro brain natriuretic peptide.

surrogate end point of interest for HF clinical trials focused on improvement in gas exchange variables and exercise hemodynamics. There is still a need for HF studies with specific EOV endpoint to identify whether HF interventions such as diuretic therapy, exercise training, phosphodiesterase inhibitors, cardiac resynchronization therapy, intensification of neurohormonal blockade, cardiac surgery or other emerging therapies such as neprilysin inhibitors will successfully attenuate EOV, and if that modification translates into improvement in underlying cardiac dysfunction and clinical outcome of HF patients.

CONCLUSION

EOV is a noninvasive and reproducible exercise parameter which is easily recognizable during submaximal cardiopulmonary exercise testing. EOV has been proven to be a strong predictor of reduced survival in HF patients irrespective of the echocardiographic and gas exchange

variables. Presence of EOV in a HF patient indicates significant impairment in resting and exercise cardiac hemodynamic parameters, especially when the cycle length of EOV is longer than one minute and when EOV occurs early during exercise. HF patients presenting with EOV may therefore need an intensification of therapy to optimize cardiac hemodynamics, and improve overall symptoms and functional capacity.

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REVIEW

Prediction of atrial fibrillation development and progression: Current perspectives

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Abstract

Atrial fibrillation (AF) is the most common arrhythmia in clinical practice. Several conventional and novel predictors of AF development and progression (from paroxysmal to persistent and permanent types) have been reported. The most important predictor of AF progression is possibly the arrhythmia itself. The electrical, mechanical and structural remodeling determines the perpetuation of AF and the progression from paroxysmal to persistent and permanent forms. Common clinical scores such as the hypertension, age ≥ 75 years, transient ischemic attack or stroke, chronic obstructive pulmonary disease, and heart failure and the congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, stroke/transient ischemic attack, vascular disease, age 65-74 years, sex category scores as well as biomarkers related to inflammation may also add important information on this topic. There is now increasing evidence that even in patients with so-called lone or idiopathic AF, the arrhythmia is the manifestation of a structural atrial disease which has recently been defined and described as fibrotic atrial cardiomyopathy. Fibrosis results from a broad range of factors related to AF inducing pathologies such as cell stretch, neurohumoral activation, and oxidative stress. The extent of fibrosis as detected either by late gadolinium enhancement-magnetic resonance imaging or electroanatomic voltage mapping may guide the therapeutic approach based on the arrhythmia substrate. The knowledge of these risk factors may not only delay arrhythmia progression, but also reduce the arrhythmia burden in patients with first detected AF. The present review highlights on the conventional and novel risk

factors of development and progression of AF.

Key words: Atrial fibrillation; Development; Progression; Risk factors; Inflammation; Fibrosis

Core tip: Atrial fibrillation (AF) is a progressive disease associated with increased morbidity and mortality. Prevention of arrhythmia progression is therefore of paramount importance. An intense rhythm control strategy will prevent structural and electrical remodelling. The modification of common risk factors of AF development and progression such as hypertension, obesity, and sleep apnoea should be additionally considered. Emerging risk factors such as inflammation and fibrosis will guide the therapeutic approach in the future.

Vlachos K, Letsas KP, Korantzopoulos P, Liu T, Georgopoulos S, Bakalakos A, Karamichalakis N, Xydonas S, Efremidis M, Sideris A. Prediction of atrial fibrillation development and progression: Current perspectives. *World J Cardiol* 2016; 8(3): 267-276 Available from: URL: http://www.wjgnet.com/1949-8462/full/v8/i3/267.htm DOI: http://dx.doi.org/10.4330/wjc.v8.i3.267

INTRODUCTION

Atrial fibrillation (AF) is the most common arrhythmia managed in clinical practice and its incidence increases sharply with age[1]. AF is associated with increased morbidity and mortality that primarily occur as a result of 2 complications: Stroke and heart failure (HF)[2]. Mortality is increased because of a combination of altered hemodynamics, atrioventricular dyssynchrony, progressive atrial and ventricular mechanical dysfunction, and thromboembolic complications. The current evidence indicates that the overall prevalence of AF is in the range of 1%-2% of the general population[3]. Its prevalence is expected to double in the next 50 years as a consequence of prolongation of life[4]. Significant interest has been directed to risk factors predicting the progression of paroxysmal to permanent AF. The knowledge of these risk factors may not only delay AF progression, but also reduce the arrhythmia burden in patients with first detected AF. The present review highlights on conventional and novel risk factors of development and progression of AF.

DEFINITION OF AF

The American College of Cardiology, the American Heart Association, the Asia Pacific Heart Rhythm Society, the European Cardiac Arrhythmia Society, the European Heart Rhythm Association, the Society of Thoracic Surgeons, and the Heart Rhythm Society classified AF as paroxysmal, persistent, longstanding persistent and permanent AF[5]. Paroxysmal AF is defined as recurrent AF (2 episodes) that terminates spontaneously within 7 d. Episodes of AF of 48 h duration that are terminated with electrical or pharmacologic cardioversion should also be classified as paroxysmal AF episodes. Persistent AF is defined as continuous AF that is sustained beyond 7 d. Episodes of AF in which a decision is made to electrically or pharmacologically cardiovert the patient after 48 h of AF, but prior to 7 d, should also be classified as persistent AF episodes. Longstanding persistent AF is defined as continuous AF of greater than 12 mo duration. The term permanent AF is not appropriate in the context of patients undergoing catheter or surgical ablation of AF, as it refers to a group of patients for which a decision has been made not to restore or maintain sinus rhythm by any means, including catheter or surgical ablation. If a patient previously classified as having permanent AF is to undergo catheter or surgical ablation, the AF should be reclassified.

CONVENTIONAL AND NOVEL RISK FACTORS OF AF DEVELOPMENT AND PROGRESSION

The development and progression from paroxysmal to persistent and longstanding persistent AF has many risk factors[6]. Several conventional and novel risk factors have been proposed (Table 1).

AF begets AF

The most important predictor of AF progression is possibly AF itself[7]. At an early stage, AF determines an atrial electrophysiological, mechanical and structural atrial remodeling by shortening, mismatching and lengthening the atrial effective refractory periods (increase of dispersion) and by the depression of intra-atrial conduction and the loss of contractile function. The electrical, mechanical and structural remodeling determines the perpetuation of AF and the progression from paroxysmal to persistent and permanent forms. The longer one waits to initiate a rhythm treatment strategy, the more difficult it is to regain sinus rhythm. Dittrich *et al*[8] showed that patients who converted to sinus rhythm within 3 mo of onset of AF were more likely to maintain sinus rhythm at 6 mo than patients who converted more than 12 mo after onset of AF (67% *vs* 27%). By shortening the atrial refractory period, reducing conduction velocity and provoking contractile and structural remodeling, AF provokes AF[9].

Valvular heart disease

Almost any valvular lesion that leads to significant stenosis or regurgitation is associated with the development of AF. In patients with degenerative mitral regurgitation in sinus rhythm at diagnosis, the incidence of AF occurring under conservative management is high and similar whether the cause of mitral regurgitation is flail leaflet or simple mitral valve prolapse. After onset of AF,

Table 1 Conventional and novel risk factors for atrial fibrillation development and progression

Well-established risk factors
AF (AF begets AF)
Valvular heart disease
Hypertension
Coronary artery disease
Heart failure
Left atrial dilatation
Diabetes mellitus
Advancing age
Sex (male)
Congenital heart disease
Acute pericarditis
Hyperthyroidism
Alcohol consumption
Less-established risk factors
Obstructive pulmonary disease
Obstructive sleep apnea syndrome
Obesity
Left ventricular diastolic dysfunction
Atrial conduction delay (PR interval prolongation)
Genetic factors
Ethnicity
Emerging risk factors
Chronic kidney disease
Fibrosis
Inflammation
Elevated natriuretic peptides

AF: Atrial fibrillation.

an increased cardiac mortality and morbidity are both observed under conservative management[10]. Rheumatic heart disease is now uncommon in developed countries. It is, however, associated with high prevalence of AF. The highest frequency of AF in rheumatic heart disease occurs in those with mitral stenosis, mitral regurgitation, and tricuspid regurgitation in combination. AF, while occurring in 29% of patients with isolated mitral stenosis and in 16% with isolated mitral regurgitation, is an infrequent finding (1%) in patients with aortic valvular disease[11]. In addition, John *et al*[12] compared patients with mitral stenosis with 24 control patients. Patients with mitral stenosis showed, not only left atrial enlargement, but also a significantly reduced biatrial voltage (left atrium 1.8 + 0.6 mV *vs* 3.6 + 0.6 mV, right atrium 1.9 + 0.6 mV *vs* 3.3 + 0.5 mV), reduced conduction velocity, and prolonged effective refractory periods. These abnormalities may clearly play a role in the increased propensity to AF in patients with mitral stenosis.

Hypertensive heart disease

The association between hypertension and AF is well established. A history of hypertension increases 1.42-fold the risk of developing AF[13]. Although the increase in risk is relatively modest (relative risk, 1.2-1.5), the high prevalence of hypertension in the general population renders it the most significant population-attributable risk factor for AF beyond age and sex. It is observed that hypertension is responsible for 14% of all cases of AF[14]. Although overt systolic hypertension is strongly related with the progression of AF, recent studies demonstrated that systolic blood pressure in the prehypertensive range (130-139 mmHg) and widened pulse pressure are also associated with increased incidence of AF[15,16]. Mean arterial pressure does not seem to be related with AF.

Coronary artery disease

AF occurs transiently in 6%-10% of patients with acute myocardial infarction, presumably due to atrial ischemia or atrial stretching secondrary to HF[17]. These patients have a worse prognosis that is mostly due to comorbidities such as older age and HF. The Coronary Artery Surgical study which included 18000 patients showed that the incidence of AF is much lower (0.6%) in patients with chronic stable coronary artery disease (CAD)[16]. These patients probably had chronic AF; the prevalence of paroxysmal AF may be higher. AF was an independent predictor of increased mortality in patients with stable CAD[18]. Coronary artery disease can promote AF *via* multiple mechanisms. Myocardial infarction often causes substantial left ventricular dysfunction and HF predisposing to AF. Acute atrial ischemia/injury promotes AF by causing important atrial conduction disturbances, likely related to impaired cell-to-cell coupling[19]. Healed atrial infarctions and persistent ischemia enhances AF by causing Ca^{2+} - handling abnormalities, resulting in delayed afterdepolarizations and triggered activity resulting in ectopic firing, along with structural remodeling and reentry[20]. Chronic atrial coronary artery occlusion in conjunction with autonomic activity promotes ectopic firing and AF.

Age and sex

Aging is accompanied by atrial structural remodeling associated with substantial conduction abnormalities[21]. Gaborit *et al*[22] showed that men have greater expression of important repolarizing ion channel subunits, which could enhance atrial repolarization, shorten atrial refractoriness, and favor reentry. Moreover, men have greater left atrial dimensions that could promote AF maintenance[23].

Diabetes mellitus

Diabetes mellitus is an independent determinant of AF prevalence but predicted incidence only among women[24]. Over a mean follow-up of 7.2 years, diabetic patients without AF at baseline developed AF at an age/sex-adjusted rate of 9.1/1000 person-years, compared with 6.6/1000 person years among non-diabetic patients. Diabetes mellitus was associated with 26% increased risk of AF among women, but diabetes was not a statistically significant factor among men. Diabetes mellitus elicits AF *via* both structural remodeling, mediated by advanced glycosylation end products[25] and autonomic nervous system remodeling[26].

HF

AF and HF often occur together and each may predispose to the other. There is continuing controversy as to whether HF is merely a common coexisting condition among patients with AF or whether it is a true causative

factor. Among patients with HF, the prevalence of AF is variable, depending in part upon the severity of HF. The association is not limited to systolic left ventricular dysfunction but also AF is combined with diastolic dysfunction of the left ventricle[27]. Isolated diastolic dysfunction is associated with an increased AF incidence, possibly reflecting shared risk factors such as advancing age and hypertension. Although the association between AF and HF is well established, the causative relationship between the two has not been fully elucidated. Probably, AF can cause reductions in cardiac output (because of shorter diastolic filling time, loss of atrial contractile function, and elevated filling pressures) and tachycardia-induced cardiomyopathy[28]. HF results in structural and electrical remodeling changes that predispose to AF.

Hypertrophic cardiomyopathy

AF has been reported in 10%-28% of patients with hypertrophic cardiomyopathy (HCM)[29]. AF is the most common arrhythmia in patients with HCM. Olivotto *et al*[30] evaluated 480 patients with HCM with a mean follow-up of 9.1 years and found the prevalence of AF to be 22%. More recently, a study in Japan examined 261 patients with HCM and found that 74 (28%) patients had documented paroxysmal AF or permanent AF[31]. The high prevalence of AF in HCM is related to atrial dilation and remodeling in the setting of diastolic dysfunction, mitral regurgitation, and atrial fibrosis[30,31]. AF is an important prognostic indicator in patients with HCM, because these patients are typically at a higher New York Heart Association functional class and have a poorer outcome. This subgroup of patients with HCM is at an increased risk of cardiovascular morbidity and mortality in the form of thromboembolic events, HF, and sudden death[32]. In a systematic review, Kumar *et al*[33] reported that in HCM brain natriuretic peptide, left atrial size (left atrial volume measured with cardiac magnetic resonance), higher left atrial mean extent of late gadolinium enhancement in cardiac magnetic resonance, left ventricular myocardial fibrosis determined by delayed contrast enhancement, sleep apnea, longer *P*-wave duration, genetic factors, and ischemia are associated with AF progression.

Dilated cardiomyopathy

AF is common in patients with dilated cardiomyopathy (DCM). Epidemiologic studies have shown that 30%-40% of patients with left ventricular dysfunction and systolic HF from any cause will develop AF during the course of their disease, and AF has been associated with increased morbidity and mortality[34-36]. In experimental subjects, the increased incident of AF is associated with atrial structural abnormalities, with increased atrial fibrosis associated with slowing conduction of velocity and conduction heterogeneity[37]. In humans, Sanders *et al*[38] also showed that AF in patients with left ventricular dysfunction is associated with widespread areas of low voltage and electrical silence consistent with scar, and with regional atrial conduction slowing with prolongation of the *P*-wave duration, in addition to altered sinus node function. Pulmonary veins are responsible for arrhythmia initiation[39]. Atrial electrical and structural remodeling outside the pulmonary veins is the substrate of maintenance of persistent AF. Rotors, or high-frequency sources within the atrium, have been recently proposed as mechanisms for both initiation and maintenance of persistent AF[40].

Peripartum cardiomyopathy

In 2007, the European Society of Cardiology working group on myocardial and pericardial diseases redefined cardiomyopathies including peripartum cardiomyopathy (PPCM), which it is defined as a form of DCM that presents with signs of cardiac failure during the last month of pregnancy or within 5 mo of delivery[41]. Limited data regarding the association of PPCM and AF exist in the literature. Biteker *et al*[42] studied 42 women with PPCM. Five of them (11.9%) had AF and AF had no apparent effect on survival or recovery of left ventricular function. Kane *et al*[43] examined 33 women with PPCM and 1 (3%) of them had AF. Finally, Isezuo and Abubakar[44] showed that 2 out of 65 women (3.1%) developed AF strengthening the observation that PPCM is associated with AF.

Chronic kidney disease

AF is more prevalent in patients with chronic renal dysfunction (CRD). AF risk increases with severity of kidney dysfunction (HR of 1.3-1.6 and 1.6-3.2 with an estimated glomerular filtration rate of 30-59 and < 30 mL/min per 1.73 m^2, respectively, *vs* estimated glomerular filtration rate ≥ 60 mL/min per 1.73 m^2)[45]. These two entities (AF and CRD) share common associated factors such as coronary heart disease, HF, hypertension, left ventricular hypertrophy and systemic inflammation. In addition, macroalbuminuria and microalbuminuria were significantly associated with higher AF risk.

Sleep apnea and obesity

Accumulating data have demonstrated a clear and significant association between obstructive sleep apnea (OSA) and AF[46,47]. The occurrence of AF in 400 middle-aged patients who had moderate or severe OSA (apnea-hypopnea index ≥ 25) was more than 3%. Furthermore, twelve of the study patients who underwent tracheostomy, bypassing the obstructed airway, had complete elimination of AF up to 6 mo later, something that clearly shows the straight correlation between AF and OSA[46]. In the largest registry until now, Gami *et al*[47] showed that OSA and AF were significantly associated. Body mass index and the decrease in nocturnal oxygen saturation were independent predictors of AF. This study, also, proves the correlation between obesity and AF. Multiple pathophysiological pathways link OSA with AF. Increased left atrial size, hypertension and diastolic dysfunction may coexist in OSA and AF[48]. AF probably occurs as a complex interaction of several hemodynamic and sympathetic consequences of OSA.

These include autonomic dysregulation[49], elevated sympathetic tone, oxidative stresses, endothelial dysfunction, and left atrial stretch[50]. OSA is associated with systemic inflammation, increased levels of C-reactive protein (CRP), serum amyloid A, and interleukins[51]. These observations makes us believe that OSA and AF share common pathways, which contribute to atrial fibrosis and structural and electrical remodeling. Finally, Al Chekakie *et al*[52] showed that central obesity and pericardial fat is associated with AF. Pericardial adipose tissue contributes to inflammation and progression to AF. Patients with paroxysmal AF had significantly greater pericardial fat volume on average than patients in sinus rhythm (93.9 mL *vs* 76.1 mL) and the persistent AF patients had a significantly larger volume of pericardial fat volume on average than the paroxysmal AF patients (115.4 mL *vs* 93.9 mL).

Congenital heart disease

AF has been reported in approximately 20% of adults with an arial septal defect[53]. AF and atrial flutter also occurs in other forms of congenital heart disease that affect the atria, including Ebstein's anomaly[54] and patent ductus arteriosus[55], and after surgical correction of some other abnormalities, including ventricular septal defect, tetralogy of Fallot, pulmonary valve stenosis, and transposition of the great vessels.

Hyperthyroidism

Patients with hyperthyroidism have an increased risk of AF progression[56]. Frost *et al*[57] showed that among 40628 patients with clinical hyperthyroidism, 8.3% had AF or atrial flutter. Increased beta adrenergic tone play a crucial role for the development of AF in hyperthyroidism, often combined with rapid ventricular response. Furthermore, hyperthyroidism increases the likelihood of AF in experimental models, even in the presence of beta receptor and vagal blockade[58]. The pathophysiology remains unknown, but may be related to an increased automaticity and enhanced triggered activity of pulmonary vein cardiomyocytes[59]. The risk for development of AF is also increased in patients with subclinical hyperthyroidism[60,61]. It remains controversial whether patients with AF associated with previous treated thyrotoxicosis are at increased risk of thromboembolism, in the absence of other known risk factors[62].

Other clinical risk factors

AF is associated with a variety of other types of cardiopulmonary disease. AF is seen in 10% to 14% of patients with documented pulmonary embolism[63]. AF also occurs in chronic obstructive pulmonary disease[64], myocarditis[65] and acute pericarditis[66]. In addition, electrolytic disturbances like hypokalemia or low serum magnesium[67] initiates AF. Alcohol consumption contributes, also, to the development of AF[68]. Finally, prior surgery, especially and coronary artery bypass grafting[69] predispose to AF.

CLINICAL RISK SCORES FOR PREDICTION OF AF DEVELOPMENT AND PROGRESSION

The HATCH score [hypertension - age (75 years and older) - transient ischemic attack or stroke (2 points) - chronic obstructive pulmonary disease - HF (2 points)] allows an instant classification of the risk of progression to persistent or permanent AF in patients with paroxysmal AF[70]. de Vos *et al*[70] showed that nearly 50% of the patients with a HATCH score more than 5 progressed persistent AF, compared with only 6% of the patients with a HATCH score of 0. Malik *et al*[71] described LADS score [left atrial diameter (0-2 points), age (0-2 points), diagnosis of stroke (0-1 point), and smoking status currently (0-1 point)], a 6-point scoring system. A score of 4 or greater was associated with a sensitivity of 85.5% and a specificity of 53.1% for progression AF. CHADS2 score [one point each for age > 75 years, hypertension, diabetes and HF or low ejection fraction, and two points for history of prior stroke or transient ischemic attack (TIA)] and CHA2DS2-VASc score [congestive HF (1 point), hypertension (1 point), diabetes mellitus (1 point), history of stroke, TIA or thromboembolism (2 points), vascular disease (history of myocardial infarction, peripheral vascular disease or aortic atherosclerosis) (1 point), age 65-74 years old (1 point), age > 75 years old (2 points), sex male (0 points), female (1 point)] has been shown to be associated with post-ablation AF recurrences[5]. Letsas *et al*[72] examined 126 patients with symptomatic paroxysmal AF who underwent left atrial ablation. Over 16 mo, 89 patients were recurrence-free (70.6%). In the multivariate analysis, both CHADS2 and CHA2DS2-VASc score were independently associated with AF recurrence. Cut-off analysis showed that a score ≥ 2 for both CHADS2 and CHA2DS2-VASc scores showed the highest predictive value for AF recurrence.

BIOMARKERS FOR PREDICTION OF AF DEVELOPMENT AND PROGRESSION

Several biomarkers have been proposed as predictors of occurrence and progression of AF. Bruins *et al*[73] were the first to propose a direct link between inflammation and AF by observing an increased frequency of AF after coronary artery bypass surgery, where AF occurred on the second and third postoperative day coinciding with the peak elevation of CRP. CRP is an acute phase protein, which is directly related to inflammation. Raised levels of CRP have been noted to be higher among patients with AF when compared with patients in sinus rhythm[74]. Persistent AF patients have a higher CRP than paroxysmal AF patients, and both groups have a higher CRP than controls. Furthermore, CRP is considered as a significant predictor of early AF relapse after successful cardioversion, even after adjustment for multiple risk factors, such as hypertension and coronary artery disease[75]. Microalbuminuria combined with an elevated

CRP raises fourfold the risk of AF[76]. Korantzopoulos *et al*[77] presented data from a study of 30 AF patients undergoing cardioversion. Patients with arrhythmia relapse exhibited an increase in fibrinogen levels compared with those who remained in sinus rhythm. In addition, there was a trend to reduced CRP levels among those patients who were successfully cardioverted compared with those who relapsed. IL-6 plays a key role in inflammation and to the progression of AF. Gaudino *et al*[78] showed that a 174G/C polymorphism of the promoter of the *IL-6* gene appears to influence the development of postoperative AF supporting the role of inflammation in the development of postoperative AF. The importance of troponin, as a biomarker, in an AF population was first described in a substudy of RELY trial[79]. The results indicated that troponin Ⅰ levels ≥ 0.01 mg/L were seen in 55% of the 6189 patients with AF and at least one risk factor for stroke. Troponin was significantly and independently associated with increased risk of stroke, systemic embolism and cardiovascular death. These results were in concordance with the ARISTOTLE biomarker study where 14892 patients with AF were treated either with apixaban or warfarin in order to reduce the risk of stroke[80]. The ARISTOTLE troponin substudy results proved that the troponin levels were related to the risk of thrombo-embolic events and cardiovascular death. Other biomarkers which are increased in wall tension such as volume or pressure overload and are related with AF is B-type natriuretic peptide (BNP) and N-terminal fragment (NT-proBNP). Ellinor *et al*[81] first described that patients with AF had elevated levels of natriuretic peptides compared with matched controls in sinus rhythm. The levels of natriuretic peptides fall rapidly following restoration of sinus rhythm[82]. Patton *et al*[83] recently reported that elevated NT-proBNP levels predict an increased risk of development of AF independent of other risk factors including echocardiographic parameters. In addition, a substudy of the RELY trial showed that the level of NT-proBNP was associated with the risk of thrombo-embolic events and cardiovascular mortality[79]. Plasma D-dimer is a marker of fibrin turnover, and is used as an index of thrombogenesis. A substudy of the ARISTOTLE trial showed that D-dimer levels were a predictor of stroke, mortality and major bleeding[84].

IMAGING FOR PREDICTION OF AF DEVELOPMENT ANA PROGRESSION

Echocardiographic parameters

Left atrial size is a well-known predictor of AF development. A left atrial size greater than 4 cm has been associated with a significantly higher AF recurrence rate[85]. The left atrial volume measured by transthoracic echocardiography is possibly superior to left atrial diameter in predicting progression to persistent AF[86]. Li *et al*[87] reported that the E/e' index (E, early transmitral flow velocity; e', early diastolic mitral annular velocity), an index of diastolic dysfunction, was the best independent predictor of AF recurrence after catheter ablation. E/e' > 11.2 before ablation has been associated with AF recurrence. Shaikh *et al*[88] showed that speckle left atrial strain and stiffness index can predict the possibility of maintenance in sinus rhythm after cardioversion for AF. Changes in longitudinal left atrial strain (peak systolic longitudinal strain) after cardioversion were significantly higher among individuals who remained in sinus rhythm when compared to individuals with recurrent AF[88].

Magnetic resonance imaging and voltage mapping

Late gadolinium enhancement-magnetic resonance imaging (LGE-MRI) allows the direct visualization of atrial arrhythmic substrate. Vergara *et al*[89] described a new staging system for AF based on the amount of left atrial enhancement on LGE-MRI, the Utah score (Utah Ⅰ ≤ 5%, Utah Ⅱ > 5%-20%, Utah Ⅲ > 20%-35%, and Utah Ⅳ > 35%). On the basis of patient stage, a more tailored approach to AF management can be taken. Patients with a previous stroke had a significantly higher percentage of left atrial fibrosis compared with those without (24.4% ± 12.4% *vs* 16.1% ± 9.8%, $P \leq 0.001$). There was a significant difference in the rate of thromboembolism between patients with stage Ⅰ and those with stage Ⅳ of atrial remodeling as assessed by LGE-MRI. In addition patients with CHADS2 score ≥ 2 had higher amounts of left atrial fibrosis. The DECAAF study showed that left atrial fibrosis contributes to the progression of AF. The more fibrosis there is, the more likely the arrhythmia will persist following ablation[90]. Atrial fibrosis estimated by LGE-MRI in 260 AF patients, including 65% with paroxysmal AF, was a significant predictor of recurrence. Each 1% increase in fibrosis was associated with a 6% increased risk of recurrence. Fibrosis was categorized as stage 1 (< 10% of the atrial wall), 2 (≥ 10%-< 20%), 3 (≥ 20%-< 30%), and 4 (≥ 30%). At one year, 88% of patients with stage 1 fibrosis were free of AF. For those with stage 2, 3, or 4 fibrosis, 69%, 55%, and 45% were free of recurrence at one year, respectively. At 475 d, 86%, 64%, 51%, and 35% of those with stage 1, 2, 3, and 4 fibrosis were free of AF, respectively. Electroanatomic bipolar voltage mapping has proved to have great correlation with DE-MRI. Jadidi *et al*[91] have demonstrated bipolar voltages of 0.63 ± 0.8 in dense DE-CMRI areas, compared with 0.86 ± 0.89 in non DE-MRI areas. Moreover, Spragg *et al*[92] have demonstrated that the mean atrial voltage in areas identified as scar by DE-MRI was 0.39 ± 0.61 mV, while in areas identified as normal by DE-CMRI was 1.38 ± 1.23 mV.

There is now increasing evidence that even in patients with so-called lone or idiopathic AF, the AF is an arrhythmic manifestation of a structural atrial disease which has recently been defined and described as fibrotic atrial cardiomyopathy (FACM). Different expressions can be found from mild (FACM Ⅰ), moderate (FACM Ⅱ) to excessive fibrosis (FACM Ⅲ), and wide clinical variations from asymptomatic to multiple arrhythmic

manifestations (including AF, left and/or right atrial re-entrant tachycardia, sinus, and/or atrioventricular node disease)[93]. Fibrosis results from a broad range of factors related to AF inducing pathologies such as cell stretch, neurohumoral activation, oxidative stress, and possibly even AF itself[94]. Stiles *et al*[95] investigated 25 patients with "lone" AF, during an electrophysiological study after at least 7 d in sinus rhythm, and found slower conduction velocity, longer effective refractory periods, and significantly lower voltages (left atrium 1.7 + 0.7 mV *vs* 3.3 + 0.7 mV, right atrium 1.7 + 0.4 mV *vs* 2.9 + 0.4 mV) compared with control patients without AF. These findings confirm a substantial chronic structural biatrial substrate since the electrical remodelling is reversible within a few days. It might be that not all patients with paroxysmal "lone" AF have an underdetected chronic substrate, but many more than assumed. The debate is whether the fibrosis is causative or merely a result of AF. Several data suggest that fibrosis is causative and that AF-induced fibrosis may be part of the vicious cycle. In animal models, reversal or prevention of fibrosis prevents AF[96]. Furthermore, AF substrate in the absence of any cellular electrophysiological abnormalities has been demonstrated in a transgenic mouse model of isolated atrial fibrosis[97].

CONCLUSION

AF is a progressive disease associated with increased morbidity and mortality. Prevention of arrhythmia progression is therefore of paramount importance. An intense rhythm control strategy may be the first step towards this direction (sinus rhythm begets sinus rhythm). The modification of common risk factors of AF development and progression such as hypertension, obesity, and sleep apnoea should be additionally considered. Emerging risk factors such as inflammation and fibrosis will guide the therapeutic approach of AF in the future.

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MINIREVIEWS

Tilt table test today - state of the art

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Abstract

A tilt table test (TTT) is an inexpensive, noninvasive tool for the differential diagnosis of syncope and orthostatic intolerance and has good diagnostic yield. The autonomic system malfunction which underlines the reflex syncope is manifested as either hypotension or bradycardia, while an orthostatic challenge is applied. The timing of the response to the orthostatic challenge, as well as the predominant component of the response help to differentiate between various forms of neurocardiogenic syncope, orthostatic hypotension and non-cardiovascular conditions (*e.g.*, pseudosyncope). Medications, such as isoproterenol and nitrates, may increase TTT sensitivity. Sublingual nitrates are easiest to administer without the need of venous access. TTT can be combined with carotid sinus massage to evaluate carotid sinus hypersensitivity, which may not be present in supine position. TTT is not useful to access the response to treatment. Recently, implantable loop recorders (ILR) have been used to document cardioinhibitory reflex syncope, because pacemakers are beneficial in many of these patients, especially those over 45 years of age. The stepwise use of both TTT and ILR is a promising approach in these patients. Recently, TTT has been used for indications other than syncope, such as assessment of autonomic function in Parkinson's disease and its differentiation from multiple system atrophy.

Key words: Syncope; Orthostatic intolerance; Tilt table test; Hypotension; Bradycardia

Core tip: A tilt table test (TTT) is a noninvasive tool for the differential diagnosis of syncope and orthostatic intolerance. The way of the response to the orthostatic challenge helps to differentiate between various forms of neurocardiogenic syncope, orthostatic hypotension and non-cardiovascular conditions. TTT can be combined with carotid sinus massage to evaluate carotid sinus hypersensitivity, which may not be present in supine position. Implantable loop recorders (ILR) have been used to document cardioinhibitory reflex syncope. The stepwise use of both TTT and ILR is a promising approach. TTT has been used to assessment of autonomic function in Parkinson's disease.

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INTRODUCTION

The tilt table test (TTT) was initially described by Kenny *et al*[1] in 1986 as a tool to diagnose syncope of unknown origin. Since then various protocols have been developed. The cornerstone of the test is an orthostatic challenge which is done with the upright tilt. Apart from its main use in the syncope workup, use of the test was described in the evaluation of the presence of autonomic neuropathy in a variety of conditions[2,3]. The main idea behind the test is that reflex syncope is due to the abnormal cardiac autonomic reflexes, which lead to inappropriate vasodilatation (vaso-depressive reflex syncope), inappropriate bradycardia (cardio-inhibitory reflex syncope) or a mixed response[4-6]. A prolonged upright position is a known trigger of reflex syncope, where, after an initial normal adaptation to standing, inappropriate vasodilatation or bradycardia appears, leading to symptoms. This is different from the orthostatic hypotension, where the initial response to standing is abnormal.

DEFINITION OF DIFFERENT TYPES OF ORTHOSTATIC INTOLERANCE

European Society of Cardiology guidelines on diagnosis and management of syncope describe 6 major types of syndromes of orthostatic intolerance, which may cause syncope[7] and the tilt test is useful for making a correct diagnosis. Four of them are different types of orthostatic hypotension. The initial orthostatic hypotension (up to 30 s since postural challenge) is caused by the mismatch between cardiac output and systemic vascular resistance. It usually happens either in young, thin patients or in elderly patients treated with medications or with carotid sinus hypersensitivity and is usually manifested by the fall in blood pressure associated with dizziness in rare syncopal episodes. Classic orthostatic hypotension takes from 30 s to 3 min, is caused by autonomic failure to increase the systemic vascular resistance while standing, with the resultant pooling of blood in lower extremities and subsequent fall in blood pressure. Sometimes, significant volume depletion may cause this type of orthostatic intolerance, even when autonomic reflexes function normally. This form of orthostatic hypotension usually occurs in elderly patients, or in association with vasodilator or volume depleting medications, with orthostatic dizziness as a main manifestation and infrequent syncope. Delayed orthostatic hypotension occurs between 3 and 30 min, is caused by a progressive fall in venous return, low cardiac output and diminished reflex vasoconstriction; however, there is no decrease in heart rate. This type is present in elderly patients with autonomic failure, vasoactive medications and comorbidities. It is manifested by a prolonged prodrome of dizziness, weakness, visual disturbances, chest, neck and back pain, followed by rapid syncope. Reflex (vasovagal) syncope takes 3 to 45 min of postural challenge to develop. It is characterized by an initially normal adaptation reflex, followed by a rapid vasovagal reaction with reflex vasodilation and bradycardia. It is manifested by prodrome, which includes dizziness, nausea and sweating (some symptoms are caused by autonomic activation), always followed by syncope and mostly occurring in young female patients. Post exercise syncope, which happens in the first minute after cessation of intense physical activity, is now understood to be a form of reflex syncope[8,9]. When investigating the exercise related syncope, the initial effort should concentrate on excluding cardiac causes of syncope such as hypertrophic cardiomyopathy, valvular disease, or channelopathies.

Elderly patients with comorbidities may have a combination of delayed orthostatic hypotension with reflex syncope. Postural orthostatic tachycardia syndrome (POTS) is manifested by a significant increase in heart rate (an increase of more than 30 bpm or a heart rate of 120 bpm or more) during postural challenge without a fall in blood pressure (it can be quite variable). The mechanism of POTS is incompletely understood and is associated with physical deconditioning, and it usually happens in young females.

THE DIAGNOSTIC VALUE OF TTT

The etiology of reflex syncope can be divided into its common form (vasovagal - where postural challenge or emotion causes the abnormal reflex) and to the situational syncope (where this reaction is caused by a specific trigger). The autonomic malfunction causing reflex syncope is either a vasodepressive response (loss of sympathetic vasoconstrictive tone with resultant hypotension), cardioinhibitory response (active para-sympathetic stimulation with resultant bradycardia or asystole) or a mixed response. Carotid sinus hyper-sensitivity is a special form of reflex syncope.

Young patients are more prone to cardioinhibitory syncope, whereas older individuals are more likely to have a hypotensive response[10-12]. Moreover, an individual patient may demonstrate different types of responses on different occasions.

Normal individuals may have syncope during the tilt test (false positive result). However, comparing normal people who have a positive tilt test with people who have a history of reflex syncope[13] demonstrated that patients with a history of syncope had less time to syncope, a more rapid and persistent fall in blood pressure and higher peak serum epinephrine levels. False negative results have been reported with a rate of up to 30%, so a negative result does not exclude reflex syncope. Prolonged electrocardiographic monitoring may later diagnose cardioinhibitory syncope in tilt test negative patients[10,14]. There is no good gold standard for

evaluation of vasodepressive syncope.

The test is relatively simple and requires a special tilt table (a bed which rapidly moves the patient from a supine to an upright position, while the patient is secured to it with a foot board and restraints). Before the test, orthostatic hypotension is usually excluded. Electrocardiogram and blood pressure are continuously monitored (mostly by noninvasive measurements). Various protocols have been published with the differences mainly in the degree of tilt (60 to 90 degrees), its duration and use of pharmacological enhancement.

After monitoring of the patient in the supine position for 5 to 20 min (a longer duration is required if the intravenous cannula is used)[7], the patient is moved to the upright position and kept there for 20 to 45 min. If symptoms develop in association with bradycardia or hypotension, the test is considered positive. Obviously, the patient is rapidly returned to the supine position. If hypotension or bradycardia develops without symptoms, the test is suggestive of reflex syncope. Additionally, orthostatic hypotension may be documented.

If the test is negative, isoproterenol infusion (the dose is titrated to increase the average heart rate by 25%) or sublingual nitrates are used[15,16] during a second tilt. These are used to blunt the adaptive response of the autonomic nervous system and further unmask abnormal reflexes. Both were reported to have similar sensitivity (61%-69%) and specificity (92%-94%)[15,16]. Sublingual nitrates are easier to administer because venous access is unnecessary. However, one study demonstrated that in the pediatric population, administration of nitrates *vs* isoproterenol was associated with lower sensitivity (24% *vs* 56%) and more severe cardioinhibitory response[17]. A recent study which compared 2 protocols of sublingual nitrate administration (with and without a 5 min rest period in the supine position before nitroglycerin administration) found no differences with positive test in 61% *vs* 60% and specificity of 92% *vs* 90%, respectively[18]. This may eliminate the use of the rest period and shorten the test. Another study demonstrated that the use of the nitroglycerin tablet *vs* the sublingual spray is more specific, the latter form of usage was associated with higher rate of false positive response in both syncope patients and control patients[19]. Efremov *et al*[20] evaluated heart rate variability in patients with previous syncope who underwent a head up tilt test. Changes in the heart rate variability parameters between the first and last 5 min of the passive tilt test predicted syncope after nitroglycerine administration. Thus, evaluation of the heart rate variability during a tilt test may obviate the need for nitrate administration and shorten the test with decrease of side effects; however, this will require additional data processing.

Other triggers described during the tilt table testing are carotid sinus massage and clomipramine administration. Carotid massage in an upright position may demonstrate hypersensitivity, which may not be present in the supine position. Clomipramine is an serotonin selective reuptake inhibitor, which causes increased stimulation of serotonin receptors and, subsequently, diminishes sympathetic tone. One study[21] demonstrated an increased rate of positive response in patients (80% *vs* 53%) without increase in false positive responses.

Indications for the tilt table testing include recurrent unexplained syncope in patients without structural heart disease[7], or in patients with structural heart disease when cardiac causes have been excluded. Patients with a single episode of syncope do not usually need a tilt table test, unless there are specific circumstances associated with high risk (lifestyle or occupational hazard, *etc.*). Patients who are diagnosed with reflex syncope on the initial assessment are usually not candidates for the tilt test. The test may be useful to differentiate syncope with jerking movements from epilepsy[22,23]. Reflex syncope and epilepsy may actually coexist, so in some cases electroencephalogram recording during TTT may be of value[23]. Tilt test is also useful to differentiate reflex syncope from orthostatic hypotension[24], to evaluate a patient with recurrent falls[25] and to diagnose patients with psychogenic syncope[26]. In this scenario, syncope during the TTT will not be preceded by hypotension and/or bradycardia. The TTT is not used to evaluate the response to treatment. It is also not useful to evaluate patients with specific triggers which cause syncope.

One study[27] assessed neuro-autonomic evaluation in elderly patients with syncope which was determined to be likely to be neurally mediated after baseline initial evaluation. A diagnosis was made in 64% of cases with a diagnostic tilt test in 50%, carotid sinus massage (CSM) in 12% and orthostatic hypotension in 20%. The study demonstrated that neuro-autonomic evaluation is useful in elderly patients with syncope and that a tilt test was the most important contributor to this evaluation.

Another study[28] evaluated the diagnostic yield of tests in syncope according to the ICD-10 discharge diagnosis. The final diagnosis was reflex syncope in 21%, cardiac in 18%, orthostatic hypotension in 10%, others in 4% and unexplained in 48%. While the overall diagnostic yield of tests was low, the tilt test had a diagnostic yield of 47% during the initial admission and 61% during the work up.

A tilt test can be used to evaluate postural tachycardia syndrome. However, its performance is similar to the active standing test. One recent study[29] comparing TTT to active standing (blood pressure and heart rate at the 3rd and 9th minute) demonstrated no difference in the presence of orthostatic intolerance (P = 0.786). Syncope or presyncope was induced in 35% of patients in both groups. The only difference was a slight fall in blood pressure after 9 min of the tilt test but not in the active standing test. Another study[30] which compared the active standing test and the tilt test using heart rate measurements after 10 and 30 min found that an increase in 30 bpm in the upright position had good sensitivity with either method, but was less specific with the tilt test (40% *vs* 67% at 10 min and 20% *vs* 53% at 30 min, respectively). Thus, clinical features of orthostatic intolerance together with positive active standing are

Table 1 Comparison of relative merits of tilt table test and implantable loop recorders

	TTT	ILR
Advantages	Noninvasive, nonexpensive Differentiates between reflex syncope, orthostatic hypotension, carotid sinus hypersensitivity and pseudosyncope Assesses function of autonomic system	Reliable diagnosis of arrhythmias causing presyncope or syncope
Disadvantages	Significant false negative response (up to 30%) Pharmacological chellenge may be required	Invasive Cannot assess nonarrhythmic causes of syncope

TTT: Tilt table test; ILR: Implantable loop recorder.

probably sufficient for the diagnosis, while a tilt test is not going to be contributory in this situation.

COMPARISON WITH AN IMPLANTABLE LOOP RECORDER

Implantable loop recorder (ILR) provides continuous rhythm monitoring and can capture spontaneous episodes of cardioinhibitory syncope. ILR may more precisely determine a cause-effect relationship between bradyarrhythmia and syncope and exclude the tachyarrhythmic cause of syncope[31-33]. In case of cardioinhibitory syncope, TTT is more likely to demonstrate hypotension and bradycardia and less asystole, whereas ILR recordings during spontaneous episodes usually demonstrate asystole[10]. Thus, an implantable loop recorder may be used for the diagnosis of the suspected cardioinhibitory syncope instead of the tilt test. The drawback of this approach will be high proportion of implanted pacemakers in patients with documented spontaneous asystolic events, whereas patients with a positive tilt test will be mostly reassured about the benign nature of their disease. ISSUE 3 trial, reported in 2012[34] demonstrated high efficacy of dual chamber pacing with a rate drop response programing in patients who are 40 years and older with at least 3 previous syncopal episodes with ILR documented cardioinhibitory syncope (asystole for more than 3 s) or asystole for more than 6 s without syncope. In this randomized placebo-controlled (sensing only pacemaker) trial pacing caused 32% absolute and 57% relative reduction of syncopal episodes. According to this data, it seems prudent to proceed with ILR without a TTT in individuals with recurrent syncopal episodes of an unexplained nature, or with a suggested cardioinhibitory response. Of note, later analysis of this cohort of patients demonstrated that the benefit pacing in this group of patients was much greater in patients with negative TTT, than with positive one (the type of positive response was not significant)[35]. Another recent study[36] used an algorithm with carotid sinus massage, followed by a tilt test, and, if it is not diagnostic, ILR implantation. Asystolic response in any of the tests led to pacemaker implantation. The recurrence rate in the pacemaker-implanted patients (about half of the total group) was 9% in 1 year and 15% in 2 years (with no difference between CSM, TTT or ILR positive patients) and was significantly lower than in patients with nondiagnostic ILR (22% in 1 year and 37% in 2 years). The significance of prolonged asystole (> 30 s) was evaluated in one study[37]. A total of 2263 patients underwent TTT, 6.5% had an asystole, 11 patients (0.5%) had asystole between 30 and 63 s. Avoidance of triggers and physical counterpressure maneuvers were recommended in all patients, no one received a pacemaker. Although no patient died, 4 patients (36%) had recurrent syncopal episodes after a median follow-up of 42 mo. The summary of relative merits of TT *vs* ILR is shown in Table 1.

BEYOND SYNCOPE: THE USE OF TTT TO ASSESS AUTONOMIC NERVOUS SYSTEM IN DIFFERENT DISEASES

Besides its main use for differential diagnosis of syncope, TTT has been utilized in a variety of different disorders. Recent studies[38,39] used TTT in Parkinson disease. One study[37] demonstrated that in Parkinson's disease patients orthostatic hypotension is associated with a combination of decreased peripheral vascular resistance and inability to increase stroke volume, which means that autonomic dysfunction, involves both vasoregulatory dysfunction and cardiac denervation. Patients with preserved cardiac autonomic response (increase in stroke volume while in upright position) did not have orthostatic hypotension during TTT, despite reduction in peripheral vascular resistance. Orthostatic hypotension was very infrequent (1 in 46 patients) in patients who elevated peripheral vascular resistance during TTT. Another study[39] demonstrated that TTT is useful in making a differential diagnosis between multiple system atrophy (MSA) with predominant Parkinsonism and Parkinson's disease. Autonomic dysfunction was much more prevalent in MSA; combination of TTT and Valsalva maneuver having 91% sensitivity and 92% specificity. TTT also documented abnormal autonomic responses in patients with persistent post-concussion syndrome[40], restless leg syndrome[41] and anorexia nervosa[42].

CONCLUSION

TTT is a time proven test with good diagnostic yield for the diagnosis of syncope. Because of its relatively low cost and noninvasive nature, TTT can be widely used.

Combined with an implantable loop recorder, TTT will provide valuable information for the physician caring for patients with syncope. Apart from syncope, TTT demonstrated efficiency in evaluation of autonomic nervous system in noncardiac disorders.

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ORIGINAL ARTICLE

Clinical Trials Study

Clinical outcomes of combined flow-pressure drop measurements using newly developed diagnostic endpoint: Pressure drop coefficient in patients with coronary artery dysfunction

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Abstract

AIM: To combine pressure and flow parameter, pressure drop coefficient (CDP) will result in better clinical outcomes in comparison to the fractional flow reserve (FFR) group.

METHODS: To test this hypothesis, a comparison was made between the FFR < 0.75 and CDP > 27.9 groups in this study, for the major adverse cardiac events [major adverse cardiac events (MACE): Primary outcome] and patients' quality of life (secondary outcome). Further, a comparison was also made between the survival curves for the FFR < 0.75 and CDP > 27.9 groups. Two-tailed χ^2 test proportions were performed for the comparison of

primary and secondary outcomes. Kaplan-Meier survival analysis was performed to compare the survival curves of FFR < 0.75 and CDP > 27.9 groups (MedcalcV10.2, Mariakerke, Belgium). Results were considered statistically significant for $P < 0.05$.

RESULTS: The primary outcomes (%MACE) in the FFR < 0.75 group (20%, 4 out of 20) was not statistically different ($P = 0.24$) from the %MACE occurring in CDP > 27.9 group (8.57%, 2 out of 35). Noteworthy is the reduction in the %MACE in the CDP > 27.9 group, in comparison to the FFR < 0.75 group. Further, the secondary outcomes were not statistically significant between the FFR < 0.75 and CDP > 27.9 groups. Survival analysis results suggest that the survival time for the CDP > 27.9 group ($n = 35$) is significantly higher ($P = 0.048$) in comparison to the survival time for the FFR < 0.75 group ($n = 20$). The results remained similar for a FFR = 0.80 cut-off.

CONCLUSION: Based on the above, CDP could prove to be a better diagnostic end-point for clinical revascularization decision-making in the cardiac catheterization laboratories.

Key words: Pressure drop coefficient; Interventional cardiology; Intermediate coronary stenosis

Core tip: In the case of intermediate coronary stenosis, fractional flow reserve (FFR) is traditionally used as a functional end-point for interventional decision making in a cardiac catheterization laboratory. In this outcomes study, it was purported that pressure drop coefficient could prove to be a better clinical end-point for decision-making in comparison to the FFR.

Effat MA, Peelukhana SV, Banerjee RK. Clinical outcomes of combined flow-pressure drop measurements using newly developed diagnostic endpoint: Pressure drop coefficient in patients with coronary artery dysfunction. *World J Cardiol* 2016; 8(3): 283-292 Available from: URL: http://www.wjgnet.com/1949-8462/full/v8/i3/283.htm DOI: http://dx.doi.org/10.4330/wjc.v8.i3.283

INTRODUCTION

Accurate assessment of the severity of intermediate coronary stenosis is a clinical challenge to the interventional cardiologists. Quantitative anatomic tools have been proposed to address the issue but their relevance is still a matter of debate. Recently, the assessment of functional coronary lesion severity using sensor-equipped guidewires has emerged as a standard diagnostic modality to provide objective evidence of myocardial ischemia during cardiac catheterization[1,2]. Coronary diagnostic indices, fractional flow reserve (FFR; pressure derived), and coronary flow reserve (CFR; flow derived) showed a high agreement with non-invasive stress testing[3-5].

FFR (ratio of pressure distal to the stenosis to the pressure proximal to the stenosis) is the current gold standard for evaluating the functional significance of an epicardial stenosis[6-8]. FFR has a lower bound of "0", representing complete vessel obstruction and an upper bound of "1" represented no obstruction and normal flow. Based on extensive clinical outcomes trials, a cut-off value of 0.75[7] for FFR was shown to indicate hemodynamic significance of coronary stenosis in the presence of single vessel disease, and 0.80 for multi-vessel disease[9-13]. The limitations of FFR include the assumption of zero central venous pressure, and its dependence on achieving maximal hyperemia. Failure to achieve peak hyperemia may result in not achieving minimal constant microvascular resistance, leading to under estimation of pressure drop and over estimation of FFR across a stenosis[14].

The flow derived parameter CFR (ratio of flow at hyperemia to flow at rest) was found to have excellent agreement with noninvasive stress testing at a cut-off value of 2.0[3]. An abnormal CFR (< 2.0) corresponded to reversible myocardial perfusion defects with high sensitivity and specificity[3]. It should be noted that CFR provides the combined effect of epicardial stenosis and microvascular dysfunction, but cannot differentiate between the two. Hence, evaluation of epicardial coronary stenosis may not be accurate in the setting of microvascular dysfunction.

FFR and CFR are based on either intra coronary pressure or flow. Therefore, they can both be confounded by the presence of extended microvascular disease and cannot differentiate between hemodynamic status of the epicardial stenosis and microvasculature[15,16]. To overcome these limitations of FFR and CFR, hybrid pressure and velocity parameters were proposed. However, these parameters were defined for detection of either epicardial stenosis, namely, hyperemic stenosis resistance index (ratio of pressure drop across the stenosis to the distal velocity during hyperemia)[4]; or for the detection of microvascular dysfunction, namely, hyperemic microvascular resistance index (ratio of mean distal pressure and velocity during hyperemia)[17].

For simultaneous detection of epicardial stenosis and microvascular dysfunction using a single diagnostic parameter, we recently introduced the functional index, pressure drop coefficient (CDP); ratio of trans-stenotic pressure drop, Δp, to distal dynamic pressure, ($1/2 \times$ blood density $\times$ APV^2), where APV (average peak flow velocity) is measured under maximal hyperemia[18]. The CDP was validated *in vitro*[18,19], and *in vivo* animal studies[18-24] to differentiate between epicardial stenosis and microvascular dysfunction. In a recent pilot clinical study[25] CDP has been shown in a patient population to distinguish between degrees of stenosis severity. Further, for making interventional decisions, CDP > 27.9[26,27] was proposed as an indicator of significant epicardial stenosis, corresponding to a FFR < 0.75 cut-off in a single vessel.

Table 1 Summary of the characteristics of the 86 recruited patients

Variable		Study/group
Sex (M/F)		77/9
Age (yr)		61 ± 9
Ejection fraction (%)		58 ± 10
Clinical history		
	Diabetes	42/86
	Hypertension	70/86
	Dyslipidemia	60/86
	Previous myocardial infarction	21/86
	Smoking history	52/86
	Family history of CAD	23/86
	LV hypertrophy	4/86
Affected artery		
	LAD	43
	LCX	17
	RCA	26

M: Male; F: Female; CAD: Coronary artery disease; LV: Left ventricle; LAD: Left anterior descending; LCX: Left circumflex; RCA: Right coronary artery.

However, for the CDP to be included into regular clinical practice, the cut-off value CDP > 27.9 need to be associated with positive clinical outcomes. Hence, the objective of this pilot study is to compare the outcomes between the CDP > 27.9 and the clinical gold standard, FFR < 0.75. The hypothesis is that the combined pressure and flow parameter, CDP will result in better clinical outcomes in comparison to the FFR group. To test this hypothesis, a comparison was made between the FFR < 0.75 and CDP > 27.9 groups in this study, for the major adverse cardiac events [major adverse cardiac events (MACE): Primary outcome] and patients' condition (secondary outcome). Further, a comparison was also made between the survival curves for the FFR < 0.75 and CDP > 27.9 groups.

MATERIALS AND METHODS

Study patients

The protocol[25] was approved by the institutional review board at University of Cincinnati (UC) and Cincinnati Veteran Affairs Medical Center (CVAMC), and informed consent was obtained from all the participants. Patients who underwent exercise testing and myocardial perfusion scans were consented based on the inclusion and exclusion criteria, as explained below. The study was registered with Clinicaltrials.gov, with the identifier NCT01719016.

The study population consisted of 86 patients enrolled at the UC and CVAMC. Table 1 summarizes the clinical characteristics of the enrolled patients. The inclusion criteria for the study were: (1) chest pain; (2) abnormal stress test; (3) an angiographically detectable stenosis of moderate severity (defined as approximately 50% by visual examination) in a major coronary artery; and (4) left ventricular ejection fraction > 25%. Patients were excluded if they had: (1) left ventricular ejection fraction < 25%; (2) non-dialysis dependent chronic kidney disease with baseline serum creatinine greater than 2.5 g/dL; (3) history of type-Ⅱ heparin induced thrombocytopenia; (4) ostial lesions, serial stenoses, significant left main stenosis; (5) significant co-morbid conditions that would make coronary angiography prohibitive and contraindicated; and (6) pregnant women.

Cardiac catheterization and hemodynamic measurement

Using standard-of-care catheterization techniques, vascular access was through the femoral approach; a 5-to-6-French catheter was introduced into the femoral sheath and advanced into the ostium of the coronary artery. Unfractionated heparin was administered using a weight-based protocol. Aortic pressure was measured through the guiding catheter. Intra coronary pressure and flow measurements were obtained across the lesions either by using a 0.014-inch-diameter guidewire (Combowire, Volcano Corporation, California, United States) that combines a standard Doppler sensor at the tip and a standard pressure sensor 1.5 cm proximal to the tip or by 0.014-inch-diameter pressure and Doppler guide wires separately. The Combowire (or pressure wire) was set at zero, calibrated, advanced through the guiding catheter and normalized to aortic pressure before insertion into the target vessel. The wire was positioned distal to the stenosis in the target vessel, with the pressure transducer at least 30 mm distal to lesion. The position of the Doppler sensor was manipulated until an optimal and stable blood velocity signal was obtained. Adenosine was then infused intravenously (140 μg/kg per minute)[25] or *via* intracoronary (20 μg for the right coronary artery and 40 μg for the left coronary artery)[28] to induce maximal coronary blood flow. Aortic pressure (P_a), coronary pressure (P_d) and average peak velocity (APV) distal to the stenosis were recorded. All signals were continuously recorded at rest and throughout induction and decline of maximum hyperemia.

CDP calculation

Percent diameter stenosis, reference diameter, and minimal lumen diameter were obtained by quantitative analysis of coronary angiograms, with the use of a validated automated contour detection algorithm (Centricity Cardiology, GE Healthcare). CDP[18,20-22,24,27] is defined as the ratio of trans-stenotic pressure drop ($\Delta P = P_a - P_d$) to distal dynamic pressure. The product of blood density (ρ), the square of APV and a constant value of 0.5, *i.e.*, $0.5 \times \rho \times APV^2$, is calculated to obtain distal dynamic pressure, measured at hyperemia. Blood density, ρ does not change significantly at hyperemia, and thus can be assumed to have a constant value (1.05 g/cm^3)[20,29].

$CDP = \Delta P/(0.5 \times \gamma \times APV^2)$(a dimensionless parameter; where $\Delta P = P_a - P_d$), P_a and P_d are mean pressures measured proximal and distal to the stenosis at hyperemia, respectively.

Patient follow-up and study endpoints

All the patients were followed-up through either chart review, a phone call, and/or a questionnaire. The period

Table 2 Summary of the primary and secondary outcomes at a minimum of 1-year follow-up period

Variable		FFR < 0.75	FFR > 0.75	CDP > 27.9	CDP < 27.9	FFR < 0.80	FFR > 0.80	CDP < 25.4	CDP > 25.4
Primary outcome	Composite of MACE								
	All-cause mortality	3/20	2/66	2/35	3/51	4/35	1/51	3/47	2/39
	Myocardial infarction	1/20	1/66	0/35	2/51	2/35	0/51	1/47	1/39
	Revascularization	0/20	1/66	0/35	1/52	1/35	0/51	1/47	0/39
Secondary outcome: All questions related to patients' condition after the procedure	Q1: Health condition	7/20	1/66	7/35	1/51	7/35	1/51	7/47	1/39
	Q2: Heart attack	0/20	0/66	0/35	0/51	0/35	0/51	0/47	0/39
	Q3: Chest pain requiring medication	6/20	6/66	7/35	5/51	6/35	6/51	7/47	5/39
	Q4: Interventional procedure	5/20	3/66	4/35	4/51	5/35	3/51	4/47	4/39
	Q5: Re-hospitalization due to cardiac condition	2/20	5/66	4/35	3/51	2/35	5/51	4/47	3/39

MACE: Major adverse cardiac events; FFR: Fractional flow reserve; CDP: Pressure drop coefficient.

of follow-up was a minimum of 1 year. Through the follow-up, the primary outcomes, consisting of MACE, were determined. MACE was defined as the composite of all-cause mortality, myocardial infarction (MI), and repeat revascularization (Table 2).

The secondary outcomes consisting of patients' condition were determined through follow-up questionnaire based on 5 questions (Table 2). Q1: How has your health condition been after procedure? Q2: Have you been diagnosed of heart attack after procedure? Q3: Have you been experiencing chest pain requiring you to take nitroglycerin, since you had the procedure? Q4: Did you have any interventional procedure done after cardiac catheterization? Q5: Have you been re-hospitalized for cardiac-condition after this cardiac procedure? The answers to these questions comprised of the secondary outcomes.

Statistical analysis

The authors had prior biostatistics background, as apparent from previous publications[13,14,17-19]. Any patient lost to follow-up was counted as censored data. The data was segregated based on the cut-off value of FFR < 0.75 and FFR < 0.80 for significant epicardial stenosis. Similarly, for corresponding significant epicardial stenosis, CDP > 27.9 and CDP > 25.4[26,27] were used as the cut-off value. For the primary outcome analysis, the %MACE in the FFR < 0.75 (n = 20) group were quantified and compared against the %MACE in corresponding CDP > 27.9 (n = 39) group. Similar comparisons were also performed between the %MACE in the FFR > 0.75 (n = 66) and CDP < 27.9 (n = 47) groups. The same analysis were also performed for FFR = 0.80 and CDP = 25.4 groups.

For the secondary outcome analysis, the responses to the five questions (please see above) were quantified as percentages and compared between the FFR and CDP groups. For Q1, the number of patients answering "not feeling well" was counted. For Q3, Q4 and Q5, any patient answering "Yes" was counted. Q2 was excluded from presentation since there were no patients diagnosed with heart attack. All the comparisons were performed using a two-tailed χ^2 test with Yates correction. As a double check, comparisons were also performed using Fisher's exact test.

Further, survival analysis was also performed to assess the performance of CDP against FFR. The time between the index procedure and the time when the patient was last contacted (last follow-up) was recorded. Any patient who reached the primary outcome (%MACE) was counted as positive. Any patient lost to follow-up or who didn't reach the outcome was entered as censored data. Based on this, Kaplan-Meier survival analysis was performed. A comparison between the survival curves for the two groups was also performed using log-rank test. All the analyses were performed using MedCalc (V10.2, Mariakerke, Belgium). Results were considered statistically significant for $P < 0.05$.

RESULTS

In order to test the effectiveness of CDP cut-off (CDP > 27.9 and CDP > 25.4) as a guide for intervention decisions, the primary and secondary outcomes in patients were quantified and compared against the FFR cut-off (FFR < 0.75 and FFR < 0.80). In addition, survival curves were also generated and compared between the groups. These results are summarized below.

Primary outcome comparison between CDP and FFR

A comparison of the %MACE between the FFR < 0.75 and CDP > 27.9 groups, and FFR > 0.75 and CDP < 27.9

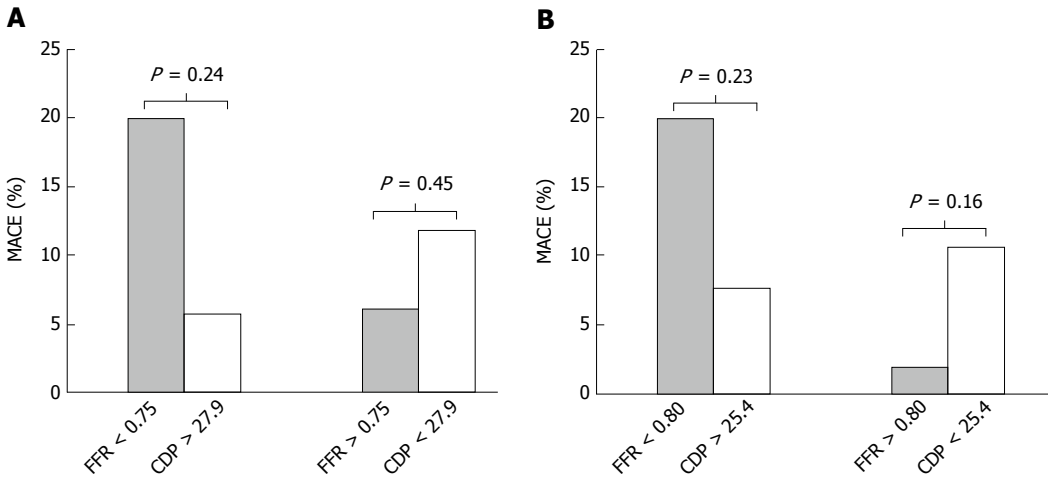

Figure 1 Comparison of % major adverse cardiac events in fractional flow reserve and pressure drop coefficient groups. MACE: Major adverse cardiac events; FFR: Fractional flow reserve; CDP: Pressure drop coefficient.

groups is summarized in Figure 1A. The %MACE in the FFR < 0.75 group (20%, 4 out of 20) was not statistically different (P = 0.24) from the %MACE occurring in CDP > 27.9 group (8.57%, 2 out of 35). Noteworthy is the reduction in the %MACE in the CDP > 27.9 group, in comparison to the FFR < 0.75 group. If a CDP-based strategy were to be implemented, the %MACE in this group would be lower (8.57%) in comparison to the FFR-guided strategy group (%MACE = 20%).

Similarly, the %MACE in FFR > 0.75 group was 6.06% (4 out of 66). This value was not statistically significant (P = 0.45) in comparison to a %MACE in the CDP < 27.9 group (11.76%, 6 out of 51).

Similar comparisons for FFR = 0.80 and CDP = 25.4 groups are presented in Figure 1B. The %MACE in the FFR < 0.80 group (20%, 7 out of 35) was not statistically different (P = 0.23) from the %MACE occurring in CDP > 25.4 group (7.69%, 3 out of 39).

Similarly, the %MACE in FFR > 0.80 group was 1.96% (1 out of 51). This value was not statistically significant (P = 0.16) in comparison to a %MACE in the CDP < 25.4 group (10.64%, 5 out of 47).

Secondary outcome comparison between CDP and FFR

The secondary outcomes, quantified through responses of the patients through follow-up questionnaire were also compared between the FFR < 0.75 and CDP > 27.9 groups, and also between the FFR > 0.75 and CDP < 27.9 groups. These results are summarized in Figures 2A and 2B, respectively.

Figure 2A summarizes the comparison between the FFR < 0.75 and CDP > 27.9 groups. In the FFR < 0.75 group patients not feeling well (Q1: 35%, 7/20) was not statistically significant (P = 0.36) in comparison to the slightly lower % of patients not feeling well in the CDP > 27.9 group (20%, 7/35). Similarly, the % of patients answering "Yes" to Q3, Q4, Q5 in the FFR < 0.75 group (Q3: 30%, 6/20; Q4: 25%, 5/20; Q5: 10%, 2/20) was not statistically different (Figure 2A) in comparison to the CDP > 27.9 group (Q3: 20%, 7/35; Q4: 11.43%, 4/35; Q5: 11.43%, 4/35).

In the FFR > 0.75 group (Figure 2B) patients not feeling well (Q1: 1.51%, 1/66) was not statistically significant (P = 0.59) in comparison to the % of patients not feeling well in the CDP < 27.9 group (1.96%, 1/51). Similarly, the % of patients answering "Yes" to Q3, Q4, Q5 in the FFR < 0.75 group (Q3: 9.09%, 6/66; Q4: 4.54%, 3/66; Q5: 7.58%, 5/66) was not statistically different (Figure 2B) in comparison to the CDP < 27.9 group (Q3: 9.8%, 5/51; Q4: 7.84%, 4/51; Q5: 5.88%, 3/51).

Figure 2C summarizes the comparison between the FFR < 0.80 and CDP > 25.4 groups. In the FFR < 0.80 group patients not feeling well (Q1: 20%, 7/35) was not statistically significant (P = 0.94) in comparison to the CDP > 25.4 group (17.95%, 7/39). Similarly, the % of patients answering "Yes" to Q3, Q4, Q5 in the FFR < 0.75 group (Q3: 17.14%, 6/35; Q4: 14.29%, 5/35; Q5: 5.71%, 2/35) was not statistically different (Figure 2A) in comparison to the CDP > 27.9 group (Q3: 17.95%, 7/39; Q4: 10.26%, 4/39; Q5: 10.26%, 4/39).

In the FFR > 0.80 group (Figure 2D) patients not feeling well (Q1: 1.96%, 1/51) was not statistically significant (P = 0.47) in comparison to the % of patients not feeling well in the CDP < 25.4 group (2.13%, 1/47). Similarly, the % of patients answering "Yes" to Q3, Q4, Q5 in the FFR < 0.80 group (Q3: 11.76%, 6/51; Q4: 5.88%, 3/51; Q5: 9.80%, 5/51) was not statistically different (Figure 2D) in comparison to the CDP < 25.4 group (Q3: 10.64%, 5/47; Q4: 8.51%, 4/47; Q5: 6.38%, 3/47).

Survival analysis

The Kaplan-Meier survival curves for the FFR < 0.75 and CDP > 27.9 groups were presented in Figure 3A. The results suggest that the survival time for the CDP > 27.9 group (n = 35) is significant (P = 0.048) in comparison to the survival time for the FFR < 0.75 group (n = 20).

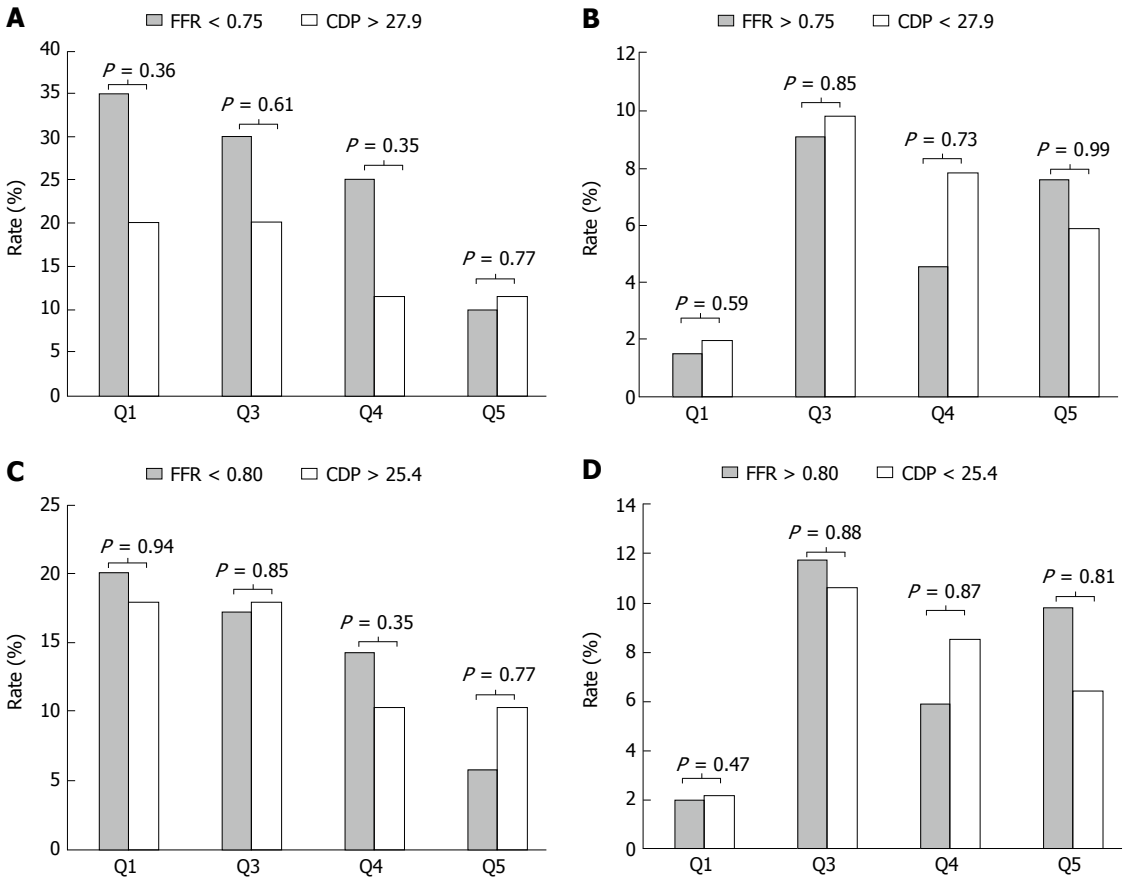

Figure 2 Comparison of patient conditions between fractional flow reserve and pressure drop coefficient groups at follow-up. A: FFR < 0.75 and CDP > 27.9; B: FFR > 0.75 and CDP < 27.9; C: FFR < 0.80 and CDP > 25.4; D: FFR > 0.80 and CDP < 25.4. FFR: Fractional flow reserve; CDP: Pressure drop coefficient.

Further, the hazard ratio between the two groups is 0.22 (95%CI: 0.06-1.24). This means that the survival expectancy in the FFR < 0.75 group is 0.22 times the survival probability in the CDP > 27.9 group. Similar results for FFR < 0.80 and CDP > 25.4 groups are presented in Figure 3B. The survival time for the CDP > 25.4 group (n = 39) is marginally significant (P = 0.066) in comparison to the survival time for the FFR < 0.80 group (n = 35).

The Kaplan-Meier survival curves for the FFR > 0.75 and CDP < 27.9 groups were presented in Figure 3C. The results suggest that the survival time for the CDP < 27.9 group (n = 51) is not significantly different (P = 0.29) in comparison to the survival time for the FFR > 0.75 group (n = 66). Further, the hazard ratio between the two groups is 1.95 (95%CI: 0.56-6.82). Similar results for FFR > 0.80 and CDP < 25.4 groups are presented in Figure 3D. The survival time for the CDP < 25.4 group (n = 47) is not significant (P = 0.094) in comparison to the survival time for the FFR > 0.80 group (n = 51).

DISCUSSION

The theoretical advantages of using a single physiological parameter that incorporates both pressure and flow measurements is well supported by ample evidence. However, the question remains whether this consideration is relevant in a clinical setting. The results of this study suggest that if clinical practice making strategy is based on CDP instead of FFR, there would be a significant increase in event free survival. Additionally, comparing patients who had CDP > 27.9 to FFR < 0.75 and CDP > 25.4 with FFR < 0.80 resulted in a trend towards reduced MACE and improved quality of life. Similar results were observed for FFR = 0.80 cut-off, with a corresponding CDP cut-off of 25.4. Purportedly the difference in clinical outcomes seen in this study reflects an enhanced accuracy in predicting ischemia.

CDP, defined as coronary trans-lesional pressure drop (Δp) to distal dynamic pressure ($0.5 \times \rho \times APV^2$) uses both pressure and flow measurements to assess stenosis severity. Additionally, it has the advantage of being a non-dimensional parameter based on fundamental fluid dynamics principles. It has been shown that coronary pressure drop (Δp) - flow relationship in a stenosed vessel is non-linear and can be described by $\Delta P = aV + BV^2$, where a and b are stenosis specific constants and V is the velocity. The Δp includes (a) viscous loss, a linear relationship of Δp and flow (or velocity), resulting from the friction between the blood flow and the lumen of the stenosis wall; and (b) loss due to the momentum change, a quadratic relationship of Δp and velocity, caused by the area change due to the stenosis.

FFR and CFR are affected in opposite directions by

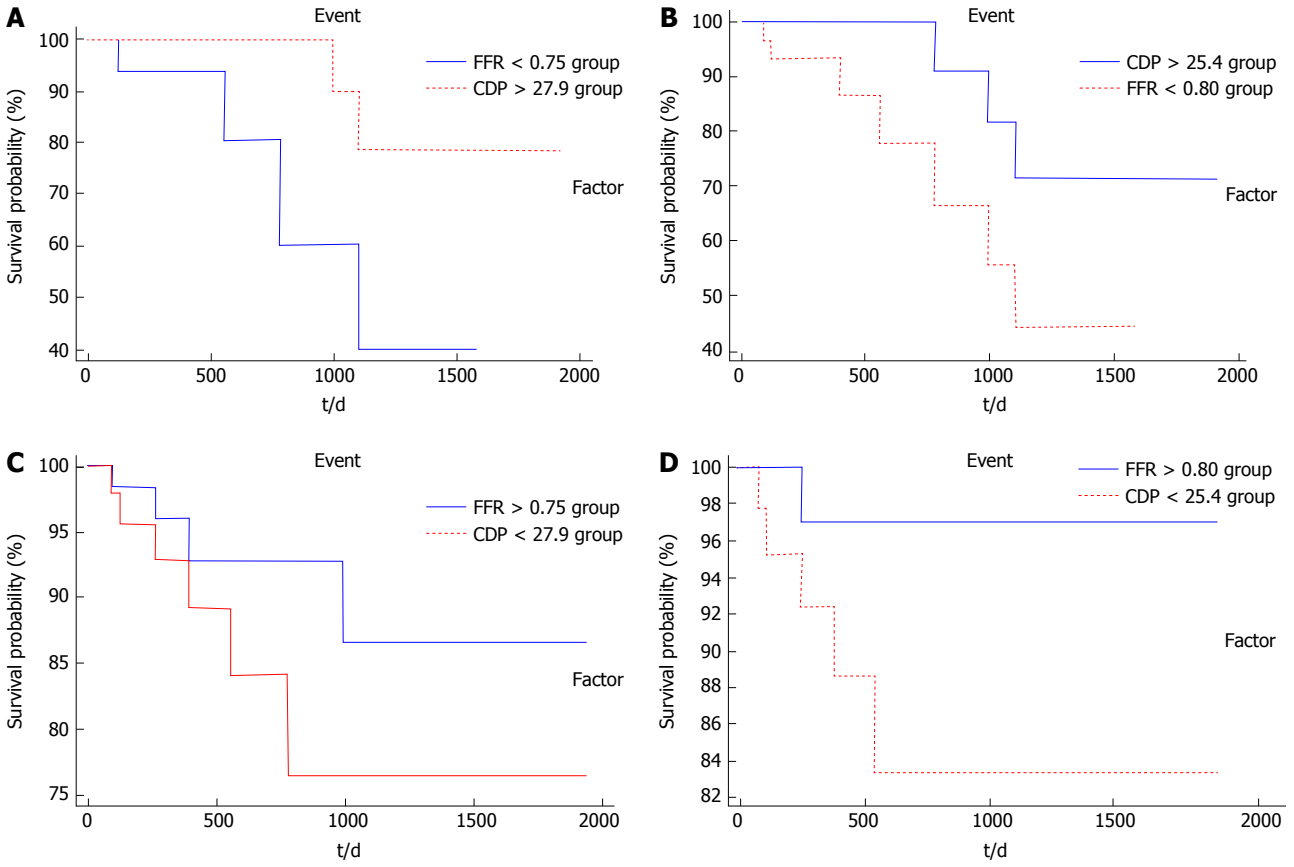

Figure 3 Survival curves. A: FFR < 0.75 and CDP > 27.9 groups (P = 0.048); B: FFR < 0.80 and CDP > 25.4 (P = 0.066); C: FFR > 0.75 and CDP < 27.9 groups (P = 0.29); D: FFR > 0.80 and CDP < 25.4 (P = 0.09). FFR: Fractional flow reserve; CDP: Pressure drop coefficient.

microvascular resistance, and assessment of ischemia by measuring FFR and CFR in the same coronary vasculature may yield discordant results in up to 40% of the cases[30]. This can be explained by the presence of diffuse epicardial disease which would lower CFR without significant impact on FFR. Conversely, a well preserved microvascular auto regulatory function may maintain CFR above the ischemic threshold while FFR is abnormal. In the presence of such conditions as diffuse lesion or concomitant microvascular disease, the complex interaction between pressure and flow might not be sufficiently explained by FFR or CFR alone, as FFR is a pressure-derived parameter and CFR is a flow-derived parameter. On the other hand, CDP combines both the pressure and flow in a single parameter and thus can distinguish between epicardial stenosis and microvascular dysfunction[22,26].

As previously mentioned, both FFR and CFR depend critically on the achievement of maximal hyperemia. Failure to achieve peak hyperemia may result in not achieving minimal constant microvascular resistance leading to under estimation of pressure drop and over estimation of FFR across a stenosis[11]. It should be noted that in the presence of microvascular dysfunction and submaximal hyperemia, pressure drop, and blood flow are affected in the same direction. Physiologically, the extent of reduction in maximal hyperemic flow due to microvascular dysfunction is higher than that due to epicardial stenosis[20]. In such circumstances, the square of maximal hyperemic flow in the denominator of CDP significantly accounts for this reduction, thus providing an increased resolving power for CDP for accurate evaluation of the status of epicardial stenosis.

Given these advantages of CDP, we believe that it can potentially have a significant role in clinical practice. However, it should be noted that the utilization of dual sensor wires for diagnostic purposes has not gained sufficient traction in cardiac catheterization laboratories partly because of the added complexity in acquiring functional data. Nevertheless, as the evidence from clinical outcome studies evolves and the technology advances further in making the dual sensor wires more steerable, less expensive and easier to use, the employment of these sophisticated concepts will be more tenable for use and application in the cardiac catheterization laboratory.

Several studies have confirmed the clinical utility of FFR in applying a "functional" PCI approach for the treatment of coronary stenosis, *i.e.,* to only revascularize the angiographic lesions that show significant FFR while deferring others. The DEFER study[11] comprised of 181 patients with stable ischemic heart disease and intermediate coronary stenosis. FFR > 0.75 was used to defer PCI and follow medical therapy in the deferred arm. At 5-year follow-up, the rate of MI or death was

significantly lower in the deferred group in comparison to the PCI group. The FAME trial[13] randomized 1005 patients to either FFR guided PCI or angiography guided PCI. The primary endpoint of MACE (MI, death, or repeat revascularization) at one year was significantly lower in the FFR guided strategy (13.2% *vs* 18.3%, $P = 0.02$).

To compare the outcomes between FFR guided PCI and optimal medical therapy alone, FAME 2[31], randomized 888 patients. The study was terminated early due to a significant difference in the primary endpoint of MACE in favor of the FFR guided strategy.

The results of these studies validate the role of FFR in guiding the clinical decision for management of coronary artery disease. Further, our study is purporting an improved accuracy for CDP over FFR in predicting major ischemic events as well as angina free survival. The reported outcomes from our analysis support the value of using CDP to make decisions regarding deferment of revascularization in clinical practice. Although statistical significance was not reached on most endpoints, the trends were robustly consistent throughout the spectrum of outcome follow-ups. Further validation in a larger cohort and a longer follow-up period may yield a stronger difference in support of CDP.

Limitations

In this study, all the clinical decisions were made on the basis of FFR only. Thus, using a larger sample size, a prospective randomized clinical trial of FFR *vs* CDP is needed to further investigate the clinical performance of CDP relative to FFR and validate the outcomes from this exploratory study.

In conclusion, in this pilot study, the primary (%MACE) and secondary (improved quality of life) outcomes between the FFR < 0.75 and CDP > 27.9 groups were compared. The %MACE in the CDP < 27.9 groups were slightly lower in comparison to the FFR < 0.75 group. However, this comparison was not statistically significant. Similarly, the secondary outcomes were not different between the FFR < 0.75 and CDP > 27.9 groups.

The event free survival in the CDP < 27.9 group was significantly ($P = 0.048$) higher in comparison the survival time in FFR < 0.75 group. Based on these, CDP could prove to be a good clinical endpoint for revascularization decision-making in a catheterization laboratory.

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COMMENTS

Background

Accurate assessment of the severity of intermediate coronary stenosis is a clinical challenge to the interventional cardiologists. Quantitative anatomic tools have been proposed to address the issue but their relevance is still a matter of debate. Hence, functional assessment of coronary lesion severity using sensor-equipped guidewires has emerged as a standard diagnostic modality to provide objective evidence of myocardial ischemia during cardiac catheterization.

Research frontiers

Pressure based parameter, fractional flow reserve (FFR) is currently being used as a clinical diagnostic marker for coronary interventions. A value of FFR < 0.80 is indicative of functionally significant coronary blockage, while a FFR > 0.80 indicates deferral of intervention to a later time. The applicability of FFR for intermediate stenosis intervention decision-making, in the presence of concomitant microvascular disease is an active research area.

Innovations and breakthroughs

This study proposes the newly developed diagnostic parameters, pressure drop coefficient (CDP), defined based on fundamental fluid dynamics. CDP combines both pressure and flow readings for interventional decision-making. Hence, it might prove to be a better parameter resulting in improved patient outcomes, as shown in this exploratory study.

Applications

The parameter CDP could be used for interventional decision-making in a cardiac catheterization laboratory, particularly in the presence of an intermediate coronary stenosis.

Peer-review

This is a nicely written article focusing on the clinical significance of different and combined flow-pressure drop measurements in coronary artery disease patients. The study is well planned and documented.

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Typical rise and fall of troponin in (peri-procedural) myocardial infarction: A systematic review

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Data sharing statement: The technical appendix, statistical code, and dataset are available from the corresponding author at diannevanbeek@hotmail.com.

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Abstract

AIM: To identify the typical shape of the rise and fall curve of troponin (Tn) following the different types of myocardial infarction (MI).

METHODS: We conducted a systematic search in PubMed and Embase including all studies which focused on the kinetics of Tn in MI type 1, type 4 and type 5. Tn levels were standardized using the 99th percentile, a pooled mean with 95%CI was calculated from the weighted means for each time point until 72 h.

RESULTS: A total of 34 of the 2528 studies identified in the systematic search were included. The maximum peak level of the Tn was seen after 6 h after successful reperfusion of an acute MI, after 12 h for type 1 MI and after 72 h for type 5 MI. In type 1 MI there were additional smaller peaks at 1 h and at 24 h. After successful reperfusion of an acute MI there was a second peak at 24 h. There was not enough data available to analyze the Tn release after MI associated with percutaneous coronary intervention (type 4).

CONCLUSION: The typical rise and fall of Tn is different for type 1 MI, successful reperfusion of an acute MI and type 5 MI, with different timing of the peak levels and different slopes of the fall phase.

Key words: Troponin; Myocardial infarction; Systematic review; Reperfusion; Coronary artery bypass grafting

Core tip: In this systematic review we aimed to identify the typical rise and fall of cardiac troponin (Tn) in the different types of myocardial infarction (MI). A total of 34 of the 2528 studies identified in the systematic search were included. The typical rise and fall of Tn is different for type 1 MI, successful reperfusion of an

acute MI and type 5 MI, with different timing of the peak levels and different slopes of the fall phase.

van Beek D, van Zaane B, Looije M, Peelen L, van Klei W. Typical rise and fall of troponin in (peri-procedural) myocardial infarction: A systematic review. *World J Cardiol* 2016; 8(3): 293-301 Available from: URL: http://www.wjgnet.com/1949-8462/full/v8/i3/293.htm DOI: http://dx.doi.org/10.4330/wjc.v8.i3.293

INTRODUCTION

Myocardial infarction (MI) is the collective term for myocardial necrosis in the setting of myocardial ischemia[1]. There are many different conditions which can result in myocardial ischemia and subsequent MI. Currently, there are five distinct types of MI defined: Type 1 spontaneous MI related to atherosclerotic plaque rupture, type 2 MI secondary to an imbalance between oxygen supply and oxygen demand, type 3 MI resulting in death when biomarkers are not available, type 4a MI related to percutaneous coronary intervention (PCI), type 4b MI related to stent thrombosis, and type 5 MI related to coronary artery bypass grafting (CABG)[1].

For all different types of MI, excluding type 3, cardiac biomarkers are the cornerstone for diagnosing its occurrence. The preferred cardiac biomarker for the detection of myocardial damage is troponin (Tn)[1]. Tn (subtypes I en T) is part of the contractile apparatus of myocardial cells only and is therefore a highly specific biomarker for myocardial damage[1]. Elevated levels of Tn can be detected within 3-12 h after the start of ischemia and they reach a peak after 12-48 h[2]. However, as Tn is a structural component of myocardial cells, Tn levels will be elevated in patients with chronic heart conditions such as heart failure as well. Therefore, to distinguish between an acute MI and chronic cardiac disease, elevation of Tn alone is not specific enough. There needs to be a significant change in the level of Tn, *i.e.,* a rise and/or a fall. In spontaneous MI a relative difference of more than 20% is considered a significant change[1]. More specifically, in spontaneous MI any level above the 99th percentile is considered a rise[1]. The cut off levels according to the third universal definition for a typical rise in PCI associated MI (> 5 times 99th percentile) and CABG associated MI (> 10 times 99th percentile) are consensus based and not evidence based[1].

The typical rise and/or fall of Tn is thus crucial for the diagnosis of MI[1]. However, the exact shape of the rise and fall curve is largely unknown. Nevertheless, understanding the shape of the rise and fall curve would allow for better timing of Tn blood sampling in clinical practice and would improve diagnostic criteria per type of MI. The aim of this systematic review was to identify the typical shape of the rise and fall curve of Tn following the different types of MI.

MATERIALS AND METHODS

Literature search

Medline (PubMed) and Embase were searched from 1966 through October 2013 for publications. We used synonyms and abbreviations for "rising", "falling", "changing", "troponin" and "myocardial infarction" as keywords (See supplementary 1 for search strategies). Based on titles and abstracts, all studies evaluating Tn in MI were included. Different types of studies were eligible, for example cross sectional studies of patients with MI, cohort studies including patients with symptoms of cardiac ischemia, randomized controlled trials concerning treatment or diagnosis of MI and case control studies where the cases had MI. We included studies in patients with MI that focused on cardiac Tn, both Tn-I and Tn-T, and that reported at least two different Tn-values with at least one sample above the cut off level. Abstracts from conference proceedings, non-human studies, non-English studies, and studies on animals, children, chronic conditions and cardiomyopathy were excluded.

First, all titles and abstracts were screened for eligibility. Second, screening was extended to full text for all studies that where either marked as relevant or when the eligibility was unclear from screening titles and abstracts. Eligibility was determined using a standardized form containing the above mentioned criteria.

The methodological quality of included studies was assessed by two observers (DvB and ML) and in case of doubt by a third observer (BvZ) using an adjusted QUADAS-tool[3] (see supplementary 2 for quality criteria). The selected items of the QUADAS-tool enabled us to examine potential sources of bias and variation[4]. The defined quality domains were; representativeness of the spectrum (*i.e.,* the representativeness of the patients in the study for clinical practice), acceptable reference standard, acceptable delay between tests, partial verification avoided, relevant clinical information, uninterpretable results reported, and withdrawals explained. We did not calculate summary scores estimating the overall-quality of included studies since it has been shown that their interpretation is problematic and may be misleading[5].

Data extraction took place using a specifically designed data extraction form. The two observers independently extracted raw data from the included studies to obtain information on Tn levels at different time points. Other elements that were extracted included the year of publication, the type of study, the research question, any subgroups, inclusion and exclusion criteria, the setting (*e.g.,* emergency department, in hospital, post-surgery) and sample size. In addition, the proportion of patients with MI, the mean or median age of patients with MI, the proportion of males with MI, any comorbidities and the diagnostic criteria used for MI were obtained. Finally, test characteristics were extracted such as the type of Tn test, the 99th percentile/upper reference limit/cut off level of the Tn test, limit of detection, number of samples per patient and the sample time points in relation to the

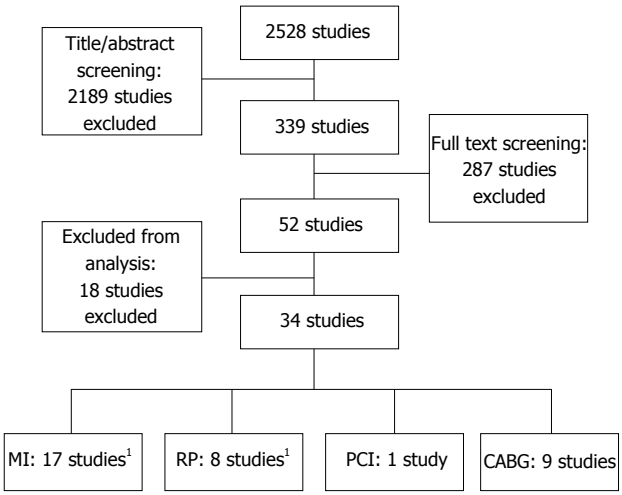

Figure 1 Flow chart. [1]Different data from one study has been included in both the MI and RP analysis. MI: Type 1 spontaneous myocardial infarction; RP: Successful reperfusion during an acute myocardial infarction; PCI: Type 4 myocardial infarction associated with percutaneous coronary intervention; CABG: Type 5 myocardial infarction associated with coronary artery bypass surgery.

event (*e.g.,* admission, surgery).

Data were considered missing if not explicitly mentioned in the text and if impossible to deduct the information directly from other information in the text. Discrepancies between the two observers were resolved by discussion.

Statistical analysis

Studies were divided into four subgroups based on the focus of the articles: Studies on type 1 spontaneous MI, studies that focused on successful reperfusion in the setting of an acute MI (where reperfusion was not initiated or its effect not evaluated), studies on MI associated with PCI (type 4a MI), and studies on MI associated with CABG (type 5 MI). Type 2 MI studies were not included in this systematic review as the etiology behind this type of MI is distinctly different.

In this review we aimed to address the general rise and fall of Tn and not the rise and fall of specific Tn tests. Therefore, all Tn levels that were obtained within 72 h were included in our analysis. If the timing of the samples was not specified, the study was excluded from analysis. If only one data source was available for a given point in time, we excluded this time-point from our analysis.

For each time point up till 72 h we conducted the following procedure. For each study, we first determined the mean and standard deviation (SD) of the Tn values. If available, mean and SD as presented in the article was used. Alternatively, when only a median was available the mean was approximated. For articles with less than 25 patients with MI, we used the formula of Hozo *et al*[6] to approximate the mean, for articles with 25 or more patients with MI, the median was used as the best estimate of the mean. Articles for which the mean could not be approximated were excluded from analysis. When the standard error (SE) was not available from the articles directly, it was calculated from SD, confidence interval (CI), or median absolute deviation. Articles for which the SE was not available nor could be calculated were excluded from the analysis.

Subsequently, in order to make the Tn levels from different studies comparable, all Tn levels were standardized. Standardization was achieved by dividing the Tn levels by the 99th percentile of that particular Tn test. If the 99th percentile was not available, we used the upper reference limit (URL) or the cut off value for standardization. Studies that did not mention a 99th percentile or an URL or a cut off value for their Tn test were excluded from analysis.

After standardization, results over studies were pooled as follows. Every study was assigned a weight according to the inverse of the variance ($1/SE^2$). The weighted mean per article was calculated by multiplying the mean with the weight. The sum of all weighted means was divided by the sum of all weights to calculate a pooled mean for every timepoint. The SE per timepoint was calculated as follows: $1/(\text{sum of the weights})^{0.5}$. From the pooled SE the 95%CI was calculated.

The pooled mean of the standardized Tn levels with the corresponding CI at different time points were analyzed and summarized using a graph.

RESULTS

Search results

Our search resulted in 2528 potentially eligible studies (Figure 1). After screening titles and abstracts 2189 studies were excluded. After reviewing and applying the in- and exclusion criteria to the full text of the remaining 339 studies, 34 studies remained for analysis. There were 17 studies on type 1 spontaneous MI, 8 on successful reperfusion, 1 on MI associated with PCI (type 4), and 9 studies on MI associated with CABG (type 5). One study could be included in the analyses for both type 1 MI and reperfusion. The baseline characteristics of the included studies are summarized in Table 1.

Quality of the included studies

Table 2 describes the results of the quality assessment. Almost all studies avoided partial verification, worked with relevant clinical information and a representative spectrum of patients with MI. Very few studies reported uninterpretable results or explained withdrawals.

Typical rise and fall of Tn

The pooled mean Tn level in type 1 MI showed an early first peak of 7.0 (95%CI: 6.0-8.0) at 1 h. This initial peak was followed by a maximum pooled mean Tn level of 84 (95%CI: 82-86) at 12 h. A third small peak followed at 24 h (2.7; 95%CI: 2.6-2.9) (Figure 2). Finally, there was a gradual fall of Tn.

The maximum pooled mean of Tn after successful reperfusion was at 6 h (1853; 95%CI: 1851-1855), another high peak followed at 24 h (1006; 95%CI: 1004-1007) (Figure 3). Subsequently, there was a pronounced fall in Tn. The pooled mean Tn in type 5 MI associated with CABG raised the first 24 h, after which

Table 1 Baseline characteristics of included studies

Ref.	Year of publication	NO. of patients	Prevalence MI *n* (%)	Males with MI *n* (%)	Diagnostic criteria MI	Tn test	Cut off level	Type of cut off level	Time points measured from
Type 1: Spontaneous MI									
Aldous *et al*[12]	2011	939	200 (21)	NA	Biomarkers ECG Imaging Symptoms	HS-TnT (T) HS-TnI (I)	(T) 0.014 μg/L (I) 0.028 μg/L	(T): 99th (I): 99th	Admission
Aldous *et al*[13]	2012	385	82 (21)	59 (72)	Biomarkers ECG Imaging Symptoms	TnI (I) HS-TnT (T)	(T): 0.014 μg/L (I): 0.028 μg/L	(T): 99th (I): 99th	Admission
al-Harbi *et al*[14]	2002	86	51 (59)	46 (90)	ECG Symptoms	TnI	0.05 ng/mL	99th	Admission
Apple *et al*[15]	2009	381	52 (13)	NA	ESC ACC	TnI	0.034 μg/ L	99th	Admission
Bahrmann *et al*[16]	2013	306	38 (12)	23 (61)	Biomarkers ECG Imaging Symptoms	HS-TnT	14 ng/L	99th	Admission
Bertinchant *et al*[17]	1996	682	48 (7)	41 (85)	WHO	TnI	0.1 μg/L	Cut off	Admission
Biener *et al*[18]	2013	459	111 (3)	82 (74)	WHO UD	HS-TnT	14 ng/mL	99th	Admission
Bjurman *et al*[19]	2013	1504	1178 (75)	716 (61)	Biomarkers ECG Imaging Symptoms	HS-TnT	40 ng/L	99th	Admission
de Winter *et al*[20]	2000	131	131 (100)	NA	Biomarkers Symptoms	TnT	0.1 μg/L	URL	Symptoms
Falahati *et al*[21]	1999	327	62 (19)	NA	WHO	TnT	0.20 μg/L	Cut off	Symptoms
Haaf *et al*[22]	2012	887	127 (14)	87 (69)	Biomarkers ECG Imaging Symptoms	HS-TnT (HT) HS-TnI (HI) TnI (I)	(HT): 0.014 μg/L (HI): 0.009 μg/L (I:) 0.009 μg/L	(HT): 99th (HI): 99th (I:) 99th	Admission
Lucia *et al*[23]	2001	82	42 (51)	32 (76)	Biomarkers ECG Symptoms	TnI	1.5 ng/mL	URL	Admission
Mohler *et al*[24]	1998	100	21 (21)	NA	Biomarkers ECG Symptoms	TnT	0.1 mg/L	Cut off	Admission
Mueller *et al*[25]	2012	863	165 (21)	121 (73)	UD	HS-TnT	14 ng/L	99th	Admission
Reichlin *et al*[26]	2011	836	108 (13)	73 (68)	Biomarkers ECG Imaging Symptoms	Hs-TnT (T) TnI-ultra (I)	(T): 0.014 μg/L (I): 0.04 μg/L	(T): 99th (I): 99th	Admission
Reichlin *et al*[27]	2013	840	120 (14)	81 (68)	Biomarkers ECG Imaging Symptoms	Hs-TnT (T) HS-TnI (I)	(T): 14 ng/L (I): 9 ng/L (I) 9 ng/L	(T): 99th (I): 99th (I): 99th	Admission
Wu[28]	2009	14	4 (29)	4 (100)	NA	TnI-ultra	0.04 μg/L	99th	Admission
Successful reperfusion during acute MI									
Abe *et al*[29]	1994	38	26 (68)	20 (77)	ECG Symptoms	TnT	0.2 ng/mL	URL	Start treatment
Apple et al[30]	1996	25	17 (68)	NA	ECG Symptoms	TnI	3.1 μg/L	URL	Start treatment
Ferraro *et al*[9]	2012	87	87 (100)	68 (78)	NA	TnI-ultra	0.04 μg/L	Cut off	Before and after PCI
Ferraro *et al*[31]	2013	856	360 (42)	253 (70)	Biomarkers ECG Symptoms	TnI-ultra	40 ng/L	99th	Before and after PCI
Mair *et al*[32]	1991	172	33 (18)	NA	WHO	TnT	0.5 μg/L	99th	NA
Ricchiuti *et al*[33]	2000	83	23 (28)	17 (74)	WHO	TnI	0.8 μg/L	URL	End of treatment
Tanasijevic *et al*[34]	1997	30	19 (63)	15 (79)	NA	TnI	0.6 ng/mL	URL	Admission
Tanasijevic *et al*[35]	1999	442	344 (78)	258 (75)	NA	TnI	0.4 ng/mL	Cut off	Before and after treatment
Type 4: MI associated with percutaneous coronary intervention									
Reimers *et al*[36]	1997	80	5 (6)	NA	Biomarkers ECG Imaging	TnT	0.1 μg/L	URL	Before PCI and after
Type 5: MI associated with coronary artery bypass grafting									
Abdel Aziz *et al*[37]	2000	50	14 (28)	14 (100)	Biomarkers	TnT	10 μg/L	Cut off	Declamping

Alyanakian *et al*[38]	1998	41	5 (12)	NA	ECG ECG	TnI	0.6 μg/L	URL	Start CPB
Benoit *et al*[39]	2001	260	8 (3)	NA	Imaging Biomarkers	TnI	0.6 μg/L	URL	Before OR, end of ECC
Fellahi *et al*[40]	1999	102	7 (7)	4 (57)	ECG Imaging ECG	TnI	0.6 ng/mL	Cut off	Admission ICU
Katus *et al*[41]	1991	45	5 (11)	NA	ECG	TnI	0.5 mg/L	URL	After surgery
Lim *et al*[42]	2011	28	9 (32)	7 (78)	UD	TnI-ultra	0.06 μg/L	99th	End of surgery
Mair *et al*[43]	1994	119	10 (8)	9	ECG	TnI (I) TnT (T)	(I): 0.10 μg/L (T): 0.10 μg/L	(I): URL (T): Cut off	Declamping
Thielmann *et al*[44]	2004	55	55 (100)	26 (74)	Biomarkers ECG	TnI	0.5 ng/mL	Cut off	Declamping
Thielmann *et al*[45]	2005	94	94 (100)	67 (71)	Biomarkers ECG	TnI	20 ng/mL	Cut off	Declamping

99th: 99th percentile; ACC: American College of Cardiology; CPB: Cardiopulmonary bypass; ECC: Extracorporeal circulation; ESC: European Society of Cardiology Criteria for MI; HS-TnI: High sensitive TnI; HS-TnT: High sensitive TnT; MI: Myocardial infarction; NA: Not available; PCI: Percutaneous coronary intervention; Tn: Troponin; UD: Universal definition of MI; URL: Upper reference limit; WHO: World Health Organization Criteria for MI.

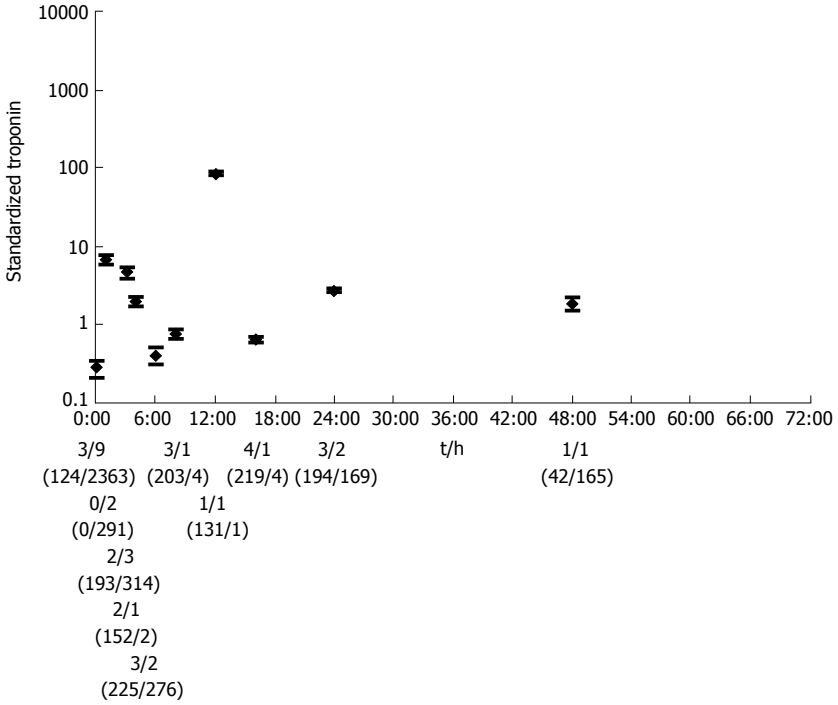

Figure 2 The pooled mean with confidence interval of standardized troponin for the different time points for type 1 spontaneous myocardial infarction. The number of articles per time point with a conventional Tn test/the number of articles with a HS-Tn test, and the number of test values (conventional Tn tests/HS-tests) are shown below the graph. Tn: Troponin; HS: High sensitive.

the Tn levels stabilized (Figure 4). The maximum pooled mean level of Tn was at 72 h (2.2; 95%CI: 1.8-2.6).

DISCUSSION

In this systematic review we identified the typical shape of the rise and fall curve of Tn following type 1 spontaneous MI, after successful reperfusion of a spontaneous MI, and after type 5 MI associated with CABG. The different types of MI resulted in a different peak level of Tn at different time points followed by distinct fall phases. Understanding these variations of Tn kinetics could result in improvement of the specific diagnostic criteria per type of MI.

It is remarkable that for type 5 MI we found the lowest pooled mean peak level of the different types of MI (2.2 compared to 84 in type 1 MI). This is in contrast with what one should expect when applying the third universal definition. In this definition for type 1 MI the recommended cut off level is defined as the 99th percentile and for type 5 MI 10 times the 99th percentile is recommended[1]. First, the relative high levels of Tn that we found for type 1 MI may be the result of the use of high-sensitive Tn tests. Second, the peak level that we have found in our review for type 5 MI is considerably lower than the optimal cut off level for diagnosing type 5 MI according to a previous published study (266 times the URL)[7]. This could be due to the fact that

Table 2 Quality of the included articles based on a modified QUADAS tool

Ref.	1	2	3	4	5	6	7
Type 1: Spontaneous MI							
Aldous *et al*[12]	+	?	-	+	+	?	-
Aldous *et al*[13]	+	+	+	+	+	?	?
al-Harbi *et al*[14]	+	?	+	+	+	?	?
Apple *et al*[15]	+	+	+	+	+	?	?
Bahrmann *et al*[16]	+	+	-	+	-	?	+
Bertinchant *et al*[17]	+	+	+	+	+	?	?
Biener *et al*[18]	+	+	+	+	+	?	?
Bjurman *et al*[19]	+	+	?	+	+	-	?
de Winter *et al*[20]	+	-	+	+	+	?	+
Falahati *et al*[21]	+	+	?	+	+	?	?
Haaf *et al*[22]	+	+	-	+	+	?	+
Lucia *et al*[23]	+	-	?	+	+	?	?
Mohler *et al*[24]	+	+	+	+	+	?	?
Mueller *et al*[25]	+	+	+	+	+	?	?
Reichlin *et al*[26]	+	+	-	+	+	?	?
Reichlin *et al*[27]	+	+	+	+	+	+	+
Wu[28]	+	+	+	+	+	?	?
Successful reperfusion during acute MI							
Abe *et al*[29]	-	+	-	+	-	?	-
Apple *et al*[30]	?	?	-	?	?	?	?
Ferraro *et al*[9]	-	?	+	+	-	-	?
Ferraro *et al*[31]	+	-	?	+	+	?	?
Mair *et al*[32]	+	+	+	+	+	?	-
Ricchiuti *et al*[33]	+	+	+	+	?	?	?
Tanasijevic *et al*[34]	?	?	?	-	?	-	?
Tanasijevic *et al*[35]	-	-	-	?	-	+	?
Type 4: MI associated with percutaneous coronary intervention							
Reimers *et al*[36]	-	+	+	+	?	?	?
Type 5: MI associated with coronary artery bypass grafting							
Abdel Aziz *et al*[37]	+	-	+	+	-	?	?
Alyanakian *et al*[38]	+	+	+	+	-	?	?
Benoit *et al*[39]	+	+	+	+	-	?	?
Fellahi *et al*[40]	+	-	+	+	-	?	+
Katus *et al*[41]	+	-	+	+	-	?	?
Lim *et al*[42]	+	+	+	+	-	+	+
Mair *et al*[43]	-	+	+	+	+	?	?
Thielmann *et al*[44]	+	+	+	+	+	?	?
Thielmann *et al*[45]	+	+	+	+	+	?	?

MI: Myocardial infarction. 1: Representativeness of the spectrum; 2: Acceptable reference standard; 3: Acceptable delay between tests; 4: Partial verification avoided; 5: Relevant clinical; 6: Uninterpretable results reported; 7: Withdrawals explained information.

many of the CABG studies included in our review used a cutoff point instead of a 99th percentile. Likely, these cut off points already take into account the expected higher levels of Tn after CABG. Since we used the cut off level for standardization of Tn if the 99th percentile was not available, this could explain the lower levels of standardized Tn in type 5 MI. In this systematic review we did not include patients without MI from the included studies; therefore we cannot make any claims regarding the optimal diagnostic cut off point.

The recommended interval between two samples to rule MI in or out is 3-6 h[1]. Our results do not support this time interval. For type 1 we found an early first peak after 1 h, followed by a short fall phase. The second rise started at 6 h. This could mean that sampling at 3-6 h might be less optimal than sampling earlier. In type 5 MI the maximum level was at 72 h. Since we did not include any time points after 72 h, we do not know whether this is a peak level or that Tn will rise further. This could mean that Tn should be monitored for more than 72 h postoperatively.

Only one study fulfilled the inclusion criteria focused on type 4 MI. We were therefore unable to analyze the typical rise and fall of Tn after type 4 MI. A review that focused on creatine-kinase M band (CK-MB) in type 4 MI found high levels of CK-MB with a CK-MB level above 10 × URL in 24% of the patients[8].

We found a very large mean peak level of Tn after successful reperfusion in acute MI at 6 h (1853), which is due to one study using a TnI-ultra test in combination with a low cut off level (0.04 μg/L)[9]. It is known that the high sensitive tests require a more pronounced change for the diagnosis MI. While the third universal definition defines a 20% change as significant[1], a rise of > 100% is needed for the high sensitive Tn test[10]. A different cut off level may also be needed for the high-sensitive tests.

This study has several limitations. First, our analysis of the typical rise and fall of Tn is not based on pooling individual patient data from different studies, which would allow for modeling entire biomarker trajectories, but on pooled estimates at different time points used in different studies. To take this into account we refrained from connecting estimates over time. It should however be noted that using individual patient data would be complex as well, given that the studies use a variety of time points; furthermore, the CIs around the pooled estimates are small, so it is rather unlikely that in a substantial number of patients the Tn pattern would be different. Second, we standardized the Tn levels preferentially by using the 99th percentile of Tn. However, the procedure of obtaining a 99th percentile of Tn tests is not uniform[11]. This could result in incorrect standardization and thus restriction of the generalizability. In addition, when the 99th percentile was not available we used the cutoff level. The argumentation for the chosen cutoff level was not always clear. However, the effect of this limitation seems minimal as it may affect the absolute levels of the standardized Tn, but not the Tn rise or fall. Third, the different studies used different criteria to define the baseline time point (0:00 h). These differences were more pronounced in type 1 MI than in type 5 MI articles. This makes the results of type 1 more difficult to interpret. Fourth, we only included studies that focused primarily on Tn levels during MI. This limited the number of included studies. However, the focus of this review was the typical rise and fall of Tn. The excluded studies measured Tn for a different purpose; the timing of the blood sampling and inclusion of the patients was therefore probably not optimal to evaluate the typical rise and fall of Tn. Fourth, Tn levels can be influenced by several patient related factors. For instance, impaired renal function is associated with higher Tn levels. Insufficient patient specific data was available to correct for such patient related factors. However, these factors are likely affecting the absolute levels of Tn and not the

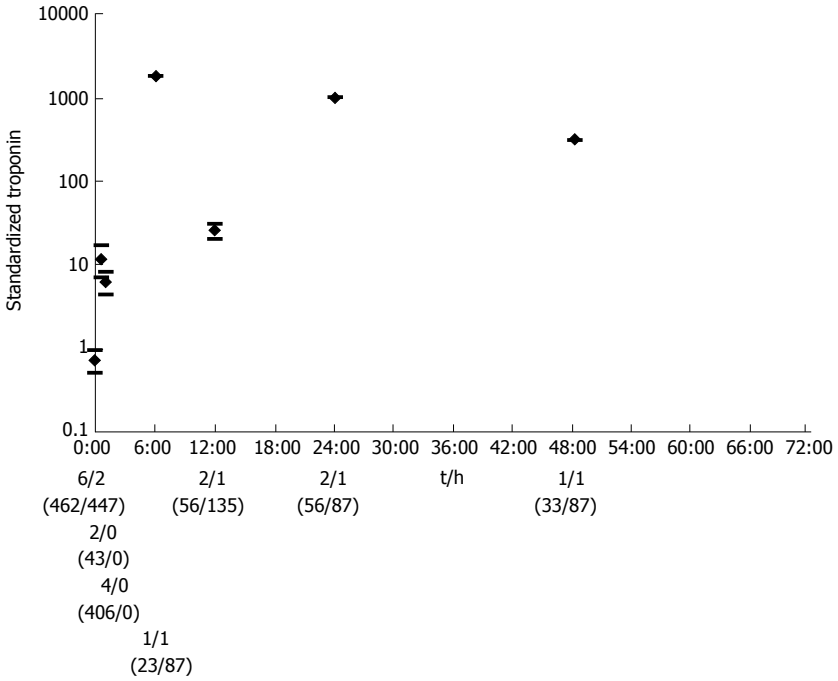

Figure 3 The pooled mean with confidence interval of standardized troponin for the different time points for successful reperfusion after acute myocardial infarction. The number of articles per time point with a conventional Tn test/the number of articles with a HS-Tn test, and the number of test values (conventional Tn tests/HS-tests) are shown below the graph. Tn: Troponin; HS: High sensitive.

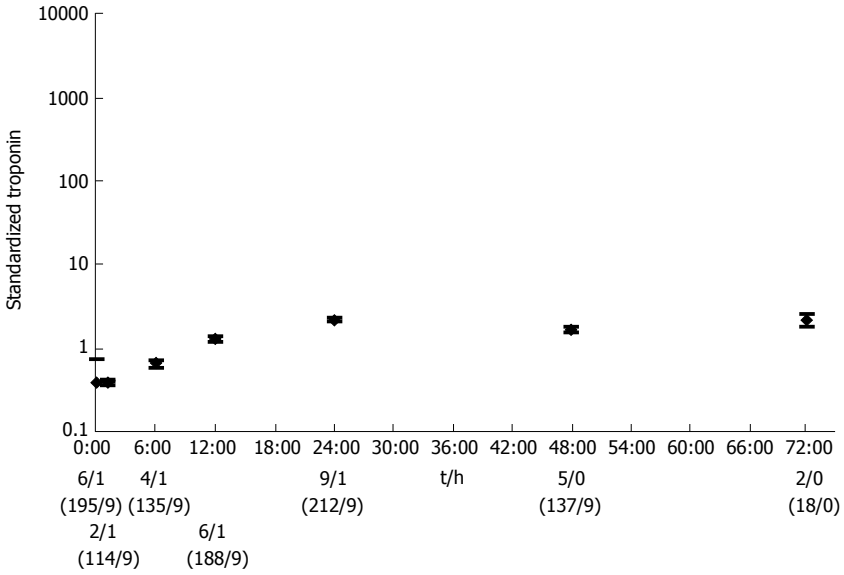

Figure 4 The pooled mean with confidence interval of standardized troponin for type 5 myocardial infarction associated with coronary artery bypass grafting. Time points with only one data source were excluded. The number of articles per time point with a conventional Tn test/the number of articles with a HS-Tn test, and the number of test values (conventional Tn tests/HS-tests) are shown below the graph. Tn: Troponin; HS: High sensitive.

shape of the rise-and-fall curve. Finally, we did not scan the reference lists or related studies identified by Medline from the retrieved studies, nor did we hand-search topic specific journals or conference proceedings. However, our study was not a systematic review focusing on diagnostic accuracy or a therapeutic effect, but merely on the kinetics of Tn. Since only studies that focused on the kinetics of Tn were included we considered that the risk of publication bias was low.

The results of this systematic review give insight in the typical rise and fall of Tn in different types of MI. This systematic review is a first step in understanding the similarities and differences in the Tn kinetics between the different types of MI. The different types of MI each seem to result in a unique rise and fall pattern of Tn. In the future this may allow for optimization of the diagnostic criteria per type of MI. Potentially, understanding the kinetics of Tn can also help in monitoring treatment effec-

tiveness.

COMMENTS

Background

An important diagnostic tool for diagnosing myocardial infarction (MI) is monitoring for dynamic cardiac troponin (Tn) levels. Tn levels are expected to rise and fall in MI. However, the exact shape of the Tn curve in MI is unknown. It is also unknown whether the shape of this curve differs for different types of MI. The aim of this systematic review was to identify the typical shape of the rise and fall curve of Tn following the different types of MI.

Research frontiers

The use of Tn in diagnosing the different types of MI was described by Thygesen *et al* in 2012. For every type of of MI a cut off level and/or the minimum required change in Tn level is suggested for the diagnoses of that particular MI.

Innovations and breakthroughs

An extensive systematic search was conducted to identify all articles concerning the kinetics of Tn in MI type 1, type 4 and type 5. Articles were screened for eligibility and data was extracted in a standardized matter independently by two of the authors. The Tn levels were standardized using the 99th percentile and a pooled mean with 95%CI was calculated for analysis of the results.

Applications

This review suggests that there are important differences in the kinetics of Tn in the different types of MI. Understanding these differences is important for optimizing the diagnostic criteria for these unique types of MI.

Terminology

Myocardial ischemia resulting in myocardial necrosis is called MI. In addition to type 1 spontaneous MI related to atherosclerotic plaque rupture, type 4 MI related to percutaneous coronary intervention and type 5 MI related to coronary artery bypass grafting are classified as distinct types of MI. Cardiac Tn is a sensitive and specific biomarker for myocardial ischemia.

Peer-review

In this systematic review, the authors presented an overview of the typical rise and fall of Tn stratified for the different types of MI.

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MINIREVIEWS

Influence of hospital volume and outcomes of adult structural heart procedures

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Abstract

Hospital volume is regarded amongst many in the medical community as an important quality metric. This is especially true in more complicated and less commonly performed procedures such as structural heart disease interventions. Seminal work on hospital volume relationships was done by Luft *et al* more than 4 decades ago, when they demonstrated that hospitals performing > 200 surgical procedures a year had 25%-41% lower mortality than those performing fewer procedures. Numerous volume-outcome studies have since been done for varied surgical procedures. An old adage "practice makes perfect" indicating superior operator and institutional experience at higher volume hospitals is believed to primarily contribute to the volume outcome relationship. Compelling evidence from a slew of recent publications has also highlighted the role of hospital volume in predicting superior post-procedural outcomes following structural heart disease interventions. These

included transcatheter aortic valve repair, transcatheter mitral valve repair, septal ablation and septal myectomy for hypertrophic obstructive cardiomyopathy, left atrial appendage closure and atrial septal defect/patent foramen ovale closure. This is especially important since these structural heart interventions are relatively complex with evolving technology and a steep learning curve. The benefit was demonstrated both in lower mortality and complications as well as better economics in terms of lower length of stay and hospitalization costs seen at high volume centers. We present an overview of the available literature that underscores the importance of hospital volume in complex structural heart disease interventions.

Key words: Hospital volume; Transcatheter mitral valve repair; Septal ablation; Septal myectomy; Transcatheter aortic valve repair; Left atrial appendage closure

Core tip: Hospital volume is regarded amongst many in the medical community as an important quality metric. This is especially true in more complicated and less commonly performed procedures such as structural heart disease interventions. We present an overview of the available literature that underscores the importance of hospital volume in complex structural heart disease interventions including transcatheter aortic valve repair, transcatheter mitral valve repair, septal ablation and septal myectomy for hypertrophic obstructive cardiomyopathy, left atrial appendage closure and atrial septal defect/patent foramen ovale closure.

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INTRODUCTION

Hospital volume is regarded amongst many in the medical community as an important quality metric. The patients are unlikely to be in a position to choose between hospitals when it comes to emergent procedures. However, in case of non-emergent procedures, volume might be an important quality measure that could guide hospital selection by patients or referring physicians. This is especially true in more complicated and less commonly performed procedures such as structural heart disease interventions. Compelling evidence from a slew of recent publications has highlighted the role of hospital volume in predicting superior post-procedural outcomes following structural heart disease interventions[1,2]. This benefit was demonstrated both in lower mortality and complications as well as better economics in terms of lower length of stay (LOS) and hospitalization costs seen at high volume centers. To address this possible relationship of hospital volume and outcomes of structural heart disease procedures, we performed the search on PubMed and Medline with the following key words: Hospital volume, transcatheter aortic valve repair (TAVR), transcatheter mitral valve repair (TMVR), septal ablation (SA) and septal myectomy for hypertrophic obstructive cardiomyopathy (HOCM), left atrial appendage closure and atrial septal defect (ASD)/patent foramen ovale (PFO) closure and included all the studies with the above key words. We present an overview of the available literature that underscores the importance of hospital volume in complex structural heart disease interventions.

VOLUME-OUTCOME RELATIONSHIP

Seminal work on hospital volume relationships was done by Luft *et al*[3] more than 4 decades ago, when they demonstrated that hospitals performing > 200 surgical procedures a year 25%-41% lower mortality than those performing fewer procedures. Numerous volume-outcome studies have since been done for varied surgical procedures[4-7]. Certain agencies such as the Leapfrog group based in Washington DC have also made attempts to lay down minimal hospital volume requirements for various surgical procedures as a part of quality control[8]. The participating employers can use incentives to motivate their employees to get healthcare in institutions meeting these volume requirements[8]. Such standards for structural heart disease interventions are however not well defined partly because of the novelty of these procedures with lack of substantial evidence regarding volume-outcome relationship.

An old adage "practice makes perfect" indicating superior operator and institutional experience at higher volume hospitals is believed to primarily contribute to the volume outcome relationship[9]. This is further associated with evolution in the process of healthcare, with higher volume hospitals more likely to have better finances to develop more robust standards of care and infrastructure[8]. Hospital volume is thus believed by some to be a surrogate for possibly superior operator experience and availability of better ancillary support[9]. Selective referral with migration of lower risk patients to higher volume hospitals could also provide a healthier patient bias for such institutions[8]. Indeed, physicians might be inclined to refer their patients for elective procedures to larger hospitals with higher procedural volume leaving low volume institutions with more emergent procedures.

TAVR

Following its approval, TAVR has rapidly evolved into a sought-after service with an increasing number of centers offering this structural intervention. However, TAVR program entails extensive resource utilization in terms of physician and ancillary manpower and other operational needs that newer lower volume centers might struggle with. A complex procedure such as TAVR should be per-

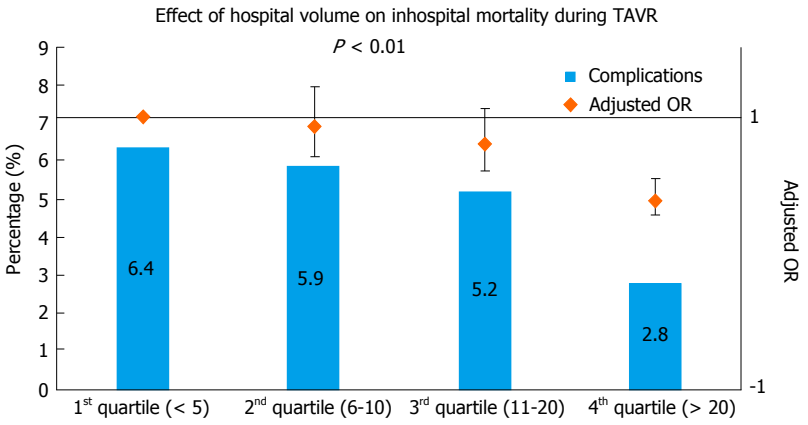

Figure 1 Effect of annual hospital volume on in-hospital mortality and procedural complication during transcatheter aortic valve repair. TAVR: Transcatheter aortic valve repair; OR: Odds ratio.

formed in specialty valvular heart disease centers lead by multidisciplinary heart valve teams. As of today, there is paucity of any evidence-based data to formulate clinical competency guidelines for TAVR. As per a sole consensus document[10], TAVR procedures can be introduced in centers that perform > 1000 catheterizations/400 percutaneous coronary interventions (PCIs) annually with TAVR interventionalists who have performed 100 structural procedures over their lifetime or at least 30 left-sided structural procedures per year. Likewise for surgical support, a minimum institutional annual volume of 50 aortic-valve replacements is recommended with surgeons who have completed 100 valve replacements over their career, with at least 10 considered high risk[10].

Previous literature on surgical valve replacement has highlighted the importance of institutional volume in predicting post-procedural outcomes[11]. Intuitively, one can reason that a similarly complex, percutaneous valve replacement procedure would also have superior results in higher volume institutions. In a recent analysis from Nationwide Inpatient Sample (NIS), we found hospital volume to be significantly predictive of lower in-hospital mortality following TAVR[12] (Table 1 and Figure 1). When compared to patients treated in lowest quartile of hospital volume, adjusted OR of in-hospital mortality in the highest quartile of hospital volume was 0.38 (0.27-0.54, $P \leqslant 0.001$). Increasing hospital volume was also independently predictive of shorter LOS and lower hospitalization costs (Table 1 and Figure 2). A separate spline analysis confirmed the significant hospital volume and outcome relationship with the predicted probability of in-hospital mortality dropping with increasing hospital volume.

TMVR/MITRACLIP

The Centers for Medicare and Medicaid (CMS) in their proposal to cover reimbursement for TMVR/Mitra-clip have laid down some operator and institutional requirements. The institution must have had ⩾ 25 total mitral valve procedures in the previous year of which at least 10 must be mitral valve repairs. In addition, there should have been ⩾ 1000 catheterizations per year performed in that institution, including ⩾ 400 PCIs per year. The individual operator should have had ⩾ 50 structural procedures per year including ASD and PFO and trans-septal punctures. Besides, it also mandates a comprehensive multi-disciplinary heart team comprised of various cardiologists, surgeons and strong ancillary support along with device-specific training as required by the manufacturer.

The National Institutes of Health in United Kingdom have minimal volume requirements for surgical mitral valve repair[13]. This is considered especially vital due to low volume of this procedure and many low volume centers perform mitral valve replacement more frequently in degenerative MR where mitral valve repair is strongly recommended[13]. Again, TMVR is a relatively new procedure with a steep learning curve and will need further studies to appraise specific volume requirements for involved operators and institutions. A more detailed competency guideline is expected in the forthcoming SCAI/AATS/ACC/STS Multisocietal Consensus Statement: Operator and Institutional Requirements for Transcatheter Valve Repair and Replacement: Part 3: Mitral Valve[13]. In another analysis from NIS (Abstract presented as poster presentation at American Heart Association Scientific Sessions 2014, Chicago, IL), we noted the highest hospital volume tertile to be significantly predictive of lower in-hospital mortality and post-procedural complications following TMVR compared to the lowest volume tertile (OR = 0.12, 95%CI: 0.06-0.23, $P < 0.001$) (Table 2 and Figure 3A). The predicted probability of mortality and complications was noted to decrease with increasing hospital volume on an additional spline analysis.

HOCM: SA, SEPTAL MYECTOMY

ACCF/AHA HOCM guideline recommends that an operator be labeled experienced in SA only after he/she has performed > 20 procedures in a facility with a cumulative volume of > 50 procedures[14]. However, given the low overall volume of SA, the maintenance of competency requires an annual operator volume of only 5 ablations with no comment on institutional volume[14].

Table 1 Multivariate regression for different outcomes during transcatheter aortic valve repair

	Multivariate simple logistic regression for mortality		Multivariate simple logistic regression for any complications and mortality		Multivariate simple logistic regression for LOS (LOS ≥ 6 d)		Multivariate simple logistic regression for disposition of transfer to short-term hospital/other facilities/home health care	
Variable	**OR (95%CI)**	***P*-value**	**OR (95%CI)**	***P*-value**	**OR (95%CI)**	***P*-value**	**OR (95%CI)**	***P*-value**
Hospital volume quartile								
1st quartile	1	Referent	1	Referent	1	Referent	1	Referent
2nd quartile	0.92 (0.70-1.21)	0.550	0.86 (0.76-0.99)	0.029	0.82 (0.71-0.94)	0.004	1.06 (0.91-1.23)	0.451
3rd quartile	0.80 (0.60-1.06)	0.114	0.70 (0.61-0.80)	< 0.001	0.91 (0.80-1.05)	0.194	0.65 (0.56-0.75)	< 0.001
4th quartile	0.38 (0.27-0.54)	< 0.001	0.71 (0.62-0.82)	< 0.001	0.85 (0.74-0.98)	0.024	0.77 (0.66-0.90)	0.001
Access								
Transfemoral	1	Referent	1	Referent	1	Referent	1	Referent
Trans-apical	1.54 (1.17-2.03)	0.002	1.44 (1.26-1.64)	< 0.001	2.27 (1.96-2.63)	< 0.001	1.37 (1.18-1.60)	< 0.001
Age (10-yr increment)	1.26 (1.07-1.47)	0.005	0.97 (0.91-1.03)	0.316	1.07 (1.00-1.14)	0.051	1.57 (1.46-1.69)	< 0.001
Gender								
Male	1	Referent	1	Referent	1	Referent	1	Referent
Female	1.09 (0.89-1.36)	0.392	1.21 (1.11-1.33)	< 0.001	1.43 (1.30-1.57)	< 0.001	1.99 (1.79-2.21)	< 0.001
Charlson score								
0	1	Referent	1	Referent	1	Referent	1	Referent
1	1.29 (0.78-2.14)	0.321	1.13 (0.92-1.38)	0.236	1.23 (1.01-1.50)	0.038	1.40 (1.14-1.72)	0.002
≥ 2	1.60 (1.01-2.55)	0.047	1.73 (1.44-2.08)	< 0.001	2.02 (1.69-2.42)	< 0.001	1.72 (1.42-2.07)	< 0.001
Bed size of hospital								
Small	1	Referent	1	Referent	1	Referent	1	Referent
Medium	0.43 (0.28-0.67)	< 0.001	0.89 (0.70-1.15)	0.386	1.18 (0.91-1.52)	0.215	1.17 (0.88-1.56)	0.279
Large	0.42 (0.29-0.61)	< 0.001	0.73 (0.58-0.91)	0.005	1.36 (1.09-1.71)	0.007	1.23 (0.96-1.58)	0.103
Model 2								
Hospital volume quartile (5 procedures increment)	0.88 (0.83-0.93)	< 0.001	0.94 (0.92-0.95)	< 0.001	0.93 (0.91-0.95)	< 0.001	0.95 (0.94-0.97)	< 0.001
Model 3								
Hospital volume quartile (10 procedures increment)	0.77 (0.69-0.86)	< 0.001	0.87 (0.84-0.91)	< 0.001	0.87 (0.84-0.90)	< 0.001	0.91 (0.87-0.95)	< 0.001

LOS: Length of stay; OR: Odds ratio.

Nonetheless, volume remains one of the many factors required to achieve satisfactory post-procedural outcomes. In a retrospective analysis from NIS, we noted highest hospital volume tertile to be significantly predictive of lower post-procedural complications following SA upon multivariate adjustment (OR = 0.51, 95%CI: 0.26-0.98, *P* = 0.04). Parallel to septal myectomy, which has been shown to have excellent outcomes when performed at centers of excellence, SA is more likely to be better performed at centers with volume and resources to care for this unique patient population. Indeed, a recent study showed a higher overall in-hospital mortality and post-procedural complication rate following septal myectomy in the real world clinical practice than that reported from selected referral centers[15]. Although, a trend was seen towards higher institutional volume being associated with better outcomes, the final results were non-significant indicating a need for further studies (Table 3).

ASD/PFO CLOSURE

Some of the initial data suggested that ASD/PFO closure could be performed safely at low-volume hospitals[16]. Relative simplicity of ASD/PFO closure that shares some of the techniques with other, more commonly preformed percutaneous interventions[17] led some to believe that volume-outcome relationship might not hold true for this

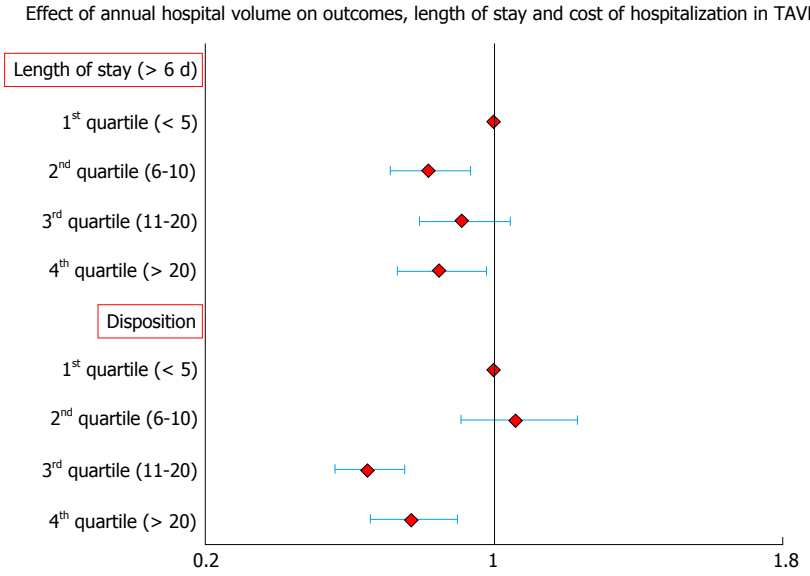

Figure 2 Effect of annual hospital volume on length of stay and cost of hospitalization in transcatheter aortic valve repair. TAVR: Transcatheter aortic valve repair.

Table 2 Multivariate predictors of primary and secondary outcomes for patients who underwent transcatheter mitral valve repair

Variable	OR (95%CI)	*P* value
Hospital volume tertile		
1st tertile	1	Referent
2nd tertile	0.23 (0.12-0.41)	0.177
3rd tertile	0.12 (0.06-0.23)	< 0.001

OR: Odds ratio.

procedure. The current ACC/AHA/SCAI guidelines recommend a minimal annual volume of > 10 ASD/PFO closure procedures for maintenance of catheterization laboratory proficiency. However, these guidelines also note the lack of sufficient evidence based data for this recommendation.

Opotowsky *et al*[18] showed the inverse hospital volume outcome relationship in an early study from the NIS database. In another study that included a larger sample size, an absolute risk reduction of 4.6% was noted when procedures were performed at hospitals with an annual procedural volume > 10[1]. An additional absolute risk reduction of 2.1% was further noticed if procedures were performed at hospitals with an annual volume > 25 indicating a need for possible revision of competency guidelines. Furthermore nearly 30% of the hospitals performing ASD/PFO closures were observed to be below the recommended threshold of 10 annual procedures (Figure 3B and C and Table 3).

LAA CLOSURE, ENDOVASCULAR STENTING OF ADULT COARCTATION

A recent study by Badheka *et al*[2] showed higher hospital volume to be inversely associated with better post-procedural outcomes as well as lower hospitalization costs and shorter LOS[2] (Figure 4 and Table 4). Hospitals with and annual volume cut-off of > 18 procedures had post-procedural complication rate, which compared favorably with trial data. This study added evidence to inverse operator volume-outcome relationship seen in the CAP registry[19]. Further studies are again needed to determine volume thresholds and lay down minimal competency requirements.

The use of stenting for adult aortic coarctation has been on the rise given the literature on favorable initial and intermediate outcomes. In a retrospective analysis, we observed significantly lower rate of post-procedural complications in hospitals performing more than 3 procedures annually (9.5% *vs* 23%, *P* = 0.002) including a lower rate of vascular complications (9.5% *vs* 20.6%) (Figure 5). Adjusted OR of post-procedural complications in hospitals with annual volume of 3 or more procedures was 0.40 (0.19-0.82, *P* = 0.013). These were further complemented by lower hospitalization costs at higher volume hospitals.

LIMITATIONS OF USING HOSPITAL VOLUME

A volume based referral strategy is not without its limitations. This could restrict the entry of newer hospitals in a highly competitive medical field, which might actually provide contractual leverage to bigger hospitals with potential cost inflation. A procedure-based strategy always has the danger of leading to inappropriate procedures by operators and institutions. Again, in order to keep up higher volumes, many institutions may forego quality improvement activities. Besides, low volume centers play an integral role in healthcare by catering to smaller communities especially in rural areas and in pre-tertiary care. The benefits of selective referral to high

Table 3 Hospital volume and primary outcome, length of hospital stay > 2 d, and predictor of highest quartile of cost of care (> $17160) following atrial septal defect/patent foramen ovale closure: Multivariate adjusted model

	Primary outcome		Length of stay		Cost of care	
	OR (95%CI)	*P* value	OR (95%CI)	*P* value	OR (95%CI)	*P* value
Hospital volume (*n* of procedure per yr)						
1st tertile (< 14)	Referent		Referent		Referent	
2nd tertile (14-37)	0.73 (0.57-0.93)	0.013	0.50 (0.36-0.69)	< 0.001	0.72 (0.49-1.07)	0.104
3rd tertile (> 37)	0.67 (0.48-0.94)	0.019	0.37 (0.24-0.57)	< 0.001	2.55 (1.54-4.20)	< 0.001

Three levels hierarchical mixed effects models were generated (patient level factors nested within hospital level factors) with the unique hospital identification number incorporated as random effects. Primary outcome (n = 6328) was adjusted for age, sex, Deyo's modification of Charlson Comorbidity Index, Median Household income, primary payer, hospital teaching status, emergent/urgent admission, weekend admission, Intracardiac Echocardiography use during procedure and hospital volume. In length of stay > 2 d (n = 6302) and predictors of highest quartile of cost (> 17160 $) ($n$ = 5389), we included all variables in primary outcome. Hospital volume were calculated based on the unique hospital identification number on year to year basis. OR: Odds ratio.

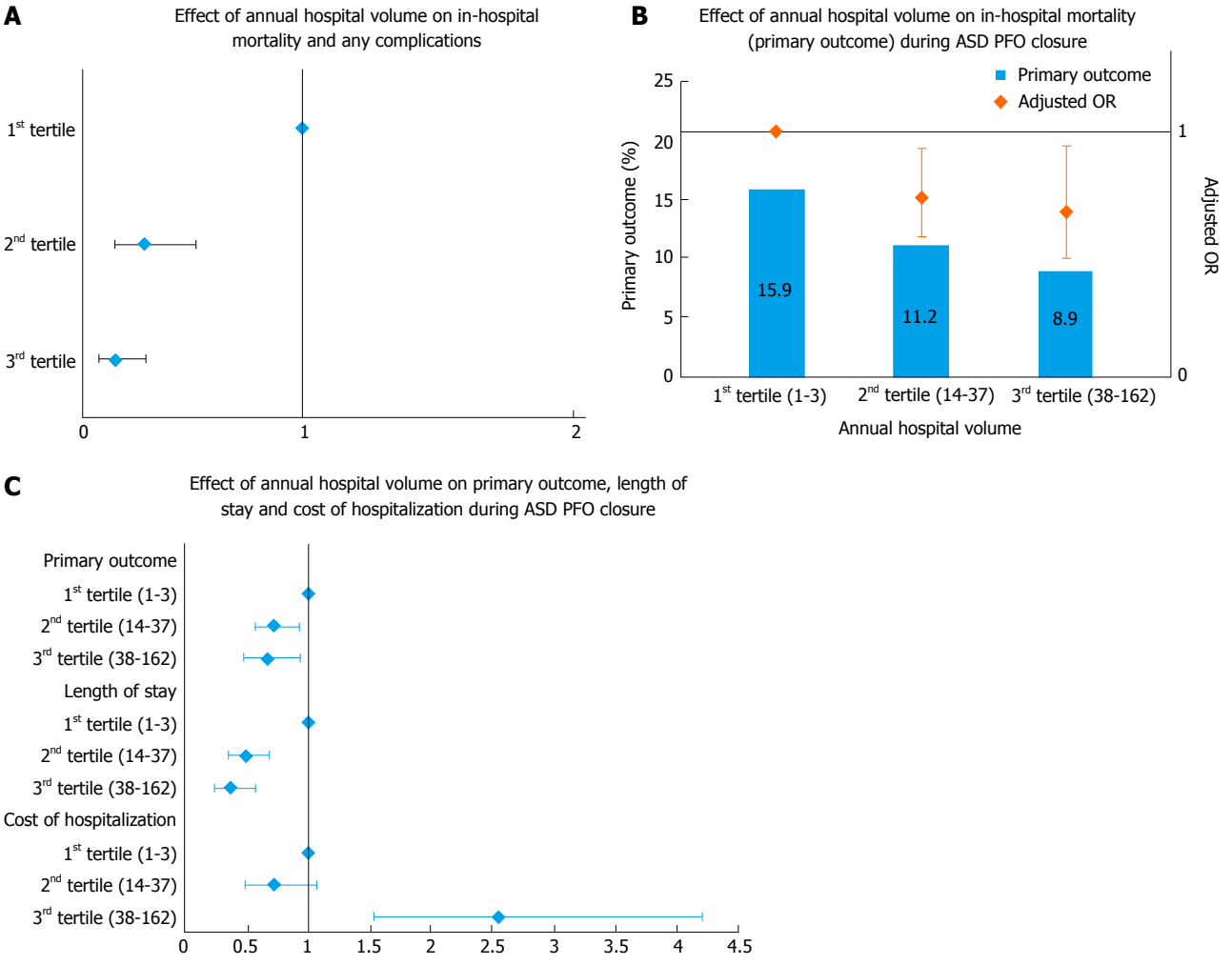

Figure 3 Effect of annual hospital volume. A: On primary and secondary outcome during transcatheter mitral valve repair; B: On in-hospital mortality (primary outcome) during atrial septal defect/patent foramen ovale closure; C: On primary outcome, length of stay and cost of hospitalization during atrial septal defect/patent foramen ovale closure. ASD: Atrial septal defect; PFO: Patent foramen ovale; OR: Odds ratio.

volume centers thus must be weighed against a potential lack of access to healthcare resulting from regionalization. However, most of the emerging structural heart disease interventions are elective procedures that could justify transfer to higher volume centers.

Some authors have also suggested the role of operator volume and experience in contributing towards effect of institutional volume on outcomes. Indeed, some studies studying outcomes of surgical procedures have shown that the institutional-volume relationship might be non-significant once operator volume is accounted for. Nonetheless, other studies have also demonstrated persistent hospital volume outcomes relationship even after adjusting for operator volume. Additionally, hospital

Table 4 Multivariate regression for different outcomes left atrial appendage closure

Any procedural complication or death (n = 264)	OR with 95%CI	P value
Hospital annual LAA closure volume (per unit increase)	0.89 (0.85-0.94)	< 0.001
Length of stay (n = 258)	HR	P value
Hospital annual LAA closure volume (per unit increase)	0.95 (0.92-0.98)	< 0.001
Cost of hospitalization (n = 250)	Estimate ($)	P value
Hospital annual LAA closure volume (per unit increase)	0.96 (0.93-0.98)	< 0.001

LAA: Left atrial appendage; OR: Odds ratio.

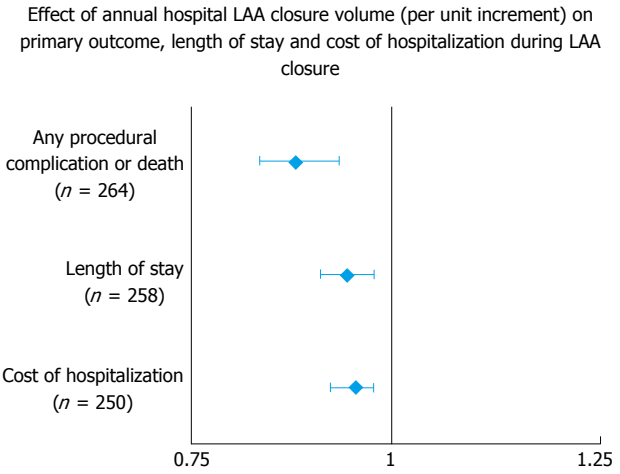

Figure 4 Effect of annual hospital left atrial appendage closure volume (per unit increment) on primary outcome, length of stay and cost of hospitalization during left atrial appendage closure. LAA: Left atrial appendage.

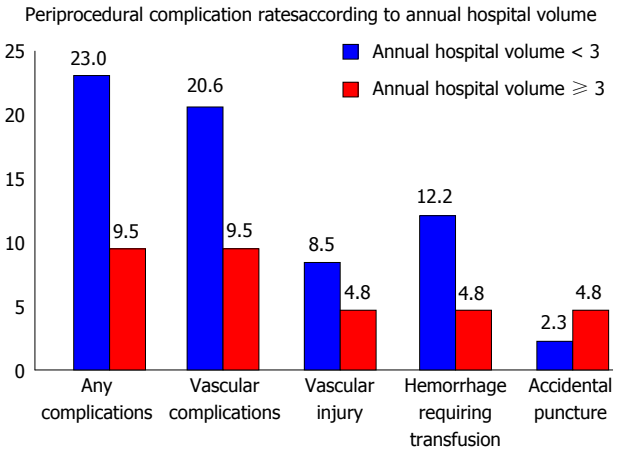

Figure 5 Peri-procedural complication rates according to annual hospital volume.

complexity in terms of range of services and technological provided can be responsible for improved outcomes as shown in a prior study by McCrum *et al*[20] and thus findings of retrospective studies should be interpreted with caution. But in the absence of detailed information on the quality of surgical procedures at a particular hospital, high hospital volume remains a valid contributor in reducing surgical mortality[21].

FUTURE DIRECTIONS

Hospital volume cannot be used as a sole quality metric since many low volume centers are known to provide safe and efficient healthcare. It is important to appraise the factors that result in superior outcomes in a subset of low-volume hospitals and further develop programs that allow other hospitals to adopt such practices. Development of newer structural heart programs with their multidisciplinary heart valve teams have lead to improved outcomes of surgical procedures in these hospital irrespective of annual procedural volume. This was demonstrated in recent analysis of improved outcomes of surgical aortic and mitral valve replacement in TAVR and TMVR capable centers respectively (abstract presented as poster presentation at SCAI 2015 Scientific Sessions, San Diego, CA). Risk-adjusted mortality rates, complication and readmission rates when considered together are some of the other important factors that can be used to assess quality of healthcare provided by different hospitals.

It has been previously demonstrated that a high coronary intervention volume does not translate into superior structural heart disease interventions outcomes[22]. Moreover, the procedural volume requirements are difficult to apply to structural disease interventions since these complex, highly specialized interventions are performed in much lower numbers. This further lends support for amendments in training requirements with a focus on procedure specific training with variable proctoring and use of simulators, in depth knowledge of the field besides annual volume recommendations. Additionally, a standardized process of certification and maintenance based on outcomes needs to be developed[20]. A plausible option is the evolution of umbrella training wherein trainees could have the opportunity to rotate through different hospitals and gain knowledge about best clinical practices.

CONCLUSION

Hospital volume is indeed a genuine predictor of post-procedural outcomes. This is important in the current era of expanding structural heart disease interventions, which are relatively complex with evolving technology and a steep learning curve. However, other quality metrics should also be accounted for in order to avoid labeling any good low-volume hospitals as underperformers. Further studies are mandatory to study the volume-outcome relationship for multiple emerging structural interventions

since current data on many such interventions is either extrapolated from other procedures or based on consensus rather than evidence.

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MINIREVIEWS

Collateral findings during computed tomography scan for atrial fibrillation ablation: Let's take a look around

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Abstract

The growing number of atrial fibrillation catheter ablation procedures warranted the development of advanced cardiac mapping techniques, such as image integration between electroanatomical map and cardiac computed tomography. While scanning the chest before catheter ablation, it is frequent to detect cardiac and extracardiac collateral findings. Most collateral findings are promptly recognized as benign and do not require further attention. However, sometimes clinically relevant collateral findings are detected, which often warrant extra diagnostic examinations or even invasive procedure, and sometimes need to be followed-up over time. Even though reporting and further investigating collateral findings has not shown a clear survival benefit, almost all the working groups providing data on collateral findings reported some collateral findings eventually coming out to be malignancies, sometimes at an early stage. Therefore, there is currently no clear agreement about the right strategy to be followed.

Key words: Collateral findings; Incidental findings; Incidentalomas; Cardiac computed tomography; Image integration

Core tip: Several cardiac computed tomography (CT) scans are performed worldwide in order to better delineate left atrial anatomy before atrial fibrillation (AF) ablation. A thorough examination of the entire field of view often discovers cardiac or extra-cardiac collateral findings, which might represent potentially malignant diseases. Early detection of such diseases may guarantee a curative treatment. Our objective is to consolidate the current literature about collateral findings detected at cardiac CT before AF ablation and to highlight the potential

implications of systematically reporting and following up such findings.

Perna F, Casella M, Narducci ML, Dello Russo A, Bencardino G, Pontone G, Pelargonio G, Andreini D, Vitulano N, Pizzamiglio F, Conte E, Crea F, Tondo C. Collateral findings during computed tomography scan for atrial fibrillation ablation: Let's take a look around. *World J Cardiol* 2016; 8(4): 310-316 Available from: URL: http://www.wjgnet.com/1949-8462/full/v8/i4/310.htm DOI: http://dx.doi.org/10.4330/wjc.v8.i4.310

IMAGE INTEGRATION IN ATRIAL FIBRILLATION ABLATION

Cardiac computed tomography (CT) is being increasingly required for a large amount of indications, such as coronary artery disease, congenital heart disease, and detection of intracardiac thrombi[1]. It is also frequently performed among patients undergoing atrial fibrillation (AF) catheter ablation, in order to achieve three-dimensional reconstruction of the left atrium (LA), which is crucial for pre-procedural planning of the ablation strategy and accurate intra-procedural catheter navigation, especially in complex cardiac anatomies[2-4].

Pulmonary vein (PV) isolation has become a cornerstone in the treatment of AF, and may represent a first-line therapy in selected cases[5-8]. However, complicated LA or PV anatomy can make it extremely difficult to access some areas, thus contributing to suboptimal success rates and hindering the successful application of this technique[9,10]. Moreover, it has been ascertained that PV anatomic variations are fairly common[11-13]. Knowledge of the conventional pulmonary venous anatomy, as well as of anatomic variants, is crucial for preprocedural planning and safer catheter navigation. Fluoroscopy alone cannot differentiate between PVs, LA and surrounding structures. On this proposal, cardiac CT has gained acceptance, among cardiac electrophysiologists, as the preferred radiological investigation in order to precisely delineate LA and PV anatomy, because of its better diagnostic gain on intrathoracic organs and vessels as compared to other investigations, such as intracardiac echocardiography[14]; moreover, cardiac CT is more widely available than magnetic resonance, requires shorter scanning times and is better tolerated by patients[2-4,15]. These characteristics made cardiac CT the gold standard exam for image integration in AF ablation.

Cardiac CT performed for AF ablation is a chest CT angiography scan acquired using multidetector CT scanners with a field of view (FOV) which usually extends vertically from the level of the carina to the diaphragm. CT scan is generally not electrocardiographically (ECG)-gated, since a consistent part of the patients may be in AF during the examination. The absence of ECG-gating is the main difference between cardiac CT scan performed for AF ablation and for coronary artery disease, since synchronization with the ECG is necessary in order to investigate coronary arteries. Scan synchronization with the contrast medium is often performed with the bolus tracking technique, that is, injecting a bolus of radio-opaque contrast media into the patient *via* a peripheral vein, tracking the volume of contrast within a region of interest, and then following it with the CT scanner after it reaches that region. After imaging the left atrium, it is possible to build a volume rendering three-dimensional image of the structures of interest, which is imported in the electroanatomical mapping system workstation and segmented using an image processing software, in order to better distinguish the left atrium from the surrounding structures. Once the segmentation process is complete, the three-dimensional representation of the left atrium is displayed in the electroanatomical mapping system and is superimposed to the three-dimensional electroanatomical map created by the operator; the electroanatomical map and the CT image are aligned to each other in order to allow the operator to move the mapping catheter within the three-dimensional representation of the left atrium.

Image integration between the cardiac CT scan (performed before the ablation) and the electroanatomical LA map (obtained intraprocedurally), allows the operator to have a detailed roadmap of the actual patient's anatomy available during the ablation procedure. This is crucial for anatomic definition of ablation targets and precise catheter navigation throughout complex anatomies, as well as for limiting collateral damage to adjacent structures, such as the esophagus (lowering the risk of atrio-esophageal fistula)[16]. This technique is particularly useful while ablating difficult targets, such as the ridge of Marshall between the left-sided PVs and the left atrial appendage, in order to avoid ablating either inside the appendage (risk of perforation) or too deep inside the PVs (risk of PV stenosis) (Figure 1). Image integration systems have been shown to reduce procedural and fluoroscopy times, and even improve procedural outcomes, thus justifying their increased procedural costs[17-19].

COLLATERAL FINDINGS DETECTED BY CARDIAC CT FOR AF CATHETER ABLATION

Cardiac CT scan usually details only a small FOV strictly around the heart, although almost the entire chest is irradiated during image acquisition. A larger FOV is then available from the unprocessed data to examine the neighboring structures, such as lungs, breasts, mediastinum, spine, and upper abdomen, with no additional X-rays exposure. While examining the entire FOV of a cardiac CT, it is frequent to encounter cardiac or extracardiac collateral findings (CFs) during the imaging study (Figures 2 and 3). The term "collateral finding" reflects an incidentally discovered mass or lesion, detected by CT, magnetic resonance imaging, or other imaging modality, which is not related to the primary objectives of the

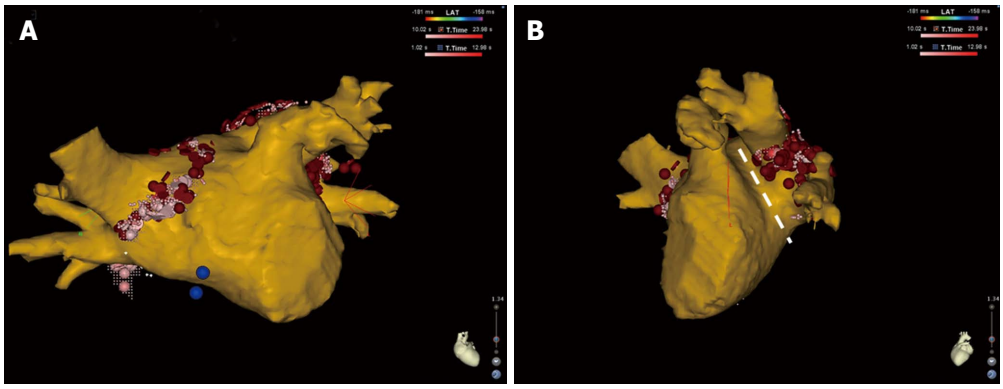

Figure 1 Antero-posterior (A) and left lateral (B) view of three-dimensional reconstruction of the left atrium and pulmonary veins after merging the cardiac computed tomography with the electroanatomical map created with the Carto 3 system (Biosense Webster, Inc., Diamond Bar, CA, United States). Note the ablation tags (red dots) placed around the pulmonary vein ostia on the computed tomography reconstruction. In the left lateral view, the narrow ridge between the left-sided pulmonary veins and the left atrial appendage can be appreciated (white dashed line).

examination; CFs are also called "incidental findings" or "incidentalomas"[20]. A collateral finding is considered "clinically significant" when its detection warrants further investigations or therapeutic measures, or causes a change in the patient management. Most encountered extra-cardiac CFs pertain to the lungs, particularly small (< 4 mm) pulmonary nodules. Other frequently met CFs are degenerative spine disease, aortic disease, swollen mediastinal or hilar lymph nodes, liver lesions.

On this basis, several working groups reported about the prevalence and clinical significance of such CFs during cardiac CT scans. The early reports mostly referred to CT studies performed in order to diagnose coronary artery disease, which is the main indication for cardiac CT scan[21-25]. The reported prevalence of CFs during 4 electron beam CT studies ranged between 7.8% to 53%, with 4.2% to 11% of scanned patients needing follow-up examinations; this wide range of prevalence can be explained by different technologies and definition of CFs used in those studies[26-29]. Along with the expanding indications for AF catheter ablation, there has been a parallel growth in the request of cardiac CT to depict LA and PV anatomy for image integration. As a consequence, some studies reporting CFs detected before AF ablation have been published (Table 1)[30-35].

Wissner *et al*[30] studied 95 patients undergoing PV isolation between 2003 and 2007 with a 16-slice and subsequently 64-slice multidetector scanner, covering an area from above the clavicle to diaphragm, and found that 53% of patients had either cardiac or extracardiac CFs. Most CFs were extracardiac (78 out of 83), and more than half (46 out of 83) were pulmonary. Fifteen patients (16%) needed additional tests, and 6 of them (6.8%) had therapeutic implications due to the detection of unexpected findings. One patient (1.1%) had an adenocarcinoma of the lung diagnosed, which was treated surgically[30].

Sohns *et al*[31] performed 64-slice multidetector CT of the chest and upper abdomen in 158 patients for identification of PV anatomy. They looked for extracardiac CFs only. A total of 198 extracardiac CFs were detected in 72% of patients, and 31% of patients had at least one clinically significant or potentially significant finding. Lung cancer was diagnosed in 2 patients (1.3%)[31].

The same group assessed the incidence of both cardiac and extracardiac CFs among an extended population of 224 AF patients. In 91% of patients an average of 3.2 cardiac findings per patient were discovered, while 619 extra-cardiac findings (2.8 per patient) were detected in 80% of patients. Thirty-two percent of the 619 extracardiac findings were classified as "clinically significant", including 2 cases of previously unknown cancers (esophageal and pulmonary, respectively; 0.9% of patients) and a newly diagnosed aortic dissection. The authors explained the relatively high incidence of extra-cardiac findings with the detailed image and the advanced age of their patients[32].

Schietinger *et al*[33] reached analogous conclusions, finding extra-cardiac CFs in 69% of patients, the majority being pulmonary, and clinically significant CFs in 24% of patients at ECG-gated multidetector CT for PV evaluation.

Martins *et al*[34] described a lower prevalence of CFs among 250 consecutive patients (23%). Half of the 76 CFs were pulmonary, including 2 lung cancers (0.8% of patients) and 2 pulmonary fibroses. Several findings led to specific disease management, but no focused follow-up was performed in order to get information about the impact of reviewing the entire FOV on patients' outcome[34].

Our group enrolled 173 patients referred for catheter ablation of AF. Fifty-six percent of the patients ha at least one CF, and 33% had clinically significant CFs warranting further follow-up or investigations. In 10% of them, the detection of a CF led to therapeutic decisions. Three cases of bronchogenic carcinoma were eventually diagnosed (1.7% of the study population)[35]. After publication of the study, two more cases of bronchogenic carcinoma were diagnosed during further follow-up chest CTs performed in patients with incidentally detected pulmonary nodules (unpublished data). All lung cancers detected among our patients were at a relatively early stage; therefore, curative treatment was possible in all the cases.

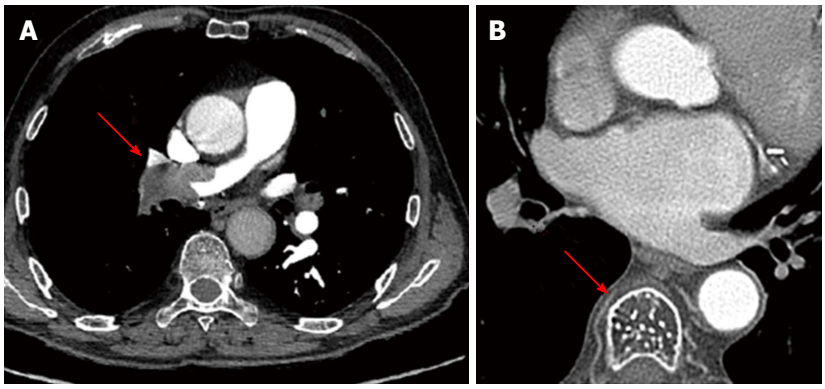

Figure 2 Examples of collateral findings detected with the preprocedural cardiac computed tomography. A: Pulmonary thromboembolism involving principal branch of right pulmonary artery (red arrow); B: Classic "polka dotted" appearance due to the thickened vertebral trabeculae, highly suspicious for vertebral hemangioma (red arrow).

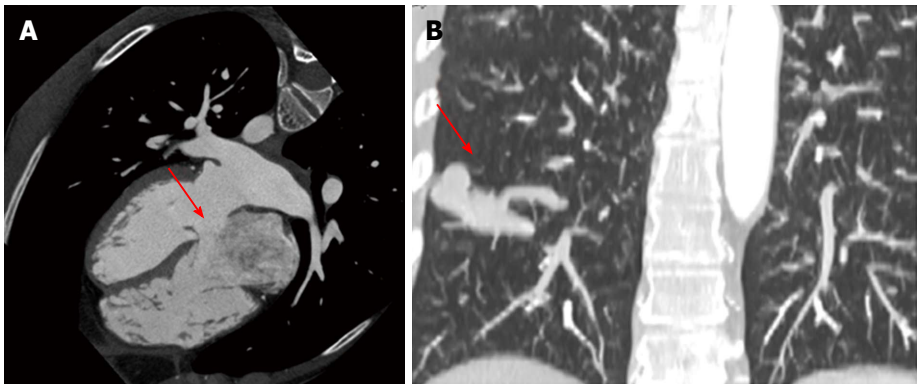

Figure 3 Examples of collateral findings detected with the preprocedural cardiac computed tomography. A: Ostium primum atrial septal defect (red arrow); B: Abnormal dilated vessels (red arrow) diagnostic for pulmonary arterovenous malformation located in the lower lobe of the right lung.

In summary, the proportion of patients with CFs is very high among the reported studies of cardiac CT performed for AF catheter ablation. Incidental findings requiring further investigations or follow-up are also quite frequent. Rather consistently, almost half of all collateral findings are represented by pulmonary nodules. Malignancy is diagnosed in a percentage ranging from 0% to 1.7% of patients.

REPORTING AND FOLLOWING UP COLLATERAL FINDINGS: AN OPEN DEBATE

Because of the large diffusion of AF catheter ablations, an increasing number of cardiac CT is being performed worldwide. The number of reported CFs is increasing, due to the growing number of cardiac CT performed and to the improved spatial resolution of the CT scanners. The main problem in reporting CFs is the subsequent flow of further investigations and procedures that are performed in order to rule out potentially deleterious pathologies. On the one hand, one should always keep in mind that in some cases, the detection of an early stage malignant disease might allow appropriate treatment and prolong or save a patient's life. However, to date robust data regarding the potential clinical benefits of reporting and following-up CFs is still lacking, and it has not been shown that reporting CFs may change the course of the disease or prolong survival, especially in the case of metastatic cancers or pathologies with an unpredictable natural history. The risk of undesirable effects carried by additional procedures, such as contrast medium-induced complications or the lifetime risk of ionizing radiation exposure-related cancer, must be kept in mind as well. This hinders the development of a widely accepted approach to such findings[36]. As a consequence, there is still disagreement about the appropriateness of reviewing and reporting extra-cardiac CFs during cardiac CT studies[37,38].

Once a CF is reported, there is also uncertainty about the decision to follow-up such findings over time. Some CFs are promptly deemed insignificant, that is, they do not require any additional examination. The dilemma about CFs follow-up arises when so-called "clinically significant collateral findings" are detected. While the anxiety for medico-legal implications from underreporting incidental findings would lead to describe and follow-up any lesion that is found in the FOV, some concern has been raised about increased financial burden in front of

Table 1 Studies about collateral findings detected at cardiac computed tomography performed for atrial fibrillation ablation

Ref.	*n* of pts	Mean age (yr)	Smoking history	Scanner	FOV	Collateral Findings, *n* (% of patients)	Cardiac (*n*)	Extracardiac (*n*)	Pulmonary (*n*)	Extra pulmonary (*n*)	Clinically significant	Malignancies
Wissner *et al*[30]	95	62 ± 10	45%	16- and 64-slice	Above clavicle to diaphragm	83 (53%)	5	78	46	37	16% of patients	1 (1.1%)
Sohns *et al*[31]	158	NR	NR	64-slice	Supraaortic region to the heart base and upper abdomen	198 (72%)	NR	198	47	151	31% of patients	2 (1.3%)
Sohns *et al*[32]	224	64 ± 10	38%	64-slice	Supraaortic region to the heart base and upper abdomen	1343	724	619	77	542	32% of extracardiac findings	2 (0.9%)
Schietinger *et al*[33]	149	55.9 ± 11	47%	16-slice	Aortic arch to diaphragm	110 (69%)	NR	102	70	32	24% of patients	0 (0%)
Martins *et al*[34]	250	55.2 ± 9.6	NR	64-slice	20-25 cm centered on the heart	58 (23%)	3	73	38	38	NR	2 (0.8%)
Casella *et al*[35]	173	59 ± 10	50%	64-slice	Carina to diaphragmatic domes	164 (56%)	14	150	74	90	33% of patients	3 (1.7%)

FOV: Field of view; NR: Not reported.

an unclear benefit while pursuing this strategy.

American guidelines on coronary artery imaging recommend a systematical review of extracardiac structures within the FOV during a CT scan, especially when risk factors for cancer exist[39]. Missing a malignant cancer, especially in a potentially curable stage, would have deleterious consequences for the patient, as well as potential medico-legal implications for the radiologist. The Fleischner Society and the American College of Radiology provided some recommendations about how to manage incidentally detected small pulmonary nodules[40] and abdominal incidentalomas[41].

The Early Lung Cancer Action Project evaluated 1000 asymptomatic smokers aged at least 60 years, finding pulmonary nodules in 23% of the patients; 12% of these patients with noncalcified pulmonary nodules had lung malignancies, which were mostly non detectable on chest radiography[42].

Nevertheless, it is still unclear whether the strategy of examining the entire FOV and reporting all CFs would be beneficial for the patients' clinical outcome. In fact, reporting all CFs translates into additional follow-up with potential further radiation exposure, increased costs and patients' anxiety, and sometimes, invasive procedures are needed in order to complete the follow-up. Most of those CFs are eventually found to be benign and have little or no clinical influence on patients' health. A large study provided a cost analysis of following-up such findings after CT scan for the screening of coronary heart disease[37]. Among 966 patients, 41.5% had extracardiac CFs. Additional diagnostic examinations required extra costs of 83.035 United States dollars. The authors concluded that reporting CFs did not provide a clear mortality benefit because CFs were not an independent predictor of noncardiac death. However, the authors did not report whether patients with a diagnosis of malignancy received life-saving or life-prolonging interventions, therefore it is not advisable to draw conclusions about difference in mortality between patients with and without CFs. Moreover, they used a too short mean follow-up (18 mo) to evaluate the course of potentially slow-progressing diseases. Sohns *et al*[32] estimated additional costs as high as about 42.543 United States dollars (190 United States dollars per patient) for subsequent diagnostic examinations (excluding invasive procedures) of incidentally detected extra-cardiac findings at cardiac CT before AF ablation. A clear clinical benefit was achieved in 1.1% of patients, however the authors did not attempt to investigate the potential clinical implications of such strategy.

Larger studies are warranted to understand the real impact on patients' outcome of CFs follow-up. In particular, a study randomizing patients with CFs to either further investigations or no follow-up would answer this question, if ethically viable.

In our opinion, on the basis of the potential detection of early stage cancers, until large studies analyze the cost-benefit ratio of such approach in a real-world scenario, the full set of abnormalities that are visible in the entire FOV should be reported, for ethical reasons. Obviously, once CFs are reported, smoking history, previous cancer, presence of first-degree relatives with history of cancer, or other known risk factors should be taken into account in the decision-making process of further follow-up.

CONCLUSION

The large number of cardiac CT performed for AF catheter ablation and the improved spatial resolution of modern CT scanners generates a huge number of serendipitously

detected collateral findings (mostly extracardiac). Collateral findings are very frequently detected during cardiac CT studies, and a consistent proportion of them may require further investigations or follow-up. The optimal strategy to manage CFs is still debated, since most CFs are eventually found to be benign at the end of a diagnostic process which implies an increased financial burden and, in some cases, even some clinical risks for the patient. Moreover, a real clinical benefit of incidentally detecting malignant diseases has not been demonstrated. However, the risk of missing an early stage malignant disease should be considered while deciding whether reporting and following-up CFs or not. Almost all the studies published so far reported some malignant cancers, which could be treated after being serendipitously diagnosed by cardiac CT. We therefore advise a thorough inspection of the entire irradiated FOV, as well as a strict cooperation between cardiologists and radiologists for a comprehensive examination of cardiac CTs, in order to avoid missing important diseases in the examined FOV.

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ORIGINAL ARTICLE

Retrospective Study

Impact of computed tomography image and contact force technology on catheter ablation for atrial fibrillation

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Abstract

AIM: To investigate the impact of using computed tomography (CT) and contact force (CF) technology on recurrence of atrial tachyarrhythmia after atrial fibrillation (AF) ablation.

METHODS: This non-randomized study included 2 groups of patients. All patients had symptomatic recurrent paroxysmal or persistent AF and were treated with at least 1 anti arrhythmic medication or intolerant to medication. The first group included 33 patients who underwent circumferential pulmonary veins isolation (PVI) for AF during 2012 and 2013 guided by CT image integration (Cartomerge, Biosense Webster, Diamond Bar, CA, United States) of left atrium and pulmonary veins into an electroanatomic mapping (EAM) system (CT group) using standard irrigated radiofrequency catheter (ThermoCool, Carto, Biosense Webster, Diamond Bar, CA, United States) or irrigated catheter with integrated CF sensor (Smart Touch, Carto, Biosense Webster, Diamond Bar, CA, United States). The second group included immediately preceding 32 patients who had circumferential PVI by standard irrigated catheter (ThermoCool) using only EAM (Carto) system (EAM group). Linear lesions were performed according to the discretion of operator.

RESULTS: Sex, age, and persistent AF were not different between groups. PVI was achieved in all patients in both groups. Linear ablations including cavo-tricuspid isthmus and or roof line ablation were

not different between groups. Free of atrial tachyarrhythmia during follow-up of 24 mo was significantly higher among CT group compared to EAM group (81% *vs* 55%; respectively; P = 0.027). When 11 patients from CT group who had ablation using Smart Touch catheter were excluded, the difference between CT group and EAM became non significant (73% *vs* 55%; respectively; P = 0.16). Sub analysis of CT group showed that patients who had ablation using Smart Touch catheter tend to be more free of atrial tachyarrhythmia compared to patients who had ablation using standard irrigated catheter during follow-up (100% *vs* 73%; respectively; P = 0.07). Major complications (pericardial effusion, cerebrovascular accident/transient ischemic attack, vascular access injury requiring intervention) did not occurred in both groups.

CONCLUSION: These preliminary results suggest that CT image integration and CF technology may reduce the recurrence of atrial tachyarrhythmia after catheter ablation for AF.

Key words: Atrial fibrillation; Catheter ablation; Image integration; Contact force

Core tip: The aim of this nonrandomized study was to determine the impact of integrating computed tomography (CT) image of left atrium into electroanatomical mapping (EAM) system and using of contact force (CF) technology on recurrence of atrial tachyarrhythmia after atrial fibrillation (AF) ablation. We found that combination of CT image integration into EAM and CF technology might reduce the recurrence of atrial tachyarrhythmia after catheter ablation for AF during follow-up period of 24 mo.

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INTRODUCTION

In treatment of symptomatic and drug refractory atrial fibrillation (AF), catheter-based pulmonary veins isolation (PVI) has been established as a standard procedure by using a single-tip ablation catheter for creating linear lesion surround ipsilateral pulmonary veins (PVs)[1]. Nevertheless, repeat procedures are required in a significant number of cases and recurrent PV conduction is responsible for most ablation failures in paroxysmal AF[2].

The durability of PVI and clinical outcome after radiofrequency (RF) ablation is affected by the contact force (CF) between the catheter tip and the tissue. Insufficient CF may result in an ineffective lesion, where as excessive CF may result in complications[3]. Catheter ablation using real-time CF technology was reported to be safe for the treatment of supraventricular tachycardia and AF[3]. In addition, understanding the anatomy of left atrium (LA) and PVs is essential for the safety and effectiveness of Procedure. Pre-procedural cardiac computed tomography (CT) helps to evaluate the three dimension (3D) and complex anatomy of LA and PVs[4].

We assume that integrating CT Image of LA/PVs into electroanatomical mapping (EAM) system and using CF technology may reduce the clinical recurrence of atrial tachyarrhythmia after ablation of AF.

MATERIALS AND METHODS

We summarized all patients who underwent circumferential PVI for AF during 2012 and 2013 guided by CT image integration into an EAM (Cartomerge, Biosense Webster, Diamond Bar, CA, United States) system (CT group). This group was compared to immediately preceding patients who had PVI using only EAM (Carto, Biosense Webster, Diamond Bar, CA, United States) system (EAM group).

All patients had symptomatic recurrent paroxysmal AF or persistent AF (less than 3 mo duration) who were treated with at least 1 anti arrhythmic drug (AAD) or intolerant to medication. All patients with paroxysmal AF were treated with IC AADs, and all patients with persistent AF were treated with amiodarone.

Ablation procedure

The procedure was performed during deep sedation with fentanyl and midazolam. Double trans-septal punctures were done with guidance of intra-cardiac echo (ICE): One for circular mapping catheter (Lasso, Biosense Webster, Diamond Bar, CA, United States) and one for ablation catheter.

The ablation catheter used was 3.5-mm standard externally - irrigated (ThermoCool, Carto, Biosense Webster, Diamond Bar, CA, United States) for all patients in EAM group and part of patients of CT group. Externally-irrigated Smart Touch catheter (ST, Carto, Biosense Webster, Diamond Bar, CA, United States) was used in the remaining patients of CT group (Figure 1). The Smart Touch catheter is capable of directly assessing CF and showing its absolute value and orientation by means of a 3D vector in real time during the procedure[5].

In the EAM group, wide circumferential ablation of ipsilateral veins pair at the antrum about 1 cm of veno-atrial junction was performed (Figure 1). The ostium and veno-atrial junction of each PV was identified by intra cardiac electrogram, dragging the ablation or Lasso catheter back under fluoroscopic guidance, and ICE. Isolation of each vein was confirmed by lasso catheter. In the CT group, the EAM was merged with 3D-anatomical chamber reconstructions of LA and PVs derived from pre procedure (up to 24 h) cardiac CT. Image integration

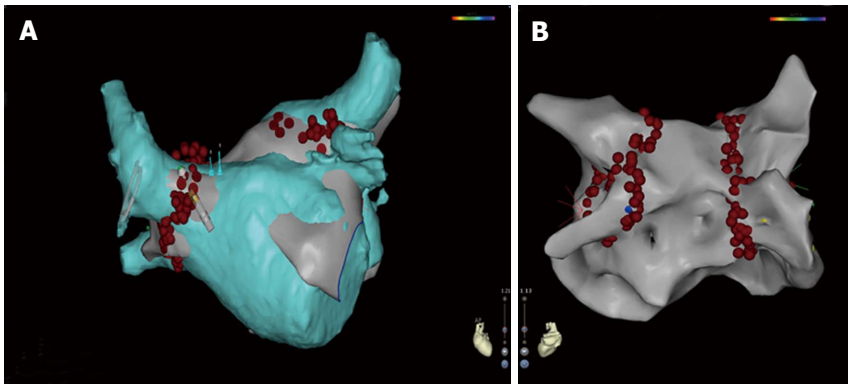

Figure 1 Carto screenshot during pulmonary veins isolation. A: Anterior-posterior view showing CT image of left atrium integrated into the electroanatomic map (CT group). The ablation in this case was performed using the Smart Touch catheter. The tip of the Smart Touch catheter is shown with 3D vector; B: Posterior-anterior view showing electroanatomic mapping (EAM group) of left atrium with ablation points around pulmonary veins. EAM: Electroanatomic mapping; CT: Computed tomography; 3D: Three dimension.

Table 1 Baseline characteristics

	EAM group (n = 32)	CT group (n = 33)	P
Sex (male)	19	24	0.3
Age (yr)	55 ± 8.8	56.7 ± 11.6	0.6
Persistent AF	5	4	0.7
CTI Ablation	7	7	0.76
Roof line ablation	8	8	0.77
Major complications	0	0	

EAM: Elecroantomic mapping; AF: Atrial fibrillation; CTI: Cavotricuspid isthmus; CT: Computed tomography.

is based on registration involving landmark points and surface alignment using the Cartomerge software as described previously[6] (Figure 1). The ablation was performed in similar way as in the EAM group by standard irrigated catheter or Smart Touch catheter. When Smart Touch catheter was used, ablation was done only when the force was at least 10 g (optimal range for ablation was considered as 10-40 g). We tried to deliver RF energy when the CF is > 10 g and is stable for at least 20 s.

RF energy was delivered at a maximum power of 25 W at a flow rate of 17 mL/min along the posterior wall, and at a maximum power of 35 W at a flow rate of 30 mL/min along the anterior wall and elsewhere in the atria. The maximum temperature was set at 43 ℃. RF ablation was continued at each site until local electrograms were abolished or for 30 s. Linear lesions including roof line and or cavo-tricuspid isthmus line were performed in some patients according to discretion of the operator. All the procedures in both groups were performed by 2 experienced operators.

All patients were followed in the outpatient clinic every 3 mo for 24 mo. Recurrence was defined as any clinical or documented atrial tachyarrhythmia lasts more 30 s after a blanking period of 3 mo. All patients were treated with anticoagulation for at least 3 mo. Anticoagulation was continued after 3 mo in high risk patients. AADs were stopped after 3 mo.

Statistical analysis

Variables are expressed as mean ± SD. Comparisons between groups were performed with Student's t test. Categorical variables expressed as numbers and percentages were compared with a χ^2 test. Kaplan - Meier survival curve was used for estimation of recurrence of atrial tachyarrhythmia during 24 mo follow-up. A P value < 0.05 was considered statistically significant. The statistical methods of the study were reviewed by biomedical statistician.

RESULTS

The EAM group included 32 patients, and the CT group included 33 patients. Baseline characteristics are similar (Table 1). The AF duration before ablation in both groups was 1-3 years.

Circumferential PVI with confirmation of isolation was performed in all patients in both groups. Cavotricuspid isthmus ablation was performed in the index procedure in 7 patients in the EAM group and in 7 patients in the CT group (P = 0.76). Roof line was performed in the index procedure in 8 patients in the EAM and in 8 patients in the CT group (P = 0.77) (Table 1).

All patients completed the 24 mo follow-up. Free of atrial tachyarrhythmia during 24 mo was significantly higher among CT group compared to EAM group (81% *vs* 55%; respectively; P = 0.027) (Figures 2-4). When 11 patients from CT group who had ablation using Smart Touch catheter were excluded, the difference became non significant (73% *vs* 55%; respectively; P = 0.16) (Figures 2 and 3).

Sub analysis of CT group showed that patients who had ablation using Smart Touch catheter tended to be more free of atrial tachyarrhythmia compared to patients who had ablation using standard irrigated catheter (100% *vs* 73%; respectively; P = 0.07) (Figure 3). Of note, all patients who had recurrence of atrial tachyarrhythmia had AF except 1 patient from CT group and 2 patients from EAM group who had atypical atrial flutter.

Major complications (pericardial effusion/tamponade,

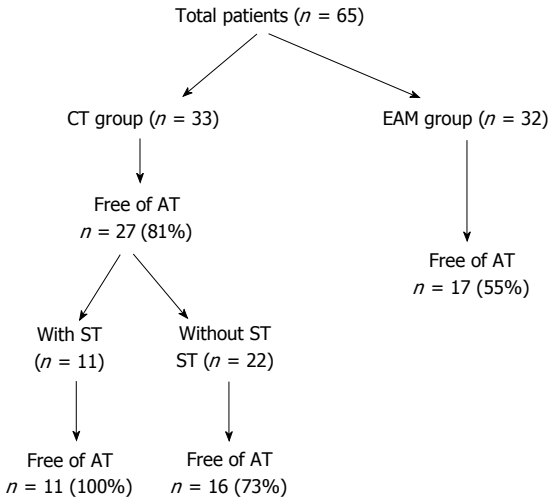

Figure 2 Flowchart reporting the different patient groups and the results. ST: Smart touch; AT: Atrial tachyarrhythmia; EAM: Electroanatomic mapping; CT: Computed tomography.

cerebrovascular accident/transient ischemic attack, and or vascular access injury requiring intervention) did not occur in both groups.

DISCUSSION

The main finding of this study was that ablation of AF guided by of CT image integration of LA/PVs into an EAM and the use of CF technology was associated with reduced recurrence of atrial tachyarrhythmia. CT image integration without CF technology was associated with non-significant reduced recurrence of atrial tachyarrhythmia. CF technology tended to reduce recurrence of atrial tachyarrhythmia among patients who underwent ablation of AF guided by of CT image integration.

Kistler *et al*[7] reported in a nonrandomized study that catheter ablation for AF guided by CT image integration (Cartomerge) was associated with reduced fluoroscopy times, arrhythmia recurrence, and increased restoration of sinus rhythm compared to a similar ablation strategy guided by a 3D mapping. Successful PV electrical isolation did not differ between the two groups. However, Kistler *et al*[8] reported in another study which was randomized study that CT image integration (Cartomerge) to guide catheter ablation for AF did not significantly improve the procedural and clinical outcome compared to EAM.

As we showed in our non-randomized study, CT image integration without CF technology was associated with non-significant reduced recurrence of atrial tachyarrhythmia compared to EAM. This result is in agreement with the randomized study of Kistler *et al*[8]. In addition, CF technology tended to reduce recurrence of atrial tachyarrhythmia among patients who underwent ablation of AF guided by CT image integration. Thus, it seems that the contribution of CF technology is significant.

In the TOCCATA study[9], patients with paroxysmal AF underwent PVI by using a RF ablation catheter with a different integrated CF sensor (TactiCath; Endosense, Geneva, Switzerland). The CF during catheter ablation for AF correlated with clinical outcome after 12 mo. Arrhythmia control is best achieved when ablation lesions were placed with an average CF of > 20 g, and clinical failure is universally noted with an average CF of < 10 g.

In the EFFICAS I multicenter study[10], a RF ablation catheter with integrated CF sensor (TactiCath; Endosense, Geneva, Switzerland) was used to perform PVI in patients with paroxysmal AF. At follow-up, an interventional diagnostic procedure was performed to assess gap location as correlated to index procedure ablation parameters. Minimum CF and minimum Force-Time Integral (FTI) values were strong predictors of gap formation. According to this study, optimal CF parameter recommendations are a target CF of 20 g and a minimum FTI of 400 g for each new lesion. In our study, we tried to keep the force at least 10 g at each site for at least 20 s until electrogram abolition or at least for 30 s.

Recently, Sciarra *et al*[5] studied 3 types of irrigated-tip ablation catheters. Sixty-three patients with paroxysmal AF underwent ablation by standard ThermoCool catheter, Smart Touch catheter, or Surround Flow catheter (Biosense Webster, Diamond Bar, CA, United States). The percentage of isolated PVs was comparable between groups. Both the Smart Touch catheter and the Surround Flow catheter significantly reduced radiofrequency and fluoroscopy times, as well as PVs reconnection rate at 30 min. Moreover, the Smart Touch catheter reduced overall duration of the procedure. However, the long term clinical significance of these results is not known.

We do not know the exact mechanism why combination of technologies is more useful. Image integration could improve clinical outcome because it helps to understand the 3D complex anatomy of LA/PV and appreciate the variant anatomy of PVs including common trunks or more than 4 veins. In addition, it could help to make the lesion set more precise. CF technology could lead to durable lesions. We think that the results of our study emphasized the fact that AF is a complex arrhythmia. The AF ablation is also a complex procedure with relatively high rate of recurrence due to PV reconnection. Many technologies were introduced to overcome this issue like steerable sheath[11]. Recently, a novel irrigated multi electrode mapping and ablation catheter (nMARQ catheter, Biosense Webster, Diamond Bar, CA, United States) was introduced for PVI with promising results[12]. However, there is no specific technology that is significantly more useful than others. We think, that combination of technologies rather than single one can lead to the best results as in this study. In addition centers and operators should choose the technologies according to their experience and according to the 3D anatomy of LA/PVs as detected by pre-procedure echocardiography, CT and or other modalities.

Limitations

This is a small non-randomized study comparing AF ablation using integrated CT/EAM with AF ablation using EAM only. We used two types of ablation catheters in the CT group, the standard irrigated catheter as in

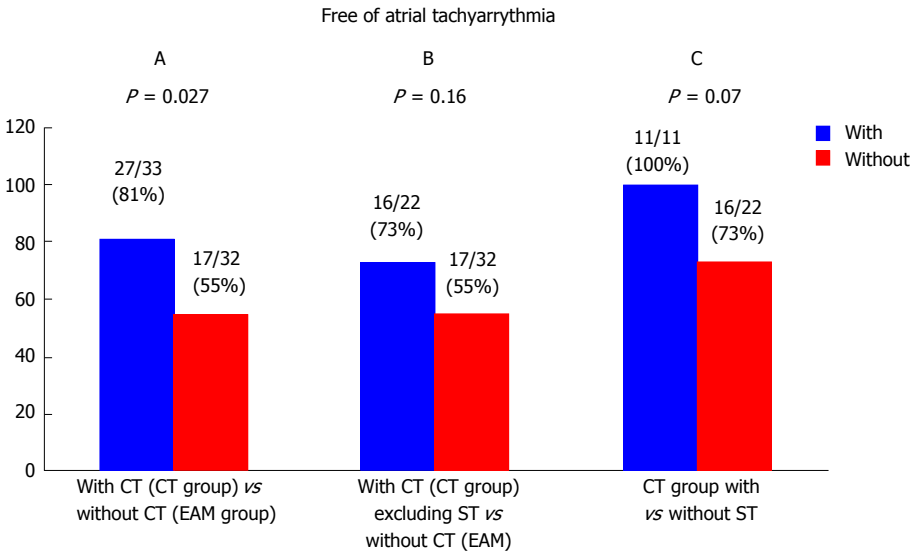

Figure 3 Free of atrial tachyarrhythmia during 24 mo. A: Among CT group *vs* among electroanatomic group; B: Free of atrial tachyarrhythmia among CT group (excluding Smart Touch) *vs* among electroanatomic group; C: Free of atrial tachyarrhythmia among CT group with or without ST. ST: Smart touch; EAM: Electroanatomic mapping; CT: Computed tomography.

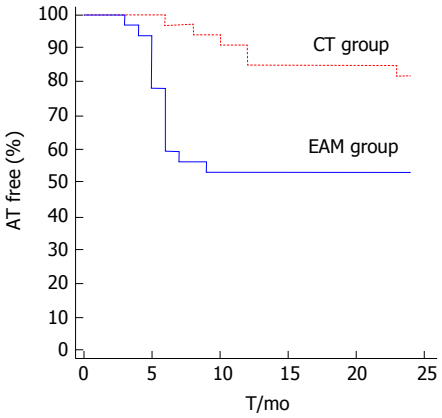

Figure 4 Kaplan-Meier estimate of recurrence atrial tachyarrhythmia during 3-24 mo after ablation for atrial fibrillation. Free of atrial tachyarrhythmia was significantly higher among CT group compared to electroanatomic mapping group. AT: Atrial tachyarrhythmia; EAM: Electroanatomic mapping; CT: Computed tomography.

EAM group and CF catheter. Only the combination of CT and CF technology was associated with significant reduction of atrial tachyarrhythmia. Thus, we could not determine the relative contribution of these technologies. Future randomized studies are needed to determine the optimal combination of technologies that gives the best procedural and clinical results of AF ablation.

In summary, these preliminary results suggest that CT image integration into EAM in combination with CF technology may reduce the recurrence of atrial tachyarrhythmia after catheter ablation for AF.

COMMENTS

Background

Recurrence of atrial arrhythmia after pulmonary vein isolation (PVI) is mainly due to recurrent pulmonary veins conduction. The durability of PVI and clinical outcome after radiofrequency ablation is affected by the contact force (CF) between the catheter tip and the tissue. In addition, understanding the anatomy of left atrium (LA) and PVs is essential for the safety and effectiveness of procedure. Pre-procedural cardiac computed tomography (CT) helps to evaluate the three dimension (3D) and complex anatomy of LA and PVs. In this study, the authors evaluated the impact of integrating CT image of LA/PVs into electroanatomical mapping system and using CF technology on clinical recurrence of atrial tachyarrhythmia after ablation for atrial fibrillation (AF).

Research frontiers

CT image integration of cardiac chamber into electroanatomic mapping (EAM) is widely used to guide catheter ablation for AF and related arrhythmias. Some studies showed that it improved the procedural and clinical outcome compared to EAM but others did not. In addition CF technology was found recently to associated with better clinical outcomes. Research is focused now in defining the parameters of CF that are universally associated with better clinical outcomes.

Innovations and breakthroughs

The authors found that combination of CT image integration into EAM and CF technology may reduce the recurrence of atrial tachyarrhythmia after catheter ablation for AF during follow-up period of 24 mo.

Applications

The authors think, that combination of technologies rather than single one can lead to the best results as in this study. Centers and operators should choose the technologies according to their experience and according to the 3D anatomy of LA/PVs as detected by pre-procedure echocardiography, CT and or other modalities.

Terminology

EAM: Electroanatomic mapping enables reconstruction of 3D anatomy of LA and PVs. Image integration: A technique to integrate a CT image of LA/PVs into EAM. CF technology: Enables assessing contact between tip of catheter and tissue and showing its absolute value and orientation by means of a 3D vector in real time during the procedure.

Peer-review

This is an interesting article analysing the influence of novel technologies (image integration and CF evaluation) on the outcome of catheter ablation of AF.

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CASE REPORT

Single lead catheter of implantable cardioverter-defibrillator with floating atrial sensing dipole implanted *via* persistent left superior vena cava

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Author contributions: All authors have contributed significantly to the submitted work and approved submission of the manuscript.

Institutional review board statement: The paper entitled "Single lead catheter of implantable cardioverter-defibrillator with floating atrial sensing dipole implanted *via* persistent left superior vena cava" has been reviewed and approved at an internal meeting of the Department of Cardiology, S. Anna Hospital, University of Ferrara, Italy for submission to the World Journal of Cardiology.

Informed consent statement: All the involved persons gave the informed consent prior to the writing of this study. Any detail that might disclose the identity of the patient has been omitted or anonymized.

Conflict-of-interest statement: The authors have no conflicting interest, including but not limited to commercial, personal, political, intellectual or religious interest, related to this study.

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Abstract

Persistent left superior vena cava (LSVC) is a congenital anomaly with 0.3%-1% prevalence in the general population. It is usually asymptomatic but in case of transvenous lead positioning, *i.e.*, for pacemaker or implantable cardioverter defibrillator (ICD), may be a cause for significant complications or unsuccessful implantation. Single lead ICD with atrial sensing dipole (ICD DX) is a safe and functional technology in patients without congenital abnormalities. We provide a review of the literature and a case report of successful implantation of an ICD DX in a patient with LSVC and its efficacy in treating ventricular arrhythmias.

Key words: Implantable cardioverter defibrillator; Left superior vena cava; Floating atrial sensing dipole

Core tip: The implantation of devices in patients with left superior vena cava is often unsuccessful. In case of single lead implantable cardioverter defibrillator with atrial sensing dipole implantation, little is known about the efficacy of the device during follow-up. This case report represents not only a successful implantation, but also the first case of effectiveness of anti-tachycardia therapy during follow-up.

Malagù M, Toselli T, Bertini M. Single lead catheter of implantable cardioverter-defibrillator with floating atrial sensing dipole implanted *via* persistent left superior vena cava. *World J Cardiol* 2016; 8(4): 323-326 Available from: URL: http://www.wjgnet.com/1949-8462/full/v8/i4/323.htm DOI: http://dx.doi.org/10.4330/wjc.v8.i4.323

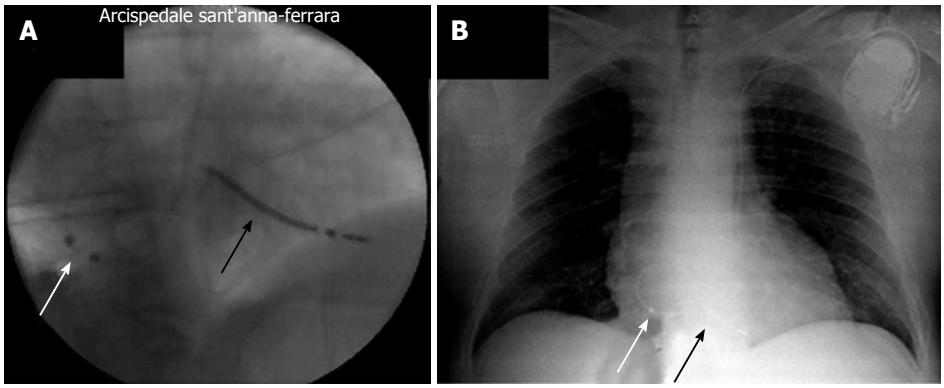

Figure 1 Final position of implantable cardioverter defibrillator sensing dipole. A: Fluoroscopic posteroanterior view during implantation; B: Chest X-ray after implantation. Note the position of atrial sensing dipole (white arrow) and defibrillation coil (black arrow).

INTRODUCTION

About 0.3%-1% of the general population has a persistent left superior vena cava (LSVC)[1,2], which drains blood from the left upper part of the body into the coronary sinus[3]. Persistence of LSVC is generally asymptomatic and may be an incidental finding, however it may also be associated with an increased risk of cardiac arrhythmias[4]. Device implantation in patients with LSVC is a challenge for two main reasons: The congenital anomaly is often an incidental finding during the procedure, leading to possible complications or implant failure. In addition, little is known on the effectiveness of shock therapy in the treatment of malignant arrhythmias.

Single lead implantable cardioverter defibrillator (ICD) with floating atrial sensing dipole (ICD DX, Biotronik SE and Co, Berlin, Germany) is a safe and functional technology in patients without congenital abnormalities[5]. Previous experiences with VDD leads with a similar floating atrial dipole, however, were burdened by instability of the atrial sensing amplitude[6]. Thus, in patient with LSVC, the presence of a floating atrial sensing dipole on the ventricular lead may result in uncorrect positioning and unsatisfactory atrial sensing. To our knowledge, only one case of successful ICD DX implantation in presence of LSVC has been previously reported, without any information at follow-up[3]. There are no data in literature about follow-up stability and effectiveness of therapy in these patients.

CASE REPORT

A 58-year-old man was referred to our cardiological institution from our heart failure center with indication to ICD implantation in primary prevention of sudden cardiac death. He suffered 14 years ago of myocardial infarction treated with medical therapy. A previous coronary angiogram showed chronic total occlusion of proximal left anterior descending artery. The electrocardiogram showed sinus rhythm with right bundle branch block and left anterior fascicular block. The echocardiogram documented a severe left ventricular dilation with reduced ejection fraction (< 35%). His NYHA functional class was between Ⅱ and Ⅲ.

During the implant procedure, the catheter inserted *via* the left cephalic vein took an anomalous route to coronary sinus. A venous angiography *via* the cubitalis vein revealed a previously unknown persistence of LSVC draining into the coronary sinus. The right superior vena cava was present, normally draining into the right atrium. We then performed ICD DX implantation with insertion of a single-coil single lead with atrial sensing dipole (Biotronik Linox Smart S DX) *via* the left cephalic vein through LSVC and coronary sinus. The catheter was positioned in the right ventricular posterior wall towards the apex, with the atrial sensing dipole into the right atrium at a postero-inferior level and with the defibrillation coil near the interatrial septum inserted beyond the tricuspid valve (Figure 1). Electrical measurements showed acceptable values of atrial and ventricular sensing (4.3 mV and 5.7 mV, respectively), as well as ventricular pacing (0.6 V pacing threshold), impedance (377 Ohm) and shock impedance (65 Ohm). Total X-ray exposure time was 26 min and 24 s. Defibrillation test was not performed. The patient was then discharged and followed-up with remote monitoring (Biotronik Home Monitoring).

During 10 mo of follow-up, several events were reported. In particular, the patient experienced 4 episodes of sustained ventricular tachycardia/ventricular fibrillation. Of these, 3 were interrupted with antitachycardia pacing (ATP) and the fourth with a single 40 Joule DC-shock (vector between right ventricular coil and anterior can), which restored sinus rhythm (Figure 2). No atrial arrhythmias were detected. Diagnostics also revealed sensing/pacing time with 90% AS-VS, which indicate spontaneous rhythm, and only few times of pacing. Remote monitoring showed acceptable values of atrial and ventricular sensing, stable over time, indicating stable position of the lead (Figure 3).

DISCUSSION

In our patient, given the posterior position of RV catheter, we expect normal or even better efficacy of ICD since

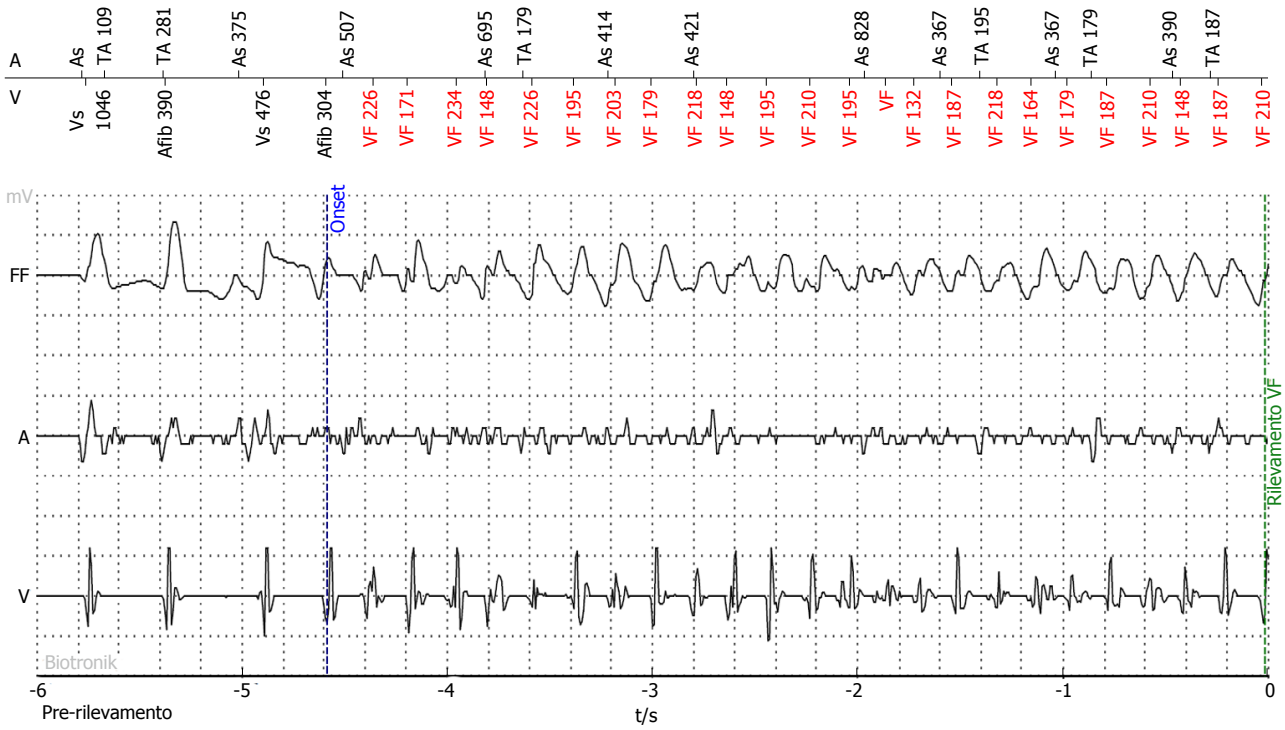

Figure 2 Ventricular fibrillation event.

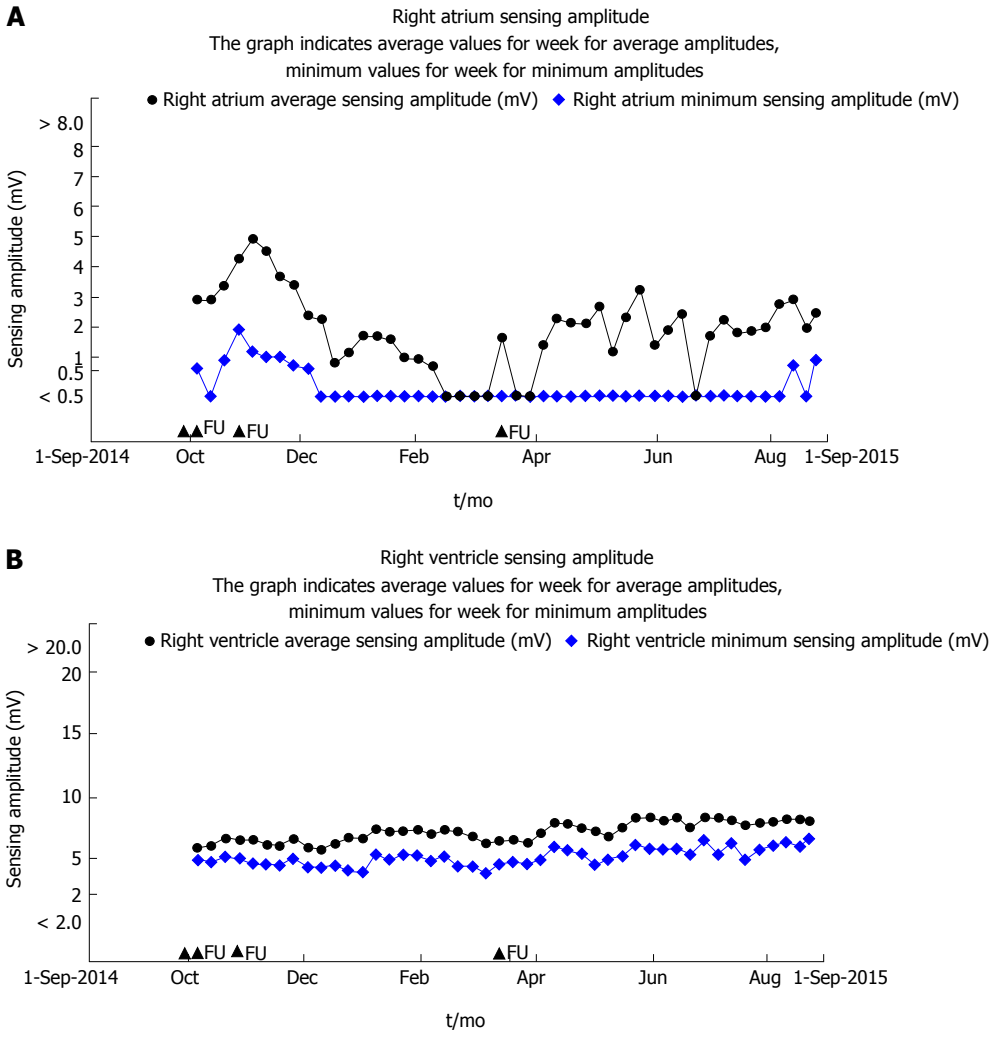

Figure 3 Trends of atrial and ventricular sensing during 10 mo of follow-up. FU: Follow-up.

defibrillation vector, directed from posterior (right ventricle) to anterior (can) could include huge critical ventricular mass. This consideration should discourage the implantation in the right side. Furthermore, in one third of cases of LSVC there is absence of right superior vena cava[1]. Therefore, in patients with LSVC it is in any case more appropriate to implant the device on the left side.

In conclusion, this case report gives a contribution to the knowledge on this subject by confirming the possibility of successful implantation and effectiveness of the therapy. During 10 mo of follow-up, our patient presented a few episodes of ventricular arrhythmias, which were effectively recognized and treated either with ATP and with DC-shock.

COMMENTS

Case characteristics

Ischemic cardiomyopathy with reduced ejection fraction, scheduled for implantation of single lead implantable cardioverter defibrillator (ICD) with atrial sensing dipole.

Clinical diagnosis

Persistent left superior vena cava (LSVC).

Imaging diagnosis

Fluoroscopy and angiography during ICD implantation.

Treatment

Single lead ICD with atrial sensing dipole implantation *via* persistent LSVC.

Related reports

Stability of lead and effective ICD therapy both with antitachycardia pacing and DC-shock during follow-up.

Experiences and lessons

Single lead ICD with atrial sensing dipole is a safe and effective technology even in patients with persistent LSVC.

Peer-review

The paper reports the implantation and follow-up data of a patient with persistent LSVC who underwent ICD implantation with a single lead capable of atrial sensing.

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MINIREVIEWS

P2Y12-ADP receptor antagonists: Days of future and past

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Abstract

Antiplatelet therapy is the cornerstone of the therapeutic arsenal in coronary artery disease. Thanks to a better understanding in physiology, pharmacology and pharmacogenomics huge progress were made in the field of platelet reactivity inhibition thus allowing the expansion of percutaneous coronary intervention. Stent implantation requires the combination of two antiplatelet agents acting in a synergistic way. Asprin inhibit the cyclo-oxygenase pathway of platelet activation while clopidogrel is a P2Y12 adenosine diphosphate (ADP)-receptor antagonist. This dual antiplatelet therapy has dramatically improved the prognosis of stented patients. However, due to pharmacological limitations of clopidogrel (interindividual variability in its biological efficacy, slow onset of action, mild platelet reactivity inhibition) ischemic recurrences remained high following stent implantation especially in acute coronary syndrome patients. Thus, more potent P2Y12-ADP receptor inhibitors were developped including prasugrel, ticagrelor and more recently cangrelor to overcome these pitfalls. These new agents reduced the rate of thrombotic events in acute coronary syndrome patients at the cost of an increased bleeding risk. The abundance in antiplatelet agents allow us to tailor our strategy based on the thrombotic/bleeding profile of each patient. Recently, the ACCOAST trial cast a doubt on the benefit of pre treatment in non-ST segment elevation acute coronary syndrome. The aim of the present review is to summarize the results of the main studies dealing with antiplatelet therapy in stented/acute coronary syndromes patients.

Key words: Clopidogrel; Prasugrel; Ticagrelor; Acute coronary syndrome; Ticagrelor; Cangrelor

Core tip: Antiplatelet therapy in coronary artery disease has dramatically changed during the past few years. From ticlodipine to cangrelor, the present review summarizes the results of the main studies dealing with this hot topic of cardiology.

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INTRODUCTION

Allowing the expansion of percutaneous coronary intervention (PCI) and considered as the cornerstone of acute coronary syndromes (ACS) treatment, anti-platelet therapy is in large part responsible for the dramatic reduction of ischemic events observed in the past decades in ischemic heart disease patients. Indeed, dual anti-platelet therapy (DAPT) is mandatory to prevent both stent thrombosis and ischemic recurrences in stented patients. Over the past decade, from ticlodipine to clopidogrel and more recently prasugrel, ticagrelor or cangrelor, anti platelet therapy's efficacy has dramatically improved resulting in clinical benefit for our patients. This evolution is the typical example of therapeutics improvements obtained thanks to pharmacology, pharmacogenomics and clinical experience. The aim of the present review is to summarize the main results of currently available P2Y12-adenosine diphosphate (ADP) receptor antagonists.

PLATELET ACTIVATION PATHWAYS

Circulating in quiescent state, platelets can be activated through several pathways leading to the thrombus formation and growth. Following platelets' adhesion, cyclo-oxygenase 1 and 2 transform arachidonic acid into prostaglandin-H2 which is then converted in thromboxane A2 which has potent vasoconstrictor properties but also activates platelets through their TPα and TPβ receptors. Through this G-protein receptor, thromboxane A2 activates the Glycoprotein Ⅱb-Ⅲa (Gp Ⅱb-Ⅲa) receptor (final stage of platelet activation) that binds to fibrin and ensures platelets aggregation resulting in the formation of a thrombus. By inhibiting the cyclo-oxygenases, aspirin blocks the platelets' activation pathway mediated by thromboxane A2.

Another critical step of platelets' activation is mediated through ADP that is produced by red blood cells and activates platelets in an autocrine/paracrine way thanks to the P2Y1 and mainly P2Y12 receptors. The binding of ADP with its P2Y12-receptor results in a decrease of the intracellular concentration of cyclic AMP which, there again, leads to the Gp Ⅱb-Ⅲa receptor activation.

Approximately 70 agonists are involved in platelets' activation such as serotonin, thrombin, epinephrine or collagen. These other agents are not actually therapeutical targets in ischemic heart disease patients; therefore they will not be discussed in this review.

TICLODIPINE

Ticlodipine was the first commercially available P2Y12 ADP-receptor inhibitor. In the nineties, this thienopyridine has demonstrated its superiority in combination with aspirin over the gold standard therapy of that time that associated aspirin to oral anticoagulant therapy in stented patients. Schömig *et al*[1] in their study that randomized more than 500 patients demonstrated a 25% reduction in the rate of major adverse cardiovascular events (MACE) including stent thrombosis thanks to the DAPT. This benefit on ischemic events was also associated with a dramatic reduction in bleedings which are associated with poor outcome in stented patients[2].

In 1998, Leon *et al*[3] published a study that compared three anti-thrombotic regimens in stented patients: Aspirin alone, aspirin plus warfarin and aspirin in combination with ticlodipine. The primary endpoint combined death, revascularization of the target lesion, angiographically evident thrombosis and myocardial infarction at 30 d was observed in 3.6% of the aspirin group, 2.7% of the aspirin-warfarin group and 0.5% in the aspirin-ticlodipine group (P = 0.001 for the comparison of all three groups). Regarding hemorrhagic complications they occurred in respectively 1.8%, 6.2% and 5.5% of the patients (P = 0.001 for the comparison of all three groups)[3]. Bertrand *et al*[4] randomized approximately 500 stented patients to aspirin-ticlodipine or aspirin-anticoagulant therapy and unlike the previous described studies used bleedings or peripheral vascular complication as primary endpoint. Again, DAPT was superior to the former gold standard demonstrating a reduction in the primary endpoint 13.5% *vs* 21% (OR: 0.23; 95%CI: 0.05-0.91, P = 0.01). Further, DAPT reduced the rate of MACE (P = 0.01) and hospital stay (P = 0.0001) compared to the aspirin-anticoagulant therapy[4].

However, concerns were raised regarding the safety of ticlodipine. Indeed, serious hematological side effects of ticlodipine were highlighted in several studies, therefore an urgent need for a new P2Y12-inhibitor emerged.

CLOPIDOGREL

Like ticlodipine, clopidogrel belongs to the thienopyridine family. This pro-drug absorbed in the intestine required a two steps hepatic biotransformation to become active. About 85% of the absorbed clopidogrel is turned into SR26334 (an inactive metabolite) by carboxylase. The rest is metabolized by cytochrome P450 iso-enzymes in the liver. During the first step CYP2C19, CYP1A2 and CYP2B6 turn clopidogrel into 2-oxoclopidogrel which is then hydrolyzed by CYP2C19, CYP2C9 and CYP3A to become R130964, the active metabolite that irreversibly inhibits the P2Y12 ADP-receptor[5-7].

The CURE trial was the first large scale randomized study that compared the combination of aspirin-clopidogrel to aspirin alone in ACS patients. In this study that included more than 12000 patients, DAPT significantly reduced the rate of MACE (9.3% *vs* 11.4%; RR 0.80, 95%CI: 0.72-0.90, P < 0.001) at the cost of an increased in major bleedings (3.7% *vs* 2.7%; RR

1.38; $P = 0.001$)[8].

Further, the PCI CURE study randomized 2600 ACS patients treated with PCI to clopidogrel pre-treatment and long term therapy *vs* aspirin (and thienopyridine for 1 mo only following PCI). There again, clopidogrel pre-treatment and long term therapy reduced the rate of MACE by 30% (RR 0.70; 95%CI: 0.50-0.97, $P = 0.03$) without any increase in major bleedings. Consistently, clopidogrel use was associated with a lower rate of Gp Ⅱb-Ⅲa inhibitors use ($P = 0.001$)[9]. Based on these findings and on the fact that unlike ticlodipine clopidogrel is devoid of hematological side effects, DAPT combining aspirin and clopidogrel quickly became the gold standard in stented and/or ACS patients.

However, our patients are not equal before clopidogrel. Järemo *et al*[10] demonstrated in 2002 that a large inter-individual variability in response to clopidogrel exists. In fact, about 30%-40% of patients are hypo responders to clopidogrel[11]. Further, Barragan *et al*[12] correlated high on-treatment platelet reactivity (HTPR) with stent thrombosis, a finding that was later confirmed in numerous studies. Several factors may be responsible for high on-clopidogrel platelet reactivity; they can act alone or combined. Genetic polymorphism has been one of the first causes of HTPR investigated. Three independent genes have clearly been related to clopidogrel hypo responsiveness: CYP2C19 (*2), CYP3A4 and ABCB1[13-18]. Drug-drug interaction with proton pump inhibitor, but also calcium channel blocker or statin (even if the evidence level is lower for the two latest)[19,20]; clinical factors (diabetes mellitus, acute coronary syndrome and obesity) or biological factors (high platelet turnover, platelet receptors up-regulation) have also been incriminated[21-24].

Beside its inter-individual platelet reactivity, clopidogrel possesses other limitations including a slow onset of action (especially in the ACS setting) and it induced a mild platelet reactivity inhibition. Therefore, new drugs devoid of these disadvantages were developed: Prasugrel and ticagrelor.

PRASUGREL

Prasugrel is defined as a third generation thienopyridine that irreversibly inhibits platelets like clopidogrel through its P2Y12-ADP receptor. Prasugrel is also a pro-drug that requires hepatic bio-transformation to become active. Following absorption it is hydrolyzed into R-95913 (a thiolactone) by esterases[25]. Then CYP3A4, CYP2B6, CYP2C19, CYP2C9, and CYP2D6 turn it into R-138727, the active metabolite[26]. Interestingly, prasugrel active metabolite possesses similar efficacy than the active metabolite of clopidogrel suggesting that its higher potency is related to its simpler metabolism[27].

The PRINCIPLE-TIMI 44 study is a phase 2 trial that demonstrated a faster onset of action and a more potent platelet reactivity inhibition with prasugrel compared to clopidogrel in patients undergoing PCI[28].

The TRITON trial compared prasugrel to clopidogrel in 13608 ACS patients treated with PCI. This study demonstrated a 19% reduction of the primary endpoint composed of myocardial infarction, stroke, and cardiovascular deaths with prasugrel compared to clopidogrel (9.9% *vs* 12.1%; HR 0.81, 95%CI: 0.73-0.90, $P < 0.001$) at the cost of increased life-threatening bleedings (1.4% *vs* 0.9%, $P = 0.01$). Further analysis of this study revealed the lack of benefit of prasugrel in elderly (⩾ 75 years) or small weighted patients (< 60 kg) and a potential harm in patients with an history of stroke or transient ischemic attack history leading to a restriction of use in the first described populations and a contra-indication in the later[29].

It is important to keep in mind that prasugrel should only be administered in ACS patients treated with PCI, once the coronary anatomy is known, given the design of the TRITON trial that randomized patients after coronary angiography.

The TRILOGY ACS study randomized more than 7000 ACS patients medically managed (*i.e.*, without revascularization) to prasugrel or clopidogrel in this clinical setting. In this study, the rate of myocardial infarction, stroke or cardiovascular death (primary endpoint) was similar between both groups (prasugrel: 13.9%, clopidogrel: 16%; HR: 0.91, 95%CI: 0.79-1.05, $P = 0.21$). Therefore, prasugrel is not recommended in this situation[30].

More recently, the ACCOAST study compared in 4033 non-ST segment elevation ACS patients the impact of a 30 mg pre-treatment of prasugrel (a half loading-dose administered after randomization, complement being administered after PCI) to a full loading dose (60 mg) once the PCI is performed. No benefit was found to pre-treat the patient. The primary endpoint composed of myocardial infarction, stroke, death from cardiovascular causes, urgent revascularization, Gp Ⅱb/Ⅲa bailout was similar in the two groups (HR pre-treatment: 1.02, 95%CI: 0.84-1.25, $P = 0.81$) but the rate of TIMI major bleeding was higher in the pre-treatment group despite the half loading dose used before coronary angiography ($P = 0.006$)[31].

TICAGRELOR

Unlike clopidogrel or prasugrel, ticagrelor does not belong to the thienopyridine family but to the cyclopentyltriazolopyrimidine family. Divergences with previous drugs go further than this classification; indeed ticagrelor is not a pro-drug and reversibly inhibits P2Y12-ADP receptor. Ticagrelor's main active metabolite (namely AR-C124910) is formed by O-de-ethylation that depends on CYP3A4. This metabolite (also active) can reach 40% of the concentration of ticagrelor[32].

The phase 2 trial ONSET/OFFSET demonstrated the faster onset of action associated with a more potent platelet reactivity inhibition of ticagrelor compared to clopidogrel in stable patients[33].

The PLATO trial compared ticagrelor to clopidogrel in 18624 patients ACS patients and founded a significant

reduction of the rate of the primary endpoint (death from cardiovascular causes, myocardial infarction or stroke) in the ticagrelor group: 9.8% *vs* 11.7% (HR 0.84, 95%CI: 0.77-0.92, $P < 0.001$). Unlike prasugrel, ticagrelor reduced the rate of death from any causes ($P = 0.001$) compared to clopidogrel. Of note, the rate of death in the clopidogrel group of the PLATO trial was 5.9% while it was 3.2% in the clopidogrel group of the TRITON trial suggesting a lower risk population included in the latter study[29,34]. Interestingly, the benefit of ticagrelor was present whatever the method of revascularization used (PCI, CABG, none).

Concerning the safety, ticagrelor administration was associated with an increased risk of major bleedings not related to CABG ($P = 0.03$).

In the ATLANTIC study, investigators evaluated the efficacy of ticagrelor pre-treatment in 1862 STEMI patients compared to the administration of the loading dose in the cath lab. In this study, both strategies resulted in a similar efficacy[35].

CANGRELOR

Cangrelor is a non-thienopyridine intra-venous agent that reversibly inhibits P2Y12 ADP-receptor. Like ticagrelor, it does not require hepatic biotransformation to become active explaining its quick onset of action. Further, half-life of cangrelor is 3-6 min while platelets resume normal reactivity 30-60 min after discontinuation of the infusion[36]. Theoretically, cangrelor seems to be an interesting drug: A rapid onset of action, a potent platelet reactivity inhibition and a rapid reversible effect. However, despite these promising properties, the CHAMPION PCI and CHAMPION PLATFORM trials failed to demonstrate any benefit of cangrelor compared to clopidogrel in patients treated with PCI[37,38].

Later, the CHAMPION PHOENIX trial redefined periprocedural myocardial infarction and used an angiographic core lab. This study that once again compared cangrelor to clopidogrel in patients treated with PCI found a significant reduction in the rate of primary endpoint (death from any cause, myocardial infarction, ischemia driven revascularization, stent thrombosis at 48 h) in the cangrelor group (4.7% *vs* 5.9%, OR 0.79, 95%CI: 0.67-0.93, $P = 0.006$) without difference regarding severe bleedings[39].

Interestingly, the BRIDGE study confirmed a better platelet reactivity inhibition with cangrelor compared to placebo without significant difference in bleedings in ACS patients that discontinued thienopyridine before CABG[40].

Thanks to its pharmacological properties, cangrelor might be interesting in patients treated with P2Y12 inhibitors that require drug discontinuation before surgery or in unconscious patients admitted for ACS, unable to take orally administered anti platelet agents or in vomiting patients, a frequent setting during STEMI or in morphine treated patients.

CONCLUSION

Therapeutics has constantly improved over the last decades for the best of our patients. However, several debates remain regarding pre-treatment or optimal duration of DAPT in ACS patients emphasizing the importance of personalized treatment in stented patients.

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Mitochondrial vasculopathy

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Abstract

Mitochondrial disorders (MIDs) are usually multisystem disorders (mitochondrial multiorgan disorder syndrome) either on from onset or starting at a point during the disease course. Most frequently affected tissues are those with a high oxygen demand such as the central nervous system, the muscle, endocrine glands, or the myocardium. Recently, it has been shown that rarely also the arteries may be affected (mitochondrial arteriopathy). This review focuses on the type, diagnosis, and treatment of mitochondrial vasculopathy in MID patients. A literature search using appropriate search terms was carried out. Mitochondrial vasculopathy manifests as either microangiopathy or macroangiopathy. Clinical manifestations of mitochondrial microangiopathy include leukoencephalopathy, migraine-like headache, stroke-like episodes, or peripheral retinopathy. Mitochondrial macroangiopathy manifests as atherosclerosis, ectasia of arteries, aneurysm formation, dissection, or spontaneous rupture of arteries. The diagnosis relies on the documentation and confirmation of the mitochondrial metabolic defect or the genetic cause after exclusion of non-MID causes. Treatment is not at variance compared to treatment of vasculopathy due to non-MID causes. Mitochondrial vasculopathy exists and manifests as micro- or macroangiopathy. Diagnosing mitochondrial vasculopathy is crucial since appropriate treatment may prevent from severe complications.

Key words: Mitochondrial disorder; Multisystem; MtDNA; Phenotype; Vasculopathy; Arteriopathy; Angiopathy; Genotype

Core tip: Recently, it has been shown that rarely also the arteries may be affected in mitochondrial disorders, known as mitochondrial vasculopathy. Mitochondrial vasculopathy manifests as either microangiopathy or macroangiopathy. Clinical manifestations of mitochondrial microangiopathy include leukoencephalopathy, migraine-like headache, stroke-like episodes, or peripheral retinopathy. Mitochondrial macroangiopathy manifests as atherosclerosis, ectasia of arteries, aneurysm formation, dissection, or spontaneous rupture of arteries. The diagnosis relies on the documentation and confirmation of the mitochondrial metabolic defect or the genetic cause after exclusion of non-mitochondrial causes. Treatment is not at variance compared to treatment of vasculopathy

due to non-mitochondrial causes.

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INTRODUCTION

It is well established that syndromic and non-syndromic mitochondrial disorders (MIDs) manifest as mitochondrial multiorgan disorder syndrome (MIMODS) in the majority of the cases, either since onset of the disease or starting later during the disease course[1,2]. Organs or tissues involved in MIMODS are numerous but some are more frequently affected than others and some are better recognised as sites of involvement than others. Among the frequently affected organs are the muscle, brain, eyes, ears, endocrine organs, and the heart. Less frequently involved are the liver, pancreas, intestines, kidneys, blood, and skin. Hardly known and appreciated as possibly affected organs in MIDs are the lung and the arteries. Here we summarise and discuss recent findings concerning the involvement of the arteries, arterioles, and capillaries in MIDs (mitochondrial vasculopathy). Mitochondrial vasculopathy may manifest in large arteries (macroangiopathy) or the small arteries (microangiopathy). Microangiopathy is defined as vasculopathy of the small arteries, arterioles, capillaries, or venules[3]. This review aims at summarising and discussing recent findings concerning mitochondrial vasculopathy.

SEARCH STRATEGY

Data for this review were identified by searches of MEDLINE, Current Contents, EMBASE, Web of Science, Web of Knowledge, LILACS, SCOPUS, and Google Scholar for references of relevant articles using the search terms "vasculopathy", "macroangiopathy", "microangiopathy", "aortic ectasia", "dissection", "rupture", "aneurysm", "megadolichobasilar artery", "migraine", "migraine-like headache", "microvascular", and "stroke-like episode" in combination with "mitochondrial", "mtDNA", "respiratory chain", "oxidative phosphorylation", and "cytopathy". Randomized (blinded or open label) clinical trials, longitudinal studies, case series, and case reports were considered. Abstracts and reports from meetings were not included. Only articles published in English, French, Spanish, or German between 1966 and 2015 were considered. Appropriate papers were studied and discussed for their suitability to be incorporated in this review. Fifty-nine papers were identified as suitable to be discussed in this review. According to these papers mitochondrial vasculopathy may be classified according to various criteria.

CLASSIFICATION OF MITOCHONDRIAL VASCULOPATHY

Mitochondrial vasculopathy may not only be classified as micro- or macro-angiopathy but also as primary or secondary. Primary mitochondrial vasculopathy is due to affection of cells constituting the vessels by the causative metabolic defect. Secondary mitochondrial vasculopathy is due to affection of vessels secondary to the development of diabetes, hyperlipidemia, or arterial hypertension due to affection of organs other than the arteries by the metabolic defect. Additionally, mitochondrial vasculopathy may go along with clinical manifestations or without and it may occur in a focal or generalised distribution. Mitochondrial macroangiopathy and microangiopathy present with various manifestations.

Microangiopathy

Microangiopathy manifests clinically or may remain subclinical. Clinical manifestations of mitochondrial microangiopathy include leukoencephalopathy, migraine-like headache, stroke-like episodes (SLEs), or peripheral retinopathy. Subclinical manifestations include morphological abnormalities in mitochondria of vascular smooth muscle cells (VSMCs), of pericytes, or of endothelial cells[4].

Leukoencephalopathy: Leukoencephalopathy is a frequent central nervous system (CNS) abnormality in syndromic as well as non-syndromic MIDs. It may be patchy or confluent. It is so far unknown if leukoencephalopathy is due to a vascular pathology or represents a primary metabolic defect of neurons or glial cells. Evidence for a vasculopathy comes from several observations. In a 13yo mitochondrial encephalomyopathy, lactic acidosis, and SLEs (MELAS) patient with leukoencephalopathy post-mortem studies revealed generalised cerebral microangiopathy[5]. In a post-mortem study of two other patients with MELAS-syndrome due to the mtDNA mutation m.3243A > G, of which one also presented with migraine, COX-negative VSMCs were most frequently found in the walls of leptomeningeal and cortical arteries over all cerebral regions[6].

Migraine-like headache: Migraine-like headache is a frequent manifestation of syndromic and non-syndromic MIDs. Best known is migraine-like headache as a manifestation of MELAS-syndrome[7] but has been also reported in adult Leigh-syndrome[8], Alpers-Huttenlocher disease[9], myoclonic epilepsy with ragged-red fibers (MERRF)-syndrome[10], mitochondrial recessive ataxia syndrome[11], chronic progressive external ophthalmoplegia (CPEO)[12], Leber's hereditary optic neuropathy (LHON)[13], cyclic vomiting syndrome[14], mitochondrial depletion syndrome[15], and non-syndromic MIDs due to POLG1 mutations[16]. Among patients

carrying the m.3243A > G mutation the prevalence of migraine was 58%[7]. In a study of two patients with MELAS-syndrome, of which on one also had migraine, COX-deficiency and heteroplasmy rates of the causative mutation were highest in cortical and leptomeningeal arteries[6]. Though the pathogenesis of migraine-like headache is poorly understood there are some studies indicating vasculopathy in these patients. Vascular pathology is characterised by episodic changes of the diameter of small cerebral arteries[17]. According to the vascular hypothesis of migraine it is assumed that initially there is vasoconstriction followed by vasodilation[17,18]. A further hypothesis suggests that activation of the calcitonin-related peptide gene is responsible for hyperperfusion and migraine[19]. Additional evidence for mitochondrial dysfunction in migraine derives from the finding that increased influx of calcium increases oxidative stress, that muscle biopsy of patients with migraine may show mitochondrial abnormalities, that mtDNA polymorphisms may be increased in migraine patients, and that riboflavin, coenzyme-Q, niacin, and carnitine, all agents used in the treatment of MIDs, exhibit a beneficial effect for migraine[20].

SLEs: SLEs are the hallmark of MELAS-syndrome but may occur in other syndromic or non-syndromic MIDs as well. They are clinically indistinguishable from ischemic strokes but may additionally manifest with seizures, headache, confusional state, or lactic acidosis[21]. The morphological correlate of a SLE is the stroke-like lesion, which is not confined to a vascular territory and most frequently located in the temporo-occipital region[22]. Concerning the MRI findings of stroke-like lesions, acute, subacute, and chronic alterations have to be differentiated. In the acute and subacute stage there may be cortical hyperintensity on diffusion weighted imaging (DWI) and hypointensity on apparent diffusion coefficient (ADC) maps (cytotoxic edema). The subcortical compound of a stroke-like lesion in this stage shows up as hyperintensity on DWI and hyperintensity on ADC in the cortical and subcortical compound (vasogenic edema)[23]. However, there are also studies showing hyperintensity on DWI and hyperintensity on ADC (vasogenic edema) in the subcortical and cortical grey matter. Fluid attenuated inversion recovery (FLAIR) sequences in the acute stage may show hyperintensity and MR angiography prominent dilatation of arteries and PWI consecutive hyperperfusion in the affected areas[24]. On the contrary, PWI studies in the acute stage in another study showed decreased cerebral blood flow as well as decreased cerebral blood volume[23,25]. Mean transit-time and time-to-peak are prolonged in lesional and non-lesional areas. The chronic stage of a stroke-like lesion may show up as hyperintensity on FLAIR sequences and as iso- or hyperintensity on ADC maps[22]. 99mTc-hexa-methyl-propyl-eneamine-oxime single-photon emission CT (HMPAO-SPECT) of a stroke-like-lesion in the chronic stage may show hyperperfusion or a mixture of hypo- and hyperperfusion[19,23,26].

Three main hypotheses have been raised to explain the phenomenon. First, SLEs result from mitochondrial vasculopathy caused by dysfunction of VSMCs of the small cerebral arteries leading to disruption of the blood brain barrier and consecutive vasogenic respectively cytotoxic edema and neuronal death[19,21,23]. Second, mitochondrial dysfunction may secondarily cause impaired cellular or mitochondrial metabolism resulting in decreased mitochondrial energy production causing neuronal damage or neuronal death[21]. Third, an initial seizure may cause oxidative stress resulting in secondary metabolic break-down. An argument for the seizure hypothesis is that SLEs are frequently associated with seizures and that appropriate antiepileptic treatment may be beneficial also for stroke-like-episodes[27].

Microangiopathy of retinal arteries: LHON is a syndromic MID with subacute onset visual impairment leading to permanent blindness. Two thirds of these patients present with microangiopathy of the retinal arteries, characterised by increased tortuosity and ectasias[28-31]. The same vascular abnormalities may be also found in non-manifesting carriers of the disease. However, the pathogenetic role of these vascular changes remains questionable since not all LHON patients develop retinal microangiopathy[28]. In rare cases, retinal microangiopathy may spontaneously regress[32].

Subclinical mitochondrial vasculopathy: Further evidence for microangiopathy in MIDs comes from a study of 3 patients with MERRF, CPEO, and migraine respectively, each carrying the m.3243A > G mutation[33]. 99mTc-HMPAO-SPECT in these three patients revealed asymmetric hypoperfusion in various cerebral regions with predominance in the temporo-occipital regions[33]. In another study of 13 MELAS patients reactivity of the median cerebral artery to hypo- or hyper-capnia was decreased on transcranial Doppler sonography and there was crossed diaschisis[34]. In a study of patients with Leigh-syndrome capillary shunting was documented by cerebral MRI[35]. In a recent study of 16 MID patients carrying the m.3243A > G mutation, the m.8344A > G mutation, or a POLG1 mutation respectively, multiple ischemic-like lesions were found in the cerebellar cortex bilaterally[36]. The findings were attributed to dysfunction of VSMCs and endothelial cells[36]. Dysfunction of endothelial cells and VSMCs was made responsible for a breakdown of the blood-brain-barrier, resulting in extravasation of plasma proteins and disruption of tight junctions of endothelial cells[36]. In a patient carrying the m.3243A > G mutation histological studies of the skin and muscle showed extra-cellular matrix mineralization in blood vessel walls[37]. There was also a correlation between SDH histochemical staining and the number of mitochondria on electron microscopy[37]. In a boy with non-syndromic MID neuropathological work-up of the brain revealed spongiform changes, swelling of endothelial cells, and increased number of mitochondria

with abnormal cristae formation in pericytes and VSMCs[4]. In a girl with MELAS-syndrome generalised microangiopathy with reduced COX-activity was found in the cerebrum, myocardium, and skeletal muscle[38]. In a histopathological study of MELAS patients COX-deficiency and heteroplasmy rates were highest in cortical and leptomeningeal arteries[6]. In case muscular arteries are subclinically affected histological studies may show SDH hyperreactivity, also known as strongly-succinate dehydrogenase-reactive vessels (SSV)[26]. SSV may occur in MELAS[39-42], CPEO[43], MERRF[44], and MERRF/MELAS overlap syndrome[45]. SSV are usually normal for COX[44] but in 5 MERRF patients SSV were COX-negative[44]. Ultrastructural investigations may show cristae swelling and increased number of mitochondria in VSMCs and endothelial cells[25]. In patients with non-syndromic MID muscle biopsy showed vasculopathy with swollen endothelial cells and swollen and dysmorphic mitochondria in VSMCs and pericytes[4]. Muscle biopsy of MID patients may also show reduced NO bioactivity particularly in endothelial cells and VSMCs of these patients[46]. When studying chronic intestinal pseudo-obstruction in MNGIE patients it turned out that mtDNA depletion due to tyrosine phosphorylase gene mutations was also present in VSMCs and endothelial cells of small arteries within the gastrointestinal walls[47].

Macroangiopathy

Premature atherosclerosis: There is increasing evidence that abnormal premature primary atherosclerosis can be a prominent feature of MIDs. Though not systematically investigated, an increasing number of patients with mitochondrial atherosclerosis is reported indicating that premature atherosclerosis particularly in patients without classical risk factors for atherosclerosis occurs. In a 54yo male with recurrent hyper-CKemia, Leriche-syndrome developed in the absence of classical risk factors for atherosclerosis and despite regular extensive physical exercise in form of frequent bicycling[48]. In a MID patient carrying the m.617G > A mutation, recurrent embolic strokes originating from an internal carotid artery stenosis in the absence of classical risk factors for atherosclerosis was reported[19]. It was concluded that mtDNA mutations might be implicated in the development of macroangiopathy in MID patients[19].

Ectasia of arteries: Ectasia of arteries in MIDs has been described for the aorta and the cerebral arteries. Aortic root ectasia: Aortic root ectasia in MID patients has been first described by Brunetti-Pierri *et al*[49] in 2011 in 10 patients with non-syndromic MIDs. These ten patients had an increased Z-score of the aortic root width, which is zero per definition in controls. One of these patients was a female and ten were males, aged 0.5 to 11.5 years[49]. A further case with non-syndromic MID and aortic root ectasia has been recently recognised. In a 84yo female with suspected non-syndromic MID, ectasia of the aortic root was diagnosed on X-ray of the lungs and confirmed by CT of the aorta. Most likely, aortic root ectasia is more frequent among MID patients than so far appreciated. However, except for the study by Brunetti-Pierri *et al*[49] no further systematic investigations regarding this issue have been conducted. It is unknown if aortic root ectasia in MIDs is associated with an increased risk of aortic dissection type A. It is also unknown if MID patients with aortic root ectasia have a worse prognosis compared to MID patients without. Ectasia of cerebral arteries: Ectasia of arteries in MIDs has not only been reported for the aorta but in a single patient also for the basilary artery[50]. In a 70yo female with suspected MID, ectasia of the basilary artery has been demonstrated[50]. Originally, the patient was admitted for an ischemic stroke in the posterior leg of the left internal capsule. Features suggesting MID in this patient included leukoencephalopathy, short stature, and hyperlipidemia[50]. Since megadolichobasilar arteries are not infrequent, these patients should undergo investigations for a MID if time of flight angiography on cerebral MRI or CT angiography show ectasia of the cerebral arteries. Additionally, patients with a MID should be investigated for ectatic cerebral arteries as a CNS manifestation of the disease. Pathogenetically, it can be suspected that there is impaired innervation of the arterioles and thus reduced tone of the vessel wall, that there is a decrease of collagen fibers, or impairment of the VSMCs due to metabolic dysfunction. It is also conceivable that arterial ectasia is congenital without progression during the further course.

Aneurysm formation: Cerebral aneurysms are the most frequent cause of subarachnoid bleeding with often poor or fatal outcome[51]. Particularly, in cases with hereditary subarachnoid bleeding with maternal trait of inheritance a MID should be suspected and affected patients investigated appropriately. Also in cases of accidental detection of a cerebral aneurysm, which is the most frequent mode how cerebral aneurysms are diagnosed, the family history is of great importance and in case there are indications for a MID in one of the family members, appropriate diagnostic work-up should be initiated also in other family members. Since cerebral aneurysms may occur in a familial distribution it appears justified not only to investigate MID patients for cerebral aneurysms but also their affected and non-affected relatives. A pseudoaneurysm of the right internal carotid artery was found in a 47yo female with MELAS-syndrome[52].

Dissection: Spontaneous dissection of the carotid artery is a rare manifestation of a MID and has been reported only in five patients thus far[37,52,53]. In a patient carrying the mtDNA mutation m.3243A > G spontaneous dissection of the internal carotid artery and of the vertebral arteries was reported[37]. Skin and muscle biopsy in this patient revealed ragged-red fibers (RRFs), regional variability of succinate-dehydrogenase (SDH) histochemical reactivity, morphologically abnormal mitochondria, and accumulations of mitochondria[37].

Similar mitochondrial abnormalities and extracellular matrix mineralisation were found in arterial walls[37]. In three further patients with suspected MID, spontaneous dissection of the carotid artery and the posterior cerebral artery have been described[53]. Muscle biopsy in these patients revealed RRFs, SDH hyporeactivity, and COX-negative fibers[53]. These abnormalities were made responsible for the development of arteriopathy with dissection. Possibly, more MID patients have experienced arterial dissection but were either not reported or a causal relation was not assumed. Neurosurgeons, vascular surgeons, and neurologists must be aware of MIDs as the cause of carotid artery dissection and each patient with carotid artery dissection but without an evident cause should be investigated for a MID as well. Treatment is not at variance from that of dissection due to non-mitochondrial causes. The fifth patients is a 47yo female with mitochondrial myopathy due to the m.3243A > G mutation who presented a right carotid artery dissection with consecutive ischemic stroke in the right median cerebral artery territory[52].

Spontaneous rupture of arteries: In a 15yo girl with MELAS-syndrome due to the m.3243A > G mutation spontaneous rupture of the aorta during insertion of a gastrostomy has been reported[54]. Rupture of the aorta was attributed to affection of the aortic wall by the metabolic defect since post-mortem histological examination had revealed disorganised layers of VSMCs, disrupted elastic layers, and decreased COX staining of VSMCs of the vasa vasorum of the aorta[54]. Additionally, PCR and RFLP revealed a mutation load of 40% in blood lymphocytes but 85% in arteries[54]. Interestingly, the family history was positive for arteriopathy since the mother of this girl had died from rupture of a major artery during angiography[54]. Unfortunately, it was not mentioned if the deceased mother also suffered from a MID or not and if she manifested in organs other than the arteries[54].

Vascular malformations: In a single patient with LHON due to the mtDNA mutation m.11778G > A in the *ND4* gene, conventional cerebral angiography after right thalamic bleeding at age 9yo revealed an arteriovenous malformation with feeders from the posterior thalamo-perforat artery[55].

Reduced flow-mediated vasodilation: Flow-mediated vasodilation (FMD) is defined as change in diameter of an artery as assessed by high-resolution ultrasound in response to the release of an inflated cuff proximal to the measurement[26]. In a study of 35 patients with MELAS-syndrome the FMD was generally reduced[26]. In a study of 12 patients with a MID the FMD was reduced compared to controls[56].

DIAGNOSIS

Diagnosing mitochondrial vasculopathy is not at variance from non-mitochondrial vasculopathy. The diagnosis relies on the documentation and confirmation of the mitochondrial metabolic defect or the genetic cause and the exclusion of non-MID causes. In case of SLEs it is advisable to additionally carry out EEG recordings.

TREATMENT

Treatment of mitochondrial vasculopathy is not at variance from treatment of non-mitochondrial vasculopathy but patients with SLE may profit from L-arginine, vitamins, and coenzyme-Q[57]. Administration of co-factors may be also beneficial for MID patients with migraine-like headache. L-arginine may improve the FMD on a long-term basis[26].

DISCUSSION AND CONCLUSION

Diagnosing mitochondrial vasculopathy is important since it has several clinical implications. First, recognition of vasculopathy of undetermined cause may lead to the diagnosis of a MID. Diagnosing MIDs is important since many MIDs are frequently non-recognised for years or under-diagnosed. Mitochondrial vasculopathy most obviously indicating a MID as the underlying pathology is a stroke-like lesion. This is evident since stroke-like lesions are hallmarks of some MIDs and do not occur in disorders other than MIDs. Mitochondrial vasculopathy second most frequently indicative of a MID as an underlying cause is migraine[7]. Migraine is a frequent phenotypic feature of several syndromic and non-syndromic MIDs[7]. It may present not always as classical migraine why it is often termed migraine-like headache. Recent studies have shown that certain mtDNA polymorphisms are increased in patients with migraine[58]. There is also a mild bias towards a maternal transmission of migraine[59]. This is why patients with migraine should be suspected to have a MID as the underlying cause, as long as other possible causes have not been definitively excluded. Second, mitochondrial vasculopathy should be included as a phenotypic manifestation of syndromic or non-syndromic MIDs. Diagnosing MIDs should urge those manging MID patients to look for mitochondrial vasculopathy in individual patients and to initiate measures of treatment and prevention. Third, patients with MIDs should be systematically investigated for mitochondrial vasculopathy. This is important since MID patients are not investigated for concomitant mitochondrial vascular disease unless it is the dominant feature or leads to the diagnosis of LHON. Systematic investigations of MID patients for mitochondrial vasculopathy are important since early diagnosis may prevent severe complications. Systematic search for mitochondrial vasculopathy may contribute to assessing the prevalence of mitochondrial vasculopathy.

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ORIGINAL ARTICLE

Basic Study

Tenascin C upregulates interleukin-6 expression in human cardiac myofibroblasts *via* toll-like receptor 4

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Author contributions: Maqbool A performed the majority of the experiments and manuscript preparation; Spary EJ performed the statistical analysis; Manfield IW was involved in purification of the Tenascin C; Ruhmann M, Zuliani-Alvarez L and Midwood KS were equally involved with the synthesis and purification of the Tenascin C recombinants; Porter KE supplied the human cardiac fibroblasts; Drinkhill MJ generated the mouse infarct model; Gamboa-Esteves FO performed the histology, immunohistochemistry and image capture; Turner NA performed some of the experiments and was involved in experimental design and manuscript preparation.

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Institutional animal care and use committee statement: All procedures involving animals were carried out in accordance with the Home Office Animals (Scientific Procedures) Act 1986 and the University of Leeds Animal Welfare and Ethical Committee.

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Data sharing statement: Complete dataset and statistical analyses available from the corresponding author at cvsam@leeds.ac.uk.

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Abstract

AIM: To investigate the effect of Tenascin C (TNC) on the expression of pro-inflammatory cytokines and matrix

metalloproteinases in human cardiac myofibroblasts (CMF).

METHODS: CMF were isolated and cultured from patients undergoing coronary artery bypass grafting. Cultured cells were treated with either TNC (0.1 μmol/L, 24 h) or a recombinant protein corresponding to different domains of the TNC protein; fibrinogen-like globe (FBG) and fibronectin type Ⅲ-like repeats (TNⅢ 5-7) (both 1 μmol/L, 24 h). The expression of the pro-inflammatory cytokines; interleukin (IL)-6, IL-1β, TNFα and the matrix metalloproteinases; MMPs (MMP1, 2, 3, 9, 10, MT1-MMP) was assessed using real time RT-PCR and western blot analysis.

RESULTS: TNC increased both IL-6 and MMP3 (P < 0.01) mRNA levels in cultured human CMF but had no significant effect on the other markers studied. The increase in IL-6 mRNA expression was mirrored by an increase in protein secretion as assessed by enzyme-linked immunosorbant assay (P < 0.01). Treating CMF with the recombinant protein FBG increased IL-6 mRNA and protein (P < 0.01) whereas the recombinant protein TNⅢ 5-7 had no effect. Neither FBG nor TNⅢ 5-7 had any significant effect on MMP3 expression. The expression of toll-like receptor 4 (TLR4) in human CMF was confirmed by real time RT-PCR, western blot and immunohistochemistry. Pre-incubation of cells with TLR4 neutralising antisera attenuated the effect of both TNC and FBG on IL-6 mRNA and protein expression.

CONCLUSION: TNC up-regulates IL-6 expression in human CMF, an effect mediated through the FBG domain of TNC and *via* the TLR4 receptor.

Key words: Tenascin C; Matrix metalloproteinase; Toll-like receptor; Interleukin-6; Cardiac fibroblasts

Core tip: Tenascin C (TNC) is transiently expressed in cardiac tissue following acute myocardial infarction (MI) and MI patients with higher serum TNC levels have worse long term prognosis. This suggests that TNC is important in ventricular remodelling, although a functional role in this process is unclear. We report that TNC stimulates interleukin-6 synthesis in cardiac myofibroblasts, an effect mediated by toll-like receptor 4. As a growing body of evidence suggests that prolongation of the post-infarction inflammatory response results in worse remodelling and dysfunction this important observation may in part explain the mechanism by which TNC induces maladaptive ventricular remodelling following MI.

Maqbool A, Spary EJ, Manfield IW, Ruhmann M, Zuliani-Alvarez L, Gamboa-Esteves FO, Porter KE, Drinkhill MJ, Midwood KS, Turner NA. Tenascin C upregulates interleukin-6 expression in human cardiac myofibroblasts *via* toll-like receptor 4. *World J Cardiol* 2016; 8(5): 340-350 Available from: URL: http://www.wjgnet.com/1949-8462/full/v8/i5/340.htm DOI: http://dx.doi.org/10.4330/wjc.v8.i5.340

INTRODUCTION

A number of cardiac pathologies including acute myocardial infarction (MI), ischaemia/reperfusion (I/R) injury, hypertensive heart disease and myocarditis are associated with activation of pro-inflammatory mediators in the heart. Sustained expression of pro-inflammatory cytokines such as tumor necrosis factor-α (TNFα), interleukin (IL)-1 and IL-6 by infiltrating/resident inflammatory cells and cardiac fibroblasts is associated with increased matrix metalloproteinase (MMP) production, adverse cardiac remodelling leading to fibrosis, left ventricular (LV) dysfunction and heart failure[1]. The mechanisms that drive the inflammatory response in the heart are not fully understood.

The matricellular protein Tenascin C (TNC) is an extracellular glycoprotein that is highly expressed during embryonic development but is absent from healthy adult tissue. It is re-expressed in adult tissue during wound healing, inflammation and cancer invasion. In the adult myocardium TNC is up-regulated in pathological conditions that are closely associated with inflammation and extensive tissue remodelling such as MI[2], myocarditis[3] and dilated cardiomyopathy[4]. TNC is synthesised by interstitial fibroblasts and is up-regulated by various pro-inflammatory cytokines (*e.g.*, IL-1, IL-4, IL-13) and growth factors, as well as by oxidative and mechanical stress[5-11]. Evidence suggests that TNC may promote wound healing by recruiting cardiac myofibroblasts (CMF) during tissue repair[12]. However, it may also contribute to adverse ventricular remodelling as it can upregulate MMP production leading to excessive extracellular matrix (ECM) degradation. This in turn could weaken the adhesion of cardiomyocytes to the ECM, leading to cardiomyocyte slippage, LV dilation and reduction in contractile function[13]. Recent studies using synovial fibroblasts demonstrated that TNC was an endogenous activator of the toll-like receptor 4 (TLR4) pathway in the arthritic joint[14].

TLRs play a key role in driving inflammation and ECM turnover. They promote innate and adaptive immune responses including induction of pro-inflammatory cytokines and MMPs[15-18]. TLR4 has been identified on cardiac myocytes and TLR4 signalling is involved in the expression of cytokines in the myocardium[19-21]. Moreover, the TLR4 signalling pathway has been implicated in maladaptive ventricular remodelling[1] and in cardiac dysfunction after global I/R[22].

In the present study we investigated the effect of TNC on IL-6, IL-1β and MMP expression in a key cell type involved in the myocardial remodelling process, namely the human CMF[23,24]. In particular we investigated the interplay between TNC, TLR4 and the pro-inflammatory cytokine IL-6.

MATERIALS AND METHODS

Reagents

All cell culture reagents were purchased from Invitrogen (Paisley, Scotland, United Kingdom), except foetal calf serum (FCS) which was from Biosera (Ringmer, East Sussex, United Kingdom). Native human TNC was obtained from AbD Serotec (#8640-0502, Oxford, United Kingdom) and recombinant IL-1α from Life Technologies (Paisley, Scotland, United Kingdom). Lipopolysaccharide (LPS) was obtained from Sigma (Poole, United Kingdom).

Purification of human TNC

Purified human TNC protein (CC065, Millipore) from the human glioma cell line U251 was used in the *in vitro* experiments. Endotoxin levels were measured using the ToxinSensor Chromogenic LAL Endotoxin Assay Kit (Genscript). The TNC protein was taken through an endotoxin removal process using Detoxi-Gel Endotoxin Removal Columns (Thermoscientific) following the manufacturer's instructions. Commercial TNC, which was initially found to have an LPS concentration of approximately 15.8 pg/μg protein by LAL test, was column purified and found thereafter to be almost devoid of contamination (*i.e.*, < 0.1 pg/μg protein, which equates to < 3 pg/mL per reaction). The levels of LPS contamination of the TNC recombinant proteins [fibrinogen-like globe (FBG) and TNⅢ 5-7] was less than 10 pg/mL as described earlier[14]. These levels of contamination were more than 300-fold lower than that required (*i.e.*, 1 ng/mL) to stimulate IL-6 mRNA expression in human CMF. Nevertheless, polymyxin B was added in our experiments to block the biological effects of LPS. There was no evidence that polymyxin B alone could trigger IL-6 mRNA expression.

Recombinant TNC fragments

Recombinant TNC fragments corresponding to the FBG and fibronectin type Ⅲ-like repeats (TNⅢ 5-7) regions of the TNC protein were synthesised and purified as described previously[14].

Cell culture

Right atrial appendage biopsies from patients undergoing elective coronary artery bypass surgery at the Leeds General Infirmary were obtained following local ethical committee approval (reference number: 01/040) and informed patient consent. All investigations conformed to the principles outlined in the Declaration of Helsinki, 1997. Human cardiac fibroblasts were harvested, characterised and cultured as we have previously described[25,26]. Cells exhibit a myofibroblast phenotype as determined by positive staining for both α-smooth muscle actin and vimentin at passage 1 through to at least passage 5[26]. Experiments were performed on cells from passage 3-5 obtained from multiple donors. Cells were serum starved for 24 h before performing experiments in basal medium (DMEM) supplemented with 0.4% FCS and polymyxin B (50 μg/mL), an LPS neutralising agent, to ensure that any residual LPS in the TNC could not elicit a signal. Cells were treated with either IL-1α (10 ng/mL, 24 h), TNC (0.1 μmol/L, 24 h) or TNC recombinant fragments (FBG, TNIII 5-7, 1 μmol/L, 24 h). Concentrations and time point were based on preliminary dose response and time course experiments (data not shown). In TLR4 neutralising experiments, cells were pre-treated with TLR4 neutralising antibody (25 μg/mL, #AF1478, R and D Systems, Minneapolis, United States) for 1 h prior to TNC addition.

Quantitative RT-PCR

Cellular RNA was extracted from cells at the end of the incubation period and cDNA was prepared as described previously[27]. Real time RT-PCR was performed in duplicate using the Applied Biosystems 7500 Real-Time PCR System. Intron spanning primers and Taqman probes for human IL-1β (Hs00174097_m1), IL-6 (Hs00174131_m1), TNFα (Hs00174128_m1), MMP-1 (Hs00233958_m1), MMP-2 (Hs00234422_m1), MMP-3 (Hs00233962_m1), MMP-9 (Hs00234579_m1), MMP-10 (Hs00233987_m1), MT1-MMP (Hs00237119_m1), TLR2 (Hs01872448_s1) and TLR4 (Hs00152939_m1) were from Applied Biosystems (www.appliedbiosystems.com). Data are presented as a relative percentage of expression of the endogenous control GAPDH (Hs999-99905_m1 primers) using the formula $2^{-\Delta C_T} \times 100$ in which C_T is the cycle threshold number.

Real time RT-PCR array for TLR expression

RNA was extracted from human CMF from 3 different donors using the Aurum Total RNA kit (BioRad). Equivalent RNA samples from each of the 3 donors were pooled before preparing cDNA and measuring expression levels of TLRs as part of a SYBR Green-based real-time PCR array (RT^2 Profiler Human Innate and Adaptive Immune Response Array, SABiosciences, Qiagen). Δ C_T values for the target genes were calculated by subtracting the mean C_T value (threshold cycle number) of the 5 housekeeping (HK) genes on the array (β2-microglobulin, hypoxanthine phosphoribosyltransferase 1, ribosomal protein L13A, β-actin and GAPDH) from the C_T value of the target genes. Data are expressed relative to the mean of HK genes using the formula $2^{-\Delta CT}$.

Western blot analysis for TLR4

Whole cell homogenates were prepared from human CMF and cultured human saphenous vein smooth muscle cells, as described previously[28]. Proteins (10 μg) were resolved by SDS-PAGE and immunoblotting performed as described previously[28] with TLR4-specific primary antibody raised in rabbit (#sc10741, Santa Cruz Biotechnology, CA, United States) and horseradish peroxidase-conjugated donkey anti-rabbit secondary antibody (#NA934V, GE Health Care, United Kingdom). Immunolabelled bands were visualised on X-ray film by

SuperSignal West Pico chemiluminescence kit (Perbio, Cramlington, United Kingdom).

Enzyme-linked immunosorbant assay

Cells cultured in 48-well plates were serum-starved for 48 h before exposure to appropriate stimuli for 24 h in a volume of 0.25 mL. Conditioned media were collected and centrifuged to remove cellular debris, and samples were stored at -40 ℃ for subsequent analysis. Enzyme-linked immunosorbant assay for IL-6 was performed according to the manufacturer's instructions (R and D Systems, Abingdon, United Kingdom) using samples diluted 1:100.

Immunocytochemistry for TLR4

Human CMF were fixed in paraformaldehyde (40 g/L) before permeabilising with Triton X-100 (1 mL/L) in PBS. Cells were blocked with bovine serum albumin and incubated with goat primary antibody to human TLR4 (sc-8694, Santa Cruz Biotechnology, CA, United States) followed by Cy3-conjugated donkey anti-goat secondary antibody (1:1000, Stratech Scientific, Soham, Cambridgeshire, United Kingdom). Labelled cells were visualised using a Zeiss Imager. Z1 Apotome microscope and Axiovision image analysis software (Zeiss, Hamburg, Germany). Cells were mounted in Vectashield with DAPI (H-1200, Vector Laboratories, CA, United States). Antibody specificity was confirmed by pre-absorption of primary antibody with TLR4 protein (8 μg/mL for 24 h, sc-8694P, Santa Cruz Biotechnology, CA, United States).

MI model

All procedures involving animals were carried out in accordance with the Home Office Animals (Scientific Procedures) Act 1986 and the University of Leeds Animal Welfare and Ethical Committee. Experiments were performed on C57BL/6 mice (25-30 g, University of Leeds). Animals were maintained at 22 ℃ on a 12 h light and dark cycle with *ad libitum* access to food and water. The animal protocol was designed to minimise pain or discomfort to the animal. Mice were anaesthetised with isofluorane. Under a dissecting microscope, a left thoracotomy was performed at the level of the 4th intercostal space to allow the left anterior descending coronary artery to be visualised. This was ligated at the edge of the left atrium with 8-0 prolene suture. Occlusion was confirmed by observation of pallor of the anterior wall of the LV.

TNC, TRL4 and α-smooth muscle actin immunohistochemistry

Three days following MI, animals were perfused with formaldehyde, hearts were removed and wax-embedded. Tissue sections (3 μm) were cut and stained for both TNC (10337, Immuno-Biological Laboratories Co. Ltd, Japan) and TLR4 (sc-10741, Santa Cruz Biotechnology, CA, United States) using the MenaPath X-Cell Plus Multiplex Double Stain Detection Kit 2 (A.MENARINI Diagnostics, Berkshire, United Kingdom) and a Mouse on Mouse Polymer IHC Kit (Abcam, Cambridge, United Kingdom). Sections were also stained for α smooth muscle actin (clone 1A4, code no. M851; Dakopatts, Glostrup, Denmark) and TLR4 in similar fashion. Tissue sections were counterstained with haematoxylin and imaged using an Axioplan Zeiss microscope and AxioVision 4.8 software (Carl Zeiss Inc.).

Statistical analysis

Results are mean ± SEM with n representing the number of experiments on cells from different patients. Data were analysed using the student's *t*-test or repeated measures one-way ANOVA and Bonferroni multiple comparison post hoc test (GraphPad Prism software, www.graphpad.com). $P < 0.05$ was considered statistically significant. The statistical methods of this study were reviewed by Dr. Emma Spary from the University of Leeds.

RESULTS

Increased expression of TNC and TLR4 in the infarcted ventricle

Three days following LAD ligation, in an experimental mouse model of MI, positive interstitial TNC immunoreactivity (brown) was observed in the infarcted side of the left ventricle but not in the remote non-infarcted regions (Figure 1A and D). Light diffuse TLR4 staining (pink) was noted throughout the myocardium on myocytes and interstitial cells (Figure 1D). On the infarcted side the TLR4 staining was more evident with scattered foci of intense staining visible on myocytes, a feature consistent with previous reports[11] as well as on CMF (Figure 1B and C).

TNC up-regulates IL-6 mRNA and protein expression in human CMF

To determine whether TNC could stimulate MMP or pro-inflammatory cytokine synthesis *in vitro*, human CMF were incubated with TNC (0.1 μmol/L TNC or vehicle for 24 h) and mRNA levels were assessed using RT-PCR. A significant increase (14 fold, $P < 0.01$) in IL-6 mRNA expression from basal levels was observed in response to TNC (Figure 2). TNC also induced an approximately 25-fold increase in MMP3 levels ($P < 0.01$), whereas neither IL-1β nor any of the other MMPs analysed by real-time RT-PCR showed significant changes in mRNA expression in response to TNC (Figure 2). Basal TNFα mRNA expression in human CMF was minimal (0.002% GAPDH) and TNC had no effect on its expression (data not shown).

TLR4 is expressed in human CMF

We examined the mRNA expression of TLR4 in human CMF by RT-PCR and TLR4 protein by both western blot analysis and immunocytochemistry. Real-time RT-PCR

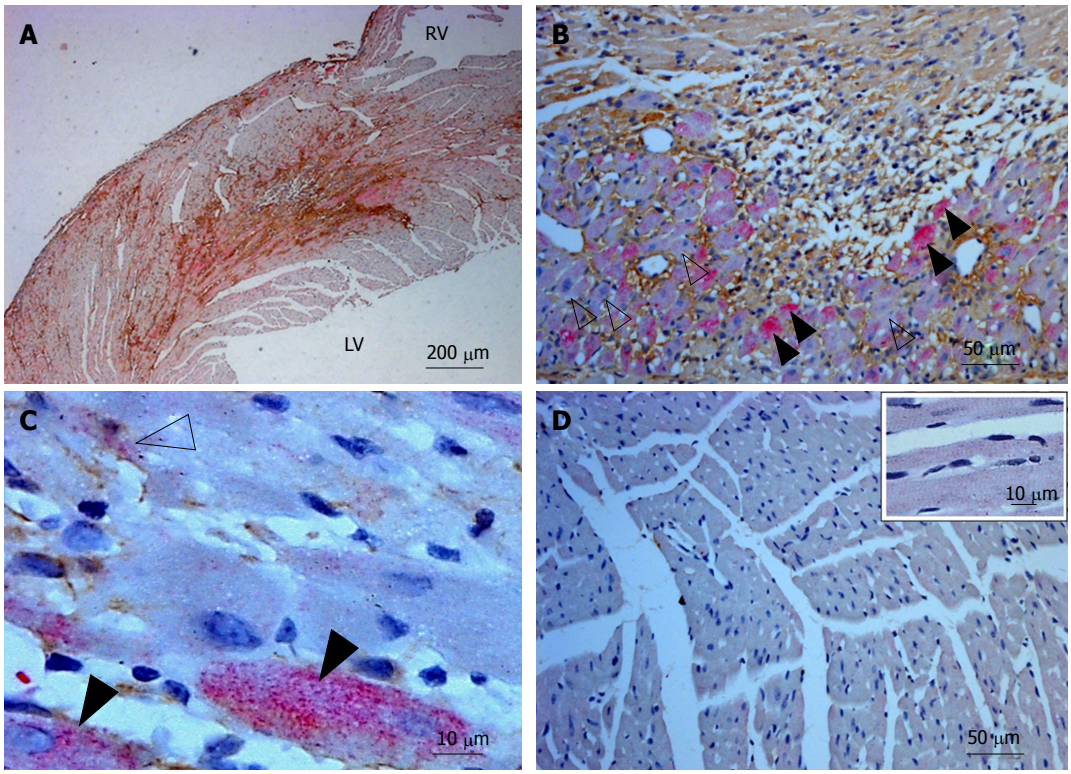

Figure 1 Tenascin C and toll-like receptor 4 staining in the murine left ventricle following infarction. A: Low power view of the infarcted mouse LV showing the proximity of TNC (brown) and TLR4 (pink) 3 d following the occlusion of the left anterior coronary artery; B: Diffuse TLR4 staining (open arrows) in myocytes and interstitial cells and intense TLR4 staining (solid arrows) in some myocytes. Interstitial TNC staining (brown) is evident around these cells; C: High powered view of TLR4 (pink) and alpha smooth muscle actin (brown) staining of cells in the infarcted LV. Intense TLR4 staining can be seen in some myocytes (solid arrow) with more diffuse staining seen in some cardiac myofibroblasts (labelled both pink and brown, open arrow); D: Low power view of the non-infarcted side of the mouse myocardium stained for TNC (brown) and TLR4 (pink). An absence of TNC staining and light diffuse TLR4 staining of the cells is observed. Inset image: a high powered view of cells in this area. In each image cell nuclei were stained with Mayer's Haematoxylin. RV: Right ventricle. LV: Left ventricle; TNC: Tenascin C; TLR4: Toll-like receptor 4.

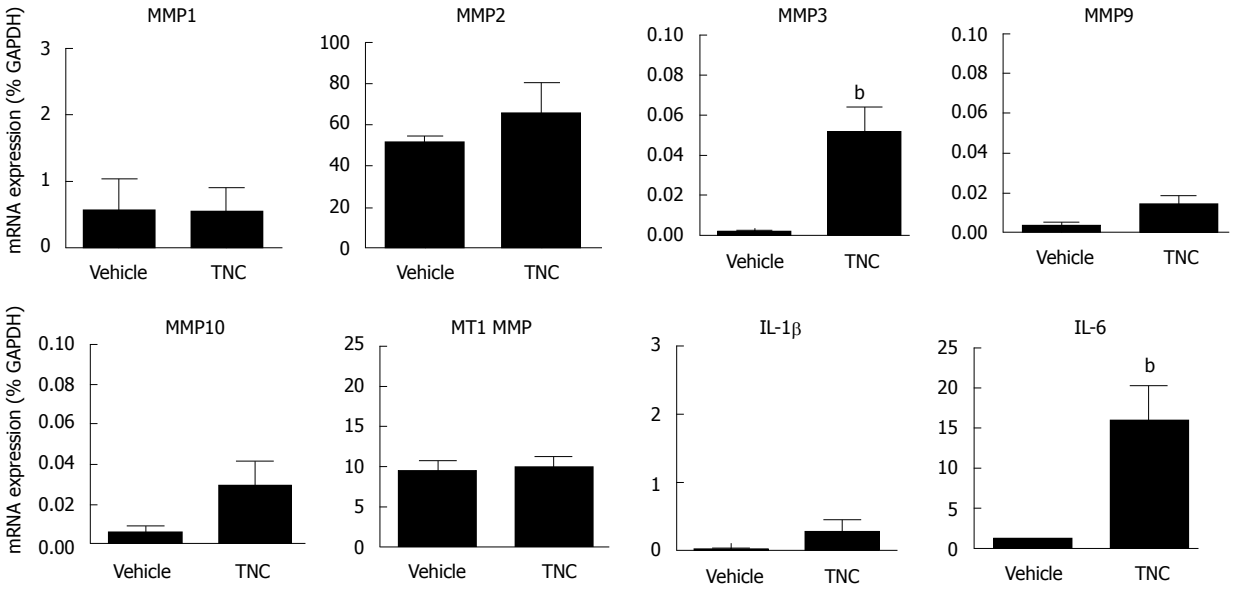

Figure 2 Changes in cytokine and matrix metalloproteinase mRNA expression in human cardiac myofibroblasts following incubation with Tenascin C. Effect of Tenascin C (TNC) (0.1 μmol/L, 24 h) on MMP1, MMP2, MMP3, MMP9, MMP10, MT1-MMP, IL-1β and IL-6 mRNA expression was assessed in human cardiac myofibroblasts (n = 4-6 donors). A significant increase in the expression of MMP3 and IL-6 was observed. Data are expressed as mean ± SEM. $^{b}P < 0.01$ *vs* vehicle (student's *t*-test). MMP: Matrix metalloproteinase; IL: Interleukin.

array analysis of TLRs 1-9 revealed that TLR4 was by far the most highly expressed TLR in human CMF at

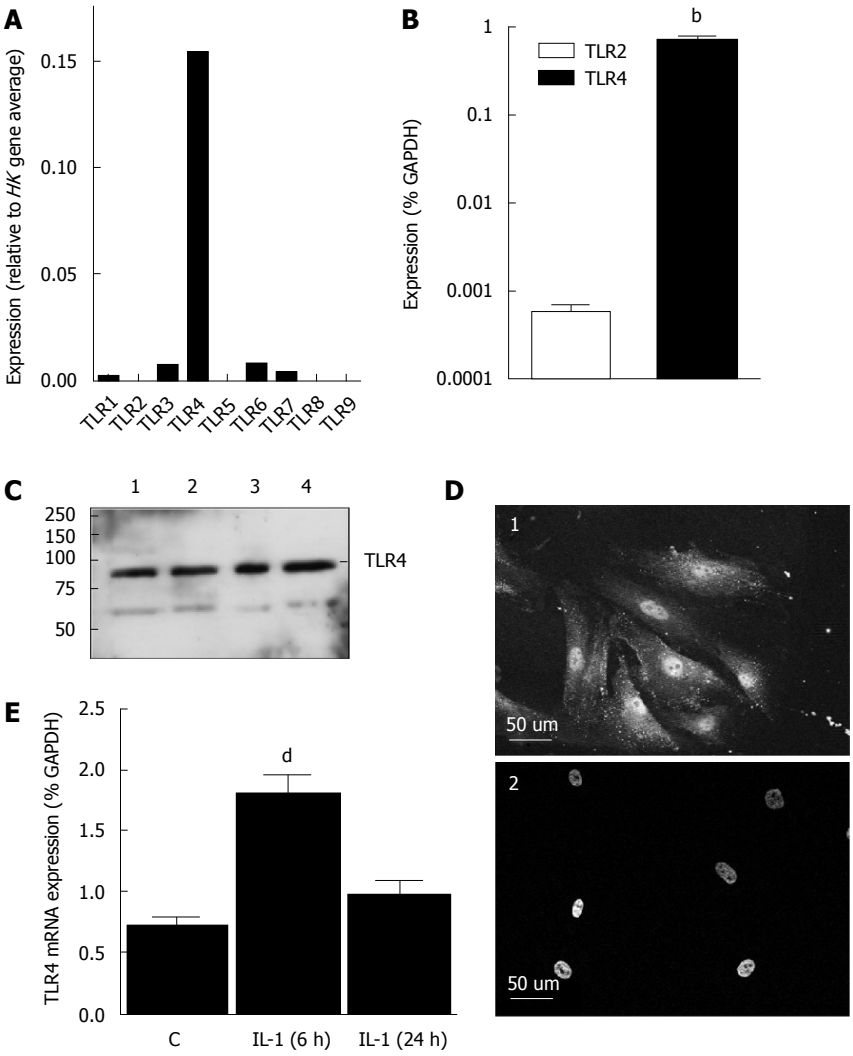

Figure 3 Toll-like receptor 4 expression in human cardiac myofibroblasts. A: Data from RT-PCR array showing abundance of TLR mRNA in a pooled sample of human CMF (n = 3 donors). Data expressed relative to 5 housekeeping genes; B: Taqman RT-PCR analysis of TLR2 and TLR4 mRNA levels in human CMF (n = 4 donors). Note log scale. $^{b}P < 0.001$ (paired t-test); C: Western blot of CMF homogenates from 4 donors probed with anti-TLR4 antibody. Fifteen micrograms protein per lane. Molecular size (kDa) on left. TLR4 = 95 kDa; D1: Immunocytochemical localisation of TLR4 in human CMF using a primary antibody to human TLR4 and a Cy3-conjugated secondary antibody; D2: Effect of pre-absorption of primary antibody with TLR4 peptide (8 μg/mL) prior to immunostaining. Nuclei are labelled with DAPI. Loss of immunostaining confirms specificity of the antibody. Scale bar 50 μm; E: Effect of IL-1α (10 ng/mL, 6 and 24 h) on TLR4 mRNA expression in human CMF (n = 4 donors). Data are expressed as mean ± SEM. $^{d}P < 0.01$ *vs* vehicle (ANOVA post-hoc). TLR: Toll-like receptor.

the mRNA level (Figure 3A). Lower levels of TLR6 > TLR3 > TLR7 > TLR1 were also observed, but TLR2 was not detected. Follow-up studies with Taqman RT-PCR (different primers) on cells from a further 4 donors confirmed the TLR4 and TLR2 data (Figure 3B). Western blot analysis revealed a single 95 kDa band corresponding to TLR4 in protein lysates isolated from human CMF from 4 different donors (Figure 3C). Immunocytochemistry with primary antibodies directed against human TLR4 revealed a pattern of punctate staining in the cytoplasm and nucleus of human CMF (Figure 3D1). Staining was not evident if the primary antibody was pre-incubated with TLR4 protein (Figure 3D2). To assess the effect of inflammatory cytokines on TLR4 mRNA expression, human CMF were incubated with IL-1α. Real-time RT-PCR analysis of TLR4 revealed a 2.5 fold increase of expression after 6 h of treatment, falling back towards basal levels after 24 h (Figure 3E).

TLR4 mediates TNC up-regulation of IL-6 in human CMF

To determine whether the effects of TNC on IL-6 mRNA expression in human CMF were mediated by TLR4, cells from 5 donors were pre-incubated with TLR4 neutralising antibodies prior to TNC treatment (100 nmol/L, 24 h). TLR4 neutralisation had no significant effect on basal IL-6 mRNA expression but did prevent TNC-stimulated expression of IL-6 (Figure 4A). These changes in IL-6 mRNA expression were mirrored by changes in IL-6 protein secretion (Figure 4B). The specificity of the TLR4 antisera for the TLR4 receptor in our *in vitro* studies was confirmed by demonstrating that pre-treating cells with TLR4 neutralising antibodies had no effect on the IL-1α induced IL-6 mRNA expression (Figure 4C).

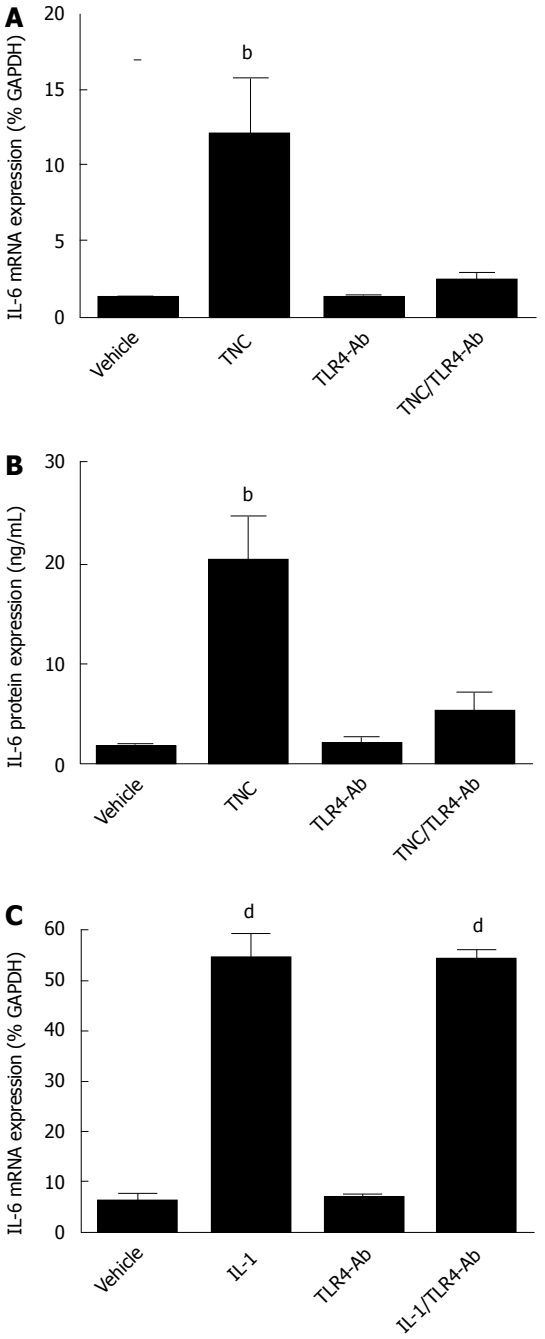

Figure 4 Tenascin C upregulates interleukin-6 expression in human cardiac myofibroblasts *via* toll-like receptor 4. A and B: Effect of TNC (0.1 μmol/L, 24 h) with and without 1 h pre-incubation in TLR4 antisera (25 μg/mL) on IL-6 mRNA (A) and IL-6 protein expression (B) in CMF (4-5 donors). Data expressed as mean ± SEM. $^{b}P < 0.01$ *vs* vehicle (ANOVA post-hoc). TNC: Stimulation with TNC alone; TLR4-Ab: Pre-incubation with TLR4 neutralising antisera; TNC/TLR4-Ab: Stimulation with TNC following TLR4 pre-incubation; C: Effect of 1 h pre-incubation in TLR4 antisera (25 μg/mL) on IL-1α (10 ng/mL, 24 h)-stimulated IL-6 mRNA expression in CMF (n = 3 donors). The TLR4 neutralising antisera had no effect on IL-1α induced IL-6mRNA expression. Data expressed as mean ± SEM. $^{d}P < 0.0001$ *vs* vehicle (ANOVA post-hoc). IL-1: Stimulation with IL-1α alone; TLR4-Ab: Pre-incubation with TLR4 neutralising antisera; IL-1/TLR4-Ab: Stimulation with IL-1α following TLR4 pre-incubation; TNC: Tenascin C; CMF: Cardiac myofibroblasts; IL: Interleukin; TLR: Toll-like receptor.

FBG domain upregulates IL-6 mRNA expression in human CMF

Previous studies have implicated the FBG domain of TNC in the promotion of cytokine production in synovial fibroblasts[14]. To determine whether a similar effect was evident in human CMF, cells were incubated with recombinant FBG protein (1 μmol/L, 24 h) and IL-6 mRNA expression assessed. FBG induced a 6-fold increase in IL-6 mRNA expression ($P < 0.01$), whereas incubation with the TNⅢ 5-7 recombinant TNC fragment had no effect, endorsing the suggestion that the FBG domain was crucial for promoting IL-6 production (Figure 5A). Neither FBG nor TNⅢ 5-7 recombinant proteins significantly increased MMP-3 expression in human CMF (Figure 5B).

TLR4 mediates FBG up-regulation of IL-6 in human CMF

To determine whether the effects of FBG on IL-6 mRNA expression in human CMF were mediated by TLR4 pathways, cells from 3 donors were pre-incubated with TLR4 neutralising antibodies prior to FBG treatment (1 μmol/L, 24 h). TLR4 antibodies had no significant effect on basal IL-6 mRNA expression but did prevent FBG -stimulated expression of IL-6 (Figure 5C).

DISCUSSION

The main finding of the present study is that TNC up-regulates IL-6 expression in human CMF and that this effect is mediated through its FBG domain and the TLR4 receptor.

Inflammation and matrix turnover are important features in cardiac remodelling post infarction. If unchecked, these can lead to chronic maladaptive LV remodelling, characterised by progressive ventricular dilatation, myocardial hypertrophy, fibrosis, cardiac dysfunction and failure. TNC is an ECM glycoprotein that is re-expressed in the heart under pathological conditions such as MI[29,30], myocarditis[3,31,32] and dilated cardiomyopathy[4,33] and is closely associated with tissue injury and inflammation[3,31,34]. Following MI, TNC has been reported to appear during the acute stage at the interface between the infarcted and intact myocardium where tissue remodelling is at its most active[2]. There is evidence that TNC is a sensitive marker for active inflammation in acute myocarditis[3]. Moreover, serum levels of TNC correlate with the severity of heart failure, LV dysfunction and remodelling in patients with dilated cardiomyopathy[35]. These observations suggest that TNC expression is maintained in cardiac pathologies in which there is ongoing inflammation and remodelling.

We previously reported that IL-1α up-regulates TNC expression in human CMF[11]. IL-1 has been identified as one of the initial stimuli that drive the acute inflammatory response following MI[36-39]. Increased levels of IL-1 have also been implicated in the inflammatory response and adverse LV remodelling seen in heart failure[40]. The observation that TNC up-regulates IL-6 expression in our present study supports the previous notion that after its initial induction TNC could drive the inflammatory response further[14].

IL-6 has previously been shown to have important roles in inflammation and remodelling in the heart

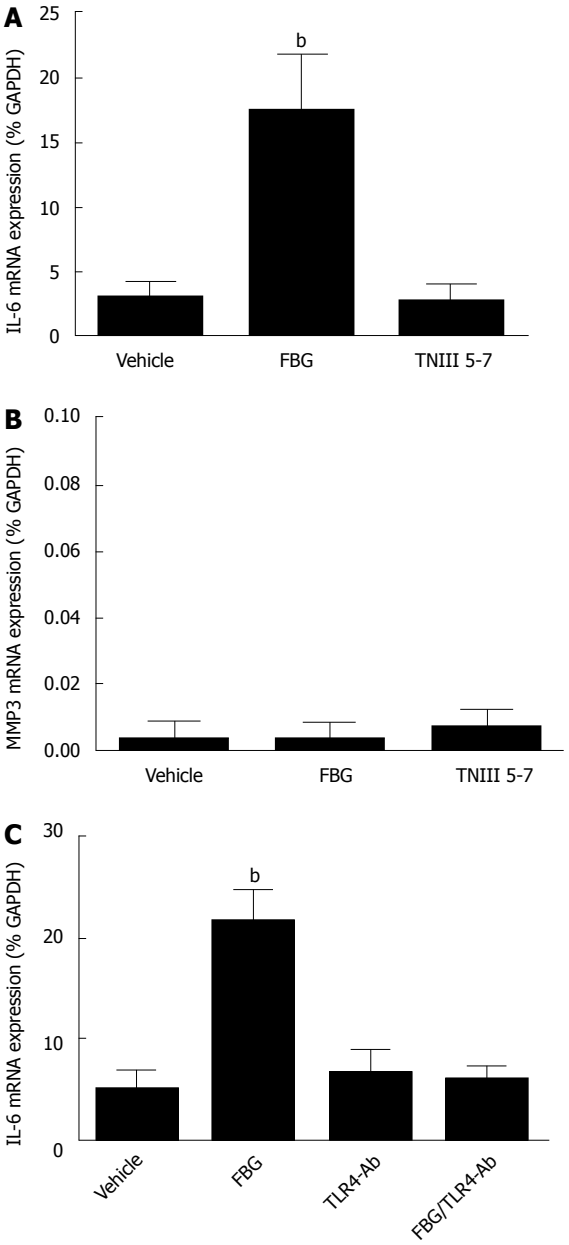

Figure 5 Fibrinogen-like globe domain of Tenascin C up-regulates interleukin-6 mRNA expression in human cardiac myofibroblasts *via* toll-like receptor 4. A and B: Effect of 1 μmol/L (24 h) recombinant protein, corresponding to either the FBG domain or the fibronectin type III domain (TNIII 5-7) of TNC, on IL-6 mRNA (A) and MMP3 mRNA (B) in human CMF (n = 3-5 donors). Data expressed as mean ± SEM. $^{b}P < 0.01$ *vs* vehicle (ANOVA post-hoc); C: Effect of 1 h pre-incubation in TLR4 neutralising antisera (25 μg/mL) alone on IL-6 mRNA expression and on FBG (1 μmol/L, 24 h) stimulated IL-6 mRNA expression in CMF (n = 3 donors). Data expressed as mean ± SEM. $^{b}P < 0.01$ *vs* vehicle (ANOVA post-hoc). FBG: Stimulation with FBG recombinant alone; TLR4-Ab: Pre-incubation with TLR4 neutralising antisera; FBG/TLR4-Ab: Stimulation with FBG following pre-incubation with TLR4 neutralising antisera. FBG: Fibrinogen-like globe; TNC: Tenascin C; IL: Interleukin; CMF: Cardiac myofibroblasts.

following injury by promoting leukocyte infiltration and activation, and by modulating fibroblast function[23,41-43]. In addition to its pro-inflammatory and fibrogenic properties, there is also evidence that IL-6 regulates ECM remodelling by enhancing cardiac fibroblast MMP expression and modulating tissue inhibitor of MMPs (TIMP) expression levels[23,42,44]. Our observations are consistent with a previous report in synovial fibroblasts, where an up-regulation of IL-6 expression following TNC stimulation was purported to play a role in the chronic inflammatory response seen in the arthritic joint[14]. In that study, the TLR4 pathway was identified as a mediator of this effect with the TLR4 receptor being activated by the FBG domain of TNC. Importantly, our study suggests that this notable mechanism may also play a role in the inflammatory response in the heart. As TLR4 signalling has long been implicated in a range of cardiac pathologies, the confirmation of such a mechanism in cardiac cells contributes to our understanding of the process of inflammation that occurs in the heart.

A regulatory role for TLR4 signalling in inflammation and ECM turnover has been established and its involvement in post-infarct maladaptive remodelling in the heart has been reported[1]. Moreover, TLR4 signalling has been implicated in myocarditis[45] and in the myocardial inflammatory response following regional or global ischemia/reperfusion[20,22,46,47]. Although TLR4 signalling contributes to cardiac dysfunction after MI in part through its influence on myocardial production of cytokines, the mechanism by which TLR4 is activated in these circumstances remains to be defined[22]. Evidence that TNC is up-regulated following oxidative stress suggests it may be a candidate ligand responsible for TLR4 signalling following ischemic injury[48]. Furthermore, our observations that the inflammatory cytokine, IL-1α, upregulates both TNC[11] and TLR4 expression (Figure 3E) in CMF and that both TNC and TLR4 are upregulated in the infarcted ventricle (Figure 1) lends support to their involvement in the cardiac inflammatory response following MI[2,14,49].

With the exception of MMP3, neither IL-1β nor any of the MMPs analysed by real-time RT-PCR showed significant changes in mRNA expression in response to TNC. In the case of MMP3, although a significant increase from basal expression was indeed observed with TNC, the mean induced MMP3 levels were only 0.05% that of the *HK* gene GAPDH. Nevertheless, this is equivalent to the mRNA level observed in response to a low concentration of IL-1 (0.1 ng/mL) in these cells which resulted in detectable MMP3 protein secretion[50]. We found no evidence, however, that FBG was responsible for the increase in MMP3 observed. The possibility that a different domain of this molecule, other than FBG or TNⅢ5-7, plays a role in MMP3 induction remains to be tested. Moreover, the recent demonstration that some of the effects of TNC are mediated *via* αVβ3 integrin, suggests that the induction of MMP3 by TNC may occur *via* a different receptor subtype[51].

The up-regulation of MMP3 by TNC would be consistent with TNC's role in the degradation of ECM following MI and the promotion of a de-adhesive state that facilitates migration of fibroblasts and other granulation tissue cells to the site of injury[52]. TNC has previously

been reported to induce cell-specific increases in MMP levels including cultured human smooth muscle cells, murine mammary cancer cells, macrophages and synovial fibroblasts[53-56].

Finally, the lack of induction of IL-1β and TNFα by TNC is consistent with previous studies which have reported that stimulation of synovial fibroblasts with TNC resulted in augmented gene expression of some pro-inflammatory cytokines (*e.g.*, IL-1α and IL-6), but not others (*e.g.*, interferon-γ, TNF-α and IL-1β)[14,56].

In conclusion, we have demonstrated that TNC up-regulates MMP3 and the pro-inflammatory cytokine IL-6 in human CMF. The latter effect of TNC is mediated *via* the TLR4 receptor and the FBG domain of the TNC. Targeting the FBG domain of TNC may provide a novel therapeutic option to counteract aberrant inflammation and maladaptive cardiac remodelling.

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COMMENTS

Background

Adverse ventricular remodelling following cardiac injury is a key determinant of heart failure. Despite major advances in the field, the number of heart failure deaths is increasing steadily. A better understanding of the processes involved in the remodelling process would enable the development of novel therapeutics.

Research frontiers

The importance of inflammation in cardiac remodelling that occurs after myocardial injury is unequivocal. The inflammatory process can cause myocardial damage, while inflammatory agents contribute to the worsening and progression of heart failure. A detailed understanding of the underlying inflammatory processes involved in cardiac remodelling, with the aim to develop better therapeutics, remains an important area in heart failure research.

Innovation and breakthroughs

Tenascin C (TNC) is highly expressed during embryogenesis but is virtually absent in the adult heart. It is re-expressed in the heart following injury where its expression correlates with the extent of inflammation and myocardial remodelling. The continued expression of TNC in pathologies associated with cardiac inflammation (*e.g.*, myocarditis, heart failure) had been recognised yet its functional significance remained elusive. This study is the first to demonstrate that TNC is able to stimulate the expression of the inflammatory cytokine interleukin (IL)-6 in human cardiac myofibroblasts (CMF) in a toll-like receptor 4-dependent fashion. This action is similar to that reported in the arthritic joint where TNC contributes to the persistent inflammation observed. As IL-6 plays an important role in myocardial inflammation and fibrosis, identification of this notable mechanism in CMF will further our understanding of the inflammatory processes occurring after myocardial stress or injury.

Application

The results provide further insight into the underlying mechanism(s) involved in cardiac inflammation and may help identify novel therapeutic targets to attenuate this in disease states.

Peer-review

This manuscript reports the effects of TNC on the expression of the pro-inflammatory cytokines in human CMF. The findings are of interest and suitable for the publication by the journal.

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CASE REPORT

Relationship between coronary artery ectasia, cocaine abuse and acute coronary syndromes

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Author contributions: Dendramis G designed the report, analyzed the data and wrote the paper; Paleologo C collected the patient's clinical data; Piraino D and Assennato P analyzed the data.

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Abstract

Coronary artery ectasia (CAE) often represents a coronary angiography finding casually detected or following the occurrence of an acute coronary syndrome. The pathogenetic role of cocaine abuse in the genesis of CAE is still little known and very few data are available in literature. We describe a case of a 31-year-old male cocaine user admitted to our department for typical acute chest pain. Coronary angiography showed diffuse coronary ectasia with slow flows and without hemodynamically significant stenosis. An increasing of matrix metalloproteinases values and a reduction of their tissue inhibitors was showed both during hospitalization and at one month after discharge. This case report emphasizes the close relationship between cocaine abuse, CAE and acute coronary syndromes in patients without hemodynamically significant coronary stenosis. As reported by Satran *et al*, cocaine abuse should be considered an important risk factor for CAE and these patients appear to be at increased risk of angina and acute myocardial infarct. Further studies that can strengthen this hypothesis would be useful to deepen and better analyze this interesting association.

Key words: Coronary artery ectasia; Acute coronary syndromes; Cocaine abuse; Matrix metalloproteinases; Inflammation

Core tip: The pathogenetic role of cocaine abuse in the genesis of coronary artery ectasia (CAE) is still little known and very few data are available in literature. This case report emphasizes the close relationship between cocaine abuse, CAE and acute coronary syndromes in patients without hemodynamically significant coronary stenosis. As reported by Satran *et al*, cocaine abuse should be considered an important risk factor for CAE and appears to be another potential mechanism of

acute coronary syndromes in cocaine users. Further studies that can strengthen this hypothesis would be useful to deepen and better analyze this interesting association.

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INTRODUCTION

Coronary artery ectasia (CAE) is a dilation of coronary arteries angiographically defined if the diameter of the artery is at least 1.5 times greater than that of the intact adjacent vascular segment.

Common causes include atherosclerosis, systemic inflammatory disease, systemic vasculitis, genetic connective tissue disorders (Marfan and Ehler-Danlos syndrome) and cocaine abuse.

CAE may have a variable clinical presentation and often represents a coronary angiography finding casually detected or following the occurrence of an atypical chest pain or an acute coronary syndrome. The mechanisms that determine the abnormal dilatation of the vascular lumen are still poorly understood and particularly the overexpression of matrix metalloproteinases (MMPs) has been associated with an excessive expansive arterial remodeling[1].

CASE REPORT

A 31-year-old caucasian man, cocaine user without other cardiovascular risk factors, was admitted to our department for typical acute chest pain started while he was climbing stairs.

At cardiac examination we found a 1/6 Levine systolic murmur at the precordium and blood pressure was 180/90 mmHg. The ECG showed a sinus rhythm with 91 bpm, ST segment depression with T negative waves from V2 to V5 and a corrected QT interval of 493 msec (Figure 1).

Leukocytosis with increasing of inflammatory markers (C-reactive protein 3.2 mg/dL) and positive Troponin I (0.3 ng/mL) were present. Transthoracic echocardiogram showed left ventricular concentric hypertrophy, ejection fraction of 60%, low mitral regurgitation and altered relaxation mitral inflow pattern.

For the persistence of typical chest pain and the high pretest probability of coronary artery disease (CAD) due to cocaine abuse, we choose an invasive diagnostic approach. Percutaneous coronary angiography (performed with 6F diagnostic catheters and right femoral artery access) showed diffuse coronary ectasia without hemodynamically significant stenosis and coronary slow flow with Timi Frame Count score of 2 and a myocardial blush grade 2 (Figure 2). For left coronary artery contrast was injected with a flow rate of 4 mL/s and a volume of 8 mL; for right coronary artery contrast was injected with a flow rate of 3 mL/s and a volume of 6 mL.

To exclude a possible role of a coronary spasm in the genesis of the acute coronary syndrome, an hyperventilation testing and an intracoronary injection of acetylcholine (with incremental doses of 20 and 50 μg into the right coronary artery and of 20, 50, and 100 μg into the left coronary artery over 20 s and with at least a 3-min interval between injections) were performed and were negative. Furthermore, to exclude a thrombophilic diathesis, a thrombophilia testing was also performed and was negative.

For the presence of diffuse CAE MMPs plasma concentrations (MMP-2 and MMP-9) and their tissue inhibitors (TIMP-1 and TIMP-2) were also quantified.

An increasing of MMPs values and a reduction of their tissue inhibitors was showed both during hospitalization (MMP-2: 538.9 ng/mL, normal plasma values 125 ± 30 ng/mL; MMP-9: 53.5 ng/mL, normal plasma values 18 ± 6 ng/mL; TIMP-1: 39.2 ng/mL, normal plasma values 356 ± 110 ng/mL; TIMP-2: 26.3 ng/mL, normal plasma values 105 ± 12 ng/mL) and both at one month after discharge (MMP-2: 492.3 ng/mL, MMP-9: 51.7 ng/mL, TIMP-1: 40.5 ng/mL, TIMP-2: 29.1 ng/mL). Because during acute phenomena these values would be physiologically altered, a double assessment was carried out to ensure that values were not affected by the acute event.

Patient was subjected to pharmacological treatment with acetylsalicylic acid, ACE inhibitors, beta-blockers, spironolactone, and statins. Others possible causes of persistent elevated levels of MMP have not been observed one month after discharge.

DISCUSSION

Cocaine is an alkaloid extracted from the leaf of the Erythroxylon coca bush which blocks the presynaptic reuptake of epinephrine, norepinephrine and dopamine, thereby increasing their postsynaptic concentrations and improving sympathetic activity. Cocaine's principal effects on the cardiovascular system are mediated *via* alpha-adrenergic stimulation with increase in the determinants of myocardial oxygen demand (increasing of heart rate and systemic arterial pressure) and with a concomitant decrease in myocardial oxygen supply caused by vasoconstriction of the epicardial coronary arteries.

Cocaine induced chest pain is a common presentation in emergency departments and premature coronary atherosclerosis with obstructive coronary artery disease often has been seen in young cocaine abusers. Focal occlusive vasospasm, diffuse coronary vasoconstriction, endothelial dysfunction and coronary thrombosis may be responsible for cocaine induced myocardial infarct in patients with normal coronary

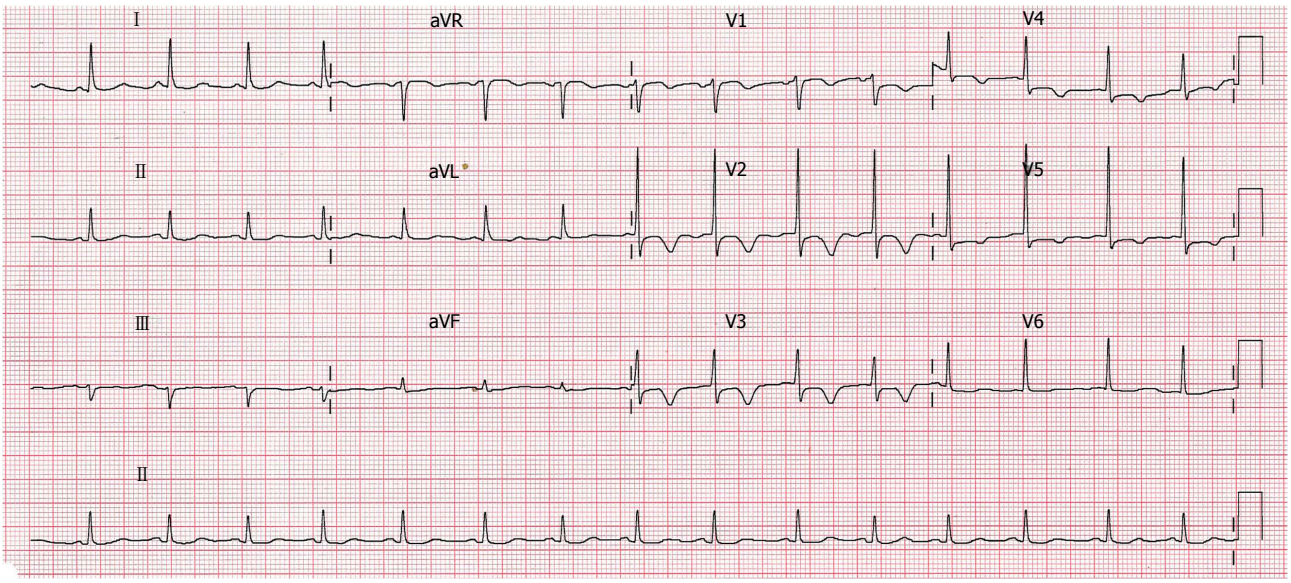

Figure 1 Electrocardiogram at the admission.

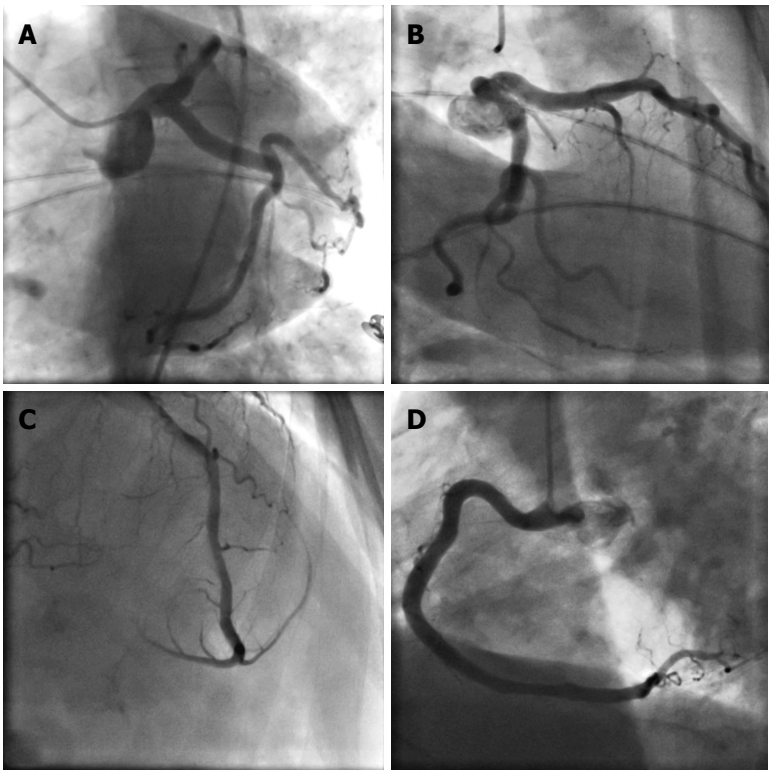

Figure 2 Coronary angiography performed with 6F diagnostic catheters showing ectasia of left anterior descending artery and circumflex coronary artery with maximum diameter of 5.8 mm (A and B), ectasia of medio-distal tract of left anterior descending artery (C), ectasia of right coronary artery with a maximum diameter of 5.6 mm (D).

arteries and cocaine use is also associated with an activation of platelets, leading to increased platelet adhesiveness and aggregation that play a major role in the development of coronary thrombi[2].

Patients with a history of cocaine abuse have also an increased prevalence of CAE. Potential mechanisms that play a major role in the development of CAE may include direct vascular smooth muscle cells apoptosis with media damage, enhanced monocyte migration and endothelium adhesion with hypersecretion of inflammatory cytokines and MMP overexpression with enzymatic degradation and hyalinization of the extracellular matrix. All this effects may cause "chronic vascular stress" (vascular inflammation, arterial remodeling and coronary ectasia) resulting in coronary slow flow and thrombosis[1].

Su *et al*[3] have demonstrated that cerebral vascular smooth muscle cells can undergo rapid apoptosis in

response to cocaine in a concentration-dependent manner, moreover Fiala *et al*[4] have shown that cocaine in vitro increases the expression of endothelial adhesion molecules, intercellular adhesion molecule-1, vascular cell adhesion molecules-1 and platelet/endothelial cell adhesion molecule-1. Moreover, both *in vitro* and *in vivo*, cocaine increases rolling white blood cell flux, leukocyte-endothelium adhesion and mononuclear cells activation with hypersecretion of inflammatory cytokines and overexpression of MMPs with consequent coronary arterial remodeling and ectasia[3,4].

In Demopoulos *et al*[5] study, history of acute myocardial infarct was reported among 39% of patients with CAE but without CAD and for the authors the presence of ectasic vascular segments would lead to a slow blood flow with greater likelihood of intracoronary thrombosis. In an interesting study Satran *et al*[6] have demonstrated as patients with a history of cocaine abuse have an increased prevalence of CAE. These patients appear also to be at increased risk of acute myocardial infarct (nearly half the patients in the cocaine group had a history of acute MI despite an average age of 43 years). Therefore CAE appears to be another potential mechanism of acute coronary syndromes in cocaine users[6].

It is known that CAE can be also caused by long lasting hypertension, but it is also known that the cocaine abuse may determines CAE[6]. In our case the patient did not reported to suffer from hypertension and his young age and lack of familiarity for hypertension does not support the hypothesis that CAE may be secondary to a possible hypertension. Moreover to exclude this hypothesis and on the basis of the echocardiography view of concentric hypertrophy we also investigated possible causes of secondary hypertension but all the exams resulted negative. No others conditions (except cocaine abuse) were present to exclude other causes of CAE.

The pathogenetic role of cocaine abuse in the genesis of CAE is still little known and very few data are available in literature. As demonstrated by Satran *et al*[6], cocaine abuse should be considered an important risk factor for CAE and furthermore these patients appear to be at increased risk of acute coronary syndromes even without hemodynamically significant coronary stenosis.

This case emphasizes the close relationship between cocaine abuse, CAE and acute coronary syndromes in patients without coronary stenosis but, being only a case report, it is not possible to draw conclusions about this association, although often in our clinical practice we see more and more cases like this. Further studies that can strengthen this hypothesis would be useful to deepen and better analyze this interesting association.

COMMENTS

Case characteristics

The authors describe a case of a 31-year-old male cocaine user and without other cardiovascular risk factors, admitted to the authors' department for typical acute chest pain.

Clinical diagnosis

At cardiac examination the authors found a 1/6 Levine systolic murmur at the precordium, blood pressure was 180/90 mmHg and the electrocardiogram showed sinus rhythm, ST segment depression with T negative waves from V2 to V5.

Differential diagnosis

Cocaine induced chest pain is a common presentation in emergency departments and premature coronary atherosclerosis with obstructive coronary artery disease, focal occlusive vasospasm, diffuse coronary vasoconstriction and coronary artery ectasia (CAE) are clinical conditions to be excluded in these patients.

Laboratory diagnosis

Leukocytosis, increasing of inflammatory markers and positive Troponin I were present; furthermore thrombophilia testing was negative and an increasing of matrix metalloproteinase (MMP) values with a reduction of their tissue inhibitors was showed both during hospitalization and at one month after discharge.

Imaging diagnosis

Coronary angiography showed diffuse coronary ectasia with slow flows and without hemodynamically significant coronary stenosis.

Treatment

Patient was subjected to pharmacological treatment with acetylsalicylic acid, ACE inhibitors, beta-blockers, spironolactone, and statins.

Related reports

A double assessment of MMP values and of their tissue inhibitors was carried out both during hospitalization and at one month after discharge to ensure that values were not affected by the acute event, furthermore others possible causes of persistent elevated levels of MMP have not been observed after discharge.

Experiences and lessons

Cocaine abuse should be considered an important risk factor for CAE and appears to be another potential mechanism of acute coronary syndromes in cocaine users; anyway further studies that can strengthen this hypothesis would be useful to deepen and better analyze this interesting association.

Peer-review

The authors reported the acute coronary syndrome accompanied with CAE in a young male cocaine user. This case report is interesting.

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MINIREVIEWS

Cardiomyopathy in becker muscular dystrophy: Overview

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Author contributions: Ho R and Nguyen ML conducted literatures search and wrote the entire manuscript; Mather P reviewed and edited the manuscript.

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Abstract

Becker muscular dystrophy (BMD) is an X-linked recessive disorder involving mutations of the dystrophin gene. Cardiac involvement in BMD has been described and cardiomyopathy represents the number one cause of death in these patients. In this paper, the pathophysiology, clinical evaluations and management of cardiomyopathy in patients with BMD will be discussed.

Key words: Becker muscular dystrophy; Cardiomyopathy; X-linked recessive disorder; Dystrophin

Core tip: Becker muscular dystrophy (BMD) is an X-linked recessive disorder involving mutations of the dystrophin gene. This condition is rare but not uncommon. However, there are limited articles on this topic. Patients with BMD can present with mental retardation and diffuse muscular dystrophy. Cardiomyopathy is the number one cause of death in BMD. This paper aims to provide a comprehensive overview of BMD pathophysiology and management. The paper will discuss both the established treatments as well as exciting new research on gene therapy.

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INTRODUCTION

Becker muscular dystrophy (BMD), first described by Doctor Peter Emil Becker in 1955, is an X-linked recessive disorder involving mutations of the dystrophin gene. The dystrophin gene located on chromosome Xp21.1, codes for a large protein that serves as a scaffolding protein in both skeletal and cardiac muscle. In BMD, the mutations allow for expression of truncated but functional dystrophin or a reduced amount of dystrophin protein. BMD is characterized by progressive skeletal muscle weakness. It affects one in 18450 males with the prevalence of at least 2.4/100000[1]. Researchers started correlating BMD with cardiac involvement in 1960s[2]. BMD patients may live until the fifth or sixth decade of life and cardiomyopathy represents the number one

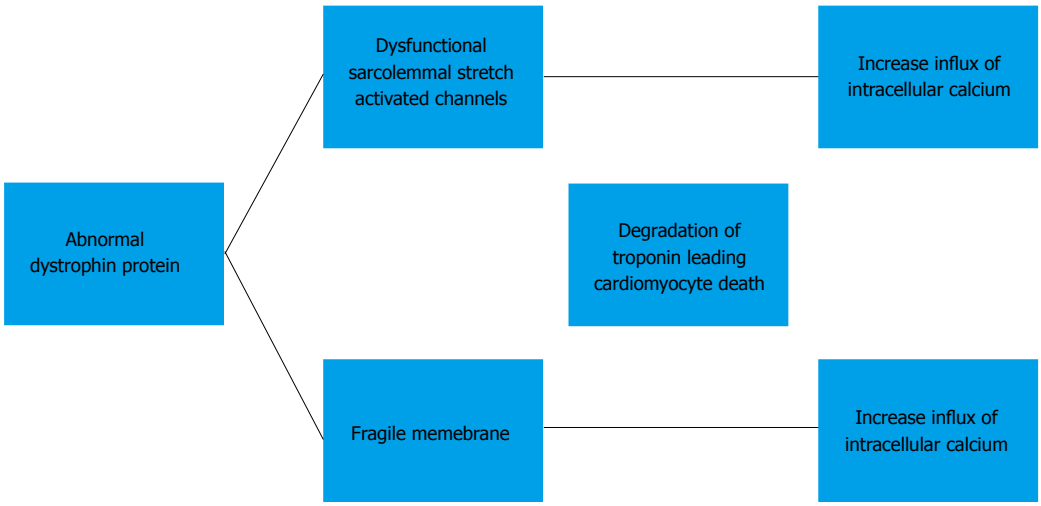

Figure 1 Proposed pathways leading to myocyte death.

cause of death in these patients[1,3].

CARDIOMYOPATHY IN BMD

The frequency of cardiac involvement in BMD is 60% to 75%[4]. The average age of onset of cardiac involvement is 28.7 ± 7.1 years[5]. Severe dilated cardiomyopathy (DCM) in patients less than 20-year-old is rare. The primary pathology of cardiomyopathy in BMD is thought to be due to diffuse degeneration and fibrosis in the ventricles especially the inferolateral region and the conduction tissue[4]. Myocardial damage preferentially in the inferolateral wall is presumed to be due to exaggerated mechanical stress and not due to limited distribution of dystrophin in this region.

There are different cardiac manifestations in BMD ranging from very subtle signs to severe cardiomyopathy requiring cardiac transplant[6]. Most of BMD patients have asymptomatic cardiac involvement. Only up to one third of patients develop DCM with symptoms of heart failure. Studies have shown that there appears to be no correlation between skeletal muscle involvement and the severity or time of onset of myocardial involvement[1,5]. The majority of BMD patients have skeletal muscle impairment before the onset of cardiac symptoms. However, there are rare cases in which cardiomyopathy may represent the initial manifestation. Ruiz-Cano *et al*[7] described a patient who was diagnosed with DCM and subsequently needed a heart transplant in less than 1 year. Eleven years after heart transplant, this patient developed lower extremities muscle weakness and was diagnosed with BMD based on muscle biopsy.

PATHOPHYSIOLOGY OF CARDIOMYOPATHY

The detailed molecular mechanism of the development of cardiomyopathy in BMD has not been well established. Currently, the mechanism is thought to be secondary to increase in intracellular calcium influx. Elevation of intracellular calcium results in mitochondrial deregulation, protease calpain-mediated necrosis and NF-κB activation. This leads to degradation of troponin I compromises the contraction of the cardiomyocyte and eventually results in cardiomyocyte death. The exact mechanism causing an increased intracellular calcium influx is subject to a debate. One proposed mechanism is that dysfunction of the sarcolemmal stretch activated channels causes an increased influx of calcium. Others believe that the absence of dystrophin causes cells to have a fragile membrane that is leaky and thus allowing intracellular calcium influx[8,9] (Figure 1).

GENOTYPE AND CARDIOMYOPATHY CORRELATION

The wide phenotypic variation in the severity of cardiomyopathy in BMD patients may be due to different mutations in the dystrophin gene. Deletions affecting the amino terminal domain or mutations resulting in disruption of spectin repeat in the rod domain of the dystrophin protein, and mutations involving exons 12 and 14 to 17 or 31 to 42 are associated with early onset of cardiomyopathy[1,10]. People with deletion mutations of exons 2 to 9 or exons 45 to 49 are at risk of developing DCM in the second and third decades of life respectively[11]. Specifically, deletion of the intron located between exon 48 and 49 is associated with cardiomyopathy. Deletion around exon 1 damages the expression and or function of dystrophin selectively in cardiac muscle. On the other hand, no cardiac abnormality is seen in patients with deletions on the 5′ side[12]. Further studies are needed to unify these findings. However, these findings suggest that BMD patients with certain mutations may have significant cardiac involvement and need more careful and regular cardiac evaluation.

Previous studies have shown that there is no correlation between the extent of cardiac and skeletal muscle disease in patients with BMD. A possible, straightforward explanation is that different genetic mutations lead to different phenotypes. However, recent findings suggest that there may be another explanation. Cardiac dystrophin may interact with proteins that are different from those of skeletal dystrophin. Johnson *et al*[13] using antibody-based immunoprecipitation, discovered that there is a different interaction between members of the dystrophin-associated protein complex (neuronal nitric oxide synthase and β2-syntrophin) with cardiac and skeletal dystrophin. Neuronal nitric oxide synthase does not interact with cardiac dystrophin while β2-syntrophin interacts with cardiac but not skeletal dystrophin. They also found that there is a unique interaction between cardiac dystrophin and Cavin-1 (polymerase I and transcript release factor), Ahnak1 (neuroblast differentiation-associated protein), Cypher (a PDZ-LIM domain Z-line protein), and CRYAB (crystalline, alpha B). The significance of these interactions remains to be determined.

CARDIOMYOPATHY IN FEMALE CARRIERS

Female carriers of dystrophin mutations may develop cardiomyopathy even without skeletal muscle disease. There are reports of electrocardiographic and echocardiographic evidence of cardiomyopathy among BMD carriers. However, the significance of cardiomyopathy in female carriers has been a source of debate, since it does not appear to affect life expectancy[14]. Hence, the benefit of routine cardiac surveillance in BMD carriers is unclear. Currently, there is no consensus on the need for regular cardiac surveillance in BMD carriers.

EKG FINDINGS

Typical EKG changes in BMD include an R:S ratio $\geqslant$ 1 in lead V1, tall R waves in the right precordial leads, deep Q waves in the inferolateral leads, short PR, and longer QTc interval. There are also conduction abnormalities including incomplete and complete right bundle branch block, incomplete and complete left bundle branch block, and infra-hisian block[1,2,12].

DEVICE THERAPY

BMD patients with cardiomyopathy can develop atrial and ventricular arrhythmias. The degree of arrhythmia is proportional to the severity of left ventricular dysfunction. The benefit of an implantable cardioverter-defibrillator (ICD) in BMD patients has not been established. Therefore, the same criteria is used for prophylactic ICD implantation in BMD patients as in other forms of nonischemic DCM[4,15]. Resynchronization therapy with biventricular pacing may also be considered to reduce heart failure symptoms[15-18].

CARDIAC TRANSPLANT

Although there were case reports dated back to the 1990s of patients with BMD who successfully underwent cardiac transplantation[19], inherited myopathies remained as a relative contraindication for heart transplant for a number of reasons. First, immunosuppression after transplant may cause progression of muscle impairment. Secondly, respiratory muscle dysfunction may make it difficult to wean off the ventilator post-operatively.

Wu *et al*[20] challenged these traditional concerns in a study comparing patients with muscular dystrophy to a matched cohort of patients with idiopathic DCM after heart transplant. The results showed that survival, rate of infection, cardiac rejection, and transplant vasculopathy post heart transplant were similar between the two groups. The limitation of this study was its small sample size and the possibility of selection bias. Nonetheless, the findings of this study suggest that BMD patients who have only mild muscular disability and no involvement of respiratory muscles may successfully undergo cardiac transplantation[7,20]. Patients with BMD may have a small additional risk of rhabdomyolysis and malignant hyperthermia reaction[21].

Cardiac rehabilitation after heart transplant in a patient with BMD has also been shown in a case report to improve cardiac function[6].

FUTURE THERAPEUTIC PERSPECTIVES

There are ongoing investigations looking at the introduction of a modified functional dystrophin gene *via* gene transfer as well as molecular correction of the mutated dystrophin gene. There are adeno-associated virus capsids that target cardiomyocytes specifically which allow gene expression in the heart even when the capsid is delivered *via* a peripheral vein. There are two types of synthetic dystrophin genes: Mini-dystrophin and micro-dystrophin. In mini-dystrophin, part of the rod domain is removed, while in micro-dystrophin, a significant portion of the rod and the C-terminal domain are removed. Mini-dystrophin transferred in a mouse model showed normalization of EKG and improved myocardial fibrosis and ejection fraction. Similarly, micro-dystrophin was able to restore normal heart rate, PR and QT interval, and cardiomyocyte integrity. The challenge of this gene therapy is the immune rejection of the viral vector or the newly expressed dystrophin protein[17].

Another gene therapy is exon skipping. In this method, antisense oligonucleotides (AONs) are used to remove mutated exons resulting in a truncated but functional protein. Applying this method in a mouse model with mutated dystrophin showed favorable echocardiographic changes[17,22-27]. Mendell *et al*[28] showed that AONs increased functional dystropin-positive fibers in an open-labeled human study. Unfor-

Table 1 Summary of current diagnostic modalities

Imaging modalities	Description
Echocardiogram	Evaluating for wall motion abnormality and cardiac function
Contrast enhanced cardiovascular magnetic resonance	Evaluating for early tissue fibrosis
Spatial mapping cardiovascular magnetic resonance	Evaluating for early tissue fibrosis

tunately, subsequent Phase Ⅲ trails failed to show clinical benefits[29]. However, Goyenvalle *et al*[25] recently showed a new class of AONs made up of tricyclo-DNA (tcDNA) might hold promise for future therapy. Using a mouse model, they showed tcDNA increases dystrophin expression in skeletal and cardiac muscles and improvement in cardio-respiratory function.

Lastly, there is sarcoplasmic reticulum calcium *ATP-ase 2a* (SERCA2a) gene therapy. The role of SERCA2a is to pump cytoplasmic calcium into the sarcoplasmic reticulum to restore calcium homeostatis and prevent cell death. Shin *et al*[26] found that increasing SERCA2a gene expression in mice using adeno-associated virus serotype-9 Lead to EKG improvement. This finding is especially encouraging because a Phase Ⅱ trail by Jessup *et al*[27] showed that SERCA2a gene therapy improved heart failure symptoms, increased functional status and improved left ventricular end-systolic and end-diastolic volume in patients with end-stage heart failure.

IMAGING FINDINGS

The echocardiogram shows a dilated left ventricle with wall motion abnormality especially in the posterior and lateral wall. There is also impaired diastolic function even in those with normal systolic function. Mitral and tricuspid regurgitation are common findings[3].

Cardiovascular magnetic resonance imaging (CMR) is beginning to be accepted as a more sensitive modality than echocardiography in providing information on ventricular size and function, and detecting regional myocardial deformation. Contrast enhanced CMR (ceCMR), using late gadolinium enhancement as an indication of myocardial damage, allows for detection of even small areas of myocardial deformation[24]. Using ceCMR, Yilmaz *et al*[1] showed that myocardial damage in BMD begins in the subepicardium of the inferolateral wall. However, Soslow *et al*[22] showed recently that spatial mapping of the longitudinal relaxation time constant (T1) CMR might be superior to ceCMR in detecting early myocardial fibrosis. As such, more research is warranted to ascertain the best modality for detecting early fibrosis in BMD.

Previously, it has been recommended that BMD patients undergo a screening ECG and echocardiogram at the time of diagnosis and every five years thereafter if the findings are normal. However, as CMR becomes widely accepted, it is recommended it be initiated at diagnosis and then at least every two years even in the case of normal findings. This rigorous screening procedure is proposed with the hope of early cardiomyopathy detection so that effective treatment can be initiated to slow the progression of cardiac dysfunction (Table 1).

OTHER ASSESSMENT METHODS

There are other methods that can either support the diagnosis or monitor left ventricular function. Chest X-ray may show cardiomegaly, pleural effusion, and pulmonary congestion. Cardiac troponin Ⅰ is a marker for myocardial damage. Brain natriuretic peptide, released following ventricular overload and increased wall stress, has been proposed as a marker for monitoring of left ventricular dysfunction[30].

PHARMACOTHERAPY

Angiotensin-converting enzyme inhibitors (ACEIs) have been shown to delay the progression of LV dysfunction, improve left ventricular function, and confer a mortality benefit. However, there is no universal guideline on the best time for the initiation of ACEI in patients with BMD. Suggestions have been made for ACEI to be given when left ventricular ejection fraction is less than 55%[31,32].

β blockers are beneficial in patients with DCM. Therefore, β blockers may have positive effects on BMD patients with cardiomyopathy. A Japanese study comparing patients with different types of muscular dystrophies on ACEI alone *vs* ACEI plus β blocker showed that the combination of ACEI and β blocker provided a significant improvement on left ventricular fractional shortening[33]. Therefore, β blockers are recommended to be used in accordance with current heart failure guidelines. Clinically, hypotension may limit the use of a β-blocker.

Corticosteroids have been shown to improve muscle strength and function. Numerous studies implicated the role of steroid in prolonging ambulation and stabilization of pulmonary function. However, corticosteroids have many adverse effects, which include Cushing's, hypertension, osteoporosis and hyperglycemia[9].

There has been no large trial examining the mortality benefit of angiotensin receptor blockers (ARBs) in BMD patients with cardiomyopathy. It is possible that ARBs are efficacious based on studies showing their benefit in other causes of heart failure. Diuretics and digoxin can be used as adjuncts for symptom reduction although no mortality benefit has been demonstrated. Aldosterone blockade can be added for patients with NYHA Class Ⅲ or Ⅳ who are already on optimal doses of an ACEI and β blocker[15]. Calcium channel blockers such as diltiazem, flunarizine, and nifedipine have not been shown to be beneficial[34].

Current data suggested that there might be a role of eplerenone in treating BMD. Raman *et al*[23] showed that eplerenone in addition to ACEIs slow down the

progression of left ventricular systolic function decline. The exact mechanism is unknown. But evidence from ceCMR suggested that it is likely secondary to eplerenone anti-inflammatory effect.

Ivabradine is a medication that selectively blocks the I(f) current in sinoatrial cells and slows heart rate. Unlike β blockers, ivabradine does not cause hypotension. Ivabradine may reverse cardiac remodeling thus providing a mortality benefit. A case report on Ivabradine in BMD cardiomyopathy has shown benefits. Randomized controlled trials are needed for further evaluation. Currently, this medication is not available in the United States[16].

CONCLUSION

There are still many unknowns regarding BMD cardiomyopathy. Imaging techniques need to be optimized further to allow for early diagnosis of CM. Different pharmacological and gene therapies currently being developed offer hope for patients with BMD cardiomyopathy.

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MINIREVIEWS

Thrombosis in ST-elevation myocardial infarction: Insights from thrombi retrieved by aspiration thrombectomy

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Abstract

In patients with ST-elevation myocardial infarction, recurrent cardiovascular events still remain the main cause of morbidity and mortality, despite significant improvements in antithrombotic therapy. We sought to review data regarding coronary thrombus analysis provided by studies using manual aspiration thrombectomy (AT), and to discuss how insights from this line of investigation could further improve management of acute coronary disease. Several studies investigated the fresh specimens retrieved by AT using techniques such as traditional morphological evaluation, optical microscopy, scanning electron microscopy, magnetic resonance imaging, and immunohistochemistry. These approaches have provided a better understanding of the composition and dynamics of the human coronary thrombosis process, as well as its relationship with some clinical outcomes. Recent data signaling to new antithrombotic therapeutic targets are still emerging.

Key words: Myocardial infarct; Aspiration; Mechanical; Thrombectomy; Thrombus; Immunohistocytochemistry

Core tip: This paper describes the importance of coronary thrombosis as a direct effector of ST-elevation acute myocardial infarction, reviewing important data provided by coronary aspiration thrombectomy regarding thrombus composition and its relationship with clinical variables. The knowledge of such data is an important basis for improving antithrombotic therapy, as it signals for potential new therapeutic targets.

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INTRODUCTION

Over the past years, improvements in antithrombotic and reperfusion therapies have been associated with

decreasing mortality in the setting of ST-elevation acute myocardial infarction (STEMI)[1]. However, coronary artery disease (CAD) remains the leading cause of death worldwide[2], so that efforts are still needed in order to better treat this condition. In most cases, STEMI is caused by the disruption of vulnerable atherosclerotic plaques associated with intense inflammatory activity of a dysfunctional endothelium. Such rupture is the trigger for platelet activation and aggregation and thrombin formation, culminating with total occlusion of the coronary artery by thrombus[3].

Because of the pivotal role of thrombus as a final effector of coronary occlusion and ischemic injury in most cases of acute coronary syndromes, many efforts have been made to improve antithrombotic therapy. For example, antithrombotic drugs like prasugrel and ticagrelor, as compared to clopidogrel, have shown to reduce ischemic events and even mortality in STEMI patients[4,5]. Recently, a large clinical trial demonstrated that double antiplatelet therapy with ASA and ticagrelor significantly reduced the risk of cardiovascular death, myocardial infarction (MI), or stroke in patients with previous MI[6].

Despite of these significant improvements in the medical treatment of patients with CAD, recurrent cardiovascular events still remain the main cause of morbidity and mortality, which justifies further studies to better understand the physiopathology of human coronary thrombosis.

ASPIRATION THROMBECTOMY

Percutaneous coronary intervention (PCI) has been shown to be the preferred method of reperfusion in patients with ST-elevation acute MI[7]. The high thrombotic burden and the subsequent compromise of coronary flow after dilatation and stent implantation in many cases stimulated the development of adjunctive devices designed to remove thrombi. The manual aspiration thrombectomy (AT) technique was the most successful of such approaches, and it has gained widespread use after the demonstration of improved angiographic results and clinical outcomes in the TAPAS trial[8]. On the other hand, enthusiasm over this technique has substantially waned after recent reports of lack of benefit in the large TASTE and TOTAL trials[9-11].

The demonstration of lack of clinical benefit of AT in these trials is not fully understood yet. One possible explanation is that manual thrombectomy was not effective enough, which is supported by a recent TOTAL substudy using optical coherence tomography[12]. In this analysis, there was no difference between the two groups of patients randomized (routine upfront manual thrombectomy *vs* PCI alone) with respect to the mean amount of thrombus, although this residual amount was relatively low on average. Another substudy, evaluating angiographic variables, found a 30% reduction in the distal embolization in favor of the thrombectomy group, being this surrogate endpoint an independent predictor of mortality[13]. Assuming that for every 10 patients who have distal embolization, maybe one or two will die related to that, we would expect a reduction of mortality in the range of 10% or 15%, a difference which no trial was powered to detect.

Regardless of the clinical appropriateness of AT in current practice, its development has made possible a new line of investigation, with the opportunity of analyzing fresh specimens of *in vivo* coronary thrombi, assessing morphology, histology, immunohistochemistry and others[14,15]. Before the availability of this procedure, studies of coronary thrombi were performed mainly by post-mortem analyzes, angioscopy or *ex-vivo* analysis[16-20]. The information derived from post-mortem studies is reliable, but it is always limited by the selection bias that occur when studying only patients who died. Angioscopy provides *in vivo* information of thrombi morphology and color, but it has been used rarely due to technical difficulties of the method. Experimental studies, like the Badimon chamber[21] and others, are limited by not evaluating the process of human coronary thrombosis *in vivo*.

On the other hand, AT is limited by the relative frequent occurrence of unsuccessful procedures, which have been reported in approximately 25% of the patients[8]. Potential causes for failing to retrieve thrombotic material are partial lyses of thrombi by pharmacological therapy administered before arrival in the catheterization laboratory, non-thrombotic lesions, distal embolization before aspiration and limitations of the current aspiration devices. Challenging anatomies for performing AT include tortuous and/or calcified vessels, bifurcations, very distal lesions and small vessels[22].

Morphology of coronary thrombi

Thrombus varies widely in shape and size. Arterial thrombi usually are about one centimeter long, arising at the site of an endothelial injury (for example, an atherosclerotic ruptured plaque) in the retrograde direction from the point of anchorage. It generally consists of a tangled network of variable amounts of platelets, fibrin, erythrocytes and degenerate leukocytes[23].

In patients with acute coronary syndromes, there are several factors associated with thrombus size, such as the intensity of anticoagulant and antithrombotic therapy[24,25], the age of the thrombus[14,26], and the presence of flow in the infarct-related artery before primary PCI[18]. Thrombus burden is an established predictor of complications during PCI with or without stents[27,28].

Another condition that may influence the characteristics of coronary thrombi is the presence of diabetes mellitus (DM). In this setting, thrombus area seems to be greater[21] and coronary plaques present greater total and distal plaque load than in those subjects without DM[16]. Moreno *et al*[29], evaluating coronary tissue retrieved by atherectomy, found a large content of lipid-rich atheroma, macrophage infiltration and subsequent

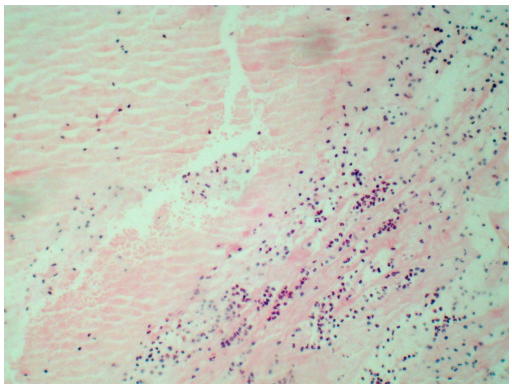

Figure 1 Recent coronary thrombus composed of fibrin, white blood cells and red blood cells, hematoxylin-eosin, 200 ×.

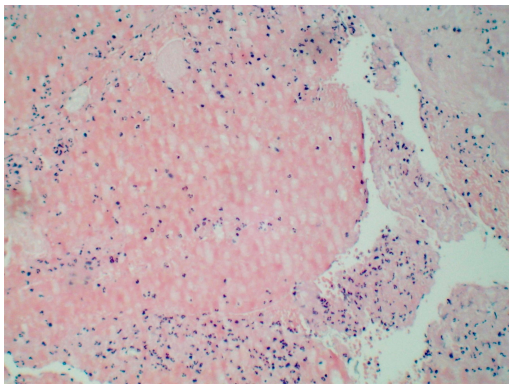

Figure 2 Coronary thrombus with lysis focuses in few neutrophils, hematoxylin-eosin, 200 ×.

thrombosis in patients with DM.

According to the macroscopic appearance, thrombi can be classified as white, red or mixed. White thrombi are mainly composed of platelets and fibrin[30]. Mizuno and cols showed that white thrombi occur when blood flow was not completely interrupted in the vessel[18]. In patients with STEMI, we have previously demonstrated that white thrombus has a smaller size when compared to red thrombus, and is associated with high fibrin infiltration, shorter ischemic times and lower mortality[31]. Red thrombi are wet, gelatinous and resemble a blood clot being formed by fibrin, erythrocytes and platelets[30], causing complete occlusion of the vessel[18].

Thrombi can also be classified according to its age: (1) recent (newly formed), composed primarily of fibrin, white blood cells and red blood cells (Figure 1); (2) lytic (intermediate), characterized by the presence of apoptosis of leukocytes (Figure 2); and (3) organized thrombi, classified mainly by presenting collagen and connective soft tissue[14,17].

Rittersma *et al*[14] assessed coronary thrombi age in 199 STEMI patients submitted to AT within 6 h after onset of chest pain. The authors found that in at least 50% of patients, coronary thrombi were days or weeks old, indicating a variable period of plaque instability and thrombus formation initiated before onset of symptoms. These findings were later confirmed by another report by Kramer *et al*[26]. In an important study with more than 1300 STEMI patients, fresh thrombus was identified in approximately 30% of the patients. The mortality rates at the 4-year follow-up were significantly higher in patients with older thrombi (16%) when compared to those with fresh thrombus (7%)[32].

Silvain *et al*[15] used magnetic resonance imaging to evaluate the composition of coronary thrombus and its association with ischemic time. It was found that fibrin content increased with ischemic time, ranging from 48% (< 3 h) up to 67% (> 6 h), whereas platelet content decreased from 21% (< 3 h) to 9% (> 6 h). Multivariate analysis indicated that ischemic time was the only predictor of thrombus composition, with a 2-fold increase of fibrin content per ischemic hour[15].

Immunohistochemical analysis

Immunohistochemistry detects surface proteins in the cells of tissues using the principle of antibodies binding specifically to antigens. It is used in specimens removed surgically or in autopsies. In the assessment of thrombi retrieved by AT, this can also be an additional tool to histopathology, in order to increase the sensitivity for recognition of thrombus components[33,34].

Ikuta *et al*[35] compared thrombotic material from individuals with stable or unstable angina with immunohistochemistry analysis. The patients with unstable coronary syndromes presented higher platelet aggregation and activation, and also increased immunoreactivity of GP Ⅱb/Ⅲa and P-selectin[35].

Iwata *et al*[36] analysed the cellular constituents of 108 thrombi aspirated from coronary lesions in 62 patients who underwent emergent intervention for the treatment of acute (< 24 h) or recent (24-72 h) STEMIs. The content of platelets, as determined by immunostaining for CD42a, presented a negative correlation with the time since the onset of chest pain. The ratio of CD34-positive cells in intracoronary thrombi had a significant positive correlation with restenosis at follow-up coronary angiography. This finding indicates that the early accumulation of primitive cells in platelet aggregates may play a role in neointimal growth after successful coronary intervention in patients with acute coronary syndromes.

Sambola *et al*[37] compared the content of thrombotic and fibrinolytic factors in thrombi of patients submitted to rescue PCI to those with successful thrombolysis. Thrombi resistant to lysis showed higher content of platelets, fibrin, P-selectin and Von Willebrand Factor, demonstrating a disturbance in thrombus structure of these patients.

Yamashita *et al*[38] examined thrombi removed within 24 h of acute MI with immunohistochemistry techniques, focusing on possible mechanisms of thrombosis in patients with DM. There was a paucity of CD34-positive cells in the specimens analyzed, suggesting that the ability of these cells to down-regulate thrombus formation and facilitate thrombus organization was

Table 1 Studies evaluating aspirated thrombus characteristics of ST-elevation acute myocardial infarction patients

Ref.	Main comparison/subject	*n*	Results
Quadros *et al*[31]	White *vs* red thrombus	113	Mortality (0% *vs* 10.1%; $P = 0.05$), size (0.4 ± 0.2 *vs* 0.6 ± 0.4 mm, $P < 0.001$), fibrin (68% ± 19% *vs* 44% ± 18%, $P < 0.001$), ischemic time (4.5 ± 2.3 h *vs* 6.1 ± 3.1 h, $P = 0.01$)
Rittersma *et al*[14]	Age of intracoronary thrombi	199	Organized: 9%, lytic changes: 35%, fresh: 49%, both fresh and organized: 7%
Kramer *et al*[26]	Older *vs* fresh thrombus	1315	All-cause mortality at 4 yr (16.2% *vs* 7.4%, hazard ratio: 1.82, 95%CI: 1.17-2.85, $P = 0.008$)
Silvain *et al*[15]	Composition of coronary thrombus and its association with ischemic time	45	Fibrin content: 48.4% ± 21% (< 3 h) up to 66.9% ± 9% (> 6 h) ($P = 0.02$)
Iwata *et al*[36]	Restenosis *vs* without Restenosis	108	CD34-positive primitive cells (5.10% ± 0.66% *vs* 1.88% ± 0.24%, $P < 0.01$)
Sambola *et al*[37]	Thrombus resistant to fibrinolysis *vs* sensible to lysis	20	Rescue PCI: Significantly higher levels of fibrin ($P = 0.016$), P-selectin ($P = 0.03$) and VWF ($P = 0.03$) than patients who were underwent to primary PCI
Yamashita *et al*[38]	Thrombosis in diabetics *vs* non diabetics	50	Paucity of CD34-positive cells and higher expression of HMGB-1 in diabetics

PCI: Percutaneous coronary intervention; VWF: Von willebrand factor; HMGB-1: High-mobility group box-1.

compromised in diabetic patients. On the other hand, the higher expression of HMGB-1 found in those with DM, in association with the thrombin-induced microvascular thrombosis accelerated by HMGB-1, may contribute to the adverse events frequently seen in these patients[38].

FUTURE PERSPECTIVES

In the previous sections of this paper, we have described several studies that aimed to investigate the physiopathology of human coronary thrombosis by studying specimens of thrombi retrieved by AT (Table 1). The majority of those studies used techniques such as traditional morphological evaluation, optical microscopy, scanning electron microscopy, magnetic resonance imaging, and immunohistochemistry. More recently, novel approaches have been described.

Ramaiola *et al*[39] applied principles of proteomics and advanced cellular microscopy to evaluate retrieved coronary thrombi. The authors showed that profilin-1 (Pfn-1) levels in the systemic circulation are directly correlated to the duration of coronary artery thrombotic occlusion. Thrombus age is an independent predictor of long-term mortality[32], and these results may suggest that measuring Pfn-1 levels could be used to assess ongoing thrombosis and occlusion time in clinical practice[39].

The immune response mediated by lymphocytes is involved in the pathogenesis of the acute coronary syndromes[3], but there is few evidence of the role of T cells in thrombus composition. Regulatory T cells (Treg) are an inherent anti-inflammatory component of adaptive immunity which exerts atheroprotective effects[40-44]. Treg were frequently identified among T cell subsets present in coronary thrombi of patients presenting with ACS[45], which raises the hypothesis of a local compensatory mechanism to attenuate inflammation[46]. The concept of expanding antigen-specific Treg to diminish vascular inflammation and atherothrombosis by immunotherapy is appealing and may represent a new line of investigation[45].

CONCLUSION

Thrombosis plays a central role in acute coronary syndromes. A better understanding of the human coronary thrombosis process *in vivo* and its relationship with clinical outcomes could be obtained by analyzes of specimens obtained by AT. Recent data signaling to new therapeutic targets has been recently provided, and insights from this line of investigation will help to further improve management of acute coronary disease.

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ORIGINAL ARTICLE

Retrospective Study

Incidence and trends of cardiovascular mortality after common cancers in young adults: Analysis of surveillance, epidemiology and end-results program

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Author contributions: Al-Kindi SG conceived the study, obtained the data, performed the statistical analysis, and drafted the manuscript; Oliveira GH conceived the study and revised the manuscript.

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Data sharing statement: Data used for this analysis are available from SEER program (seer.cancer.gov).

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Abstract

AIM: To describe the incidence of cardiovascular mortality (CVM) in survivors of major cancers and identify its trends over the past two decades.

METHODS: We used the surveillance, epidemiology and end-results 19 registry to identify young adults (20-49 years), diagnosed with the following major primary cancers: Lung, breast, liver/intrahepatic bile duct, pancreas, prostate, colorectal, and ovarian from 1990 through 2012 and identified the cumulative incidence of CVM after adjusting for confounding factors.

RESULTS: We identified a total of 301923 cancers (breast 173748, lung 38938, colorectal 31722, prostate 22848, ovary 16065, liver 9444, pancreas 9158). A total of 2297 (0.8%) of patients had incident CVM. Lung (10-year cumulative CVM 2.4%) and liver (1.73%) cancers had the highest incidence of CVM, while breast (0.6%) and prostate (1.2%) had the lowest CVM mortality, even after multiple adjustments (P < 0.001). Overall, there was a significant improvement in CVM since 1990 [2005-2012 *vs* 1990-1994, adjusted HR 0.63 (0.54-0.72), P < 0.001]. This was driven by improvements in CVM in lung cancers (P = 0.02), breast (P < 0.001), and a trend in ovarian cancer (P = 0.097).

There was no statistically significant improvement in CVM among survivors of colorectal, pancreatic, liver, or prostate cancers.

CONCLUSION: The risk of CVM differs among different cancers, and is highest among survivors of lung and liver cancers. The incidence of CVM has decreased over the past 2 decades mainly among survivors of lung and breast cancers.

Key words: Cardiovascular disease; Cancer; Trends; Cardiovascular mortality; Type of cancer

Core tip: Cancers and cardiovascular diseases share many risk factors. Premature cardiovascular mortality (CVM) has been described in cancer survivors. However, the trends of CVM in cancer survivors are largely unknown. Using a large national cancer registry in the United States, we show that CVM has decreased in survivors of breast and lung cancers, but not other cancers. Surprisingly, more than half of all cardiovascular deaths occur before age of 50 years. It is likely that interventions targeted at decreasing CVM in cancer survivors will decrease the overall mortality in those patients.

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INTRODUCTION

Cardiovascular diseases and cancers are the leading causes of death in the United States[1]. They often coexist due to similar risk factors (*e.g.*, smoking, advanced age, chronic inflammation). We have previously shown that preexisting cardiovascular diseases are prevalent in patients with cancers and may be undertreated[2].

Patients with cancer may have subclinical cardiac disease even prior to cardiotoxic therapy[3]. In addition, many of cancer therapies (including chemotherapy, radiation therapy, and surgery) can directly or indirectly impact cardiovascular health[4-8]. As a result, patients with different cancers have been shown to have increased cardiovascular morbidity and mortality compared with the general population[6,9-11].

There is wide variability in cardiovascular risk between different cancer populations[2]. Recent advances in cancer and cardiovascular therapies have resulted in overall improved population survival[12,13], however, it is unclear if these advances translate into decreased CVM among cancer survivors. The current study was done to analyze the incidence of CVM after major cancers and report the changes over the past 2 decades in the United States.

MATERIALS AND METHODS

Data source

We used the surveillance, epidemiology and end-results (SEER) 19 database for this study. SEER 19 research data is a program of the national cancer institute and includes incidence and individual-level data collected from 19 cancer registries on patient demographics, histopathology, staging, geographic areas, treatments, follow-up and causes of death on all cancers diagnosed 1973-2012. Data are de-identified and are accessible through an online software (SEER*Stat). Based on November 2014 submission, SEER includes 8689771 cases. Causes of death are reported in broad categories that are coded from a list of International Classification of Diseases (ICDs). SEER data includes public-access deidentified data only, and thus institutional review board approval was not required.

Cohort selection

For this study, we identified young adults (20-49 years at diagnosis), diagnosed with the following major primary cancers using the 3rd edition of the ICDs for Oncology site codes: Lung (C34.0 to C34.9), breast (C50.0 to C50.9), liver/intrahepatic bile duct (C22.0 to C22.1), pancreas (C25.0 to C25.9), prostate (C61.9), colorectal (C18.0 to C18.9; C19.9 to C20.9) and ovarian (C56.9) diagnosed from 1990 through 2012.

Outcomes

Outcomes include cardiovascular mortality (CVM) stratified by type of cancer and by era of diagnosis. We defined CVM to include the following ICD codes: ICD 9 (1979 to 1998): 390 to 398, 402, 404, 410 to 429; and ICD 10 (1999þ): I00 to I09, I11, I13, I20 to I513.

Statistical analysis

Continuous variables are presented as mean ± SD and compared using *t*-test. Categorical variables are presented as numbers and percentages and compared using χ^2 test. Cox-proportional hazard models were used for survival adjusting for age, gender, race, year of diagnosis, surgery, radiation, SEER stage, and cancer site; censoring for loss to follow-up or death from other causes. All test were two sided and $P < 0.05$ was considered significant.

RESULTS

We identified a total of 301923 cancers (breast 173748, lung 38938, colorectal 31722, prostate 22848, ovary 16065, liver 9444, pancreas 9158). Mean age at cancer diagnosis for the entire cohort was 43 ± 5.6 years, 24.4% were male, and 74.3% were white; 45.3% had local disease, 78.8% had surgery, and 35.4% had beam

Table 1 Characteristics of patients by cancer type

	Breast	Colorectal	Liver	Lung	Ovary	Pancreas	Prostate	All
Age (yr)	42.6 ± 5.3	42.2 ± 6.2	43.4 ± 6.1	44.0 ± 5.1	40.5 ± 7.5	43.5 ± 5.4	46.4 ± 2.8	43.0 ± 5.6
Sex								
Female	99.6%	48.3%	22.2%	46.0%	100.0%	42.3%	0.0%	75.6%
Male	0.4%	51.7%	77.8%	54.0%	0.0%	57.7%	100.0%	24.4%
Race								
White	75.8%	72.7%	61.0%	73.8%	77.9%	74.5%	68.4%	74.3%
Black	12.9%	16.3%	14.9%	18.4%	9.4%	16.6%	25.9%	15.0%
Other	10.5%	10.0%	23.6%	7.5%	12.0%	8.5%	2.9%	9.9%
Unknown	0.8%	0.9%	0.5%	0.3%	0.7%	0.4%	2.8%	0.9%
Year of diagnosis								
1990-1994	9.8%	8.9%	7.9%	13.1%	12.1%	9.1%	3.6%	9.7%
1995-1999	12.7%	11.4%	13.5%	13.9%	13.6%	12.4%	9.2%	12.5%
2000-2004	28.8%	28.8%	31.4%	31.4%	29.0%	28.7%	29.6%	29.3%
2005-2012	48.8%	50.8%	47.3%	41.6%	45.4%	49.7%	57.6%	48.5%
Surgery								
No	3.8%	7.8%	63.5%	63.1%	5.4%	61.8%	23.4%	17.0%
Yes	94.2%	89.7%	23.5%	26.9%	92.1%	28.2%	68.2%	78.8%
Unknown	2.1%	2.4%	13.0%	10.0%	2.5%	9.9%	8.4%	4.2%
Stage								
Local	53.3%	29.2%	33.9%	11.6%	35.6%	8.8%	90.7%	45.3%
Regional	38.7%	37.2%	27.2%	22.8%	8.5%	26.3%	0.0%	31.2%
Distant	6.1%	29.1%	21.5%	58.7%	50.6%	57.3%	3.4%	19.5%
Unstaged	2.0%	4.5%	17.3%	6.9%	5.3%	7.7%	5.9%	4.0%
Radiation								
None	47.8%	94.0%	91.0%	46.7%	97.1%	76.1%	79.3%	59.7%
Beam	47.0%	4.1%	4.6%	48.9%	1.6%	20.3%	10.5%	35.4%
Other	0.7%	0.1%	1.0%	0.4%	0.2%	0.2%	8.0%	1.1%
Unknown	4.4%	1.9%	3.4%	4.0%	1.1%	3.4%	2.3%	3.7%

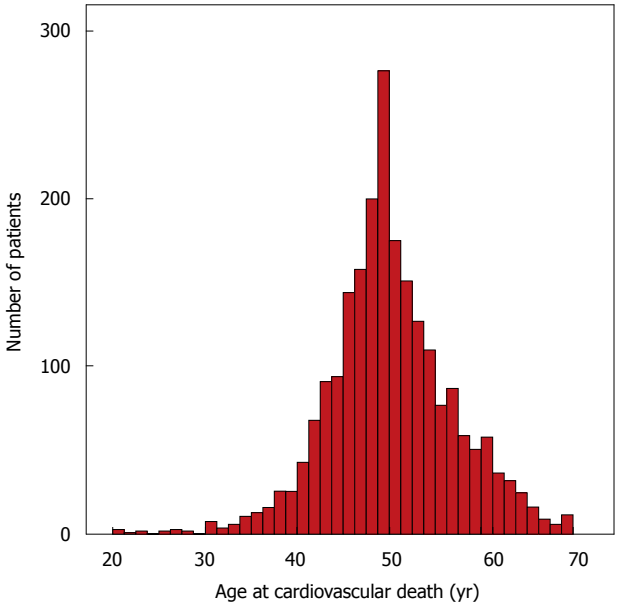


Figure 1 Age at cardiovascular death for all patients (*n* = 2297).

radiation. Table 1 shows the characteristics of study population by cancer type.

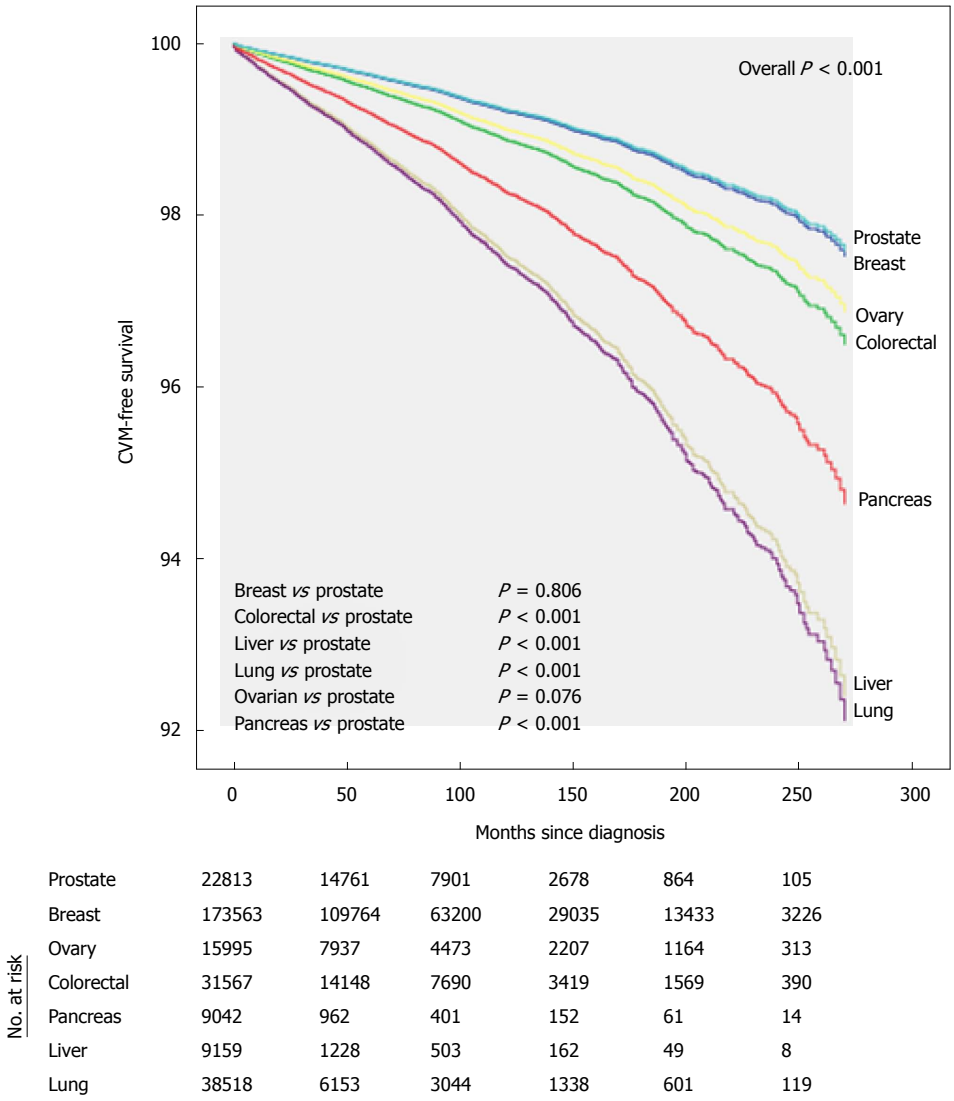
A total of 2297 (0.8%) of patients had incident CVM. Majority were females (60.4%), white (64.7%), with mean age at cancer diagnosis of 44.7 ± 4.6 years. Majority were survivors of breast cancer (40%), followed by lung (25%), colorectal (11.8%), prostate (11.4%), liver and ovary (4.3% each), and pancreas (3.2%). CVM occurred at a mean 5.3 ± 5.2 years after diagnosis of cancer. Mean age at cardiovascular death was 50.1 ± 6.8 years (range 20-70 years). The distribution of age at death is shown in Figure 1.

Cumulative CVM varied by cancer type: Lung (10 year cumulative CVM 2.4%) and liver (1.73%) cancers had the highest incidence of CVM, while breast (0.6%) and prostate (1.2%) had the lowest CVM mortality, even after multiple adjustments ($P < 0.001$, Figure 2).

Overall, there was a significant improvement in CVM between era 4 and era 1 [2005-2012 *vs* 1990-1994, adjusted HR 0.63 (0.54-0.72), $P < 0.001$], era 4 *vs* era 2 [2005-2012 *vs* 1995-1999, adjusted HR 0.67 (0.58-0.79), $P < 0.001$] and era 4 *vs* era 3 [2005-2012 *vs* 2000-2004, adjusted HR 0.79 (0.70-0.90), $P < 0.001$] (Table 2 and Figure 3). When taken as a continuous variable, there was an average decrease in CVM of 3% per year [adjusted HR 0.97 (0.96-0.98) per year, $P < 0.001$]. This was driven by improvements in CVM in lung cancers (2005-2012 *vs* 1990-1994, adjusted HR 0.69, $P = 0.02$), breast (2005-2012 *vs* 1990-1994, adjusted HR 0.58, $P < 0.001$), and a trend in ovarian cancer (2005-2012 *vs* 1990-1994, adjusted HR 0.46, $P = 0.097$). There was no statistically significant improvement in CVM among survivors of colorectal ($P = 0.331$), pancreatic ($P = 0.119$), liver ($P = 0.696$), or prostate cancers ($P = 0.148$), Figure 4.

DISCUSSION

Our findings suggest that young adults remain at high



No. at risk

Prostate	22813	14761	7901	2678	864	105
Breast	173563	109764	63200	29035	13433	3226
Ovary	15995	7937	4473	2207	1164	313
Colorectal	31567	14148	7690	3419	1569	390
Pancreas	9042	962	401	152	61	14
Liver	9159	1228	503	162	49	8
Lung	38518	6153	3044	1338	601	119

Figure 2 Adjusted cumulative cardiovascular mortality by cancer site.

risk for CVM following cancer diagnosis and this risk varies by type of cancer. Half of all cardiovascular deaths occur before age of 50; however, the incidence of CVM has decreased over the last 2 decades, mainly among survivors of lung and breast cancers.

We provide the first evidence that CVM has been decreasing over the past decades in lung and breast cancers, but not others. We have previously shown that these trends were also seen among young adults with early stage Hodgkin lymphoma[14], and were also recently reported in survivors of childhood cancers[15]. This is likely due to recognition of cardiovascular disease in cancer survivors, improvements in cardiovascular screening and treatment options, in addition to better, less cardiotoxic cancer treatment. Oncocardiology, a field of cardiovascular disease management and assessment in cancer patients, has played a role in comprehensive assessment and follow-up in patients with cancer[1,4,16]. The availability of newer imaging techniques in detecting subclinical myocardial dysfunction (*e.g.*, strain imaging, cardiac magnetic resonance imaging), helped identify patients earlier, and thus provide opportunities for treatment or prevention, especially in patients receiving anthracyclines and HER2 antagonists[17,18].

It is important to note, however, that there has been no significant reduction in CVM among patients with prostate, liver, colorectal, and pancreas. It is likely that this is due to high utilization of non-anthracycline chemotherapy, whose cardiotoxic effects have not been well studied. It is also possible that these patients have higher prevalence of comorbidities not accounted for in this analysis. These findings are hypothesis generating and require further investigation.

Our multivariable model suggests that patients with advanced cancers (regional or metastatic) have and those inoperable cancers have higher rates of CVM. The reasons for this finding remain speculative, but it is possible that patients with advanced diseases may receive more cardiotoxic chemotherapy and/or radiation, which have been shown to impact long-term survival. These findings were also observed in young adults with Hodgkin lymphoma[14].

Table 2 Multivariable model for cardiovascular mortality

	HR	2.5th-ile	97.5th-ile	*P*-value
Cancer type				
Breast *vs* prostate	1.026	0.837	1.258	0.806
Colorectal *vs* prostate	1.456	1.196	1.773	< 0.001
Liver *vs* prostate	3.221	2.495	4.158	< 0.001
Lung *vs* prostate	3.348	2.797	4.007	< 0.001
Ovarian *vs* prostate	1.298	0.973	1.731	0.076
Pancreas *vs* prostate	2.248	1.675	3.016	< 0.001
Demographics				
Age at diagnosis (per year)	1.078	1.068	1.089	< 0.001
Black *vs* white	2.397	2.18	2.635	< 0.001
Other *vs* white	0.79	0.662	0.942	0.009
Unknown *vs* white	0.428	0.203	0.903	0.026
Female *vs* male	0.678	0.595	0.773	< 0.001
Year of diagnosis (per year)	0.97	0.962	0.978	< 0.001
Radiation				
Beam radiation *vs* no radiation	0.814	0.737	0.9	< 0.001
Other radiation *vs* no radiation	0.463	0.304	0.703	< 0.001
Unknown *vs* no radiation	0.867	0.673	1.119	0.273
Surgery				
Surgery *vs* no surgery	0.424	0.368	0.489	< 0.001
Unknown *vs* no surgery	0.937	0.78	1.127	0.491
Stage				
Regional *vs* local	1.394	1.254	1.548	< 0.001
Distant *vs* local	1.705	1.472	1.976	< 0.001
Unstaged *vs* local	1.304	1.093	1.555	0.003

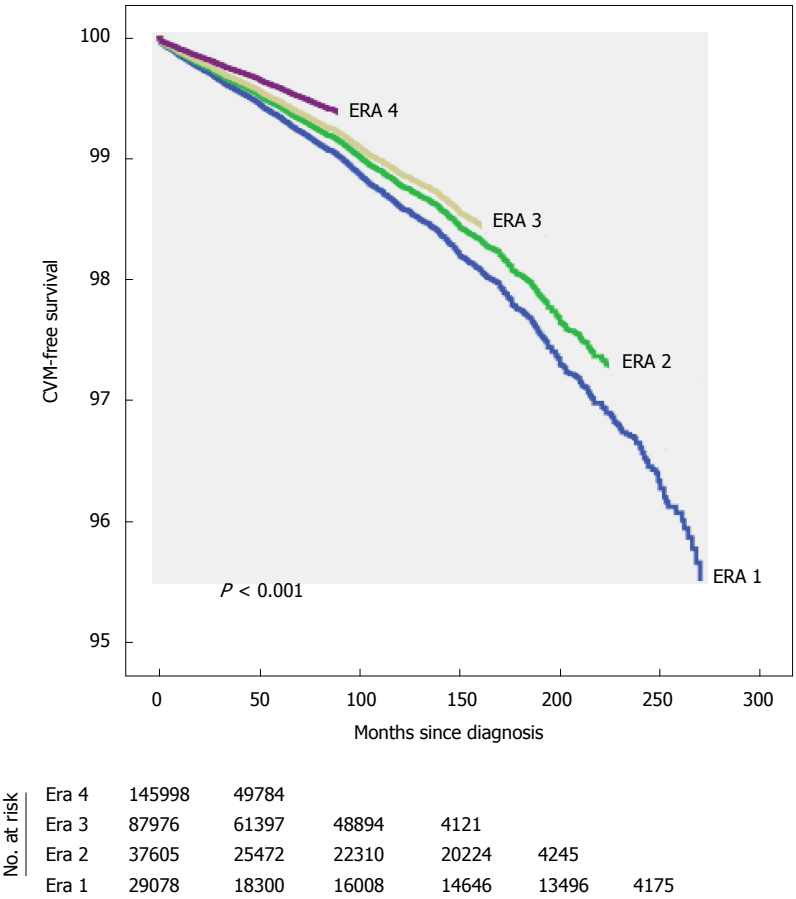


Figure 3 Adjusted overall cardiovascular mortality-free survival across eras.

It is surprising that half of all cardiovascular deaths occurred before age of 50 years, suggesting premature cardiac death. The implication of this finding is that improving cardiovascular health with early monitoring

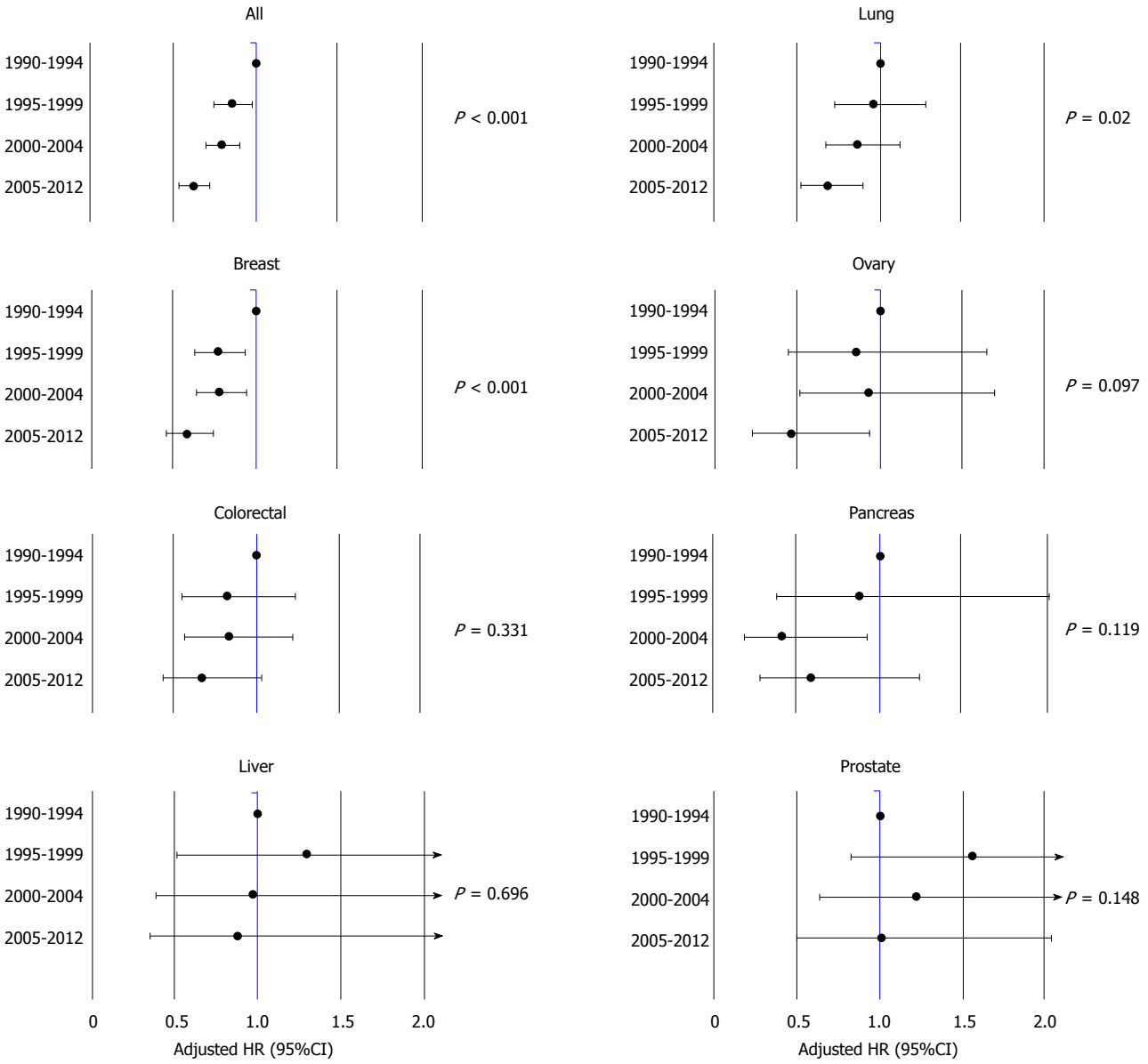


Figure 4 Adjusted HR of cardiovascular mortality by year of cancer diagnosis.

and prevention strategies may significantly decrease the overall mortality in patients with cancer. This can be accomplished through development of non-cardiotoxic targeted therapies, reduced heart radiation-dose, and modulation of cardiovascular risk factors before, during and after treatment.

This report highlights the need for intensive management of cardiovascular risk factors and cardiovascular disease in patients with cancer diagnosis, particularly lung and liver. Early involvement of cardiologists, through oncocardiology practices, may prove helpful in patients at high risk, especially those with preexisting heart disease or those undergoing cardiotoxic therapies. Future studies should focus on the impact of cardiovascular disease management on long-term outcomes in these cancers.

While this is a very large cohort of patients, this study has limitations that need to be acknowledged. First, we do not have data on cardiovascular risk factors in patients (such as smoking, diabetes, hypertension) and cardiovascular medications. Second, we don't have data on cardiotoxic chemotherapy, and radiation doses which may impact the development of cardiovascular disease. Hence, we were unable to ascertain the etiology of CVM. Also, we did not have granular data on the exact causes of death. Therefore, it is imperative to study these factors in a prospective fashion.

CVM is highest among survivors of lung and liver cancers and lowest among prostate and breast cancer survivors. The incidence of CVM has significantly decreased over the past 2 decades mainly among survivors of lung and breast cancers.

COMMENTS

Background

Cancers and cardiovascular diseases share many risk factors. Premature cardiovascular mortality (CVM) has been described in cancer survivors.

However, the applicability of improved CVM in the general population to cancer survivors is largely unknown.

Research frontiers

The impact of preexisting cardiovascular disease on overall survival in cancer survivors need to be investigated. In addition, the role of primary and secondary prevention for cardiovascular disease in this cohort needs to be studied.

Innovations and breakthroughs

The authors show, for the first time, that survivors of cancers of breast and lung, but not others, have a decreasing risk of CVM over the past 2 decades.

Applications

The implications of the current study help raise awareness about the cardiovascular disease in cancer survivors. Efforts should be focused on decreasing cardiovascular disease in patients with cancers of liver, pancreas, colorectal, and ovarian cancers.

Terminology

CVM is death due to any cardiovascular disease which include but not limited to: Ischemic heart disease, heart failure, stroke, thrombosis. Cardiotoxic chemotherapy is any chemotherapy (mainly anthracyclines and HER2 antagonists) that has a negative direct or indirect effect on the myocardium.

Peer-review

The authors present here a nice paper on CVM and cancer. The manuscript is well written and pretty interesting, even with its (recognized) inherent limitations.

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CASE REPORT

Asymptomatic post-rheumatic giant left atrium

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Abstract

A 78-year-old asymptomatic woman was referred to our clinic for a second opinion regarding indication for mitral valve surgery. An echocardiogram showed a moderate mitral stenosis with a concomitant severe regurgitation. The most striking feature, however, was a giant left atrium with a parasternal anteroposterior diameter of 79 mm and a left atrial volume index of 364 mL/m². There are various echocardiographic definitions of a giant left atrium, which are mainly based on measurements of the anteroposterior diameter of the left atrium using M-mode in the parasternal long axis view. Since the commonly accepted method for echocardiographic evaluation of left atrial size is left atrial volume index, we propose a cut-off value of 140 mL/m^2 for the definition of a "giant left atrium".

Key words: Giant; Left; Atrium; Postrheumatic; Mitral; Valve; Stenosis; Regurgitation

Core tip: There are various echocardiographic definitions of a giant left atrium, which are mainly based on measurements of the anteroposterior diameter of the left atrium using M-mode in the parasternal long axis view. Since the commonly accepted method for echocardiographic evaluation of left atrial size is left atrial volume index, we propose a cut-off value of 140 mL/m^2 for the definition of a "giant left atrium".

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INTRODUCTION

Early in the 20th century Owen and Fenton[1] presented "A

case of extreme dilatation of the left auricle of the heart". The patient initially presented because of dyspnea, which after clinical examination was thought to be due to a right sided pleural effusion. However, paracentesis produced pure blood. Postmortem examination showed a severely enlarged left atrium occupying the entire thoracic cavity that was accidentally punctured during paracentesis. To our knowledge, this is the first published case of a so called "giant left atrium", a term that was introduced by Fisher *et al*[2] in 1956.

It is well known that various cardiac conditions such as valvular heart disease, systolic or diastolic dysfunction of the left ventricle, atrial fibrillation and others can cause an enlargement of the left atrium. However, an enlargement fulfilling the criteria for "giant left atrium" is most commonly due to mitral valve pathology, in particular mitral valve stenosis[3].

CASE REPORT

A 78-year-old woman with known atrial fibrillation and arterial hypertension was referred to our clinic for a second opinion regarding indication for mitral valve surgery. As a child she had suffered from rheumatic fever and subsequently developed mitral valve dysfunction. However, having been asymptomatic ever since, she refused surgery in the past - even when an endocarditis of the mitral valve with enterococcus coli in 2013 was detected. The endocarditis was treated conservatively at that time.

At presentation the patient denied any cardiac symptoms such as dyspnea, nocturia, chest pain or palpitations. She was able to walk two floors without a break and was perfectly capable of mastering her daily life.

Physical examination showed an alert and oriented patient. The pulse was irregular with 53 beats per minute, respiration rate was normal and systolic blood pressure was elevated with 167/83 mmHg. A 2/6 holosystolic heart murmur was present at the left sternal border and at the apex with radiation to the left axilla. The lungs were clear to auscultation with no crackles or wheezes. No signs of volume retention such as distension of the jugular veins, peripheral edema or positive hepatojugular reflux were present.

The electrocardiogram showed atrial fibrillation with a heart rate of 56 beats per minute and a left anterior fascicular block. Apart from a slightly reduced kidney function with an estimated glomerular filtration rate of 61 mL/min (CKD-EPI 2009) and an elevated proBNP of 1345 ng/L (normal < 738 ng/L) there were no pathologic findings.

On the treadmill exercise test the patient reached 5.2 metabolic equivalent of task without cardiac symptoms or significant ECG changes. The test had to be abandoned due to joint pain in the knees.

An echocardiogram showed a moderately dilated left ventricle (end-diastolic volume index: 88 mL/m^2) with a moderately reduced ejection fraction of 38% due to global hypokinesis. The mitral annulus was calcified. In a pattern consistent with post-rheumatic changes the mitral valve leaflets were thickened and partially calcified. Moderate mitral stenosis with a mean diastolic pressure of 7 mmHg and a concomitant severe regurgitation was present. The estimated pulmonary pressure was slightly elevated (41 mmHg), the dimension and function of the right ventricle normal. The most striking feature, however, was a giant left atrium with an anteroposterior diameter of 79 mm (Figure 1), a left atrial circumference of 88 cm^2, a total volume of 525 mL and a left atrial volume index (LAVI) of 364 mL/m² (see audio core tip).

DISCUSSION

Left atrial size is influenced by increased left atrial pressure and its duration. Hence, left atrial dilatation occurs under various cardiac conditions such as mitral valve disease, left ventricular systolic as well as diastolic dysfunction and others. In general it can be assumed that the more severe and chronic the cardiac condition, the larger the left atrium. The chronicity might be a key factor why the patient presented such a dilated atrium, having suffered from rheumatic fever as a child and subsequently developed mitral stenosis (and regurgitation). The persistent atrial fibrillation as well as arterial hypertension certainly contributed to the severity of left atrial enlargement.

There are several empirical definitions of giant left atrium, but no established diagnostic criteria[4] so far. Piccoli *et al*[5] published a paper in 1984 using a cardiothoracic ratio > 0.7 on chest X-ray in combination with an echocardiographic and angiographic evidence of aneurysmal dilatation of the left atrium to define giant left atrium. The measured atrial anteroposterior diameters ranged from 7 to 12 cm. Isomura *et al*[6] defined a left atrium as giant, if the echocardiographic diameter exceeded 6.0 cm. In 1991 Minagoe *et al*[7] used another arbitrary anteroposterior diameter of 65 mm in the parasternal long axis view using M-mode echocardiography as a cut-off value (Figure 1). To our knowledge this is the generally used echocardiographic criteria for a giant left atrium. All echocardiographic cut-off values have in common that they are based on a single, monoplane, linear measurement.

In clinical practice, however, we occasionally are confronted with severely enlarged and anatomically distorted left atria, making it difficult to find a correct angle for an adequate measurement of the anteroposterior diameter in M-mode. This can even lead to different values between measurements in M- and B-mode (Figures 1 and 2). Moreover, since the left atrium is a three dimensional structure, we think that the LAVI is a more suitable method for evaluating its size.

Interestingly, no definition of a giant left atrium based on indexed left atrial volume is available. An anteroposterior atrial diameter below 40 mm is regarded normal, a value above 65 mm "giant", corresponding

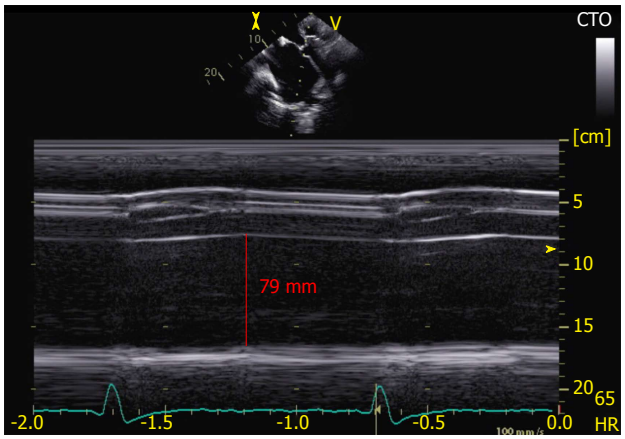

Figure 1 Parasternal long axis view in M-mode at the level of the aortic valve and left atrium. The dilated diameter of the left atrium (79 mm) is shown.

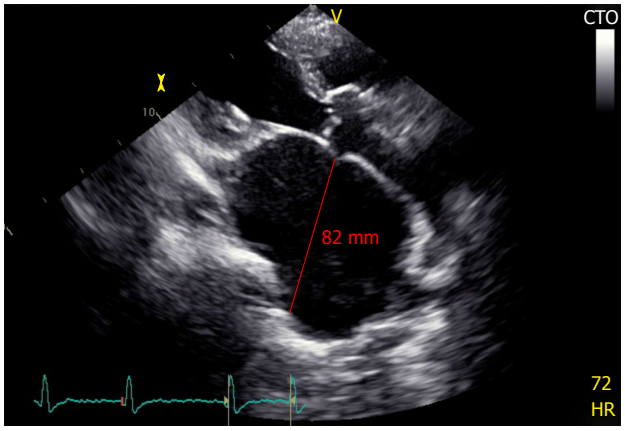

Figure 2 Modified parasternal long axis view in B-mode showing the dimension of the giant left atrium (82 mm).

to 1.6 times the normal value. A LAVI below 34 mL/m^2 is regarded as normal[8]. Thus, LAVI being a three dimensional measurement, one might extrapolate a LAVI of more than 140 mL/m^2 as a cut off for a giant left atrium (> 1.6 times of the length in each of the three spatial directions: 34 mL/m² × 1.6³). However, this cut off is arbitrary and the prognostic relevance, whether an atrium is severely dilated or "giant left atrium", is unknown. This has to be explored in future studies.

COMMENTS

Case characteristics

A 78-year-old patient with rheumatic heart disease and no cardiac symptoms such as dyspnea, nocturia, chest pain or palpitations.

Clinical diagnosis

Irregular heart beat with a rate of 53 beats per minute, elevated blood pressure with 167/83 mmHg and a 2/6 holosystolic heart murmur at the left sternal border and the apex with radiation to the left axilla.

Differential diagnosis

Severely enlarged left atrium because of mitral valve pathology due to rheumatic heart disease, persistent atrial fibrillation and arterial hypertension.

Laboratory diagnosis

Reduced estimated glomerular filtration rate of 61 mL/min as a sign of chronic kidney disease stage 2 and increased proBNP of 1345 ng/L as a marker for chronic heart failure.

Imaging diagnosis

Echocardiography showed a giant left atrium with a left atrial total volume of 525 mL and an indexed volume of 364 mL/m².

Treatment

Medication for chronic heart failure, *i.e.*, ACE-inhibitor, beta-blocker and loop diuretic and a vitamin K antagonist for atrial fibrillation.

Related reports

Rheumatic heart disease is defined by the world heart federation as a chronic heart condition caused by rheumatic fever due to a preceding group A streptococcal infection that can cause fibrosis of heart valves, leading to crippling valvular heart disease, heart failure and death.

Term explanation

M-mode is an echocardiographic modality (M for motion) with high temporal resolution of up to 1000 Hz that allows detailed analysis of rapidly moving structures.

Experiences and lessons

Obtaining a correct anteroposterior diameter in the parasternal long-axis view using M-mode echocardiography can sometimes be difficult. The authors therefore propose to measure left atrial volume index and suggest a cut-off value of greater than 140 mL/m² for the definition of giant left atrium.

Peer-review

The authors present a case of a giant aneurysm in a 78-year-old patient with prior history of rheumatic fever and subsequent mitral disease and mitral endocarditis medically treated. The evolution of both entities to a chronic severe mitral regurgitation might probably lead to dilate the left atrium to that extent. The paper is well written.

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CASE REPORT

Successful extracorporeal life support in sudden cardiac arrest due to coronary anomaly

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Author contributions: Bang DW, Hyon MS and Lee MH designed and reviewed the report; Lee JH and Kim KS collected clinical data; Park JW and Park BW designed and wrote the report; all co-authors read and approved the final report.

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Abstract

Extracorporeal life support (ECLS) has recently been reported to have a survival benefit in patients with cardiac arrest. It is now used widely as a lifesaving modality. Here, we describe a case of sudden cardiac arrest (SCA) in a young athlete with an anomalous origin of the right coronary artery from the left coronary sinus. Resuscitation was successful using ECLS before curative bypass surgery. We highlight the efficacy of ECLS for a patient with SCA caused by a rare, unexpected aetiology. In conclusion, ECLS was a lifesaving modality for SCA due to an anomalous coronary artery in this young patient.

Key words: Coronary vessels anomalies; Extracorporeal circulation; Cardiac arrest

Core tip: We describe the case of an adolescent with out-of-hospital cardiac arrest during intense physical activity; this patient had an anomalous origin of the right coronary artery from the left coronary sinus. He was resuscitated successfully using extracorporeal life support (ECLS). This case highlights the utility of ECLS for a young patient with refractory sudden cardiac arrest due to this rare, unexpected aetiology.

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INTRODUCTION

Coronary artery anomalies are rare, but they may be fatal and can cause sudden cardiac arrest (SCA). In such cases, the most common cause of cardiac arrest is functional stenosis of the anomalous artery between the pulsatile great vessels, especially in young athletes during or after intense physical activity[1].

It was recently reported that extracorporeal life support (ECLS) confers a survival benefit in patients with prolonged cardiac arrest when conventional cardiopulmonary resuscitation (CPR) fails[2]. We herein describe the case of an adolescent with out-of-hospital cardiac arrest during intense physical activity; this patient had an anomalous origin of the right coronary artery (RCA) from the left coronary sinus confirmed by cardiac computed tomography (CT) and coronary angiography. He was resuscitated successfully using ECLS. This case highlights the utility of ECLS for a young patient with refractory SCA due to this rare, unexpected aetiology.

CASE REPORT

A 17-year-old male patient was brought to the emergency room (ER) for urgent treatment of SCA that had occurred while playing basketball. His medical history was non-contributory. There was no family history of sudden cardiac death, collagen vascular disease, or congenital heart disease. In the ambulance, defibrillation was performed four times for ventricular fibrillation, and CPR was continued for about 25 min before arrival at the ER.

On arrival, the patient was in a coma, and his vital signs could not be checked. CPR was continued for an additional 30 min in the ER. However, this was not successful, and refractory cardiac arrest with ventricular fibrillation continued. To restore the systemic circulation and adequate organ perfusion, ECLS was planned with a veno-arterial approach using the femoral artery and vein. After starting ECLS, the ventricular fibrillation subsided spontaneously without further cardiac arrest. The vital signs stabilised (blood pressure *via* a left radial artery line, 112/54 mmHg; pulse rate, 94/min; respiratory rate, 16/min; body temperature, 33 ℃). The low body temperature was due to hypothermia therapy.

An initial electrocardiogram after ECLS implementation showed atrial fibrillation with ST depression in leads Ⅱ, Ⅲ, and aVF, indicating myocardial ischaemia. Echocardiography showed severe left ventricle (LV) systolic dysfunction (ejection fraction, 30%) with global hypokinesia, a dilated LV (LV diastolic dimension, 54 mm), and mild pulmonary hypertension (estimated pulmonary artery pressure, 32 mmHg; inferior vena cava size, 14.7 mm). On laboratory testing, the levels of troponin T (0.291 ng/mL; normal, < 0.1 ng/mL) and creatine kinase-MB (8.74 ng/mL; normal, < 6 ng/mL) were elevated, and blood gas analysis showed metabolic acidosis. A chest X-ray showed interstitial pulmonary oedema. One hour after starting ECLS, the oxygen pressure (PaO_2) *via* the left radial artery was 81.7 mmHg, and the oxygen saturation (SaO_2) was 91.8%. Forty-eight hours later, his vital signs remained stable and he was alert with no neurological deficit. The pulmonary oedema resolved.

The electrocardiogram showed normal sinus rhythm. Follow-up echocardiography 24 h later showed improved LV function (ejection fraction, 42%) without LV ballooning (LV diastolic dimension, 47 mm) or pulmonary hypertension (estimated pulmonary artery pressure, 26 mmHg). The mean central venous pressure *via* the left subclavian vein was 6 mmHg, and the pulse pressure *via* the left radial artery was maintained during ECLS. On the second day, ECLS was removed successfully with normalised LV function (ejection fraction, 63%). Cardiac CT and coronary angiography were performed to evaluate the aetiology of the SCA. CT and coronary angiography showed that the RCA originated from the left coronary sinus and ran between the aorta and pulmonary trunk, causing severe functional stenosis of the proximal segment of the RCA (Figure 1). Nine days after SCA, neo-ostium formation of the RCA with a saphenous vein graft was conducted without complications (Figure 2), and the patient was discharged on day 33. One and a half years later, he was well with no neurological deficits or complications.

DISCUSSION

An estimated 350000 deaths occur annually due to SCA in the United States. Despite advances in emergency care, only 3% to 10% of patients with SCA survive after successful resuscitation[3]. However, new techniques such as ECLS and hypothermia therapy have improved the outcome of SCA. ECLS can serve as bridging therapy for the recovery of cardiac and respiratory function, replacing heart function while minimising myocardial work and improving organ perfusion. ECLS has a survival rate 36% higher than that expected from traditional CPR[4]. Because our patient had SCA with refractory ventricular fibrillation despite optimal resuscitation, ECLS was initiated as soon as possible to allow for the recovery of cardiac function.

SCA is uncommon in people with no history of cardiac problems. In the young, congenital coronary anomalies remain an important cause of SCA, especially during or after extreme exercise. Therefore, we must evaluate the possibility of coronary artery anomalies systemically in all such cases[5]. There are no advance warnings of impending SCA in 55% to 93% of patients with coronary anomalies[6].

SCA due to an anomalous coronary artery is presumed to occur with the collapse of the anomalous coronary artery along its route between the great vessels with pulmonary hypertension occurring after extreme exercise. Collapse of the coronary artery results acute myocardial ischaemia over a wide territory, which causes SCA. With ECLS, the right ventricle load

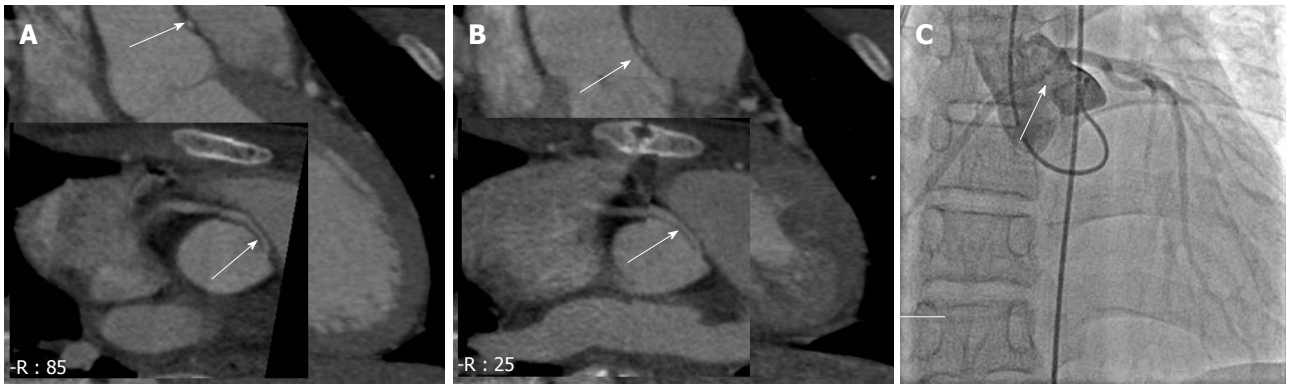

Figure 1 Coronary computed tomography shows coronary anomaly; right coronary artery from left coronary sinus running between aorta and pulmonary trunk causing functional stenosis of proximal segment (white arrow). A: Diastole state; B: Systole state. The coronary artery at diastole state is more occlusion. Coronary angiography (C, white line arrow) shows right coronary artery originated from the left sinus of valsalva and suspicious significant stenosis of right coronary artery ostium.

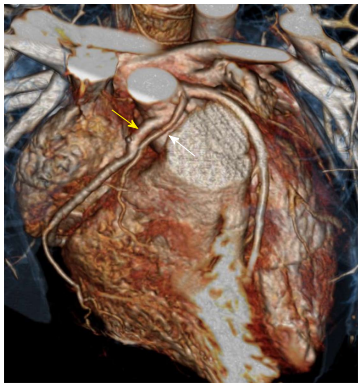

Figure 2 Coronary computed tomography after neo-ostium formation of right coronary artery with saphenous vein graft operation. Yellow arrow is the graft vessel and white arrow is the original right coronary artery.

is decreased and pulmonary hypertension is improved, which obviates the requirement for catecholamines and improves the perfusion of other organs[7]. However, ECLS has some disadvantages. First, severe cardiac dysfunction, excessive ECLS support, or inadequate preload can increase the afterload and induce pulmonary trunk expansion, which leads to functional stenosis of the anomalous coronary artery[8]. In our case, although the pulmonary arterial pressure was not monitored by Swan–Ganz catheterisation, the central venous pressure and maximum pressure of tricuspid regurgitation by echocardiography were not elevated during ECLS, which reflects improved pulmonary arterial hypertension. Maintained pulsatility *via* the left radial artery and improved LV systolic function without LV ballooning might exclude inadequate LV decompression by ECLS. Second, ECLS may result in a zone of deoxygenated blood in the aortic root and hypoxic blood perfusion in the coronary arteries[9]. In our case, the oxygen saturation *via* the left radial artery was maintained at > 90%, which excluded coronary hypoperfusion after ECLS.

To our knowledge, this is the first report of successful resuscitation by immediate implantation of ECLS in a young patient with SCA due to a coronary anomaly. ECLS can be considered a lifesaving modality for SCA due to anomalous coronary arteries in the young.

ECLS is a viable alternative to CPR and should be considered early and instituted rapidly in cases of SCA in institutions where it is available. Congenital coronary anomalies remain an important cause of SCA in the young and should be evaluated systematically in all such cases.

COMMENTS

Case characteristics

A 17-year-old man with no significant medical history presented with a sudden cardiac arrest (SCA) which was occurred by coronary anomaly: Right coronary artery (RCA) from left coronary sinus.

Clinical diagnosis

When the patient was arrived, his pulse was asystole, with coma mental status.

Differential diagnosis

Because of the patient was young adult, we have to be differential diagnosis include coronary artery anomalies of wrong sinus origin, hypertrophic cardiomyopathy, myocarditis, arrhythmia include Brugada syndrome, and ion channelopathies.

Laboratory diagnosis

Cardiac marker include troponin T and creatine kinase-MB were elevated, and blood gas analysis showed metabolic acidosis.

Imaging diagnosis

Coronary computed tomography and coronary angiography shows coronary anomaly; RCA from left coronary sinus running between aorta and pulmonary trunk causing functional stenosis of proximal segment.

Treatment

Extracorporeal life supporting (ECLS) was applied to maintain the patient's cardiac function, after that neo-ostium formation of the RCA with a saphenous vein graft was conducted.

Related reports

SCA due to an anomalous coronary artery is uncommon in people with no history of cardiac problems, and survivor rate is poor. ECLS can serve as

bridging therapy for the recovery of cardiac and respiratory function, replacing heart function while minimising myocardial work and improving organ perfusion.

Experiences and lessons

ECLS is a viable alternative to cardiopulmonary resuscitation and should be considered early and instituted rapidly in cases of SCA in institutions where it is available. Congenital coronary anomalies remain an important cause of SCA in the young and should be evaluated systematically in all such cases.

Peer-review

The authors reported the case of a patient with anomalous origin of RCA, successful saved from cardiac arrest. There are other cases in literature, that described the use of ECLS as support in cardiac arrest and this case further attest the utility of this support. We congratulate the authors for this well described case.

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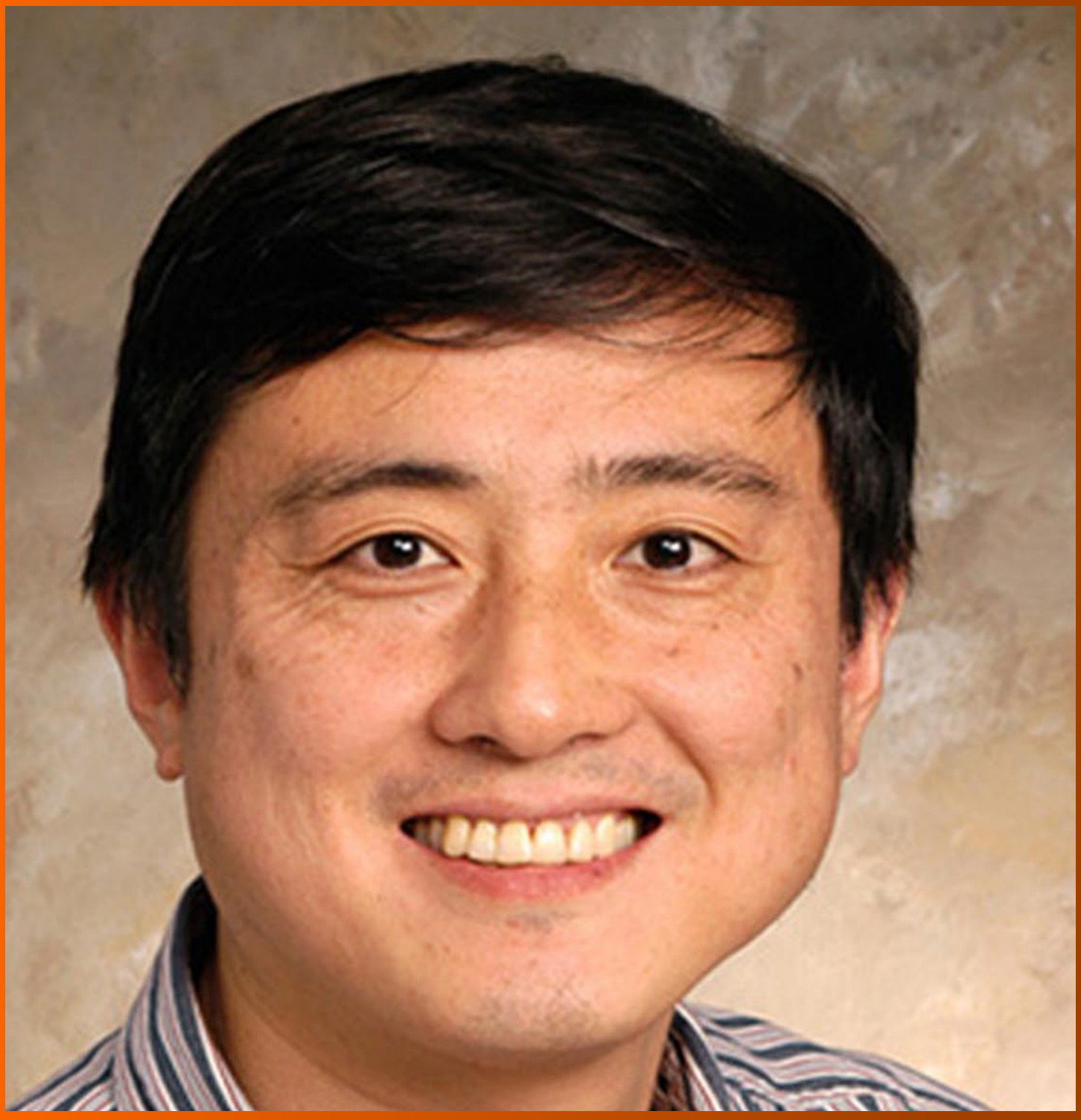

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Transcranial Doppler ultrasonography: From methodology to major clinical applications

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Abstract

Non-invasive Doppler ultrasonographic study of cerebral arteries [transcranial Doppler (TCD)] has been extensively applied on both outpatient and inpatient settings. It is performed placing a low-frequency ($\leqslant$ 2 MHz) transducer on the scalp of the patient over specific acoustic windows, in order to visualize the intracranial arterial vessels and to evaluate the cerebral blood flow velocity and its alteration in many different conditions. Nowadays the most widespread indication for TCD in outpatient setting is the research of right to left shunting, responsable of so called "paradoxical embolism", most often due to patency of foramen ovale which is responsable of the majority of cryptogenic strokes occuring in patients younger than 55 years old. TCD also allows to classify the grade of severity of such shunts using the so called "microembolic signal grading score". In addition TCD has found many useful applications in neurocritical care practice. It is useful on both adults and children for day-to-day bedside assessment of critical conditions including vasospasm in subarachnoidal haemorrhage (caused by aneurysm rupture or traumatic injury), traumatic brain injury, brain stem death. It is used also to evaluate cerebral hemodynamic changes after stroke. It also allows to investigate cerebral pressure autoregulation and for the clinical evaluation of cerebral autoregulatory reserve.

Key words: Transcranial Doppler ultrasonography; Lindegaard ratio; Paradoxical embolism; Microembolic signals; Middle cerebral artery; Patent foramen ovale; Cryptogenic STroke; Vasospasm; Acute subarachnoid

hemorrhage; Ischemic stroke

Core tip: Non-invasive Doppler ultrasonographic study of cerebral arteries [transcranial Doppler (TCD)] has been extensively applied on both outpatient and inpatient settings. Nowadays the most widespread indication for TCD in outpatient setting is the research of right to left shunting, responsable of so called "paradoxical embolism", most often due to a patency of foramen ovale which is responsable of the majority of cases of cryptogenic stroke occuring in patients younger than 55 years old. In addition TCD has found many useful applications in neurocritical care practice. It is useful on both adults and children for day-to-day bedside assessment of critical conditions including vasospasm in acute subarachnoid hemorrhage, traumatic brain injury, brain stem death.

D'Andrea A, Conte M, Cavallaro M, Scarafile R, Riegler L, Cocchia R, Pezzullo E, Carbone A, Natale F, Santoro G, Caso P, Russo MG, Bossone E, Calabrò R. Transcranial Doppler ultrasonography: From methodology to major clinical applications. *World J Cardiol* 2016; 8(7): 383-400 Available from: URL: http://www.wjgnet.com/1949-8462/full/v8/i7/383.htm DOI: http://dx.doi.org/10.4330/wjc.v8.i7.383

INTRODUCTION

Non-invasive Doppler ultrasonographic study of cerebral arteries [transcranial Doppler (TCD)] was introduced in clinical practice in 1982[1], since then it has been extensively applied in both outpatient and inpatient settings.

TCD ultrasonography is performed placing a low-frequency (≤ 2 MHz) transducer on the scalp of the patient, in order to visualize the intracranial arterial vessels through specific acoustic windows, where bone is thinner, and evaluate cerebral blood flow velocity (CBFV) and its alteration in different cerebrovascular diseases and traumatic brain injuries.

It is inexpensive, repeatable, and can be used in neurocritical intensive care to continually monitor CBFV at bedside[2].

Nowadays the most widespread indication for TCD in an outpatient setting is the research of right to left shunting (RLS), responsible of so called "paradoxical embolism", most often due to a patency of foramen ovale, mostly occurring in people younger than 55 years of age[3,4] with ischemic stroke or TIA of unknown origin.

For this purpose it is necessary to inject an ultrasonographic contrast medium in an upper limb vein. The finding of typical artifacts in middle cerebral artery (MCA) Doppler tracing after a provocative manoeuvre is diagnostic for RLS.

In addition TCD has found many useful applications in neurocritical care practice. In particular, its principal use is in the assessment of vasospastic reaction after subarachnoid haemorrhage[5] (caused by aneurysm rupture or traumatic injury)[6,7], both in adults and children. It is used also to evaluate cerebral hemodynamic changes after stroke. Moreover TCD is able to provide a non-invasive estimate intracranial pressure (ICP) and to study cerebral autoregulatory function, thus helping to adjust cerebral perfusion pressure and mechanical ventilation in the single patient. Finally it represents an adjunctive test for the confirmation of brain death.

In this review we will describe in the first place physical principles, scanning proceedings, acoustic windows used in standard TCD examination, then will be discussed flow indices most frequently used in clinical practice. Finally we will focus on the incremental diagnostic role of TCD in Cryptogenic Stroke and the main critical care indications for this imaging modality.

ANATOMY OF MAIN INTRACRANIAL ARTERIES

For better understanding of TCD findings and its applications in clinical setting, can be useful to make a brief description of the anatomy of intracranial arteries of major clinical interest: Internal carotid artery (ICA), MCA, anterior cerebral artery (ACA) and posterior cerebral artery (PCA).

The ICA, together with the external carotid artery is the terminal branch of the common carotid artery. It starts at C3 and C5 vertebral level, and it has been subdivided into seven segments (named from C1 to C7): (1) cervical segment; (2) petrous (horizontal) segment; (3) lacerum segment; (4) cavernous segment; (5) clinoid segment; (6) ophthalmic (supraclinoid) segment; and (7) communicating (terminal) segmen. The ICA gives rise to two terminal branches which are the MCA and the ACA.

The MCA is the most frequently insonated artery during TCD examinations. It arises from the ICA and runs into the lateral sulcus where it then branches and gives blood to many parts of the lateral cerebral cortex. It can be subdivided into 4 tracts. The sphenoidal segment, M1 is also called the horizontal segment, because of its origin and its lateral course on sphenoid bone. The insular segment, M2 segment, is situated anteriorly on the insula. The opercular segments, M3 segment, extend laterally and exteriorly from the insula towards the cortex. The Cortical segments, the M4 terminal segments, irrigate cortex.

The ACA is smaller than MCA, and arches anteromedially to run anterior to genu of the corpus callosum, where the artery divides into its two major branches, pericallosal and callosomarginal.

The PCA represents the terminal branches of the basilar artery (BA) and irrigate the occipital lobes and posteromedial temporal lobes.

PROBE AND SCANNING PROCEDURES

In clinical practice the most frequently used transducer is a pulsed Doppler sectorial probe with a 2.0-3.5 MHz emission frequency capable of changing the size of the sample volume in order to adapt to the diameter of major intracranial arteries, moreover the angle and position of insonation should be adjusted to provide/determinated the highest quality Doppler signal.

The probe can then be fixed to the scalp with a headband so that the same angle of insonation for continuous flow velocity recordings is maintained throughout the exam. TCD can be conducted using two acquisition modalities.

The first is transcranial color-coded duplex sonography (TCCS), in which it is displayed a two-dimensional color-coded image[8] and, once the desired blood vessel is insonated, blood flow velocities may be measured using PW Doppler.

The second method is conventional TCD, using only Doppler probe function. The TCDS with combined ColorFlow and power Doppler provides more useful data than TCD since it allows direct imaging of the intracranial arteries, their anatomic course, diameter and relationships with the adjacent structures. Although the use of TCCS can be considered superior to TCD, no substantial differences were found when the two methods were compared in their accuracy to detect vasospasm in the setting of acute subarachnoidal haemorrhage (SAH)[1,9].

In order to get a better quality of the Doppler signal in spite of background noises, the TCD devices are equipped with a larger sample volume compared to other PW Doppler probe. Specific Doppler settings used in TCD examination include also the emission power between 10 and 100 mW/cm^2 second and a pulse repetition frequency (PFR) up to 20 kHz with a focus depth between 40 and 60 mm[10].

In clinical practice can be found two channel TCD transducers with dual emission frequency (2.0 MHz and 2.5 MHz, Embo-Dop). In standard TCD examination should be recorded bilateral PW-Doppler tracing lasting at least 10 cardiac cycles after a 30-s stabilized recording period.

ACOUSTIC WINDOWS AND SCANNING PLANE

The transmission of an ultrasound beam through skull is influenced by structural characteristics of the diploe bone: The almost complete absence of bone spicules makes penetration of the ultrasound similar to conventional "acoustic windows" consenting the visualization of intracranial vessels. First of all the patient should be lying in supine position, with his head and shoulders on a pillow.

In general terms transcranial United States study is performed using two main scanning planes: The axial and coronal planes at a depth that allows to display also the contralateral vessels (14-16 cm depth), with the brain stem structures remaining in the middle of the scanning plane.

The axial scan is the one most commonly used and it allows two different types of imaging planes: The mesencephalic and diencephalic views. The mesencephalic plane is obtained by positioning the probe parallel to the zygomatic arch. At this level can be identified the hypoechogenic "butterfly-shaped midbrain", located about half of the scanning plane. In the 75% of cases, can be also detected the posterior communicating arteries if they have enough relevant diameter. In the middle of the diencephalic plane, which is obtained by slightly tilting the transducer 10 degrees upwards, can be seen the Ⅲ ventricle: Behind it can be identified hyperechogenic pineal gland, while the thalamus and internal capsule are located anteriorly to it. The lateral ventricles can be also detected.

The coronal scan is obtained by rotating the probe of 90° from the axial position. In this view are shown the Ⅲ ventricle, the lateral ventricles, the thalamus and internal capsule. The examination carried out on this plane is mainly useful for assessment of the shift of the median line caused by space occupying lesions (ischaemic area, haemorrhage and tumors). For what concerns the Doppler Study of Intracranial arteries, in clinical practice there are four acoustic windows that can be used for TCD and TCDS.

The temporal window is situated above the zygomatic arch, anterior to the tragus, using an axial plane in order to obtain a mesencephalic view, with the patient's head in the antero-posterior position (Figure 1). This window can be divided in an anterior, middle and posterior zone and allows to identify the MCA, in particular M1 and M2 tracts. From this approach can be also visualized A1 segment of the ACA, P1 and P2 segments of the PCA and C1 segment of the carotid siphon (CS) (Figure 2). In this temporal view can be also seen the communicating arteries - anterior and posterior - and the distal end of the BA. It should be noted that about 10%-20% of subjects have poor and unsuitable trans-temporal acoustic views, depending on patient age, female sex, and other factors affecting the temporal bone thickness[2,11,12].

In the occipital window, the probe must be positioned on the median sub-occipital line and the patient should be sitting or lying down with the head turned to opposite direction respect to the operator with the chin lowered toward the shoulder. With US beam passing through the foramen magnum in this window it can be visualized the intracranial segment of the two vertebral arteries (VA) and the basilar trunk. All these three vessels dispose in a Y shape with their flow, depicted in blue color, moving away from the probe. In this view, with slight lateral movements it is possible to display also both the inferior cerebellar arteries, the posterior and the anterior[13].

When TCD examination is performed from the orbital window, transducer is put perpendicularly to the eyelid, with patient's eye closed and looking on the opposite side respect to the probe. This approach allows to insonate

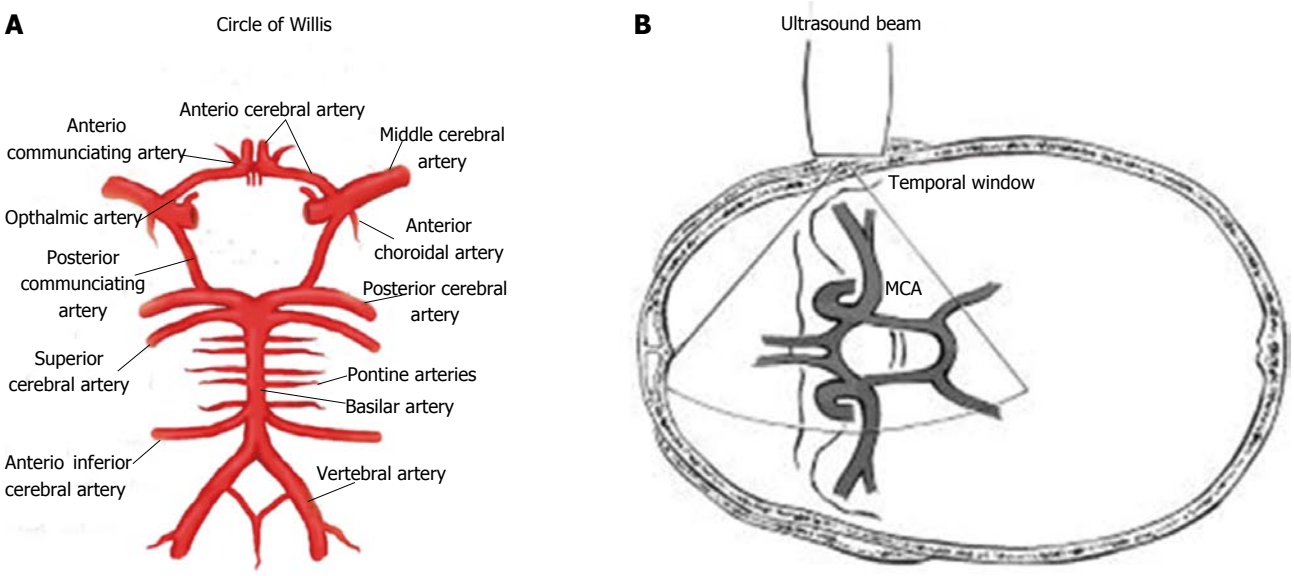

Figure 1 Circle of Willis and Ultrasonographic study by transcranial Doppler ultrasound. A: Circle of Willis; B: Transmission of ultrasound beam through skull using pulsed Doppler sectorial probe with a 2.0-3.5 MHz emission frequency. Probe is positioned on temporal window. MCA: Middle cerebral artery.

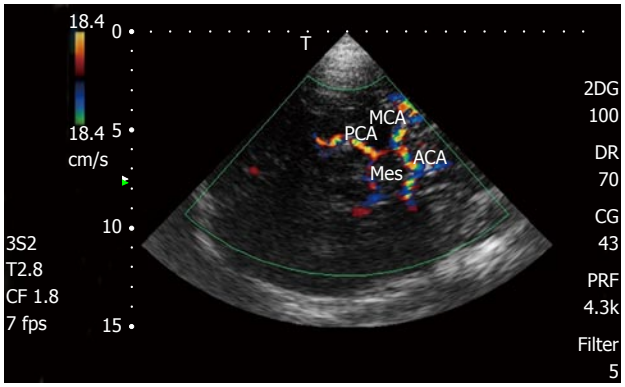

Figure 2 Transcranial Doppler color Doppler study of intracranial arteries. MCA: Middle cerebral artery; PCA: Posterior cerebral artery; ACA: Anterior cerebral artery; Mes: Mesencephalon.

the ophthalmic artery and the C2, C3 and C4 segments of the carotid syphon, through the foramen of the ocular cavity. The limitation of this approach is represented by the potential retinal injuries caused by the US beam: It is advisable to reduce 10%-15% power of the device respect to transtemporal scan.

In addition to the above mentioned views it can be also used the submandibular window, putting the transducer underneath the angle of the mandible, in front of the masseter muscle, inclinating the probe toward the skull. This window allows only the detection of the terminal segment (C5-C6) of the ICA (CI) and of the C1 segment of the CS. So, this approach is employed in case of impossibility to realize the TCD examination using the other standard windows for hemodynamic assessment of the Circle of Willis.

MCA

The most frequently examined intracranial vessel in clinical practice is the MCA, it is easily delineated through the temporal window above the zygomatic arch. The 60%-70% of the ICA blood flow is directed to MCA, so its TCD evaluation can be taken to represent almost total blood flow to ipsilateral hemisphere. MCA is detected at a depth of 45-60 mm, and the blood flow is directed toward the probe[14]. The identification of the sphenoid bone, through the "butterfly wing sign", leads to a easy MCA visualization in almost all patients, with a constant depth of 59 ± 3 mm[15]. The time to achieve an adequate echographic image of MCA is about 50 ± 20 s[15].

TCD: PHYSICAL PRINCIPLES AND TCD INDICES

TCD examination, as explained above, is executed placing on the surface of the skull a probe of a range-gated ultrasound Doppler instrument, which allows to determine flow velocities in the intracranial arteries[16]. The attenuation of US beam due to bone and soft tissues requires a low emission frequency in order to provide satisfactory recordings of intracranial CBFVs, usually a 2-MHz frequency is adopted[16].

In physical terms, the probe trasmits an ultrasonic beam that crosses the skull and is reflected back from the erythrocytes flowing in blood vessels, when a sound wave hits a moving object, the wave of reflection shows a shift in its frequency (the Doppler shift *f*) that proportionally corrrelated to the velocity (V) of the same object. The Doppler shift represents the difference between the transmitted and received signal frequency while the time interval from pulse emission and reception determines the depth at which any Doppler frequency shift is detected[16].

In the intracranial vessels, as in the arteries of other vital organs (liver, kidney, and heart), the Doppler signal shows a prominent diastolic component of blood flow.

The following equation derived from Doppler pri-

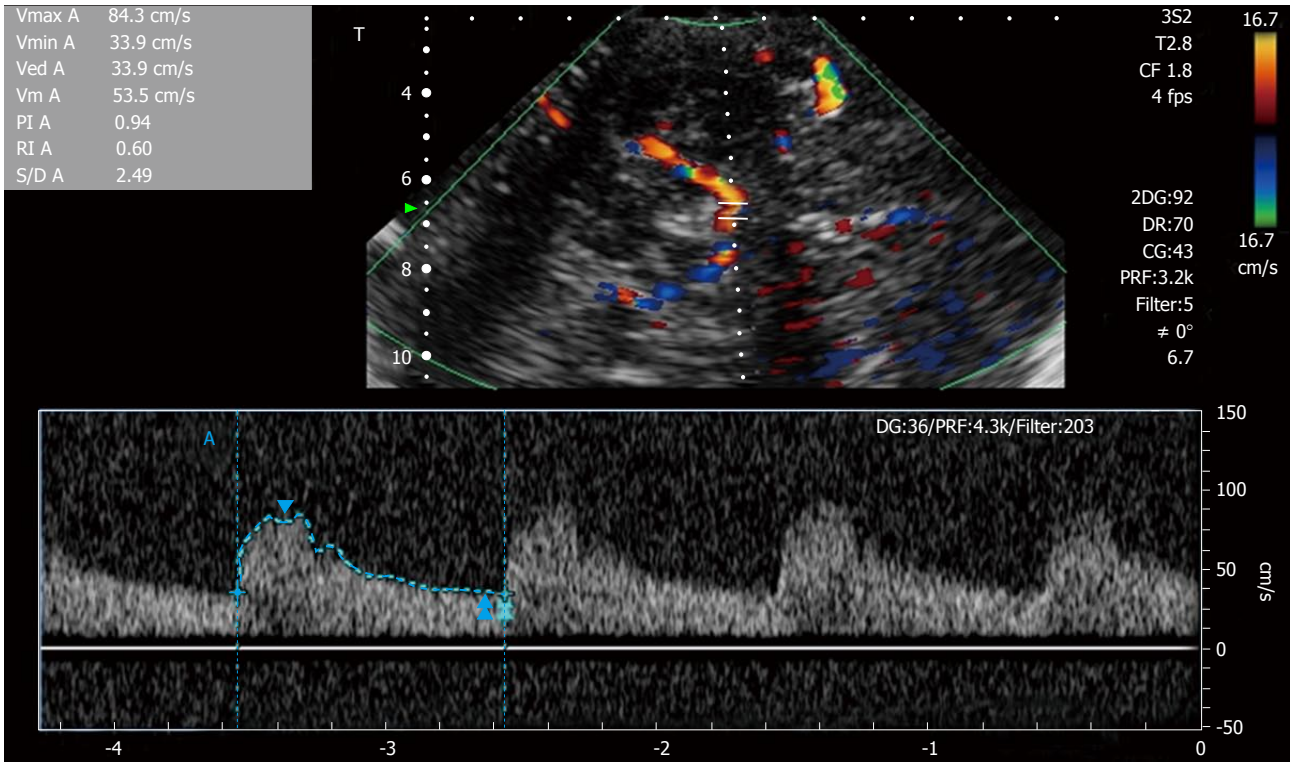

Figure 3 Transcranial Doppler spectral Doppler study of intracranial middle cerebral artery.

nciples described above, is used for estimation of CBFV with TCD:

$$v = [(c \times f)/(2 \times fo \times \text{costheta})]$$

Where c represents the speed of the US Wave emitted from probe, *fo* represents the emitted Wave pulse frequency, theta represents the angle of formed by reflected wave relatively to the initial US emission beam[17].

When performing the TCD examination the operator should keep a Theta angle of 15° or less, because the cosine remains 0.96 or more so that any error caused by changes in the angle is less than 4%.

Mean CBFV is derived through the spectral envelope of Doppler Signal, as indicated by following formula:

$$\text{Mean CBFV} = [\text{PSV} + (\text{EDV} \times 2)]/3,$$

Where PSV is peak systolic velocity, and EDV is end-diastolic blood flow velocity[18,19] (Figure 3).

By the Bernoulli principle, the correlation between velocity and pressure exerted by blood flowing, is characterized by a decrease of pressure exerted by the fluid as the velocity of flow increases. Moreover, it should be remembered that by the continuity principle the CBFV in a given artery is inversely related to the cross-sectional area of the same artery[19,20]. So, TCD gives an indirect evaluation of the diameter of intracranial vessel through the analysis of blood flow velocity[19]. It should be also considered that there are many physiologic factors affecting CBFV: Age, hematocrit, gender, fever, metabolic factors, pregnancy, menstruation, exercise, and brain activity[21-24] (Tables 1 and 2).

In clinical practice an higher mean CBFV is suggestive of hyperdynamic flow, stenotic arterial disease or vasospastic reaction. On the other hand, a decreased value of this parameter could be suggestive of low intracranial perfusional pressure, or increased ICP or even brain stem death[21]. Stenosis or vasospasm in an arterial segment is defined as an increase in mean CBFV of more than 30 cm/s, within a tract 5 to 10 mm long on one side, if confronted with the healthy corresponding contralateral arterial tract[25].

The Lindegaard ratio (LR) permits to differentiate between hyperdynamic arterial blood flow and vasospasm. It is obtained by the following equation:

LR = MCA mean CBFV/extracranial ICA mean CBF-V[26].

This ratio tends to increase in relation to the severity of symptomatic vasospasm (VSP). Normal reference range is from 1.1 to 2.3 and in the absence of vasospasm is lower than 3[26]. When the CBFV is elevated but the LR ratio is lower than 3, the elevation is considered to be caused by hyperemia, because patients after acute subarachnoidal haemorrhage (aSAH) are often treated following so called triple-H therapy: Hypertension, hypervolemia, hemodilution. In case of a ratio more than 6, there is a severe VSP[20,27,28]. So, in summary, LR defines the severity of vasospasm: MCA mean CBFV/extracranial ICA mean CBFV > 3 mild to moderate VSP; MCA MEan CBFV/extracranial ICA mean CBFV > 6 severe VSP.

Table 1 Factors influencing cerebral blood flow velocit

Factor change in CBFV	
Age	Increase up 6-10 yr then decrease
Sex	Women > men
Pregnancy	Decrement in the Ⅲ Trimester
Hematocrit	Increase with decreasing Hct
PCO_2	Increase with increasing PCO_2
Main	Arterial pressure increase with increasing MAP

CBFV: Cerebral blood flow velocity; MAP: Mean arterial pressure.

Table 2 Mean cerebral blood flow velocity (cm/s) related to age

Artery	Age 20-40 yr	Age 40-60 yr	Age > 60 yr
Anterior cerebral artery	56-60	53-61	44-51
Middle cerebral artery	74-81	72-73	58-59
Posterior cerebral artery P1	48-57	41-56	37-47
Posterior cerebral artery P2	43-51	40-57	37-47
Vertebral artery	37-51	29-50	30-37
Basilar artery	39-58	27-56	29-47

Moreover, for detecting the severity of BA vasospasm it is calculated the modified LR: BA mean CBFV/left or right extracranial VA Mean CBFV; LR modified: 2 to 2.49 possible VSP; LR modified: 2.5 to 2.99 moderate VSP; LR modified: > 3 severe VSP (Table 3).

Incremental diagnostic role in cryptogenic stroke

The American Academy of Neurology states that TCD main clinical indications include ischaemic cerebrovascular disease, neurointensive care and periprocedural applications in the setting of carotid and intracranial vascular interventions[29].

In this section we shall focus on the role of TCD ultrasonography for the research of the so-named "paradoxical embolism" through patent foramen ovale (PFO) which has been recognized as a relevant aetiologic factor for cryptogenic stroke, mainly when occurring in patients younger than 55 years old[30,31]. In fact TCD can be used to detect a cardiac source of embolism due to right-left intracardiac or pulmonary shunts (*e.g.*, patency of foramen ovale or pulmonary arterio-venous malformations). It also allows to classify the grade of severity of such shunts using the so called "microembolic signals (MES) grading score"[32,33].

PARADOXICAL EMBOLISM: PFO AND CRYPTOGENIC STROKE

PFO can be considered a remnant of the fetal circulation. During the fetal life, it allows the transit of blood flow from the right cardiac chambers to the left cardiac chambers, determining a so-called right-left shunt. The presence of a PFO in adult life can be considered persistence of such fetal communication between right and left atrium, it usually appears as an oblique, slit-shaped defect which looks like a tunnel. The cause of its incomplete closure after birth is not known, but it appears to be associated with multifactorial inheritance. In some patients such interatrial communication can be associated with a thinner and redundant interatrial septum which shows mono or bidirectional movement during cardiac cycle [atrial septal aneurysm (ASA)].

Table 3 Intracranial arteries: Severity of vasospasm

	MFV (cm/s)	LR	LR modified
MCA or ICA vasospasm			
Mild (< 25%)	120-149	3-6	
Moderate (25%-50%)	150-199	3-6	
Severe (> 50%)	> 200	> 6	
BA vasospasm			
Possible vasospasm	70-85		2-2.49
Moderate (25%-50%)	> 85		2.5-2.99
Severe (> 50%)	> 85		> 3

MCA: Middle cerebral artery; ICA: Internal carotid artery; LR: Lindegaard ratio; BA: Basilar artery; MFV: Mean flow velocity.

Frequency of such lesion in general adult population varies between 25% to 30%: The prevalence and size of the defect are similar for males and females[33-35] and decrease progressively with age. In detail, PFO is diagnosed into 34% of patients 30's old, into 25% between 30's and 80's old, and finally into 20% over 80's old and this trend is inversely related to the dimensions of the defect. Moreover the average dimensions increase progressively from 3.4 mm in the first decade of life, to 5.8 mm after the ninth decade[36]. The explanation of this phenomenon is probably that larger defects tend to persist while those of smaller dimensions go towards spontaneous closure with time[36].

Most individuals with a PFO remain asymptomatic, but in some cases it has been associated with several clinical manifestations due to transient RLS, such as decompression sickness in scuba divers[37] or platypnea-orthodeoxia syndrome[38]. But, the most important potential manifestations related to PFO are represented by cryptogenic stroke due to paradoxical embolism, and migraine and vascular headache, although the causal relationship between PFO and migraine is not yet completely understood and is still object of research.

The clinical significance and the pathogenic role of PFO in patients with cryptogenic stroke is still a matter of debate: About 40% of ischemic strokes that occur in people under the age of 55 are cryptogenic[31,39]. Cryptogenic stroke is defined as an ischemic stroke which takes place without any clearly identifiable etiology from cardioembolic source or large vessel atheromasia. This kind of cerebrovascular accident has an embolic origin and typically shows a distribution pattern that is not consistent with small vessel involvement.

Prevalence of PFO is higher among subjects hit by a cryptogenic stroke: In a prospective study (the PFO-ASA study) were included 581 patients with a cryptogenic cerebrovascular ischemic accident of less than 55 years of age (mean 42), 37% had PFO and 9% had PFO associated with ASA[39].

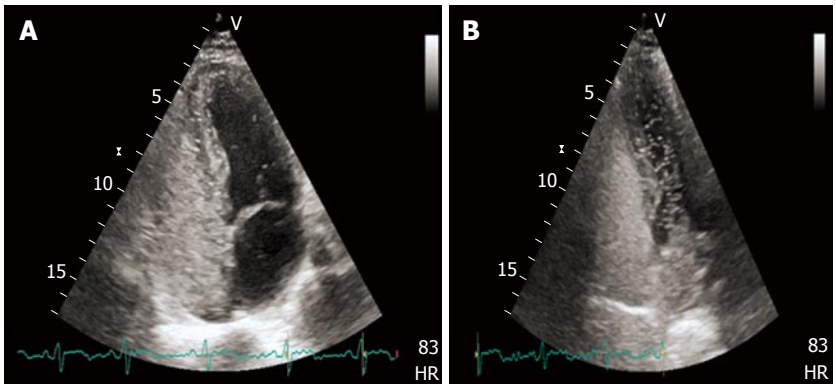

Figure 4 Transthoracic echocardiography showing high grade right to left shunt with evident micro-bubbles in the left heart after intravenous contrast administration (A and B).

In the PFO in Cryptogenic Stroke study was found an analogous prevalence of PFO (39%) in 250 patients with a mean age of 59 years[40]. Moreover patients with cryptogenic stroke showed significantly higher rate of a large PFO compared to patients with a stroke of known cause (20% *vs* 9.7%)[40]. The pathophysiological mechanism underlying stroke of cryptogenic origin in PFO carriers probably consists in a paradoxical embolism in the setting of a transient right to left shunt. In detail when the right atrial pressure is higher than the pressure in the left atrium, a transient right-to-left shunt possibly occurs through a PFO that becomes a pathway for the passage of emboli from venous to arterial circulation (paradoxical embolism).

Thus, a transitory occurrence of interatrial right-to-left pressure gradient can cause paradoxical shunting and can commonly be elicitated using specifical maneuvers in patients with no baseline RLS (including both subjects without net shunt at all or with a left-to-right shunt). In particular a short-lived right-to-left gradient can be present in normal individuals during early ventricular systole and after release of maneuvers which raise intra-abdominal pressure (such as Valsalva maneuver, defecation, cough, lifting or pushing heavy objects). In a community based study of 148 subjects carriers of a PFO, 57% showed resting right-to-left shunt, and 92% showed elicitable RLS after Valsalva maneuver or cough[41]. In summary PFO represents a possible cardioembolic source responsible of cryptogenic stroke and a risk factor for neurological events.

ROLE OF THE TCD METHODOLOGY AND DIAGNOSTIC ACCURACY

The diagnosis of PFO, in order to achieve a clinical significance, should provide both an anatomic description and a physiologic assessment of a potential RLS. The first is usually obtained by transesophageal echocardiography (TEE) or by intracardiac echocardiography while the physiologic assessment of an RLS is usually obtained using contrast transthoracic echocardiography (TTE) or TCD. A definite ultrasonographic diagnosis of temporary right-left shunting requires the use of contrast enhancement. In clinical practice the most frequently used ultrasonographic contrast medium is represented by agitated saline solution. In fact the different density present at the interface separating gas-containing micro-bubbles from sorrounding tissue modifies the "acoustic impedance" of such interface: The higher impedance the higher echogenicity at the same level. Moreover gas microbubbles work very effectively as contrast medium, since they are 100000 times less dense than blood[42].

Traditionally, TEE supported by agitated saline contrast-enhancement has always been considered the gold standard techinque both for demonstration of a right-to-left shunt through a PFO and for morphological description of interatrial septum. It should be noted that micro-bubbles with a diameter smaller than 9 μm are not able to pass through pulmonary capillary network, so the finding of any micro-bubble after intravenous contrast administration is diagnostic for RLS.

Contrast enhancement for the research of paradoxical interatrial shunting has been applied also to TTE (Figure 4), with a reported sensitivity and specificity similar to that of c-TEE[43,44]. This was also due to the introduction of harmonic imaging, which improved image quality of TTE[45]. In recent times contrast enhanced TCD (c-TCD) has gained a growing role for the diagnosis of transient RLS, which allows to recognize the passage of intravenously injected micro-bubbles directly in cerebral circulation. As stated above about TEE, also with c-TCD the finding of a single microbubble in cerebral arterial circulation (usually MCA) is considered diagnostic of RLS. C-TCD represents a low cost, widely available, non-invasive imaging techinque, of easy interpretation, which also permits to semiquantitatively estimate severity of venous-arterial shunt[46].

In order to highlight RLS a contrast medium, usually agitated saline is injected into a peripheral vein, usually right antecubital vein in three boluses, at the same time the Doppler signal is recorded while the patient performs a Valsalva maneuver. The contrast agent is obtained by combining 9 mL of normal saline solution with 1 mL of air and then it is usually shaken up about 10 times through a system constituted by two 10 mL syringes

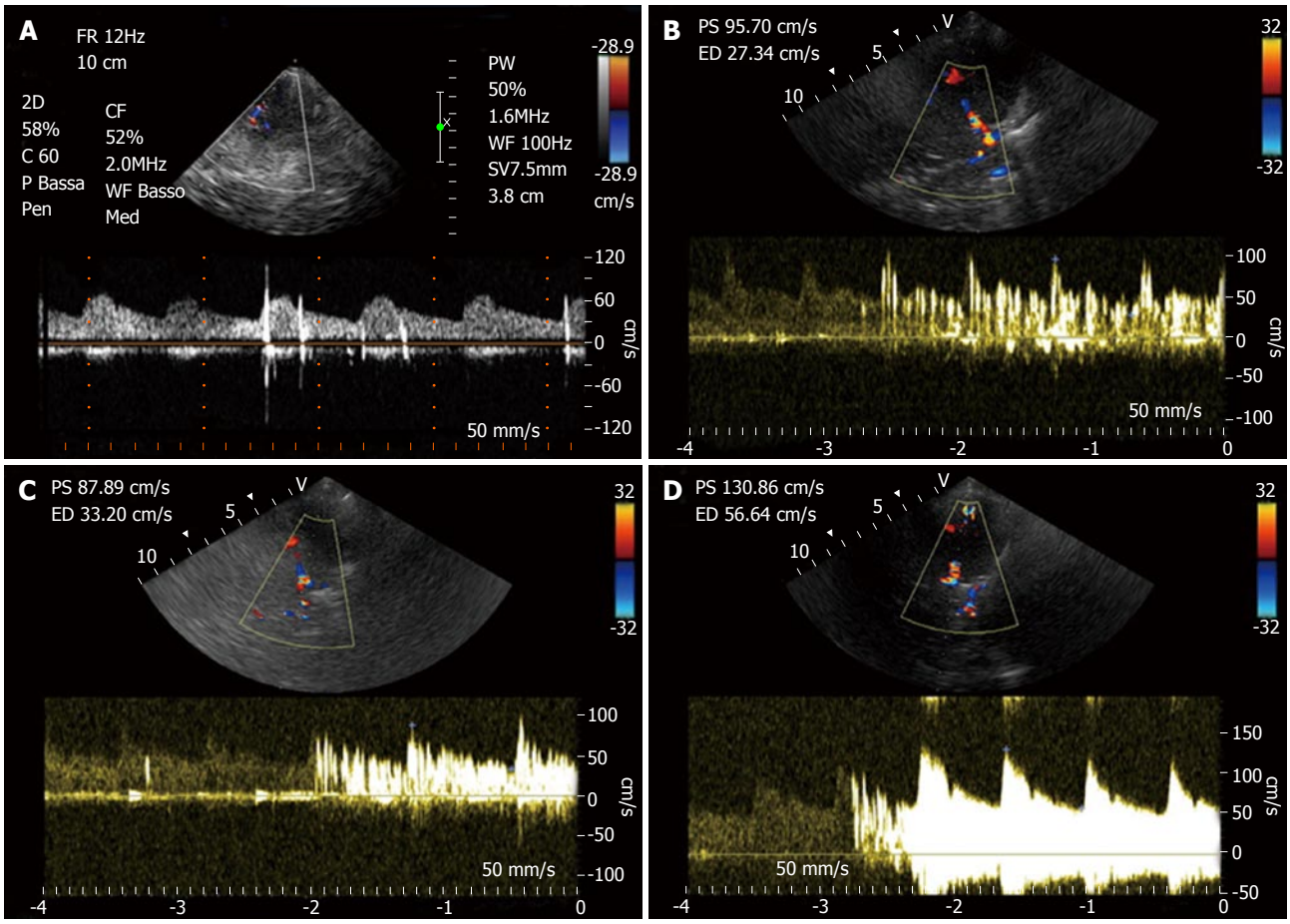

Figure 5 Right to left shunt with microembolic signals. A: Low grade shunt; B: Moderate grade shunt; C: High grade shunt (shower); D: Curtain effect.

Table 4 Grade of transient right to left shunting based on microembolic signals grading score

Grade transient shunt	MES
No shunt	0
Low grade shunt	1-10
Moderate grade shunt	11-25
High grade shunt	> 25 (shower) or uncountable (curtain effect)

MES: Microembolic signals.

linked by a 3-way stopcock. The agitated solution is then administrated into the antecubital vein by an 18-gauge. The patient is then invited to perform a forced expiration against the closed glottis for a minimum of 10 s (Valsalva Maneuver). When a right to left shunt is present the air microbubbles constituting ultrasonographic contrast medium will directly pass from venous to systemic circulation and will be visualized in cerebral arterial vessels as so called MES.

In addition it is possible to evaluate the entity and functional relevance of a paradoxical RLS through the MES grading score, based on the number of Doppler signals provoked by microbubbles that reach MCA (Figure 5 and Table 4). Moreover the entity of right to left shunt is directly associated with the risk of stroke[33,47]. It should be noted that when the number of microbubbles passing through a RLS is very low, they may not be able to reach the MCA giving a false negative result of absent RLS. But on the other hand clinical relevance of such small entity of shunt is uncertain. A very large amount of microbubbles reaching MCA is responsible on the Doppler Spectrum of the so called "Curtain effect", characterized by impossibility to identify on Doppler spectrum a single MES. In the work of Serena *et al*[48], "Curtain effect" is characteristically found in patient hit by cryptogenic stroke, so the identification of this Doppler aspect in a subject could denote a higher risk of cerebrovascular events, thus providing useful information for the clinician in order to differentiate "innocent" from "harmful" shunts information[48].

Nowadays there is no consensus about a definite time interval from contrast administration until recording of the first MES on MCA Doppler spectrum. In a recent work, twenty-six patients with stroke (16 with PFO *vs* 10 without PFO, diagnosed by cTEE) after a positive cTCD test were evaluated for three parameters: The amount of MES, latency time (LT) before the first MES and the duration time of MES, looking for any difference between PFO carriers and no-PFO. The presence of more than 9 MES with a LT of less than 9 s (so called rule of nine) can be considered a marker for PFO diagnosis by cTEE, providing a specificity and positive predictive value (PPV) of 100%[49].

Table 5 Diagnostic role of transcranial Doppler and its accuracy

Ref.	No. of patients	Sensitivity (%)	Specificity (%)	Accuracy (%)	Cut-off for RLS
Serena *et al*[48], 1998	55	100	100	100	⩾ 1 MES[1]
Lange *et al*[49], 2010	26	31	100	65.5	⩾ 9 MES
González-Alujas *et al*[52], 2011	93	97	98	97.5	⩾ 1 MES
Mojadidi *et al*[51], 2014	1968	97	93	95	Meta-analysis[2]

[1]In this study c-TCD performs better than c-TEE; [2]This study is a large meta-analysis comprising 27 studies. TCD: Transcranial Doppler; c-TCD: Contrast enhanced TCD; TEE: Transesophageal echocardiography; RLS: Right-to-left shunting; MES: Microembolic signals.

To increase the test sensitivity for identification of the right to left shunt [PFO detection can be increased by asking patient to cough or by releasing a sustained Valsalva manoeuvre (VM)] the patient may be asked to cough or to perform a prolonged VM, since in the release phase of these strain maneuvres a RLS can be elicitated when the right atrial chamber is filled with blood from the abdominal cavity, while the left atrial chamber is still volume depleted before passage of increased blood return through pulmonary circulation[50]. VM should be always performed for the research of RLS, it is started 5 s after agitated saline administration (because it represents the avarage time interval required for the injected solution to reach right atrium from the cubital vein).

Effectiveness of VM strength can be assessed through peak flow velocity of the MCA Doppler Spectrum, which tends to decrease during a well executed VM[44]. Mojadidi *et al*[51] have published an extensive bivariate meta-analysis of 27 prospective studies with a total of 1968 patients comparing PFO detection with TCD to the c-TEE as gold standard. Starting from these data they could determine sensitivity in FOP identification for TCD (index test) and TEE (considered reference test) according to type of contrast medium, different provocative maneuvers, different quantitative microembolic cutoffs, different time of onset of provocation maneuver, and insonation of a single or both MCA. No difference in sensitivity and specificity was found between each contrast medium (agitated saline, Echovist, and gelatin-based solutions, $P > 0.05$). No significant difference between cough or Valsalva as provocative maneuvre was evident ($P > 0.7$). When cut-off number of 10 microbubbles instead of 1 was chosen to define TCD positivity study specificity was showed a significant improvement from 89% to 100% ($P = 0.04$), nevertheless this approach did not result in a substantial improvement in sensitivity (from 98% to 97%, $P = 0.29$).

Duration of Valsalva strain, more or less than 5 s, did not show a significant influence sensitivity or specificity of TCD ($P > 0.50$). Finally a not significant trend towards an improvement of specificity when a single MCA was insonated instead of both (95% specificity *vs* 89% respectively, $P = 0.09$), while no significant difference was seen regarding sensitiviy ($P = 0.15$).

In conclusion Mojadidi found an overall sensitivity of 97% and a specificity of 93% for detection of RLS with c-TCD compared with c-TEE[51]. Increasing the number of microbubbles needed for a positive TCD from 1 to 10 resulted in a predictable significant improvement in specificity. TCD showed a good diagnostic performance with an overall LR+ of 13.51 and LR- of 0.04 and a disease probability of 93%-94% after a positive test and of 4% after a negative test[51].

In Table 5 are summarized sensitivity, specificity and diagnostic accuracy of c-TCD for the research of RLS in patients with cryptogenic stroke in different studies, which adopted TEE as a gold standard. So in the context of a cryptogenic stroke, the clinician is called to choose the best diagnostic technique between c-TCD, c-TEE or c-TTE in order to detect a RLS.

TEE provides detailed morphological description of interatrial septum and is able to identify anatomic characteristics of a PFO. In particular a diameter greater than 4 mm or the coexistence of an aneurysm of interatrial septum is associated with recurrent ischaemic cerebrovascular accidents. These c-TEE may be useful in guiding management towards an interventional strategy instead antithrombotic treatment in patient hit by cryptogenic stroke[52]. On the other hand recent published data suggest that TEE should not be considered the true gold standard imaging technique for the detection of RLS. In fact in the case of really small shunts (of 1 to 3 bubbles), c-TCD may show a better sensitivity, because such a small number of microbubbles may me missed on a single tomographic echocardiographic plain[53]. Moreover TEE is an high cost, semi-invasive technique characterized by poor patient's compliance, it is not always available and contrast administration may be inconclusive or be followed by falsely negative results[53], mainly due to inability of the patient to carry out an effective Valsalva maneuvre[54-57].

A lower sensitivity of c-TEE compared with c-TTE and c-TCD was reported by the work of González-Alujas *et al*[52] (86% sensitivity for TEE, *vs* 100% for TTE and 97% for TCD, $P < 0.001$), while here was no significant difference in sensitivity between TTE and TCD. These results may have a clinical impact, because they confirm that TEE is not the most accurate diagnostic technique as it was commonly considered in the past years.

Higher sensitivity shown by c-TCD is also due to its positive results also in presence of extracardiac shunts, such as pulmonary arterio-venous malformations. TCD is not able to show the exact anatomic position of the RLS, although LT from contrast injection in antecubital

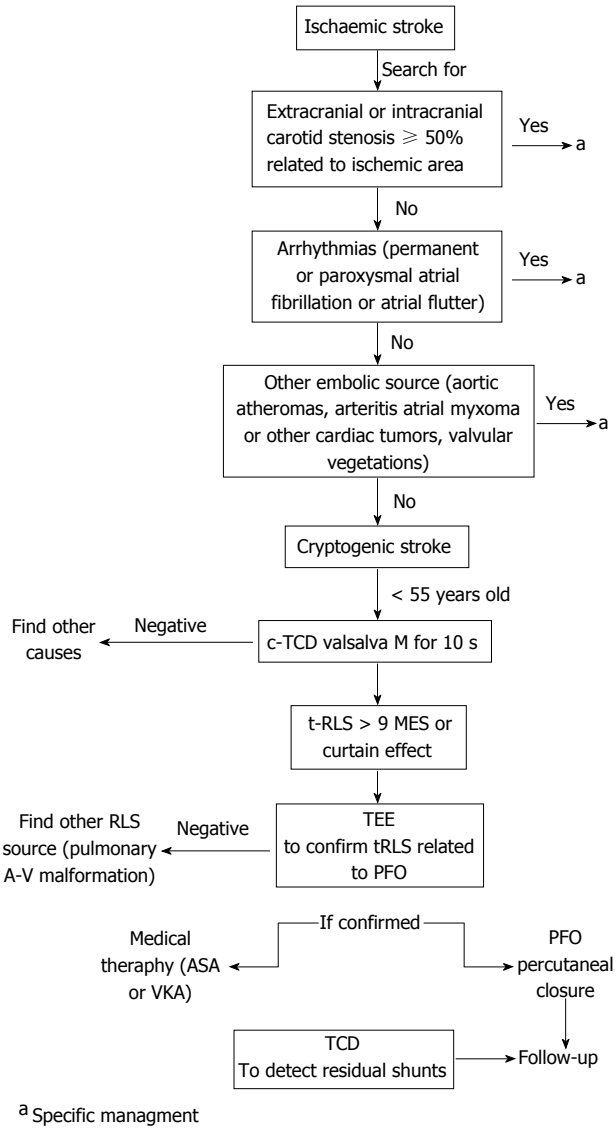

Figure 6 Contrast enhanced transcranial Doppler as a first line screening tool in the setting of a cryptogenic ischemic stroke. TCD: Transcranial Doppler; c-TCD: Contrast enhanced TCD; TEE: Transesophageal echocardiography; RLS: Right-to-left shunting; PFO: Patent foramen ovale; ASA: Atrial septal aneurysm; MES: Microembolic signals; VKA: Vitamin K antagonist.

vein to the appearance of MES in the setting of an intracardiac shunt is about 11 s, while in presence of a pulmonary artero-venous malformation is about 14 s[58]. Interestingly as reported in the work of Gonzalez-Aluja[52], c-TTE performed simultaneously with TCD was able to confirm presence of an artero-venous pulmonary malformation in a positive TCD, showing the entrance of microbubbles in left atrium from a pulmonary vein.

RECOMMENDATIONS

American Academy of Neurology confers a class Ⅱ indication for both c-TCD and TEE for interatrial shunt detection[29,58]. On the other hand Italian stroke guidelines (SPREAD) consider TCD a better screening tool than TEE in the population of patient with suspect shunt through a foramen ovale[59].

In a consensus document published on behalf of Italian society of interventional cardiology by Pristipino *et al*[60] in 2010 TCD was proposed as first-choice screening tool for RLS in the setting of a cryptogenic stroke in subjects 55 years old or younger, while in patients older than 55 TEE was recommended as first-line test.

In conclusion our suggestion in the setting of a cryptogenic ischemic stroke is to use c-TCD as a first line screening tool, due to its higher sensitivity and its better tolerability. TEE may be considered as a complementary imaging technique for a more detailed anatomic definition of interatrial septum, especially when PFO closure is contemplated (Figure 6). Moreover TCD is also useful for follow-up of patients after PFO closure in order to identify those with residual shunting[61] due also to its repeatability and its sensitivity for the detection of small entity residual shunts[62].

Principal applications in neurocritical care unit

TCD examinations have gained an important role in the very early phase of critical cerebral pathologies, as well during follow-up of patients with chronic cerebrovascular diseases.

In neurocritical care bedside TCD examination provides the clinician useful information to guide the management of patients with SAH, allowing to recognize vasospasm both in adult and paediatric patients. Moreover TCD represents an additional non-invasive tool for cerebral hemodynamic monitoring, which is particularly of interest in the follow-up of patients with ischemic stroke. It allows to investigate cerebral pressure autoregulation and for the clinical evaluation of cerebral autoregulatory reserve[63]. TCD has important clinical application in the management of patients with sickle-cell disease, traumatic brain injury (TBI), brain stem death[64], raised ICP[65].

VASOSPASM AFTER SAH: DIAGNOSIS AND MONITORING ON TCD

Symptomatic vasospasm (VSP) is a frequent complication of aSAH, secondary to intracranial aneurysm rupture (aSAH). It should be considered that 25% of patients affected by aSAH develops clinical delayed ischemic deficits due to vasospasm[6,11,66-68].

The retarded vasospasm of intracranial arteries is reported by angiographic studies to occur in about 70% of patients affected by SAH and in most cases it develops between 4-17 d following the acute episode[20,69]. When it's still present up to day 20 by TCD[70], morbidity and mortality are considered to increase significantly up to 20%[8,71,72].

VSP is characterized by a decrease in blood flow through cerebral regions after aSAH secondary to reflex vasoconstriction of intracranial arteries[20]. The exact mechanism causative of delayed cerebral ischemia (DCI) is not clearly understood, and several theories have been proposed[73]. Clinically, the terms "delayed ischemic neurologic deficit and DCI" have been introduced to

describe symptomatic VSP.

Angiographic study is considered as the gold standard for the detection of intracranial vasospastic reaction but it is invasive diagnostic exam and cannot be used for continuous monitorization[2,74]. Angiographic VSP, identified by digital subtraction angiography and computed tomography angiography (CTA) has been diagnosed up to 50% to 70% of patients affected by aSAH and about half of them showed clinical symptoms[73,75].

TCD ultrasonography is a noninvasive, repeatable, and relatively inexpensive imaging test and it could be used in patients affected by aSAH for diagnosing and monitoring of VSP[16,76]. It can identify cerebral hemodynamic changes, diagnosing VSP before appeareance of clinical neurologic deficits, and can suggest earlier intervention[77].

So, in NCCU daily TCD monitoring is warranted for the management of patient affected by aSAH: The timing of the development and resolution of VSP can guide therapeutic strategies such as triple-H therapy (hypertension, haemodilution, and hypervolaemia). TCD also can monitor the efficacy of interventional procedures such as transluminal balloon angioplasty[78] and can identify patients at higher risk of developing DCI.

TCD is able to recognize vasospastic reactions in MCA and BA with a good sensitivity and specificity. A systematic analisys collecting 26 works, which compared TCD with angiographic exam has shown that a Mean CBFV > 120 cm/s in MCA detected by TCD carries 99% specificity and 67% sensitivity for identification of angiographic vasospasm of $\geqslant$ 25%[79]. For MCA vasospasm it is calculated as MCA mean CBFV/extracranial ICA mean CBFV (Table 3). MCA mean CBFV/extracranial ICA mean CBFV > 3 indicates mild to moderate VSP. MCA mean CBFV/extracranial ICA mean CBFV > 6 indicates severe VSP. Thus TCD, compared with angiography as gold standard, showed high specificity and high PPV for MCA vasospasm detection, making it a very useful diagnostic tool in this setting[79].

TCD criteria for BA VSP have not been universally defined yet (Table 3). Sviri *et al*[75] argued that the CBFV ratio (LR BA/VA) between the BA and the extracranial VA is related to the degree BA narrowing (0.648, P < 0.0001). A BA/VA ratio (LR BA/VA) over 2.5 with BA velocity higher than 85 cm/s was 86% sensitive and 97% specific for BA narrowing of more than 25%. A BA/VA ratio over 3.0 with BA velocities higher than 85 cm/s was 92% sensitive and 97% specific for BA narrowing of more than 50%. The investigators so concluded that the BA/VA ratio increases the sensitivity and specificity of BA VSP diagnosis by TCD. Therefore, the reported evidences indicate that TCD is highly predictive of angiographically demonstrated VSP in the MCA, but its diagnostic accuracy is lower to identify VSP in the BA[80,81]. For VSP detection after aSAH in ACA and PCA territory, TCD's diagnostic performance has revealed quite insufficient. In a study involving 57 patients undergone TCD study within 24 h of cerebral angiographic exam, a mean CBFV superior to 120 cm/s in ACA showed a 18% sensitivity and 65% specificity to detect VSP and a CBFV superior to $\geqslant$ 90 cm/s in PCA had 48% sensitivity and 69% specificity to detect VSP[82]. Therefore, caution should be used to make therapeutic decisions based only on the absence of VSP of ACA or PCA by TCD. So, an increased mean CBFV on TCD is highly predictive of VSP of main intracranial arteries after aSAH. It is of critical importance to evaluate day-to-day changes in CBFV: Mean CBFV raising of 50 cm/s or more within 24-h[83] or mean CBFV increases of > 65 cm/s per day from day 3 to 7[11] indicates high risk for DCI (delayed cerebral ischaemia DCI), which is related to adverse outcome.

In conclusion, the association of clinical examination and different imaging techniques such as computed tomography and TCD should be used for diagnosis of VSP after aSAH instead of the single independent tests[84].

The American Heart Association states that TCD could be considered a valid diagnostic tool to identify and to monitor the development of vasospasm on the management of aSAH[85].

TCD STUDY OF CEREBRAL AUTOREGULATION: IT'S APPLICATION IN ASAH, CAROTID DISEASE, AND SYNCOPE

Cerebral autoregulatory mechanism is a homeostatic function of local brain circulation which keeps CBF constant throughout a wide range of Cerebral Perfusion Pressure (estimated between 50 to 150 mmHg)[28]. Dysfunction of cerebrovascular autoregulation was shown in TBI[86], ischemic cerebrovascular accidents[87], carotid atherosclerosis[88], and in syncope, although for the latter there is still uncertainity about its pathophysiological role[89]. Evaluation of cerebrovascular autoregulation can give useful prognostic information in these conditions[90]. The first evidences regarding physiologic cerebral circulatory autoregulation cam from works which adopted a static approach measuring CBF after a pharmacologic modification of[90]. Following the introduction of TCD, CBFV could be used as an estimate of CBF, allowing dynamic monitoring of local cerebral blood flow.

TCD performed simultaneously with thigh cuff deflation was used for the first times by Aaslid[91] in 1989, after this many different nonpharmacologic stimuli were adopted in order to provoke a pressure modification, like pressure over carotid artery[92], Valsalva manoevre[93], head-up tilting[94], and application of negative pressure to lower portion of the body[89,95]. In particular the static autoregulatory index (sARI), which is calculated as the percent of change in cerebrovascular resistence (CVR) divided by the percent of change in cerebral perfusional pressure (CPP).

sARI[96] = % change in CVR/% change in CPP

This index is used to classify autoregulatory function

going from 0 (no response) to 1 (full response). Anyway it should be kept in mind that static methods need pharmacologic or mechanical stimulations which may not be allowed in critically ill patients[87,90,97]. Regarding dynamic study a cerebral autoregulatory function, there is no index which can be considered as gold standard[98]. The Mx index expresses the relationship among CPP and m CBF-V: A positivity of this index means that cerebro-vascular flow is pressure-dependent and absent autoragulation, a negative correlation is found when autoregulary function is preserved[97,99].

Tiecks *et al*[96] introduced the dynamic autoregulatory index (dARI), a parameter which is obtained constructing,through graphic representations, a CBFV response curve following pressure modifcation and adapting it to 10 of ipothetical models CBFV, ranging from curve 0 (no autoregulatory function) to curve 9 (fully unaffected autoregulation)[96].

In subjects affected by ICA stenosis, derangement of autoregulatory function can represent a marker of high risk of stroke and so it can be used to guide treatment decision making towards revascularization[88,100]. In fact significant decrease in dARI and increase in Mx indexes have been reported in patients with ipsilateral steno-occlusion of ICA, with a significant correlation with the severity of stenotic lesions[88,101]. On the other hand altered dARI and Mx indexes were only found in subjects with severely (> 80%-90%) stenotic carotid arteries and Mx index wasn't significantly different in symptomatic confronted with asymptomatic subjects[88,101].

In the setting of severe SAH, Lang *et al*[100] studied cerebral autoregulation through continuous monitoring of BP and CBFV recording in 12 patients, confronted with 40 controls. Autoregulatory function was impaired when compared with control subjects ($P < 0.01$ for days 106, and $P < 0.001$ for days 7013). They suggested that TCD could evaluate the entity of autoregulatory dysfunction in patients SAH and a derangement of autoregulation foretells VSP. Moreover the presence of VSP was associated with worsening of autoregulatory response and the degree of cerebral autoregulatory dysfunction in the first days after the event (days 1-6) has a negative prognostic value.

In stroke patients TCD showed a consistent ipsilateral cerebral autoregulation dysfunction, which was associated with the need of surgical decompression, the severity of neurological damage and poor outcome[101]. Many methodological issues of TCD, limit the application of this technique in clinical practice for the evaluation of cerebrovascular autoregulation.

The presence of many different static and dynamic stimuli used in many different studies of this subject, without a reference gold standard methodology to confront with and the absence of a single reference value to define an impairment autoregulatory function impede the comparison and synthesis of different study results[87,89,102]. Moreover many published works have been conducted with small samples and are statistically underpowered[89].

In addiction since the majority of TCD studies is focused on MCA, alterations of autoregulatory function of posterior cerebral vasculature or in regional cortical vessels may be overlooked[87].

In conclusion, TCD imaging represents a promising technique for the study of cerebral autoregulatory function, thanks to its good temporal resolution, non invasive approach, and good cost-benefit ratio.

TCD IN ACUTE ISCHAEMIC STROKE: DIAGNOSIS AND PROGNOSIS

The American Academy of Neurology Report of the Therapeutics and Technology Assessment Subcommittee states that TCD can accurately identify acute MCA occlusions with a sensitivity, specificity, PPV and NPV higher than 90%[29], while for occlusion of ICA siphon, Vertebral Artery (VA) and BA shows 70% to 90% sensitivity and PPV and very high specificity and NPV[29].

In the setting of acute stroke TCD has been confronted with magnetic resonance angiography (MRA) and CTA[103-105]: It has been especially used to assess steno-occlusive pathology of intracranial vessels, such as the terminal ICA, ICA siphon, and MCA. TCD is 100% specific and 93% sensitive for identification of MCA lesions, while MRA had a sensitivity of 46% and a specificity of 74% in the assessment of intracranial arteries. In the emergency department in patients with suspected acute cerebral ischemia, bedside TCD can give real-time information about cerebral blood flow adjunctive to that obtained by CTA[105].

In ischemic stroke, TCD evidence of complete intracranial arterial occlusions predicted worse neurologic outcome, disability, or death after 90 d in 2 studies[106,107]. Normal TCD findings instead predicted early neurological improvement[29,108].

Performing a TCD examination in the first 24 h of stroke symptom onset greatly increases the accuracy of early stroke subtype diagnosis (hemorrhagic *vs* ischemic). Moreover early and accurate detection of arterial occlusion guides emergency management in patients with acute ischemic cerebrovascular accident. It is universally recognized that clinical course of stroke may present either spontaneous improvements or worsening in relation to dynamic changes in cerebral blood flow. Thus the detection of such haemodynamic changes with the use of TCD may have an important prognostic role.

Cerebral blood flow before and after the administration of thrombolytic agents in ischemic cerebrovascular accident, is described by the thrombolysis in brain ischaemia (TIBI) score[108]. Post-trombolysis flow is classified ranging from 0: Absent flow to 5: Normal flow[109].

TIBI grade and its increase post-thrombolysis correlate with severity, survival, and clinical recovery in ischemic stroke[11,109-112]. As shown by a meta-analysis, reopening of the occluded vessel within a time window of 6 h from stroke symptoms onset, assessed by TCD imaging, portends a better clinical outcome at 48 h (OR

= 4.31, 95%CI: 2.67-6.97) and better functional status at 3 mo (OR = 6.75, 95%CI: 3.47-13.12)[113].

Moreover a sudden improvement of TIBI score or its gradual improvement over 30 min denotes more effective vessel recanalization and has been correlated to a better early outcome, whereas those in whom flow restoration takes place after more than 30 min show a significantly worse clinical outcome[111].

Furthermore, applying TIBI score to TCD, early re-occlusion (flow decrease ⩾ 1 TIBI grade, within 2 h) after thrombolysis can be recognized. It has been found in about 34% of cases of initial reperfusion[112] and has been associated with a worse outcome at 3 mo and a reduction of survival when confronted with patients experiencing stable reperfusion of occluded artery[112].

So, daily TCD examinations can be useful to recognize dynamic changes in cerebral circulation more time-effectively than a single neuroradiological study. Seriated evaluation of cerebral hemodynamics in patients with acute cerebral ischemia improves the diagnostic accuracy and gives valuable information about monitoring and decision making.

In conclusion, TCD represents a low-cost and readily repeatable diagnostic imaging test characterized by sensitivity and specificity > 80% for ICA and MCA occlusion[99,101].

It also gives useful information about prognosis in MCA occlusion[99,103,104]. However, CTA and MRA should still be used as first-line imaging tests in ischaemic stroke because TCD is operator dependent and has low diagnostic accuracy for posterior circulation occlusive pathology[114].

Sickle cell disease and ischemic stroke

Subjects affected by sickle cell anemia carry a high risk for brain cerebrovascular injuries including stroke and subclinical infarction and haemorrhagic accidents. The rate of ischemic cerebrovascular accidents in this setting is 600 for 100000 patient years[115].

More frequently involved intracranial arteries are ICA, proximal MCA and ACA, adhesion of sickle cells to the vascular endothelium of these vessels results in progressive stenotic or occlusive phenomena.

Asymptomatic children with CBFV > 200 cm/s show an higher rate of stroke events reported as 10000 per 100000 patient-years[116]. Blood transfusions can effectively lower the rate of stroke by > 90%[117]. So for children between 2- and 6-year-old affected by sickle cell anaemia it is recommended to perform a screening by TCD on semestral or annual basis.

On TCD screening peak mean CBFV among major intracranial vessels is measured[118]. Subjects showing a peak time averaged CBFV in all the above mentioned vessels lower than 170 cm/s are considered at low risk[118]. Whereas a CBFV higher than 200 cm/s in any artery demandates blood transfusion aiming to obtain a rate of pathologic haemoglobin lower than 30% in order to decrease the risk of stroke[118].

The Stroke Prevention Trial in Sickle Cell Anemia (STOP Trial) showed that chronic red-cell transfusion reduced the risk of a first stroke by 90% and TCD can be used to screen and identify children at greatest risk of cerebrovascular disease.

TBI AND BRAIN STEM DEATH

Trauma represents, among neurological conditions, the principal cause of morbidity and mortality in people under 45 years of age[119]. It is characterized by thriphasic pattern in cerebral blood flow: Hypoperfusion at time 0, hyperperfusion between 24 to 72 h, vasospasm from days 4 to days 15, and finally by raised ICP[119,120].

Final outcome of patients depends on two main causes: (1) the initial traumatic injury, which takes place at time of accident; and (2) the secondary consecutive pathogenic responses which represents consecutive pathologic processes starting at the moment of trauma and leads to late clinical manifestations (*e.g.*, DCI due to VSP and intracranial hypertension are the most important secondary injuring factors).

TCD allows non invasive and repeatable bedside assessment of post-traumatic cerebrovascular hemodynamic alterations, providing useful prognostic information and has relevant implications for management of TBI patients[8,29].

Moreover TCD in this setting may be useful as a non-invasive mean of calculating of CPP. Czosnyka *et al*[102] studied the reliability of CPP using TCD-measured CBFV in MCA (mean and diastolic) in 96 patients with TBI (Glasgow Coma Scale < 13). The CPP measured by TCD and the calculated CPP (MAP minus ICP, measured using an intraparenchymal sensor) were compared. The results showed that in 71% of the studies, the estimation error was less than 10 mmHg and in 84% of the examinations, the error was less than 15 mmHg. The TCD method had a high positive predictive power (94%) for detecting low CPP (< 60 mmHg).

Although TCD study allows non-invasive estimation of ICP and CPP, and is widely considered a valuable alternative to invasive monitoring[2], too many formulae have been proposed for this application, often carrying too wide confidence intervals and in many cases without full validation[2,8]. Thus TCD is more properly used to monitor dynamic changes in CPP instead of its real value in the setting of TBI[2].

Cerebral hypoperfusion is correlated with outcome at 6 mo after TBI, so non invasive measurement of CBF through TCD has proven to give information about prognosis similar to invasive CBF assessment[121].

During the 72 h post TBI, a reduced cerebral blood flow state, characterized by an MCA mean-CBFV lower than 35 cm/s has been associated with unfavourable outcome at 6 mo evaluated by Glasgow Outcome Score.

In addition, a worse outcome at 6 mo (GOS 1–3) was demonstrated in 50 patients with head injury in which TCD monitoring showed vasospasm and hyperaemia identified by interrogation of the MCA, ACA, and BA within 7 d from traumatic brain event, respect to the

absence of alterations in blood flow velocity[122].

Peak mean-CBFV was also an independent predictor of outcome with higher CBFV values carrying an increased risk for worse outcome evaluated by Glasgow Outcome Score[123].

Diagnosis of brain stem death is usually derived from physical examination and prolonged monitoring[124]. It can be confirmed with the use of ancillary diagnostic modalities, such as EEG, radionuclide scans, and angiography. TCD ultrasonography can be also used to support diagnosis of brain death. In addition it may be of great value in this indication, as it is portable, less time consuming, and can be performed at bedside. Arrest in cerebral circulation is a condition before the terminal state of brain stem death, and it can be evidenced by TCD if one of specific Doppler spectra listed below is obtained insonating BA and ICA or MCA of both sides in two different studies performed at least 30 min apart[125]: (1) an oscillating waveshape (equal systolic anterograde flow and diastolic retrograde flow, *i.e.,* zero net flow); (2) small systolic spikes of lasting less than 200 ms and with a PSV of less than 50 cm/s with no diastolic flow; or (3) The absence of intracranial flow not with concomitant specific findings in extracranial arteries. These peculiar findings come after the progressive increase in ICP which occurs after necrosis of a critically large amount of cerebral tissue.

In detail, when ICP reaches the level of diastolic arterial pressure, then cerebral perfusion will happen exclusively during systole, while with the increase of ICP at the level of systolic arterial pressure there will be no net cerebral blood flow. In this phase TCD will show an oscillatory Doppler signal, as mentioned above, with equalization of area under the envelope of forward and backward Doppler spectra, so that resulting net flow is zero: This pattern has been correlated with angiographic evidence of brain circulatory arrest. Fourteen Later ICP will continue to rise above the level of systolic arterial pressure, at this stage only systolic spikes can be recorded on Doppler spectrum and absence of diastolic flow.

Successively the amplitude of systolic those Doppler signals will progressively decrease, so that in the final stage blood flow will be completely abolished and no Doppler signal can be recorded. In this case the diagnosis of brain death needs to be confirmed by Doppler exploration of extracranial arteries (Common Carotid, ICA and VA). Compared with arteriography as gold standard TCD showed a 100% agreement for diagnosis of brain stem death[126]. A meta-analysis performed by the American Academy of Neurology have demonstrated for this technique a sensitivity of 89%-100% and a specificity of 97%-100%[29,127].

The consensus document of Neurosonology Research Group of the World Federation of Neurology on diagnosis of cerebral circulatory arrest using Doppler-sonography confirms that extracranial and intracranial Doppler sonography is useful as a confirmatory test to establish irreversibility of cerebral circulatory arrest. Although optional, TCD is of special value when the therapeutic use of sedative drugs renders EEG unreliable[128]. This statement also mentions that the absence of flow in MCA precedes complete loss of brain stem functions. The AAN considers TCD a confirmatory test of brain death along with clinical testing and other allied tests[129].

CONCLUSION

To conclude, in NCCU TCD examination should be routinely recommended as a non invasive tool, which allows early identification of patients progressing to VSP secondary to aSAH and TBI. Moreover TCD can be used in NCCU for bed side assessment of CPP with acceptable reliability. The frequency with which TCD should be performed may be guided by patient clinical presentation, risk factors for VSP, and early clinical course. The presence and temporal profile of CBFVs in all available vessels must be detected and serially monitored. The high sensitivity of TCD to identify abnormally high CBFVs due to the onset of VSP demonstrates that TCD is an excellent first-line examination to identify those patients who may need urgent aggressive treatment. Several features of TCD assessment of VSP are similar to cerebral angiography. Most likely, validation of new TCD criteria for VSP and combination of different physiologic monitoring modalities that includes TCD, electroencephalography, brain tissue oxygen monitoring, cerebral microdialysis, and near-infrared spectroscopy will improve TCD accuracy to predict clinical deterioration and infarction from DCI.

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REVIEW

Novel role of phosphodiesterase inhibitors in the management of end-stage heart failure

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Abstract

In advanced heart failure (HF), chronic inotropic therapy with intravenous milrinone, a phosphodiesterase Ⅲ inhibitor, is used as a bridge to advanced management that includes transplantation, ventricular assist device implantation, or palliation. This is especially true when repeated attempts to wean off inotropic support result in symptomatic hypotension, worsened symptoms, and/or progressive organ dysfunction. Unfortunately, patients in this clinical predicament are considered hemodynamically labile and may escape the benefits of guideline-directed HF therapy. In this scenario, chronic milrinone infusion may be beneficial as a bridge to introduction of evidence based HF therapy. However, this strategy is not well studied, and in general, chronic inotropic infusion is discouraged due to potential cardiotoxicity that accelerates disease progression and proarrhythmic effects that increase sudden death. Alternatively, chronic inotropic support with milrinone infusion is a unique opportunity in advanced HF. This review discusses evidence that long-term intravenous milrinone support may allow introduction of beta blocker (BB) therapy. When used together, milrinone does not attenuate the clinical benefits of BB therapy while BB mitigates cardiotoxic effects of milrinone. In addition, BB therapy decreases the risk of adverse arrhythmias associated with milrinone. We propose that advanced HF patients who are intolerant to BB therapy may benefit from a trial of intravenous milrinone as a bridge to BB initiation. The discussed clinical scenarios demonstrate that concomitant treatment with milrinone infusion and BB therapy does not adversely impact standard HF therapy and may improve left ventricular function and morbidity associated with advanced HF.

Key words: Milrinone; Advanced heart failure; Bridge to beta blocker; Combination therapy; Inotrope support

Core tip: Heart failure (HF) patients requiring chronic inotropic support are considered hemodynamically labile and may escape the benefits of evidence based HF therapy (HFTx). Chronic milrinone infusion may be bene-

ficial as a bridge to introduction of HFTx. We discuss evidence that intravenous milrinone support may allow introduction of beta blocker (BB). We propose that HF patients who are intolerant to BB therapy may benefit from intravenous milrinone as a bridge to BB initiation. When used together, BB mitigates cardiotoxic effects and decreases the risk of arrhythmias associated with milrinone. Whereas, milrinone does not attenuate the clinical benefits of BB therapy.

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INTRODUCTION

Heart failure (HF) is a chronic progressive disease with high morbidity and in advanced stages with an annual mortality > 50%; and prevalence is projected to rise[1-3]. Although the long-term benefit of beta-blocker (BB) in advanced HF is well established[4], many patients may be intolerant due to the negative hemodynamic impact of acute therapy and escape the benefits of HF therapy[4-7]. In such patients with advanced HF, chronic inotrope support is used as a bridge to transplantation, ventricular assist device, or palliation strategy for clinical and hemodynamic improvement. However, the use of chronic inotrope therapy as a bridge to introduction of HF therapy, specifically BB therapy, has not been effectively explored. Furthermore, chronic inotropic support is discouraged in advanced HF patients due to increased sudden death and accelerated disease progression[8,9]. In inotrope dependent advanced HF patients, combination therapy with intravenous milrinone infusion and BB provide a unique opportunity.

Concomitant therapy with BB and inotropes has been reported; however only type ⅢA phosphodiesterase inhibitors (PDEI) such as milrinone and enoximone (an PDEI agent available in oral and intravenous formulations in Europe) have demonstrated a positive impact on hospitalization and functional status[10-15]. Both milrinone and enoxamone have shown to improve left ventricular ejection fraction (LVEF) when used in combination with BBs[12,16,17]. However, latest HF management guidelines do not comment on this dual therapy approach and recommends intravenous milrinone infusion only as bridge to advanced management or palliation in refractory end-stage HF[2,18,19].

This review discusses the beneficial effects of combining milrinone infusion and BB therapy in advanced HF. When used together, BB attenuates the cardiotoxicity and accentuates the hemodynamic effect of milrinone. Wherein, milrinone provides the hemodynamic support for introduction of BB therapy. Further, BB therapy decreases the risk of adverse arrhythmias associated with chronic PDEI. Finally, molecular pathways supporting beneficial effects of combination therapy with milrinone infusion and BB therapy are discussed. The index cases to be discussed demonstrate improvement in LVEF after concomitant treatment with carvedilol and chronic milrinone infusion in end-stage HF with severe functional limitation.

Intravenous milrinone therapy in HF

Intravenous milrinone is typically used in patients with acute systolic HF with signs or symptoms of end organ hypoperfusion[2,18,19]. However, inotropic support may be difficult or impossible to wean and prolonged support may be required.

The earliest use of chronic inotropic infusion as viable management option in end-stage HF patients was in 1987[20]. Mehra *et al*[21] reported a 72% survival on long-term milrinone support with a mean duration of 160 d in advanced HF patients awaiting transplantation. Brozena *et al*[22] found similar results in a study of 60 patients committed to home milrinone with an 88.3% survival rate to heart transplantation. In a prospective randomized study that included 19 hospitalized patients who received milrinone therapy, Aranda *et al*[23] showed that 84% survived to receive heart transplantation with a mean waiting of 60 ± 45 d.

In advanced HF patients who are transplant ineligible, success of long-term inotrope therapy has been modest. Harjai *et al*[24] reported a decrease in the number of hospital admissions from 2.7 ± 2.6 to 1.3 ± 1.3 (P = 0.056) and length of hospital stay from 20.9 ± 12.7 to 5.5 ± 5.4 d (P = 0.0004) with improvement in NYHA functional class from 4.0 ± 0.0 to 2.7 ± 0.9 (P < 0.0001) in 24 patients with LVEF < 30%, chronic inotrope-dependence and intolerance to oral HF agents. The benefit of therapy was at the expense of eight deaths (38%) after 2.8 ± 1.7 mo of home Ⅳ inotropic therapy. Hershberger *et al*[25] showed a 3, 6 and 12 mo mortality of 51%, 26% and 6%, respectively, in 36 inotrope-dependent patients with refractory HF on high-dose milrinone (mean dose: 0.6 ± 0.3 mcg/kg per minute). Additionally, using Medicare data, Hauptman *et al*[26] reported reductions in hospital days at all time points (30, 60 and 180 d) but was negatively counterbalanced by a mortality rate exceeding 40% at 6 mo in 331 patients on chronic inotrope therapy. In a single center retrospective analysis of 56 inotrope dependent, transplant ineligible HF patients, Gorodeski *et al*[27] reported 62% mortality and 48% hospitalization during a median follow-up of 130 d. However, in a recent single center study of 197 contemporary HF patients, Hashim *et al*[28] reported an overall median survival of 18 mo on continuous inotropic therapy. Median survival was 9 mo in whom inotrope therapy was intended as palliation, with a 1-year actuarial survival of 48% and a 2-year actuarial survival of 38%. Among all patients placed on inotropes, those on milrinone had a better survival than on dobutamine. The authors proposed that the modest improvement in survival compared to prior studies may be related to

utilization of HF medical therapy and electrophysiologic devices that treat arrhythmias.

In the largest study to date, the PROMISE (Prospective Randomized Milrinone Survival Evaluation) trial randomized 1088 HF patients with NYHA functional class Ⅲ or Ⅳ to placebo or oral milrinone[29]. The milrinone group had 28% higher mortality at 6 mo. However, it is noteworthy that patients did not have defibrillators, and those requiring BB were excluded. Moreover, the study did not evaluate hemodynamics at enrollment with milrinone therapy. Secondary analysis of the Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure (OPTIME-CHF) study revealed a neutral to beneficial effect of milrinone on 60 d cardiovascular hospitalizations and composite of death and readmission in nonischemic cardiomyopathy but harmful effect in ischemic cardiomyopathy[30]. In addition, it is not clear whether the mortality on chronic inotropic therapy is above and beyond that of patients with end-stage HF where medical options are limited, specifically those with resting hemodynamic decompensation who are not candidates for advanced management[9].

In the light of existing evidence (Table 1), the American Heart Association/American College of Cardiology HF management consensus guideline classifies chronic inotrope infusion in refractory HF as a class Ⅱb indication/level of evidence B due to a lack of randomized controlled trials supporting morbidity and mortality benefits[2,18].

Combination of intravenous milrinone infusion with beta-blocker

Patients whose BB dosages have to be reduced or stopped have worse clinical outcomes than those in whom BB is maintained[31]. The use of intravenous PDEI permits successful initiation and up titration of BBs in HF patients who are intolerant to BB therapy[13,32-34]. Milrinone provides hemodynamic support by improving systolic and diastolic function, along with decreasing afterload and filling pressures, correcting some of the adverse effects of acute BB therapy[14]. Whether these hemodynamic benefits translate into clinical improvement has not been extensively studied. Kumar *et al*[33] assessed the tolerability of carvedilol titration and ability to wean inotrope support in a retrospective review of 32 patients with HF. Seventeen patients with NYHA functional class Ⅲb/Ⅳ HF (group Ⅰ) who received intermittent milrinone infusion were compared to 15 patients with NYHA functional class Ⅱ/Ⅲa symptoms (group Ⅱ) who did not. Both groups were started on carvedilol 3.125 mg twice daily and titrated to 25 mg twice daily every 2 wk as tolerated. Milrinone infusion had no impact on carvedilol titration (88% *vs* 93%). At 8 wk, 53% patients in group Ⅰ were successfully weaned off milrinone infusion. Those who could not be weaned had a 50% decrease in the frequency of infusions. The majority (63%) of group Ⅰ patients improved by one or more functional class at the end of follow-up. Another retrospective review assessed BB tolerability in 16 patients with stage D HF on continuous milrinone infusion[35]. Twelve patients were started on metoprolol tartrate or carvedilol and the remaining four received only milrinone. After 6 mo, 92% of patients on milrinone were able to tolerate dual therapy with a BB. No significant changes in blood pressure and heart rate after were noted BB initiation. One patient in each group died, and rates of hospitalization for HF were similar (0.83/pt in combination group *vs* 0.5/pt in BB alone). While these studies suggest tolerability and symptomatic improvement with dual therapy, results cannot be unequivocally extrapolated due to the small sample sizes.

In a retrospective analysis, Zewail *et al*[36] reported hemodynamic and clinical outcomes of long-term combination therapy with intravenous milrinone and BB in 65 patients with severe HF (NYHA class IV and LVEF < 25%) refractory to oral medical therapy. Fifty-one patients (78%) successfully tolerated BB therapy while on intravenous milrinone, while 14 patients did not and thus received milrinone monotherapy. Functional class improved from NYHA class Ⅳ to Ⅱ-Ⅲ with combination therapy. While no patients in the milrinone-only arm could be weaned off, 47% patients (24/51) in the combination arm were successfully weaned off. The corrected QT interval was significantly prolonged in the monotherapy group (mean ± 436 ± 13 ms before *vs* 469 ± 28 ms after; $P = 0.002$), whereas the interval remained unchanged in the combination group. Most notably, survival at 3 years was 59% higher in the combination group *vs* the milrinone monotherapy group ($P < 0.001$). One died of sudden cardiac death on treatment day 116 in the combination group. Jiménez *et al*[10] carried out an observational study of 26 inotrope dependent patients (> 8 wk home inotrope support) with end stage HF, with 17 patients as bridge to transplantation and 9 patients as destination therapy. They reported an 85% survival at an average of 10 mo home inotropic therapy. The reported mortality rates in the above nonrandomized studies were consistent with randomized studies of similar HF patients[37].

Gattis *et al*[38] conducted a post-hoc analysis comparing patients receiving BB at the time of hospitalization to those who did not using the OPTIME-CHF study. The 949 patients with acute HF exacerbation were randomized to receive 48-72 h of intravenous milrinone *vs* placebo. In patients who were continued on BB on admission, there was no difference in the primary endpoint regardless of assignment to milrinone or placebo. Patients whose BB were withdrawn upon randomization to milrinone had worse outcomes (mortality 28.6% *vs* 7.7%, *P*-value not reported). Furthermore, patients who received both milrinone and BB during hospitalization had the lowest 60-d mortality (5.8%).

The findings of above studies suggest that combination therapy may reduce mortality and facilitate discontinuation of inotropic support in advanced HF. However, retrospective design and small sample sizes preclude firm conclusions on the impact of combination therapy on mortality, hospitalization, and symptomatic improvement. Further, as there is substantial evidence

Table 1 Clinical studies evaluating phosphodiesterase Ⅲ inhibitors in heart failure

Ref.	Aim of study	Background beta blocker therapy	Study size *n* (total)	HF symptoms	Trial duration	Major findings/conclusion	Impact of therapy on LVEF	Complications/adverse events	Inotrope weaning rate
Packer *et al*[29], 1991	Effect of oral milrinone on mortality of pts with symptomatic chronic HF on conventional therapy	No	1088	100% NYHA Ⅲ-Ⅳ 42% NYHA Ⅳ	Median F/U duration 6.1 mo (stopped early due to adverse effects)	28% increased mortality with milrinone (30% *vs* 24%)	Not reported	Syncope palpitations hypotension headache blurry vision	Not reported
Böhm *et al*[16], 1997	Metoprolol restores the reduction of the inotropic effect of the cAMP-phosphodiesterase inhibitor milrinone, independent of beta-adrenoceptor	Yes (100%)	15	NYHA Ⅱ or Ⅲ	6 mo	Treatment with metoprolol increased LVEF, fractional shortening and submaximal exercise tolerance and reduced heart rate, plasma norepinephrine concentrations After metoprolol treatment, milrinone increased fractional shortening but had no effect before beta-blocker treatment Effect of dobutamine was completely antagonized by treatment with metoprolol	Addition of metoprolol improved EF (%) from 24.6 ± 1.5 to 40.3 ± 3.6	Not reported	Not reported
Shakar *et al*[12], 1998	Clinical impact of combined therapy with enoximone and beta blocker	Yes (80%)	30	NYHA Ⅳ	Mean duration of combination therapy was 9.4 ± 1.8 mo; mean length of F/U was 20.9 ± 3.9 mo	Combination therapy with enoximone and beta blocker improved EF and functional status in severe HF	LVEF increased from 17.7 ± 1.6% to 27.6 ± 3.4% (P = 0.01) NYHA improved from 4 to 2.8 (P = 0.0001)	2 sudden deaths	48% were weaned off enoximone
Yamani *et al*[67], 2001	Clinical outcome and economic cost of dobutamine-based and milrinone-based therapy in patients with ADHF	Yes 20% (18% milrinone grp)	329 (60 milrinone grp)	100% NYHA Ⅳ	Retrospective review of ADHF admissions	No difference in the in-hospital mortality rate or clinical outcomes	Not reported	No difference in adverse effects between the grps (20% pts in milrinone grp with either NSVT or VT)	Not reported
Lowes *et al*[32], 2001	Efficacy of milrinone *vs* dobutamine in patients with decompensated heart failure on chronic carvedilol therapy	Yes (100%)	20	100% NYHA Ⅱ-Ⅳ	Acute therapy	Dobutamine has less favorable hemodynamic effects in patients treated chronically with carvedilol	Not reported	Not reported	Not reported
Kumar *et al*[33], 2001	Carvedilol titration in NYHA class Ⅲb/Ⅳ on milrinone therapy as compared to class Ⅱ/Ⅲa CHF without milrinone	Yes (90%)	32	Class Ⅱ-Ⅳ	Mean: 24 wk	Successful carvediolol uptitration in NYHA Ⅲ-b/Ⅳ can be achieved at similar rates as in NYHA Ⅱ/Ⅲa in the presence of stable chronic milrinone therapy	Not reported	No statistical difference in adverse events among the two grps	53% patients were weaned off milrinone infusions in a mean of 8.4 ± 8.4 wk

Metra *et al*[13], 2002	Hemodynamic effects of dobutamine and enoximone before and after 9-12 mo of beta-blocker therapy with metoprolol or carvedilol in chronic HF	Yes (100%)	34	NYHA Ⅱ-Ⅳ	9-12 mo	Beta blockers significantly inhibit the favorable hemodynamic response to dobutamine. No attenuation occurred with beta blockers and enoximone	Not reported	Not reported	Not reported
Cuffe *et al*[68], 2002	Short-term milrinone in addition to standard therapy to improve outcomes in pts with ADHF	Yes (22%)	949	93% NYHA Ⅲ-Ⅳ	Treatment for up to 72 h, 60 d F/U	Milrinone was associated with higher rate of treatment failure at 48 h due to AE (12.6% *vs* 2.1%)	Not reported	Hypotension, (SBP < 80 mmHg); 10.7% with milrinone Significant atrial arrhythmias during index hospitalization; 4.6%	Not reported
Felker *et al*[30], 2003	To assess the interaction between HF etiology and response to milrinone in ADHF	Yes (23%)	949	93% NYHA Ⅲ-Ⅳ	Treatment up to 72 h with 60 d F/U	In ischemic HF, milrinone was associated with worse outcomes: 60 d mortality or hospitalization: 42% *vs* 36% placebo; in-hospital mortality 5% *vs* 1.6% placebo In nonischemic HF, benefit was derived from milrinone: 60 d mortality or hospitalization: 28% *vs* 35% placebo; in-hospital mortality 2.6% *vs* 3.1% placebo	Not reported	No difference in atrial or ventricular arrhythmias and hypotension in both grps	Not reported
Aranda *et al*[23], 2003	Clinical outcomes and costs associated dobutamine *vs* milrinone in hospitalized pts awaiting cardiac transplantation	Yes (41% in dobutamine grp; 74% in milrinone grp)	36	Not reported presumably NYHA Ⅲ-Ⅳ	Enrollment 17 mo	No difference between milrinone and dobutamine with respect to clinical outcomes or hemodynamic measures Beta blocker use in dobutamine grp was associated with worsened pulmonary pressures and PCWP	Not reported	No difference in death of length of hospital stay	Not reported
Brozena *et al*[22], 2004	Feasibility and safety of continuous IV milrinone therapy administered at home in pts listed as status IB for heart transplant	Yes (73%)	60	NYHA Ⅱ-Ⅲ Peak VO_2 11.4 mL/kg per minute	43 mo F/U	88.3% of pts underwent OHT 3.2% died before transplant	Not reported	8% hospitalized for IV line infection	1 pt weaned off based on clinical improvement
Abraham *et al*[69], 2005	In-hospital mortality in ADHF pts receiving treatment with 1 of 4 vasoactive meds (NTG, nesiritide, milrinone, dobutamine)	Yes (56% milrinone grp)	2021 (milrinone)	100% NYHA Ⅳ	10/01-7/03	Worse inpatient mortality and longer LOS with IV inotropes	N/A	N/A	N/A
Feldman *et al*[70], 2007	Whether low-dose oral enoximone could wean pts with end-stage HF from IV inotropic support	Yes (40%)	201	100% NYHA Ⅲ-Ⅳ	26 wk	30 d after weaning, 51% of placebo pts and 61.40% enoximone pts were alive and free of IV inotropic therapy	Not reported	Dyspnea, 5% enoximone *vs* 0% placebo, $P < 0.05$	

						At 60 d, the wean rate was 30% in placebo grp and 46.5% in enoximone grp Kaplan-Meier curves demonstrated a trend towards decreased in time to death or reinitiation of IV inotropic therapy over the 182-d study period and a reduction at 60 d and 90 d after weaning in the enoximone grp			
Elkayam *et al*[71], 2007	Six month risks of all-cause mortality and all-cause mortality plus rehospitalization associated with the use of vasodilators, inotropes, and their combinations	Yes (62%)	433; 75 (vasodilator); 133 (IV inotrope); 47 (both); 178 (neither inotrope/ vasodilator)	Mean peak VO_2 10.0	N/A	Worse 6 mo mortality and either mortality/re-hospitalization with inotropes (whether alone or with vasodilator)	Not reported	N/A	N/A
Gorodeski *et al*[27], 2009	Relationship between choice of dobutamine or milrinone and mortality in inotrope dependent stage D HF pts	Yes [5% (dob) *vs* 34% (mil)]	112	Not reported presumably NYHA Ⅲ-Ⅳ	Median F/U of 130 d	Higher mortality in the dobutamine grp; No difference in mortality between inotrope type in propensity matched cohort	Not reported	Not reported	Not reported
Metra *et al*[37], 2009	Effects of low dose enoximone on symptoms, exercise capacity, and major clinical outcomes in pts with advanced HF who were also treated with beta blockers and other guideline recommended background therapy	ESSENTIAL Ⅰ Yes (83%) ESSENTIAL Ⅱ Yes (90%)	ESSENTIAL Ⅰ: 904 ESSENTIAL Ⅱ: 950	100% NYHA Ⅲ-Ⅳ	Median F/U duration 16.6 mo	No difference in first co-primary endpoints: All cause mortality, all-cause mortality and CV hospitalizations	Not reported	Palpitations 8% enoximone *vs* 5% placebo, $P = 0.01$	N/A

AE: Adverse event; dob: Dobutamine; F/U: Follow-up; grp: Group; HF: Heart failure; mil: Milrinone; NYHA: New York Heart Association; OPTIME-CHF: The Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure study; OHT: Orthotopic heart transplant; PCWP: Pulmonary capillary wedge pressure; pts: Patients; SBP: Systolic blood pressure; IV: Intravenous; cAMP: Cyclic adenosine monophosphate; ADHF: Acute decompensated heart failure; CV: Cardiovascular; LVEF: Left ventricular ejection fraction; LOS: Length of stay; EF: Ejection fraction; NSVT: Non sustained ventricular tachyarrhythmia; NTG: Nitroglycerin; VT: Ventricular tachyarrhythmia; VO_2: Peak oxygen consumption; ADHERE: The Acute Decompensated Heart Failure National Registry; EMOTE: The EnoxiMone in intravenous inOTropE-dependent subjects study.

on BBs in mortality reduction, it would be unjustified to randomize BB *vs* placebo in milrinone treated patients with refractory HF. Larger observational studies would further elucidate the potential clinical benefits of combining BB with milrinone.

MOLECULAR PATHWAYS SUPPORTING COMBINATION THERAPY

Defective calcium (Ca^+) handling is thought to be a major contributor to mechanical and electrical dysfunction in HF (Figure 1)[39]. The increased mortality associated with PDEI therapy in HF is attributed to a proarrhythmic effect[29,40,41], contributing to increased sudden cardiac death and direct cardiomyocyte toxicity related to cyclic adenosine monophosphate (cAMP) mediated Ca^+ overload and sustained beta-1-receptor pathway signaling (Figure 2)[21]. Recent investigations suggest that modulation of

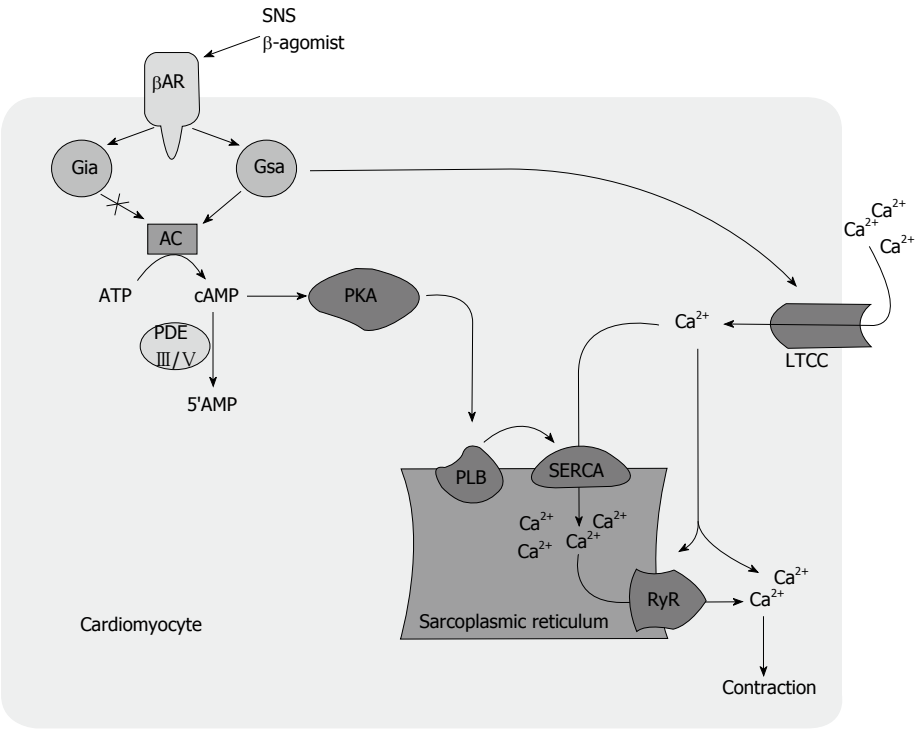

Figure 1 Beta-adrenoreceptor mediated signal transduction leads to the activation of both G stimulatory alpha protein and G inhibitory alpha protein. Activated Gαs activates adenylyl cyclase (AC) which converts ATP into cAMP while activated Gαi inhibits AC. Activated Gαs also leads to calcium (Ca^{2+}) mobilization into cardiomyocyte by activating L-type calcium channel (LTCC) independent of AC. This increase in intracellular Ca^{2+} concentration leads to activation of ryanodine receptor (RyR) which causes further release of Ca^{2+} from SR, a phenomenon known as calcium-induced calcium release. Elevated cAMP activates phosphokinase A (PKA) that inhibits phospholamban (PLB) by phosphorylating it. Phosphorylation of PLB increases uptake of Ca^{2+} from cytosol into the SR through sarcoplasmic reticulum calcium ATPase (SERCA). This enhanced Ca^{2+} entry into SR has positive impact on both systolic and diastolic function. In diastole, decreased intracellular Ca^{2+} causes relaxation. In systole increased release of Ca^{2+} from SR store through RyR activation increases inotropy. In the failing myocardium, chronic stimulation of βAR results in ineffective activation of AC, persistent activation of L-type calcium channel that increases Ca^{2+} influx, and decreased Ca^{2+} uptake into the SR due to decreased SERCA activity. This translates into systolic and diastolic dysfunction and increased arrhythmogenicity. βAR: Beta-adrenoreceptor; ATP: Adenosine triphosphate; cAMP: Cyclic adenosine monophosphate; Gαi: G inhibitory alpha protein; Gαs: G stimulatory alpha protein; PDE: Phosphodiesterase; SNS: Sympathetic nervous system.

Ca^{+} handling may result in improvements in inotropy and lusitropy without increasing arrhythmogenesis and cardiotoxicity[39,42-44]. BBs have shown to attenuate these molecular responses[45-48] and may attenuate adverse effects associated with PDEIs (Figure 3)[49,50].

In the presence of BB, the harmful sustained B-receptor pathway signaling associated with HF, mediated through cAMP-independent G-a-stimulating protein coupling of Ca^{+} channels[51], is eliminated. The inotropic effect of PDEIs is still maintained through the phosphorylation of phopholamban on the sarcoplasmic reticulum (SR)[52-54]. Inotropic agents that act through inhibition of phospholamban are desirable and best tolerated[14,55]. Phospholamban phosphorylation causes decreased inhibition of SR calcium ATPase (SERCA) activity, resulting in its increased SR calcium uptake in diastole and subsequent increased release in cytosol in systole for augmented myocardial performance. This, in turn, results in increased diastolic and systolic functions[14]. Improvement in Ca^{+} handling, through targeted *SERCA* gene expression has shown to retard development of action potential duration alternans and hence decreased arrhythmogenesis[56]. This is further supported by an improved systolic and diastolic function without increase in heart rate in phospholamban knockout models, a maneuver that mimics phospholamban phosphorylation[57,58]. In addition, the delivery of pseudo-phosphorylated mutant of phopholamban into sheep heart using a viral vector reversed chronic pacing induced HF[59]. On the contrary, phosphorylation of L-type Ca^{+} channel leads to an increased Ca^{+} influx during the plateau phase of the action potential, resulting in increased intracellular Ca^{+} during both diastole and systole that causes a detrimental effect on diastolic function and arrhythmogenesis[14].

Using an extracorporeal circulation cardioplegia reperfusion model, Usta *et al*[60] showed evidence of decreased apoptosis with low dose milrinone on *ex vivo* human right auricle cardiomyocytes compared with controls. At lower concentrations, the most likely pharmacological target of PDEI is phopholamban as both are localized to SR[61,62]. A twelve-week treatment with lower dose of enoximone (≤ 50 mg three times daily) increased exercise capacity without increasing ventricular arrhythmias. This approach demonstrated favorable effects on degree of dyspnea and physician assessments of clinical status compared to placebo[61]. A contemporary observational study suggested better survival on low dose intravenous milrinone at 0.296 ± 0.092 mcg/kg per minute[28]. Although the short-term benefits have been documented, long-term efficacy and safety of low-dose PDEI remains to be demonstrated in controlled

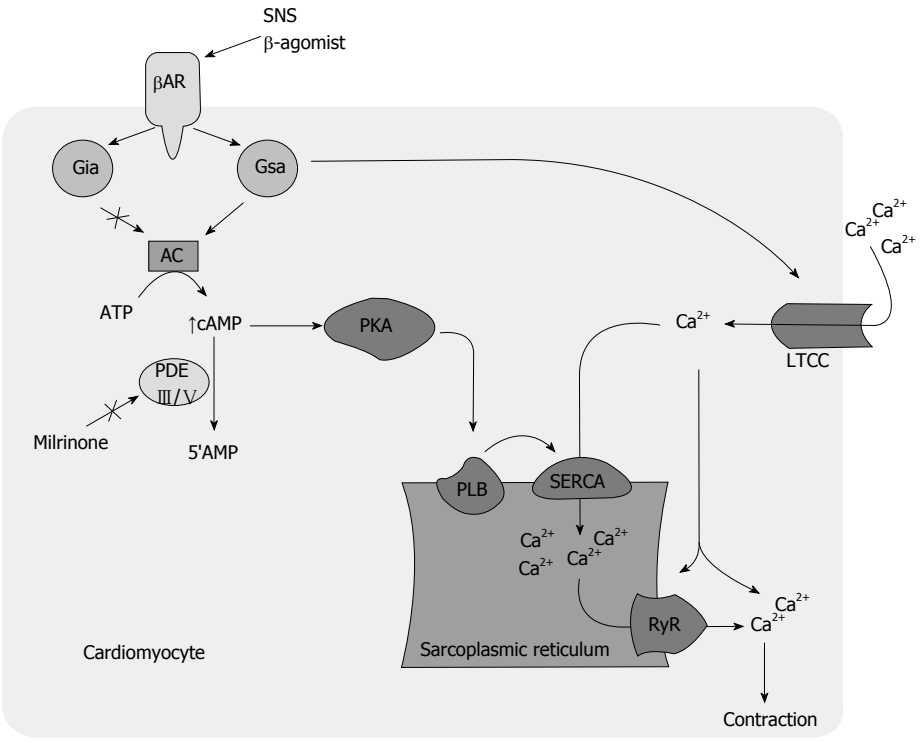

Figure 2 Milrinone causes inhibition of phosphodiesterase Ⅲ enzyme which decreases cyclic adenosine monophosphate concentration by converting later into inactive 5'adenosine monophosphate. Increased cyclic adenosine monophosphate (cAMP) activates phosphokinase A (PKA) that inhibits phospholamban (PLB) by phosphorylating it. Inhibition of PLB increases uptake of calcium (Ca^{2+}) from cytosol into the SR through sarcoplasmic reticulum calcium ATPase (SERCA). This enhanced Ca^{2+} entry into SR has positive impact on both systolic and diastolic function. During diastole, decreased cytosolic Ca^{2+} causes relaxation. During systole increased release of Ca^{2+} from SR store through ryanodine receptor (RyR) activation increases inotropy. However, unchecked chronic stimulation of beta-adrenoreceptor (βAR) causes inhibition of AC through Gαi protein and increases intracellular Ca^{2+} influx by activation of L-type calcium channel (LTCC). Activated LTCC indirectly increases intracellular Ca^{2+} through activation of RyR mediated release of Ca^{2+} from SR. This increased intracellular influx of Ca^{2+} is associated with increased arrhythmogenicity. ATP: Adenosine triphosphate; Gαi: G inhibitory alpha protein; Gαs: G stimulatory alpha protein; PDE: Phosphodiesterase; SNS: Sympathetic nervous system.

trials. In patients with advanced HF who do not tolerate BB therapy, we choose intravenous milrinone continuous infusion at low dose (< 0.5 μg/kg per minute) as this strategy is shown to augment cardiac function to permit BB therapy[61].

In addition, when used in combination, BB may enhance hemodynamic effects related to PDEI therapy by decreasing activity of upregulated inhibitory G-alpha-inhibitory protein activity[12,63]. The choice of BB to use in combination with a PDEI is uncertain. The use of B1-selective agent is suggested to be preferable as its blockade leads to increased B2-receptor-mediated signal transduction through cross-regulatory mechanisms[64], which is less cardiomyopathic[65] and may even prevent apoptosis[66]. The vasodilator effect of carvedilol can be additive to that of milrinone. However, this combination may be not desirable in patients with marginal blood pressures. The vasodilator property is less pronounced and response to milrinone is not compromised by additional vasodilation once the patient becomes stable[17].

Clinical scenario

Case1: A 67-year-old man with chronic cardiomyopathy with severely reduced systolic function with LVEF < 15% without significant epicardial coronary artery disease was impaired by six hospitalizations in five months and New York Heart Association (NYHA) class Ⅳ functional status. Due to inability to tolerate HF medicines and inadequate diuretic response, invasive hemodynamic assessment was performed. Elevated biventricular filling pressures and decreased cardiac output were noted, both of which improved 20% after milrinone bolus (0.5 mcg/kg per minute over 10 min) (Table 2). Due to refractory cardiomyopathy and hemodynamic findings, he was started on long-term continuous home milrinone infusion. Consequently, the patient tolerated carvedilol initiation and up-titration on outpatient follow-up. His functional class improved to NYHA class Ⅱ-Ⅲ and HF hospitalizations decreased to three in the subsequent nine months. Defibrillator interrogation throughout did not reveal significant arrhythmias. Nine months into treatment, LVEF improved to 35%-40% and milrinone was discontinued (Video core tip). The patient continued to thrive independent of milrinone therapy.

Case 2: A 50-year-old man with chronic cardiomyopathy with severely reduced LVEF 10%-15% without significant epicardial coronary artery disease was admitted for decompensated HF with acute renal insufficiency and inadequate diuretic response. Invasive hemodynamics revealed elevated biventricular pressure with severely decreased cardiac output (Table 2). Intravenous mlri-

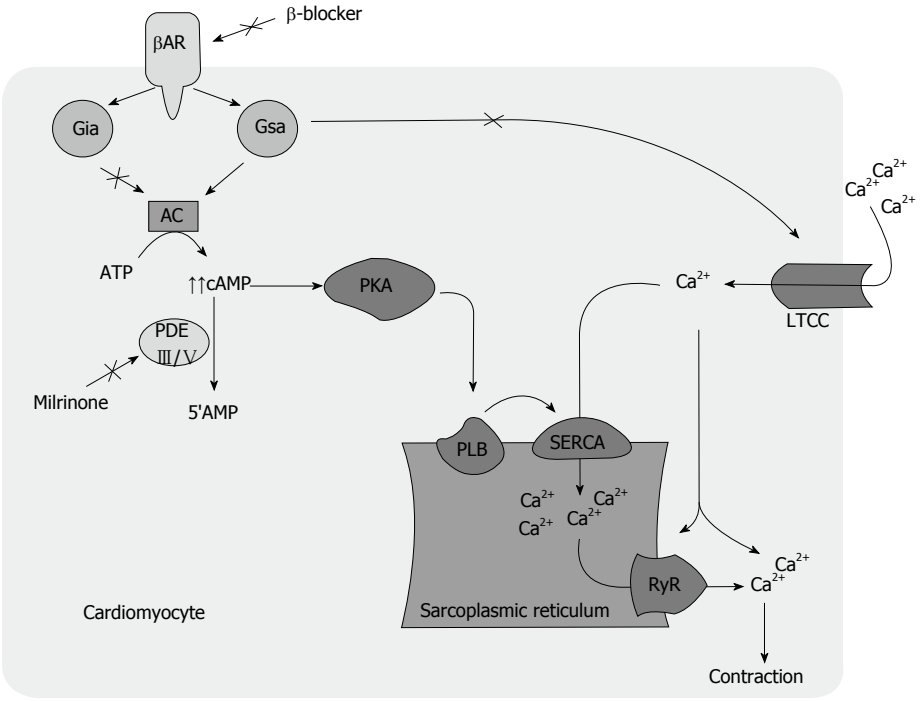

Figure 3 Concomitant use of beta blocker and milrinone causes inhibition of G inhibitory alpha protein which is an inhibitor of adenylyl cyclase and phosphodiesterase Ⅲ enzyme, both results in increased cyclic adenosine monophosphate concentration. Increased cAMP inhibits phospholamban (PLB) resulting in efficient movement of calcium (Ca^{2+}) from cytosol into the SR through sarcoplasmic reticulum calcium ATPase (SERCA). This PLB mediated Ca^{2+} handling results in improved systolic and diastolic function. In addition, BB inhibits beta-adrenoreceptor (βAR) mediated increased Ca^{2+} influx through L-type calcium channel (LTCC) that is associated with increased arrhythmogenicity. ATP: Adenosine triphosphate; cAMP: Cyclic adenosine monophosphate; Gαi: G inhibitory alpha protein; Gαs: G stimulatory alpha protein; PDE: Phosphodiesterase; SNS: Sympathetic nervous system; BB: Beta blocker; AC: Adenylyl cyclase.

Table 2 Hemodynamic parameters at baseline and after milrinone loading

Hemodynamic parameters	Patient 1		Patient 2		Reference values
	Baseline	Post-milrinone loading	Baseline	Post-milrinone loading	
RA (mmHg)	15		15		5-7
RV (mmHg)	54/15		Dec-58		15-30/1-5
PA (mmHg)	53/33 (40)	56/21 (34)	61/37 (45)		15-30/4-10; mean < 20
PA O_2 saturation	49.50%		57%		60%-80%
PCWP (mmHg)	29	15	30		< 12
Cardiac output (L/min)	5.1	7.1	3.3	6	4-8
Cardiac index (L/min per meter squared)	2.1	2.95	1.64	3.03	2.6-4.2
PVR (WU)	2.68	2.16	4.54		< 3 WU
Hemoglobin (g/dL)	10.2	10.2	11.7		13.5-17.5

PA: Pulmonary artery; PCWP: Pulmonary capillary wedge pressure; PVR: Pulmonary vascular resistance; RA: Right atrial; RV: Right ventricle; WU: Wood units.

none was initiated, permitting diuresis that led to a net 40-pound weight loss during the two-week hospitalization. The patient also underwent biventricular pacemaker implantation for cardiac resynchronization therapy. Over the ensuing year post-milrinone therapy, his ambulatory status improved from < 100 feet to > 6 city blocks. Defibrillator interrogation throughout the treatment duration did not reveal significant arrhythmias. Repeat LVEF after 10 mo improved to 20%-25% (Video core tip).

CONCLUSION

In patients with advanced HF, use of a combination therapy with low-dose intravenous milrinone infusion and BB offers an appealing strategy. In the treatment of advanced HF, we propose that chronic milrinone infusion be regarded as a "bridge to BB" in addition to the traditional bridge to advanced options or palliation strategy. Attempt at initiation and up-titration of BBs should be underscored in such patients. Milrinone provides hemodynamic support to initiate and up-titrate BB in the presence of BB-intolerance. Moreover, dual therapy improves symptoms and decreases hospitalization. Lastly, LVEF may improve with this approach without any ill-effects and significant arrhythmias, suggesting that this is a safe and effective therapeutic strategy in advanced refractory HF. Our experience with cases discussed above

shows improvement in LVEF after concomitant use of BB and intravenous continuous low-dose milrinone. It is possible that the cases might not have been adherent to prescribed HF medications prior to use of intravenous milrinone, and the increased LVEF is purely a reflection of medical compliance. Systematic exploration involving large cohorts is required for further understanding as the population with advanced HF continues to expand.

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REVIEW

Takotsubo syndrome: Advances in the understanding and management of an enigmatic stress cardiomyopathy

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Abstract

Takotsubo cardiomyopathy is a syndrome mimicking an acute myocardial infarction in absence of obstructive epicardial coronary artery disease to explain the degree of the wall motion abnormalities. Typically more common in the elderly women, this condition is usually triggered by unexpected emotional or physical stress situations, and is associated with electrocardiogram abnormalities and slight elevation of cardiac biomarkers. The pathophysiological mechanism is not clear yet, but it is believed that a high circulating concentration of catecholamines causes an acute dysfunction of the coronary microcirculation and metabolism of cardiomyocytes, leading to a transient myocardial stunning. Typically, it presents with acute left ventricular systolic dysfunction that in most cases is completely resolved at short term. Recurrences are rare and it is thought that the long-term prognosis is good. We present here a review of the clinical features, pathophysiology and management of this enigmatic condition.

Key words: Takotsubo cardiomyopathy; Stress; Review; Myocardial stunning; Left ventricle systolic dysfunction

Core tip: Takotsubo cardiomyopathy is a syndrome mimicking an acute myocardial infarction in absence of obstructive epicardial coronary artery disease to explain the degree of the wall motion abnormalities. Typically more common in the elderly women, this condition is usually triggered by unexpected emotional or physical stress situations, and presents with acute left ventricular systolic dysfunction that in most cases is completely resolved at short term. Recurrences are rare and it is thought that the long-term prognosis is good. We present here a review of the clinical features, pathophysiology and management of this enigmatic condition.

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INTRODUCTION

Takotsubo cardiomyopathy (TTC) was first described in Japan at the beginning of 90's[1]. Patients with this condition present signs and symptoms resembling those with an acute coronary syndrome (ACS), but the angiographic appearance of the epicardial coronary arteries do not explain neither the grade of the left ventricle systolic dysfunction (LVSD) nor the wall motion abnormalities typically observed in this syndrome[2]. The term "takotsubo" was used to remind the octopus trap form of the left ventricle during systole in the acute phase of disease, as result of the wall motion abnormalities in the mid-apical segments with hyperkinetic motion of the base. Along the first years of its description, it was observed that most affected people were post-menopausal women after suffering a stress situation. However, cases in men and young people have been progressively reported. Although the left ventricle mid-apical dysfunction is the pattern most frequently found, transient abnormalities in other myocardial segments have been described, such as mid-ventricular and "inverted" forms. On the other hand, there is a significant percentage of patients in whom a trigger is not identified. Therefore, currently it is recognized that TTC is a multifaceted disease with a wide spectrum[3].

Many names have been used for calling this syndrome, including stress cardiomyopathy, transient apical dyskinesia, broken heart syndrome, apical ballooning or transient cardiomyopathy, but a consensus to define an universal name is lacking. Due to different forms of presentation, it seems more appropriate to use the term "takotsubo cardiomyopathy"[4]. Recently, it has been proposed include TTC as part of the so-called syndrome of "acute myocardial infarction without obstructive coronary atherosclerosis"[5].

Throughout this review, based in our experience and that of the other authors, we will discuss the clinical, epidemiological and electrocardiographic features of this syndrome with an approach to the pathophysiological hypotheses and advances in the understanding of this enigmatic disease.

CLINICAL FEATURES AND EPIDEMIOLOGY

TTC has been increasingly recognized along last two decades[6-8], but it is still a rare condition. The true incidence of this syndrome is unknown. Several studies have estimated an incidence ranging 1.2%-2% among patients undergoing coronary angiography with a presumptive diagnosis of ACS[9,10]. Near 90% of patients with TTC are women, most of them at postmenopausal period with a mean age around 70 years[11]. Hypertension is the predominant cardiovascular risk factor (CVRF), while prevalence of diabetes is low[12], specially compared with those patients with ACS in whom diabetes is present at least as twice (30%)[13]. In Spain, most patients with TTC have no more than 2 CVRF (68.7%)[14]. The high predominance of female gender and the cardiovascular risk profile support the notion that coronary atherosclerosis in this syndrome does not seem to play a key role in the primary mechanisms, as in fact it happens in ACS.

Regarding clinical picture, chest pain is the most common presentation symptom, affecting 54%-80% of patients, followed by dyspnea[14-18]; among patients presenting with chest pain, typical rest angina is by far the most common symptom (59%)[14]. A triggering factor can be identified in 70%-86% of cases, being the distribution between emotional and physical stressful situations very variable among different case series studies. Within emotional triggers, the unexpected death of a loved one and family matters are very frequent, while severe acute illness and post-operative states are very common within physical triggers[14,18]. Psychological factors may play a key role in the triggering mechanisms of TTC. A high prevalence of psychiatric disorders (acute or chronic) has been recently reported, being the affective disorders, specially depression and chronic anxiety, a common finding[18,19]. TTC patients suffer psychiatric disorders more than twice than patients with ACS. These observations may lead to propose the chronic affective disorders as predisposing factors to develop TTC.

Of note, some epidemiological features such as the incidence, the most prevalence in women, the average age around 70 years, the low prevalence of diabetes, and the chest pain as the most common symptom are concordant between the published series along worldwide (Table 1). However, concerning other epidemiological data such as frequency of triggering factors, differences between those emotional and physical triggers, and incidence of specific electrocardiographic (ECG) abnormalities are very variable, which might suggest some ethnic variations of the disease or a more aggressive diagnostic approach in some countries.

Some study has found a relation between seasonal variation and incidence of TTC, with a higher frequency in winter[16], but this finding has not been confirmed in other series[14]. Typically, TTC mimics an anterior-ST-segment elevation myocardial infarction (STEMI); some of the main clinical differences between these are listed in Table 2.

PATHOPHYSIOLOGY

Different hypotheses have been proposed to explain the pathophysiological mechanisms in TTC, but no one seems to be conclusive[9]. Studies in animals and humans using cardiac magnetic resonance (CMR), nuclear testing, endomyocardial biopsy, advanced echocardiography

Table 1 Epidemiological and clinical features of takotsubo cardiomyopathy

	Tsuchihashi *et al*[15]	Núñez *et al*[14]	Kurowski *et al*[13]	Eshtehardi *et al*[16]	Parodi *et al*[11]	Ahmed *et al*[17]	Templin *et al*[18]
Country	Japan	Spain	Germany	Swiss	Italy	United States	Europe and United States
Year of publication	2001	2015	2007	2009	2007	2013	2015
Subjects, *n*	88	202	35	41	36	620 (systematic review)	1750 (international registry)
Age (yr)	67 ± 13	70 ± 12.5	72 ± 9	65 ± 11	75 ± 7	67	66.8 ± 13
In percentage (%)							
Reported incidence[1]	---	1.2	1.2	1.7	2	---	---
Women	86	90	94	85	100[6]	91	89.8
Hypertension	48	67	74	56	50	---	65
Diabetes	12	15	23	5	5.5	---	14
Hyperlipidemia	24	41	34	39	39	---	31
Current smoking	---	15	20	27	19	---	20
Apical type	100[3]	---	60	---	---	---	81.7
Emotional/psychological trigger	20	50	43	46	---	41	27.7
Physical (acute diseases, exercise, surgery and medical procedures) trigger	53	20	43	17	---	45	36
No identified triggering factor	26	27	14	37	28	14	28.5
Chest pain	67	80	---	76	100[2]	54	76
Dyspnea	7	45	---	24	---	26	47
Syncope	---	9	---	---	---	---	7.7
ST segment elevation	90	62	69	39	100[2]	39	43.7
T wave inversion	97	94.4	---	46	---	31	41[5]
In hospital mortality	1	2.4[4]	9	0	---	4	4.1
Long term mortality from all causes	---	---	8.6 (at 12 mo)	2 (23 ± 10 mo)	3 (at 6 mo)	---	5.6 (per patient-year)
Recurrences	2.7	0	6	5	---	---	1.8 (per patient-year)

[1]Incidence is based on patients with acute coronary syndrome; [2]This case series included only patients with chest pain and ST segment elevation; [3]Included only the typical form (apical ballooning); [4]All from noncardiac causes; [5]On admission; [6]Only included women.

techniques, biochemical testing, intracoronary imaging, physiological studies of coronary microcirculation and pharmacological tests have attempted to elucidate the origin of the ventricular dysfunction and the selective impairment of myocardial segments without reaching a definitive conclusion. TTC is an enigmatic disease and very little is known yet about its primary mechanism.

The cause seems to be multifactorial and probably a single way is not enough to explain all findings. However, it is accepted that an intense release of catecholamines could be the initial trigger that finally leads to myocardial stunning, although the mechanisms that occur into the halfway are not clear yet.

A significant proportion of TTC patients have a stressor condition (emotional or physical) shortly before the appearance of symptoms. On the other hand, patients with pheochromocytoma are susceptible to suffer similar cardiomyopathy during catecholamine crisis[20-22]. Together, those observations suggest an exaggerated response of the sympathetic system, causing a high serum catecholamine levels that initiate the cascade of events that ultimately hit the cardiomyocytes. In fact, higher levels of catecholamines have been demonstrated in TTC compared with ACS[23]. Moreover, the absence of permanent late gadolinium enhancement on CMR and the complete recovery of the ventricular dysfunction support the myocardial-stunning phenomenon in TTC patients.

One of the first hypotheses, which emerged after ruling out obstructive coronary artery disease, was the spasm of multiple epicardial coronary arteries triggered by high levels of catecholamines[1]. This theory has not been demonstrated or reproduced reliably[24]. Attempts to induce vasospasm with acetylcholine in patients with TTC have been successful in a proportion of patients that is not enough to draw definitive conclusions[25]. Also, it is well known that some patients with definitive TTC have shown persistent ST-segment elevation without simultaneous evident coronary spasm at the angiography. Furthermore, a significant proportion of patients does not report symptoms such as chest pain or syncope that would be expected to find if epicardial coronary vasospasm would be involved.

The rupture of an atherosclerotic plaque in a long and recurrent left anterior descending (LAD) coronary artery, with thrombus formation and spontaneous lysis early aborting myocardial infarction[26], also seems unlikely, since most patients have normal both coronary angiography and intracoronary imaging. Optical coherence tomography (OCT) have ruled out any suspicion of plaque rupture and other injuries that may go unnoticed on angiography[27]. In fact, the extent of the

Table 2 Clinical comparison between takotsubo cardiomyopathy and STEMI

	TTC	STEMI
Predominant gender	Women	Men
Myocardial segments involved	Extent beyond one coronary artery	Corresponding to culprit vessel
Peak of troponin	Lower	Higher
Left ventricle dysfunction recovery	Complete and at short term	Variable
Long term mortality	Lower	Higher

TTC: Takotsubo cardiomyopathy; STEMI: ST-segment elevation myocardial infarction.

left ventricle wall motion abnormalities exceeds the subtended myocardial territory of a recurrent LAD.

Myocarditis was another hypothesis. The strongest argument to rule out myocarditis is the absence of both clinical signs and permanent late enhancement on CMR demonstrated in the majority of patients with TTC.

Otherwise, nuclear studies have been of outstand relevance to investigate the potential mechanisms at metabolic level. PET studies have found a markedly reduced uptake of F-18 fluorodeoxyglucose (an analogue of glucose) at the apical segments in patients with typical TTC[28]. Moreover, it has been found a concordance between the myocardial wall motion abnormalities and the myocardial region with an impairment of glucose uptake[13]. However, this latter seems to be more severe and extensive than the corresponding myocardial perfusion defect, which is called a mismatch between metabolism and perfusion abnormalities[29]. Similar results have been obtained with fatty acids, another energy source, in terms of reduced uptake and mismatch in the apical zone of TTC patients[30,31]. Why this reduced uptake of energy sources is produced is not well understood, but a metabolic disorder, derived from myocardiocytes injury by the cathecolamines storm probably plays a key role in the mechanisms of TTC, causing a metabolic stunned myocardium.

On the other hand, coronary microvascular dysfunction (CMD) has been strongly highlighted as a key pathophysiologic mechanism. A decreased coronary flow velocity reserve and a short diastolic deceleration time, measured with intracoronary Doppler, have been found in TTC patients[32]. This findings have been supported by non-invasive studies, such as the assessment of coronary flow reserve through transthoracic Doppler, finding that in TTC patients, there is a transient impairment of the microcirculation at the acute phase, demonstrated by a reduced CFR[33]. Other studies have documented indirect signs of CMD, such as abnormal myocardial blush grade and TIMI frame count[13,34-36]. Such abnormalities have been found not only in the LAD subtended myocardial territory but also in the other main epicardial vessels, which may suggest that CMD may occur at multivessel level. Therefore, it seems that the coronary microvascular integrity is impaired, but what is not clear yet is if myocardial stunning is consequence of metabolic disorder or CMD[23]. Another relevant question is why other people subjected to stress conditions do not develop this syndrome. Some argue that TTC patients are unprotected at molecular level to facing the acute storm of cathecolamines within context of stress situation. Recently, d'Avenia *et al*[37] have found that mutation of BAG3, a gene involved in the epinephrine-induced apoptosis of altered cardiomyocytes, may play a role in the impaired response of myocardium to supraphysiological levels of cathecolamines.

There are many questions still unanswered. Nowadays, we do not know for sure why this disease predominantly affects postmenopausal women, but epidemiological data invite us to think that estrogens in women may play a protective role. Why the left ventricle apical segments are the most affected and why the basal segments behave hyperkinetic are issues not clearly answered today, but it is believed that heterogeneous distribution and variable response of beta-receptors along myocardial segments are involved[38,39].

Based on the myocardial dysfunction beyond one single coronary artery and the absence of concordant abnormalities in the epicardial arteries, the mechanism of myocardial stunning in TTC seems to overstep the frontiers of the epicardial coronary vessels, which lead us to search the cause in the coronary microcirculation or even at a molecular level.

DIAGNOSIS

Typical form of TTC affects the mid and apical segments of the left ventricle with compensatory hyperkinesis of the basal segments, but in any case, the myocardial wall motion abnormalities extend more than a single epicardial coronary artery distribution. Unlike what happens in ACS, the peak of troponin in TTC is disproportionately lower compared to the extent of the myocardial dysfunction. Ruling out severe obstructive coronary artery disease and acute plaque rupture must be a priority before diagnosing this syndrome. Currently, it is recognized that TTC is, by definition, a completely reversible disease. So, it is mandatory to confirm a full recovery of the ventricular wall motion abnormalities along follow-up. Table 3 shows the most recognized diagnosis criteria for this syndrome[15].

VARIANTS

The left ventricular dysfunction in TTC includes not only the classical apical ballooning form but also different angiographic patterns that have been increasingly reported along last decade (Figure 1). The "mid-ventricular shape" respects both the apex and base[40]. The "reversed takotsubo", in which there are wall motion abnormalities of the base and mid segments with preserved motion/hiperkinesis of the apex, is very rare[41]. Furthermore, some case reports have documented simultaneous abnormalities at both left and right ventricles up to in third of cases[42-44], but the isolated involvement of the

Table 3 Diagnosis criteria for takotsubo cardiomyopathy

Patients must satisfy all the following	
ECG	New abnormalities: ST-segment elevation and or T waves inversion
Blood test	Modest peak of troponin
Imaging	Transient wall motion abnormalities (with or without apical involvement) that extend beyond a single epicardial coronary artery
Angiography	Normal or near normal epicardial coronary arteries and no evidence of plaque rupture
Excluding other diseases	Pheochromocytoma, myocarditis

Based on Mayo Clinic Criteria (2008). ECG: Electrocardiographic.

right ventricle is very uncommon[45,46]. Recently, it was described the first case of "double takotsubo", in which the typical pattern was followed by the reversed type[47]. Thus, TTC may hit different myocardial walls, but in any case, this extends beyond a single epicardial coronary artery.

IMAGING TECHNIQUES IN TTC

Two-dimensional echocardiogram

This is an imperative imaging technique in the course of diagnosis and follow-up of TTC patients. Due to its ready availability, two-dimensional echocardiogram allows quantify the severity of the LVSD from the onset, which is usually not achieved with other imaging technique by time availability. This is key for supporting diagnosis, taking into account that sometimes the wall motion abnormalities improve very quickly (in some cases, it have been reported a complete recovery in less than 48 h)[48,49]. Dynamic left ventricular outflow tract obstruction (DLVOTO) due to systolic anterior motion (SAM) of mitral valve and intracavitary thrombi (mainly in the apex) are complications that can be early detected by this imaging technique, which determine specific strategies of treatment[50]. Moreover, advanced echocardiographic techniques, such as speckle-tracking and coronary flow assessment with transthoracic Doppler, are providing pathophysiologic insights about this syndrome[51].

Cardiac catheterization

Coronary angiography is warranted to exclude severe obstructive coronary disease as the cause of ventricular dysfunction. However, it is important to note that the presence of coronary atherosclerosis not exempt TTC. Indeed, near to 15% of patients has coronary artery disease[7,18]. Intracoronary imaging techniques, such as OCT, have been useful to definitively rule-out structural abnormalities in the epicardial vessels that may go unnoticed on angiography, including plaque rupture, eroded intimae, dissections or residual thrombus, supporting the need for searching an alternative pathophysiological mechanisms[27]. Left ventriculography has been traditionally used to describe the pattern of TTC (Figure 1).

CMR

This imaging technique has become an important tool to advance in understanding the pathophysiological mechanisms involved in TTC. The main contribution has been the demonstration of transient myocardial edema, mainly at the apex, which is related to the degree of ventricular dysfunction, even with the repolarization electrocardiographic abnormalities[52-56]. T2-weighted imaging has shown a non-coronary distributed apical edema without contrast enhancement, which confirms that myocardial abnormalities extend beyond one single coronary artery. In clinical practice CMR is key to exclude other differential diagnosis, such as myocarditis[57]. Recently, it has been found with CMR a profound diastolic dysfunction in the acute phase, that takes more time to resolve compared with the rapid recovery of the left ventricular systolic dysfunction[58].

Nuclear imaging: Single-photon emission computed tomography and positron emission tomography (PET) allow a precise assessment of myocardial perfusion and metabolism, ventricular function and even sympathetic innervations of the heart by using different radiotracers[59,60]. This techniques have been mainly used to study the pathophysiological mechanisms involved in TTC, showing that coronary flow reserve and myocardial blood flow are globally impaired, not only restricted to the dysfunctional segments, indicating a microcirculatory dysfunction at least in the acute phase[61].

ELECTROCARDIOGRAPHIC FEATURES OF TTC

T waves

In our experience, up to 90% of patients develop T waves inversion at some point of evolution. This is frequently seen from the onset (38.8%), either as single finding or with ST-segment abnormalities, but they typically appear when ST-segment begins to normalize. Compared with anterior-STEMI, negative T waves in TTC are usually deeper, wider and more diffuse, affecting a greater number of leads. In patients with inverted T waves from the onset without ST-segment elevation, the absence of negative T waves on V1 and positive T waves on aVR should raise suspicion of TTC[62]. T waves inversion is less frequently found on atypical forms[63].

ST-segment abnormalities and comparison with AMI

ST-segment elevation is the second most common finding observed in our large registry (62%)[14]. However, as it can be seen on Table 1, there is a different incidence along worldwide, which may be explained by ethnic variations or a more aggressive diagnostic approach in some countries[64]. Because the apical region of the left ventricle is the most affected, the ST-segment elevation is more frequently found on the LAD subtended myocardial territories[65], while it is uncommon in V1 because the right ventricle is respected mostly times. On the other

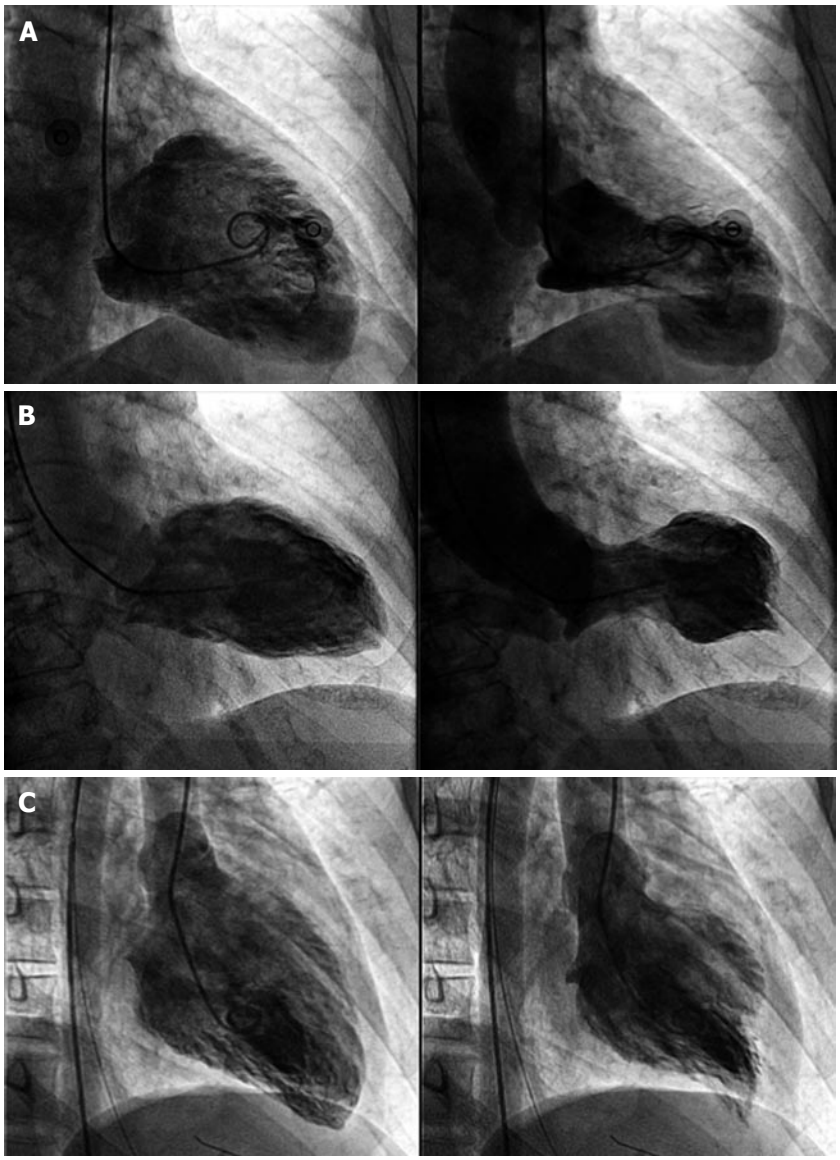

Figure 1 Left ventriculography showing different types of takotsubo cardiomyopathy. A: Takotsubo cardiomyopathy (TTC) typical form. On systole the left ventricle presents akinesis of the apex and hyperkinesis of the basal segments; B: Mid-ventricular variant. On systole the mid-segments are akinetic while the apical and basal segments are normal; C: "Inverted TTC". Basal and mid-segments are akinetic on systole while the apex is hyperkinetic.

hand, ST-segment reciprocal depression in the inferior leads is uncommon compared with anterior-STEMI[66]. Moreover, ST-segment depression as the unique find is the least frequent ECG abnormality on TTC, and is very uncommon compared with ACS[18].

Evolution of the ECG abnormalities

The repolarization changes follow a pattern very similar to STEMI, but the normalization of ST-segment and the appearance of T waves inversion usually occur more rapidly in TTC. Therefore, one can not rule out that patients presenting with T waves inversion in the first ECG, have previously had a short unnoticed phase with ST-segment elevation. In general, the evolution of the main ECG abnormalities described in TTC patients is, in order: ST-segment elevation, development of negative T waves while ST-segment is normalizing, and prolongation of QT-interval. The time to resolve both T waves inversion and prolonged QT-interval is highly variable, it could be take few weeks or several months[67]. Interestingly, the ECG abnormalities take more time to resolve than the wall motion impairment. Other electrocardiographic abnormalities have been described, including a high prevalence of low QRS voltage and attenuation of the amplitude of QRS complexes, which might help to support the suspicion of TTC[68].

QT-interval

Although a prolonged QT-interval is very common (47.7% by Templin *et al*[18]; 78.8% by Núñez *et al*[14]), the incidence of ventricular arrhythmias is very low, which highlight a benign prognosis of this form of acquired long QT-interval. Interestingly, Gopalakrishnan *et al*[69] found a strong correlation between prolonged-QTc interval at presentation and overall outcome.

Q-waves

Given the full recovery of myocardial damage, it is ex-

Table 4 Electrocardiographic findings in takotsubo cardiomyopathy

T waves inversion	ST-segment	QRS complex	Q waves
Are the most frequent finding along ECG evolution	Makes priority rule out obstructive coronary artery disease	aVR lead is especially sensible to changes in voltage because it "faces" the apex	Permanent pathological Q waves are exceptional
Appear mainly in precordial leads (V2-V6)	More frequent on precordial leads, except V1		
Negative T waves are deep, symmetrical and widespread	Reciprocal depression is less frequent than in STEMI		
Progressive QT-interval prolongation	Suspicious combinations: ST-depression in aVR plus no elevation in V1 (91% sensitivity, 96% specificity)[87] The sum of elevation in V4-V6/V1-V3 ⩾ 1 (77% sensitivity, 80% specificity)[65]		
No negative T wave in V1 plus positive T wave in aVR must raise suspicion (95% sensitivity, 97% specificity)[62]	Level of ST segment elevation lesser than in anterior STEMI		

ECG: Electrocardiogram; STEMI: ST-segment elevation myocardial infarction.

ceptional to find permanent pathological Q waves on previously normal hearts in patients with TTC[70].

The similarities between TTC and anterior-STEMI have aroused a great interest on scientific community in searching of electrocardiographic features that help to distinguish them from the onset[65,66,71,72]. Although some ECG signs have been described in patients with TTC (Table 4), more studies are needed, particularly prospective, rigorously comparing the electrocardiographic findings with anterior-STEMI[9]. Currently, there are no ECG signs which alone may rule out a culprit coronary artery stenosis[73]. Figure 2 shows an example of the most common ECG findings in TTC patients.

Arrhythmias

Incidence and type of arrhythmias observed in different TTC series varies widely, but it has in common that usually resolve after overcoming the acute setting. In our registry, paroxysmal atrial fibrillation is the more common sustained tachyarrhythmia (11%). Sinus bradycardia and different degrees of atrioventricular block have been observed. Ventricular arrhythmias such as ventricular tachycardia (4.8%) and ventricular fibrillation (VF) (0.7%) are uncommon in the acute phase in our experience[14], which is concordant with other observational studies[18]. Torsades de pointes have rarely been reported. However, among patients with TTC who present prolonged QT-interval, male sex has been associated with more risk of Torsades de pointes, as well as severe left ventricular systolic dysfunction, bradycardia, hypokalemia and use of QT-prolonging agents[74]. Some patients debut with sudden death due to VF[75,76], although in these cases it is unclear if VF is a trigger or consequence of TTC[77].

TREATMENT

Because pathophysiologic mechanisms are not clear yet, there is no consensus on specific treatment to this condition. In fact, treatment consists mainly on treatment of heart failure and its complications. Based on the theory of high catecholamine levels, use of beta-blockers seems reasonable, but caution must be taken due to the high frequency of heart failure on these patients[78]. However, it is striking that in some case series a significant percent of patients were on treatment with beta-blockers at the time of debut. Furthermore, in patients with recurrences, there are no differences regarding incidence among those who were being treated with beta-blockers and those without. Beta-blockers do not appear to have a protective effect for this syndrome based on these results[18,79].

Anticoagulation is indicated to the management of ventricular thrombus and should be maintained at least until confirm its resolution. it must be considered an early anticoagulation therapy irrespective of the presence of ventricular thrombus at admission, specially in patients with high risk of thromboembolic events[9,80].

Patients with hemodynamic instability may require positive inotropic drugs and circulatory support devices such as intra-aortic balloon pump counterpulsation or extracorporeal life support in case of refractory cardiogenic shock. However, it is not clear the benefit of exogenous catecholamines taking into account the pathophysiology of this syndrome, so positive inotropic drugs should be used with caution with the minimum dose required to maintaining an acceptable hemodynamic status[78,81].

Echocardiography is very useful to guide the treatment in patients with TTC. In presence of DLVOTO, SAM and hemodynamic instability, beta-blockers and/or intravenous fluids are preferred (in absence of significant pulmonary congestion) instead of positive inotropic drugs[9,82-84].

Typically, TTC patients are initially treated with the standard of care for ACS at the moment of presenting to the emergency department, due to the similarities among these two diseases. This decision implies that TTC patients must receive dual antiplatelet and anticoagulation therapy until coronary angiography is

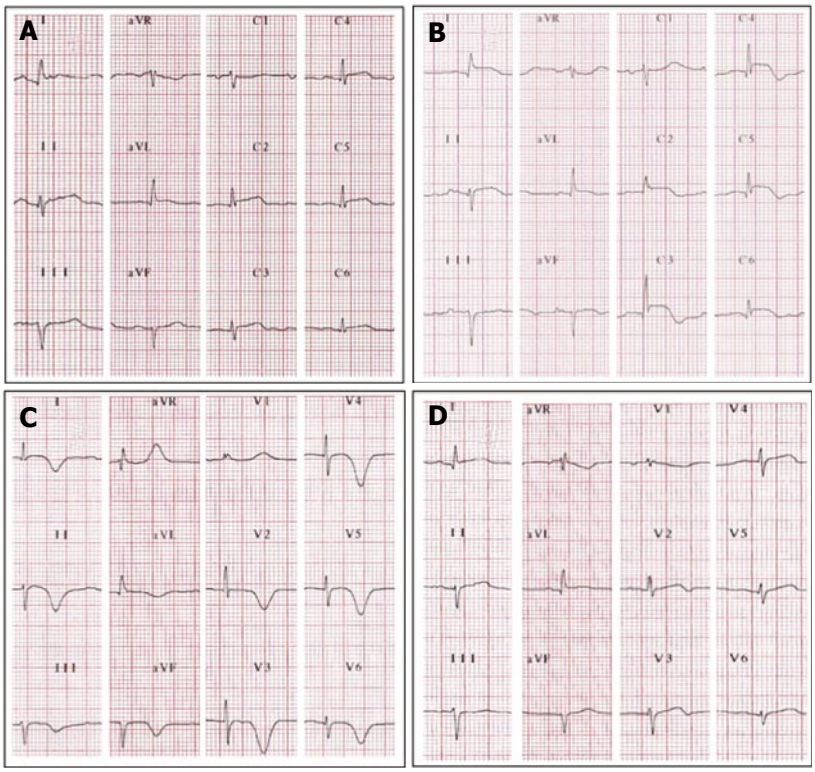

Figure 2 Electrocardiographic evolutionary changes in a 65-year-old woman with typical takotsubo cardiomyopathy. A: Initial electrocardiographic (ECG) after 3 h of symptoms. There is diffuse ST-segment elevation (DI, aVL and all precordial leads except on V1); B: ECG after 24 h of symptoms. The ST-segment elevation seems to be more prominent. Note ST-segment depression on aVR. The T waves start to invert on leads with ST-segment elevation, except on V1 where there is a more prominent positive T wave; C: Third day. The ST-segment is almost normal. The T waves are now inverted, deep, wide and symmetrical on all leads except on aVR and V1 where they are positive. The corrected QT-interval is prolonged (520 milliseconds); D: ECG 3 wk later, outpatient. The T waves are almost normal and the QT-interval is not prolonged.

performed and culprit coronary obstructive disease is discarded.

Finally, angiotensin-converting-enzyme inhibitors and angiotensin-receptor blockers have been associated with better survival[18].

PROGNOSIS

By definition, TTC left ventricular dysfunction is completely reversible. The involvement of the right ventricle is occasional. Serious complications and recurrences are infrequent. So, TTC has been traditionally considered as a benign cardiac syndrome in absence of significant comorbid conditions[79,85,86]. However, this syndrome significantly contributes to morbidity and mortality. Some recent large observational studies have shown that TTC has a poorer prognosis than it was believed, comparable with ACS[7,18], and related to the patient's risk profile such as frailty and associated comorbidities. Templin *et al*[18] found that elderly patients with emotional triggers have a low risk of significant cardiovascular events, while younger patients with physical triggers and acute neurologic or psychiatric diseases have an increased risk of acute complications. The risk of mortality seems to be higher in men and patients with underlying critical illness[8].

The recurrence of TTC is low; Elesber *et al*[79] have reported an average yearly recurrence rate of 2.9% in the first few years, decreasing later to 1.3% per year, which is similar to the recurrence rate reported by Templin *et al*[18] (1.8% per patient-year).

CONCLUSION

TTC is a wide spectrum syndrome that clinically mimics an ACS in absence of significant epicardial coronary artery disease to explain the extent of the wall motion abnormalities. Nowadays, there have not been clearly identified electrocardiographic signs to reliably differentiate TTC from ACS in the acute phase. Therefore, knowledge of the coronary anatomy is mandatory. The pathophysiological mechanism is not well understood, but it seems that an intense release of catecholamines triggers myocardial stunning. In the midway, CMD and abnormalities on myocardium metabolism have been highlighted as potential involved mechanisms. Treatment in the acute phase should be directed to treat complications, including heart failure, arrhythmias and ventricular thrombus, while long-term medical therapy remains empirical due to limited available data. Although it was thought that prognosis is good, it seems increasingly evident that TTC patients may have poorer outcomes, even similar with patients with ACS. Angiotensin-converting-enzyme inhibitors and angiotensin-receptor

blockers have been associated with improved survival. We need more rigorous prospective studies to continue on the way of understanding this enigmatic disease.

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ORIGINAL ARTICLE

Retrospective Cohort Study

Impact of clinical and procedural factors upon C reactive protein dynamics following transcatheter aortic valve implantation

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Abstract

AIM: To determine the effect of procedural and clinical factors upon C reactive protein (CRP) dynamics following transcatheter aortic valve implantation (TAVI).

METHODS: Two hundred and eight consecutive patients that underwent transfemoral TAVI at two hospitals (Imperial, College Healthcare NHS Trust, Hammersmith Hospital, London, United Kingdom and San Raffaele Scientific Institute, Milan, Italy) were included. Daily venous plasma CRP levels were measured for up to 7 d following the procedure (or up to discharge). Procedural factors and 30-d safety outcomes according to

the Valve Academic Research Consortium 2 definition were collected.

RESULTS: Following TAVI, CRP significantly increased reaching a peak on day 3 of 87.6 ± 5.5 mg/dL, $P < 0.001$. Patients who developed clinical signs and symptoms of sepsis had significantly increased levels of CRP ($P < 0.001$). The presence of diabetes mellitus was associated with a significantly higher peak CRP level at day 3 (78.4 ± 3.2 *vs* 92.2 ± 4.4, $P < 0.001$). There was no difference in peak CRP release following balloon-expandable or self-expandable TAVI implantation (94.8 ± 9.1 *vs* 81.9 ± 6.9, $P = 0.34$) or if post-dilatation was required (86.9 ± 6.3 *vs* 96.6 ± 5.3, $P = 0.42$), however, when pre-TAVI balloon aortic valvuloplasty was performed this resulted in a significant increase in the peak CRP (110.1 ± 8.9 *vs* 51.6 ± 3.7, $P < 0.001$). The development of a major vascular complication did result in a significantly increased maximal CRP release (153.7 ± 11.9 *vs* 83.3 ± 7.4, $P = 0.02$) and there was a trend toward a higher peak CRP following major/life-threatening bleeding (113.2 ± 9.3 *vs* 82.7 ± 7.5, $P = 0.12$) although this did not reach statistical significance. CRP was not found to be a predictor of 30-d mortality on univariate analysis.

CONCLUSION: Careful attention should be paid to baseline clinical characteristics and procedural factors when interpreting CRP following TAVI to determine their future management.

Key words: Aortic stenosis; Transcatheter aortic valve implantation; C reactive protein; Inflammation

Core tip: Transcatheter aortic valve implantation (TAVI) results in increases in serum C reactive protein (CRP) levels reaching a peak at day 3 in all patients. CRP increase is further increased in patients with diabetes mellitus, those that underwent pre-TAVI balloon aortic valvuloplasty and patients that suffered major vascular complications. In addition to the bedside evaluation of patients, careful attention should be paid to baseline clinical characteristics and procedural factors when interpreting CRP to aid in the management and risk assessment of patients following TAVI.

Ruparelia N, Panoulas VF, Frame A, Ariff B, Sutaria N, Fertleman M, Cousins J, Anderson J, Bicknell C, Chukwuemeka A, Sen S, Malik IS, Colombo A, Mikhail GW. Impact of clinical and procedural factors upon C reactive protein dynamics following transcatheter aortic valve implantation. *World J Cardiol* 2016; 8(7): 425-431 Available from: URL: http://www.wjgnet.com/1949-8462/full/v8/i7/425.htm DOI: http://dx.doi.org/10.4330/wjc.v8.i7.425

INTRODUCTION

Aortic stenosis (AS) is the most common valvular pathology in the elderly population with a prevalence of approximately 4.6% in patients greater than 75 years of age[1]. Whilst asymptomatic AS is associated with a low mortality[2], in those who develop symptoms, prognosis is very poor with a mortality of 50% within 2 years without treatment[3]. Whilst surgical aortic valve replacement (SAVR) remains the "gold standard" treatment, many of these elderly patients present with many co-existent comorbidities that render them inoperable or high-risk for SAVR. The emergence of transcatheter aortic valve implantation (TAVI) has revolutionised the treatment of these patients[4-8]. The transfemoral (TF) route is now the preferable TAVI vascular route due to shorter procedure and recovery times, and better clinical outcomes[9].

In spite of TAVI being less invasive, these frail, elderly patients are at increased risk of developing complications resulting in adverse outcomes. Post-procedural infection is a potentially life-threatening complication and has been reported to occur in approximately 20% of all patients[10,11]. In combination with the clinical evaluation of patients, the C reactive protein (CRP), an acute phase protein synthesized and released by the liver is commonly measured to aid in diagnosis. However, the CRP is non-specific for infection and misinterpretation can result in misdiagnosis, inappropriate antibiotic therapy (and associated adverse effects) and prolonged in-hospital stay.

CRP is also a measure of inflammation that is thought to play a critical role in both the underlying pathogenesis of AS[12,13] with persistently high levels of circulating plasma inflammatory proteins following aortic valve intervention associated with increased cardiovascular and all-cause mortality[14,15]. SAVR results in greater activation of inflammatory pathways in comparison to TAVI with the TF access route being associated with the most attenuated inflammatory response[16]. Understanding CRP dynamics following TF TAVI is therefore critical in both the post-procedural management of these patients and predicting outcome.

The aim of this study was therefore to characterise CRP dynamics following TF TAVI and to identify clinical or procedural factors that may impact upon them.

MATERIALS AND METHODS

Study population

Consecutive patients that underwent TF TAVI at two hospitals (Hammersmith Hospital, Imperial College Healthcare NHS Trust, London, United Kingdom and San Raffaele Scientific Institute, Milan, Italy) were included. All patients were treated for native severe AS with patients treated with TAVI devices for aortic regurgitation and for bioprosthesis degeneration excluded. A dedicated multidisciplinary "Heart Team" consisting of interven-

Table 1 Baseline patient characteristics

Variable	All patients (n = 208)
Age (yr)	81.4 ± 0.9
Female (%)	57 (27.4)
Diabetes mellitus (%)	34 (16.3)
Hypertension (%)	122 (58.7)
Dyslipidemia (%)	65 (31.3)
History of smoking (%)	34 (16.3)
NYHA Ⅲ or Ⅳ (%)	94 (45.2)
Previous MI (%)	24 (11.5)
Previous CABG (%)	37 (17.8)
Previous PCI (%)	40 (19.2)
Cerebrovascular disease (%)	19 (9.1)
eGFR < 60 mL/min per 1.73 m^2 (%)	42 (20.2)
Logistic EuroScore (%)	14.8 ± 1.4

NYHA: New York Heart Association; MI: myocardial infarction; CABG: Coronary artery bypass grafting; PCI: Percutaneous coronary intervention; eGFR: Estimated glomerular filtration rate.

tional cardiologist, cardiac surgeons, imaging specialists, general physicians and cardiac anaesthetists, discussed the management of all patients. All patients included in the study were of high surgical risk or inoperable on the basis of surgical risk scores (*e.g.*, Euroscore) and clinical judgement to allow for other patient factors including frailty.

Daily venous plasma CRP levels were measured for up to 7 d following the procedure (or up to discharge) using.

Informed consent was provided by all patients for the procedure, subsequent clinical follow-up and analysis of data collected.

TAVI procedure

Pre-operatively, all patients were evaluated with multi-slice computed tomography or invasive angiography to determine the presence or absence of coronary artery disease and for the characterisation of the peripheral vasculature. The choice of prosthesis (balloon expandable Edwards Sapien XT or Sapien 3 (Edwards LifeSciences, Irvine, CA, United States) or self-expandable Medtronic CoreValve or Evolut R (Medtronic, Minnesota, MN, United States) and size was at the operator's discretion. Patients treated with other devices were excluded due to their unavailability at both sites. At the time of TAVI, no patients had any clinical signs, symptoms of biochemical evidence of infection. All procedures were carried out under general anaesthesia or conscious sedation provided by a cardiac anaesthetist and were performed when possible by a fully percutaneous approach utilizing the cross-over technique and suture-mediated closure devices (Proglide and Prostar, Abbott Laboratories, IL, United States). Antibiotics were not administered to any patient routinely during the peri-operative period.

Patient follow-up

Procedural outcomes in-hospital clinical outcomes were prospectively collected in a dedicated TAVI database. Longer-term follow-up was conducted by clinic visits. All definition of the clinical endpoints used were in concordance with the Valve Academic Research Consortium 2 (VARC-2) definitions[17]. Patients were deemed to have infection on the basis of clinical symptoms (*e.g.*, dysuria), signs of infection (*e.g.*, fever) and objective evidence (*e.g.*, elevated white cell count, positive blood culture). The administration and choice of antibiotics was at the discretion of the treating physician.

Statistical analysis

Continuous variables are presented as the mean ± standard error of the mean. Normality of each continuous variable was tested with the Kolmogorov-Smirnov test and differences were compared using the paired *t*-test. Categorical variables are presented as numerical values and percentages and were compared using the Fisher's exact test. Cox proportional hazards regression analysis was performed to determine predictors of mortality. Receiver-operator characteristic (ROC) analysis was performed to identify the threshold for CRP as a binary classifier. All reported *P*-values were 2-sided, and values of $P < 0.05$ were regarded as statistically significant. Analyses were performed with SPSS version 21.0 (SPSS Inc., Chicago IL, United States) and GraphPad Prism version 5.0 (GraphPad, San Diego, CA, United States).

RESULTS

Patient population

Two hundred and eight patients underwent TF TAVI at both institutions during the study period and were included in the final analysis. The baseline characteristics of all patients are summarised in Table 1. As expected, the patient group were elderly (age: 81.4 ± 8.5 years) and of high surgical risk standard Euroscore 14.8% ± 10.4%.

Procedural characteristics and outcomes

All patients underwent TF TAVI with an overall procedural success rate of 98.1%. Procedural characteristics are summarised: Forty-nine percent of patients received a balloon expandable device [Edwards Sapien XT (27.4%) and Edwards Sapien 3 (21.6%)] and 51% of patient received a self-expandable prosthesis [Medtronic Corevalve (37.5%) and Medtronic Evolut R (13.9%)]. Seventy-three (35.1%) patients underwent pre-TAVI balloon aortic valvuloplasty (BAV). Thirty-seven patients (17.8%) required post-dilatation following TAVI for AR with 27 patients (13%) with residual grade ⩾ 2 AR at the end of the procedure. Four patients (1.9%) required emergency cardiac surgery, one patient for coronary artery obstruction, two patients for left ventricular perforation and one patient for right ventricular perforation following temporary wire placement. There were 10 (4.8%) peri-procedural deaths. Thirty-day outcomes according to the VARC-2 criteria are summarised in Table 2.

CRP dynamics

The baseline CRP (measured in 87.7% of patients) was

Table 2 Thirty-day outcomes

	All patients (n = 208)
All-cause death	12 (5.8)
Coronary obstruction (%)	1 (0.05)
Stroke	9 (4.3)
PPM implantation	38 (18.3)
Minor vascular complication	8 (3.8)
Major vascular complication	8 (3.8)
Minor bleed	34 (16.3)
Major bleed	23 (11.1)
Life-threatening bleeding	8 (3.8)
Valve related dysfunction	0 (0)

PPM: Permanent pacemaker implantation.

8.9 ± 2.5 mg/dL for total study population. Following TAVI this significantly increased reaching a peak on day 3 of 87.6 ± 5.5 mg/dL (measured in 77.6% of patients), $P < 0.001$ (Figure 1A). As would be expected, patients who developed clinical signs and symptoms of sepsis had significantly increased levels of CRP (n = 8) when compared to all patients which at day 3 was 187.7 ± 6.1 representing a 21-fold increase when compared to baseline levels ($P < 0.001$, Figure 1B).

Clinical impact upon CRP dynamics

Following exclusion of patients with clinical evidence of infection, peak (day 3) CRP levels were compared to determine the impact of baseline clinical factors upon maximal CRP release following TAVI. The presence of diabetes mellitus was associated with a significantly higher peak CRP level at day 3 (78.4 ± 3.2 *vs* 92.2 ± 4.4, $P < 0.001$). The presence of hypertension (75.2 ± 4.1 *vs* 93.1 ± 3.2, $P = 0.22$), previous PCI (70.6 ± 3.9 *vs* 82.2 ± 5.2, $P = 0.39$), previous cardiac surgery (87.4 ± 3.1 *vs* 93.9 ± 3.4, $P = 0.65$) or smoking (99.6 ± 3.7 *vs* 78.1 ± 3.3, $P = 0.31$) did not impact upon the peak CRP following TAVI.

Procedural impact upon CRP dynamics

There was no difference in peak CRP release following balloon-expandable or self-expandable TAVI implantation (94.8 ± 9.1 *vs* 81.9 ± 6.9, $P = 0.34$) or if post-dilatation was required (86.9 ± 6.3 *vs* 96.6 ± 5.3, $P = 0.42$). There was a difference in maximal CRP release when pre-TAVI balloon aortic valvuloplasty was performed (110.1 ± 8.9 *vs* 51.6 ± 3.7, $P < 0.001$). Peak CRP was not found to be different between patients with residual $\geqslant$ 2 AR and those that had residual < 2 AR (71.9 ± 7.4 *vs* 88.9 ± 7.9, $P = 0.28$). The development of a major vascular complication did result in a significantly increased maximal CRP release (153.7 ± 11.9 *vs* 83.3 ± 7.4, $P = 0.02$) and there was a trend toward a higher peak CRP following major/life-threatening bleeding (113.2 ± 9.3 *vs* 82.7 ± 7.5, $P = 0.12$) although this did not reach statistical significance.

CRP as a predictive tool

Both CRP levels at baseline [hazard ratio (HR) per unit increase 0.98, 0.94-1.03, $P = 0.42$] and peak levels at day 3 (HR per unit increase: 1.01, 0.98-1.02, $P = 0.18$) were not found to be predictors of 30-d mortality on univariate analysis. We also did not find the magnitude of change in CRP (the difference between peak and baseline levels) to be a predictor of 30-d mortality (HR per unit increase: 0.92, 0.83-1.14, $P = 0.33$). ROC analysis further confirmed that both baseline [area under the curve (AUC): 0.42] and peak levels (AUC: 0.48) of CRP was a poor predictive tool for 30-d mortality in this study population.

DISCUSSION

The principal findings are: (1) CRP universally increases following TAVI reaching a peak at day 3; (2) the presence of diabetes mellitus was associated with a significant increase in the peak CRP following TAVI; (3) procedurally, the use of balloon aortic valvuloplasty during the procedure and the development of a major vascular complication resulted in a significant increase in the peak CRP; and (4) the peak CRP did not predict 30-d adverse outcomes.

Inflammation plays a central role in the pathogenesis and progression of AS[13,18,19]. The treatment of AS also results in activation of inflammatory pathways with more invasive treatment options (*e.g.*, SAVR) associated with more inflammation in comparison to less invasive treatment options (*e.g.*, TF TAVI)[16]. In addition to the magnitude of inflammation, persistently elevated markers of inflammation have been shown to be negatively associated with outcomes including mortality[14,20,21]. In agreement with previous reports, we found that CRP increased in all patients following TF TAVI reaching a peak level at day 3[16,22].

CRP in diabetes mellitus has been shown to be a predictor of cardiovascular events and outcomes[23,24]. After excluding patients with clinical signs and symptoms of infection we found that the presence of diabetes mellitus resulted in a significantly increased peak release in CRP following TAVI. This may explain worse outcomes in this patient sub-group[25] and should be considered when interpreting CRP results following TAVI and also when counselling patients with regards to risk pre-procedurally. We did not find any other baseline clinical characteristic (*e.g.*, smoking, hypertension) to have an impact upon CRP dynamics following TAVI.

The impact of specific procedural factors upon CRP dynamics is poorly characterised in patients undergoing TF TAVI. We did not find a difference in the peak CRP between patients that were treated with a BE or SE valve possibly suggesting that they are both equally traumatic. Interestingly, the use of pre-implantation BAV was associated with a significant increase in the peak CRP at

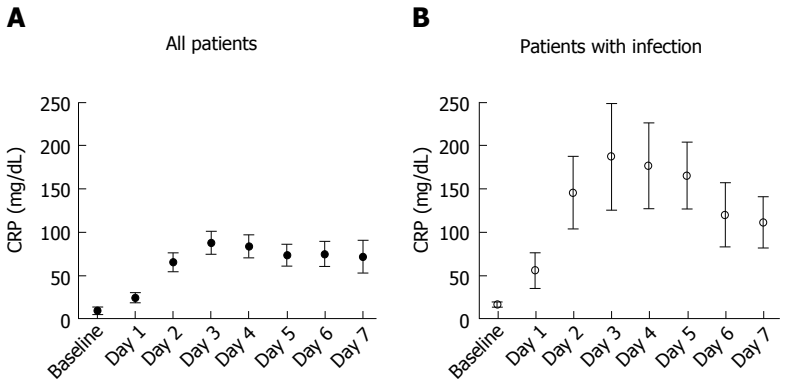

Figure 1 C reactive protein dynamics following transcatheter aortic valve implantation. C reactive protein (CRP) dynamics of total patent study population (A) and between patients who had clinical signs and symptoms of infections and those that did not (B).

day 3, whilst the requirement for post-dilatation or the extent of residual AR did not impact upon maximal CRP release. This finding may represent the increased trauma to the native valvular apparatus and systemic debris shower resulting in greater release of CRP, although this may also reflect disease severity of the native valve that required a BAV rather than direct valvular implantation. Nonetheless, it is important for physicians managing patients following TAVI to be aware of the procedural specifics when interpreting CRP results in the post-operative period.

Unsurprisingly, the development of a major vascular complication resulted in a greater release of CRP, likely reflecting further trauma associated with peripheral vessel intervention and also longer procedural times. The requirement for a blood transfusion, in our study population, did not impact upon CRP dynamics in the post-procedural period.

CRP has been shown to be a useful prognostic tool[22] following TAVI, however in our study population, this was not found to be the case, possibly due to the relative small numbers of patients and short follow-up.

Study limitations

This study has some limitations. This was a retrospective study with treatment strategy (*e.g.*, prosthesis selection, use of BAV) at the operator's discretion and so the effect of selection bias cannot be excluded. Patient numbers were relatively small with limited follow-up and so the study may be underpowered to detect the predictive value of CRP upon outcomes. Finally, we did not measure the role of other markers of inflammation that in combination with CRP may have augmented its usefulness, although this study reflects routine clinical practice and makes the results directly applicable to a contemporary TAVI service.

In conclusion, TAVI results in increases in serum CRP levels reaching a peak at day 3 in all patients. CRP increase is further increased in patients with diabetes mellitus, those that underwent pre-TAVI BAV and patients that suffered major vascular complications. In addition to the bedside evaluation of patients, careful attention should be paid to baseline clinical characteristics and procedural factors when interpreting CRP to aid in the management and risk assessment of patients following TAVI.

COMMENTS

Background

Transcatheter aortic valve implantation (TAVI) is now the established treatment of choice for the management of patients presenting with severe symptomatic aortic stenosis (AS) who are deemed inoperable or of high surgical risk. The post-procedural management of these patients is complex due to their concomitant co-morbidities. In combination with the clinical evaluation of patients, the C reactive protein (CRP), is commonly measured to aid in diagnosis. However, the CRP is non-specific for infection and misinterpretation can result in misdiagnosis, inappropriate antibiotic therapy (and associated adverse effects) and prolonged in-hospital stay. Understanding CRP dynamics following TAVI is therefore critical in the post-procedural management of these patients.

Research frontiers

The role of inflammation in both the pathogenesis of AS and its roles in repair, recovery and predicting outcomes following TAVI are currently important areas of investigation in this area.

Innovations and breakthroughs

This study demonstrates that CRP levels increase in all patients following TAVI but we here identify both specific patient and procedural factors that may result in a greater magnitude of change in CRP, that should be considered in the management of these complex patients in the post-operative period.

Applications

The findings of this study highlight the importance of taking into consideration not only the clinical condition of the patient but also baseline patient characteristics and procedural factors when interpreting CRP levels following TAVI. Into the future, research will focus on interventions to reduce inflammation peri- and post-procedurally to investigate if this will have an effect on outcomes.

Terminology

TAVI is a technique by which a bioprosthetic aortic valve can be implanted in a minimally invasive fashion by delivering a catheter-mounted valve to the aortic annulus. The CRP is an acute phase protein synthesized and released by the liver.

Peer-review

The study was nicely executed and the text is well written.

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CASE REPORT

Rare presentation of intralobar pulmonary sequestration associated with repeated episodes of ventricular tachycardia

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Author contributions: Rao DS had suggested the line of management; Barik R had done the procedure and written the manuscript.

Institutional review board statement: This case report was won the approval of the institutional ethical committee and the Review Board standards at Nizam's Institute of Medical Sciences, Hyderabad, India.

Informed consent statement: The patient involved in this study gave her written informed consent authorizing use and disclosure of her protected health information.

Conflict-of-interest statement: None.

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Abstract

Arterial supply of an intralobar pulmonary sequestration (IPS) from the coronary circulation is extremely rare. A significant coronary steal does not occur because of dual or triple sources of blood supply to sequestrated lung tissue. We present a 60-year-old woman who presented to us with repeated episodes of monomorphic ventricular tachycardia (VT) in last 3 mo. Radio frequency ablation was ineffective. On evaluation, she had right lower lobe IPS with dual arterial blood supply, *i.e.*, right pulmonary artery and the systemic arterial supply from the right coronary artery (RCA). Stress myocardial perfusion scan revealed significant inducible ischemia in the RCA territory. Coronary angiogram revealed critical stenosis of proximal RCA just after the origin of the systemic artery supplying IPS. The critical stenosis in the RCA was stented. At 12 mo follow-up, she had no further episodes of VT or angina.

Key words: Coronary steal; Coronary artery disease; Ventricular tachycardia; Angioplasty; Intralobar pulmonary sequestration

Core tip: The intralobar pulmonary sequestration (IPS) of right lower lobe of the lung (RLL) is less than 10% of all the pulmonary sequestration. It is rare to encounter that right coronary artery is being the source of systemic arterial supply to IPS of RLL. This anomalous artery was the reason for ischemia in the area subtended by right

coronary artery (RCA) by coronary steal phenomenon. A significant stenosis of RCA just distal to origin of the anomalous artery supplying the IPS is extremely rare which was further worsening ischemia by incremental steal. We felt excessive stealing from RCA was the reason for ischemic ventricular tachycardia in this patient. Angioplasty of right coronary stenosis relieved ischemia in the area subtended by RCA by removing obstruction and reducing coronary steal.

Rao DS, Barik R. Rare presentation of intralobar pulmonary sequestration associated with repeated episodes of ventricular tachycardia. *World J Cardiol* 2016; 8(7): 432-435 Available from: URL: http://www.wjgnet.com/1949-8462/full/v8/i7/432.htm DOI: http://dx.doi.org/10.4330/wjc.v8.i7.432

INTRODUCTION

Pulmonary sequestration consists 0.5%-6.4% of all congenital malformation of lung[1]. Intralobar pulmonary sequestration (IPS) accounts for 75%-90% of the total pulmonary sequestration[1,2]. Right lower lobe is involved in 20% of cases of IPS[3]. The non-functioning mass of lung tissue that lacks normal communication with the tracheobronchial tree is supplied by systemic circulation (nutritional branches from abdominal or thoracic aorta) or dual arterial supply (systemic artery and pulmonary artery)[4] or triple arterial supply (systemic, pulmonary and bronchial artery)[5]. Pulmonary sequestration supplied by a normal coronary artery is extremely rare with significant coronary steal[6] or coronary artery disease[7]. Right coronary artery (RCA) is very rarely being the source of blood supply when compared to the left circumflex coronary artery.

CASE REPORT

A 60-year-old female was referred to us for repeated episodes of monomorphic ventricular tachycardia (VT) in the last 12 mo. She had undergone recently radiofrequency ablation (RFA) for VT. Coronary angiogram prior to RFA was reported to have mild RCA disease as was mentioned in referral slip. Her past history reveals she was a known case of right lower lobe IPS accidentally detected in contrast enhanced computed tomography (CECT) of chest when she was under evaluation for right lower lobe pneumonia. The detail of arterial supply to sequestration was evident from the report of past CECT chest. At admission, 12 leads electrocardiography and echocardiogram were normal. A chest X-ray revealed nonhomogenous opacity of right lower lobe. Myocardial stress perfusion scan was positive for inducible ischemia in the RCA territory. Her coronary angiogram showed critical stenosis of proximal dominant RCA (Figure 1A). The anomalous artery to the right sided IPS was just before the critical RCA stenosis (Figure 1B). The follow-up in levophase confirmed normal pulmonary venous drainage [Video core tip: Selective RCA angiogram in left anterior oblique 48 degrees (LAO 48°) showed the normal venous drainage from IPS to right lower pulmonary vein]. The lesion in RCA was stented using a drug eluting stent, 3 mm × 12 mm, Xience V (Abbott's Vascular) with predilatation with a noncompliant coronary balloon (Figure 2). Angioplasty of right coronary stenosis relieved ischemia in the area subtended by RCA by removing obstruction to forward flow and coronary steal. At 12 mo follow-up, she had no further episodes of VT and angina. The elective resection of IPS was planned in future as the patient was not willing to undergo surgery at present.

DISCUSSION

In most cases, IPS has a single feeding artery. Sometimes, there are multiple systemic arteries supply to IPS. Arterial supply of pulmonary sequestration mainly originates from thoracic aorta (46.1%-86.1%) and abdominal aorta (6.9%-31.6%)[8-10]. The other feeders are intercostal artery, phrenic artery, branches from aortic arch, subclavian artery, pulmonary artery, left gastric artery, coronary artery, celiac trunk and renal artery[8-10]. Several complications related to IPS include recurrent pulmonary infections, haemoptysis and heart failure from persistent left-to-right shunt. The natural history of sequestration supplied by a coronary artery remains unknown because of rare incidence. In absence of complications, surgical resection is controversial[11] and the exact timing of such surgery is not known[12]. A recent series suggest surgical resection is safe in such cases because of very lower complication rate[13]. Recently, some researchers suggest to resect the sequestration to avoid unpredictable fatal haemoptysis[14]. Surgical resection is recommended for recurrent pulmonary infections or coronary steal. In our case, the detection of IPS was incidental, *i.e.*, detection during evaluation for pneumonia. Significant coronary artery disease of the of the feeder that nourishes IPS is extremely rare[15]. The unique finding in our case was significant coronary steal due to critical stenosis of RCA just distal to the origin of artery which was feeding IPS contributing to significant ischemia in the area subtended by RCA which is the very reason for ischemic VT in our case. The various management approaches in a case are option 1: Surgical resection of IPS, ligation of abnormal feeder t and distal RCA graft; option 2: Angioplasty of RCA and elective resection of IPS with ligation of feeder; or option 3: Coil embolization of feeder artery during angioplasty of RCA and elective resection of sequestration. The patient was not willing for lung surgery during current admission, therefore, the best option was coiling of feeder to IPS during angioplasty of RCA. As there was one episode of pneumonia in our patient, we proceeded with the angioplasty of RCA which was the needed most at the time presentation. Therefore, our future plan for our patient is ligation of the

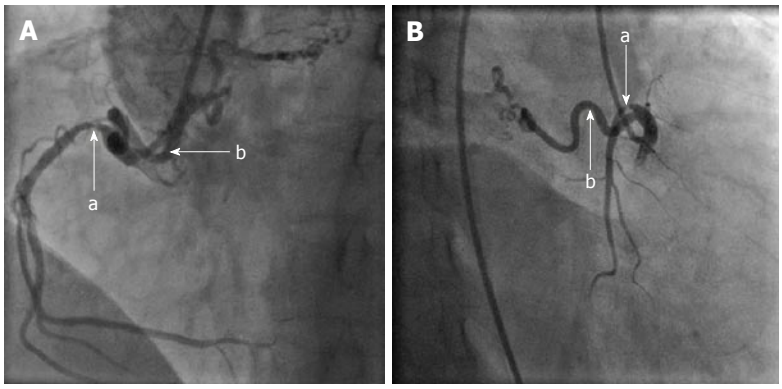

Figure 1 Selective right coronary angiogram from right femoral approach in left anterior oblique 48 degrees and right posterior caudal view showed tight right coronary artery (A) and aberrant blood supply to right lower lobe intralobar sequestration which the branch of right coronary artery (B).

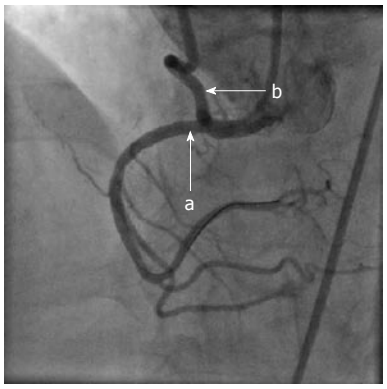

Figure 2 Selective right coronary angiogram after stenting the proximal lesion left anterior oblique 48 degrees (a) which resulted in significant reduction of flow in aberrant blood supply to right lower lobe intralobar sequestration (b).

feeder artery during the resection of IPS.

COMMENTS

Case characteristics

This is 62-year-old female with previous diagnosis of intralobar sequestration of right lower lobe presented with repeated episodes of ventricular tachycardia (VT) without any response to radiofrequency ablation therapy.

Clinical diagnosis

Repeated episodes of VT.

Differential diagnosis

Coronary artery disease, ischemic VT, idiopathic VT and cardiomyopathy.

Laboratory diagnosis

Right lower lobe intrapulmonary sequestration associated with critical stenosis of right coronary artery (RCA).

Imaging diagnosis

Selective coronary angiogram confirms the diagnosis of critical RCA stenosis associated a branch of right coronary supplying right intralobar pulmonary sequestration (IPS).

Pathological diagnosis

Contrast enhanced computed tomography is suggestive of right lower lobe intrapulmonary sequestration.

Treatment

RCA angioplasty with future plan of resection of intrapulmonary sequestration.

Related reports

Symptomatic IPS should undergo elective surgical resection with ligation of systemic arterial supply to the sequestrated lung.

Term explanation

Pulmonary sequestration is a rare congenital malformation of the lower respiratory tract. It consists of a nonfunctioning mass of normal lung tissue that lacks normal communication with the tracheobronchial tree, and that receives its arterial blood supply from the systemic circulation. It is of three types: IPS, extralobar pulmonary sequestration and bronchopulmonary-foregut malformation.

Experiences and lessons

RCA as source of systemic blood supply to the right IPS is rare. If the same coronary artery acquires coronary artery stenosis distal to the systemic feeder artery to sequestration, it further worsens the ischemia in the RCA territory. The resection of sequestrated lung, ligation of systemic artery to sequestration and coronary artery bypass graft is the ideal treatment in such situation.

Peer-review

This is an interesting and very unusual case.

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REVIEW

Renal sympathetic denervation in therapy resistant hypertension - pathophysiological aspects and predictors for treatment success

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Abstract

Many forms of human hypertension are associated with an increased systemic sympathetic activity. Especially the renal sympathetic nervous system has been found to play a prominent role in this context. Therefore, catheter-interventional renal sympathetic denervation (RDN) has been established as a treatment for patients suffering from therapy resistant hypertension in the past decade. The initial enthusiasm for this treatment was markedly dampened by the results of the Symplicity-HTN-3 trial, although the transferability of the results into clinical practice to date appears to be questionable. In contrast to the extensive use of RDN in treating hypertensive patients within or without clinical trial settings over the past years, its effects on the complex pathophysiological mechanisms underlying therapy resistant hypertension are only partly understood and are part of ongoing research. Effects of RDN have been described on many levels in human trials: From altered systemic sympathetic activity across cardiac and metabolic alterations down to changes in renal function. Most of these changes could sustainably change long-term morbidity and mortality of the treated patients, even if blood pressure remains unchanged. Furthermore, a number of promising predictors for a successful treatment with RDN have been identified recently and further trials are ongoing. This will certainly help to improve the preselection of potential candidates for RDN and thereby optimize treatment outcomes. This review summarizes important pathophysiologic effects of renal denervation and illustrates the currently known predictors for therapy success.

Key words: Renal sympathetic denervation; Sympathetic nervous system; Predictors; Hypertension; Renal hypertension

Core tip: The initial enthusiasm for renal sympathetic denervation (RDN) has disappeared. However, the detailed effects of RDN on the complex pathophysiological

mechanisms underlying therapy resistant hypertension are only partly understood and are part of ongoing research. Moreover, a number of promising predictors for successful RDN treatment have been identified recently which could help to improve future trial design. This review summarizes important pathophysiologic effects of renal denervation and illustrates the currently known predictors for therapy success.

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BACKGROUND

Many forms of human hypertension are associated with an increased systemic sympathetic activity[1]. Especially the sympathetic nervous system of the kidney plays a key role in the pathogenesis and perpetuation of hypertension. An activation of efferent renal nerve fibers leads to salt and water retention *via* stimulation of α_{1B}-adrenoceptors, activation of the renin-angiotensin-aldosterone system *via* β_1-adrenoceptors causing thereby an increased systemic blood pressure (BP)[1,2]. The release of vasoactive peptides present in renal nerve fibers is also controlled by efferent sympathetic fibers[3,4]. *Via* afferent fibers, the kidney itself affects systemic sympathetic activity[1].

One option to reduce the systemic sympathetic activity is renal sympathetic denervation (RDN). Once introduced as a surgical treatment for hypertension in the past century[5,6], this interesting therapeutic approach lost clinical relevance since medical antihypertensive treatment was introduced to practice. As the burden of cardiovascular diseases associated with hypertension increased over the last decades, RDN experienced a renaissance, now as a catheter-based interventional treatment option[7]. After the first promising trial results, the initial enthusiasm for this therapy strategy was markedly dampened, when the results of the sham-controlled randomized Symplicity-HTN-3 trial did not show any significant effect on BP of RDN-treated *vs* sham-treated patients[8]. The results of this particular trial are part of an ongoing debate and further trials to allow definite conclusion on the effect of RDN on BP are on the way[9]. In contrast to the extensive use of RDN in treating hypertensive patients within or without clinical trial settings over the past years, the detailed effects of RDN on the complex pathophysiological mechanisms underlying therapy resistant hypertension are only partly understood.

In the following review we present a short overview of the manifold effects described for RDN so far (Table 1).

EFFECTS OF RDN

BP

The main indication for RDN in the past decade and in the past century has been therapy resistant hypertension. Therefore, BP as an end point has been included in nearly every single trial regarding RDN. In almost any trial, controlled, uncontrolled or sham-controlled, a significant BP reduction was found after RDN[7,10-14] (Table 2). However, the largest randomized sham-controlled trial to date, the Symplicity-HTN-3 trial, failed to show any superiority of RDN over sham-control, mostly through an unexpected drop in BP in the sham-treated arm of the trial[8].

Another sham-controlled randomized approach, excluding most of the confounding factors which might have blurred the results of Symplicity-HTN-3 by careful patient selection, the ongoing SPYRAL-HTN trial (NCT02439775), will hopefully give a definite answer to this issue soon.

It is of particular interest, that many of the effects attributed to RDN result in a reduced BP: A diminished systemic vascular tone leading to a reduced afterload, sympathetic mediated alterations in cardiac output, altered sodium- and volume-state or (*via* the renin-angiotensin-aldosterone axis) humoral-mediated changes. Which and how much these effects contribute to a RDN-induced BP drop and how they are counter-regulated remains an unresolved issue that needs to be clarified in future RDN-trials.

Besides other confounders, a constant observation in clinical trials is that a proportion of patients does not respond to RDN, which might in part contribute to the negative results in Symplicity-HTN3. Interestingly, the problem of non-responsiveness to renal denervation seems to be as old as the procedure itself: Even for surgical sympathectomy a high proportion of non-responders (ranging between 55% and 68%) has been described[5,6]. Despite that, a strong positive effect on long-term mortality was found in a large series of 1200 patients[5]. This leads to the question which other beneficial effects besides BP reduction RDN might have in humans, which might explain this discrepancy.

Renal function and sodium excretion

A potential deterioration of renal function - either by renal artery stenosis or by changes in intrarenal hemodynamics - is an often raised concern regarding RDN. On the contrary, as renal blood flow and salt/water retention is influenced by sympathetic activity[2], RDN might have nephroprotective effects.

Two larger non-randomized analyses found glomerular filtration rates (GFR) to be unchanged after RDN[15,16]. Interestingly, one trial could even show a decrease in albuminuria, consistent with an improvement of hypertension-induced end-organ damage[16]. In another study, examining the effects of RDN in patients with impaired renal function, the authors were able to show that the hypertension-related deterioration of renal

Table 1 Effects of renal sympathetic denervation

Ref.	Year	*n* (RDN/control)	Effector	Effect	Control
Ott *et al*[15]	2013	19/-	Renal blood flow	None	None
Pöss *et al*[19]	2015	137/-	Renal sodium excretion	Increased sodium excretion, less pronounced in responders	None
Mahfoud *et al*[24]	2014	55/17	Left ventricular mass	Reduced left ventricular mass after RDN	Medical therapy
Doltra *et al*[25]	2014	5/23			Medical therapy
McLellan *et al*[26]	2015	14/-			None
Lu *et al*[27]	2016	139/-			Meta-analysis
McLellan *et al*[26]	2015	14/-	Atrial conduction	Improved atrial conduction after RDN	None
Qiu *et al*[31]	2016	21/-	Persistent atrial fibrillation	Reduced heart rate after RDN	None
Armaganijan *et al*[36]	2015	10/-	Ventricular arrhythmia	Reduced frequency of ventricular arrhythmia episodes	None
Ott *et al*[15]	2013	19/-	Central hemodynamics	Reduced central BP and augmentation index after RDN	None
Brandt *et al*[38]	2012	110/10		Reduced aortic pulse pressure, pulse wave velocity and augmentation index	Medical
Mortensen *et al*[39]	2012	21/-			None
Hering *et al*[40]	2013	40/10		Reduced augmentation index	Medical
Okon *et al*[41]	2016	23/-		Unchanged invasive pulse wave velocity after RDN	None
Donazzan *et al*[51]	2015	11/-	Sympathetic activity	Reduced cardiac sympathetic activity after RDN	None
van Brussel *et al*[52]	2016	21/-		Unchanged cardiac sympathetic activity after RDN	None
Tsioufis *et al*[53]	2014	14/-		Reduced heart rate and arrhythmia burden and improved heart rate variability after RDN	None
Vink *et al*[55]	2014	13/-			None
Brinkmann *et al*[56]	2012	12/-		Unchanged muscle sympathetic nervous activity after RDN	None
Hering *et al*[57]	2013	10/25		Reduced muscle sympathetic nervous activity after RDN	Medical
Dörr *et al*[58,59]	2015	150/-		Reduced Neuropeptide Y and transiently reduced brain derived neutrophic factor after RDN	None
	2015	100/-			
Dörr *et al*[63]	2015	60/-	Inflammation	Reduced systemic inflammation after RDN	None
Mahfoud *et al*[65]	2011	37/13	Insulin sensitivity	Improved insulin sensitivity after RDN	Medical
Verloop *et al*[66]	2015	29/-		Unchanged insulin sensitivity	None
Ewen *et al*[71]	2014	50/10	Exercise testing	Reduced Exercise BP after RDN	Medical
Ukena *et al*[69]	2011	37/9			Medical
Fengler *et al*[70]	2016	22/26			Sham
Lenski *et al*[72]	2013	36	Orthostatic reaction	None	None

BP: Blood pressure; RDN: Renal sympathetic denervation.

function could be halted with RDN over a follow up of three years[17]. This suggests overall beneficial effects of RDN on renal function, especially in these patients who already suffer from hypertension-induced end-organ damage, which will clearly improve long-term mortality.

Despite the known vasoconstrictive effects of systemic sympathetic activity on the arterial vasculature[2] and significant alterations in an animal study[18], RDN does neither seem to improve nor deteriorate renal blood flow in humans[15]. Presumably, this can be explained by the auto-regulative capacities of the renal vessels outweighing any RDN-induced changes.

The putative effect of RDN on renal sodium excretion is a promising therapeutic goal. The only human trial investigating this hard-to-assess endpoint however showed mixed results, as patients with stronger BP response after RDN showed a diminished effect on sodium excretion compared to those with less BP changes[19]. To some extent this might be explained by a compensatory dietary sodium intake which was not assessed in the study. Therefore, this interesting aspect of RDN needs to be investigated thoroughly by additional rigorous assessment of dietary sodium intake. An additional MRI-based quantification of tissue sodium and water might be helpful here as elevated concentrations are observed in patients with essential hypertension. Sodium and water tissue content might therefore represent an interesting diagnostic and therapeutic goal[20,21].

Cardiac and hemodynamic changes

Left-ventricular-mass and fibrosis: An elevated left-ventricular mass is a frequent finding in hypertensive subjects[22]. Its presence and its regression through therapeutic interventions significantly affects patients' outcomes[22,23]. Therefore, it is a worthwhile therapeutic target in the treatment of human hypertension.

Several smaller studies and one recent meta-analysis describe a reduction of left-ventricular mass after RDN[24-27]. In one of them an additional improvement in left-ventricular strain and ejection fraction was observed in patients with reduced values at baseline[24]. Besides reversal of myocyte hypertrophy left-ventricular fibrosis might be altered by renal denervation, as the absolute extracellular volume was found to be reduced

Table 2 Blood pressure effects of renal sympathetic denervation

Ref.	Year	Control	*n* (RDN/control)	Systolic office BP (mmHg)	P-value	Systolic ambulatory BP (mmHg)	*P*-value
Krum *et al*[7]	2009	None	50	-22	< 0.001[a]	NA	NA
Esler *et al*[11]	2010	RDN *vs* medical	106 (52/54)	-32 *vs* 1	< 0.00001[b]	-11/-7 *vs* -3/-1	NA
Bhatt *et al*[8]	2014	RDN *vs* sham	535 (364/171)	-14 *vs* -12	0.26[b]	-6.8 *vs* -4.8	0.98[b]
Desch *et al*[10]	2015	RDN *vs* sham	71 (35/36, intention to treat) 63 (29/34, per protocol)	NA NA	NA NA	-8.5 *vs* -4.7 -8.3 *vs* -3.5	0.06[b] 0.04[b]
Rosa *et al*[13]	2015	RDN *vs* intensified medical treatment	106 (52/54)	-12 *vs* -14	< 0.001[a]/0.60[b]	-8.6 *vs* -8.1	< 0.001[a]/0.87[b]
Azizi *et al*[14]	2015	Stepped-care antihypertensive treatment with *vs* without RDN	106 (53/53)	-15 *vs* -9	0.15[b]	-15.8 *vs* -9.9	0.03[b]
Böhm *et al*[12]	2015	None	998	-12	< 0.00001[a]	-6.6	< 0.00001[a]

[a]*P*-value for within group change; [b]*P*-value for between group change. BP: Blood pressure; RDN: Renal sympathetic denervation; NA: Not available.

after RDN[25]. This finding might be supported by a reduced cellular matrix turnover assessed by collagen pro-peptides in patients after renal denervation in an upcoming laboratory study[28].

Atrial fibrillation: Associated with BP reduction, RDN has been shown to improve atrial conduction[26]. This might allow a look-out on renal denervation as an alternative or additional option for the treatment of symptomatic atrial fibrillation. This concept is supported by two recent animal studies in dogs, where RDN could impede the induction of atrial fibrillation[29,30]. Also, for persistent atrial fibrillation, RDN was found to reduce the heart rate in a small case-series of symptomatic patients[31]. Beyond this, several in-human trials regarding this issue are currently ongoing which will certainly help to improve our understanding of the intracardiac effects of RDN (NCT01635998, NCT01990911, NCT02064764).

Ventricular arrhythmia: As ventricular arrhythmias are more likely to occur under an elevated sympathetic activity, using RDN as a treatment for refractory ventricular arrhythmia seems a reasonable endeavor[32]. Animal studies show promising effects for RDN in ischemia-induced arrhythmias when compared to a sham procedure[33,34], while inducibility of ventricular arrhythmias cannot be prevented by RDN in healthy animals[35]. Also a first in-man cohort of 10 patients with mainly non-ischemic cardiomyopathies reveals a dramatic drop in arrhythmia burden after RDN[36]. Nonetheless, further prospective, randomized trials are needed to confirm this scope of application for RDN.

Hemodynamics and volume changes: Since the effects of RDN on renal water/sodium excretion and systemic vasculature are likely to be associated with changes in systemic volume status, it would be interesting to assess changes in intra-cardiac pressure and pressure-volume relations. Also, changes in central and peripheral hemodynamics in patients undergoing RDN are of particular interest, as they determine the incidence of heart failure and potentially the course of cardiovascular remodeling[37].

Several trials investigated central hemodynamics using non-invasive methods[15,38-40]. Herein, alterations of cardiac afterload, namely a significant reduction in central pulse pressure and aortic augmentation index after RDN could be demonstrated. Also, a reduction of non-invasively assessed pulse-wave velocity, indicating decreased arterial stiffness after RDN, was observed, even if this is conflicting with the results of a smaller cohort with unchanged invasively acquired pulse-wave-velocity 6 mo after RDN[41]. As arterial stiffness is - to some extent - a BP-dependent parameter, any changes observed after RDN have to be interpreted with caution.

An explicit effect of RDN on cardiac hemodynamics, including changes in preload, filling and contractility, has - to the present date - not been described. Assessment of hemodynamic changes can be achieved *via* echocardiography, which was part of virtually all protocols of bigger studies examining treatment effects of RDN. The paucity of published data regarding echocardiographically assessed hemodynamic changes in patients treated with RDN might imply negative findings (assuming a publication bias), might be a consequence of the limited sensitivity of echocardiography in detecting cardiac filling pressures or might just have been neglected so far. Therefore - besides invasive measurements - other non-invasive methods like MRI-based analyses (*e.g.*, the left atrial transit time) could provide additional information here[42].

Furthermore, given the described impact of RDN on the LV musculature and the arterial system, an improvement of ventricular-atrial coupling could be assumed after treatment.

However, as cardiac loading underlies marked intra-individual changes, reliable assessment of changes in central hemodynamics depend on testing of patients instantaneously under different physiologic conditions (such as rest and exercise) or under longitudinal observational trial settings.

Central and peripheral nervous changes

As illustrated above, mediated through afferent central nervous fibers RDN also affects the central nervous system. Interestingly, overall successful treatment of essential hypertension is associated with improved neuropsychological performance and to some extent with alterations in regional cerebral blood flow response to working memory tasks at short-term follow up[43]. To date, this has not been assessed for patients undergoing RDN but might be a promising task for future trials, especially since uncontrolled hypertension is a well-known risk factor for cerebrovascular diseases and might contribute to cognitive decline[44].

The link between central-nervous and peripheral sympathetic-nervous alterations in hypertensive patients could further be investigated in assessing to which extent central nervous changes are mediated indirectly by BP alterations or by increased sympathetic overdrive and afferent signaling itself.

The role of a potential sympathetic re-innervation after RDN[45,46] warrants further investigation as it might partly explain non-responsiveness and lead to negative trial results. However, BP reductions in response to effective RDN seems to be long-lasting in the data published so far[47-49].

Systemic sympathetic activity

Direct measurement of the systemic sympathetic activity is difficult to perform and is therefore underrepresented in clinical trials of RDN[50]. Indirect assessment, however, is feasible with different techniques and has been used in various trials.

Cardiac scintigraphy: Two small trials (including only 23 and 11 patients) examined alterations in the cardiac sympathetic nervous system activity after RDN using scintigraphy[51,52]. Their results were conflicting, as in one trial with only a non-significant BP drop in ambulatory BP-measurements in the RDN patients, no significant alterations in cardiac sympathetic activity were found. The other trial found a remarkable impact of RDN on ambulatory measured BP and also found a strong reduction in cardiac sympathetic activity. Since the results are inconclusive at present, further evaluation in larger, adequately powered cohorts is necessary.

Heart rate variability: Another way to measure systemic sympathetic activity is assessing heart rate variability (HRV). In a small case series, Tsioufis and coworkers were able to show RDN achieved a significant reduction in patient's HRV and arrhythmia burden, suggesting a reduced systemic sympathetic activity in the treated patients[53].

Muscle sympathetic nerve activity: Muscle sympathetic nerve activity is known to be elevated in hypertensive subjects[54], indicating a direct link to systemic sympathetic activity. Hence, direct intraneural recordings could be considered as a good marker for treatment success after RDN. So far this hypothesis has been investigated in two smaller case series which failed to show any alterations through RDN[55,56]. In contrast, a prospective controlled trial in 35 patients found significant alterations in single- and multi-unit muscle sympathetic nerve activity[57]. Despite the latter results, overall the role of muscle sympathetic activity as an outcome marker in RDN trials is not fully determined and warrants further research.

Laboratory markers: Dörr *et al*[58] investigated the role of Neuropeptide Y, a neurotransmitter that is co-released with norepinephrine and up-regulated during sympathetic activity. They were able to show a significant drop of Neuropeptide Y after RDN which can be interpreted as an expression of a reduced systemic sympathetic activity.

Successful RDN also leads to a transient down-regulation of serum brain-derived neurotrophic factor immediately after denervation[59]. Since brain-derived neurotrophic factor is a neuronal growth factor, this adds further evidence for true downregulation of the sympathetic nervous system on a neuronal base through RDN.

Overall, despite the lack of data for a direct assessment of systemic sympathetic activity in RDN-trials, indirect markers strongly indicate that RDN results in significant changes of systemic sympathetic activity.

Inflammation

Arterial hypertension is associated with chronic vascular inflammation and remodeling[60-62]. In a prospective analysis of 60 patients undergoing RDN, a significant reduction of pro-inflammatory cytokine interleukine-6 and high-sensitive C-reactive protein was achieved[63]. This is in particular encouraging, as it might be related to beneficial long-term effects of RDN. It has however to be debated, if the observed changes are rather related to the BP lowering effects of RDN, which might attenuate the pathologic immune response, rather than to RDN itself.

Metabolic effects

Insulin sensitivity: An elevated sympathetic activity seems to be associated with an altered insulin sensitivity[64]. Therefore, RDN might help to improve the glucose metabolism in patients with a high sympathetic overdrive. The first trial to investigate this relation, a pilot-study in 50 patients, found a significant change in glucose metabolism and insulin sensitivity[65]. Notably, only 40% of these patients were diagnosed with diabetes mellitus and only 36% had an impaired glucose tolerance at baseline. In contrast, a smaller, uncontrolled prospective trial did not find any changes in insulin sensitivity after a follow up of 12 mo in 29 patients with metabolic syndrome[66]. Therefore, the role of RDN for improvement of insulin sensitivity remains equivocal.

However, if an effect of RDN on this very relevant end point could be proven, it could tremendously affect patients' long-term prognosis.

Exercise testing: Exercise BP, an important risk factor for future cardiovascular events[67,68], was found to be reduced after RDN in two non-randomized studies and one sham-controlled trial[69-71]. Also beneficial effects for exercise capacity and duration are described for RDN without affecting chronotropic competence in treated patients[69,71].

Orthostatic effects: Safety concerns regarding potential unfavorable orthostatic effects of RDN can largely be ruled out due to the lack of the occurrence of orthostatic side effects in the large RDN treatment trials and a smaller trial which did not find any pathologic alterations in tilt table testing for RDN-treated patients[72].

Conclusion

Beyond the still debated effects of RDN on BP in hypertensive patients, a wide range of promising effects has been shown. Most of these changes could importantly change long-term morbidity and mortality of the treated subjects, even if their BP remained unchanged. To determine the value of non-BP effects of RDN for clinical practice, further long-term data with multiple cardiovascular endpoints is needed.

Until then, it seems prudent to optimize BP outcome in RDN trials through the identification of predictors for treatment success. In the following we will give a brief overview of such predictors that have been identified so far.

PREDICTORS FOR SUCCESSFUL RDN

Baseline BP

High BP prior to renal denervation has most frequently been described as the strongest predictor of BP reduction after RDN[12,73]. However, whether this is related to a higher sympathetic activity in patients with higher baseline BP or a manifestation of the regression to mean phenomenon remains controversial and is an unresolved issue to date[74]. Thus, other predictors for treatment success in RDN are needed.

Anatomy and technological aspects

Anatomy: The anatomy of the renal arteries seems to have considerable influence on the BP response to RDN. Importantly, the anatomy of human renal vessels shows a high variability[75]. Accessory renal arteries or an early bifurcation occurs in approximately one of three patients[75]. This is important, as the presence of accessory or early bifurcated vessels seems to influence outcome negatively[76]. In principle it seems prudent to exclude these patients from renal denervation. Nevertheless, in the ongoing SPYRAL-HTN trial (NCT02439775) denervation of accessories with a diameter above or equal 3 mm is planned. This will hopefully clarify the role of accessory arteries and early bifurcations soon.

As the sympathetic nerve fibers are closer to the lumen in the distal part of the renal vessel[77], ablation of the distal main artery or even the side branches are also thought to improve outcome[78,79].

Technological aspects: One of the major shortcoming of RDN is the lack of a direct feedback mechanism during intervention[50]. Despite many promising approaches, including direct intravascular and (sub-)cutaneous measurements of renal sympathetic activity, the challenging task of a direct *in-vivo* feedback for renal denervation success is still far away from clinical practice. Nevertheless, once a direct assessment method for renal sympathetic activity is established this will be a milestone in improving renal denervation success[50].

Another technological aspect for future trial designs is that denervation success seems to be dependent of the number of ablation points as well as the experience of the interventional physician[73]. Therefore, RDN should only be performed by trained interventionalists and as many ablations as possible should be delivered to optimize BP outcome.

Most clinical trials regarding RDN were carried out using radiofrequency based catheters. The role of other devices, like ultrasound-based[80-82] or chemical approaches[83,84], remain uncertain, as head-to-head comparisons of different techniques are lacking. Nevertheless, ultrasound treatment appears to be a promising treatment option, as recent work from our group suggests: Treatment of 24 non-responders to radiofrequency based RDN with an ultrasound denervation system significantly improved BP[85].

Obesity

Obesity seems to be associated with an elevated sympathetic activity, even in normotensive subjects[86]. Therefore, it might be a good predictor for BP responsiveness to RDN. In contrast, according to one singular study[87] obesity seems to be a predictor for non-responsiveness to RDN. The results of this trial are however somewhat questionable, as this constellation was neither found in any other trial[8,73] nor in the even large multicenter Global Simplicity Registry[12]. Moreover, in two smaller trials a higher body mass index was found to be a predictor for responsiveness to RDN[47,88]. To date, obesity should not be considered to have any predictive value for RDN success until reevaluation in larger, adequately powered cohorts has been performed.

Gender

So far the effect of RDN seems to be independent of gender. Nevertheless, due to the higher incidence of hypertension and therapy resistant hypertension in men, women are strongly underrepresented in any clinical trial regarding RDN. The percentage of women included in trials of renal denervation ranges between 23 and

Table 3 Predictors for blood pressure change after renal sympathetic denervation

Ref.	Year	Patients	Predictor
Böhm *et al*[12]	2015	998	Higher baseline BP predicts better BP response to RDN
Kandzari *et al*[73]	2015	364	
Id *et al*[76]	2013	74	Less BP response to RDN if accessories are present
Ewen *et al*[89]	2015	126	Better BP response in patients with combined vs isolated systolic hypertension
Okon *et al*[41]	2016	58	Lower pulse wave velocity predicts BP response
Zuern *et al*[88]	2013	40	Better BP response in patients with impaired baroreflex sensitivity

BP: Blood pressure; RDN: Renal sympathetic denervation.

41[8,10,13,14,47]. Realizing a meta-analysis of prospective trials could clarify the role of gender for RDN success.

Age

The age of the treated patients itself was not found to have a good predictive value for the success of RDN[73]. In contrast, considerable evidence was found for vascular aging and stiffening as a predictor for renal denervation over the last years[41,89].

Vascular aging and stiffness

Arterial stiffening is associated with a high cardiovascular mortality in hypertensive patients[90,91]. It also can be regarded as a cause for essential hypertension[92,93]. Ewen *et al*[89] found, that the presence of isolated systolic hypertension - characterized by increased aortic stiffness - is associated with a diminished response to RDN. In line with these data, our group also found an increased aortic stiffness, assessed by invasive pulse wave velocity, to be an independent predictor for poor BP response to renal denervation[41]. This is a promising finding, as isolated systolic hypertension and pulse wave velocity, among other markers of vascular aging and aortic stiffness, can easily be assessed non-invasively and thereby could help improving the preselection of patients available for renal denervation. To some extent, this might also explain why a trial by Vink *et al*[94] found the presence of cardiovascular diseases (a composite of stroke, transient ischemic attack and coronary artery disease), which are associated with increased vascular stiffness, to be a predictor for BP response to RDN.

Baroreflex

An impaired cardiac baroreflex occurs frequently in hypertensive subjects[95]. This might be explained by sympathetic overactivity[88]. Therefore, the presence of an impaired cardiac baroreflex as an indicator for high sympathetic overdrive could be a good predictor for renal denervation success. This hypothesis was already confirmed by a trial in 50 patients[88], but has not been applied in other prospective trials to date.

Renal function

Patients with renal diseases have often been excluded from clinical trials for safety reasons. Despite these considerations, patients with impaired renal function show an elevated sympathetic activity[96,97], and therefore might be good candidates for RDN. Consequently, Vink *et al*[94] found an inverse relation between the estimated GFR and the change in BP after RDN in a hypertensive population off antihypertensive medication. However, when analyzing patients on antihypertensive medication, no significant predictive value for estimated GFR was observed. These interesting findings warrant further investigation, as - besides enlightening the predictive role of renal function - they might partly explain why and how antihypertensive drugs interact with the effectiveness of RDN. Several trials investigating the effect of renal denervation in chronic kidney disease are currently recruiting patients (*e.g.*, NCT02002585, NCT01442883).

Conclusion

Despite the disappointing results of the SYMPLICITY-HTN3 trial, the canon of published data identifies RDN as a promising therapeutic option for hypertensive patients. Besides direct BP-lowering effects RDN has been shown to affect a broad range of pathophysiological mechanisms and might even be a viable treatment option for patients with other conditions such as heart failure or arrhythmias.

Although various predictors for the success of RDN have been identified (Table 3), an optimization for the prediction of RDN response is highly desired and several trials are ongoing which hopefully will improve treatment success and future RDN-trial design.

Verification of specific treatment effects of RDN in carefully and well-designed trials bare the hope to secure the role for RDN in treating arterial hypertension and ideally in reducing cardiovascular morbidity and mortality in the future.

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12-lead electrocardiogram features of arrhythmic risk: A focus on early repolarization

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Abstract

The 12-lead electrocardiogram (ECG) is still the most used tool in cardiology clinical practice. Considering its easy accessibility, low cost and the information that it provides, it remains the starting point for diagnosis and prognosis. More specifically, its ability to detect prognostic markers for sudden cardiac death due to arrhythmias by identifying specific patterns that express electrical disturbances of the heart muscle, which may predispose to malignant arrhythmias, is universally recognized. Alterations in the ventricular repolarization process, identifiable on a 12-lead ECG, play a role in the genesis of ventricular arrhythmias in different cardiac diseases. The aim of this paper is to focus the attention on a new marker of arrhythmic risk, the early repolarization pattern in order to highlight the prognostic role of the 12-lead ECG.

Key words: Ventricular repolarization; Cardiovascular diseases; Arrhythmic risk; Early repolarization; Arrhythmia

Core tip: By identifying specific patterns which are an expression of ventricular repolarization alterations, the 12-lead electrocardiogram plays an important role in the diagnosis of electrical disturbances and in the risk stratification of death due to arrhythmias. This review focuses the attention on the new early repolarization marker of arrhythmic risk and its prognostic implications.

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INTRODUCTION

More than 100 years after its invention, the 12-lead electrocardiogram (ECG) is still the most used tool in cardiology clinical practice. Moreover, it represents the

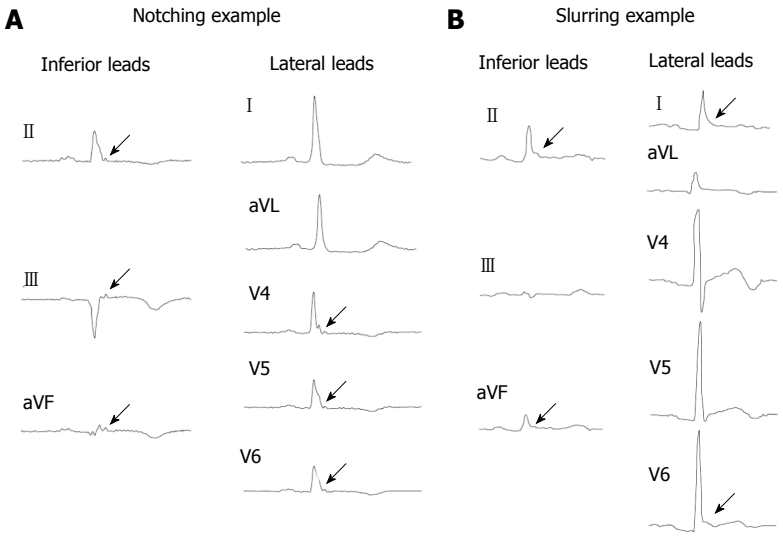

Figure 1 Notching and slurring example of early repolarization. A: Notching example; B: Slurring example.

starting point for diagnosis, given its easy accessibility and low cost.

Its ability to predict sudden cardiac death (SCD) due to arrhythmias by identifying specific patterns that express electrical disturbances of the heart muscle, which may predispose to malignant arrhythmias, is universally recognized.

On a surface 12-lead ECG it is possible to recognize a phase of ventricular depolarization, represented by the QRS complex, and a phase of ventricular repolarization (VR), that conventionally begins at the QRS wave and ends at the T waves. VR is made up of the J-wave, ST-segments and T-waves and U-waves[1,2]. Over the years several studies have analyzed the characteristics of VR and have recognized visible alterations as characteristic patterns on 12-lead ECG, emphasizing the role of the latter in the genesis of ventricular arrhythmias in different cardiac diseases[3-6].

From a pathophysiological point of view, it has been shown that changes in the process of VR can lead to malignant ventricular arrhythmias through abnormalities occurring in the action potential (AP) and in the refractory period of cardiac cells, thus leading to spatial heterogeneity and temporal fluctuations in repolarization, favoring the onset of arrhythmias[7,8].

However, an ECG can also be modulated by genetic factors which can determine an arrhythmogenic substrate that leads to an increased risk of SCD. This effect is particularly evident in inherited arrhythmogenic disorders such as long QT syndrome, short QT syndrome and Brugada syndrome, where the ECG can identify not only specific diagnostic alterations, but also prognostic indicators. This emphasizes the role of the ECG as an instrument not only for diagnostic but also for prognostic purposes[9].

The aim of this review is to focus the attention on a new marker of arrhythmic risk, *i.e.*, the early repolarization (ER) pattern. The notions presented in the literature will be revised and the prognostic and predictive role of the 12-lead ECG will be highlighted, by recognizing, characterizing and carefully studying VR disturbances in the context of the ER pattern.

DEFINITION AND FAMILY FORM OF ER, A NEW ELECTROCARDIOGRAPHIC MARKER OF ARRHYTHMIC RISK

The early ER pattern as a 12-lead ECG marker of arrhythmic risk is a more recent discovery. It is characterized by a J-point elevation of at least 1 mm in two contiguous leads with a "notching" type appearance, *i.e.*, a positive J-deflection inscribed in the S wave, or a "slurring", *i.e.*, a gradual transition of the QRS to the ST segment in the inferior, lateral or inferolateral leads, as defined by Haissaguerre in 2008[10] (Figure 1).

The J-point on the ECG waveform is historically defined as the junction between the end of the QRS complex and the beginning of the ST-segment[11].

In the 1953, Osborn[12] described the association between hypothermia and the appearance of positive deflections due to J-point elevation associated with VF. They were considered currents of injury. They became known as J-waves bearing his name (Osborn waves) and have become a generally accepted marker for clinical hypothermia.

In 1961, it was defined by Wasserburger *et al*[13] as an elevated take-off of the ST segment at the J-junction with downward concavity of the ST segment and symmetrical T waves. This elevation is manifested either as QRS slurring or notching in at least two inferior or lateral leads.

This definition remained in place until 2008 when Haissaguerre[10] shifted the focus from the ST-segment elevation to the J-point. J-point elevation was defined as being an elevation of at least 1 mm in two contiguous leads with a "notching" appearance, *i.e.*, a positive J-deflection inscribed in the S wave, or "slurring", *i.e.*, a gradual transition of the QRS to the ST segment in the inferior, lateral or infero-lateral leads. The simultaneous

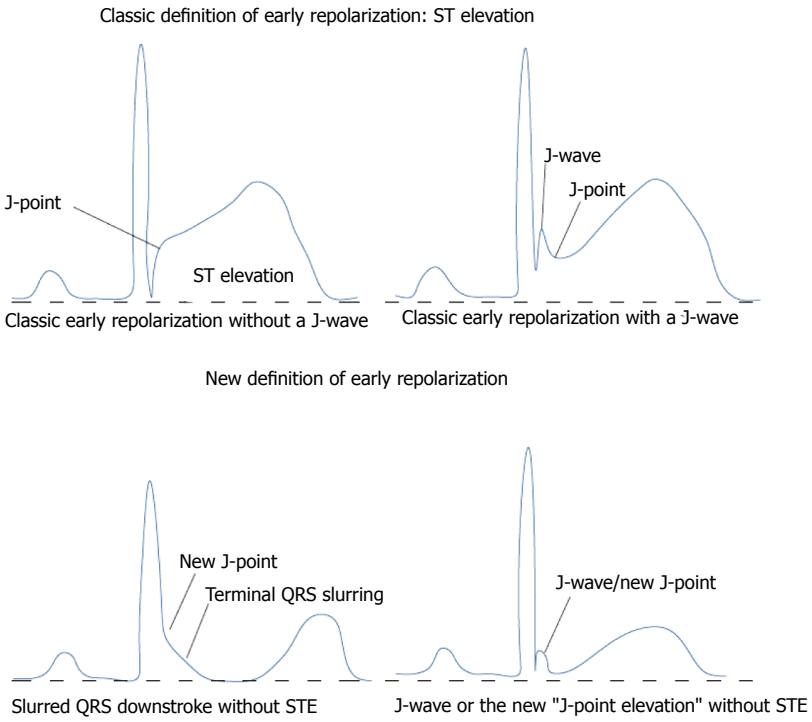

Figure 2 Old and new definition of early repolarization. STE: ST elevation.

presence of ST-segment elevation is not necessary for diagnosis (Figure 2).

ER was historically considered a benign ECG variant, commonly seen in the anterolateral leads of young male athletes of black ethnicity but also in adolescents, accentuated by vagal tone and hypothermia[14-18]. In effect, an increase in vagal activity is known to cause an ST-segment elevation whereas sympathetic agonists normalize the ST segment[19].

A prevalence of between 1% and 5% has been estimated in healthy adults[13,20-22]. Furthermore, an intermittent pattern of ER is commonly observed, being only rarely present in all the ECGs performed successively on the same patient. It then becomes less common with age[23]. This evidence could be explained by the direct correlation of ER pattern with elevated testosterone plasma levels, as it is observed in young males. This would also explain the absence of the ER in older subjects[24].

Although not considered a marker of cardiovascular disease, ER has a practical importance because it may mimic the ECG of acute myocardial infarction, pericarditis, ventricular aneurysm, hyperkalemia or hypothermia. A dilemma may occur when a patient with ST variant presents with chest pain and no prior available ECG[25-28]. Unnecessary or incorrect diagnostic tests, therapeutic decisions, including administration of thrombolytic drugs[29], and hospital admissions might result from misinterpretation.

The available literature also provides evidence of a possible hereditary pattern of ER. In particular, a study of 500 families showed that subjects with at least one parent with ER were twice as likely to have the same ECG alteration. Family transmission is more frequent when the mother has the ER pattern, both for notching forms and for those in the lower location[30]. Such families have been shown to have a high incidence of sudden death, probably linked to ER.

There are also very rare forms of autosomal dominant inheritance[31]. In this context it was suggested that the Valsalva maneuver can unmask forms of ER which are not spontaneous on the surface ECG. The sensitivity of this maneuver, however, is considered to be low.

The question of whether family forms have a worse prognosis than sporadic forms remains.

PATHOPHYSIOLOGICAL BACKGROUND OF J-WAVE AS AN ARRHYTHMIC MARKER

An ER pattern with the characteristics of the J-point elevation of at least 2 mm and a horizontal or descending pattern of the ST segment appears to increase the risk of developing ventricular arrhythmias, especially in structurally abnormal hearts. In fact, ER creates a kind of gradient of repolarization between adjacent areas that results in re-entry phenomena that cause the onset of arrhythmias.

The J-wave comes from an alteration of the AP involving the epicardial, but not the endocardial, cells during phase 1 of the AP. In this period (ER phase) there are two ion currents of repolarization: Potassium tends to leak out (current Ito) and chlorine tends to enter into the cell (current ICl) while the front sodium current (INa-late) is gradually attenuated until it disappears. As a result of the loss of positive charges (K^+) and the acquisition of negative charges (Cl^-), the transmembrane potential is reduced to less positive

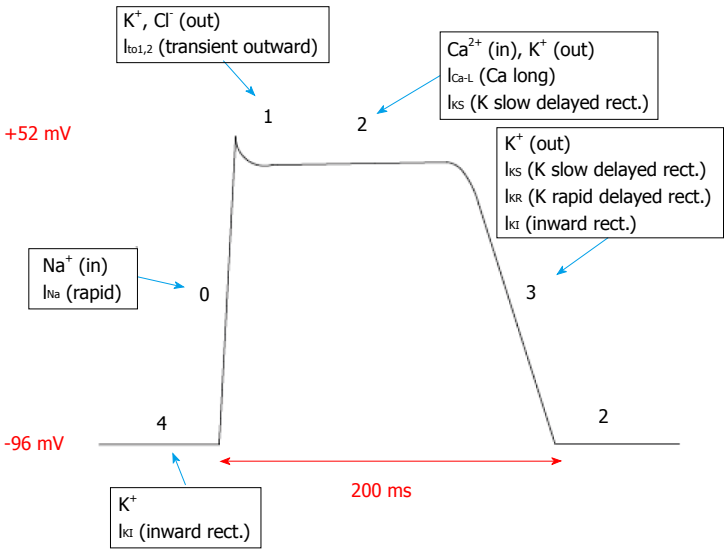

Figure 3 Action potential in physiological condition.

values, from +30 to approximately 0 mV. The incoming sodium current (INa-late) has the opposite effect to that of Ito and ICl and, by bringing positive charges within the cell, it slows down the repolarization. However, since it is quickly depleted, its importance is relatively modest in physiological conditions (Figure 3). In subjects who have the ER patterns, repolarization proceeds more quickly than normal during phase 1, with a rapid reduction in the potential which passes from +30 to 0 mV or negative values[32]. The imbalance between outward and inward positive currents during phase 1 of the AP and thus the propagation of the AP dome from sites where it is maintained and to sites at which it is lost, might lead to a local re-excitation *via* phase-2 re entry which, in turn, may facilitate the development of premature beats. An increase in transmural dispersion might facilitate transmural propagation of the extrasystole predisposing to the development of polymorphic VT and VF[33] (Figure 4).

CLINICAL EVIDENCES OF ER/J WAVE AS A MARKER OF ARRHYTHMIC RISK

It is important to identify ECG characteristics that differentiate the "benign ER" pattern from the "malignant ER"[34,35] (Table 1). In fact, for the first time, an English case-control study has demonstrated the arrhythmogenic potential of ER by putting in relation the ER with the idiopathic ventricular fibrillation (IVF). In fact 206 subjects under the age of 60 with IVF, were compared with a control group of 412 healthy patients. The results suggested a correlation between ER and sudden cardiac arrest. It was observed that most of the subjects with the characteristic patterns were young males, with a history of unexplained syncope or cardiac arrest during sleep. In addition, at baseline ECG, ER was present mainly in the inferior-lateral leads[10].

Tikkanen also considered the importance of defining a benign form of ER from a malignant one[35,36]. He studied a group of young athletes with ECG patterns of ER. Most of these presented an aspect of "rapidly ascending ST-segment blending with T-wave". Naturally, this has been regarded as the benign form of ER. On the other hand, a minority of the athletes showed a pattern with an ST segment that remained flat, horizontal, or even descending towards the T-wave. The authors considered this to be the malignant variant of ER which is associated with arrhythmic mortality during long-term follow up. Moreover, subjects with an elevation of at least 2 mm of the J-point in the inferior leads had an increased risk of cardiac death. The study showed a relationship between mortality and ER and revealed that the risk of death was influenced by the seat, more common in the inferior leads, and the amount of elevation of the J-point, for values greater than 2 mm. In addition, Tikkanen *et al*[35,36] demonstrated that benign ER (ascending/upsloping ST segment) is associated with a significantly shorter QTc interval compared to the malignant form (horizontal/descending ST segment) which is associated with a significantly longer QRS duration (a prolonged QTc interval was defined as at least 440 ms for men and at least 460 ms for women). Therefore, benign ER appears to reflect earlier onset of repolarization, but malignant ER may reflect abnormal depolarization, possibly with underlying subtle structural disease[35,36].

The supposition of Tikkanen was later supported by a study that compared 21 athletes with a history of previous cardiac arrest of unknown etiology with more than 300 healthy athletes[37]. The study proved that athletes with a horizontal pattern of ER and ST were 11 times more at risk of cardiac arrest. Furthermore, recent studies have shown that patients with an ER pattern have a higher risk of having ischemic events and ischemic VF[38-40]. More specifically, the ER pattern with a horizontal ST segment was an independent predictor of sudden death[41]. As regards the malignant form of ER, the pattern of ER in the inferior lateral leads must be

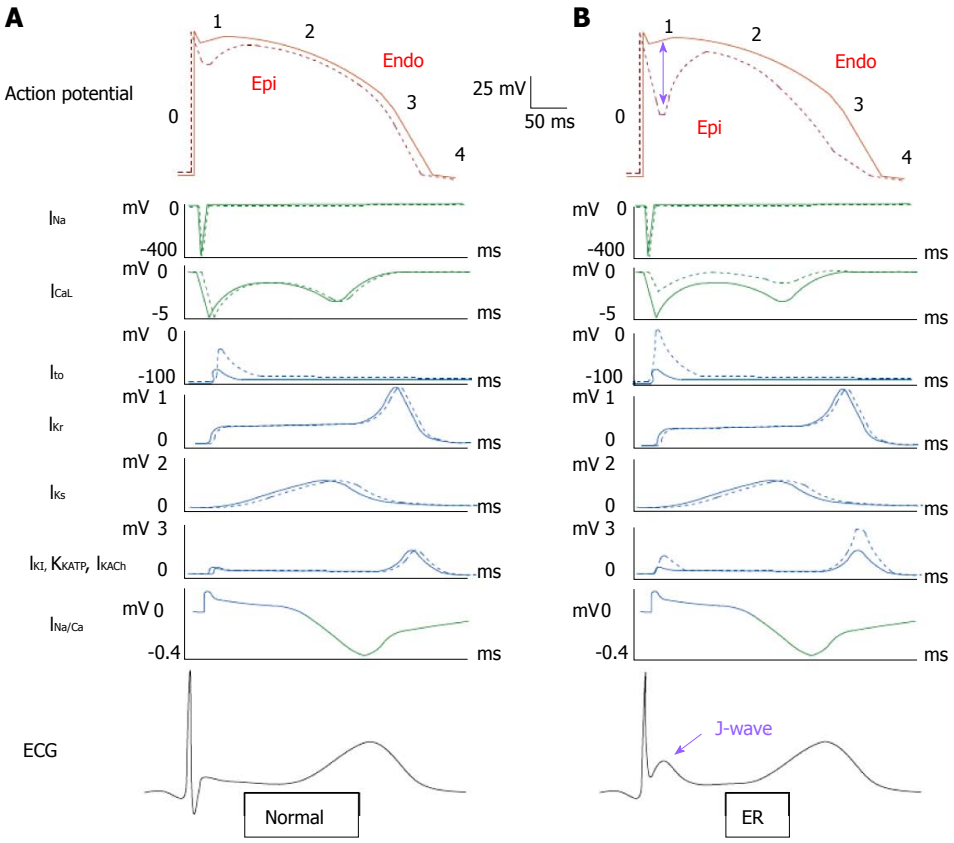

Figure 4 The pathophysiological background of J wave. A: The normal action potential, underlying currents and corresponding ECGs. Epicardial (Epi) action potential and current are shown by dotted lines and endocardial (Endo) by solid lines. Depolarizing currents are depicted downward in green and repolarizing currents upward in blue. The Epi action potential has a characteristic notch caused by larger phase -1 Ito compared with Endo; B: Exaggeration of the Epi notch results from enhancement of net outward current. Phase-1 current flow from Endo to Epi produces the J-wave. The various ionic mechanisms that are believed to produce ER are shown with purple stars. INa: Inward sodium current; ICaL: Inward calcium currents; INa/Ca: Sodium calcium exchange; Ito: Transient outward current; IKs: Slow delayed rectifier current; IKr: Rapid delayed rectifier current; IK1: Inward rectifier current; IKATP: Adenosine triphosphate-sensitive current; IKACh: Acetylcholine-activated current; ECG: Electrocardiogram.

carefully considered. It is characterized by a deflection in the R-wave (slurred pattern) descending in the terminal part of the QRS in at least two inferior leads (Ⅱ, Ⅲ, aVF), in two lateral leads (Ⅰ, aVL, V4-V6), or both. Numerous studies have demonstrated the association between a pattern of ER in these locations, especially in the inferior leads, and the presence of idiopathic VF (IVF)[26,29,42]. However, contrasting results in the available literature should be considered. In fact, in one study of nearly 30000 outpatients, with a mean follow up of 7 years, the negative prognostic effect of the ER patterns was not confirmed[43]. The only meta-analysis available of this emphasizes the correlation of ER with a higher risk of arrhythmic death but not of cardiac death or death from other causes[44].

In 1992 a Japanese study assessed the dynamicity of J-wave associated with idiopathic VF by analyzing its pause-dependent increase.

The J-wave amplitude was measured in the beat immediately after a pause and compared with the mean J-wave measured in almost three beats before the pause. The pause was considered as an abnormal sudden prolongation of the interval R-R, induced by arrhythmias such us sinus arrest, sinoatrial block, atrioventricular block, or atrial and ventricular premature beats.

It is interesting to note that the pause-dependent increase of J-wave was observed only in patients with idiopathic VF and in none of the control patients and this augmentation was associated with depression of the ST-segment or inversion of the T-waves. This dynamicity could be well explained by the pause-dependent augmentation in transient outward current (Ito) of the AP. In conclusion the authors suggested that the pausedependent augmentation was highly predictive of arrhythmic events and proposed a description of the characteristics of the "J-wave" potentially associated with IVF[45].

The same authors have further analyzed the J-wave dynamicity in the general patient population, with no symptoms and no history of IVF. They have observed an increase in amplitude of J-wave at high frequency but not at low frequencies and this may be due to a delay conduction[46].

So the analysis of the J-wave variations according to RR interval can be used to characterize the J-wave and use it for the arrhythmic risk stratification.

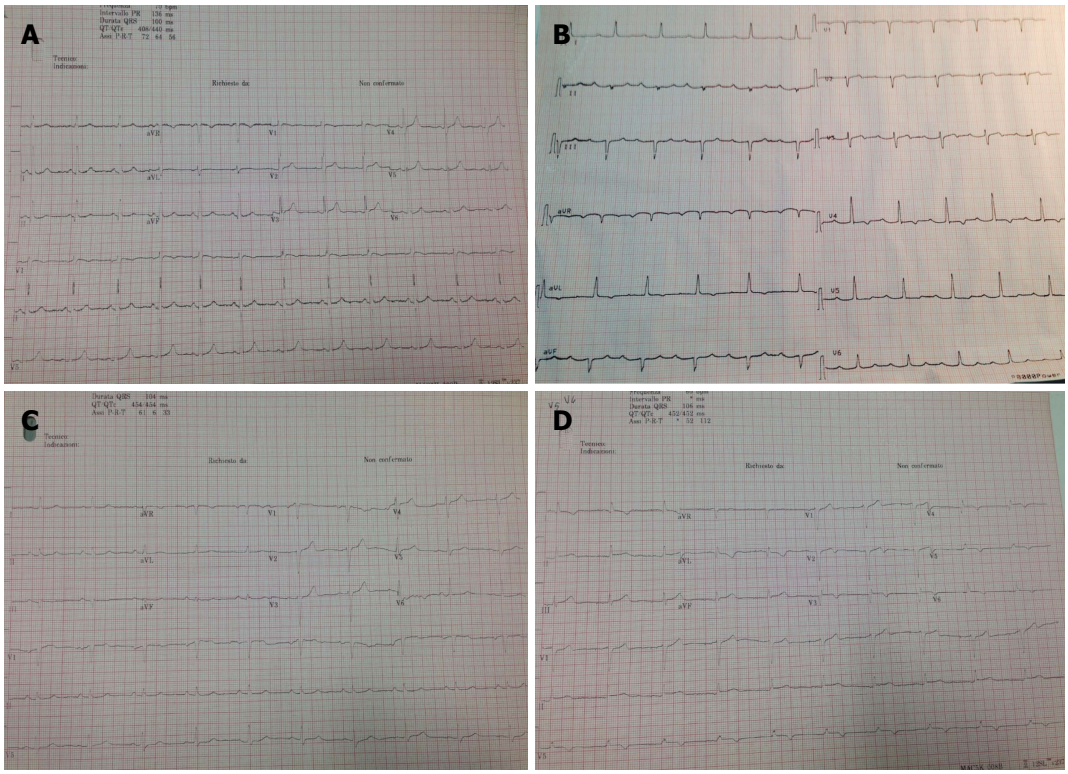

Figure 5 Early repolarization in clinical practice. A: Example of ER pattern "notching tipe" in Inferior-lateral leads (D2, D3, aVF, V5, V6). Width: 1 mm; B: Example of ER pattern "slurring tipe" in lateral leads (D1, aVL, V5, V6). Width: 1 mm; C: Example of ER pattern "notching tipe" in Inferior leads (D2, D3, aVF). Width: 1.5 mm; D: Example of ER pattern "notching tipe" in lateral leads (V5, V6). Width: 1.8 mm. ER: Early repolarization.

Focus on ECG features

Given the conflicting results between the different studies analyzed, possibly due to the non-uniformity of the case histories of patients treated, it is reasonable to think that, in addition to the seat and extent of the J-point changes, a key role is played by the characteristics of the segment elevation ST, as Tikkanen first demonstrated in his study, where the presence of a rapidly ascending ST was not associated with an increased risk of death from arrhythmia causes, unlike the detection of a horizontal or descending ST. The maximum risk was achieved by the combination of an ER pattern in the inferior leads with an ST-segment elevation at J-point greater than 2 mm and a horizontal-descending ST[35,36]. It is also interesting to note that patients with rapidly ascending ST were mostly young, had low blood pressure, and signs of left ventricular hypertrophy.

The literature shows that subjects with a good prognosis, who are young and athletic, with no evidence of structural heart disease have a high prevalence of an ER pattern with rapidly ascending ST elevation. Conversely, individuals with a poor prognosis, due to advanced age, and who have had a myocardial infarction with or without arrhythmic complications, have a high prevalence of an ER pattern with a horizontally-downward ST[47].

It is also important to evaluate the J-wave dynamicity in order to recognize ECG features predictive of arrhythmic risk, which are the pause dependent augmentation, the large amplitude and the concomitant horizontal-descending ST-segment[45].

CONCLUSION

In conclusion, there is a correlation between 12-lead ECG VR patterns and cardiac death due to arrhythmias, especially in inferior or inferolateral localized forms, associated with a J-point elevation of at least 2 mm and a horizontal ST pattern. This pattern is more common in a poor prognosis population, *i.e.*, in older subjects with a history of myocardial infarction or heart disease. Although ER is a common ECG finding, ER syndrome (ER with IVF) is rare[42].

Even in middle-aged individuals with an inferior ER of > 0.2 mV, the 3-fold increased SCD risk was not apparent until 10 years after the index ECG[35,36].

There have been no risk stratifies for asymptomatic ER subjects and, to date, no primary prevention strategy has been established. It is currently impossible to make recommendations based on this incidental ECG finding in an asymptomatic individual.

In fact, if it is simple and almost automatic to propose defibrillator implantation for a patient with a personal history of cardiac arrest and an ECG showing a typical framework, it is much less easy to take a decision if the same ECG is recorded by chance in an asymptomatic subject. The research carried out to date has highlighted some aspects of the problem but does not offer a one-size fits all approach. Moreover, it is not recommended

Table 1 The main studies evaluating the relationship between early repolarization pattern and death due to arrhythmia

Ref.	No. of patients	Study population	ER pattern	Results
Tikkanen *et al*[36], 2009	10.864	Community-based general population of middle-aged subjects	ER was stratified according to the degree of J-point elevation (> or = 0.1 mV or > 0.2 mV) in either inferior or lateral leads	ER pattern in the inferior leads is associated with an increased risk of death from cardiac causes in middle-aged subjects
Tikkanen *et al*[35], 2011	565 young healthy athletes-10 864 middle-aged subjects	565 young healthy athletes compared with ECGs from a general population of 10864 middle-aged subjects	ER pattern with horizontal/descending or rapidly ascending/upsloping	ST-segment morphology variants associated with ER separates subjects with and without an increased risk of arrhythmic death in middle-aged subjects. Rapidly ascending ST segments after the J- point, the dominant ST pattern in healthy athletes, seems to be a benign variant of ER
Uberoi *et al*[43], 2011	29281	Resting ambulatory ECGs	J-point elevation ⩾ 0.1 mV-notching and slurring type in at least 2 lateral or inferior-lateral leads	No significant association between any components of early repolarization and cardiac mortality
Haïssaguerre *et al*[10], 2008	206	Patients who were resuscitated after cardiac arrest due to IVF	Elevation of the QRS-ST junction of at least 0.1 mm inferior or lateral lead-QRS slurring or notching	Correlation between ER and sudden cardiac arrest
Nam *et al*[41], 2008	1410	1595 controls and 15 patients with IVF	J-point elevation ≥ 0.1 mV-notching and slurring type in at least 2 lateral or inferior leads	ER pattern is indicative of a highly arrhythmogenic substrate
Rosso *et al*[42], 2008	290	45 patients with idiopathic VF were compared with 124 age- and gender- matched control subjects and with 121 young athletes	J-point elevation ⩾ 0.1 mV-notching and slurring type in at least 2 lateral or inferior-lateral leads	J-point elevation is found more frequently among patients with idiopathic VF than among healthy control subjects. The frequency of J-point elevation among young athletes is intermediate
Rosso *et al*[29], 2011	8980	331 patients with IVF and 8.649 controls	J waves > 2 mm	The presence of J waves > 2 mm in amplitude in asymptomatic adults is associated with a threefold increased of arrhythmic death
Aizawa *et al*[45], 2012	116	Forty patients with J-wave-associated idiopathic VF compared with 76 non-VF patients	J-wave amplitude was measured in the beat immediately after a pause and compared with the mean J-wave measured in almost three beats before the pause. J waves were defined as those ⩾ 0.1 mV above the isoelectric line	Pause-dependent augmentation of J waves was confirmed in about one-half of the patients with idiopathic VF after sudden R-R prolongation. Such dynamicity of J waves was specific to idiopathic VF and may be used for risk stratification
Cappato *et al*[37], 2010	386	21 athletes with a history of previous cardiac arrest of unknown etiology compared with more than 300 healthy athletes	ER pattern with horizontal/descending or rapidly ascending/upsloping	Athletes with a horizontal pattern of ER and ST were 11 times more at risk of cardiac arrest
Naruse *et al*[38], 2012	220	patients with AMI	elevation of the QRS-ST junction of > 0.1 mV - 2 inferior or lateral leads- QRS slurring or notching	The presence of ER increased the risk of VF occurrences within 48 hours after the AMI onset
Rudic *et al*[40], 2012	60	Patients with AMI	J-point elevation ⩾ 0.1 mV-notching and slurring type- in at least 2 lateral or inferior leads	Early repolarization pattern seems to be associated with ventricular tachyarrhythmias in the setting of acute myocardial infarction
Tikkanen *et al*[39], 2012	964	432 consecutive victims of SCD because of acute coronary event and 532 survivors of such an event	elevation of the QRS-ST junction of > 0.1 mV - 2 inferior or lateral leads- QRS slurring or notching	The presence of ER increases the vulnerability to fatal arrhythmia during acute myocardial ischemia
Wu *et al*[44], 2013		meta-analysis		Correlation of ER with a higher risk of arrhythmic death but not of cardiac death or death from other causes

ER: Early repolarization; IVF: Idiopathic ventricular fibrillation; AMI: Acute myocardial infarction; SCD: Sudden cardiac death.

that athletes should stop exercising or adopt specific preventive measures[48]. In addition, it should be noted that the usefulness of an electrophysiological study in these subjects is low considering that the inducibility of arrhythmias was observed in only 28% of cases[49]. In symptomatic subjects the etiology of symptoms should be evaluated. In cases of unexplained syncope with ER, an ECG may arouse suspicion if there is also a family history of sudden death or the occurrence of palpitations before syncope. Ventricular arrhythmias, if confirmed, clearly require the delivery of a defibrillation system in primary prevention[50]. It is still unclear if there is a different prognosis for patients presenting with notching or slurring patterns.

A greater characterization of the prognostic value of the ECG pattern of ER is necessary, but there is no doubt regarding the correlation between 12-lead ECG VR patterns and cardiac death due to arrhythmias and that the higher risk was achieved by the combination of an ER pattern in the inferior leads with an ST-segment elevation at J-point greater than 2 mm and a horizontal-descending ST. This pattern is also more common in a poor prognosis population, *i.e.*, in older subjects with a history of myocardial infarction or heart disease.

Conversely, subjects with a good prognosis, who are young and athletic, with no evidence of structural heart disease show a high prevalence of an ER pattern with rapidly ascending ST elevation.

Moreover, the evidence of pause-dependent increase in J-wave amplitude, highlighted in patients with idiopathic VF, has proved to be highly specific and high predictive of arrhythmic events. This simple phenomenon may be used for the stratification of arrhythmic risk in patients with J-wave.

So, in conclusion, given the increased risk of major arrhythmic events in these subjects, it becomes important for the cardiologist to recognize the "malignant ER" pattern in order to improve the risk stratification of these patients (Figure 5).

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MINIREVIEWS

Application of appropriate use criteria for percutaneous coronary intervention in Japan

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Abstract

The aim of this review was to summarize the concept of appropriate use criteria (AUC) regarding percutaneous coronary intervention (PCI) and document AUC use and impact on clinical practice in Japan, in comparison with its application in the United States. AUC were originally developed to subjectively evaluate the indications and performance of various diagnostic and therapeutic modalities, including revascularization techniques. Over the years, application of AUC has significantly impacted patient selection for PCI in the United States, particularly in non-acute settings. After the broad implementation of AUC in 2009, the rate of inappropriate PCI decreased by half by 2014. The effect was further accentuated by incorporation of financial incentives (*e.g.*, restriction of reimbursement for inappropriate procedures). On the other hand, when the United States-derived AUC were applied to Japanese patients undergoing elective PCI from 2008 to 2013, about one-third were classified as inappropriate, largely due to the perception gap between American and Japanese experts. For example, PCI for low-risk non-left atrial ascending artery lesion was more likely to be classified as appropriate by Japanese standards, and anatomical imaging with coronary computed tomography angiography was used relatively frequently in Japan, but no scenario within the current AUC includes this modality. To extrapolate the current AUC to Japan or any other region outside of the United States, these local discrepancies must be taken into consideration, and scenarios should be revised to reflect

contemporary practice. Understanding the concept of AUC as well as its perception gap between different counties will result in the broader implementation of AUC, and lead to the quality improvement of patients' care in the field of coronary intervention.

Key words: Appropriate use criteria; Acute coronary syndrome; Percutaneous coronary intervention; Japan; Stable ischemic heart disease

Core tip: The concept of appropriate use criteria (AUC) regarding percutaneous coronary intervention (PCI) has significantly impacted patient selection for PCI in the United States, particularly in non-acute settings. In Japan, when the United States-derived AUC were applied to Japanese patients, about one-third of elective cases were classified as inappropriate. This is largely due to the perception gap between American and Japanese experts. To extrapolate the current AUC to Japan or any other regions outside of the United States, these local discrepancies must be taken into consideration, and scenarios should be revised to reflect contemporary practice.

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INTRODUCTION

To improve the quality of care, such as indications for and performance of various procedures, appropriate use criteria (AUC) have been developed. The concept of AUC has been widely accepted to aid in quantifying and improving the quality of care, and AUC have become available in various diagnostic and therapeutic modalities[1-3]. In the field of coronary intervention, the potential overutilization of percutaneous coronary intervention (PCI) has come under harsh criticism, particularly after the initial report of the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial[4]. In this setting, AUC for coronary revascularization were developed in 2009 and revised in 2012 in the United States[5,6].

In this review, we aimed to provide an overview of the concept of AUC for coronary revascularization and its impact on the selection of patients undergoing PCI in the United States. Furthermore, we sought to clarify the appropriate ratings of PCI indications in Japan based on the current United States-derived AUC. Finally, we discuss issues that remain to be resolved when extrapolating the current AUC to Japanese clinical practice and propose the future direction of this concept in Japanese cardiovascular society. This minireview will aid in the broader implementation of the concept of AUC in various countries outside of the United States, and will lead to improve the quality of care, especially patients' selection, in PCI.

ROLE OF CORONARY INTERVENTION IN STABLE ISCHEMIC HEART DISEASE

PCI providing emergent or urgent recanalization of acute thrombi has played a crucial role in treating patients with acute coronary syndrome (ACS). The so-called "open artery hypothesis" proposes that early reperfusion through infarcted coronary arteries leads to better clinical outcomes than nonreperfusion. Reopening an occluded coronary artery would minimize myocardial injury, preserves cardiac function, and may ultimately improve overall survival.

From the same scientific rationale for improving patient longevity, preventing future acute coronary syndrome, and relieving anginal symptoms, PCI was also widely implemented in stable ischemic heart disease (SIHD) patients for a fairly short time period. However, in the past decade, increasing scientific evidence has highlighted the unclear benefit of PCI on SIHD, and expectations for PCI have been tempered[7]. This issue was further underscored by the publication of the COURAGE trial[8], a multicenter study that recruited most of its patients from the Veterans Administration Hospital Network and failed to demonstrate clear benefits of PCI for hard endpoints (mortality and/or myocardial infarction) in comparison with optimized medical therapy alone in patients with SIHD. Concern towards overuse of PCI has emerged, and the above neutral results for PCI in the non-acute setting provoked a debate in the reconsideration of the indications for elective PCI.

Under these circumstances, 6 professional societies in the United States [American College of Cardiology Foundation (ACCF)/Society for Cardiovascular Angiography and Interventions (SCAI)/Society of Thoracic Surgeons (STS)/American Association for Thoracic Surgery (AATS)/American Heart Association (AHA)/American Society of Nuclear Cardiology (ASNC)] have presented their own "appropriate use" provisions in order to solve this problem. The original criteria were developed in 2009, and the revised version was published in 2012[5,6].

DEVELOPMENT OF AUC

The process of evaluating appropriateness was based on the RAND approach, which blends scientific evidence, guidelines, and practical experience by engaging a technical panel in a modified Delphi exercise. In brief, nationally recognized experts were recruited, and the panel included interventional cardiologists, cardiovascular

surgeons, and general cardiologists. Over 200 clinical scenarios were prepared. Initially, the members independently rated the appropriateness of performing PCI in these clinical scenarios using a 9-point scale, with 1 point regarded as being the most inappropriate and 9 points as being the most appropriate, based on different combinations of the following items: (1) Anatomical information [left main trunk (LMT), 3-vessel disease (VD), 1- or 2-VD with/without proximal left anterior descending artery (LAD) involvement]; (2) Evaluation of the presence and severity of preoperative ischemia (treadmill, exercise myocardial scintigraphy, and stress echocardiography); (3) Presence and severity of symptoms [asymptomatic, Canadian Cardiovascular Society (CCS) scale 1-4]; and (4) Presence of optimal medical therapy. An example would be as follows.

Asymptomatic patient with diabetes; after screening electrocardiography performed at an annual health check-up revealed abnormalities, coronary computed tomography angiography (CCTA) findings indicated severe stenosis in the mid-right coronary artery; myocardial scintigraphy revealed mild ischemia in the relevant area, which was consistent with the finding of CCTA; drugs administered: Aspirin (100 mg), rosuvastatin (2.5 mg).

When this scenario is evaluated using the 4 evaluation points for AUC, the patient would be classified as having "asymptomatic single-vessel disease without proximal LAD involvement and mild ischemia, and no optimal medical therapy". According to the AUC, each evaluation committee member determines the appropriateness of PCI based on such a simplified scenario. The panel then met for a face-to-face discussion, and the panel members independently re-provided their final scores for each indication. Each panel member had equal weight in producing the final result. The median score was documented for each scenario. Based on the median score for each indication (range, 1-9), they were categorized as "appropriate" (median, 7-9), "uncertain" (4-6), or "inappropriate" (1-3).

CURRENT STATUS OF APPROPRIATE RATINGS IN THE UNITED STATES

A set of AUC was initially proposed to review clinical decisions made by medical teams in each facility. In addition, after its publication and initial phase of implementation, attempts have been made to assess the appropriateness of the indications for PCI in actual clinical practice by applying these AUC to large-scale registry data[9,10]. The results of the analysis of PCI appropriateness in the United States revealed that in acute settings, the procedure was generally adapted appropriately. By contrast, in non-acute settings, 11.6% of PCIs were deemed to be inappropriate (by 2009 AUC), and when using the revised 2012 AUC, as many as 26.2% of PCIs were evaluated as inappropriate, indicating the overuse of PCI for SIHD (Figure 1).

At the same time, the following changes were observed from 2009 to 2014[10], which were thought to popularize the concept of AUC: (1) The rates of patients with serious symptoms (CCS 3 or 4), patients with severe ischemia, and patients receiving optimal medical therapy increased; (2) The annual trend revealed that the rate of inappropriate PCI decreased from 26.2% to 13.3% (Figure 1), and the ratio of elective PCI patients decreased 30% overall; and (3) The variance of appropriateness among facilities also improved.

In the United States, on the basis of a study by Hachamovitch *et al*[11] demonstrating that PCI-related prognostic improvement could only be obtained in cases with > 10% ischemic area, pre-procedural evaluation of the extent of ischemia is deemed almost essential. Furthermore, reflecting the COURAGE trial, clinical guidelines also emphasize the use of optimal medical therapy prior to revascularization. From such evidence, PCI in cases of 1- or 2-VD without proximal LAD involvement and optimal medical therapy is not accepted regardless of patient symptoms. Additionally, coronary artery bypass graft (CABG) is considered to be a more appropriate therapeutic strategy than PCI for multivessel CAD, based on the findings of the Synergy between PCI with Taxus and Cardiac Surgery (SYNTAX) trial[12] and the Future Revascularization Evaluation in Patients with Diabetes Mellitus: Optimal Management of Multivessel Disease (FREEDOM) trial[13].

Consequently, according to the CathPCI registry (National Cardiovascular Data Registry), there was a significant 33.8% reduction in the volume of non-acute PCI procedures from 2010 (89704) to 2014 (59375)[10]. Similarly, analysis of the Clinical Outcomes Assessment Program also demonstrated a 43% decline in the number of PCIs for elective indications (from 3818 in 2010 to 2193 in 2013)[14].

APPLICATION OF THE CURRENT AUC IN JAPAN

The number of PCI procedures has continued to increase in Japan. More than 250000 procedures in > 800 hospitals were performed in 2014, which is estimated to be > 14 times greater than the number of CABG procedures. The proportion of elective procedure accounts for < 40% of all PCI in the United States, and as many as three-fourths of PCIs are performed in non-acute settings in Japan[15,16].

To document the rate of appropriate vs. inappropriate PCI in Japanese practice, we applied US AUC scenario ratings to patients registered in the Japan Cardiovascular Database - Keio interhospital Cardiovascular Studies (JCD-KiCS). JCD-KiCS is an ongoing prospective multicenter registry built to collect clinical background and outcome data on consecutive PCI patients in 15 centers affiliated with Keio University Hospital (11258 patients registered from 2008 to 2013)[17-22].

Similar to the results in the United States, PCI was

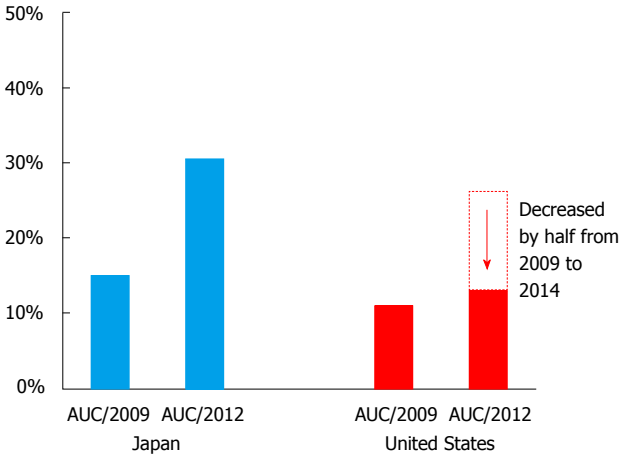

Figure 1 The rates of inappropriate percutaneous coronary intervention in non-acute settings in Japan and in the United States. In Japan, when evaluated under the original criteria developed in 2009 (AUC/2009), 15% of PCIs were categorized as inappropriate, and 30.7% of PCIs were classified as inappropriate under the revised criteria (AUC/2012) (blue bars). By contrast, in the United States, 11.6% of PCIs were deemed to be inappropriate by AUC/2009, and when using the AUC/2012, 26.2% of PCIs were classified as inappropriate (red bars). Additionally, the rates of inappropriate PCI decreased by half from 2009 to 2014, owing to the publication of AUC. PCI: Percutaneous coronary intervention; AUC: Appropriate use criteria.

generally performed appropriately in acute settings. However, in non-acute settings, 15% of PCI cases were classified as inappropriate under the 2009 AUC, and 30.7% of PCI cases were categorized as inappropriate under the revised 2012 AUC. As mentioned earlier, when the 2009 AUC was applied, the rate of inappropriate PCI in the United States was 11%, and when the revised 2012 AUC was used, the rate ranged from 13% to 26%; based on these findings, the rate of inappropriate PCI in Japan is high (Figure 1).

This higher rate of inappropriate PCIs in Japan compared with the United States is mostly driven by differences in the therapeutic strategy toward patients with low-risk ischemia. In contrast to the United States practice, where indications for PCI are strictly limited to cases with > 10% ischemia, PCI for low-risk patients is considered acceptable in Japan. The Japanese Stable Angina Pectoris (JSAP) trial evaluated the effectiveness of PCI for such stable low-risk CAD patients compared with medical therapy in Japan, and the results were strikingly different from those of the COURAGE trial. In the JSAP trial, the long-term benefit of PCI compared to conservative management was observed[23]. The JSAP trial enrolled 384 patients with low-risk CAD consisting of 1- or 2-VD from 78 institutions in Japan. This trial was conducted in a randomized fashion, and patients were randomly allocated to a medical therapy only group or PCI plus medical therapy group. The primary end point was the composite of all-cause death, ACS admission, cerebrovascular accidents, and emergency hospitalization. During the 3.3-year follow-up, the incidence of the primary composite end point was significantly lower in the PCI plus medical therapy group compared to the initial medical therapy-only group, which demonstrated the effectiveness of PCI for stable CAD patients at low-risk for cardiovascular events.

However, the JSAP trial had several concerns. First, the benefit of PCI was only recognized in the composite end point and disappeared for all-cause death. This discrepancy could obscure the prognostic impact of PCI for this low-risk population. Furthermore, in this trial, the medical therapy was not optimal in either group. The prescription rates of statin and beta-blocker were 45.2% and 51.6%, respectively, even in the medical therapy group. From the insight of the COURAGE trial[8], implementation of the optimal medical therapy was an equivalent therapeutic option for the management of low-risk CAD patients, and the findings of the JSAP trial should be cautiously interpreted.

We have also previously evaluated the appropriateness of PCI, based on both the United States and Japanese AUC, and compared the ratings[18]. Japanese AUC was developed in the line with the United States AUC; however, several issues have merged since the establishment of J-AUC. J-AUC was published in 2007, and this was before the publication of COURAGE trial. Therefore, the importance of optimal medical therapy was not highlighted in the clinical practice guidelines then. Furthermore, the J-AUC panel was weighted more toward coronary interventionists (7, in comparison to 2 cardiac surgeons). Thorough revision is needed for the application of J-AUC, but it reflected consensus toward the indication of PCI in Japan to some extent. Naturally, the rate of inappropriate PCI under J-AUC in JCD-KiCS was substantially lower (5.2%) than that using the US AUC (15%); the rating discrepancies between the US- and J-AUC were largely due to difference in the interpretation of revascularization in asymptomatic, low- or intermediate-risk patients without proximal LAD involvement. This discrepancy may be related to multiple factors including cultural differences and the unique Japanese healthcare system. It also underscores the need for revision of AUC according to their associated culture and healthcare system.

Lastly, the variability of the appropriate ratings among institutes is also an issue that remains to be resolved. When the current United States AUC was applied to our registered dataset (JCD-KiCS registry), the rate of inappropriate PCI varied across institutes, ranging from 17.5% to 50% (Figure 2). This finding suggests uneven care in the field of coronary intervention in Japan, which should be resolved to improve the quality of care. Hospital-level variation in the proportion of PCIs classified as inappropriate was also found in the United States. However, since the launch of the AUC in 2009, it has substantially improved[10]. The concept of AUC has tremendous potential to improve patient selection for PCI, and is expected to gain wider acceptance in Japanese clinical practice.

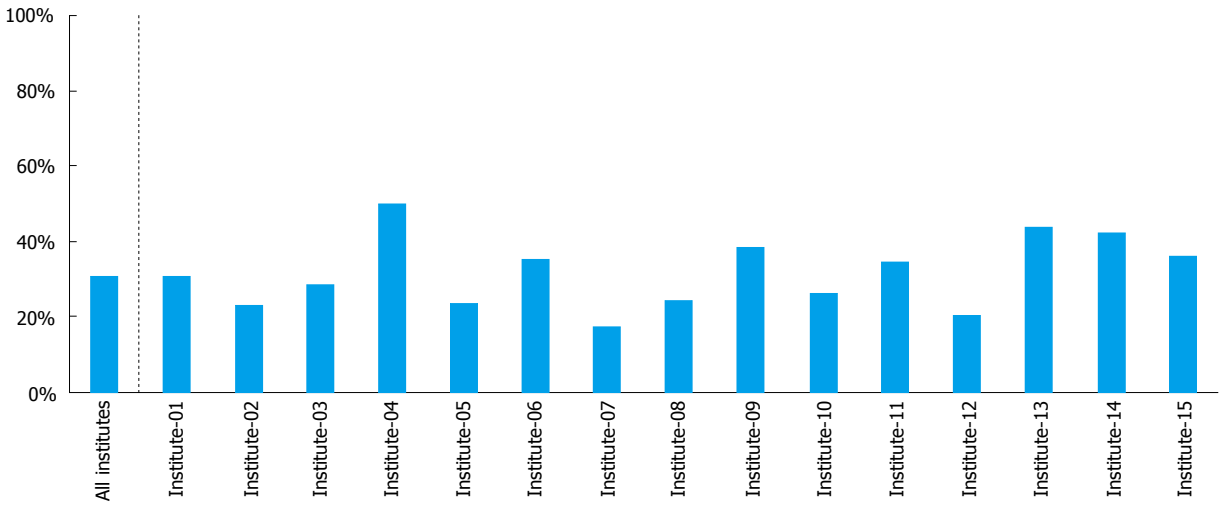

Figure 2 The variability of inappropriate ratings in elective percutaneous coronary interventions among institutes participating in the JCD-KiCS registry (15 centers). When the current AUC (developed in 2012) was applied to the JCD-KiCS registry, 30.7% of elective PCIs were classified as having inappropriate indications. This rate varied across institutes, ranging from 17.5% to 50%. AUC: Appropriate use criteria; PCI: Percutaneous coronary intervention.

PROBLEMS EXTRAPOLATING THE CURRENT AUC TO DAILY PRACTICE IN JAPAN

Can the current United States-derived AUC be directly applied to daily clinical practice in Japan? There are several problems concerning this issue. First, the modalities for evaluating CAD differ between the United States and Japan. In the United States, stress testing, including treadmill, myocardial scintigraphy, and stress echocardiography, is generally used to assess ischemia. However, in recent years, CCTA has become widespread in Japan, and fractional flow reserve (FFR) is often used to assess ischemia. Since appropriateness criteria assign high value to functional information, reflecting a strong tilt toward physiological assessment of ischemia in the United States, CCTA, which only provides anatomical information, is not recognized as one of the prior non-invasive tests under these criteria. We previously indicated that due to the popularity of CCTA and FFR, Japanese PCI cannot be adequately evaluated under the current AUC developed in the United States (Figure 3)[17], and an editorial published from the American perspective entitled "lessons learned from Japan" also mentions this problem[24].

Second, as quoted previously, the therapeutic strategy toward patients with low-risk ischemia differs greatly between the United States and Japan. Clearly, further studies involving the Japanese population are needed to close the perception gap for PCI indications that lack sufficient scientific underpinning.

Finally, there is room for improvement in the current AUC proposed in the United States. For example, clinical scenarios involving PCI for chronic total occlusion (CTO) are limited to "chronic total occlusion of 1 major epicardial coronary artery, without other coronary stenosis"; therefore other types of CTO-PCI cannot be accurately evaluated[5,6,19]. In addition, although the use of FFR is limited to cases with moderate stenosis, it should be widely accepted in evaluating various lesions. Based on the results of the FFR *vs* angiography for multi-vessel evaluation Ⅱ (FAME2) study[25], the prevalence of FFR-guided PCI substantially increased[17,26]. Because FFR enables the evaluation of the significance of CAD in the cardiac catheterization laboratory, pre-procedural tests might have been omitted in some patients; therefore, patients evaluated only by FFR are likely to be classified as having inappropriate PCI, unless such cases are properly assigned to FFR-related scenarios. However, in the current AUC, ischemic evaluation by FFR is accepted only for 1- or 2-vessel CAD with borderline stenosis of "50% to 60%", and the use of FFR in coronary artery stenosis greater than 60% was not adjudicated[5,6].

Previously, we discussed such issues concerning the current AUC with United States investigators in the form of correspondence to the paper by Inohara *et al*[27] and Brandley *et al*[14,28]. We mainly insisted on the validity of performing CCTA as a pre-procedural evaluation. However, although they agreed that AUC comprise a living document and require frequent revision to incorporate evolving evidence, they disagreed with our opinion, since pre-procedural evaluation using CCTA was performed in only 0.5% of all PCIs registered in their dataset. When considering such perception gaps, it is impractical to extrapolate the current AUC advocated in the United States to daily clinical practice in Japan. In order to popularize the concept of appropriate ratings in Japan, further effort is needed to refine and correct the disconnection between the current AUC and Japanese clinical practice.

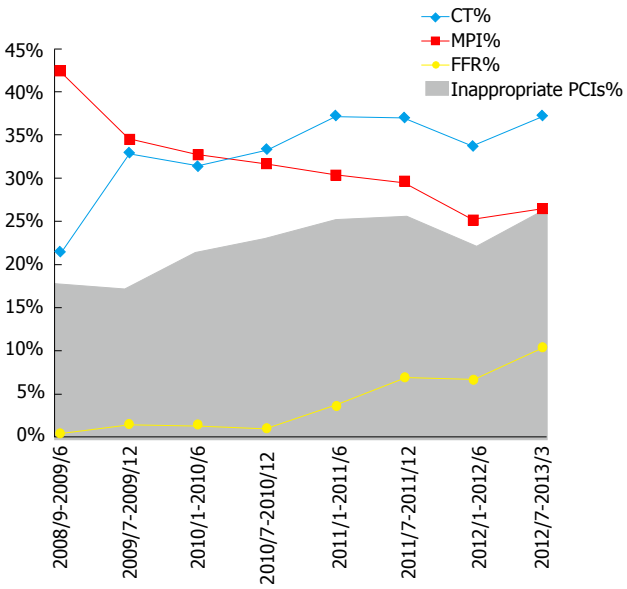

Figure 3 Association between temporal trends in non-invasive tests and frequency of inappropriate ratings. The proportion of patients evaluated with CCTA and FFR substantially increased (both *P* for trend < 0.001), which coincided with a decrease in utilization of stress myocardial perfusion imaging over the course of 5 years (*P* for trend < 0.001). Contemporaneously, the proportion of inappropriate PCIs increased (*P* for trend = 0.003) in parallel with the increase in utilization of CCTA. The gray area indicates the percentages of inappropriate procedures based on original appropriateness criteria (AUC/2009). From Inohara *et al*[17]. CCTA: Coronary computed tomography angiography; MPI: Myocardial perfusion imaging; FFR: Functional flow reserve.

TOWARDS THE INTERNATIONAL APPLICATION OF AUC

Although the revision of the current AUC in accordance with the daily clinical practice in Japan will require some effort, the effects that the concept of AUC brings are expected to be extremely large. As previously discussed, the application of AUC in the United States led to a reduction in the number of elective PCI by half.

A recent study by Chinese investigators demonstrated that the medical records of many patients undergoing PCI lacked documentation of important process measures needed to assess quality of care[29]. AUC can serve as a foundation to guide future efforts on quality improvement in the use of PCI in such cases. Variation in quality of care across hospitals has also been noted in European countries. In a hospital-level international comparison of patients with acute myocardial infarction admitted to hospitals in Sweden and the United Kingdom, inter-hospital variation in the use of primary PCI, antiplatelet treatment, and statin at discharge were important in explaining variation in 30-d mortality[30]. The results of this study suggest that more consistent adherence to new treatment guidelines across all hospitals would deliver improved outcomes, and standardizing the appropriateness of the revascularization procedures could aid in facilitating this adherence.

In Japan, the Japanese Association of Cardiovascular Intervention and Therapeutics (CVIT) has developed a nationwide registry designed to collect clinical variables and outcome data on PCI patients (J-PCI), which is also linked to medical specialty boards. Therefore, it is feasible that the construction of a feedback system *via* such a registry will lead to the popularization and practical use of AUC in daily clinical practice in Japan. However, issues concerning the balance between the professionalism and autonomy of physicians are deeply involved, making it difficult to reach a conclusion regarding the role of physician discretion in the decision to perform PCI. Looking at various past examples in Japan, the Japanese public appears to have developed a negative attitude toward organizations, including specialized professional groups that have failed to perform self-auditing. For this reason, we believe that some sort of restriction toward the indication of PCIs such as AUC will be implemented in the near future.

CONCLUSION

The concept of AUC has shown great value as a quality measure and led to improved patient selection for PCI in the United States. Although several issues remain to be resolved in order to extrapolate the current AUC to Japanese clinical practice, this concept should be introduced to improve the quality of care in Japan and other countries.

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ORIGINAL ARTICLE

Retrospective Cohort Study

Rationale and design of the cardiorespiratory fitness and hospitalization events in armed forces study in Eastern Taiwan

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Institutional review board statement: The study was reviewed and approved by the Institutional Review Board of Mennonite Christian Hospital in Taiwan.

Informed consent statement: Participants were not required to give informed consent to this retrospective study since the analysis of baseline characteristics used anonymous clinical data that were obtained after each patient agreed to share with the results by written informed consent.

Conflict-of-interest statement: The authors declare that they have no conflict of interest.

Data sharing statement: No additional data are available.

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Abstract

AIM

To investigate the association between cardiorespiratory fitness and hospitalization events in a cohort of large voluntary arm forces in Taiwan.

METHODS

The cardiorespiratory fitness and hospitalization events in armed forces (CHIEF) is a retrospective cohort consisting of more than 4000 professional military members aged 18-50 years in Eastern Taiwan. All participants received

history taking, physical examination, chest radiography, 12-lead electrocardiography, blood tests for cell counts and fasting glucose, lipid profiles, uric acid, renal function and liver function in the Hualien Armed Forces General Hospital during 2014. In addition, participants were required to undergo two indoor resistant exercise tests including 2-min push-up and 2-min sit-up, both scored by infrared sensing, and one outdoor endurance 3000-m none weight-bearing running test, the main indicator of cardiorespiratory fitness in the Military Physical Training and Testing Center in Eastern Taiwan in 2014.

RESULTS

Hospitalization events for cardiovascular disease, acute kidney injury, rhabdomyolysis, severe infectious disease, acute psychiatric illness, diabetes, orthopedic surgery and mortality will be identified in the National Insurance Research Database for 10 years.

CONCLUSION

CHIEF will be among the largest Eastern Asian armed forces cohort, in which physical status was strictly evaluated to follow up the hospitalization events for severe illness.

Key words: Cardiorespiratory fitness; Hospitalization; Voluntary armed forces

Core tip: Whether rigorous physical trainings including endurance and resistance exercises for professional young adults in armed forces associated with well or poor cardiovascular outcomes in their middle ages is unknown. In addition, several unhealthy factors such as cigarette smoking and depressive mood are prevalent among arm forces, which may affect the physical performance and increase the risk of hospitalization for severe illness. In this case, we will investigate the association of cardiorespiratory fitness with hospitalization events in a retrospective armed forces cohort consisting of about 4000 professional military members aged 18-50 years in Eastern Taiwan for more than 10 years.

Lin GM, Li YH, Lee CJ, Shiang JC, Lin KH, Chen KW, Chen YJ, Wu CF, Lin BS, Yu YS, Lin F, Su FY, Wang CH. Rationale and design of the cardiorespiratory fitness and hospitalization events in armed forces study in Eastern Taiwan. *World J Cardiol* 2016; 8(8): 464-471 Available from: URL: http://www.wjgnet.com/1949-8462/full/v8/i8/464.htm DOI: http://dx.doi.org/10.4330/wjc.v8.i8.464

INTRODUCTION

Professional military members are required to take regular rigorous physical trainings including endurance and resistance exercise to maintain their outstanding fitness. Frequent exercise training and well physical fitness have been associated with lower risk of cardiovascular disease and mortality in the general population[1-3]. However, current evidence showed conflicting results regarding the cardiovascular outcomes in those taking repetitive strenuous exercises[4,5]. For instance, cardiac remodeling such as left ventricular muscle hypertrophy, chamber dilatation, mitral valve regurgitation, and arrhythmia, which have been well regarded as poor prognostic predictors of acute cardiac events among patients with conventional atherosclerotic risk factors are commonly present in elite athletes[6-8]. Whether these physiological cardiac adaptations to repetitive vigorous training on future cardiovascular disease and mortality are beneficial or hazardous to armed forces remain unknown. In addition, several unhealthy behaviors and environments such as cigarette smoking, alcohol intake, stress, insomnia, and depressive mood are prevalent among arm forces, which may affect the physical performance by reducing cardiopulmonary function and increase the risk of hospitalization for acute illness[9,10]. However there were few studies using large military cohorts, particularly of Asian young adults, with detailed data of demographics, laboratory exams, and cardiopulmonary function evaluations at baseline, to follow up the incidence of cardiovascular disease and other severe illness events. Therefore the aim of our study is to retrospectively investigate the association between cardiorespiratory fitness and hospitalization events in a large voluntary arm forces cohort in Eastern Taiwan.

MATERIALS AND METHODS

Study population

The cardiorespiratory fitness and hospitalization events in armed forces (CHIEF) is a retrospective cohort consisting of voluntary military members aged 18-50 years in Eastern Taiwan during 2014.

Measurements of the health examinations

All participants had to undergo physical examinations, anthropometric measurements for height, weight, and waist circumference at standing position, hemodynamic status including pulse rate and blood pressures, which were automatically measured by the PARAMA TECH FT-201 blood pressure monitor over right upper arm at sitting position, after taking rest for at least 15 min, chest radiography [posteroanterior (PA) standing view], 12-lead electrocardiography which was interpreted mainly according to the computerized Minnesota Code classification system[11], urinalysis, blood tests for cell counts and concentrations of fasting glucose, total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglycerides, serum uric acid, blood urea nitrogen, creatinine, estimated glomerular filtration rate (eGFR) which was defined on the basis of the Chronic Kidney Disease Epidemiology Collaboration equation[12], aspartate transaminase (AST), alanine transaminase (ALT), and surface antigen of

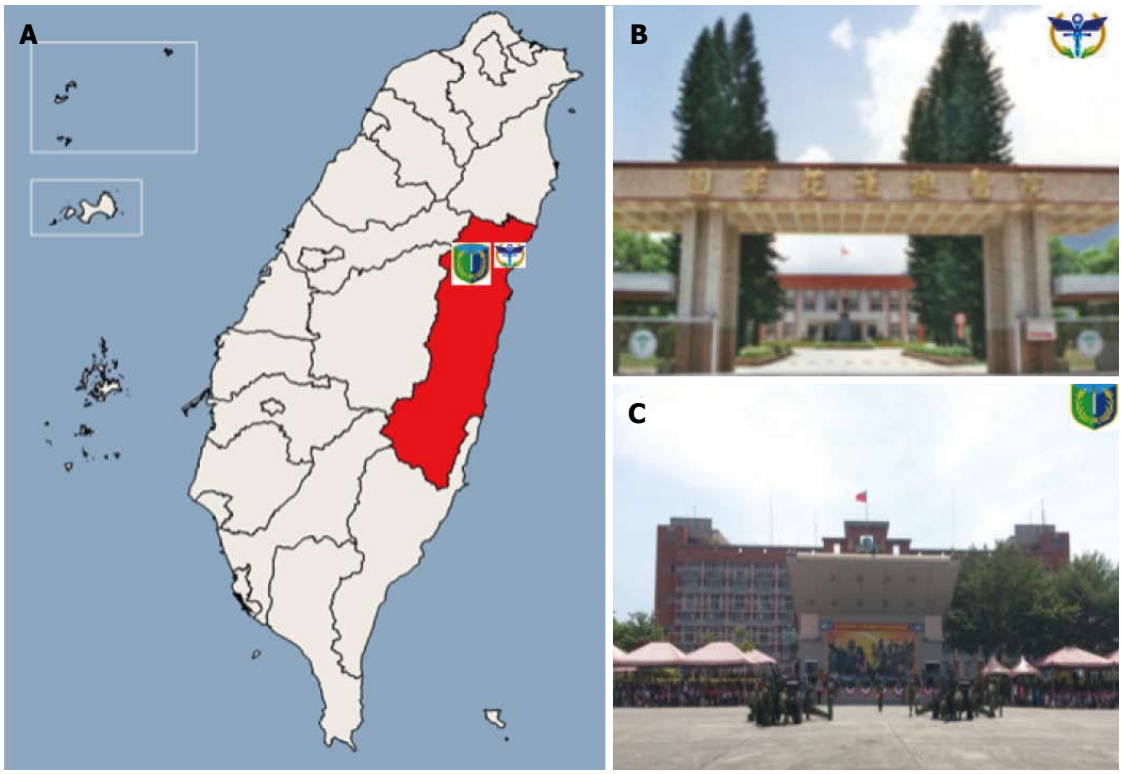

Figure 1 Geographic institutions of the cardiorespiratory fitness and hospitalization events in armed forces study performed. (A) The map of Hualien County in Taiwan is highlighted in red, and the symbols represent (B) the Hualien-Armed Forces General Hospital and (C) the Military Physical Training and Testing Center in the Army HuaDong Defense Command.

viral hepatitis B in the Hualien Armed Forces General Hospital where is the only military referral center for the professional armed forces in Hualien, Taiwan to perform the whole body health exams in 2014 (Figure 1). With regard to history taking, all participants were asked to self-report a questionnaire including demographic information, personal and third degree relatives medical history, current cigarette smoking status, current alcohol intake status, current betel chewing status, frequency of exercise persisting for at least 30 min in the past half year (never, occasionally, 0-1 time/wk, 3-5 times/wk), ever experienced any discomfort related to exercise (dizziness, chest tightness, dyspnea, or palpitation), and Brief Symptom Rating Score (BSRS-5)[13,14] which is a 5-item Likert scale [scores of 0 (none), 1 (mild), 2 (moderate), 3 (severe), 4 (extremely severe)] for measurement of the severity of psychological distress. A higher score indicates poorer mental health[13]. The full scale contained the following five items of psychopathology: (1) feeling tense or keyed up (anxiety); (2) feeling low in mood (depression); (3) feeling easily annoyed or irritated (hostility); (4) feeling inferior to others (interpersonal hypersensitivity: Inferiority); and (5) having trouble falling asleep (insomnia); and an additional question, "do you have any suicide ideation?" was added at the end of the questionnaire.

Measurements of the physical fitness

In addition, participants were also required to undergo 2 indoor resistant exercise tests including 2-min push-up and 2-min sit-up and one outdoor endurance 3000-m none weight-bearing running exercise test, the main indicator of cardiorespiratory fitness in the Military Physical Training and Testing Center in Eastern Taiwan during 2014. Both 2-min push-up and 2-min sit-up contests were computerized scoring and whole courses were recorded by video. The procedure of 2-min push-up was scored only when the participants' body upward movement achieving the initial resting set height levels of shoulder and buttock simultaneously detected by infrared sensors (Figure 2A). The test would be early aborted once either elbows or knees touched down on the ground before time out. The procedure of 2-min sit-up was scored only if participants' body bended forward and elbows blew the touch sensors on both thighs (Figure 2B). With regard to 3000-m none weight-bearing running exercise test, whole course was recorded by video as well. All 3000-m none weight-bearing running tests were only allowed to be held at 16:00 pm when the risk coefficient of heat stroke, the product of outdoor temperature (℃) and relative humidity (%) × 0.1, was less than 40 or it was not raining.

Follow-up for the outcome of interests

After 2014, those retained in annual health or physical fitness exams will be followed up longitudinally. The outcome of interest will be the hospitalization events for cardiovascular disease, acute kidney injury, rhabdomyolysis, severe infectious disease, acute psychiatric illness, type 2 diabetes mellitus, orthopedic surgery, and mortality respectively. Hospitalization events will be identified in the National Insurance Research Data-

Figure 2 Illustrations of standardized procedure for push-up and sit-up tests in the cardiorespiratory fitness and hospitalization events in armed forces study, respectively. A: A participant prepared for the push-up test surrounded by four flared sensors and a computerized monitor was ahead of him. A supervisor squatted aside by him to watch for all his procedure; B: A participant prepared for the sit-up test with two touch sensors were bound on both thighs and a computerized monitor was opposite to him. A supervisor stood aside by him to watch for all his procedure.

base and followed up for at least 10 years. This study was approved by the Institutional Review Board of the Mennonite Christian Hospital in Hualien, Taiwan and written informed consent was obtained from all participants.

Statistical analysis

The armed forces in Eastern Taiwan who did not receive health examinations or undergo exercise tests in the index centers of Hualien during 2014 were excluded. Figure 3 shows the flow diagram to select the CHIEF study cohort. Demographic characteristics and exercise performances of men and women were reported as mean ± SD or percent for continuous and categorical variables, respectively. The analysis will use the time for follow-up at January 1, 2014 with censoring at first occurrence of hospitalization events for specific severe illness, death, or end of follow-up (December 31, 2024). Kaplan-Meier analysis will be used to assess the sex-specific association of each exercise test performances (2-min push-up, 2-min sit-up, and 3000-m none weight-bearing running) with incident hospitalization events for specific severe illness. Cox proportional hazard regression analyses will be used to assess the sex-specific multivariable association between each exercise test performance and incident hospitalization events, adjusting for potential confounders. A 2-tailed value of *P*-value < 0.05 will be considered significant.

RESULTS

The historical CHIEF cohort consists of 4080 participants who received both health exams and underwent at least one exercise test during 2014. The administrative rates for 2-min sit-up, 2-min push-up, and 3000-m none weight-bearing running test were 99.5%, 98.8% and 88.6%, respectively. The descriptive statistics of baseline profiles, medical and family history, laboratory and 12-lead electrocardiographic findings, BSRS scores, and each exercise test performance of men and women were shown in Tables 1-4 respectively. Of these participants, men accounted for about 89.9% and the mean age of men and women were about 29 and 28 years, respectively.

DISCUSSION

Previous studies have demonstrated the benefit of leisure time exercise which may reduce inflammatory response, viscosity, and the risk of cardiovascular disease in the general population[15-18]. However, it is not clear the relationship of what kinds of exercise, how the dosing of exercise, and the performance of physical fitness in young adults with future health status in their middle age. In addition, for a population with rigorous exercise training daily for work such as athletes and professional military members, the question of exercise training and physical fitness on the health status has not been answered yet, since there were too few large cohort studies to investigate the association. Therefore the CHIEF study will be one of the largest retrospective military cohort ever in the world to retrospectively follow up the severe illness events.

In CHIEF, the anthropometric profile of men was characterized by an average overweight value defined by the body mass index criteria for Eastern Asian individuals (> 24.0 kg/m^2), but within a non-obese waist circumference limit defined to be < 85 cm for Asian male populations[19,20]. This may reflect that muscle mass may account for a higher proportion of body weight in men, which was also supported by a higher proportion of electrocardiographic left ventricular hypertrophy (17%) in men. In contrast, both levels of body mass index and waist circumference in women were within non-obese levels suggested for Asian female populations[20]. Unlike elite athletes, many unhealthy behaviors such as cigarette smoking and alcohol consumption were prevalent in men (about 40%) and in women (10%-20%). In addition, about 40% of men reported mild to extremely severe depression or anxiety and 50% of women reported those negative psychological symptoms. Because of the specialty of armed forces, all these confounders should

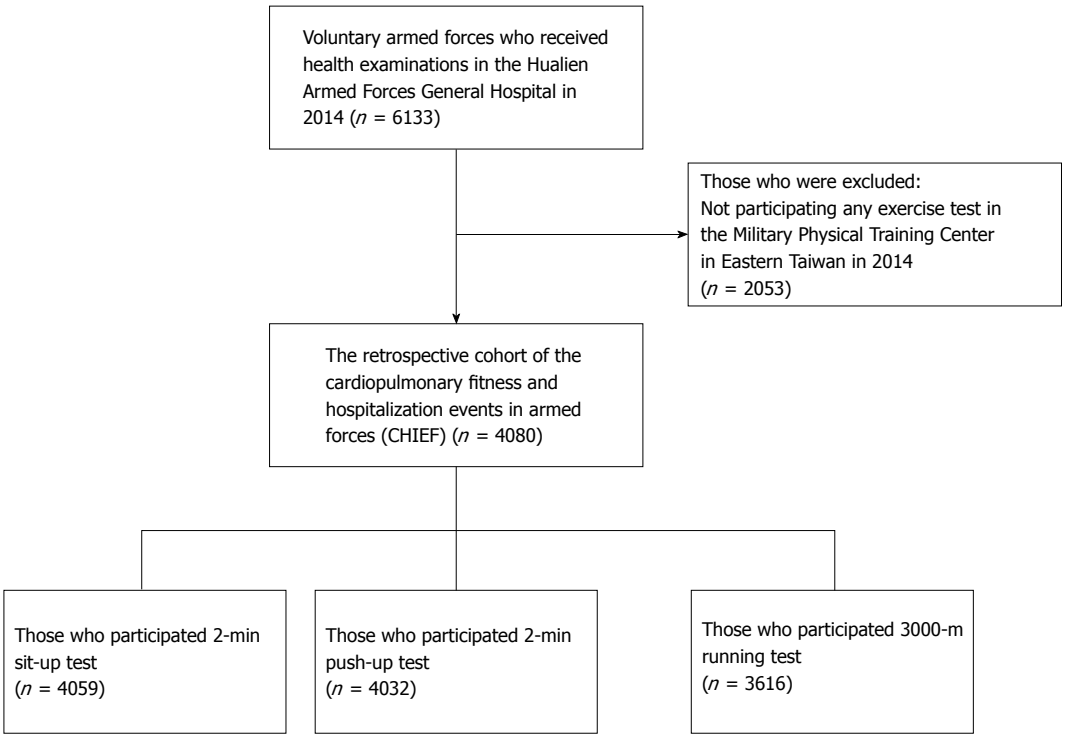

Figure 3 Flow diagram to select the eligible cardiorespiratory fitness and hospitalization events in armed forces cohort during 2014.

Table 1 Baseline demographics, hemodynamics, medical and family history, and habit of exercise of men and women in the cardiorespiratory fitness and hospitalization events in armed forces study

	Men (*n* = 3669)	Women (*n* = 411)
Age (yr)	29.3 ± 5.9	28.1 ± 6.5
Specialty (%)		
Air force	28	23.6
Army	50.5	61.6
Navy	21.5	14.8
Height (cm)	171.8 ± 5.8	160.5 ± 4.4
Weight (kg)	73.5 ± 10.2	58.1 ± 8.1
Body mass index (kg/m^2)	24.9 ± 3.1	22.5 ± 2.9
Waist circumference (cm)	83.4 ± 8.0	73.3 ± 7.4
Pulse rate (times/min)	72.2 ± 10.8	75.7 ± 10.1
Systolic blood pressure (mmHg)	118.4 ± 13.1	106.5 ± 12.4
Diastolic blood pressure (mmHg)	70.6 ± 10.1	65.2 ± 9.1
Current smoking (%)	38.1	12.2
Current alcohol intake (%)	44.7	17.1
Current betel chewing (%)	12	1.2
Medical history (%)		
Hypertension	1.5	0.2
Symptomatic arrhythmia	1.1	1.7
Chronic hepatitis B	3.4	1.7
Family history of cardiovascular disease within 3rd relatives (%)	3.4	4.6
Frequency of exercise (%)		
Never or occasionally	19.7	30.5
1-2 times/wk	38.2	42.9
Over 3-5 times/wk	42.2	26.6
Cardiopulmonary distress symptoms related to exercise (%)	8.9	15.4

Data were presented as the mean ± SD and percentage (%).

be taken into account the association between physical fitness and severe illness events.

Push-up and sit-up performance were used to assess musculoskeletal fitness. Push-up exercise is a strengthening exercise for building up strength and endurance in the muscles of the upper arm and shoulders, and sit-up exercise is performed to enhance abdominal muscular endurance. Mota *et al*[21] showed that low push-up and sit-up test performance is associated with increased risk for obesity and metabolic risk in adolescent girls. Furthermore, Katzmarzyk *et al*[22] found that sit-up but not push-up performance is predictive of mortality in the Canadian population. Performance in 3000-m (middle distance) running mainly depends on maximal aerobic power (VO_2max)[23], which are related to several physiological parameters including maximal oxygen uptake, running economy, velocity at 4 mmol/L blood lactate concentration, and the minimal velocity at which VO_2max occurs[24-28]. Accordingly, the performance of 3000-m none weight-bearing running test in armed forces could be regarded as a good surrogate for their cardiorespiratory fitness. As is known, adolescent cardiorespiratory fitness has been associated with adult fatness[29]. Several previous studies in the Western countries demonstrated that superior cardiorespiratory fitness may be associated with lower risk of hospitalization events for incident hypertension, diabetes mellitus, coronary heart disease, stroke, cataract, and diverticular complications[30-35]. Moreover, a relationship between cardiorespiratory fitness and all-cause and cardiovascular mortality has been well

Table 2 Baseline laboratory and electrocardiographic findings of men and women in the cardiorespiratory fitness and hospitalization events in armed forces study

	Men (n = 3669)	Women (n = 411)
Blood routine		
Hemoglobin (g/dL)	15.2 ± 1.0	13.0 ± 1.0
Mean corpuscular volume (fl)	85.1 ± 6.3	85.2 ± 6.8
RBC count (10^6/μL)	5.3 ± 0.5	4.7 ± 0.4
WBC count (10^3/μL)	6.8 ± 1.7	6.6 ± 1.7
Platelet count (10^3/μL)	252.9 ± 50.5	274.5 ± 53.1
Blood biochemistry		
Fasting glucose (mg/dL)	93.6 ± 13.4	89.1 ± 7.5
Total cholesterol (mg/dL)	174.4 ± 34.0	167.4 ± 29.1
LDL-cholesterol (mg/dL)	106.0 ± 29.7	93.5 ± 25.3
HDL-cholesterol (mg/dL)	47.9 ± 9.8	56.9 ± 11.0
Triglycerides (mg/dL)	115.1 ± 100.3	77.7 ± 38.9
BUN (mg/dL)	12.9 ± 2.8	10.7 ± 2.4
Creatinine (mg/dL)	1.0 ± 0.1	0.7 ± 0.1
eGFR (mL/min per 1.73 m^2)	99.8 ± 14.2	109.4 ± 18.4
Uric acid (mg/dL)	6.7 ± 1.3	4.7 ± 0.9
AST (U/L)	20.7 ± 8.9	16.2 ± 5.2
ALT (U/L)	23.1 ± 17.7	12.5 ± 7.3
Urinalysis (%)		
Protein > 1+	10.3	10.5
RBC > 1+	5.3	17.4
Occult blood > 1+	3.4	17.8
WBC > 6-10	2.1	11.2
Bacteria > 1+	2.6	22.4
12-lead electrocardiography (%)		
LVH/RVH/IVCD	17.3/1.0/0.2	2.0/0.2/0
LAE/RAE	0.2/0.2	0.2/0
ICRBBB/CRBBB	3.9/0.5	0.73/0
LAFB/LPFB	0.7/0.2	0/0
1st degree atrioventricular block	3.8	3.4
PACs/PVCs	0.4/0.6	0.2/0.2

Data were presented as the mean ± SD and percentage (%). ALT: Alanine transaminase; AST: Aspartate transaminase; BUN: Blood urea nitrogen; CHIEF: Cardiopulmonary fitness and hospitalization events in armed forces; CRBBB: Complete right bundle branch block; eGFR: Estimated glomerular filtration rate; HDL: High-density lipoprotein; ICRBBB: Incomplete complete right bundle branch block; IVCD: Intraventricular conduction delay; LAE: Left atrial enlargement; LAFB: Left anterior fascicular block; LPFB: Left posterior fascicular block; LDL: Low-density lipoprotein; LVH: Left ventricular ventricular hypertrophy; PACs: Premature atrial contractures; PVCs: Premature ventricular contractures; RAE: Right atrial enlargement; RBC: Red blood cell; RVH: Right ventricular hypertrophy; WBC: White blood cell.

Table 3 Brief symptom rating score of men and women in the cardiorespiratory fitness and hospitalization events in armed forces study

	Men (n = 3669)	Women (n = 411)
Anxiety (%)		
None (0)	69.52	59.72
Mild (1)	25.1	32.2
Moderate (2)	4.7	7.6
Severe (3)	0.4	0.2
Extremely severe (4)	0.3	0.2
Depression (%)		
None (0)	72	63.2
Mild (1)	23	28.1
Moderate (2)	4.1	7.8
Severe (3)	0.7	0.7
Extremely severe (4)	0.3	0.2
Hostility (%)		
None (0)	65.7	55.1
Mild (1)	27.3	33.9
Moderate (2)	5.8	9.8
Severe (3)	0.9	0.7
Extremely severe (4)	0.3	0.5
Insomnia (%)		
None (0)	63.5	58.8
Mild (1)	28	29.5
Moderate (2)	6.7	9.5
Severe (3)	1.4	1.2
Extremely severe (4)	0.4	1
Interpersonal hypersensitivity: Inferiority (%)		
None (0)	79.3	73,2
Mild (1)	16.5	21
Moderate (2)	4	5
Severe (3)	0.5	0.2
Extremely severe (4)	0.2	1
Suicide ideation (%)		
None (0)	96.4	95
Mild (1)	2.4	3.7
Moderate (2)	0.6	1.5
Severe (3)	0.4	0
Extremely severe (4)	0.3	0

Data were presented as percentage (%).

established in the general population[1-3]. On the contrary, outstanding cardiorespiratory fitness is highly related to rigorous exercise training which may lead to hazardous cardiovascular events such as sudden death and severe cardiac arrhythmia, rhabdomyolysis, and orthopedic illness in armed forces[36]. It is important to know how to prevent exercise related lethal complications and to obtain the best physical fitness.

The strength of the study includes that: (1) the data of the historical cohort is complete since both whole body health examinations and physical exercise tests are scheduled for all professional military members annually unless those who receive these examinations elsewhere; (2) the procedures of health examinations and physical exercise tests are standardized and performed in central labs which could avoid systemic bias completely; (3) as compared with previous studies for the association of physical fitness with severe illness, the baseline data of CHIEF includes not only demographic characteristics but also a series of laboratory and imaging findings, which could be further adjusted to prevent potential bias; and (4) both health examinations and physical exercise tests will be held annually that provide the opportunity for us to follow up the interval change of the physical fitness and investigate the association with severe illness. On the contrary, we have several limitations in the study. First, there were about one third (33.5%) of the military members in armed forces who received health examinations but did not undergo any physical exercise test in Hualien during 2014. Although the baseline characteristics of drop-out individuals were similar to those enrolled in CHIEF, we could not completely exclude

Table 4 Exercise performances of men and women in the cardiorespiratory fitness and hospitalization events in armed forces study

	Men		Women	
	n	Performance	*n*	Performance
2-min sit-up	3651	47.5 ± 8.2	408	37.7 ± 8.1
2-min push-up	3641	49.1 ± 11.7	391	33.9 ± 10.6
3000-m non-weight bearing running (s)	3296	859.9 ± 72.7	320	1007.1 ± 76.9

Data were presented as the mean ± SD.

the selection bias. Second, women account for only 10% of the CHIEF cohort and we may not have enough power to make a conclusion at last. Third, since CHIEF is a retrospective study, some potential confounders such as systemic inflammatory markers, cardiac biomarkers, nutritional support, diet, and the type of daily regular exercise trainings performed, which may affect the physical performance and hospitalization events for severe illness, will not be available without prospective collection.

In summary, physical fitness as an independent predictor of mortality and cardio-metabolic risk in the general population has not been confirmed in young military members of armed forces who have many traditional vascular risk factors. The CHIEF study is thus designed to be one of the largest military cohorts in the world and will retrospectively investigate the association of each physical fitness performance, the interval change of each physical fitness, and incident hospitalization events for severe illness. The result of CHIEF could be applied to the military members in armed forces to improve the physical trainings effectively and prevent the adverse effect related to heavy exercises in the future.

COMMENTS

Professional military members are required to take regular rigorous physical trainings to maintain their physical fitness. However, several unhealthy factors such as cigarette smoking are prevalent among arm forces, which may affect the exercise performance and increase the risk of severe illness.

Research frontiers

Frequent exercise training and well physical fitness have been associated with lower risk of cardiovascular disease and mortality in the general population. Current evidence in the Western countries showed conflicting results for the cardiovascular outcomes in those taking repetitive strenuous exercises.

Innovations and breakthroughs

There were few studies using large military cohorts, particularly of Asian young adults, with detailed data of demographics, laboratory exams, and cardiopulmonary function evaluations at baseline, to follow up the incidence of cardiovascular disease and other severe illness events such as infectious and orthopedic disease. The cardiorespiratory fitness and hospitalization events in armed forces (CHIEF) is a retrospective cohort consisting of more than 4000 professional military members aged 18-50 years in Eastern Taiwan. CHIEF will be among the largest Eastern Asian armed forces cohort, in which physical status was strictly evaluated to follow up the hospitalization events for specific severe illness.

Applications

The result of CHIEF could be applied to the military members in armed forces to improve the physical trainings effectively and prevent the adverse effect related to heavy exercises in the future.

Peer-review

The authors present here the protocol of a study about cardiorespiratory fitness in a military population. It is well written and seems to me it will make a fine study when finished.

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ORIGINAL ARTICLE

Observational Study

Noninvasive model including right ventricular speckle tracking for the evaluation of pulmonary hypertension

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Abstract

AIM

To find parameters from transthorathic echocardiography (TTE) including speckle-tracking (ST) analysis of the right ventricle (RV) to identify precapillary pulmonary hypertension (PH).

METHODS

Forty-four patients with suspected PH undergoing right heart catheterization (RHC) were consecutively included (mean age 63.1 ± 14 years, 61% male gender). All patients underwent standardized TTE including ST analysis of the RV. Based on the subsequent TTE-derived measurements, the presence of PH was assessed: Left ventricular ejection fraction (LVEF) was calculated by Simpsons rule from 4Ch. Systolic pulmonary artery pressure (sPAP) was assessed with continuous wave Doppler of systolic tricuspid regurgitant velocity and regarded raised with values ⩾ 30 mmHg as a surrogate parameter for RA pressure. A concomitantly elevated PCWP was considered a means to discriminate between the precapillary and postcapillary form of PH. PCWP was

considered elevated when the E/e' ratio was > 12 as a surrogate for LV diastolic pressure. E/e' ratio was measured by gauging systolic and diastolic velocities of the lateral and septal mitral valve annulus using TDI mode. The results were then averaged with conventional measurement of mitral valve inflow. Furthermore, functional testing with six minutes walking distance (6MWD), ECG-RV stress signs, NT pro-BNP and other laboratory values were assessed.

RESULTS

PH was confirmed in 34 patients (precapillary PH, *n* = 15, postcapillary PH, *n* = 19). TTE showed significant differences in E/e' ratio (precapillary PH: 12.3 ± 4.4, postcapillary PH: 17.3 ± 10.3, no PH: 12.1 ± 4.5, *P* = 0.02), LV volumes (ESV: 25.0 ± 15.0 mL, 49.9 ± 29.5 mL, 32.2 ± 13.6 mL, *P* = 0.027; EDV: 73.6 ± 24.0 mL, 110.6 ± 31.8 mL, 87.8 ± 33.0 mL, *P* = 0.021) and systolic pulmonary arterial pressure (sPAP: 61.2 ± 22.3 mmHg, 53.6 ± 20.1 mmHg, 31.2 ± 24.6 mmHg, *P* = 0.001). STRV analysis showed significant differences for apical RV longitudinal strain (RVAS: -7.5% ± 5.6%, -13.3% ± 4.3%, -14.3% ± 6.3%, *P* = 0.03). NT pro-BNP was higher in patients with postcapillary PH (4677.0 ± 7764.1 pg/mL, precapillary PH: 1980.3 ± 3432.1 pg/mL, no PH: 367.5 ± 420.4 pg/mL, *P* = 0.03). Patients with precapillary PH presented significantly more often with ECG RV-stress signs (*P* = 0.001). Receiver operating characteristics curve analyses displayed the most significant area under the curve (AUC) for RVAS (cut-off < -6.5%, AUC 0.91, *P* < 0.001), sPAP (cut-off > 33 mmHg, AUC 0.86, *P* < 0.001) and ECG RV stress signs (AUC 0.83, *P* < 0.001). The combination of these parameters had a sensitivity of 82.8% and a specificity of 17.2% to detect precapillary PH.

CONCLUSION

The combination of non-invasive measurements allows feasible assessment of PH and seems beneficial for the differentiation between the pre- and postcapillary form of this disease.

Key words: Echocardiography; Right ventricle function; Pulmonary arterial hypertension

Core tip: We investigated the value of speckle-tracking (ST) analysis of the right ventricle (RV) in patients with suspected pulmonary hypertension. It focuses on a non-invasive model including parameters derived from standard transthorathic echocardiography (TTE) and ST, as well as electrocardiogram (ECG), six minutes walking distance and NT-pro BNP in order to distinguish the precapillary and postcapillary forms of PH. ST-derived apical RV longitudinal strain (RVAS < -6.5%), TTE-derived systolic pulmonary artery pressure (sPAP > 33 mmHg) and ECG RV stress signs were associated with precapillary PH, their combination had a sensitivity of 82.8% and a specificity of 17.2% for the detection of precapillary PH.

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INTRODUCTION

Pulmonary arterial hypertension (PAH) is a precapillary form of pulmonary hypertension (PH). This severe disease is characterized by raised intrapulmonary pressures and changes in pulmonary haemodynamics that lead to high right ventricular (RV) afterload and chronic RV load[1]. The natural course of PAH is fatal within two to three years if missed and left untreated. Since heterogenous pathophysiological mechanisms[2] lead to elevated intrapulmonary pressures, it is crucial to distinguish the precapillary forms from the postcapillary forms of PH in order to initiate adequate therapy. According to current guidelines, the standard procedure for definite diagnosis is right heart catheterization (RHC)[3]. This invasive diagnostic mean is not widely available and inapplicable for routine follow-up (FU), due to its invasive nature and entails the risk of rare but serious complications. Therefore, a non-invasive diagnostic scheme that is reliable in: (1) diagnosing PAH; and (2) discriminating between the precapillary and postcapillary forms of PH would be of significant clinical benefit.

Recent research has aimed to detect different non-invasive diagnostic means that meet these requirements when combined. Thus, the design of our study was based on several considerations: A combination of electrocardiographic (ECG) criteria and N-terminal pro-Brain Natriuretic Peptide (NT pro-BNP) has been reported sufficient to rule out precapillary PH[4]. Transthorathic echocardiography (TTE) is a widespread, non-invasive and cost-effective instrument routinely used to assess left and right ventricular function. Speckle tracking (ST) analysis is a novel quantitative ultrasound technique that allows an angle-independent estimation of myocardial deformation[5] and function. We added ST analysis to our approach in order to level out the most important limitation of TTE, its angle- and observer-dependence.

The utility of echocardiography and ST analysis of the RV as an implement to assess presence and severity of PH has been the focus of current studies[6-8]. Due to its variable clinical presentation and difficult treatment, PH presents a clininal picture that needs functional assessment in its course, most commonly evaluated by six minutes walking distance (6MWD).

The aim of this study was to investigate the predictive significance of a non-invasive algorithm including parameters derived from ECG, echocardiography including RV strain analysis, functional testing with determination of 6MWD, lung function test and spirometry as well as NT pro-BNP and blood count for the diagnosis and

discrimination of pre- and postcapillary PH in a patient cohort with known RHC results, which were unknown to the assessor of the non-invasive measurements.

MATERIALS AND METHODS

Patients

Between April 2013 and April 2014 50 patients with suspected PH were prospectively included after undergoing RHC. All patients underwent informed consent and the study was approved by the Ethics Committee of the University Hospital of Bonn.

Right heart catheterization and definition of PH

Invasive hemodynamic parameters were evaluated during RHC according to current guidelines[9], defining precapillary PH as mean pulmonary arterial pressure (mPAP) $\geqslant$ 25 mmHg and pulmonary capillary wedge pressure (PCWP) of $\leqslant$ 15 mmHg and postcapillary PH as mPAP $\geqslant$ 25 mmHg and PCWP > 15 mmHg.

Non-invasive measurements

Non-invasive measurements consisting of TTE with special focus on the RV function and hemodynamics including speckle tracking analysis of the RV. Functional testing includes lung function test and 6MWD, as well as laboratory testing with the assessment of blood count, bilirubin, uric acid, serum creatinine, creatinine clearance and NT pro-BNP.

TTE and right ventricular speckle tracking

All participants underwent a complete echocardiographic examination including two-dimensional (2D) and Doppler echocardiography performed with commercially available ultrasound scanner with a 2,5-MHz phased array transducer (Vivid 7, General Electric Medical Health, Waukesha, Wisconsin, United States; iE 33 Philips Medical Systems, Koninklijke N.V.) according to the standard echocardiography protocol used at our clinic. The echocardiographic views were obtained in 2D and color tissue Doppler imaging (TDI) modes. In addition to parasternal long- and short-axis and apical two- and four-chamber (4CV) views, RV-focused views were obtained. The following measurements derived from TTE were utilized to assess the presence of PH considering a concomitantly elevated PCWP as a means to discriminate between the pre- and postcapillary forms of PH.

Left ventricular ejection fraction (LVEF) was calculated using Simpson's formula. Systolic pulmonary artery pressure (sPAP) was measured with continuous wave Doppler of systolic tricuspid regurgitant velocity and regarded raised with values $\geqslant$ 30 mmHg. PCWP was considered elevated when the E/e' ratio was > 12 as a surrogate for LV diastolic pressure. E/e‘ ratio was measured according to recommendations of the American Society of Echocardiography by gauging systolic and diastolic velocities of the lateral and septal mitral valve annulus using TDI mode. These measurements were then averaged with conventional measurement of mitral valve inflow[10].

The combination of sPAP > 30 mmHg and E/e‘ <12 was deemed to reflect precapillary PH, while sPAP > 30 mmHg and E/e‘ ratio >12 indicated postcapillary PH. Tricuspid annular plane systolic excursion (TAPSE) was obtained using M-Mode in the apical 4-Ch- view of the longitudinal excursion of the lateral tricuspid annulus towards the RV apex[11]. Additionally, diastolic interventricular septal thickness (IVSd), endsystolic (ESV) and enddiastolic volume (EDV) were measured. TTE derived parameters of our study population are shown in Table 1.

2DST analysis of the RV was performed using a routine grayscale apical 4-Ch view and a commercially available software (TomTec Imaging Systems GmbH, Unterschleissheim, Germany). As the region of interest, the RV endocardial border was manually delineated and was tracked by the 2D strain software. In order to ensure precise tracking of segments, visual assessment during cine loop playback was applied. The RV was divided visually in a basal, midventricular and apical segment and six corresponding time-strain curves were generated. Following the approach of Dambrauskaite[12] and Lopez-Candales[13] longitudinal lateral apical RV (RVAS) strain and global longitudinal RV strain (RVGS) entered further analysis. The longitudinal strain of the RV free wall, was calculated as the average of each of the three regional peak systolic strains along the entire right ventricle. An example for RV speckle tracking analysis is depicted in Figure 1.

Functional testing and assessment of clinical impairment

All our patients underwent a set of non-invasive testing in order to estimate the extent of their physical impairment due to PH. Shortness of breath was classified according to the World Health Organization (WHO) functional class score and gauged by 6MWD, using walking aids or portable oxygen if necessary. Standard 12-channel-ECG was screened for signs of RV strain such as RV hypertrophy, right axis deviation, right bundle block or signs of right atrial dilation[14]. Furthermore, pulmonary function was measured with spirometry and bodyplethysmography including total lung capacity, residual volume, vital capacity, forced expiratory volume and tiffeneau index. Blood count, bilirubin, uric acid, serum creatinine, creatinine clearance and NT pro-BNP were registered one to six weeks after RHC.

Statistical analysis

Data analysis was exploratory, variables underwent no adjustments. Normal distribution of continuous variables was examined employing the Kolmogorov-Smirnov test. Continuous data was expressed as mean values ± standard deviation. Two-tailed *P*-values were computed and regarded significant if ranging below 0.05 (95%CI). Two group comparisons were done using student's-*T*

Table 1 Echocardiographic and invasive measurements

	All patients (n = 44)	No PH (n = 10)	Precapillary PH (n = 15)	Postcapillary PH (n = 19)	P
TTE					
EF, %	61.3 ± 13.8	62 ± 9.5	67 ± 10.3	56.5 ± 16.7	0.28
EDV, mL	92.8 ± 36.1	87.8 ± 33.1	73.6 ± 34	110.6 ± 31.8	0.04
ESV, mL	37.4 ± 24.6	32.2 ± 13.6	25 ± 15	49.9 ± 29.6	0.04
IVSd, cm	1.2 ± 0.4	1.1 ± 0.2	1.1 ± 0.6	1.3 ± 0.4	0.12
LAV, mL	84.0 ± 52.7	82.4 ± 55.2	79.9 ± 64.9	85.2 ± 48.7	0.6
sPAP, mmHg	51.1 ± 24.4	31.2 ± 24.6	61.2 ± 22.3	53.6 ± 20.4	0.003
RVDs, cm	2.4 ± 1.1	2.2 ± 1.0	2.4 ± 1.1	2.3 ± 1.1	0.8
RVDd, cm	3.3 ± 1.4	3.0 ± 1.2	3.4 ± 1.6	3.3 ± 1.3	0.36
TAPSE, cm	1.8 ± 0.6	2.1 ± 0.6	1.8 ± 0.5	1.8 ± 0.6	0.23
E/e' ratio	14.4 ± 7.8	12.1 ± 4.5	12.4 ± 4.4	17.3 ± 10.3	0.13
RVGS, %	-11.5 ± 5.9	-13.3 ± 7.6	-10.8 ± 4.6	-11.2 ± 6	0.82
RVAS, %	-11.6 ± 5.9	-14.3 ± 6.3	-7.5 ± 5.6	-13.3 ± 4.3	< 0.001
RHC					
mPAP, mmHg	40.1 ± 17.5	20.9 ± 3	51.8 ± 20.6	40.9 ± 8.9	< 0.001
sPAP, mmHg	55.0 ± 17.6	35.3 ± 8.5	60.3 ± 17.4	53.5 ± 17.4	0.04
PCWP	16.1 ± 7.2	11.4 ± 4.1	11.4 ± 2.1	22.3 ± 6.3	< 0.001
CO, L/min	3.6 ± 3.8	3.3 ± 3.7	3.2 ± 3.3	3.4 ± 4.2	0.46
RV systolic pressure, mmHg	63.9 ± 26.3	37.1 ± 14.3	86.7 ± 25.4	66.3 ± 17.4	< 0.001
RV diastolic pressure, mmHg	5.3 ± 5.8	4.9 ± 5.3	4.3 ± 5.8	5.6 ± 5.8	0.07
RV mean pressure, mmHg	9.4 ± 8.6	7.5 ± 6.5	11.9 ± 12.1	8.6 ± 7.1	0.04
RA mean pressure, mmHg	13.5 ± 13.1	13.2 ± 9.3	12.7 ± 5.4	13.8 ± 14.7	0.69
WHO class					0.56
Ⅰ, n (%)	2 (4.3)	2 (20)	0 (0)	0 (0)	
Ⅱ, n (%)	10 (21.7)	3 (30)	2 (13.3)	5 (26.3)	
Ⅲ, n (%)	29 (63)	5 (50)	11 (73.3)	13 (68.4)	
Ⅳ, n (%)	3 (6.5)	0 (0)	2 (13.3)	1 (5.3)	

EF: Ejection fraction; EDV/ESV: End-systolic/diastolic volume; IVSd: Diastolic interventricular septum diameter; LAV: Left atrial volume; s/mPAP: Systolic/mean pulmonary arterial pressure; RVDs/d: Systolic/diastolic right ventricular diameter; TAPSE: Tricuspid annular plane systolic excursion; RVGS/RVAS: Global/apical right ventricular longitudinal strain; PCWP: Pulmonary capillar wedge pressure; CO: Cardiac output; RV/RA: Right ventricle/atrium; WHO: World Health Organization.

test for paired samples or Wilcoxon signed rank test for paired continuous variables. Categorical data was tested with Fisher's exact test. SPSS for Windows (PASW statistic, Version 21.0.0, SPSS Inc., Chicago, Illinois, United States) and MedCalc statistical software (MedCalc Software, Version 11.4.1.0, Mariakerke, Belgium) were utilized for statistical analysis.

Afterwards, a diagnostic model including RVAS, sPAP and E/e' ratio was generated by calculating associated ROC curves for the assumed possibilites. The corresponding AUCs along with 95%CI were calculated.

RESULTS

Six patients were excluded from the study population because of insufficient transthorathic image quality (n = 2), incomplete RHC results (n = 3) or withdrawal of consent (n = 1).

In total, 44 prospective patients [age 63.11 ± 14 years, 27 (61%), male], were consecutively included in our study. According to RHC, precapillary PH was diagnosed in 15 (34%), postcapillary PH in 19 (43%) and PH was excluded in 10 (23%) patients. Demographic baseline characteristics of the study cohort are shown in Table 2.

Echocardiography and speckle-tracking analysis

Echocardiographic measures on RV and LV functions differed significantly between patients with PH and those without PH concerning measures on LV diastolic function (E/e' ratio: Precapillary PH, 12.3 ± 4.4; postcapillary PH, 17.3 ± 10.3; no PH, 12.1 ± 4.5; P = 0.02), and LV volumes (ESV: 25.0 ± 15.0 mL, 49.9 ± 29.5 mL, 32.2 ± 13.6 mL, P = 0.027; EDV: 73.6 ± 24.0 mL, 110.6 ± 31.8 mL, 87.8 ± 33.0 mL, P = 0.021). Furthermore, sPAP showed significant differences between the patient groups (61.2 ± 22.3 mmHg, 53.6 ± 20.1 mmHg, 31.2 ± 24.6 mmHg, P = 0.001). Concerning RV function analysis, ST analysis of the RV free wall showed significant differences for apical RV longitudinal strain (RVAS: -7.5% ± 5.6%, -13.3% ± 4.3%, -14.3% ± 6.3%, P = 0.03), but not for global longitudinal RV strain (P > 0.05). All other measures on LV and RV function did not differ relevantly between the groups Table 1.

Functional testing and non-invasive measurements

Patients with precapillary PH presented significantly more often with ECG changes indicating RV stress (precapillary PH: 87%, postcapillary PH: 58%, no PH: 20%, P = 0.001). Functional status did not differ between patients with or without PH when comparing measures on 6MWD (375.3 ± 187.8 m, 319.5 ± 132.0 m, 372.5 ± 127.5 m,

Table 2 Baseline characteristics

	All patients (*n* = 44)	No PH (*n* = 10)	Precapillary PH (*n* = 15)	Postcapillary PH (*n* = 19)	*P*
Age, yr	63.11 ± 14.2	60.3 ± 16.9	60.2 ± 13	66.9 ± 13.3	0.71
Male gender, *n* (%)	27 (61)	5 (50)	8 (53)	14 (74)	0.33
AHT, *n* (%)	30 (60)	8 (61)	7 (53)	15 (62)	0.82
Diabetes mellitus, *n* (%)	11 (22)	2 (15)	3 (23)	6 (25)	0.57
CAD, *n* (%)	26 (52)	7 (53)	7 (53)	12 (50)	0.44
HLP, *n* (%)	15 (30)	4 (31)	6 (25)	5 (38)	0.33
Nicotine, *n* (%)	10 (20)	3 (23)	5 (21)	2 (15)	
Specific PAH Therapy, *n* (%)	15 (34)	0 (0)	15 (100)	0 (0)	< 0.001
ECG RV strain, *n* (%)	26 (59)	2 (20)	13 (87)	11 (58)	0.001
NT pro-BNP (pg/mL)	2778.3 ± 5681.3	367.5 ± 420.4	1980.3 ± 3432.1	4677 ± 7764.8	0.44
Hemoglobine, mg/dL	12.8 ± 3.6	11.4 ± 0.9	12.2 ± 2.5	12.6 ± 3.4	0.09
Bilirubin, mg/dL	0.7 ± 0.5	0.5 ± 0.2	0.9 ± 0.8	0.8 ± 0.3	0.08
Uric acid, mg/dL	7.1 ± 2.6	6.0 ± 1.7	6.9 ± 2.6	7.9 ± 2.8	0.13
Serum creatinine, mg/dL	1.3 ± 0.3	1.0 ± 0.2	1.3 ± 0.4	1.2 ± 0.2	0.25
Creatinine clearance, mL/min	55.3 ± 13.4	53.2 ± 8.9	50.5 ± 11.4	57.2 ± 6.3	0.48
6MWD, m	351.9 ± 153.2	372.5 ± 127.5	375.3 ± 186.8	319.5 ± 131.9	0.55

AHT: Arterial hypertension; CAD: Coronary artery disease; HLP: Hyperlipoproteinemia; PAH: Pulmonary arterial hypertension; ECG: Electrocardiogram; RV: Right ventricular; NT pro-BNP: N-terminal pro brain-natriuretic-peptide; 6MWD: 6 min walking distance.

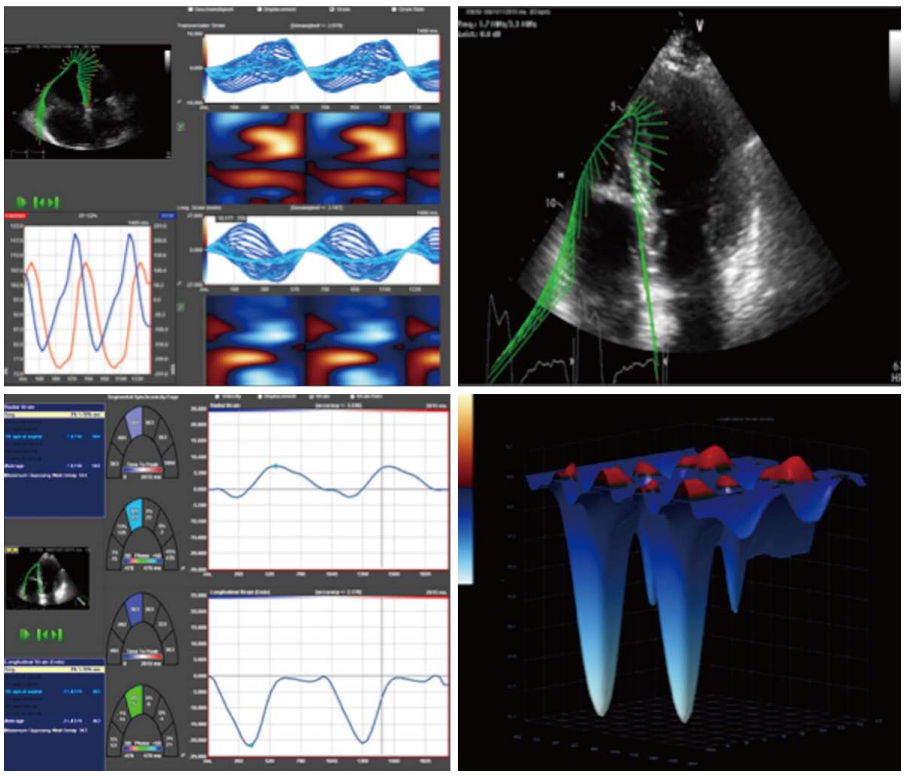

Figure 1 Example of right ventricular speckle tracking and three dimensional visualisation of longitudinal right ventricular strain values. RV: Right ventricular; 3D: Three dimensional; RVSI: Right ventricular longitudinal strain.

P > 0.05) and pulmonary function (Table 2).

Serum NT pro-BNP was significantly higher in patients with postcapillary PH (4677.0 ± 7764.1 pg/mL) as compared to patients with (precapillary PH (1980.3 ± 3432.1 pg/mL), or no PH (367.5 ± 420.4 pg/mL, *P* = 0.03). All other laboratory values did not show significant differences between the subgroups (Table 1). Notably, patients with elevated pulmonary pressures had a higher WHO functional class compared to patients without PH (*P* = 0.04) (Table 1, Figure 2).

Factors predicting PAH

In order to define cut-off values for the identification of precapillary PH, ROC analyses of variables with significant differences between the patient groups were done subsequently. Only measures on regional RV function with

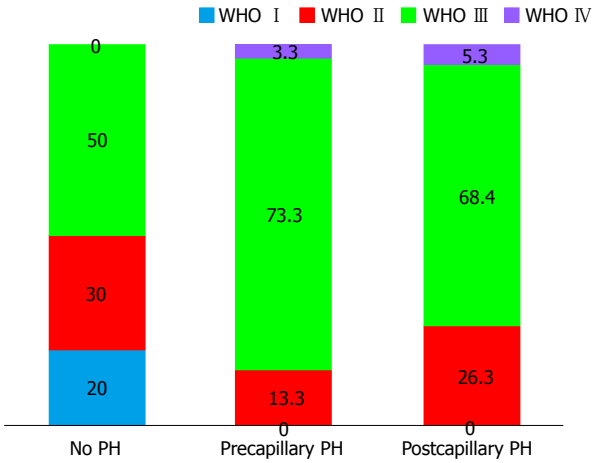

Figure 2 Distribution of World Health Organization classes in the study cohort, separated by etiology of pulmonary hypertension.

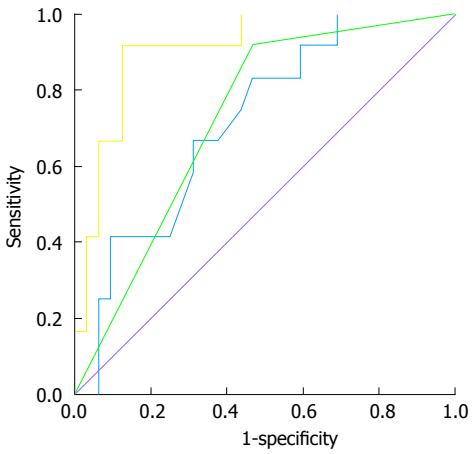

Figure 3 Incremental diagnostic value of the combination of non-invasive measures for identification of patients with precapillary pulmonary hypertension. Green curve, ECG RV stress signs alone; blue curve, apical right ventricular longitudinal strain alone; sand-colored curve, combination of non-invasive measures. RV: Right ventricle; ECG: Electrocardiograph.

strain imaging [RVAS: cut-off < -6.5%, area under the curve (AUC) 0.91, $P < 0.001$], RV hemodynamics (sPAP: cut-off > 33 mmHg, AUC 0.86, $P < 0.001$) and ECG RV stress signs (AUC 0.83, $P < 0.001$) were associated with precapillary PH.

A combination of the cut-off values showed a sensitivity of 82.8% and a specificity of 17.2% for the confirmation of precapillary PH (Figure 3).

DISCUSSION

According to current guidelines invasive testing with RHC is necessary for the diagnosis of PAH and the indication for RHC is based only on functional and clinical status in patients with persistent dyspnea of unknown cause.

Therefore, there is an unmet need for patient identification with a widespread, cost-effective and non-invasive tool[7]. Our group showed recently, that echocardiography might enable direct, easy and noninvasive diagnosis of PAH by combining non-invasive measures on RV hemodynamics utilizing sPAP, RV function RVAS and E/e' ratio as a parameter for LV diastolic function. In this study we intended to verify and extend this approach in a prospective fashion, integrating it into the newly suggested screening model for PAH in order to prove its clinical applicability.

Most importantly, the present study indicates that (1) the combined consideration of sPAP, RVAS, E/e' ratio and ECG RV stress signs seems to be a promising and easily applicable tool to discriminate between pre-, post-capillary and to some extent no PH; and (2) our data provide preliminary evidence that there does not seem to be an additional clinical benefit of functional testing with 6MWD, and/or pulmonary function tests in a preselected, severely ill patient cohort.

Need for early diagnosis of PAH

Current studies suggest the possibility of an improved long-term outcome in PAH patients when diagnosed and treated early[15,16]. Due to the unspecific symptoms of early stage PH and the limitations of routinely used screening methods, definite diagnosis is often delayed. Despite increased efforts in the early detection of PAH associated with connective tissue disease[17] and other known risk factors including bone morphogenic protein receptor 2 mutations[18], there is still a lack of general recommendations concerning screening algorithms for PAH in non-high risk populations. While 6MWD, NT pro-BNP and changes in WHO functional class have been described as significant predictors of outcome in patients with idiopathic PAH[19], Graspa *et al*[20] could demonstrate, that RV dysfunction, moderate to severe tricuspid regurgitation, a low cardiac index and elevated right atrial pressures are independent predictors in mortality in a large prospective study with patients suffering from PAH. The Registry to Evaluate Early and Long-Term Pulmonary Arterial Hypertension Disease Management (REVEAL) detected an elevated pulmonary vascular resistance (PVR), WHO functional class Ⅲ-Ⅳ, elevated mean right atrial pressure, 6MWD and Brain Natriuretic Peptide as predictive factors in PAH[21].

Right ventricular speckle-tracking in patients with pulmonary hypertension

Although clinical trials on RV strain analysis are rare, evidence proving its feasibility and prognostic value is constantly growing[5-8,13,22,24,28]. Whilst this study failed to show a significant correlation between RVGS and PH status, Rajagopal *et al*[5] were able to detect a sufficient relation between RVGS and functional status of patients suffering from PH applying a RV-centered echocardiographic approach. However, they included 40, mainly female (85%), patients, who in contrast to our cohort had a lower WHO functional class (73% WHO FC Ⅰ and Ⅱ, 27% WHO FC Ⅲ and Ⅳ). More importantly, other studies confirmed the diagnostic value of measuring regional alterations in strains derived from the RV free wall[22], namely the averaged RV peak strain as functional measure for RV ejection fraction

in adults and children suffering from different etiologies of RV impairment. However, there is still no study to verify the correlation between RV-derived strain and WHO functional class in a large patient cohort with determined PH.

Fukuda *et al*[6] were able to show a significant correlation between ST of the RV free wall with invasively measured mPAP and PVR as well as RV ejection fraction and RV end-systolic volume determined by cardiac magnetic resonance imaging and exercise tolerance by 6MWD thus implying RV ST as a suitable method to assess patients with PH. More recently, Sano *et al*[23] established RV ST analysis to describe reverse remodeling as a marker for long-term outcome of PH and Vitarelli *et al*[24] were able to affirm the diagnostic accuracy of two- and three-dimensional ST parameters, including RVAS as a surrogate for hemodynamic assessment and thus predictor of outcome in chronic pulmonary hypertension.

Screening for PAH

Humbert *et al*[18] suggested an elaborated screening algorithm for patients at risk for developing pulmonary hypertension, clearly delineating the lack of a standardized diagnostic approach in unselected patients.

Parent *et al*[25] found evidence for a combination of echocardiographic markers, 6MWD and NT-proBNP in patients with sickle-cell anemia associated PAH, whereas Allanore *et al*[26] proposed a combination of echocardiographic assessment of sPAP, serum NT-pro BNP, erythrocyte sedimentation rate and the diffusing capacity for carbon monoxide/alveolar volume in patients with systemic sclerosis. Although annual echocardiography is recommended in high risk populations[14,27], implementation of ST based RV functional analysis has not yet found consideration in order to refine the diagnostic value of TTE. Of note, the prognostic value of RV ST has been demonstrated for patients suffering from PH irrespective of its etiology by Haeck *et al*[28].

The drawbacks of all studies are the relatively small patient numbers, which may lead to biased conclusions and thus may lack general extrapolation. Therefore, the findings of the prospective DELPHI-2 study, which follows asymptomatic carriers of the bone morphogenic protein receptor 2 mutation and will provide their hemodynamic, echocardiographic and functional characteristics, will elucidate this topic in a relevant bigger cohort of patients at high risk of developing PAH.

COMMENTS

Background

Definite diagnosis of pulmonary hypertension (PH) in general and the distinction between the precapillary and postcapillary form of this disease in is often delayed due to unspecific symptoms and the necessity of invasive testing. The authors' study results verified a useful estimation of pulmonary pressure with transthorathic echocardiography (TTE). Combined with speckle-tracking (ST) analysis of the apical right ventricle (RV) and electrocardiogram (ECG) RV stress signs it seems to be of value to strengthen the suspicion of the rare but malignantly proceeding precapillary form of PH and therefore should be considered as a diagnostic tool in patients with suspected pulmonary arterial hypertension (PAH).

Research frontiers

Although the ST assessment of our cohort was performed blinded to the results of right heart catheterization (RHC), our approach was still retrospective. Therefore, confirmation of the study result needs to be acquired in a fully prospective study. Another weakness of this trial is the relatively small number of patients included, in order to reaffirm our findings, future research should aim to comprise larger numbers of patients of the different PH subgroups. Since there are multiple differential diagnoses to pulmonary hypertension that lead to RV strain and alterations of the RV geometry and contractility that have not been considered in our analysis, a prospective study design could compare RV speckle-tracking analysis of patients with PH ideally scrutinizing the diverse etiologies of PH and disparate right heart impairments. Ultimately, as the software available to perform ST-analysis was primarily produced for the left ventricle, newly developed software specialized on the complex geometry of the RV could refine the data.

Innovations and breakthroughs

The data in this study suggests that a combination of non-invasive measurements including echocardiography and speckle-tracking analysis allows feasible estimation of PH with a sensitivity of 82.8%. Taking into consideration all our findings a model for future assessment of suspected PH could provide an incrementally invasive examination beginning with TTE and ECG on the first level, adding NT pro-BNP on a second level and only after evaluating these results, a recommendation for timely RHC should be given.

Applications

In this study, ST showed only a specificity of 17.2% for detection of precapillary PH. Therefore, it does not seem to reliably identify PAH at this point and the definite diagnosis has still to be made by invasive RHC. However, ST has become more applicable in echocardiographic examination and it should be considered as an additional diagnostic tool for patients before invasive RHC. Our study results indicate a necessity for timely RHC assessing PAH if a patient shows RVAS < -6.5%, sPAP > 33 mmHg and electrocardiographic RV stress signs. In a second step, NT pro-BNP could help to determine the necessity of RHC in patients with RVAS > -6.5%. Since sPAP < 33 mmHg, no signs of RV stress in ECG and NT pro-BNP < 1000 pg/mL seemed not to correlate with PH, suggestion for RHC should be made reluctantly and other causes of dyspnea should be considered. However, given our small sample size, this model has yet to be tested in a larger patient cohort.

Terminology

The clinical classification of PAH comprises a heterogenous group of disease patterns that show unspecific clinical presentation due to elevated pulmonary pressures and right ventricular stress. ST is a relatively novel ultrasound technique that allows estimation of myocardial deformation as thus assessment of right ventricular function which is compromised in both pre- and post-capillary forms of pulmonary hypertension.

Peer-review

Recent studies focus on the value of ST-analysis in patients with suspected pulmonary hypertension, especially as to its potential to discriminate between pre- and postcapillary forms of PH. This work provides a comprehensive literature review on this topic. PAH is caused by heterogenous etiologies and often associated with rare diseases, therefore, the majority of papers available on ST in patients with PAH are centered on a specific etiology. The study included patients with suspected PAH regardless its etiology. The results are interesting and provide evidence of the utility of right ventricular ST in patients with suspected PAH.

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ORIGINAL ARTICLE

Observational Study

Relationship between coronary calcium score and high-risk plaque/significant stenosis

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Abstract

AIM

To investigate the relationship between coronary calcium score (CCS) and vulnerable plaque/significant stenosis using coronary computed tomographic angiography (CCTA).

METHODS

CCTA was performed in 651 patients and these patients were divided into the four groups (CCS 0, 1-100, 101-400 and > 400). We studied the incidence of high-risk plaque, including positive remodeling, low attenuation plaque, spotty calcification, and napkin-ring sign, and significant stenosis in each group.

RESULTS

High-risk plaque was found in 1.3%, 10.1%, 13.3% and 13.4% of patients with CCS 0, 1-100, 101-400 and > 400, respectively ($P < 0.001$). The difference was only significant for patients with zero CCS. The incidence of significant stenosis was 0.6%, 7.6%, 13.3% and 26.9% for each patient group, respectively ($P < 0.001$), which represented a significant stepwise increase as CCS increased. The combined incidence of high-risk plaque and significant stenosis was 1.9%, 17.7%, 26.9% and 40.3% in each patient group, respectively ($P < 0.001$), again representing a significant stepwise increase with CCS. The rate of major coronary event was 0%, 4.0%, 7.9% and 17.2% in each patient group, respectively ($P < 0.001$), another significant stepwise increase as CCS increased.

CONCLUSION

Stepwise increased risk of coronary events associated with increasing CCS is caused by increasing incidence of significant stenosis, while that of high-risk plaque remains the same.

Key words: Coronary calcium score; Coronary stenosis; High-risk plaque; Low attenuation plaque; Napkin-ring

sign; Positive remodeling; Spotty calcification

Core tip: Coronary computed tomographic angiography was performed in 651 patients and these patients were divided into the four groups according to coronary calcium score (CCS): 0, 1-100, 101-400 and > 400. The incidence of high-risk plaque was not significantly different among the three groups, except patients with zero CCS. The incidence of significant stenosis increased stepwise as CCS increased, as did the rate of major coronary event. Therefore, the stepwise increased risk of coronary events associated with increasing CCS is caused by an increasing incidence of significant stenosis, while that of high-risk plaque remains the same.

Iwasaki K, Matsumoto T. Relationship between coronary calcium score and high-risk plaque/significant stenosis. *World J Cardiol* 2016; 8(8): 481-487 Available from: URL: http://www.wjgnet.com/1949-8462/full/v8/i8/481.htm DOI: http://dx.doi.org/10.4330/wjc.v8.i8.481

INTRODUCTION

Coronary artery calcification represents the presence of coronary atherosclerosis and there is a strong relationship between the extent of coronary artery calcification and the total coronary plaque burden[1-3]. Many studies demonstrate that coronary calcium score (CCS) is the powerful predictor of coronary events and provide incremental risk stratification beyond traditional risk scores[4,5]. In contrast, patients with no calcium show a very low risk of coronary events[6]. However the precise mechanism of this increased risk associated with increased CCS has not been fully elucidated. Generally, most coronary events are caused by significant stenosis or vulnerable plaque. Many studies have demonstrated that significant stenosis increases the risk of coronary events[7,8]. In addition, recent studies demonstrate that 70%-80% of cardiac death and myocardial infarction are caused by rupture of vulnerable plaque, which often has non-significant stenosis[9,10].

Thus, we hypothesized that both significant stenosis and vulnerable plaque were associated with increased coronary events as CCS increased. We investigated the relationship between CCS and vulnerable plaque/significant stenosis using coronary computed tomographic angiography (CCTA).

MATERIALS AND METHODS

Patients

From September 2010 through September 2014, 981 patients underwent CCTA. We excluded: (1) patients who underwent coronary revascularization before CCTA; (2) patients who developed acute coronary syndrome before CCTA; (3) patients who have coronary artery disease (CAD); and (4) patients with inadequate image quality because of motion artifacts, blooming artifacts, or severe calcification. Finally, we studied 651 patients. Most patients underwent CCTA for the evaluation of CAD because of multiple risk factors and/or symptom of chest pain.

CCTA

For CCTA, we used a sixty-four multi-detector computed tomography (MDCT) scanner (SOMATOM Sensation 64 Cardiac, Siemens Medical Solutions, Erlangen, Germany). Before the scan, we administered 20 mg metoprolol if patients had a heart rate more than 70 beats/min. We administered sublingual nitroglycerin 0.8 mg for all patients.

We performed a scan without contrast dye to measure the coronary calcium burden. The detail of the CCTA procedure was reported in the previous study[11].

CCTA image interpretation

For image analysis, we transferred CT data sets to a workstation (Aquarius NetStation, Terarecon Inc, San Mateo, CA, United States). We calculated total calcium score and expressed as Agatston score[12]. We divided our patients into the four groups according to the usual CCS risk classification definitions: CCS 0, 1-100, 101-400 and > 400. We defined high-risk CCS as CCS > 400.

Two reviewers, who were blinded to the patients' clinical characteristics, evaluated the CCTA data, with maximum intensity and curved multiplanar reconstruction (CMPR) techniques. We regarded positive remodeling as the ratio of plaque site diameter divided by reference segment diameter more than 1.1[13]. We regarded spotty calcification as its size less than 3 mm on CMPR images and one side occupied on cross-sectional images[13]. We regarded low attenuation plaque as the lowest CT number less than 30 HU on axial images[13]. We regarded napkin-ring sign as a ring of high attenuation around coronary artery plaque and CT attenuation of a ring higher than that of the adjacent plaque but no greater than 130 HU[14]. We regarded high-risk plaque as the plaque with positive remodeling, low attenuation plaque, spotty calcification, or napkin ring sign. Percent aggregate plaque volume was measured according to Nakazato's method[15]. Two reviewers identified coronary segments and these segments were classified into normal, non-significant stenosis, or significant stenosis. Normal segment was defined as smooth parallel or tapering borders. Non-significant stenosis was defined as luminal irregularities or % diameter stenosis less than 50%. Significant stenosis was defined as % diameter stenosis more than 50%.

Major coronary event

The duration of follow-up was 2.1 ± 1.3 years (median 1.9 years). Major coronary event was defined as cor-

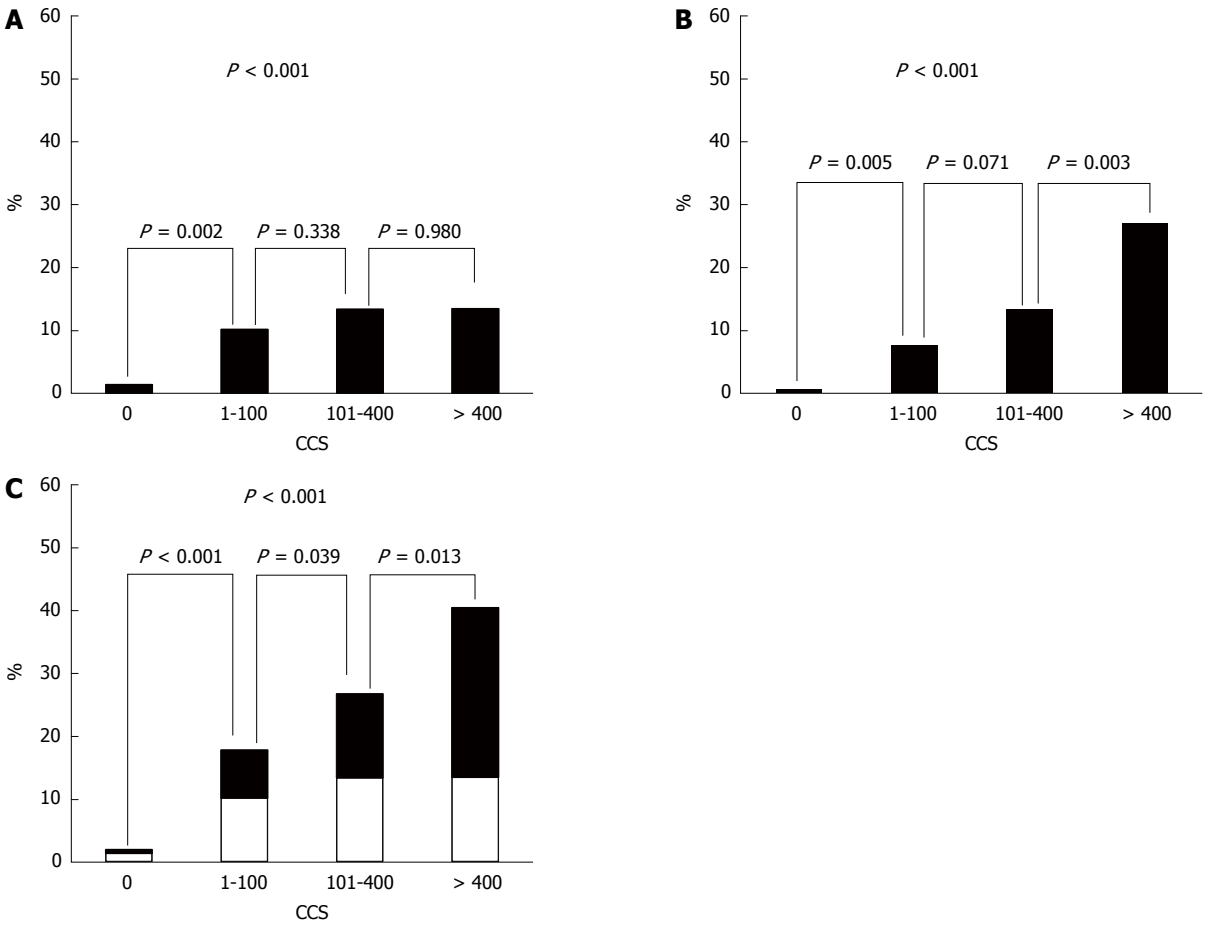

Figure 1 Prevalence of high-risk plaque and significant stenosis among the four groups. A: Prevalence of high-risk plaque; B: Prevalence of significant stenosis; C: Prevalence of combined high-risk plaque and significant stenosis. CCS: Coronary calcium score.

onary death, myocardial infarction, and coronary revascularization.

The Institutional Review Board of Okayama Kyokuto Hospital reviewed and approved this study. All patients provided informed consent.

Statistical analysis

We described continuous variables as mean ± SD. We compared continuous variables by two group *t*-test between the two groups and by one-factor ANOVA among the four groups. We described discrete variables as counts or percentage. We compared discrete variables by the χ^2 or Fisher's exact test between the two groups and by the χ^2 test for independence among the four groups. We investigated predictors of high-risk plaque, significant stenosis, and high-risk CCS by a multiple logistic regression analysis, including age, sex, and all risk factors. A *P*-value < 0.05 was regarded as statistically significant. The biomedical statistician performed statistical review of this study.

RESULTS

The patients' clinical characteristics are shown in Table 1. Figure 1 shows the incidence of high-risk plaque and significant stenosis among the four groups. The high-risk plaque was found in 1.3%, 10.1%, 13.3% and 13.4% of patients with CCS 0, 1-100, 101-400 and > 400, respectively (Figure 1A). The difference was only significant for patients with zero CCS. The incidence of significant stenosis was 0.6%, 7.6%, 13.3% and 26.9% in each patient group, respectively (Figure 1B), which represented a stepwise increase as CCS increased. The combined incidence of high-risk plaque and significant stenosis was 1.9%, 17.7%, 26.9% and 40.3% in each patient group, respectively (Figure 1C), again representing a significant stepwise increase as CCS increased.

Table 2 shows the incidence of high-risk plaque among the four groups. Apart from patients with zero CCS, there were no significant differences in the incidence of high-risk plaque, positive remodeling, low attenuation plaque, spotty calcification, and napkin-ring appearance among the three groups. In addition, the incidence of multiple high-risk plaques was not significantly different among the four groups. The percent aggregate plaque volume was not significantly different among the four groups. Table 3 shows the predictors of high-risk plaque, significant stenosis, and high-risk CCS by stepwise increased rate of major coronary event was observed. The rate of coronary revascularization also increased stepwise. The rate of coronary death and myocardial infarction was not significantly different among the four

Table 1 Clinical characteristics of studied patients *n* (%)

CCS	0	1-100	101-400	> 400	*P*
n	154	198	165	134	
Age	63.1 ± 11.7	68.2 ± 8.5	69.6 ± 9.8	71.5 ± 8.1	< 0.0001
Male sex	76 (49.4)	137 (69.2)	121 (73.3)	98 (73.1)	< 0.0001
Risk factor					
Hypertension	85 (55.2)	125 (63.1)	115 (69.7)	99 (73.9)	0.0045
Dyslipidemia	88 (57.1)	124 (62.6)	105 (63.4)	82 (61.2)	0.6484
Diabetes	53 (34.4)	76 (38.4)	65 (39.4)	76 (56.7)	0.0007
Stroke	36 (23.4)	58 (29.3)	58 (35.2)	58 (43.3)	0.0024
CKD	30 (19.5)	47 (23.7)	47 (28.5)	43 (32.1)	0.07
BMI (kg/m^2)	25.7 ± 3.7	24.4 ± 2.6	24.2 ± 3.7	23.8 ± 4.8	0.2514
Laboratory data					
HbA1c (mmol/mol)	46.1 ± 13.4	47.4 ± 14.5	48.5 ± 13.0	48.9 ± 12.0	0.3286
BS (mmol/L)	7.43 ± 2.37	7.73 ± 2.44	7.94 ± 2.39	8.52 ± 2.99	0.0333
TC (mmol/L)	5.24 ± 0.99	5.13 ± 0.99	4.95 ± 0.98	4.72 ± 0.87	0.0054
TG (mmol/L)	1.69 ± 1.12	1.63 ± 1.01	1.73 ± 0.94	1.72 ± 0.90	0.8925
HDL-C (mmol/L)	1.50 ± 0.51	1.47 ± 0.43	1.29 ± 0.30	1.41 ± 0.39	0.0084
LDL-C (mmol/L)	3.18 ± 0.86	2.93 ± 0.91	2.96 ± 0.85	2.68 ± 0.72	0.0023
Cr (μmol/L)	69.0 ± 28.3	73.4 ± 19.4	75.1 ± 17.7	78.7 ± 21.2	0.0481
Medication					
ARB/ACE-I	70 (45.5)	101 (51.0)	98 (59.4)	97 (72.4)	< 0.0001
CCB	53 (34.4)	98 (49.5)	96 (58.2)	95 (70.9)	< 0.0001
Diuretics	5 (3.2)	10 (5.1)	9 (5.5)	7 (5.2)	0.7883
Beta-blocker	3 (1.9)	5 (2.5)	3 (1.8)	4 (3.0)	0.9096
Aspirin	37 (24.0)	60 (30.3)	61 (37.0)	60 (44.8)	0.0013
Statin	85 (55.2)	119 (60.1)	100 (60.6)	79 (59.0)	0.7559
Oral diabetics	51 (33.1)	76 (38.4)	65 (39.4)	76 (56.7)	0.0004
Insulin	10 (6.5)	15 (7.6)	16 (9.7)	19 (14.2)	0.112

CCS: Coronary calcium score; ACE-I: Angiotensin converting enzyme inhibitor; ARB: Angiotensin receptor blocker; BMI: Body mass index; BS: Blood sugar; CCB: Calcium channel blocker; DM: Diabetes mellitus; HbA1c: Hemoglobin A1c; HDL-C: High-density lipoprotein cholesterol; LDL-C: Low-density lipoprotein cholesterol; TC: Total cholesterol; TG: Triglyceride.

Table 2 Incidence of high-risk plaque among the four groups *n* (%)

CCS	0	1-100	101-400	> 400	*P*
n	154	198	165	134	
High-risk plaque	2 (1.3)[b]	20 (10.1)	22 (13.3)	18 (13.4)	0.0171
Positive remodeling	2 (1.3)[d]	20 (10.1)	21 (12.7)	18 (12.7)	< 0.001
Low attenuation plaque	0 (0)[e]	7 (3.5)	4 (2.4)	1 (0.7)	0.0217
Spotty calcification	0 (0)[h]	13 (6.6)	11 (6.7)	8 (6.0)	< 0.001
Napkin-ring sign	0 (0)[i]	7 (3.5)	2 (1.2)	1 (0.7)	0.0474
Multiple plaques	0 (0)	4 (2.0)	3 (1.8)	3 (2.2)	0.166
%APV	30.5 ± 24.3	42.5 ± 9.0	44.8 ± 9.2	42.2 ± 7.8	0.2537

[b]*P* = 0.0016 compared with group with CCS 1-100; [d]*P* = 0.0016 compared with group with CCS 1-100; [e]*P* = 0.0486 compared with group with CCS 1-100; [h]*P* = 0.0031 compared with group with CCS 1-100; [i]*P* = 0.0486 compared with group with CCS 1-100. CCS: Coronary calcium score; %APV: Percent aggregate plaque volume.

groups (Table 4).

DISCUSSION

Our results showed that the incidence of high-risk plaque was not significantly different among the three groups with CCS of 1-100, 101-400 and > 400. However, the incidence of significant stenosis increased stepwise as CCS increased. Thus, the combined incidence of high-risk plaque and significant stenosis increased significantly as CCS increased. These results suggest that the stepwise increased risk of coronary events associated with increasing CCS would be due to an increasing incidence of significant stenosis, while the incidence of high-risk plaque remains the same except in patients who have zero CCS.

High-risk plaque

Recently, CCTA characteristics of vulnerable plaque are reported to be positive remodeling, low attenuation

Table 3 Predictors of high-risk plaque, significant stenosis, and high-risk coronary calcium score by multivariate analysis

	OR	95%CI	*P*
High-risk plaque factor			
Male	4.93	2.07-11.7	0.0003
Hypertension	2.2	1.13-4.28	0.0204
Significant stenosis factor			
Hypertension	2.66	1.44-4.89	0.0017
Dyslipidemia	2	1.15-3.47	0.0137
Diabetes	2.32	1.42-3.79	0.0008
High-risk CCS factor			
Age	1.06	1.03-1.08	0.00001
Male	1.54	1.02-2.34	0.0414
Diabetes	2.46	1.68-3.59	0.0001

CCS: Coronary calcium score.

plaque, and spotty calcification[13]. In addition, the napkin-ring sign is regarded as another sign of vulnerable plaque[14]. Thus, we regarded high-risk as the plaque with positive remodeling, low attenuation plaque, spotty calcification, or napkin-ring sign.

The incidence of high-risk plaque was 9.5% in our patients. Motoyama *et al*[16] detected positive remodeling and/or low attenuation plaque in 6.8%. Fujimoto *et al*[17] detected positive remodeling and low attenuation plaque in 6.3%. Their incidence is similar to our results.

In our study, the incidence of high-risk plaque was not significantly different among the three groups with CCS $\geqslant$ 1. No previous studies demonstrated this association. Fujimoto *et al*[17] studied the incidence of positive remodeling and low attenuation plaque in 1139 patients without symptoms or with atypical symptoms. High-risk plaque was detected in 0%, 4.3% and 15.5% in the low-, intermediate- and high-risk Framingham scores groups, respectively. For patients of the intermediate-risk group, the incidence of high-risk plaque was 3.3%, 4.9%, 9.8% and 6.5% in patients who have CCS of 0, 1-250, 251-500 and > 500, respectively. For patients of the high-risk group, it was 7.0%, 20.0%, 17.1% and 12.5% in the respective CCS groups. They found that the incidence of high-risk plaque was lower for CCS > 500 and > 250 in the intermediate- and high-risk groups, respectively. However, when we recalculated their results, we found that the incidence of high-risk plaque was 3.7%, 9.1%, 13.2% and 9.5% in the respective CCS categories. There were no significant differences apart from patients with zero CCS. These results are very similar to ours. Because extensive calcification appears at a later stage of atherosclerotic progression, the incidence of high-risk plaque may not increase in extensively calcified lesions.

Patients who have a high CCS may have multiple plaques compared to those with a modest CCS. Thus, we investigated the incidence of multiple plaques in each group, but there were no significant differences among the four groups. The percent aggregate plaque volume was also not significantly different among the 4 groups.

Significant stenosis

Our results also showed that the incidence of significant stenosis increased stepwise as CCS increased. Rosen *et al*[18] performed CCS measurement and coronary angiography and found a close association between baseline calcium mass score and stenosis severity in each coronary artery. Ho *et al*[19] performed CCS measurement and CCTA in 664 patients and found that the frequency of significant stenosis increased as CCS increased, being 7.9%, 8.3%, 14.5% and 27.2% in those with CCS of 1-100, 101-400, 401-1000 and > 1000, respectively. These results are consistent with ours.

Zero CCS

Our study showed that, in patients who have zero CCS, the incidence of non-calcified plaque, high-risk plaque, and significant stenosis was 13.6%, 1.3% and 0.6%, respectively. Previously, we found non-calcified plaque in 11.1% of 224 asymptomatic low-risk patients with zero CCS[20]. Hausleiter *et al*[21] detected non-calcified plaque in 15.9% of intermediate risk patients. The CONFIRM registry reported that the incidence of significant stenosis was 1.4% in patients with zero CCS[22]. Their results are consistent with ours.

Predictors of high-risk plaque, significant stenosis, and high-risk CCS

In our study, multivariate analysis demonstrated that the predictors of high-risk plaque were male sex and hypertension, while those of significant stenosis were hypertension, dyslipidemia, and diabetes. Furthermore, the predictors of high-risk CCS were age, male sex, and diabetes. These predictors are conventional coronary risk factors.

Limitations

There are several limitations to our study. The number of patients was not large enough. We need a larger patient population to confirm our results. Although the rate of major coronary event differed significantly among the four groups, this difference was caused by the difference in coronary revascularization. We selected coronary revascularization only for patients with either moderate or severe ischemia by myocardial perfusion imaging or fractional flow reserve less than 0.75. Many studies demonstrate that these patients are at increased risk of coronary events, and benefit from coronary revascularization[23,24]. We think that it is difficult to demonstrate differences in hard cardiac events among the 4 groups, because the number of patients and follow-up period were not sufficient. In addition, our patients are basically at low to intermediate risk for coronary events, because these patients have no known CAD, which means subclinical CAD. Moreover, we prescribed high-intensity statin therapy for patients with high-risk plaque. Therefore, we think that these are the reasons why there are too few events in our study.

Table 4 Major coronary event among the four groups *n* (%)

CCS	0	0-100	101-400	> 400	*P*
n	154	198	165	134	
MCE	0 (0)	8 (4.0)[a]	13 (7.9)[c]	23 (17.2)[f]	< 0.001
Coronary death	0 (0)	0 (0)	0 (0)	1(0.8)	0.6345
Myocardial infarction	0 (0)	1 (0.5)	1 (0.6)	3 (2.2)	0.4584
Revascularization	0 (0)	7 (3.5)[g]	12 (7.3)[i]	19 (14.2)[k]	< 0.001

[a]P = 0.0306 compared with group with CCS 0; [c]P= 0.1188 compared with group with CCS 1-100; [f]P = 0.0141 compared with group with CCS 101-400; [g]P = 0.0486 compared with group with CCS 0; [i]P = 0.1114 compared with group with CCS 1-100; [k]P = 0.0333 compared with group with CCS 101-400. CCS: Coronary calcium score; MCE: Major coronary event.

Our results demonstrate that the stepwise increased risk of coronary events in association with an increased CCS would be caused by an increasing incidence of significant stenosis, while the incidence of high-risk plaque remains the same, except patients with zero CCS. Thus, the combined incidence of high-risk plaque and significant stenosis increased stepwise as CCS increased.

COMMENTS

Background

Coronary calcium score (CCS) is the most powerful predictor of cardiac events beyond conventional risk factors. However, the precise mechanism of increased risk of coronary events associated with increasing CCS is not fully elucidated.

Research frontiers

Many studies have demonstrated that most cardiac death and myocardial infarction are caused by rupture of vulnerable plaque, which often has non-significant stenosis. Recent studies demonstrate that the characteristics of vulnerable plaque by coronary computed tomographic angiography, which is called high-risk plaque, are positive remodeling, low attenuation plaque, spotty calcification, and napkin-ring sign.

Innovation and breakthroughs

The authors showed that stepwise increased risk of coronary events associated with increasing CCS is caused by increasing prevalence of significant stenosis, while that of high-risk plaque remains the same. There was each study which investigated the relationship between CCS and significant stenosis, and CCS and high-risk plaque, respectively. However, the authors comprehensively showed the relationship between CCS and high-risk plaque/significant stenosis.

Applications

The higher the CCS, the more the authors have a chance to find significant stenosis in these patients. For patients with significant stenosis, non-invasive stress test to detect myocardial ischemia is needed. The authors also must pay attention to high-risk plaque even for patients with low CCS.

Terminology

Napkin-ring sign is defined as the presence of a ring of high attenuation around certain coronary artery plaque and the CT attenuation of a ring presenting higher than those of the adjacent plaque and no greater than 130 HU.

Peer-review

Very nice and interesting study, well performed.

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SYSTEMATIC REVIEW

Acquired aortocameral fistula occurring late after infective endocarditis: An emblematic case and review of 38 reported cases

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Abstract

AIM

To delineate the features and current therapeutic option of congenital and acquired aortocameral fistulas (ACF) secondary to iatrogenic or infectious disorders.

METHODS

From a PubMed search using the term "aortocameral fistula", 30 suitable papers for the current review were retrieved. Reviews, case series and case reports published in English were considered. Abstracts and reports from scientific meetings were not included. A total of 38 reviewed subjects were collected and analyzed. In addition, another case - an adult male who presented with ACF between commissures of the right and non-coronary sinuses and right atrium as a late complication of Staphylococcus aureus infective endocarditis of the AV - is added, the world literature is briefly reviewed.

RESULTS

A total of thirty-eight subjects producing 39 fistulas were reviewed, analyzed and stratified into either congenital (47%) or acquired (53%) according to their etiology. Of all subjects, 11% were asymptomatic and 89% were symptomatic with dyspnea (21 ×) as the most common presentation. Diagnosis was established by a multidiagnostic approach in 23 (60%), single method in 14 (37%) (echocardiography in 12 and catheterization in 2), and at autopsy in 2 (3%) of the subjects. Treatment options included percutaneous transcatheter closure in 12 (30%) with the deployment of the Amplatzer duct or septal occluder and Gianturco coil and surgical correction in 24 (63%).

CONCLUSION

Acquired ACF is an infrequent entity which may occur late after an episode of endocarditis of the native AV. The management of ACF is generally by surgical correction but non-surgical device intervention has recently been introduced as a safe alternative.

Key words: Aortic-atrial shunt; Aortic-atrial fistulas; Infective endocarditis; Late complication; Surgical correction

Core tip: Aortocameral fistula is an uncommon complication of native aortic valve (AV) endocarditis, which is associated with high morbidity and mortality. Acquired aortocameral fistulas (ACF) may originate from any of the three sinuses of Valsalva. Audible continuous murmur may raise suspicion for the presence of ACF. Congenital fistulas are less commonly reported than the acquired types. Acquired ACF may occur late after an episode of endocarditis of the native AV. The management of ACF is generally by surgical correction but non-surgical device intervention has recently been introduced as a safe alternative. Another case is added and the world literature is briefly reviewed.

Said SAM, Mariani MA. Acquired aortocameral fistula occurring late after infective endocarditis: An emblematic case and review of 38 reported cases. *World J Cardiol* 2016; 8(8): 488-495 Available from: URL: http://www.wjgnet.com/1949-8462/full/v8/i8/488.htm DOI: http://dx.doi.org/10.4330/wjc.v8.i8.488

INTRODUCTION

Aortocameral fistulas (ACF) may be congenital[1] or acquired complicating acute aortic dissection[2] following an intimal tear in the vicinity and proximity of the aortic root or after aortic valve (AV) replacement[3]. ACF is an uncommon complication of native AV endocarditis, which is associated with high morbidity and mortality. ACF may originate from any of the three sinuses of Valsalva. Audible continuous murmur may raise suspicion for the presence of ACF[4]. The clinical manifestations of ACF may include exertional dyspnea[2,5], chest pain[6,7], palpitation[6,8], congestive heart failure[9,10] and recurrent respiratory tract infection[11,12]. ACF may incidentally be found during routine preoperative examination[13]. Untreated ACF may cause significant morbidity and early mortality. The surgical correction of ACF is the treatment of choice but percutaneous transcatheter device intervention has recently been successfully introduced for the closure of ACF[5,6,8,9]. Acquired ACF is an infrequent entity which may occur late after an episode of endocarditis of the native AV. Another case of our own is added and the world literature is briefly reviewed.

MATERIALS AND METHODS

Literature search

From the PubMed search using the term "aortocameral fistula", 30 suitable papers for the current review were retrieved (Table 1). Reviews, case series and case reports published in English were considered. Abstracts and reports from scientific meetings were not included. From 30 publications, 38 reviewed subjects were collected and analyzed. Data were analyzed using descriptive statistics.

Statistical analysis

In contrast to classic meta-analysis, the outcome is defined here as the percentages of an event (without comparison) in observed patients.

Additional clinical case

An adult male presented with ACF between the junction of RCS-NCS and RA as a late complication of Staphylococcus aureus infective endocarditis (IE) of the native AV, is added.

A 44-year-old male survivor of a prior episode of *Staphylococcus aureus* IE of the native AV (1998) presented with a recent history of rapid fatigability (2008) during sporting activities. He was afebrile and a continuous murmur was heard. Laboratory results and chest X-ray were normal. Resting ECG depicted sinus rhythm with signs of left ventricular hypertrophy (LVH). Two-dimensional transthoracic Doppler echocardiography revealed mild LVH, the right ventricle (RV) was dilated and normokinetic, and the tricuspid AV had no vegetation. Color flow mapping revealed evidence of a high velocity shunt between the commissures of the right coronary sinus (RCS) and non-coronary sinuses (NCS) terminating into the right atrium (RA) (Figure 1, Supplementary material online, Video 1). Cardiac catheterization demonstrated a shunt between the aorta and the RA and normal left ventricular kinetics (Figure 2, Supplementary material online, Video 2). Hemodynamic evaluation revealed a significant left-to-right shunt (Qp: Qs = 2.0:1.0) with normal pulmonary vascular resistance, normal intracardiac pressures and high resting cardiac output of 10 L/min. Computed tomography and cardiovascular magnetic resonance were not available at that time. The fistula was surgically closed (2008). The fistula was surgically closed (2008). After establishing median sternotomy, extracorporeal circulation was performed through standard cannulation of the aorta and right atrium. The heart was arrested with antegrade and selective blood cardioplegia. On inspection, no infectious masses or evidence of abscess or vegetations were visible. Further inspection revealed that the ascending aorta was not dilated or calcified and the LV showed moderate hypertrophy. After aortotomy, the AV could be inspected, which was tricuspid with mild thickening and the fistula was clearly visible between the RCS and NCS terminating into RA. The fistula was closed with 4.0 prolene suture and pledgets. The patient could easily be weaned off after an uneventful procedure. Postoperative transesophageal echocardiography revealed no rest shunt flow. The patient had an uneventful postoperative course. The patient had uneventful postoperative course and regained his non-professional sporting activities without any limitations. After 8 years of follow-up, he remains free of symptoms. The fistula was closed by 4.0

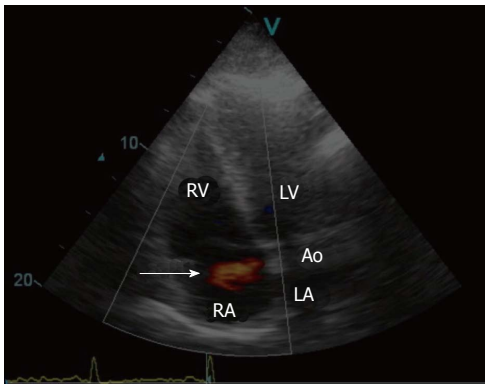

Figure 1 A frame of colored Doppler trans-thoracic echocardiography, five-chamber view illustrating the aortic-atrial fistula (arrow). Ao: Aorta; RA: Right atrium; LA: Left atrium; RV: Right ventricle; LV: Left ventricle.

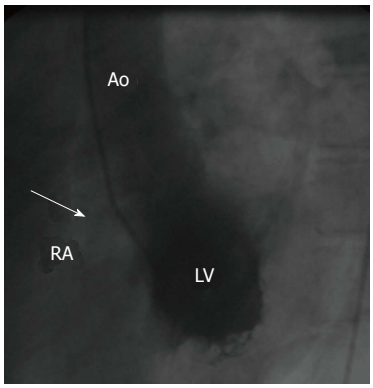

Figure 2 Levo-ventriculogram in the left anterior oblique view demonstrating the fistula (arrow) between the right and non-coronary sinuses communicating with the right atrium. RCS/NCS: Right and non-coronary sinuses; LV: Levo-ventriculogram; RA: Right atrium.

prolene suture and pledgets. The patient had uneventful postoperative course and regained his non-professional sporting activities without any limitations. After 7 years of follow-up, he remains free of symptoms.

RESULTS

A total of 38 subjects were reviewed [21 males (55%) and 17 females (45%)], with a mean age of 36.8 years (range 3-70 years). The etiology was congenital in 18 (47%) and acquired in 20 (53%). They all had 39 fistulas. Of those, 37 had a single and 1 had dual origin, with a similar outflow distribution of 37 single and one dual termination. Their origin was NCS in 21 (54%), RCS in 10 (26%), left coronary sinus (LCS) in 4 (10%) and the thoracic aorta in 4 (10%) of the subjects. The termination was into RA in 29 (74%), left atrium (LA) in 6 (15%), RV in 2 (5%), pulmonary artery in 1 (3%) and right ventricular outflow tract in 1 (3%). Four subjects (11%) were asymptomatic. In the symptomatic subjects (89%), the most common presentations were dyspnea (21 ×), followed by congestive heart failure (6 ×), chest pain (7 ×), palpitations (7 ×), IE (6 ×) with *Streptococcus mitis*[14] and *Staphylococcus epidermidis*[15]. Although syncope, hematuria, hemoptysis and recurrent respiratory tract infection are rarely reported, sudden death has also been observed[16].

Diagnosis was established by multidiagnostic approach in 23 (60%), a single method in 14 (37%) (echocardiography in 12 and catheterization in 2), and at autopsy in 2 (3%)[17] of the subjects. IE was found in 6 (16%) subjects, all originating from the NCS and communicating with the RA in 5 and the LA in one. Treatment included percutaneous transcatheter closure in 12 (30%) and surgical correction in 24 (63%) and there were 3 mortalities (7%) (Table 1).

DISCUSSION

An aortic-atrial fistula is an aortocameral fistula presenting as an extracardiac vascular communication that may be congenital[1] or acquired[2]. ACF is an uncommon complication of native AV endocarditis, which is associated with high morbidity and mortality. In 1963, Kuipers *et al*[18] reported spontaneous ruptured aortic dissection into the right atrium. Congenital fistulas are less commonly reported than the acquired types. ACF may originate from any of the 3 sinuses of Valsalva. Acquired ACF may occur following bacterial endocarditis[19], acute aortic dissection[2], ruptured sinus of Valsalva aneurysm (RSVA)[19], and post-cardiovascular surgical procedures associated with[5] or without infective endocarditis (IE)[20-22]. Furthermore, ACF may occur after coronary artery bypass grafting[23], after mitral valve replacement[23], following repeat AV replacement[24] or secondary to iatrogenic endovascular injury during an invasive diagnostic procedure[4].

ACF may incidentally be found during routine preoperative examination[13] or presented with severe heart failure[2]. The surgical correction of ACF is the treatment of choice but percutaneous transcatheter device intervention has recently been successfully introduced for the closure of ACF[5,6,8,9].

In 1831, Hope[25] described a ruptured aneurysm of a sinus of Valsalva into the right atrium. Congenital or acquired aortic-atrial fistulas are rare anomalies. In 1924, a large autopsy series (n = 4000) revealed aorta to atrium fistula as an incidental finding; rupture was found in 1197, of which 13 were into the RA due to infectious, traumatic and atherosclerotic causes[26]. ACF may be congenital[1] or acquired complicating acute aortic dissection[2] following an intimal tear in the vicinity and proximity of the aortic root or after AV replacement[3] (Table 2). ACF may occur in patients with infective endocarditis[19], as was the case in the current patient and in 16% of the reviewed subjects.

Clinical presentation

Audible continuous murmur may raise suspicion for the presence of ACF[4]. The clinical manifestations of ACF may include exertional dyspnea[2,5], chest pain[6,7], palpitation[6,8], congestive heart failure[9,10] and recurrent respiratory tract infection[11,12]. Our patient presented with reduced physical fitness as the only symptom, occurring

Table 1 Clinical presentations and management of 39 subjects

Ref.	Age gender	ACF	Diagnostic modality	Clinical presentation/etiology	Management
Jung *et al*[19], 2011	49 M	NCS-right atrium	TTE	Dyspnea and high fever Ruptured sinus of Valsalva Infective endocarditis (Enterococcus gallinarum)	Patch repair AVR/TVR
Raufi *et al*[21], 2002	50 M	RCS-right atrium	TEE aortography cardiac cath	Dyspnea and chest pain Post-repair of aneurysm of right sinus of Valsalva	Repair of the ruptured sinus of Valsalva Closure of the fistula
Hsu *et al*[2], 2000	67 M	False lumen-Right atrium	TTE cardiac cath ioTEE	Dyspnea Acute aortic dissection	Fistula repair Bentall procedure
Chung *et al*[20], 2000	52 M	AAR-right atrium	TTE cardiac cath angiography MRI	Dyspnea and hemoptysis Post-repair (ARR) of acute aortic dissection	Closure of the fistula New composite aortic root graft
Ananthasubramaniam *et al*[24], 2005	66 M	LCS-left atrium	TTE TEE ioTEE	Dyspnea post-AVR	Surgical closure of the fistula/repair
Haddad *et al*[22], 2008	66 M	NCS-right atrium	TTE	Dyspnea post-repair of acute aortic dissection	Fistula repair Bentall procedure
Estévez-Loureiro *et al*[5], 2012	44 M	NCS-left atrium	TTE TEE MDCT CAG 3-D TEE	Dyspnea Infective endocarditis post-AVR (Streptococcus viridans)	Percutaneous Amplatzer vascular plug III occluder
Bouchez *et al*[13], 2012	61 M	LCS-left atrium	io TEE 3-D TEE	Asymptomatic	Conservative
Mundo-Sagardía *et al*[14], 2006	22 M	NCS-right atrium	TTE TEE	Infective endocarditis (Streptococcus mitis). Complex congenital heart disease. Perforation of sinus Valsalva aneurysm (NCS)	Closure/repair
Ladowski *et al*[4], 1984	56 F	NCS-right atrium	angiography	Iatrogenic dissection	Surgical closure/repair
Vydt *et al*[36], 2002	43 M	NCS-right atrium	TTE TEE cardiac cath angiography aortography	Chest pain, DOE, ruptured sinus Valsalva aneurysm	Surgical closure
Moiduddin *et al*[12], 2009	5 F	NCS-left atrium	TEE angiography cardiac cath	Amplatzer atrial septal occluder ASD PDA	Surgical closure/repair
Chandra *et al*[1], 2011	12 F	RCS-right atrium	TTE CTA aortography angiography cardiac cath	Dyspnea, palpitation	Percutaneous Amplatzer duct occluder
Noureddine *et al*[16], 2001	21 F	NCS-right atrium	TTE TEE	Dyspnea	Sudden death
Przybojewski *et al*[39], 1983	27 M	RCS/right atrium and right ventricle	Phonocardiography TTE cardiac cath angiography aortography	Dyspnea; biventricular heart failure, ruptured sinus Valsalva aneurysm (RCS)	Surgical closure/repair
Mujanovic *et al*[35], 2010	41 F	NCS-right atrium	TTE angiography	Heart failure; ruptured sinus Valsalva aneurysm (NCS)	Surgical closure/repair
Mello *et al*[33], 2005	16 F	NCS-left atrium	TTE TEE aortography	Asymptomatic, post-placement of Amplatzer atrial septal occluder (ASO) for ASDII	Surgical closure/repair
Grayburn *et al*[7], 2005	41 F	Aorta-right atrium	TTE TEE	Chest pain, post-placement of Amplatzer atrial septal occluder (ASO) for ASD	Surgical closure/repair
Chun *et al*[30], 2003	10 M	NCS-right atrium	TTE TEE	Asymptomatic, post-placement of Amplatzer atrial septal occluder (ASO) for ASD	Surgical closure/repair
Knirsch *et al*[32], 2005	3 M	NCS-left atrium	TTE	Asymptomatic, post-placement of Amplatzer atrial septal occluder (ASO) for ASD	Surgical closure/repair
Jang *et al*[31], 2005	54 F	NCS-right atrium	TTE	Dyspnea, palpitation, hematuria, post-placement of Amplatzer atrial septal occluder (ASO) for ASDII	Surgical closure/repair
Ozay *et al*[45], 2007	22 F	NCS-right atrium	TTE TEE aortography cardiac catheter	Palpitation post-surgical repair of VSD and ASDII	Surgical closure/repair/correction
Elwatidy *et al*[46], 2003	3 F	Aortic isthmus-RA	TTE cardiac catheter	Presented as a case of PDA	Surgical closure/repair/correction
Akowuah *et al*[10], 2002	52 F	NCS-right atrium	TTE cardiac catheter	CHF, IE, TV, Staphylococcus aureus MRSA	Surgical TVR correction
Darwzah *et al*[15], 2006	23 M	NCS/LCS-right atrium	TTE	PVE of AVR Staphylococcus epidermidis	Surgical Re-re AVR correction
Russo *et al*[47], 2001	70 F	NCS-right atrium	TTE TEE	Chest pain, dyspnea, CHF complication of AAD type 1	Surgical closure/repair/correction
Onorato *et al*[9], 2005	48 F	NCS-right atrium	TTE TEE ICE aortography cardiac catheter	Dyspnea, CHF, ruptured sinus Valsalva aneurysm	ADO catheter closure

Chang *et al*[8], 2006	47, 22 F (2 ×) and 22,18M (2 ×)	NCS-RA (1 ×) RCS-RA (1 ×) and RCS-RV (2 ×)	4 × TEE 4 × aortography	Closure of VSD and AVR, IE (1 ×) Dyspnea and palpitation (3 ×)	ADO catheter closure (3 ×) and Gianturco coil (1 ×)
Szkutnik *et al*[6], 2009 congenital (4 ×) and acquired (1 ×)	51, 23, 41 M (3 ×) and 18, 28 F (2 ×)	RCS-RVOT (3 ×), RCS-RA (1 ×) LCS-PA (1 ×) and NCS-RA (1 ×)	TTE TEE MDCT	Dyspnea, chest pain, palpitation and syncope	ADO (5 ×) and ASO (1 ×) catheter closure
Oram *et al*[17], 1955	36, 67 M (2 ×)	NCS-RA RCS-RA, RV	Catheterization, autopsy	Chest pain, palpitation, dyspnea Chest pain, dyspnea	Post-mortem
Said and Mariani 2016	44 M	NCS-RCS-RA	TTE, aortography cardiac cath, angiography	Easy fatigability	Surgical closure

AAD: Acute aortic dissection; ACF: Aortocameral fistula; AAR: Aneurysm of the aortic root; ADO: Amplatzer duct occlude; ARR: Aortic root replacement; ASD: Atrial septal defect; ASO: Amplatzer atrial septal occlude; AVR: Aortic valve replacement; CHF: Congestive heart failure; CP: Chest pain; CTA: Computed tomography angiography; D: Dyspnea; DOE: Dyspnea on exertion; F: Female; ICE: Intra-cardiac echocardiography; IE: Infective endocarditis; io: Intra-operative; LCS: Left coronary sinus; M: Male; MDCT: Multi-detector computed tomography; MRI: Magnetic resonance imaging; NCS: Non-coronary sinus; PA: Pulmonary artery; PDA: Patent ductus arteriosus; PVE: Prosthetic valve endocarditis; RA: Right atrium; RCS: Right coronary sinus; RV: Right ventricle; RVOT: Right ventricular outflow tract; TEE: Transesophageal echocardiography; TTE: Transthoracic echocardiography; TV: Tricuspid valve; TVR: Tricuspid valve replacement; VSD: Ventricular septal defect.

Table 2 Etiology of aortocameral fistulas

Etiology	Condition/references
Congenital	Congenital RCS-RA fistula[1] and aortic isthmus-RA fistula[46]
Acquired-iatrogenic (post-surgical and non-surgical intervention/infectious/diagnostic procedures)	Iatrogenic aorta-right atrial fistula: late (14 years) post-surgical repair of VSD and ASD[45]
	Post-corrective surgery of sinus of Valsalva aneurysm[21]
	Post-CABG[23,48]
	Post-AVR[3,8]
	Post-MVR[23]
	Post-ARR, after operating on a type A dissection[20,47]
	Following ASO closure of the secundum ASD II [30]
	NVE[10], RCS/NCS-right atrial fistula (current case) secondary to NVE
	PVE[5,15]
	ACF associated with diagnostic cardiac catheterization (NCS-RAA)[4]
Acquired-accidental/traumatic	ACF post-non-penetrating thoracic injury[49] has been reported
Spontaneous	RSVA[27]
	Rupture of ascending aorta aneurysm[18]

ACF: Aortocameral fistula; ARR: Aortic root replacement; ASD: Atrial septal defect; ASO: Amplatzer atrial septal occlude; AVR: Aortic valve replacement; CABG: Coronary artery bypass grafting; MVR: Mitral valve replacement; NCS: Non-coronary sinus; NVE: Native valve endocarditis; PVE: Prosthetic valve endocarditis; RA: Right atrium; RAA: Right atrial appendage; RCS: Right coronary sinus; RSVA: Ruptured sinus Valsalva aneurysm; VSD: Ventricular septal defect.

late after the index native valve endocarditis. Among the 38 reviewed subjects, four (11%) were asymptomatic and the majority (89%) were symptomatic.

ACF may originate from any of the three sinuses of Valsalva, but origin from the NCS was infrequently reported[27]. Congenital aneurysms (origin RCS 65%-85%, NCS 10%-30% and LCS < 5%) of the sinus of Valsalva have a tendency to rupture, mainly into the right cardiac chambers (termination RV 63%, RA 32%), resulting in an ACF[28,29]. Congenital aneurysms of the sinus of Valsalva may be associated with other defects including bicuspid AV, ventricular septal defect and coarctation of the aorta[21].

ACF may occur between the aorta and right atrium[2], as was the case in our current patient, or left atrium[24]. Congenital ACF may be incidentally found in asymptomatic adult subjects[13]. There have been a few reports of iatrogenic acquired fistula formation associated with the percutaneous device closure of atrial septal defects with an Amplatzer septal occluder[30-33].

Congenital aortic-atrial fistulas are extremely rare. Acquired ACF are related to prosthetic valve disorders after aortic root repair associated with[5,15] or without infective endocarditis[22]. The current patient had a prior IE of the native AV. ACF may appear as an early[34], immediate[22] (10 d) or late (4 years)[5] postoperative complication.

Diagnostic modalities

Echocardiography [transthoracic (TTE), transesophageal (TEE) and 3-D TEE][7,32,35] is the first diagnostic modality of choice to precisely delineate the fistula components. With complete right and left cardiac catheterization and aortography of the aortic root, the fistula can be appropriately evaluated and the exact location indi-

cated[21,36]. TTE, TEE and 3-D TEE comprise a useful non-invasive diagnostic modality with which to delineate the fistula characteristics. With 2-D echocardiography, TEE, the clinical diagnosis of ACF may be established but ascending aortography is essential for confirmation and to differentiate from other disorders such as ruptured sinus of Valsalva aneurysm[36], aorta-right atrial tunnel[11] and acquired[37] or congenital[38] coronary cameral fistulas.

A multimodality imaging strategy confirms the diagnosis of ACF. Echocardiography (TTE and TEE), selective coronary angiography and retrograde aortography are used for visualization of the coronary ostia and demonstration of the course of the fistula[12,36]. This was the chosen approach in two-third (60%) of the reviewed subjects and in the presented case.

Computed tomography (CT) scan and cardiovascular magnetic resonance imaging (MRI): These diagnostic modalities were not widely applied among the reviewed subjects. In only few cases, CT scan[1,5,6] was performed and MRI technique was found in the case reported by Chung[20]. In our current case, CT and cardiovascular magnetic resonance were not available at that time and moreover, echocardiography and aortography provided adequate imaging quality of the ACF making further investigations unnecessary.

The most common termination sites of "spontaneously" ruptured aneurysms of coronary sinus of Valsalva are into the RA or RV[27,39]; more rarely, the left ventricle[27] may be involved, ensuing acute volume overload of the involved cardiac chamber. Our patient had an acquired aortic-right atrial connection.

The origin of congenital aneurysm is generally related to the right coronary sinus (65%-85%)[1,28,29,39] and those associated with infective endocarditis ensue from the left coronary sinus[40], RCS[41] or NCS[42].

Management

The first successful surgical correction of ruptured sinus Valsalva aneurysm (RSVA) was reported in 1957[43]. In 1966, Temple *et al*[44] described the successful surgical repair of aortic-right atrial fistula in an adult symptomatic male. ACF may be closed by surgical intervention[2] or by transcatheter device[5]. The treatment of choice is early surgical repair, which is necessary to prevent the development of severe symptoms and complications. Untreated ACF may cause significant morbidity and early mortality. Recently, percutaneous transcatheter treatment of ACF has been reported which is considered a novel method for selected cases[5]. Percutaneous transcatheter closure of ACF, using the Amplatzer duct occluder, Gianturco coil or Amplatzer septal occluder, has proven to be a safe technique which is gaining territory in the non-surgical management of ACF[5,6,8,9]. Our patient had a successful surgical repair with uneventful postoperative recovery.

Our current patient survived infective endocarditis of the AV occurring years prior to presentation. He remains well 7 years following the surgical correction.

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COMMENTS

Background

Aortocameral fistulas (ACF) may be congenital or acquired complicating acute aortic dissection following an intimal tear in the vicinity and proximity of the aortic root or after aortic valve (AV) replacement. ACF is an uncommon complication of native AV endocarditis, which is associated with high morbidity and mortality.

Research frontiers

ACF may originate from any of the three sinuses of Valsalva. Audible continuous murmur may raise suspicion for the presence of ACF. The clinical manifestations of ACF may include exertional dyspnea, chest pain, palpitation, congestive heart failure and recurrent respiratory tract infection. ACF may incidentally be found during routine preoperative examination. Untreated ACF may cause significant morbidity and early mortality.

Innovations and breakthroughs

The surgical correction of ACF is the treatment of choice but percutaneous transcatheter device intervention has recently been successfully introduced for the closure of ACF. Acquired ACF is an infrequent entity which may occur late after an episode of endocarditis of the native AV.

Applications

This paper presents a case of acquired aortic-atrial fistulas occurring late after infective endocarditis of the aortic valve, the author reviewed 30 suitable papers and summarized the clinical feature, diagnostic modalities and management of such a disease.

Peer-review

The authors reviewed the published literature on the aortic-atrial fistulae, but also included several cases of similar connections that occurred between the aorta and other chambers including the ventricles, the left atrium and the pulmonary artery. The interesting side of the manuscript is the review rather than the clinical case. The review is well written and reports a total of 38 cases, presented in different clinical scenario.

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Intra-cardiac distribution of late gadolinium enhancement in cardiac sarcoidosis and dilated cardiomyopathy

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Abstract

Cardiac involvement of sarcoid lesions is diagnosed by myocardial biopsy which is frequently false-negative, and patients with cardiac sarcoidosis (CS) who have impaired left ventricular (LV) systolic function are sometimes diagnosed with dilated cardiomyopathy (DCM). Late gadolinium enhancement (LE) in magnetic resonance imaging is now a critical finding in diagnosing CS, and the novel Japanese guideline considers myocardial LE to be a major criterion of CS. This article describes the value of LE in patients with CS who have impaired LV systolic function, particularly the diagnostic and clinical significance of LE distribution in comparison with DCM. LE existed at all LV segments and myocardial layers in patients with CS, whereas it was localized predominantly in the midwall of basal to mid septum in those with DCM. Transmural (nodular), circumferential, and subepicardial and subendocardial LE distribution were highly specific in patients with CS, whereas the prevalence of striated midwall LE were high both in patients with CS and with DCM. Since sarcoidosis patients with LE have higher incidences of heart failure symptoms, ventricular tachyarrhythmia and sudden cardiac death, the analyses of extent and distribution of LE are crucial in early diagnosis and therapeutic approach for patients with CS.

Key words: Magnetic resonance imaging; Late gadolinium enhancement; Sarcoidosis; Dilated cardiomyopathy; Diagnosis

Core tip: Late gadolinium enhancement (LE) in magnetic resonance imaging is a critical finding in the diagnosis of cardiac sarcoidosis (CS), but it is also observed in dilated cardiomyopathy (DCM). We review the significance of LE distribution in comparison with DCM. LE distributed into

all ventricular segments and myocardial layers in CS, whereas it was localized predominantly in the midwall of ventricular septum in DCM. Transmural, circumferential, and subepicardial and subendocardial LE were highly specific in CS. Since patients with LE have more adverse cardiac events, the analyses of extent and distribution of LE are crucial for diagnosis and management of CS.

Sano M, Satoh H, Suwa K, Saotome M, Urushida T, Katoh H, Hayashi H, Saitoh T. Intra-cardiac distribution of late gadolinium enhancement in cardiac sarcoidosis and dilated cardiomyopathy. *World J Cardiol* 2016; 8(9): 496-503 Available from: URL: http://www.wjgnet.com/1949-8462/full/v8/i9/496.htm DOI: http://dx.doi.org/10.4330/wjc.v8.i9.496

INTRODUCTION

Sarcoidosis is a multi-organ granulomatous disorder of undetermined aetiology. Cardiac involvement is identified clinically only in few percentage (%) of patients with systemic sarcoidosis, while post-mortem investigations have found myocardial lesions in around 60%[1]. Necropsies exhibited that cardiac involvement was mostly non-transmural and lesions were located predominantly in the basal left ventricle (LV) and subepicardial myocardium[2,3]. Patients with cardiac sarcoidosis (CS) have a poor prognosis due to congestive heart failure with impaired LV function, and sudden cardiac death associated with lethal ventricular tachycardia (VT) or conduction disturbance[4].

Although endomyocardial biopsy has been the gold standard in diagnosing CS, it has limited sensitivity and certain procedural risks[5]. Actually, the results of endomyocardial biopsy were frequently false negative because of the patchy distribution of the lesions. Therefore, patients with cardiac involvement of systemic sarcoidosis (sCS) and with isolated CS (iCS) are not always positive for endomyocardial biopsy. As a result, a certain part of patients may be diagnosed with normal or dilated cardiomyopathy (DCM), and do not receive immunosuppressive therapies. Since a corticosteroid therapy can improve long-term prognosis of CS[6,7], an earlier diagnosis of CS with non-invasive cardiac imaging is clinically significant.

The recent development of various imaging modalities including magnetic resonance imaging (MRI) and 18F-fluorodeoxyglucose-positron emission computed tomography (FDG-PET) has enabled more precise diagnosis of CS. The LV wall in most patients with CS has late gadolinium enhancement (LE) in MRI[5,8-10], and the novel guideline of Japanese Ministry of Health and Welfare (JMH) considers the presence of LE to be a major criterion in CS (Table 1)[11]. However, LE is non-specific and frequently observed in other cardiomyopathies including DCM.

We have been investigating the patterns of LE distribution in various cardiomyopathies and trying to confirm the values for differential diagnosis, clinical features, and prognosis[12-18]. Here we describe the value of LE in patients with CS, particularly the diagnostic and clinical significance of LE distribution in comparison with DCM.

Table 1 Clinical cardiac findings in Diagnostic Standard and Guideline for Sarcoidosis-2015-Japanese Society of Sarcoidosis and Other Granulomatous Disorders

(1) More than two of five major findings are satisfied
(2) One of five major findings and more than two of three minor findings are satisfied
Major findings
Advanced atrioventricular block (including complete atrioventricular block) or sustained ventricular tachycardia
Basal thinning of the interventricular septum or morphological ventricular abnormality (ventricular aneurysm, wall thinning of other ventricular region, wall thickening)
Impaired left ventricular contraction (LVEF < 50%) or regionally abnormal wall motion
Abnormal cardiac uptake in gallium-67 citrate scintigraphy or fluorine-18 fluorodeoxyglucose PET
Late myocardial enhancement in gadolinium enhanced magnetic resonance imaging
Minor findings
Non-sustained ventricular tachycardia, multifocal or frequent premature ventricular contractions, bundle branch block, axis deviation, or abnormal Q wave in electrocardiography
Defect on myocardial perfusion scintigraphy
Endomyocardial biopsy: Interstitial fibrosis or monocyte infiltration over moderate grade

LVEF: Left ventricular ejection fraction; PET: Positron emission tomography.

LE DISTRIBUTION IN CS AND DIFFERENTIAL DIAGNOSIS FROM DCM

Patient characteristics

We initially enrolled 21 patients with CS who had LE in the myocardium between 2003 and 2015. Among them, the intra-cardiac and intra-mural distribution of LE were analyzed in 14 (67%) patients (13 sCS and 1 iCS) who showed reduced LV ejection fraction (LVEF: < 50%). The clinical characteristics and LE features were compared with 30 patients with DCM who were diagnosed by the World Health Organization/International Society and Federation of Cardiology definition of cardiomyopathies[19]. The present study was performed in accordance with the Declaration of Helsinki and the protocol was approved by an institutional review board. All study participants provided informed consent.

Patients with CS included more female patients and were younger, but there were no differences in symptoms, ECG findings and medications excluding corticosteroids (Table 2). Patients with CS had less decreased LVEF and smaller LV end-systolic volume index, while LV end-diastolic volume index and LV mass index did not differ from those in DCM. The LV segment number with LE was also greater in patients with CS. Figure 1 shows LE-MRI images (left) and corresponding

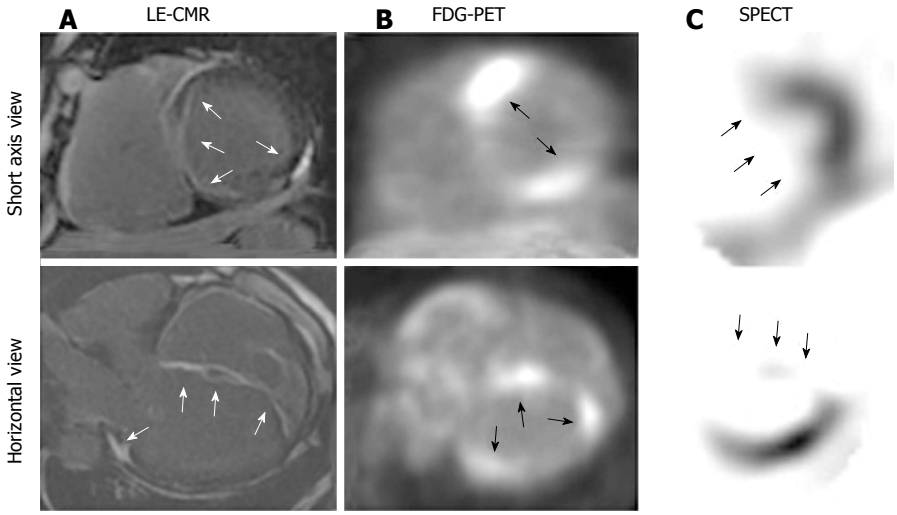

Figure 1 Non-invasive cardiac imaging in a 61-year-old male patient with cardiac involvement of systemic sarcoidosis. LE-CMR (A) shows diffuse LE in the subepicardium (RV side) and subendocardium (LV side) of basal to apical ventricular septum and patchy LE in the midwall of posterior LV (white arrows); Corresponding FDG-PET (B) demonstrates focal uptake in basal and apical ventricular septum and posterior LV wall (black arrows); ^{99m}Tc-sestamibi SPECT (C) exhibits a defect only in ventricular septum (black arrows). CMR: Cardiac magnetic resonance; FDG-PET: ^{18}F-fluorodeoxyglucose-positron emission computed tomography; LE: Late gadolinium enhancement; LV/RV: Left and right ventricles; SPECT: Single photon emission computed tomography.

FDG-PET (middle) and ^{99m}Tc-sestamibi single photon emission computed tomography (SPECT: right) in a 61-year-old patient with sCS. LE-MRI exhibits diffuse LE in the subepicardium (RV side) and subendocardium (LV side) of basal to apical ventricular septum and patchy LE in the midwall of posterior LV (white arrows). FDG-PET demonstrates focal uptake in basal and apical ventricular septum and posterior LV wall (black arrows). ^{99m}Tc-sestamibi SPECT shows a defect only in ventricular septum (black arrows).

Intra-LV and intra-mural LE distribution

The intra-LV LE distribution was analyzed using the 17-segments model[16]. Next, we visually divided the intra-mural LE distribution into subepicardial, midwall and subendocardial distribution. Then, the extent of LE in each segment was determined with a five-point scoring system (0 = no LE, 1 = 1%-25%, 2 = 26%-50%, 3 = 51%-75%, 4 = 76%-100% of transmural extent of LE). The segment with score 4 was defined as "transmural" distribution[16]. LE in patients with CS existed predominantly in the basal and mid septum, but also distributed throughout LV segments. While in patients with DCM, LE was localized mostly in the basal and mid septum[13,16]. In addition, LE distributed across all the myocardial layers in patients with CS, but was predominantly localized at the midwall in those with DCM (Figure 2). The averaged LE score in each LV segment was significantly higher in CS than that in DCM [0.95 ± 0.67 *vs* 0.42 ± 0.43, mean ± standard deviation (SD), $P < 0.05$].

Typical LE distribution profiles

Previous reports have also shown that transmural (nodular) distribution, circumferential subepicardial distribution, and subepicardial and subendocardial distribution (with spared midwall) are highly charac-

Table 2 Clinical features and magnetic resonance imaging parameters in patients with cardiac sarcoidosis and with dilated cardiomyopathy

	CS	DCM	*P* values
Number	14	30	
Sex (M/F)	M4/F10	M23/F7	0.001
Age (yr)	59.8 ± 13.5	69.2 ± 12.6	0.03
Syncope *n* (%)	2 (14.3)	6 (20.0)	0.65
Palpitation *n* (%)	7 (50.0)	17 (56.7)	0.74
NYHA	8/5/1/0	8/11/6/5	0.08
(I/II/III/IV)	(57.1%/35.7%/ 7.1%/0%)	(26.7%/36.7%/ 20%/16.7%)	
ECG findings			
PQ duration	188.4 ± 26.0	188.1 ± 40.9	0.91
1st/2nd AVB	7/1 (50.0%/7.1%)	7/0 (23.3%/0%)	0.14
QRS duration	118.6 ± 22.9	128.4 ± 36.3	0.18
Abnormal Q waves *n* (%)	6 (42.9)	3 (10.0)	0.09
RBBB/LBBB	3/5 (21.4%/35.7%)	2/15 (6.7%/50%)	0.57
VTs *n* (%)	7 (50.0)	15 (50.0)	0.74
Medications *n* (%)			
Corticosteroids	7 (50.0)	0 (0)	< 0.001
ACEI/ARB	9 (64.3)	20 (66.7)	0.73
β blockers	7 (50.0)	23 (76.7)	0.07
AADs	4 (28.6)	14 (46.7)	0.51
Diuretics	7 (50.0)	18 (60.0)	0.32
MRI			
LVEDVI (mL/m^2)	107.0 ± 45.8	135.5 ± 43.4	0.08
LVESVI (mL/m^2)	74.2 ± 44.5	106.3 ± 42.1	0.04
LVMI (g/m^2)	60.1 ± 24.9	67.1 ± 28.9	0.34
LVEF (%)	33.9 ± 11.0	22.8 ± 10.0	0.003
LE segment number	8.6 ± 4.6	5.3 ± 3.1	0.04

The categorical variables were expressed as number and percentage (%) and compared by χ^2 test. The continuous variables were expressed as means ± SD and examined by unpaired *t* test. CS: Cardiac sarcoidosis; DCM: Dilated cardiomyopathy; M/F: Male/female; NYHA: New York Heart Association; ARB: Angiotensin receptor blockers; ACEI: Angiotensin converting enzyme inhibitors; AVB: Atrioventricular block; AAD: Anti-arrhythmic drugs; MRI: Magnetic resonance imaging; LVEDVI and LVESVI: Left ventricular end-diastolic and end-systolic volume indices; LVEF: LV ejection fraction; LE: Late gadolinium enhancement; L/RBBB: Left/right bundle branch blocks; LVMI: LV mass index; VT: Ventricular tachycardia.

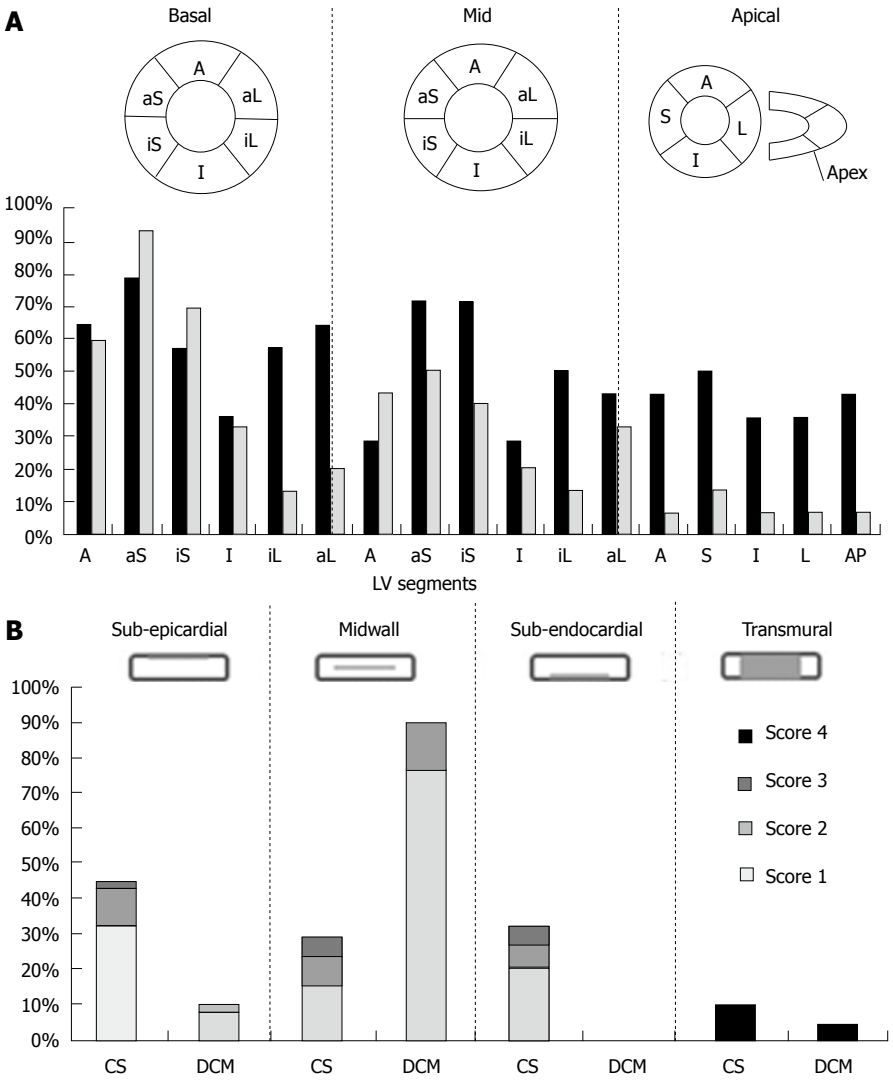

Figure 2 Intra-left ventricles (A) and intra-mural (B) late gadolinium enhancement distribution in patients with cardiac sarcoidosis and with dilated cardiomyopathy. A: Columns indicate prevalence of LE at each LV segment in patients with CS (black) and with DCM (gray). A: Anterior; aL: Antero-lateral; aS: Anterior septal; I: Inferior; iL: Infero-lateral wall in basal, mid and apical LV; AP: LV apex; B: Columns consist of prevalence of LE with scores 1 to 3 at different intra-mural distribution in patients with CS and with DCM. Score 4 indicates the transmural distribution. CS: Cardiac sarcoidosis; DCM: Dilated cardiomyopathy; LV: Left ventricles.

teristic in CS, whereas striated distribution in midwall is typical in DCM (Figure 3A)[5,10]. In our analysis, transmural (nodular), circumferential, and subepicardial and subendocardial LE distribution were highly specific in patients with CS, although the prevalence of those distribution patterns was low. In contrast, the prevalence of striated midwall LE distribution was high in both groups, but the specificity was low (Figure 3B and Table 3).

DISCUSSION

We initially demonstrated typical findings of various cardiac imaging in a patient with CS. Many reports have exhibited the correlations among LE-MRI, SPECT and FDG-PET in the evaluation of CS. The intra-mural extent of LE was quite concordant with perfusion defects in ^{201}Tl- or ^{99m}Tc-sestamibi-SPECT[9,13]. On the other hand, FDG-PET exhibits focal or focal on diffuse type of hot spots in CS[20-22]. While LE and defects in SPECT reflect irreversible fibro-granulomatous replacement, the hot spots in T2-weighted black-blood imaging (T2WBB), ^{67}Ga-SPECT and FDG-PET express active inflammatory change. The hot spots can be targeted for an endomyocardial biopsy if tissue diagnosis is required, and be adopted for an evaluation of corticosteroid therapy[21,23]. Since FDG-PET can give higher sensitivity and specificity than SPECT, we recommend the combination of LE-MRI and FDG-PET for assessing CS[20,21]. LE sometimes overlaps with hot spots in FDG-PET or T2WBB according to the disease progression or recurrence. Thus, it is important to carefully interpret findings in LE-MRI and other imaging modalities[24].

LE distributions in CS

Managing patients with reduced LV contraction who are suspected CS without histologic manifestation is a critical issue, since these cases may be diagnosed

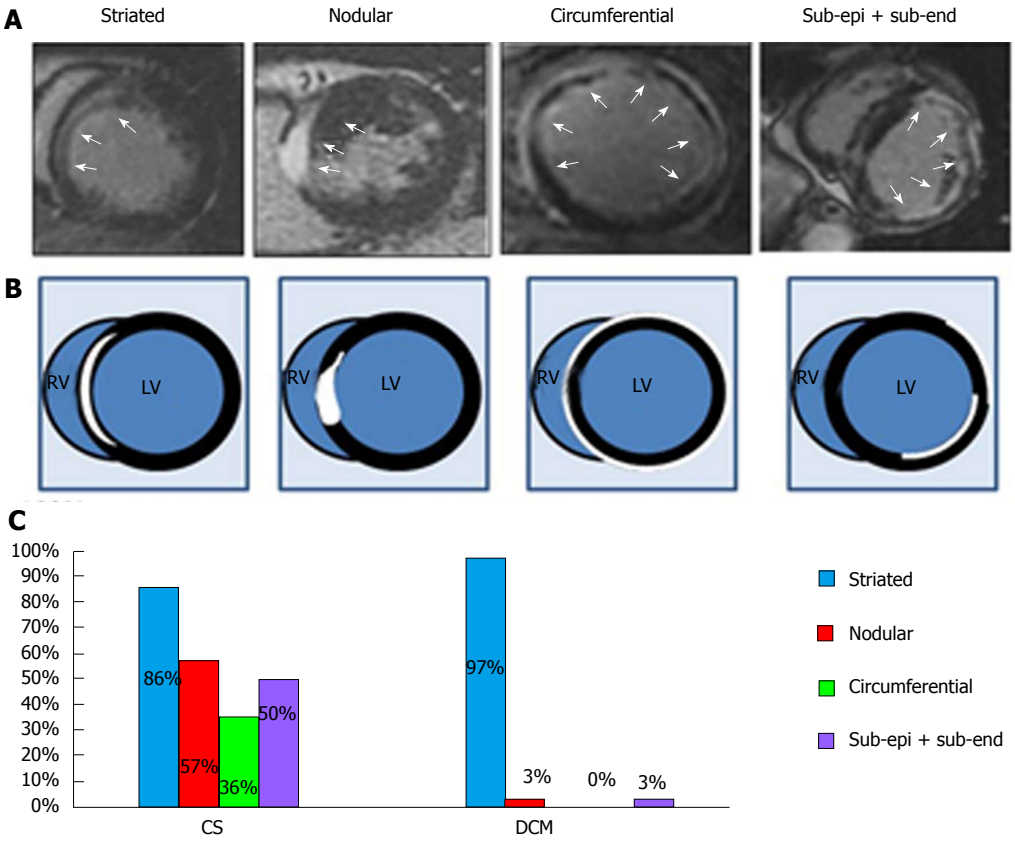

Figure 3 Typical late gadolinium enhancement distribution profiles. Characteristic patterns of LE distribution in LE-MRI (A) and the cartoons (B). Striated: Striated LE distribution in midwall; Nodular: Nodular (transmural) LE distribution; Circumferential: Subepicardial LE distribution in > 50% circumferential LV wall; Sub-epi + sub-end: Subepicardial and subendocardial LE distribution with spared midwall (white arrows); C: The prevalence of characteristic patterns of LE distribution in patients with CS and with DCM. CS: Cardiac sarcoidosis; DCM: Dilated cardiomyopathy; LE: Late gadolinium enhancement; LV/RV: Left and right ventricles; MRI: Magnetic resonance imaging.

Table 3 Diagnostic value of characteristic late gadolinium enhancement distribution patterns to differentially diagnose cardiac sarcoidosis from dilated cardiomyopathy

LE patterns	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Striated	85.7	3.3	29.3	33.3
Nodular	57.1	96.7	88.9	82.9
Circumferential	35.7	96.7	83.3	76.3
Subepi + subend	50.0	96.7	87.5	80.6

PPV and NPV: Positive and negative predictive values; Sub-epi + sub-end: Subepicardial and subendocardial distribution with spared midwall; LE: Late gadolinium enhancement.

with DCM, and do not receive corticosteroid therapy[25]. Oppositely, the inclusion of the presence of LE in the novel JMH guideline (Table 1) may cause an increase in false positive patients. Although FDG-PET can be an additional tool for diagnosing CS, it is not always available in all hospitals and patients. Therefore, more detailed analyses of LE-MRI are required to differentiate CS from DCM.

Many previous studies have clarified the characteristic LE distribution in CS (Table 4). In general, LE in CS is polymorphic and heterogeneous; a classic pattern of midwall or subepicardial LE can be seen, but subendocardial or transmural LE as in patients with ischemic cardiomyopathy is also possible. LE may correspond to the location of wall thinning, wall motion abnormalities and myocardial edema[5,8,10,13,25-30]. Tezuka *et al*[25] reported that there was no difference in LE distribution between sCS and iCS.

In our analysis, transmural (nodular), circumferential, and subepicardial and subendocardial LE distribution were highly specific in patients with CS, although the prevalence of those distribution patterns was low. In contrast, the prevalence of striated midwall LE distribution was high in both groups, but the specificity was low. Although the mechanisms of these types of LE distribution remain unknown, more aggressive examination for CS such as serological tests, ^{67}Ga-SPECT and FDG-PET should be considered, when patients with reduced LVEF showed diffuse and characteristic features of LE distribution.

Clinical implications of LE

In general, LE in patients with cardiomyopathies correlates with all-cause mortality, heart failure hospitalization, and sudden cardiac death. Thus, detection of LE by LE-MRI has excellent prognostic significance and may help guide risk stratification and management in patients with various cardiomyopathies[17,31].

In sarcoidosis, previous reports showed that patients

Table 4 Reports for patterns of late gadolinium enhancement distribution and clinical relevance of late gadolinium enhancement in cardiac sarcoidosis

Ref.	Patients	LE distribution		Clinical relevance
		Intra-cardiac	Intra-mural	
Smedema *et al*[8]	12 CS	Mostly basal and lateral LV wall	Any	Diagnostic
Matoh *et al*[13]	5 sCS	Mid ventricular septum	Midwall to subepicardial	Correlations between LE area and LVEDV, LVESV and LVEF
Ichinose *et al*[10]	10 CS	Any, but mostly basal LV wall	Any, but mainly subepicardial	Correlations between sum of LE score and BNP, LVEF, LVEDV
Manis *et al*[26]	11 CS	Ventricular septum	Patchy	Diagnostic
Patel *et al*[5]	21sCS	Any, but mainly basal ventricular septum, rarely RV wall	CAD; subendo-cardial non-CAD; mid wall, subepi-cardial, patchy	Higher rate of adverse events and cardiac death
Watanabe *et al*[27]	19 CS	NA	Subepicardial, transmural	Correlations between total LE segments, and reduced LV function and duration of extra-cardiac lesions
Greulich *et al*[28]	39 sCS	Any, but mainly ventricular septum (RV side)	Patchy, intramural to transmural	Higher Hazard ratio for MACE than other clinical parameters
Yang *et al*[29]	6 sCS	Ventricular septum, LV free wall, papillary muscle	Patchy	Decreased T2 (inactive phase)
Pöyjönen *et al*[30]	8 CS	Basal ventricular septum	Multifocal	Diagnostic
Tezuka *et al*[25]	9 sCS and 4 iCS	Any, but mainly anterior ventricular septum	Any, but mainly subepicardial	No difference between sCS and iCS in LE distribution and clinical features

BNP: Serum brain natriuretic peptide level; CAD: Coronary arterial disease type; CS: Cardiac sarcoidosis; iCS: Isolated CS; LV/RV: Left/right ventricles; LVEDV/ESV: LV end-diastolic/systolic volume; LVEF: LV ejection fractionl; MACE: Major adverse cardiac events; NA: Not available; sCS: Cardiac involvement of systemic sarcoidosis.

with LE in myocardium had high prevalence of heart failure symptoms, ECG abnormalities and lethal arrhythmias[5,28]. There are significant correlations between LE burden, and LV volume and function[5,8,10,27]. Regions of granulomatous infiltration evolving into scar tissue serve as substrates for re-entrant tachyarrhythmia[32,33]. Murtagh *et al*[34] exhibited that increased LE burden and right ventricular dysfunction can identify patients at highest risk of sudden cardiac death and VT. The efficacies of implantable cardioverter defibrillator (ICD) and catheter ablation were also reported for preventing sudden cardiac death and VT storm[35,36]. Therefore, not only the presence of LE, but also the LE burden and distribution should be considered for the risk stratification and therapeutic approach for CS. Although the smaller LE burden or non-specific scarring may be associated with a benign outcome[37], patients with LE should be carefully followed up, even when they had preserved LV function because of certain risks for sudden cardiac death and VT.

Tezuka *et al*[25] mentioned that the clinical features and prognosis did not differ between patients with sCS and iCS, whereas Kandolin *et al*[38] showed poorer outcomes in patients with iCS. The total segments with LE may correlate with the duration of extra-CS[27]. LE in CS mostly reflects irreversible myocardial scarring, and previous reports failed to show a decrease in LE volume after corticosteroid therapy[5,8,29]. The serial FDG-PET imaging is valuable to evaluate the effect of corticosteroid therapy for cardiac and systemic sarcoid lesions[21,39].

Limitations

Initially, MRI is not always available in all hospitals and patients, and has a problem of cost. Patients with pulmonary congestion cannot tolerate long data acquisition time of MRI. MRI has been prohibited in patients who have had device implantation. Therefore, patients who required urgent pacemaker or ICD implantation because of atrioventricular blocks or VT were excluded from the analyses of MRI. MR conditional pacemakers can be implanted in patients who may need MRI after device implantation[40,41]. Gadolinium cannot be injected to patients with chronic renal failure, because there is a risk of nephrogenic systemic fibrosis. Finally, different determination thresholds (> 2 SD to > 5 SD) and difficult quantification of LE are also limitations.

CONCLUSION

Although LE in myocardium has become a major criterion in the novel JMH guideline for CS, the present article suggests that more diffuse and characteristic patterns of LE distribution (in combination with abnormal wall motion and morphology) may be helpful for differentiating CS from DCM in patients with reduced LVEF. Future large and longitudinal follow-up studies are necessary to define characteristic patterns of LE distribution in CS as well as those prognostic values.

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REVIEW

Novel concepts in radiation-induced cardiovascular disease

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Abstract

Radiation-induced cardiovascular disease (RICVD) is the most common nonmalignant cause of morbidity and mortality among cancer survivors who have undergone mediastinal radiation therapy (RT). Cardiovascular complications include effusive or constrictive pericarditis, cardiomyopathy, valvular heart disease, and coronary/vascular disease. These are pathophysiologically distinct disease entities whose prevalence varies depending on the timing and extent of radiation exposure to the heart and great vessels. Although refinements in RT dosimetry and shielding will inevitably limit future cases of RICVD, the increasing number of long-term cancer survivors, including those treated with older higher-dose RT regimens, will ensure a steady flow of afflicted patients for the foreseeable future. Thus, there is a pressing need for enhanced understanding of the disease mechanisms, and improved detection methods and treatment strategies. Newly characterized mechanisms responsible for the establishment of chronic fibrosis, such as oxidative stress, inflammation and epigenetic modifications, are discussed and linked to potential treatments currently under study. Novel imaging modalities may serve as powerful screening tools in RICVD, and recent research and expert opinion advocating their use is introduced. Data arguing for the aggressive use of percutaneous interventions, such as transcutaneous valve replacement and drug-eluting stents, are examined and considered in the context of prior therapeutic approaches. RICVD and its treatment options are the subject of a rich and dynamic body of research, and patients who are at risk or suffering from this disease will benefit from the care of physicians with specialty expertise in the emerging field of cardio-oncology.

Key words: Radiotherapy; Radiation; Cardiovascular; Atherosclerosis; Cardiomyopathy; Pericarditis; Valvular; Hodgkin; Breast cancer; Radiation fibrosis

Core tip: Radiation-induced cardiovascular disease is a common complication of mediastinal radiotherapy and often occurs years or decades after treatment. It most commonly manifests as chronic pericarditis, cardiomyopathy, and valvular or coronary heart disease. Its pathophysiology is chiefly that of radiation fibrosis, fueled by chronic states of inflammation and oxidative stress. Conventional risk factors impose additive risk to these patients and must be addressed as early as possible. Development of more sensitive imaging modalities is enabling detection at earlier stages of the disease and creating opportunities for novel treatment strategies. Percutaneous interventions have an increasing role in the treatment of symptomatic vascular and valvular disease.

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INTRODUCTION

Mediastinal radiotherapy (RT) has been successfully used to decrease mortality and recurrence of a number of thoracic malignancies for decades, particularly early Hodgkin's lymphoma (HL) and breast cancer. Thanks to advances in chemotherapeutics and radiation oncology, HL is now eminently curable, with 20-year survival approaching 80%[1], while 15-year breast cancer survival is nearing the same threshold[2]. Increased longevity has unintended consequences, however, including radiation-induced cardiovascular disease (RICVD). Where the heart was once thought to be insensitive to radiation, RICVD is now known to be the chief non-malignant cause of death in these patients, responsible for between one-quarter and one-third of their mortality[1,3-5]. The intervening decades have witnessed significant decreases in the amount of radiation to which patients are exposed, but injury to the pericardium, myocardium, valvular architecture, and vasculature continue to impose significant challenges to patients and clinicians entrusted with their care. Here, we will briefly review the epidemiology and basic characteristics of the cardinal types of RICVD, focusing on emerging concepts in the pathophysiology, prevention, and treatment of this disease.

EPIDEMIOLOGY AND BASIC CHARACTERISTICS

The epidemiology of RICVD is complicated by the continual improvements in radiation dosimetry and shielding that tend to reduce cardiovascular exposure and the latent effects of radiation, which take years or decades to manifest. Thus, RICD is an inherently dynamic disease process, and while clinicians continue to cope with radiation-induced comorbidities afflicted by older and higher-dose radiation regimens, data derived from patients treated decades ago will tend to overestimate incidences and morbidities, *etc.*, of newly evolving cases. Updated epidemiologic data is therefore of critical importance to inform both patients and clinicians. Several large studies have been published over the last few years that analyzed the outcomes of RT administered between one and four decades ago. In the following section, these data will be presented in reference to the four cardinal radiation-induced cardiovascular pathologies, as well as a brief overview of the gross anatomic and histopathologic derangements known to occur over the given timelines and at the described doses.

Acute and chronic pericarditis

Radiation-induced pericarditis is the earliest form of RICVD to occur following mediastinal radiation. It may occur in either of two forms, early and acute or delayed and chronic, which should be regarded from a histopathological standpoint as two distinct disease entities. As an early complication of very high dose radiation, early pericarditis is extremely rare today due to implementation of dose reducing techniques. It occurs either during RT or in the days or weeks after in response to irradiation in excess of the "tolerance dose" of the organ, which is variably described as a mean heart dose of greater than 36 or 40 Gy, or a > 50 Gy dose administered to > 30% of the heart[6-8]. The effect of these doses on histopathology is profound in the short-term. In the acute setting, the pericardium becomes porous, resulting in a neutrophilic infiltrate and collection of a high-protein exudate[9]. Nearly half of affected patients develop hemodynamically-significant effusions, although in most cases they are self-limited. The development of apparently benign pericardial effusions in the acute stage may predispose the patient to chronic pericarditis of delayed onset, however[10].

Chronic pericarditis is the most common cardiac complication of radiation therapy, observed in some 70%-90% of necropsy cases[11,12]. The effect is highly dose-dependent, with incidence increasing from < 10% to > 50% as the total dose is increased from 50 to 60 Gy[7]. The incidence of symptomatic chronic, delayed pericarditis has decreased dramatically since the 1970s, falling from 20% to 2.5% with the application of just a few of the radiation-sparing techniques that are used today[13]. Nevertheless, even the low-dose radiation to which contemporary cohorts are exposed increases the incidence of chronic pericarditis by a factor of 1.6 when comparing patients undergoing left- *vs* right-sided RT[14]. This finding suggests that through the early 2000s, breast cancer survivors were accruing excess risk of chronic pericardial disease despite modern dose-schedules.

The time to onset of symptoms in chronic pericar-

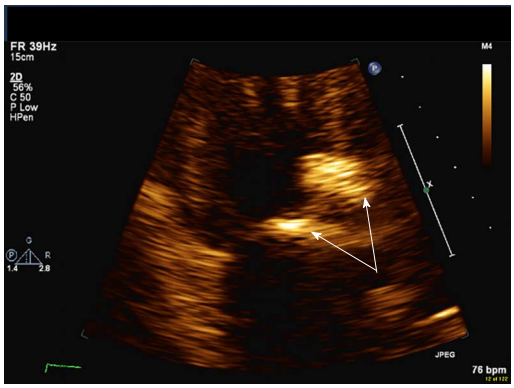

Figure 1 Severe calcification of proximal aorta and aortic leaflets (arrows) resulting in moderate aortic regurgitation and stenosis.

ditis can range from three months to over a decade, with one year being the median[8]. In the months prior to presentation, these patients will experience fibrous thickening of the pericardium and replacement of pericardial fat by collagen[11]. In nearly 20% of cases, pericardial thickening is severe enough to cause a chronic constrictive pericarditis[15], which, when it becomes symptomatic, does so much later, requiring pericardiectomy at a median of 11 years after RT according to one recent study[16].

Radiation-induced cardiomyopathy

According to the latest epidemiologic data, radiation-induced cardiomyopathy (RICM) occurs at a 40-year cumulative incidence rate of 24.8%, though most of these cases evolve following a distinct cardiac insult such as valvular disease or myocardial infarction (MI)[17]. The risk of RICM increases after 5 years, but it can evolve decades after initial RT[18]. Higher doses of radiation exposure are required to instigate this level of injury; rat hearts display a tolerance dose of 15-20 Gy[19], whereas the tolerance dose of human myocardium is approximately 40 Gy[7]. That said, asymptomatic myocardial perfusion defects have been detected as soon as 6 mo following irradiation at the much lower mean heart radiation doses used in the contemporary treatment of breast cancer[20]. In the latter study, defects were observed in about 40% of patients within two years, suggesting that RICM will continue to be a significant late adverse effect of RT in the coming decades despite reductions in radiation exposure.

Pathologically, RICM is characterized by inflammation followed by the development of a diffuse, patchy interstitial fibrosis of the myocardium, and effacement of the peri-myocyte endothelium[21]. Perfusion defects can often be detected by nuclear medicine studies in the early years following RT. They lie in the irradiated regions and do not follow the major coronary artery distributions, reinforcing the view that microvascular injury is central to this pathology[22]. As the heart becomes fibrotic it loses compliance, resulting in diastolic dysfunction[23]. Wall-motion abnormalities follow, occurring in 18% and 29% of patients in their second and third decades after RT, respectively, *vs* 5% in non-irradiated age-matched subjects in the Framingham population[24]. In the same study, a decline in left ventricular mass and wall thickness was also noted, which runs contrary to the trend seen in normal aging. Impairment of systolic function occurs last and should be considered a sign of late RICVD.

Valvular heart disease

The natural history of valvular heart disease (VHD) varies with radiation dose and, by extension, the decade in which the patient was treated. A study of HL survivors irradiated under obsolete protocols between 1965 and 1995 revealed 13- and 30-year cumulative incidences of 10% and 20%, respectively. Prior history of RT increased the risk of VHD for these patients 7-fold[18]. Unfortunately, VHD progresses in more than 30% of irradiated HL survivors throughout the second and third decades following treatment in this dose range[25]. More recently, researchers at the Netherlands Cancer Institute found a stepwise decrease in 30-year cumulative incidence of VHD corresponding to diminishing doses of RT, from 12.4% at doses greater than 40 Gy to 3.0% at doses less than 30 Gy[26]. At the lower end of this steep dose-response curve, where most treatment regimens are dosed currently, the absolute difference in 30 year VHD risk in irradiated *vs* non-irradiated patients was estimated to be 1.4%. Nevertheless, patients treated in past decades will continue to experience higher rates of VHD in the coming decades, particularly those exposed to high doses of radiation in the remote past.

With respect to the gross pathology of VHD, the earliest change appears to be the formation of valvular retractions and accompanying regurgitation preferentially involving the mitral and aortic valves, occurring within the first 10 years. The progression to fibrotic thickening and calcification of the valves occurs much later, with stenosis often appearing 20 years after RT[25]. Mitral and aortic valve regurgitation are the most common defects, and when stenosis occurs, it most commonly afflicts the aortic valve (Figures 1 and 2).

Radiation-induced coronary heart disease

Radiation-induced coronary heart disease (CHD) is currently the most active area of RICVD research. Until the 1990s, its existence was controversial, but it has been unmasked by longer survivorships and mass epidemiological studies in the ensuing decades. The disease burden it imposes is significant, in part because it can be induced by radiation doses that are well less than 10% of the tolerance dose of other cardiac tissues; thus, it more frequently complicates the course of breast cancer treatment than other forms of RICVD[7]. A large case control study of breast cancer survivors in Denmark and Sweden undertaken in 2013 found that the risk of a major CHD event begins to increase

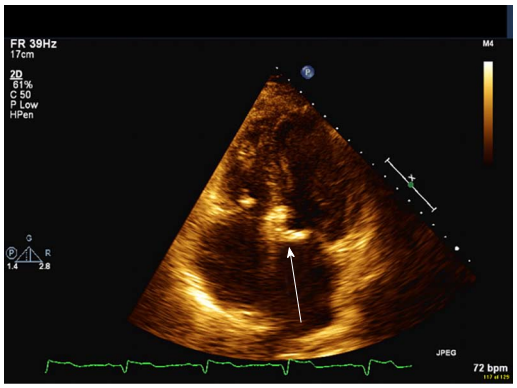

Figure 2 Apical four chamber view of mitral annular calcification (arrow).

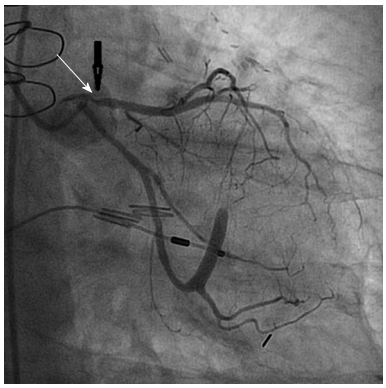

Figure 3 Severe proximal stenosis of the left anterior descending coronary artery (arrow).

within the first 5 years post-treatment and continues to significantly exceed that of the general population through at least 20 years of follow-up[27]. These patients experienced increased risk of angina pectoris, MI, and sudden cardiac death despite having been treated with a modest mean heart dose of 3.6 Gy RT between 1958 and 2001. Patients receiving radiation doses of < 2 Gy, 2-4 Gy, 5-9 Gy and > 10 Gy experienced dose-dependent excess risks of 10%, 30%, 40% and 116%, respectively, *vs* carefully matched controls. Another large study of women in Denmark and Sweden (n = 35000) comparing incidences of MI in breast cancer survivors observed an incidence ratio of 1.22 in patients undergoing left-sided *vs* right-sided RT[14]. In that study, the mean heart dose in patients with right-sided tumors was 2.7 Gy (*vs* 6.3 Gy for left-sided tumors), so the incidence ratio likely underestimates the true excess risk of RT compared with the general population. Concerning higher-dose radiotherapy, a 2015 study from the Netherlands Cancer Institute found a 40-year cumulative CHD incidence of 22.9%, amounting to a 4- to 7-fold increase in risk and 475 excess cases per 10000 person-years as compared to the general population[18].

The gross pathology of radiation-induced CHD differs from that of ordinary CHD in certain key respects. Radiation-induced coronary artery lesions tend to be longer and to preferentially involve the ostium, and they are therefore more challenging to treat percutaneously[28-30]. The left anterior descending (LAD) coronary artery is often preferentially involved because of its proximity to the radiation field (Figure 3).

This is particularly so in treatment of breast cancer where, while average heart doses are currently 1-5 Gy, the maximum LAD doses may exceed 20 Gy[31]. With respect to histopathology, these lesions tend to differ little from those of ordinary atherosclerosis and are characterized by intimal thickening, lipid accumulation, inflammation, and thrombosis[13]. They are often, however, somewhat more fibrous, with reduced lipid content, and the vessels involved tend to be more friable[23]. Other great vessels are likewise subject to radiation-induced friability, and the aorta and carotid artery have been known to rupture following RT on occasion[21]. Moreover, the carotid arteries have been noted to demonstrate early and rapid formation of unstable plaques following irradiation in rat models[7].

PATHOPHYSIOLOGY

Our basic understanding of the pathophysiology of RICVD has changed little since the seminal work of Fajardo *et al*[9,10] in the 1960s and 1970s. It has long been understood that irradiated pericardial, myocardial, endocardial, or endothelial tissue is prone to inflammation, which later results in tissue fibrosis and loss of capillaries at the microvascular level[10]. Until the early 2000s, studies in animal models and *in vitro* human tissues primarily focused on the mechanisms by which these changes occurred in the acute setting. Since the turn of the century, emphasis has shifted to the manner in which the acute inflammatory state gives way to chronic, pathological fibrosis. This section will begin with an overview of the inflammatory response, followed by a discussion of novel research into the mechanisms by which chronic and long-lasting profibrotic states become realized.

Acute inflammation

The mechanisms of tissue injury in the acute setting of radiation-induced pericarditis, valvular disease, cardiomyopathy and coronary disease are essentially the same and appear to be largely mediated by damage to the endothelium. Whether in the visceral pericardium, the highly vascular myocardium - which has a capillary density of 2800 capillaries/mm^2 as compared to 350/mm^2 in skeletal muscle[32] - or the small and medium-sized vessels that perfuse the heart, the endothelium is site of initial damage. Within minutes of irradiation, endothelial cells become hyperpermeable. By the passing of the second hour, the endothelium has begun to display membrane-bound molecules such as E- and P-selectin, which are involved in leukocyte cell rolling, and ICAM-1 and PECAM-1, which are involved in leukocyte arrest and transmigration[7].

These activities stimulate the neutrophilic response that predominates acutely, with these first-responders releasing pro-inflammatory cytokines such as tumor necrosis factor, monocyte chemotactic factor, and interleukin (IL)-8, resulting in recruitment of additional inflammatory cells[33]. While this pro-inflammatory activity of granulocytes and other immune cell types was once thought to be the chief, if not the sole cause of acute inflammation and fibrosis[34], inflammatory chemokine secretion by the endothelium itself has garnered much research interest in recent years. *In vitro* studies of cultured human microvascular endothelial cells have confirmed a radiation-induced increase in IL-6, IL-8, human fibroblast growth factor, and adhesion molecules such as ICAM-1, in the absence of immunologic cells. This suggests an immunologic and secretory functionality of the vascular endothelium that contributes to the pro-inflammatory state[35,36].

Finally, the contribution of coagulation to this acute endothelial inflammatory response merits consideration. The presence of early fibrin deposits in the capillary networks within radiation-exposed myocardium was noted in the initial studies of RICVD[37]. This is now known to result from impaired endogenous fibrinolysis, likely due in part to thrombomodulin inhibition by transforming growth factor-beta (TGF-β), and perhaps by RT itself[38]. The role of hyperacute coagulation in the eventual development of chronic fibrosis is as yet unknown. Certain coagulation factors such as thrombin, however, can induce endothelial secretion of chemokines such as IL-8 and monocyte chemoattractant peptide, which in turn promote chemotaxis of neutrophils and expression of adhesion molecules to upregulate inflammation[39,40].

Fibrosis

Fibrosis is the chief process by which chronic radiation damage occurs. At the biochemical level, fibrosis is the result of abnormal deposition of collagenous extracellular matrix (ECM) by activated myofibroblasts. The manner in which this comes about is still the subject of investigation. Cardiovascular fibrosis is a chronic but dynamic process that is propagated by pro-fibrotic cytokines, phenotypic alterations in various cell types, and the presence of chronic hypoxia and oxidative stress. Central to this process is the terminal differentiation of fibroblasts into myofibroblasts, which secrete more type Ⅰ and Ⅲ collagen, as well as alpha-smooth muscle actin, another ECM protein, than do their progenitors[41]. Stimuli that may lead to myofibroblast formation in radiation injury include pro-inflammatory cytokines, matricellular signals, and epigenetic reprogramming.

Pro-fibrotic cytokines such as platelet-derived growth factor (PDGF), IL-13, IL-4, and TGF-β are secreted in abundance by neutrophils and other immune cell types recruited to irradiated tissues. TGF-β in particular has many pro-fibrotic activities, including both the promulgation of myofibroblasts and the inhibition of collagenases[40,41]. IL-13 and IL-4 are chiefly secreted by Th2 lymphocytes and act at a variety of tissues to stimulate collagen deposition[34,42]. They have chiefly been studied in the context of hepatic and pulmonary fibrosis but are active in vascular tissues as well[43-45].

Matricellular signals also contribute to pro-fibrotic phenotypic changes. One such ECM protein that may constitute a future therapeutic target in RICVD is connective tissue growth factor (CTGF), which is induced by TGF-β and promotes differentiation of mesenchymal cells and resident fibroblasts into myofibroblasts[46-48]. Moreover, CTGF can continue to stimulate myofibroblasts to secrete ECM even after TGF-β levels have normalized, thus perpetuating fibrosis long after the initial insult has passed[49,50]. Indeed, knockdown of CTGF expression in human cardiac fibroblasts decreased fibroblast growth, and CTGF inhibition was shown to reverse fibrosis, decreasing vascular stiffness and myocardial dysfunction in rodent models, though this finding has not yet been replicated in irradiated models[51].

As terminally-differentiated cells, myofibroblasts are destined to undergo apoptosis rather than mitosis during normal wound healing. This typically results in a self-limited and acellular scar[52]. They persist in radiation-induced fibrosis, however, and a growing body of evidence links this to epigenetic reprogramming. DNA methylation is the most studied mode of epigenetic modification in radiation-induced fibrosis[53]. In murine fibroblasts, expression of the α-smooth muscle actin gene, a marker of myofibroblast differentiation, was reported to be regulated by methylation of CpG islands in the gene promoter[54]. Moreover, TGF-β-induced suppression of DNA methyltransferase expression contributed to induction of the α-smooth muscle actin gene and thus myofibroblast differentiation. In contrast, induction of α-smooth muscle actin expression during hypoxia was reported to be associated with DNA hypermethylation and upregulation of DNA methyltransferases[55]. This and other studies suggest that regulation of fibroblast differentiation *via* epigenetic DNA methylation is complex and context-specific[56,57].

Hypermethylation of genes involved in apoptosis has been observed following irradiation and is associated with decreased cell death, which could promote fibrosis[58]. Moreover, the patterns of DNA methylation predating irradiation may be a determinant of radiation fibrosis. Human dermal fibroblasts taken from patients who later developed radiation-induced fibrosis demonstrated decreased methylation of two intragenic sequences of the diacylglycerol kinase alpha gene, a regulator of fibrosis-associated signaling pathways[59]. Moreover, decreased DNA methylation at these sites correlated with future development of profibrotic fibroblast activation, highlighting the potential prognostic value of epigenetic modifications with respect to radiation-induced fibrosis. Methylation-inhibiting agents may hold promise in the treatment or prevention of RICVD and are currently in clinical trials. Aberrations in

two other modes of epigenetic modulation - microRNA activity and histone modifications - have been linked to fibrosis in various tissues, including the heart (for a detailed review, see Weigel *et al*[53]), but we know very little about their contributions to RICVD at this time.

Oxidative stress

In addition to directly inflicting cellular injury, radiation-induced oxidative stress is thought to play a key role in the transition from acute inflammation to chronic inflammation and fibrosis[60]. Reactive oxygen species (ROS) are acutely generated by the direct action of radiation and subsequently produced by both macrophages and the inflamed endothelium, which are replete with ROS-generating enzymes[61]. Macrophages produce large quantities of superoxide and nitric oxide, the latter *via* inducible nitric oxide synthase[62,63]. Superoxide and nitric oxide react to form peroxynitrite, a toxic source of free radical injury[64]. The decreased availability of nitric oxide resulting from this conversion promotes vascular dysfunction and tissue hypoxia, which further exacerbates oxidative stress[63].

Once initiated, oxidative stress propagates inflammation through several mechanisms. For example, oxidative stress promotes chemotaxis by upregulating expression of adhesion molecules such as ICAM[65] and by increasing monocyte chemotactic protein-1 and TNF-α levels[66]. Moreover, ROS increase thrombin activity by inactivating thrombomodulin, potentially promoting inflammation as previously described[67]. Though a causal link between radiation-induced oxidative stress and inflammatory cytokine production is difficult to establish, anti-oxidant studies are informative. For example, administration of alpha-lipoic acid prior to irradiation was reported to decrease local levels of IL-1, IL-6, and metalloproteinases in mice[68], while melatonin decreased levels of IL-1, TNF-α, and TGF-β[69].

ROS also promote inflammation *via* their complex interaction with NF-κB, a transcription factor responsible for such critical functions as immune regulation and cell survival. In the setting of RICVD, NF-κB activation by ROS results in increased adhesion molecule, cytokine, and chemokine production[70]. An association with fibroblast stimulation and collagen deposition has also been demonstrated. Importantly, NF-κB upregulation was detected from week 4 through week 500 post-irradiation in small vessels of the neck in humans[71], suggesting that NF-κB might be a critical element in the transition from acute inflammation to chronic fibrosis (Figure 4).

Free radicals produced by macrophages result in increased pro-fibrotic TGF-β production in irradiated animals[72]. This change is preceded by tissue hypoxia, which follows in RICVD from capillary effacement and diminished perfusion. Additionally, ROS have been reported to cleave TGF-β from its anchorage sites in the ECM, which in turn promotes myofibroblast differentiation and ECM deposition[61]. Lastly, free radicals establish a preference for the Th2 lymphocyte phenotype over the Th1 response[73,74], thus skewing the lymphocyte population towards those that preferentially secrete IL-4, IL-13, TGF-β, *etc*. These and other chemical signals act in concert to stimulate myofibroblast hyperactivity and disordered ECM deposition.

PREVENTION

The cardiovascular morbidity and mortality of RT can be forestalled through primary prevention, which consists of dose reduction and radioprotection, and secondary prevention, which consists of screening and radiomitigation. No pharmaceuticals are currently approved by the Food and Drug Administration for either purpose, although Amifostine, a scavenger of free radicals, was recently approved for the reduction of radiation-induced xerostomia[75]. This discussion will therefore focus on dose-reduction, screening, and risk modification, ending with a brief discussion of novel uses of existing pharmaceuticals, such as statins and ACE inhibitors.

The most important means of prevention is reduction in radiation exposure. Advances in radiation oncology have resulted in decreases in absolute 15-year cardiac mortality from 13% in the mid-1970s to 5.8% in the late 1980s for breast cancer survivors[76]. Meanwhile, the incidence of major CHD events in HL survivors has remained roughly unchanged during the same period despite dramatic increases in utilization of cardiotoxic chemotherapeutics[18]. Recent reviews have dealt with the techniques by which this has been achieved[77,78]. Some of these strategies involve manipulating the patient so as to exclude as much of the myocardium from the treatment field as possible; for instance, use of breast boards or prone positioning may reduce the volume of myocardium traversed by the radiation beam. Likewise, deep inspiration and inspiratory gating are two techniques by which radiation oncologists exploit the heart's tendency to fall inferiorly and posteriorly out of the radiation field. Perhaps the most important advancement is the use of intensity-modulated RT, in which 3-D CT images are used in conjunction with multileaf collimators that can be manipulated to deliver radiation beams that conform closely to the shape of the tumor. With respect to HL, reductions in radiation exposure are mainly attributable to dose fractionation, and to the shift from mantle field radiation, which encompasses much of the neck, mediastinum, and axilla, to more limited, involved fields[79]. All of these techniques presuppose superior imaging and software technologies that deliver radiation more accurately - often to within several millimeters of the desired target - and with much smaller margins than were used in the in the previous century.

Despite these improvements, excess risk of morbidity and mortality persist. It is therefore imperative that cardio-oncologic care be coordinated prior to initiation of RT for the establishment of appropriate cardiac baselines and for continued surveillance throughout the

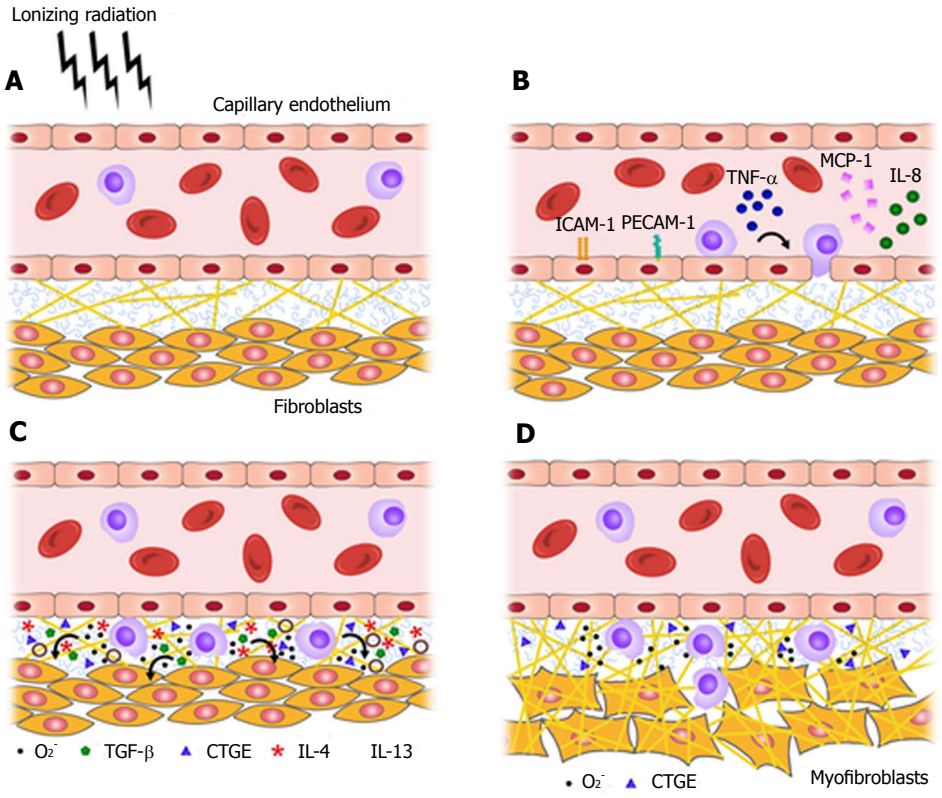

Figure 4 Radiation injury and the transition from acute inflammation to chronic fibrosis, as mediated by pro-fibrotic cytokines and reactive oxygen species. A-C: Normal tissue (A) becomes inflamed within hours of irradiation (B), and a pro-fibrotic cytokine profile predominates within days-to-weeks (C); D: Represents the chronic state of fibrosis characteristic of radiation injury. O_2^-: Reactive oxygen species; TNF-α: Tumor necrosis factor alpha; MCP-1: Monocyte chemotactic protein-1; CTGF: Connective tissue growth factor; TGF-β: Tumor growth factor beta; IL: Interleukin.

patient's lifetime. The younger the patient is at time of treatment, the more critical the need for surveillance, as both their relative risk of RICVD and their survivorship with respect to cancer are greater[18]. Cardio-oncologic care should begin with risk factor modification, as conventional CHD risk factors are particularly hazardous in this population. Indeed, traditional risk factors have been shown to more than double the relative risk of CHD events in these patients as compared to matched patients in the general population[80]. Thus, hypertension, hyperlipidemia, and diabetes mellitus should be managed aggressively, and patients should be counseled regarding smoking cessation, weight loss, and exercise where appropriate.

Screening and detection

The cardiac morbidity and mortality associated with RT can be reduced if treated early, which justifies the need for screening and early detection of RICVD[81]. Prospective data regarding cost- and risk-benefit analyses with respect to screening are lacking, however. Although evidence-based guidelines are unavailable, several expert consensus statements have been derived based on the available randomized trials and epidemiological studies. In 2014, the American College of Radiology Appropriateness Criteria Report made a case for the importance of surveillance but stopped at recommending personalization[82]. The expert panel of the National Comprehensive Cancer Network (NCCN) called for aggressive management of cardiovascular risk factors with annual blood pressure and biannual lipid screening in their expert consensus statement released in 2015. They also recommended considering a baseline stress test or echocardiogram every 10 years after treatment[83]. Some experts have proposed that irradiation should be considered an additional CHD risk factor in the presence of hypertension, hyperlipidemia, or diabetes[81].

Finally, the most rigorous set of screening recommendations came from the European Association of Cardiovascular Imaging and the American Society of Echocardiography in 2013, which recommend aggressive risk factor modification and yearly physician visits. The statement went further, however, recommending baseline echocardiography prior to RT, followed by repeat echocardiography 10 years after treatment and every five years thereafter in heart-healthy patients[84]. For patients with one or more conventional risk factors, screening echocardiography was recommended in the fifth year after treatment, and noninvasive stress testing was recommended 5-10 years after treatment and at 5-year intervals, with a preference for stress echocardiography in these patients.

The prospective data supporting these statements was largely derived from a series of studies by Heidenreich *et al*[24], who screened asymptomatic HL

survivors for RICVD. Their study of echocardiography in asymptomatic patients uncovered a 29% prevalence of significant valve disease in HL patients as compared to 3% in the general population[24]. Diastolic dysfunction was detected in 14% of the HL patients at a mean of 14 years post-RT[23]. While the cost-benefit ratio of screening for heart failure with preserved ejection fraction (EF) is uncertain due to the lack of effective treatment, a disproportionate number of patients thus afflicted also demonstrated stress-induce ischemia on subsequent stress echocardiogram or nuclear perfusion imaging (23%). Finally, Heidenreich *et al*[85] evaluated stress echocardiography and radionuclide perfusion imaging as screening tests for asymptomatic CHD after RT. They observed a 2.7% prevalence of severe, multivessel or proximal coronary stenosis, and a 7.5% prevalence of coronary stenosis greater than 50% at a mean 15 years after RT. The cohort overall had a documented 8% prevalence of coronary insufficiency or death. The generalizability of these data is limited by the high radiation doses employed in the cohort; the mean heart dose in the three trials was 43-44 Gy, which is much higher than most HL patients receive today. Nevertheless, these findings are likely pertinent to patients irradiated prior to the 1990s, or to more recently treated patients receiving mean heart doses greater than 35 Gy.

Thus, current literature supports use of transthoracic echocardiogram as the screening tool of choice to evaluate baseline left ventricular EF, diastolic function and VHD. Echocardiography is also important in the assessment of restrictive cardiomyopathy and constrictive pericarditis. Ultrasonographic technologies are constantly evolving, leading to improvements in the ability to detect subtle signs of RICVD disease *via* echocardiography. Using cardiac MRI as the gold standard, 3D echocardiography was reported to exhibit greater sensitivity than 2D echocardiography to detect left ventricular EFs less than 50% (53% *vs* 25%, respectively)[86]. Deformation imaging using speckle tracking or tissue Doppler velocities may be even more sensitive to detect subtle abnormalities in left ventricular function[87,88]. Reductions in systolic myocardial deformation were detected immediately and 2 mo after RT, in the absence of detectable reductions in EF[89]. Speckle tracking echocardiography demonstrated abnormal global longitudinal and global circumferential strain in 33% and 21.7%, respectively, of patients who underwent RT, while depressed EF was detected by 3D echocardiography in only 5.7% of patients at a median 22.6 years[90]. While no gold standard was applied, abnormal longitudinal strain was correlated with reduced quality of life and lower mean 6-min walk distances, even when it was the sole abnormal finding. Thus, while reduced EF is a late finding in RICVD, abnormal strain measurements may herald early onset disease and are increasingly being incorporated into screening protocols (Figure 5).

Though it is not a first-line screening tool, cardiac MRI is helpful in evaluation of left ventricular EF and, with the addition of myocardial tagging, may be utilized for better evaluation of constrictive pericarditis. This modality is particularly well-suited to detection of the patchy fibrosis that may be associated with micro-vascular insufficiency even in the absence of classical ostial coronary stenosis, ischemia, or infarction[91]. The pattern of late gadolinium enhanced MRI images can help differentiate between MI, diffuse myocardial fibrosis, and constrictive pericarditis as the underlying mechanism of the cardiomyopathy[92,93].

Newer screening modalities for radiation-induced vascular disease have also been evaluated, including coronary artery calcium (CAC) imaging. In a cohort of 47 HL survivors who received a mean cardiac dose of 40.6 Gy, CAC imaging demonstrated a strong association between severity of CAC and the presence of coronary artery disease verified by angiography[94]. The proportion of patients with CAC scores of zero was much lower in the HL cohort than in the general population. Another study using CT angiography in HL survivors detected nearly twice as many atherosclerotic lesions in pre-cranial blood vessels contained within the radiation field as compared with a non-irradiated control group; the percentages of calcified *vs* non-calcified lesions were similar in the HL and control groups, suggesting that atherosclerosis, but not calcification, is a radiospecific finding[95]. Interestingly, this study also found that elevated total cholesterol, measured soon after RT, correlated strongly with later incidence of coronary artery disease. While these studies suggest a role for CT in screening for vascular disease in HL survivors, their generalization is limited by the high doses of radiation to which these older cohorts were exposed. Indeed, a larger study of CAC screening in 236, 12-year breast cancer survivors who had been exposed to lower doses of radiation did not find any excess CAC, though the duration of follow-up may have been too short to detect late occurrences[96]. Thus, CT imaging may be of greater utility in detection of CHD in cancer survivors who are in their second or third decade post-RT.

Laboratory monitoring is another important component of screening for RICVD. The importance of identification and management of hyperlipidemia in cancer survivors with a history of RT is emphasized by data showing a direct correlation between the presence of hypercholesterolemia soon after RT and atherosclerosis[95,96]. Chen *et al*[97] (2009) applied a decision-analytic model to perform a cost-benefit analysis in a hypothetical cohort of HL survivors to establish the cost-effectiveness of screening intervals for hyperlipidemia. Applying an assumed relative risk of cardiac mortality of 3.2 to a theoretical cohort that otherwise differed little from that of the general population, the optimal interval for screening for hyperlipidemia was determined to be every three years. With respect to biomarker screening, elevation of troponin-I and brain natriuretic peptide have been

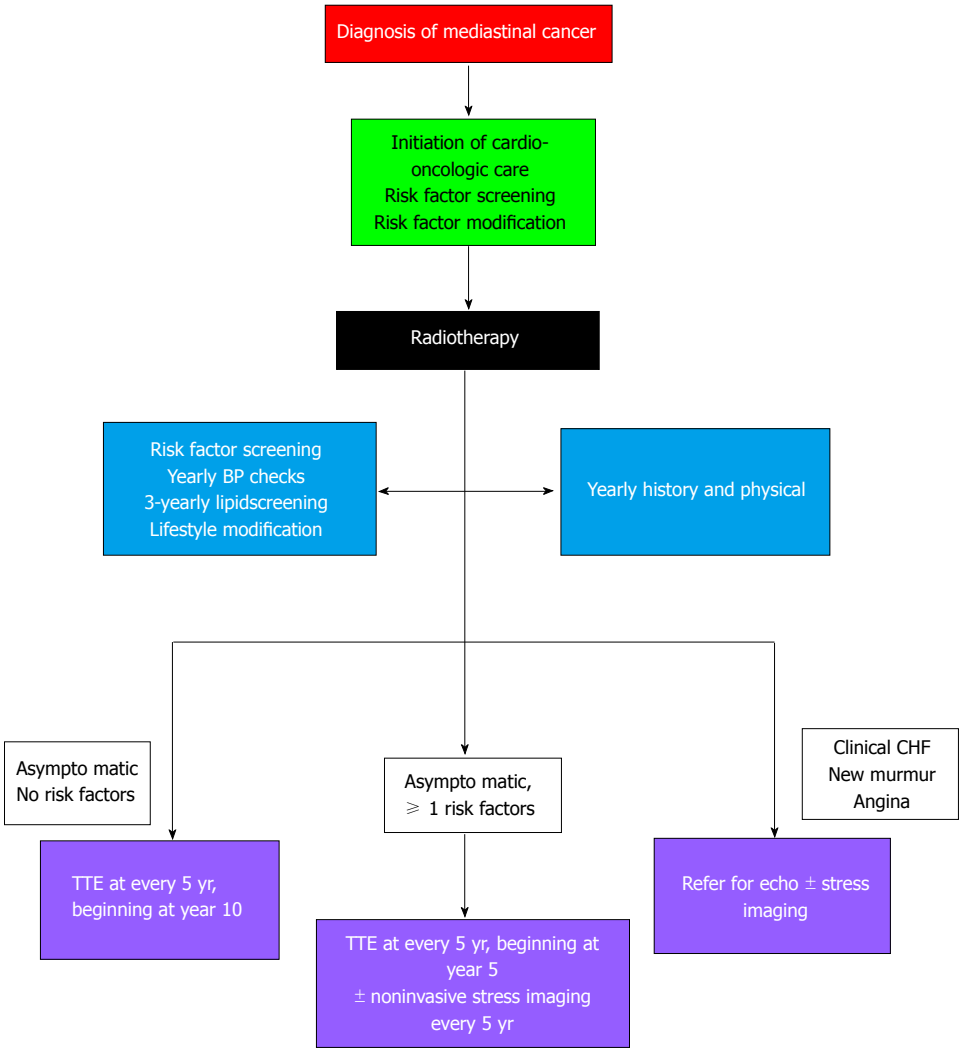

Figure 5 Proposed algorithm for cardio-oncologic screening following mediastinal radiotherapy[84]. CHF: Congestive heart failure; TTE: Transthoracic echocardiography.

demonstrated in patients during and immediately following RT in a small cohort of breast or lung cancer patients[98]. A later study found subacute elevations of high-sensitivity troponin-T following RT that were dose-dependent[99]. This study also detected echocardiographic evidence of interventricular septal thickening and prolonged diastolic deceleration time in patients who experienced a greater than 30% increase in troponin levels from baseline, suggesting that elevated high-sensitivity troponin-T correlates with subtle abnormalities of cardiac function after RT. The implications for the utility of high-sensitivity troponins in screening for future cardiac disease are unknown but may become clearer after the planned follow-up with this cohort.

Radioprotection and radiomitigation

As to the role of pharmaceuticals, several commonly prescribed agents are currently being evaluated in primary and secondary prevention after promising results were observed in animal trials. Statins have been studied extensively in rodent and *in vitro* human models and have shown promise through several of the mechanisms discussed in the Pathophysiology section. Pravastatin has been found to inhibit the activity of CTGF by modulating associated proteins such as Ras-homologous (Rho) GTPases[100]. Rho-family proteins regulate cellular responses to pro-fibrotic cytokines such as TGF-β, and to oxidative stress[46]. They also increase cell adhesion and contribute to the reorganization of the ECM[100,101]. Some of the statins' anti-fibrotic activities may also be related to attenuation of radiation-induced NF-κB activity, which depends upon activation by Rho-family GTPases[102]. Additionally, statins upregulate thrombomodulin expression in human endothelium, decreasing the pro-inflammatory activities of thrombin as described previously[103]. Lastly, atorvastatin has been found to reduce injury to and apoptosis of the vascular endothelium[104]. Notably, several trials of statins in young patients who were treated with RT are underway[105]. Although surrogate endpoints, such as detection of endothelial function and carotid intimal-medial thickness, will be employed, these studies nevertheless may begin to illuminate the role of early

statin therapy in reducing the long-term risk of RICVD.

Angiotensin converting enzyme (ACE) inhibitors are another commonly prescribed class of drug with radioprotective and radiomitigating potential. Rats treated with captopril shortly after radiation of the lung demonstrated dramatically increased survival and improved vasoreactivity, as well as decreased perivascular fibrosis and inflammatory cell infiltration[106]. Similar findings with respect to the pulmonary vasculature have been reported in rats treated with ACE inhibitors two weeks after irradiation[107]. More recently, rats treated with captopril exhibited reduced diastolic dysfunction and perivascular necrosis in the left ventricle following radiation exposure[108]. Although these data are intriguing, prospective studies evaluating the efficacy of ACE inhibitors in patients undergoing RT have not been reported.

Lastly, antioxidant approaches are the subject of much investigation. Amifostine was previously mentioned in connection with its indication for treatment of xerostomia, but in a small rodent study of RICVD, this drug was found to reduce myocardial fibrosis and impairment of aortic and coronary blood flow[75]. Melatonin is also being evaluated for this use, as it is known to act both as a scavenger of free radicals and as a stimulant of antioxidants[109,110]. It was reported to reduce the development of vasculitis, myocyte necrosis, and fibrosis following high-dose radiation in a rat model[111]. These and several other antioxidant strategies such as the use of selenium[112] show promise and warrant further exploration in animal studies.

TREATMENT

Acute and chronic pericarditis

Acute pericarditis is extremely rare thanks to reductions in the mean heart dose during RT. The clinical presentation may occur during treatment or in the following weeks. In the former instance, pericarditis is typically the result of the presence of a heavy tumor burden adjacent to or extending into the pericardium, and the subsequent tumor lysis. In both instances, the presentation is similar to that of idiopathic acute pericarditis, characterized by fever, pleuritic chest pain, and a pericardial friction rub. ECG may demonstrate low QRS voltage and diffuse ST or T wave changes. Standard transthoracic echocardiography typically demonstrates a pericardial effusion. This syndrome is usually self-limited and responds to treatment with NSAIDs and colchicine, but it may progress to tamponade physiology[37]. Pericardiocentesis is indicated in the event of hemodynamic compromise.

Radiation-induced chronic pericarditis is a more unique disease entity, in that it frequently presents as fibrinous constrictive pericarditis. The most common presentation is as an incidentally discovered asymptomatic effusion, however. This type of pericarditis rarely progresses to tamponade because of its chronicity, and the presentation is similar to that of acute pericarditis. The imaging modality of choice is echocardiography in these patients, for reasons of cost, ease of use, and reproducibility. The latter advantage is critically important in the case of recurrent effusions and symptomatic constrictive pericarditis, which may help the clinician to make appropriate referral for invasive procedures[84]. Cardiac CT and MR, on the other hand, have proven to be more sensitive in the diagnosis of constrictive pericarditis owing to better visualization of pericardial thickening and calcifications. Moreover, cardiac MR is more specific in the diagnosis of constrictive pericarditis, distinguishing it from transient constriction due to active inflammation and effusive-constrictive pericarditis. This can be useful in assessing prognosis and in determining whether or not to proceed with a high-risk pericardiectomy[93].

Recurrent symptomatic effusions may require pericardiectomy, which is also the mainstay treatment of symptomatic constrictive pericarditis. While the procedure does provide benefit to irradiated patients, these patients have poor prognoses, with a 21% perioperative mortality and a 7-year survival rate of just 27%[16,113]. In one study, zero of five patients survived beyond five years[114]. Unfortunately, these mortality rates may reflect both the technical difficulties in operating on the irradiated heart and progression of other forms of RICVD that inevitably follow from large radiation exposures.

RICM

RICM may remain asymptomatic for years before presenting as a typical clinical heart failure syndrome with shortness of breath and other symptoms of volume overload. Diastolic dysfunction is typically the earliest imaging finding in RICM, followed by abnormalities pertaining to strain and strain rate such as discussed in the screening and detection section. Therefore, this new echocardiographic modality is optimal for establishing an early diagnosis of RICM. When a reduction in EF occurs, it is often a late finding. Cardiac MR is appropriate for use in patients with poor acoustic windows and not only detects reductions in EF, but also visualizes the inciting myocardial inflammation and fibrosis[84]. Once RICM has been confirmed, treatment should be initiated per the ACC/AHA guidelines, as there are no drugs specifically approved to treat radiation-induced myocardial inflammation or fibrosis. This is also the case with respect to implantable cardioverter-defibrillator (ICD) placement, as the indications for its use have not been specifically evaluated in RICM. As to the location of ICD implantation, it has been suggested that a sub-pectoral approach may be preferred in order to avoid instrumenting the irradiated superficial tissues[5].

In patients with biventricular heart failure due to radiation-induced restrictive cardiomyopathy, cardiac transplant may be performed as a last resort. Several case series have been published in recent years detailing the outcomes of these cases. The largest was

a 2012 study of patients undergoing transplant for restrictive cardiomyopathy, which included a subgroup of 35 patients with RICM. This group demonstrated 1-, 5- and 10-year transplant survival rates of 71%, 47%, and 32%, respectively - the poorest survival rates amongst all of the subgroups[115]. A 12-subject cohort of patients transplanted for RICM reported a lower mortality, with a 5- and 10-year survival of 75% and 47%[116]. Of note, eight of these patients were transplanted for treatment of restrictive cardiomyopathy. Given the limitation in donor hearts eligible for transplantation, and the large numbers of patients currently on waiting lists, cardiac transplantation is likely to play a very limited role in patients with end-stage RICVD.

VHD

Little has been written about peculiarities of the clinical presentation of radiation-induced VHD. Echocardiographic studies have demonstrated that it typically begins as an asymptomatic regurgitation of the mitral and/or aortic valves, progressing to include aortic stenosis in 39% of patients[25]. Radiation-induced VHD is most commonly diagnosed after a long latent period[117] and in the context of clinical symptoms of heart failure[18], to which valvular insufficiency is either contributing or responsible. When VHD is suspected, *i.e.*, on the basis of a new murmur, transthoracic Doppler echocardiography is the first line of investigation, with transesophageal echocardiography reserved for when the initial evaluation is non-diagnostic[84].

The frequency of radiation-induced VHD is significantly greater than seen in the general population. In a cohort of HL patients, the standardized incidence ratio for valve surgery was found to be 9.19 when compared to the estimated expected national incidence in the United States, though this may be an overestimate, as some of these patients were irradiated under older protocols[118]. Aortic valve replacement was the most common procedure in this cohort, though mitral and tricuspid valve disease may also require intervention. Crestanello *et al*[119] reported that 32% of previously irradiated patients who underwent mitral and/or tricuspid valve repair experienced severe valve deterioration, likely because of progression of radiation-induced tissue injury. In light of these findings and the known dangers of reoperation in this cohort, the authors concluded that mitral and tricuspid valve replacement may be superior to repair in patients with RICVD.

Over the past several years, transcutaneous aortic valve replacement (TAVR) has proven equal or superior to surgical valve replacement in high-risk patients[120,121]. As valve technology and techniques for TAVR have evolved, favorable outcomes are now also being observed in intermediate risk patients. Approximately 5% of patients enrolled in recently published TAVR trials have a history of prior chest wall radiation, with initial favorable results[122]. However, long-term results are unavailable. Nevertheless, TAVR is likely to play an increasingly prominent role in treatment of patients with radiation-induced aortic disease given the associated surgical morbidity/mortality in this high-risk population.

CHD

There is currently no basis of evidence to suggest specific deviations from treatment guidelines for the medical management CHD in patients with a history of mediastinal irradiation. The increased risk of CHD in patients with a history of RT may prompt a more aggressive approach where the etiology of chest pain is in question and/or diagnostic findings are ambiguous. As always, coronary angiography is the gold standard, and clinicians should have a lower threshold to consider it in this population. On the other hand, both percutaneous interventions (PCI) and surgical revascularization are often more challenging and less effective in this population, which must be taken into account. As noted previously, coronary artery lesions tend to be proximal or ostial in this population, and may not be readily amenable to PCI. A prospective study of bare metal stent placement in HL survivors was conducted between 1993 and 2003 and revealed in-stent restenosis in 86% of irradiated patients within the first six months, with an odds ratio for this event of 21.7[123]. Moreover, revascularization of the target vessel with balloon angioplasty was required in 67% of the RT cohort at six months per coronary angiography. However, most of these patients were treated with early generation stents and single antiplatelet therapy. A larger case control study in which 36% of patients received newer drug-eluting stents, and all patients received dual antiplatelet therapy, found no difference in the rate of in-stent restenosis requiring revascularization between irradiated and non-irradiated patients[124]. Drug-eluting stents did not outperform bare metal stents in this study; nevertheless, use of newer generation drug-eluting stents is usually preferred in this population.

Surgical revascularization of the irradiated heart is often necessary, but is not without complication. Operative mortality rates of 6% have been reported, and one- and five-year actuarial survival has been estimated to be 87% and 72%, respectively[125]. Sixty-two percent of patients in the latter cohort required valve surgery concomitantly or after the initial surgery, suggesting that valvular dysfunction is a significant contributor to mortality in this population. In another, larger study of cardiothoracic surgical outcomes in irradiated patients, a dose-dependence was observed with regard to post-operative and long-term mortality data[126]. At lower doses of radiation exposure, breast cancer patients undergoing open-heart surgery were found to approach, but not reach, the levels of 4-year survival expected of the general population, while the outlook for HL patients was much worse (73%, 64% and 57% survival at 1-, 2- and 4-years, respectively). Lastly, irradiated patients often exhibit friability of the left internal mammary artery, a well-known com-

plication encountered when that vessel lies in the irradiated field, which compromises its use as a bypass conduit and diminishes the overall benefit of bypass surgery in patients with RT.

CONCLUSION

Despite advancements in radiation oncology, it appears that cancer survivors treated with breast and mediastinal radiotherapy will continue to present with complicated cardiovascular problems for the foreseeable future. Further research is needed to elucidate pro-fibrotic mechanisms and identify promising therapies that can be implemented early during the course of treatment. The phenotypic shift from fibroblast to myofibroblast is a result of the complex interplay of radiation-induced oxidative stress, inflammation, cell signaling, and epigenetic modifications, which requires further study in animal models. Medications such as ACE inhibitors and statins favorably impact many of these pathways and have shown promise in animal models of RICVD; these agents are just now beginning to be tested in patients who have undergone RT. Novel imaging approaches, such as 3D echocardiography, strain imaging, and CT/MRI scanning, are enabling the detection of early-stage RICVD, which will help to better evaluate risk and facilitate future interventional trials. Evolution of PCI (*i.e.*, transcutaneous valve replacement and drug-eluting stents) holds great potential for improving treatment of patients with RICVD, and these techniques are rapidly gaining favor given their encouraging outcomes and lower complication rates as compared to surgical interventions. Although evidence-based guidelines with respect to screening, prevention and treatment of RICVD are lacking, algorithms have been developed by experts in the field that favor a more aggressive approach than was typically pursued in prior decades. Coordination of care between oncologists, cardiologists, and primary care physicians for the purpose of early detection, risk factor modification and treatment provides the best hope of reducing the morbidity and mortality associated with RICVD.

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REVIEW

Noninvasive diagnosis of vulnerable coronary plaque

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Abstract

Myocardial infarction and sudden cardiac death are frequently the first manifestation of coronary artery disease. For this reason, screening of asymptomatic coronary atherosclerosis has become an attractive field of research in cardiovascular medicine. Necropsy studies have described histopathological changes associated with the development of acute coronary events. In this regard, thin-cap fibroatheroma has been identified as the main vulnerable coronary plaque feature. Hence, many imaging techniques, such as coronary computed tomography, cardiac magnetic resonance or positron emission tomography, have tried to detect noninvasively these histomorphological characteristics with different approaches. In this article, we review the role of these diagnostic tools in the detection of vulnerable coronary plaque with particular interest in their advantages and limitations as well as the clinical implications of the derived findings.

Key words: Atherosclerosis; Vulnerable coronary plaque; Diagnosis; Cardiac computed tomography; Cardiac magnetic resonance

Core tip: Noninvasive diagnosis of vulnerable coronary plaque has become of major interest in preventive cardiology. Certain histological features have been related with an increased risk of plaque rupture. Coronary computed tomography has been largely used for this aim, and some lesion characteristics have been consistently associated with acute coronary syndrome

in several studies. Moreover, a growing body of evidence suggests the potential role of cardiac magnetic resonance and positron emission tomography in high-risk lesion detection. These promising results should be put in perspective to select the high-risk population that may benefit the most from the use of coronary vulnerable plaque imaging screening.

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INTRODUCTION

Atherosclerosis constitutes the leading cause of morbidity and mortality in the developed countries, mostly secondary to acute coronary syndromes (ACS)[1]. Moreover, the progressive aging of the population forecasts an exponential growth of the prevalence of cardiovascular disease[2]. In this clinical scenario, detection of patients at risk of suffering an ACS has become one of the major goals in cardiology. Traditional cardiovascular risk factors have been extensively used for this aim. Nevertheless, they fail to anticipate the occurrence of an ACS, especially in certain populations[3,4], so myocardial infarction and sudden cardiac death (SCD) are frequent first manifestations of coronary disease. This situation has boosted the interest in subclinical detection of atherosclerosis. In this regard, quantification of calcium score with coronary computed tomography (CCT)[5] as well as ultrasound evaluation of carotid atherosclerosis[6,7] have demonstrated their utility for cardiovascular risk reclassification[8,9]. In any case, in spite of a very common detection of coronary atherosclerosis in autopsy series among young adults[10] the incidence of ACS in this population is very low[1]. Thus, the onus should be shifted onto the detection of lesions that are prone to develop a coronary event.

VULNERABLE CORONARY PLAQUE: DEFINITION, HISTOPATHOLOGICAL FEATURES AND RATIONALE FOR NONINVASIVE DIAGNOSIS

Classical studies supported that ACS were caused mainly by lesions with severe stenosis[11]; however, PROSPECT trial[12], a prospective intravascular ultrasound (IVUS) and virtual histology (VH) follow-up of non-culprit lesions after ACS, revealed that most of the events are derived from angiographically mild stenosis (< 50%). Again autopsy studies have provided relevant information regarding the atherosclerotic plaque characteristics in culprit lesions. The most frequent presentation is plaque rupture, followed by plaque erosion[13]. Rarely (2%-7% of the cases) the ACS are related with a calcified nodule morphology[14]. These lesions are unfailingly associated with a variable amount of thrombus[15]. Given that plaque rupture is the most common substrate of acute coronary events, vulnerable plaques are defined as lesions at the greatest risk of rupture, with subsequent thrombosis or rapid stenosis progression (Table 1)[16]. Therefore, they are also named high-risk or thrombosis-prone plaques.

When ruptured plaques leading to acute coronary events were studied in necropsies, they usually presented a large necrotic core with a thin overlying fibrous cap together with inflammatory cells and little calcification[17]. Moreover, unlike lesions related to stable disease, these plaques showed expansive or positive remodeling not causing significant narrowing of the coronary lumen[18]. Thus, plaques with these histomorphologic features but intact fibrous cap, named thin-cap fibroatheroma (TCFA), were assumed to be prone to rupture. This concept was evaluated in a detailed histologic analysis of atherosclerotic plaques from a large series of patients who suffered SCD[19]. This study established a relevance hierarchy of morphological features that may influence plaque rupture. In a general analysis a thin fibrous cap (< 84 μm) was able to exclude stable lesions. Interestingly, among TCFA with a cap thickness < 54 μm cross-section area stenosis was most likely < 74%. Finally, when fibrous cap thickness was not considered in the analysis, inflammation, characterized by macrophage plaque infiltration, as well as a large necrotic core emerged as typical features of potentially unstable lesions. In this regard, aforementioned PROSPECT trial[12] was able to confirm these findings *in vivo* with IVUS. In this study plaque burden $\geqslant$ 70%, minimal luminal area $\leqslant$ 4 mm^2 and TCFA characteristics on VH were independently associated with subsequent major adverse cardiovascular events (MACE) derived from non-culprit lesions.

Some considerations should be kept in mind to understand the clinical relevance of vulnerable plaque detection. All the plaque ruptures do not inevitably cause an ACS[20], whereas disruption and healing is the typical mechanism of plaque stenosis growth[21,22]. Thus, a perfect storm scenario, with confluence of plaque vulnerability, inflammatory state, platelet activation and impaired fibrinolysis, is necessary for ACS occurrence[23]. However, given that substrate presence is a *conditio sine qua non* and the other involved factors (homeostasis disbalance and thrombogenicity) are difficult to establish and/or variable in time, noninvasive detection of vulnerable plaques may be clinically relevant[24], especially in very high risk patients[25].

Hence, in this paper we review the different noninvasive diagnostic tools to evaluate vulnerable coronary plaques, with a detailed description of the relevant information they provide as well as their particular strengths and limitations (Table 2). We focus specially

Table 1 Concepts related to vulnerable coronary plaque[16]

Culprit lesion	Coronary lesion considered to be responsible for the clinical event, usually plaque complicated by intraluminal thrombosis
Thrombosed plaque	Plaque with an overlying thrombus extending into the vessel lumen either occlusive or non-occlusive
Eroded plaque	Thrombosed plaque (mainly fibrotic or proteoglycan-rich) due to loss or dysfunction of endothelial cells without associated rupture
Plaque with calcified nodule	Heavily calcified protruding plaque with loss or dysfunction of endothelial cells
Vulnerable, high-risk or thrombosis prone plaque	Plaque at increased risk of thrombosis and rapid stenosis progression TCFA: Inflamed plaque with a thin cap covering a lipid-rich necrotic core
Vulnerable patient	Patient at high-risk to experience a cardiovascular ischemic event due to a high atherosclerotic burden, high-risk plaques and/or thrombogenic blood

TCFA: Thin-cap fibroatheroma.

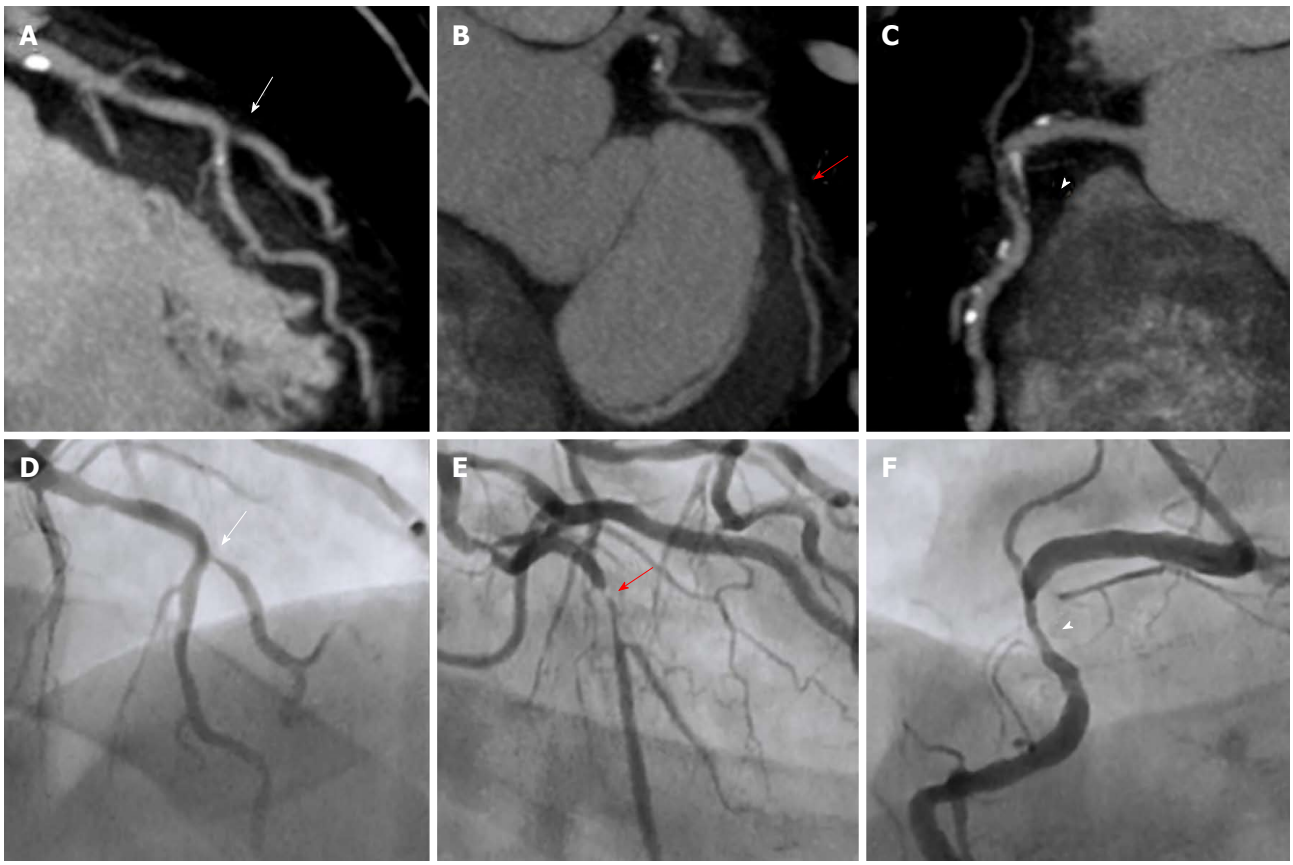

Figure 1 Coronary computed tomography stenosis evaluation compared with invasive coronary angiography. Case of a patient with 3-vessel disease. Maximum intensity projection CCT findings are shown in the upper row with the corresponding ICA projections in the lower row. (A) demonstrates a significant stenosis in the ostium of the diagonal branch (arrow) at the level of its take-off from the mid-LAD in both CCT and ICA (D); In (B) CCT shows a subtotal occlusion in the proximal LCx (red arrow) that corresponds to a critical lesion at the same level in ICA (E); In CCT image from (C) a mixed plaque is detected in proximal RCA causing a significant stenosis (arrowhead), as corroborated by ICA (F). CCT: Coronary computed tomography; ICA: Invasive coronary angiography; LAD: Left anterior descending coronary artery; LCx: Left circumflex coronary artery; RCA: Right coronary artery.

on the technique with the greatest evidence in this field, CCT, mentioning other available imaging tools with promising perspective such as cardiac magnetic resonance (CMR) imaging and positron emission tomography (PET).

CCT

CCT general information with predictive value

CCT not only provides information about the presence of significant stenoses with a high diagnostic accuracy[26] (Figure 1) but also allows a sensitive noninvasive direct evaluation of coronary atherosclerosis[27]. Coronary calcium score determination[28] as well as non-calcified plaque detection, even in the absence of significant stenosis[29-31], have demonstrated their value to predict MACE. Moreover, a large and systematic meta-analysis highlighted the relevance of luminal stenosis severity assessment with CCT[32], showing an increasing risk of the composite end-point of cardiac death or myocardial

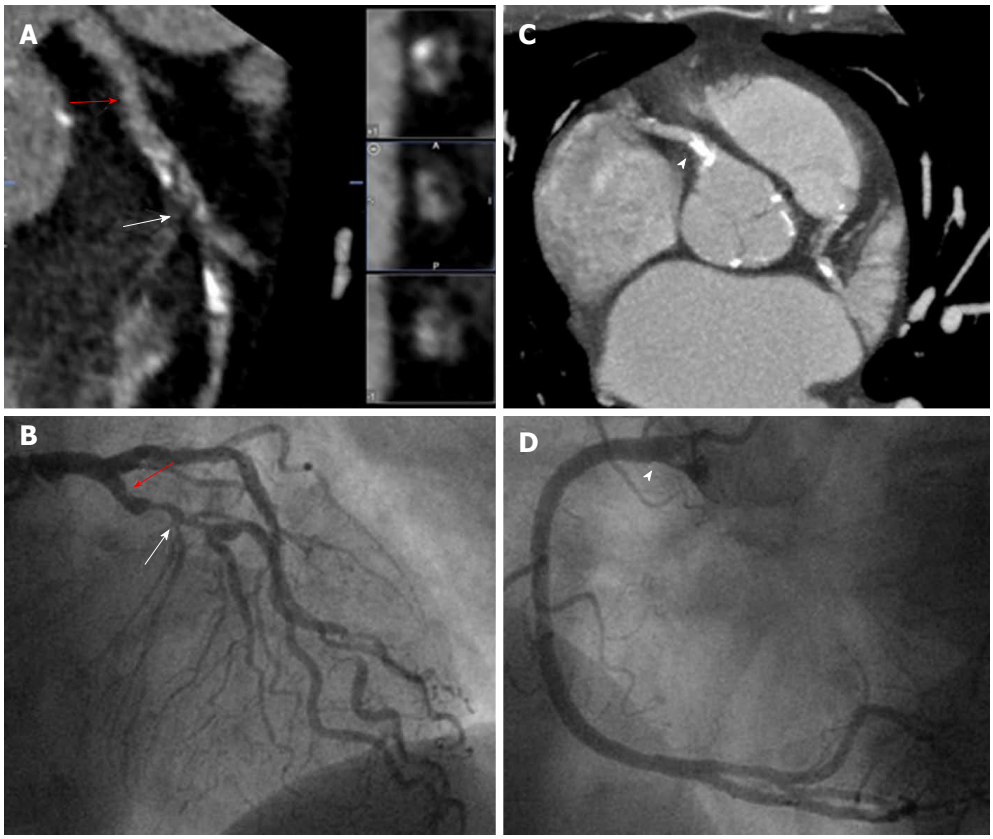

Figure 2 Coronary plaque categories by coronary computed tomography. Patient with chest pain referred for CCT. A: LAD in multiplanar reconstruction with a mixed plaque in the mid segment (arrow) that causes significant stenosis confirmed in the ICA (B, arrow). Note that there is also a nonsignificant noncalcified plaque in the proximal segment (red arrow) that is barely seen in coronariography (B, red arrow); C: A maximum intensity projection that demonstrates a severely calcified plaque in the ostial RCA (arrowhead), which does not allow luminal stenosis evaluation. However, ICA (D) confirms the absence of significant stenosis at the same level (arrowhead). CCT: Coronary computed tomography; LAD: Left anterior descending coronary artery; ICA: Invasive coronary angiography; RCA: Right coronary artery.

Table 2 Diagnostic tests for noninvasive evaluation of coronary vulnerable plaque

	CCT	CMR	PET
Plaque characterization	Plaque morphology	Plaque morphology Tissue characterization of plaque	Inflammation (FDG) Macrophage infiltration (new tracers)
Vulnerable features	Positive remodeling Low attenuation Spotty calcification Napkin-ring sign	Positive remodeling T1 hyperintensity Late gadolinium enhancement	Increased tracer uptake
Clinical relevance	Strong association with ACS Prediction of slow-flow after PCI Evaluation of response to statins	Initial data of association of T1 hyperintense plaques with slow-flow, ACS and response to statins	Differentiation between ACS and stable coronary disease
Limitations	Radiation exposure Heavy calcification Overlap in attenuation ranges Inability to detect plaque erosion	Direct relation between spatial resolution and acquisition time Susceptibility to motion artifacts	Low spatial and temporal resolution Myocardial background uptake Expensive and limited availability

CCT: Coronary computed tomography; CMR: Cardiac magnetic resonance; PET: Positron emission tomography; ACS: Acute coronary syndrome; PCI: Percutaneous coronary intervention; FDG: Fluorodeoxyglucose.

infarction for absence (0.04%), non-obstructive (1.29%) and obstructive (6.53%) coronary artery disease. It has shown a particular utility in chest pain evaluation at the emergency room[33]. There is also data supporting the capacity of CCT to evaluate coronary anatomy to determine the best revascularization strategy[34].

Coronary plaque characterization with CCT

Certainly, the most relevant information is derived from the direct evaluation of coronary plaque with CCT. By consensus[35] the lesions are classified in 3 categories: Non-calcified, calcified and mixed plaques (Figure 2). In this regard, for a further assessment of CCT

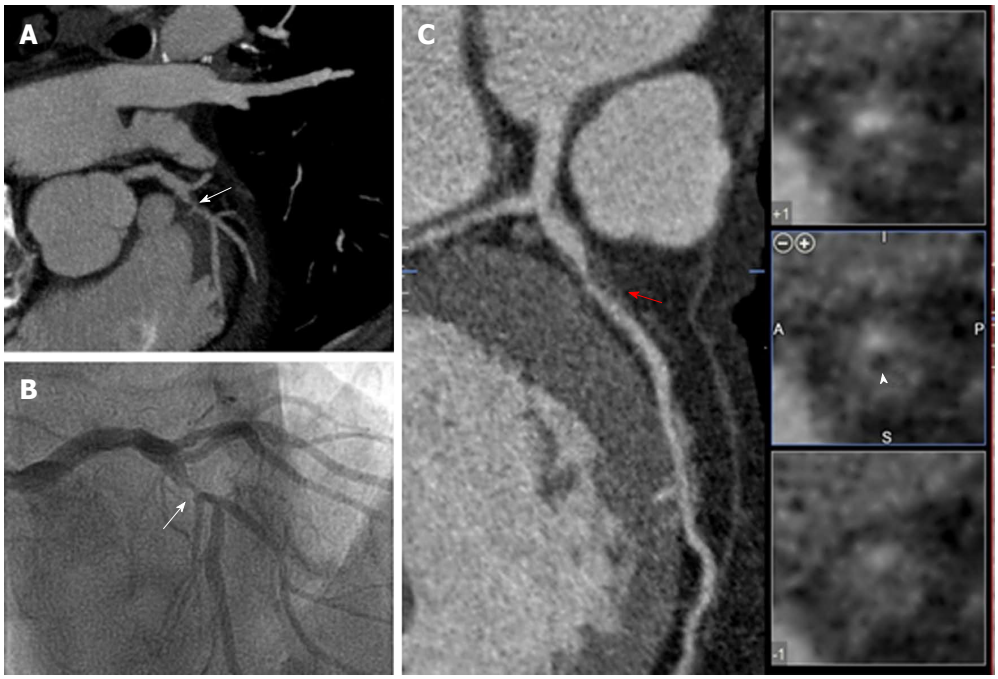

Figure 3 Vulnerable coronary plaque features by coronary computed tomography. Patient with unstable angina who underwent CCT followed by ICA. A severe stenosis (arrows) in mid-LAD just before the origin of the second diagonal was detected in CCT (A) and subsequently confirmed by ICA (B); A detailed analysis of multiplanar reconstruction of CCT (C) revealed the presence of positive remodeling (red arrow) and low attenuation (arrow head) at the level of the culprit lesion, both signs associated with vulnerable coronary plaque. CCT: Coronary computed tomography; ICA: Invasive coronary angiography; LAD: Left anterior descending coronary artery.

accuracy in coronary plaque qualitative analysis, head-to-head comparisons with VH have been performed. Pundziute *et al*[36] found a good correlation between both diagnostic tools in plaque characterization, with more fibrotic and fibro-fatty components in non-calcified plaque. Besides, the majority of TCFA in IVUS corresponded to mixed plaques in CCT. Hereof, Choi *et al*[37] established that plaques with > 10% necrotic core by VH showed significantly lower HU values in CCT. All the studies have shown a good agreement in non-calcified plaque quantification between both techniques[38-40]. However, there were contradictory results in plaque composition analysis using predefined Hounsfield unit (HU) ranges, due to overlapping in these values[38,40]. On the other hand, optical coherence tomography (OCT) has also been used as reference intravascular imaging technique. Kashiwagi *et al*[41] divided plaques in TCFA and non-TCFA according to OCT findings and studied the CCT plaque characteristics. Positive remodeling, lower attenuation values and ring-like enhancement (napkin-ring sign) on CCT were significantly more common in OCT-derived TCFA lesions. The later feature showed a good diagnostic accuracy for high-risk plaque detection and was independently associated with acute events. Moreover, napkin-ring sign has been independently associated with necrotic/lipid core area, non-core plaque area and total vessel area in post-mortem histopathological correlation[42]. However, although the presence of low attenuation and positive remodeling in CCT could identify rupture plaques in another study[43], they failed to differentiate plaque erosions leading to ACS from stable lesions. Lastly, CCT accuracy for plaque composition characterization was also evaluated with near-infrared spectroscopy (NIRS), showing a good correlation of plaque burden and non-calcified plaque area and density with cholesterol deposition in the coronary wall[27].

Thereby, even with first generation 16-rows scanners, culprit lesion characteristics could be evaluated in ACS[44]. When these lesions were compared with those in patients with stable angina, positive expansive remodeling, low attenuation (< 30 HU) non-calcified plaques and spotty calcification were detected more frequently (Figure 3). Furthermore, the combination of these three features increased the positive predictive value to 95%. These findings were corroborated with a prospective multimodal imaging protocol in acute coronary events[45]. Again lower radiological density with lower calcium score and larger remodeling index were more common in culprit lesions. Interestingly, these plaque characteristics were confirmed with IVUS and VH.

Beyond the classical tools for CCT analysis, there are new approaches with promising results in coronary plaque evaluation. Fujimoto *et al*[46] showed that the presence of delayed plaque enhancement in serial CCT acquisition was associated with high-risk plaque features. They hypothesized that this finding may be explained by plaque neovascularization and/or inflammation. In the same direction, a contrast agent formed by iodinated nanoparticles has been probed to detect macrophages in a preclinical model of atherosclerosis[47].

Prognostic relevance of plaque characterization with CCT

The hypothesis that aforementioned morphological patterns are able to identify thrombosis-prone plaques was evaluated in prospective studies. Motoyama *et al*[48] analyzed for the first time CCT plaque characteristics associated with the incidence of ACS in the follow-up. In this study, the presence of positive remodeling and/or low attenuation plaque was independently associated with ACS (HR = 22.8; $P < 0.001$) (Figure 3). Napkin-ring sign is another feature that has been associated with thrombosis-prone plaque. In a large series this sign was the strongest predictor of ACS among the vulnerable plaque characteristics[49]. On the other hand, a case-control study[50] demonstrated that when a semiautomated quantitative analysis of CCT was implemented, total and relative plaque volume and non-calcified plaque were significantly higher in patients who suffered an acute coronary event. This method of evaluation also had additive value to classical cardiovascular risk factors and conventional CCT reading for ACS prediction. Nevertheless, on top of the some methodological limitations[51], there is contradictory results in large prospective series. Among patients derived from ROMICAT Ⅱ cohort[52], acute chest pain in emergency room, presence of a least one of high risk features (positive remodeling, low attenuation, spotty calcification and napkin-ring sign) was an independent predictor of ACS, even after adjustment by clinical risk factors and > 50% or > 70% stenosis[52]. Conversely, when stable patients were evaluated, plaque feature analysis, although improved predictive accuracy, did not significantly increase model discrimination index for acute coronary events[53]. Interestingly, the relevance of high-risk plaque detection on CCT was analyzed in another important cohort from a patient-based and lesion-based perspective[54]. In the former, vulnerable plaque was independently associated with prognosis. However, presence of high-risk features failed to predict ACS in a lesion-based analysis. Additionally, when serial CCT was available, plaque progression emerged as an independent predictor of events. Putting all these data in perspective, although vulnerable plaque CCT features may predict ACS the clinical relevance of these finding still needs to be clarify.

Influence of CCT plaque characteristics in percutaneous coronary interventions outcome was evaluated as well. The incidence of slow-flow phenomenon in patients with stable coronary disease was related with the presence of circumferential plaque calcification, a higher positive remodeling index and a lower plaque density in previous CCT[55]. In fact, circumferential plaque calcification showed the strongest independent association with this complication.

Finally, when CCT was used to evaluate the response to statin therapy[56] a greater decrease of total plaque volume, due to reduction in low attenuation plaque, was detected among patients under treatment, without differences in lumen volume and remodeling index changes between the groups. Thus, CCT may play a role in evaluation of the response to lipid-lowering drugs.

Limitations of CCT in coronary plaque evaluation

Despite the promising data, CCT is far from be free of limitations in vulnerable coronary plaque analysis. First, precise definition of plaque components is hampered by inherent limited spatial resolution of this imaging technique. Thus, results of non-calcified plaque quantification may be inconsistent[39,57]. Moreover, as previously mentioned, CCT plaque characterization is restricted by the overlap in radiological attenuation ranges for the different types of lesions[58,59] (Figure 4). In this regard, dual-source CCT, whose 2 different energies provide differing attenuation of materials, have shown to improve differentiation of necrotic core and fibrous plaque *ex vivo*[60]. Nevertheless, these results worsened when applied *in vivo*[38,60]. Thus, CCT acquisition technology needs to be refined to establish a generalizable HU-based categorization for accurate evaluation of components of the coronary plaque. Second, heavily calcified plaque may obscure detailed plaque evaluation due to partial volume effect. Finally, as previously mentioned, CCT has failed to detect plaque erosion[43], which constitutes the second more frequent presentation of culprit lesions[13].

CMR

CMR not only allows a precise ventricular volume quantification[61] and myocardial tissue characterization[62,63], but also is able to detect the presence of significant (> 50%) coronary atherosclerosis with similar accuracy than CCT[64,65] (Figure 5). In any case, in CMR spatial resolution is directly proportional to scan time. Thus, the necessary high resolution for coronary imaging carries an inherent increased susceptibility to motion artifacts[66]. The most effective measure to optimize image resolution without affecting artifact susceptibility is to reduce the field of view[67], which is difficult if a whole coronary tree analysis is pursued. Apart from that, several strategies have been implemented to avoid aforementioned limitation: Techniques to accelerate image acquisition[68,69], cardiac[70] and respiratory[71] motion compensation and new sampling methods[72,73]. However, even with the last technical advances a whole-heart coronary CMR angiography still takes at least 5 min[74,75], which limits its translation to clinical practice.

Although the aforementioned limitations make the acquisition challenging, non-contrast black-blood sequences have shown a good correlation with IVUS in luminal area and coronary plaque burden determination[76,77]. Interestingly, methemoglobin produced during clot maturation has the potential of shortening T1 relaxation time, which allows coronary thrombus detection with T1-weighted sequences[78,79]. The diagnostic accuracy of this noninvasive technique was

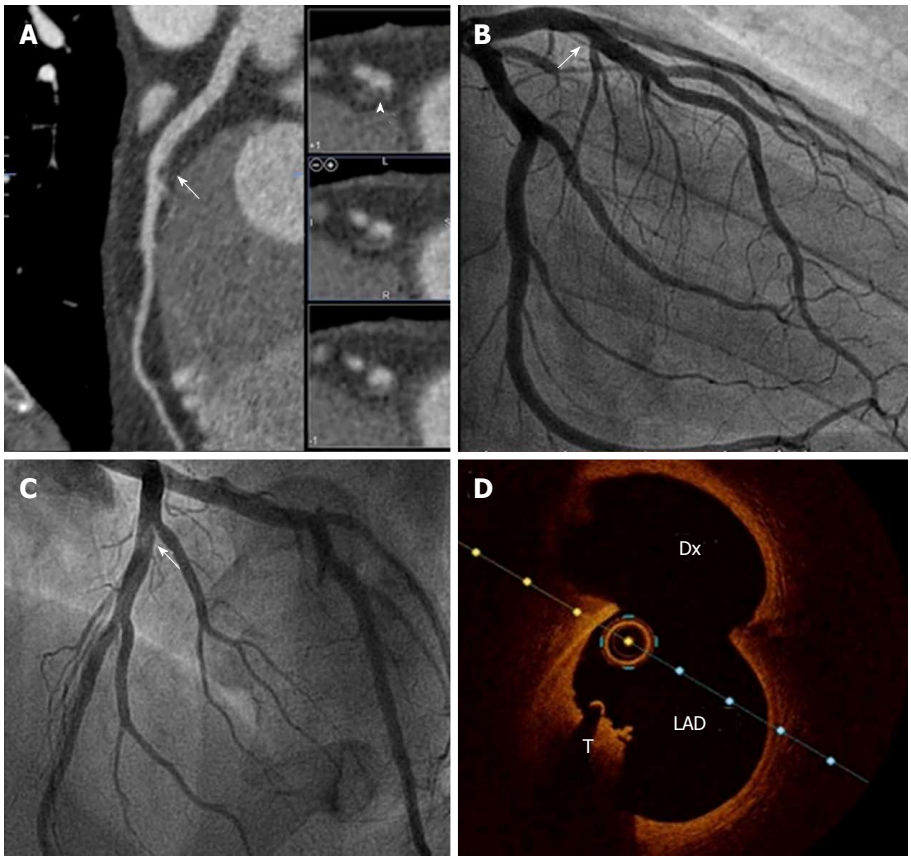

Figure 4 Coronary computed tomography characterization of plaque components. Multimodal evaluation of a mid-LAD lesion in bifurcation with a Dx branch. A: CCT multiplanar reconstruction demonstrates a nonsignificant luminal narrowing in the mid LAD (arrow), and when short axis was evaluated the lesion fulfills noncalcified plaque features (arrowhead); B and C: ICA: The same nonobstructive lesion is observed in mid-LAD (arrow), which seems hyperlucent on LAO cranial projection (C); D: OCT confirms the presence of a red intracoronary thrombus (T) in the same location. CCT: Coronary computed tomography; LAD: Left anterior descending artery; Dx: Diagonal branch; ICA: Invasive coronary angiography; OCT: Optical coherence tomography.

proven to be high when it was evaluated against invasive coronary angiography[80] and OCT[81] (Figure 6). On the other hand, in a head-to-head comparison with CCT the presence of high intensity lesions on T1 sequences was associated with features of vulnerable plaque, such as positive remodeling, low attenuation and spotty calcification[82]. Moreover, this CMR finding was also associated with prognosis: Higher incidence of slow-flow phenomenon after percutaneous coronary intervention[82], coronary events during the follow-up[83], and regression of plaque in response to statin therapy[84]. Finally, T2-weighted sequences have demonstrated their ability to detect coronary vessel wall edema, in probable relation with plaque neovascularization, in initial studies[85,86].

Targeted as well as non-targeted contrast agents have been used to evaluate coronary arteries with CMR. When nonspecific gadolinium contrast is used, the presence of hyperenhancement has been linked to the severity of coronary atherosclerosis[79]. Additionally, a progressive reduction of coronary hyperenhancement has been noted in serial CMR after acute myocardial infarction[87]. Contrarily, many targeted contrast agents, directed to specific components of the plaque, are currently under investigation. Among them some have already reached positive data for coronary evaluation in large animals and/or humans: Fibrin-specific[88-90] and elastin-specific[91] contrast agents, gadofluorine[92,93], albumin-binding[94-96] contrast agent, and iron oxide-based[97] contrast. However, due to the growing field of molecular imaging a detailed discussion of these agents exceed the scope of this review.

PET

Besides the detailed morphological characterization provided by CCT and CMR, quantification of inflammation is a key feature in vulnerable coronary plaque evaluation. In this regard, nuclear imaging techniques have been extensively used for this purpose in atherosclerosis[98,99]. PET is the preferred tool, due to its superior spatial resolution over single photon emission tomography (SPECT), and is usually combined with computed tomography for a better anatomical definition. Fluorodeoxyglucose (FDG) is the most widely used tracer in this field. However, coronary evaluation is hampered by the significant myocardial uptake of FDG. To override this limitation, free fatty myocardial metabolism was favored with a low-carbohydrate high fat preparation[100]. This strategy was initially proven to detect coronary plaque inflammation[101]. Moreover, when coronary PET was evaluated in ACS as well as in stable angina

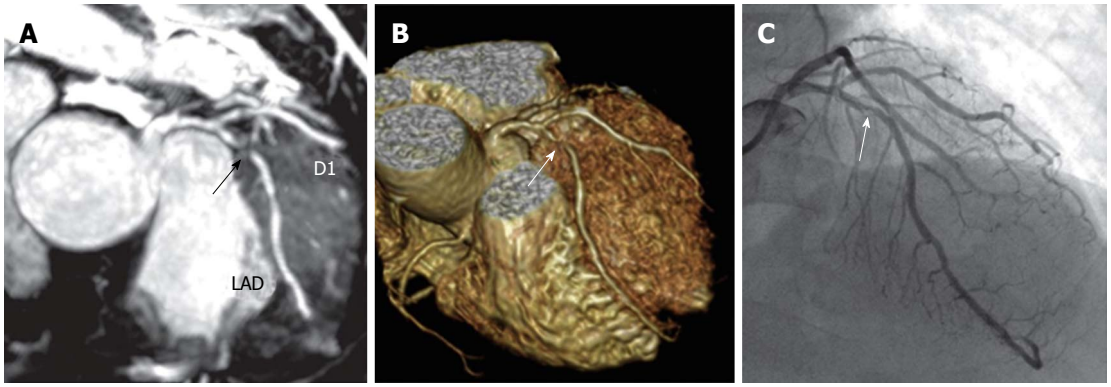

Figure 5 Unenhanced Whole-Heart coronary cardiac magnetic resonance angiography. Correlation of unenhanced whole-heart coronary CMR angiography (A, maximum intensity projection image, and B, volume-rendered image) with invasive coronary angiography (C) in a in a 50-year-old male patient with chest pain on effort. Note the presence of significant stenosis in proximal LAD (arrows). Adapted with permisssion from Nagata *et al*[75]. LAD: Left anterior descending coronary artery; D1: First diagonal branch; CMR: Cardiac magnetic resonance.

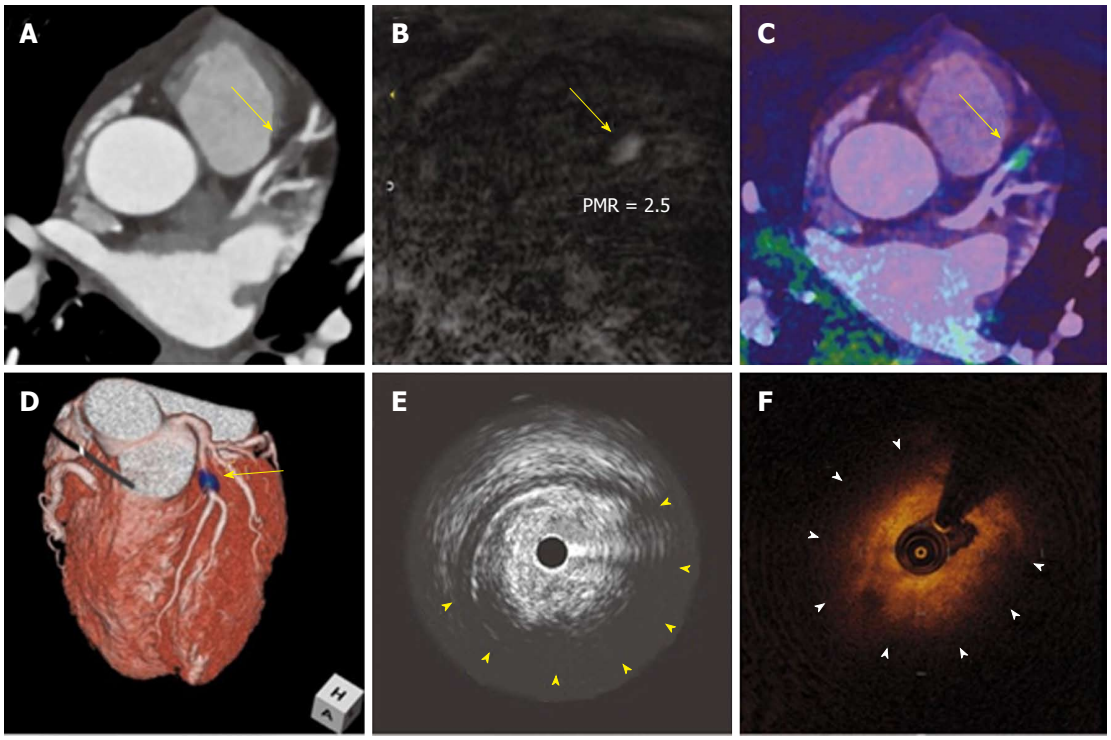

Figure 6 T1 hyperintense coronary plaques in cardiac magnetic resonance. Noninvasive and invasive coronary imaging of a significant plaque in proximal LAD. CCTA (A) showed a noncalcified plaque in LAD causing significant stenosis. When noncontrast T1-weighted CMR imaging was performed (B) a hyperintense lesion was detected. Afterwards, CMR images were fused with CCTA (C and D) and this lesion was found to correspond with the previously described coronary stenosis. Interestingly, during the subsequent coronary angiography it showed a large lipid component in IVUS (E) as well as OCT (F). Adapted with permission from Asaumi *et al*[106]. LAD: Left anterior descending coronary artery; CCTA: Coronary computed tomography; CMR: Cardiac magnetic resonance; IVUS: Intravascular ultrasound; OCT: Optical coherence tomography; PMR: Plaque to myocardium signal intensity ratio.

after stent implantation, a higher FDG uptake was noted not only in the culprit lesions but also in the left main and ascending thoracic aorta of the patients with acute coronary events (Figure 7)[102]. This suggests the presence of spread arterial wall inflammation in the former group. Conversely, Dweck *et al*[103] demonstrated the ability of the new tracer 18F-sodium fluoride to detect coronary atherosclerosis without the limitation of myocardial metabolism artifact. Increased uptake was also associated with coronary calcium score, Framingham risk score, prior cardiovascular events and angina. Lastly, new tracers targeted against other markers of inflammation such as macrophage infiltration (11C-PK11195[104] and 68Ga-DOTATATE[105]) have been successfully tested.

CONCLUSION

Noninvasive imaging tools have shown their capacity to detect features related with vulnerable coronary

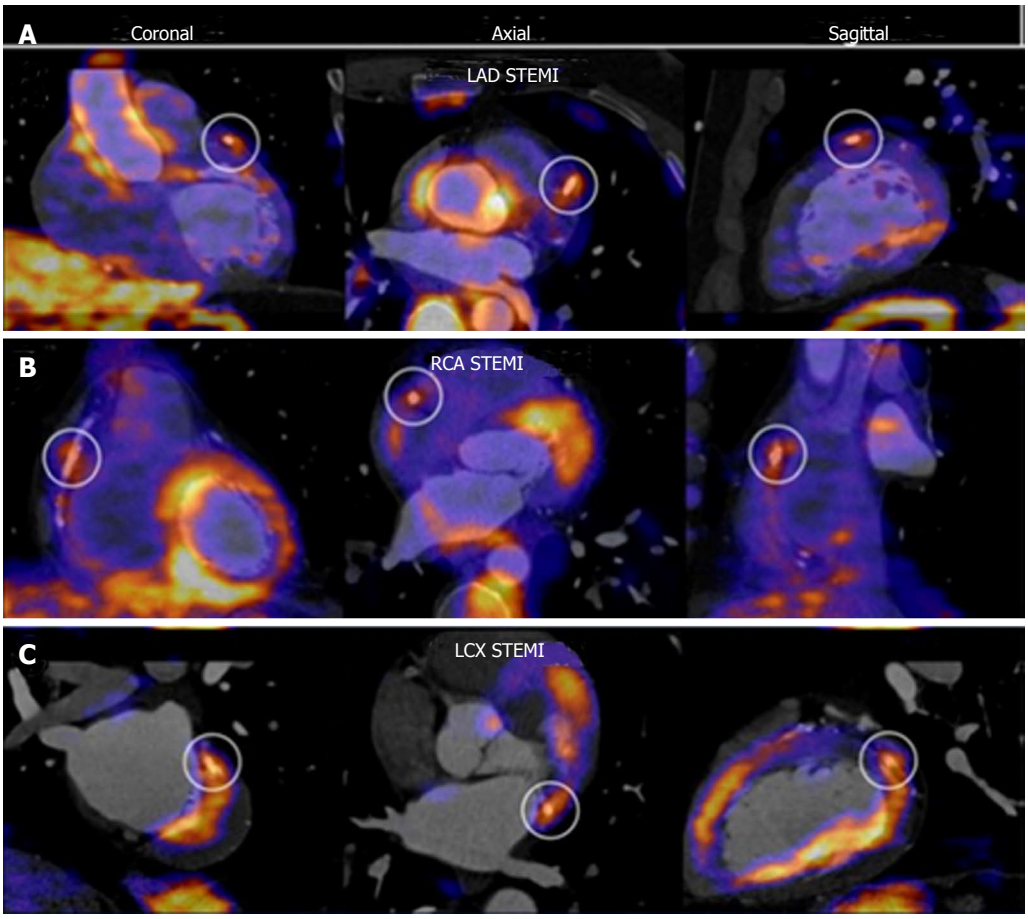

Figure 7 Fluorodeoxyglucose positron emission tomography of the coronary arteries. PET CT fusion imaging in three cases of patients with STEMI. An increased ^{18}F-FDG uptake at stent site is shown in different culprit vessels, from A to C: LAD, RCA and LCX. Adapted with permission from Cheng *et al*[107]. This research was originally published in JNM. ©by the Society of Nuclear Medicine and Molecular Imaging, Inc. FDG: Fluorodeoxyglucose; PET: Positron emission tomography; STEMI: ST elevation myocardial infarction; LAD: Left anterior descending coronary artery; RCA: Right coronary artery; LCX: Left circumflex coronary artery.

plaque. CCT has been largely tested with this aim. Certain plaque characteristics, such as positive remodeling, low attenuation, spotty calcification and napkin-ring sign, have been systematically associated with ACS occurrence. Regarding CMR, results of plaque morphology characterization are similar than CCT but the inherent acquisition limitations hampered its extension to clinical practice. Moreover this technique allows tissue characterization of the coronary plaques through T1- and T2-weighted sequences and contrast-enhanced imaging. Finally, PET has emerged as a promising molecular imaging technique being able to detect coronary inflammation and even macrophage infiltration *in vivo*. In any case, given that the presence of vulnerable plaque features is not irredeemably linked to the occurrence of an ACS, larger studies are needed to clarify the patient subgroup that may benefit from non-invasive detection of high-risk plaques. This aspect is of special interest due to the large population that may be the target of a noninvasive imaging strategy for acute coronary events prevention. In this regard, cost-effectiveness should also be evaluated carefully in the future.

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REVIEW

Role of radionuclide imaging for diagnosis of device and prosthetic valve infections

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Abstract

Cardiovascular implantable electronic device (CIED) infection and prosthetic valve endocarditis (PVE) remain a diagnostic challenge. Cardiac imaging plays an important role in the diagnosis and management of patients with CIED infection or PVE. Over the past few years, cardiac radionuclide imaging has gained a key role in the diagnosis of these patients, and in assessing the need for surgery, mainly in the most difficult cases. Both ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT) and radiolabelled white blood cell single-photon emission computed tomography/computed tomography (WBC SPECT/CT) have been studied in these situations. In their 2015 guidelines for the management of infective endocarditis, the European Society of Cardiology incorporated cardiac nuclear imaging as part of their diagnostic algorithm for PVE, but not CIED infection since the data were judged insufficient at the moment. This article reviews the actual knowledge and recent studies on the use of ^{18}F-FDG PET/CT and WBC SPECT/CT in the context of CIED infection and PVE, and describes the technical aspects of cardiac radionuclide imaging. It also discusses their accepted and potential indications for the diagnosis and management of CIED infection and PVE, the limitations of these tests, and potential areas of future research.

Key words: Device; Endocarditis; Fluorodeoxyglucose; Imaging; Infection; Leukocytes; Positron emission tomography/computed tomography; Prosthetic valve; Radionuclide; Scintigraphy

Core tip: Cardiovascular implantable electronic device infection and prosthetic valve endocarditis remain a diagnostic challenge. This review article describes the evolving role of cardiac radionuclide imaging in the diagnosis and management of cardiac infections. It focuses on recent published studies, indications and limitations of both ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography and

radiolabelled white blood cell single-photon emission computed tomography/computed tomography.

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INTRODUCTION

Cardiovascular implantable electronic device (CIED) infection and prosthetic valve endocarditis (PVE) carry significant morbidity and mortality as well as substantial financial burden to the society[1]. In some cases, establishing the diagnosis might be challenging since cultures are not always positive and they do not necessarily imply that the device/leads or heart valves are infected. Since device/lead extraction and repeat cardiac surgery are associated with significant risks, it is important to confirm the diagnosis and to plan the appropriate treatment. Cardiac imaging plays an important role in the pre-operative evaluation of patients with CIED infection and PVE. Radionuclide imaging has evolved over the past few years as an additional tool to confirm or exclude prosthetic infection and to guide the most appropriate clinical management, either complete removal or conservative treatment. In their 2015 guidelines for the management of infective endocarditis (IE), the European Society of Cardiology (ESC) addressed the use of nuclear medicine imaging for the diagnosis of IE[1]. The main objectives are to position ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT) and white blood cell single-photon emission computed tomography/computed tomography (WBC SPECT/CT) imaging in clinical practice and to review the actual knowledge and recent studies as well as to address areas of future research.

CLINICAL PRESENTATION AND DIAGNOSIS OF CARDIAC INFECTIONS

CIED infection and PVE remain a diagnostic challenge. The clinical presentation can be highly variable because of multiple potential causative microorganisms, the presence of documented heart disease, cardiac devices or prosthetic valves, different modes of presentation, and sometimes non-specific symptoms at the time of initial presentation. The modified Duke criteria are considered the gold standard for the diagnosis of endocarditis[2,3]. However, the early diagnostic accuracy is often suboptimal with several patients being misclassified[4]. This is true mainly in patients with CIED infection and PVE. The early diagnosis of IE is imperative since postponement of antibiotic therapy and/or surgery can lead to a poor outcome[5,6].

A high level of expertise is required and it often includes cardiologists, nuclear medicine specialists, electrophysiologists, cardiac surgeons and infectious disease specialists. The concept of a "Heart Team approach" or "Endocarditis Team" has been proposed to improve the diagnosis and management of CIED infection and PVE. The use of a multidisciplinary task force with a well-defined protocol has been shown to decrease the 1-year mortality of patients with IE from 18.5% to 8.2%[7].

In addition, cardiac imaging plays an essential role in the diagnosis and management of IE. In recent guidelines, transthoracic echocardiography (TTE) and transesophageal echocardiography (TEE) remain the initial recommended imaging techniques for the diagnosis of IE (class I indication, level of evidence B)[1]. Some echocardiographic information is included as major criteria for the diagnosis of IE. The sensitivity for the identification of vegetations with TTE is 75% for native valves, but may be lower in patients with poor echogenicity or prosthetic valves or very small vegetations[8]. On the other hand, the sensitivity of TEE is superior at 85%-90%. However, a negative echocardiography does not rule out IE, and it has been recommended to repeat the TEE 3 to 5 d later or sooner when there is a high suspicion of IE or a change in the clinical status (class I, level of evidence B)[9]. In addition, non-infective vegetations such as strands or thrombi on valvular prosthesis or leads can lead to a false diagnosis of IE in up to 15% of cases[4]. These findings highlight the limitations of echocardiography and the potential benefits of other imaging techniques in such instances.

Investigation of patients with IE can also include other imaging techniques, such as multislice computed tomography for detection of abscesses or pseudoaneurysms, magnetic resonance imaging for detection of cerebral lesions, ^{18}F-FDG PET/CT, and radiolabelled WBC hybrid SPECT/CT imaging.

USE OF CARDIAC NUCLEAR IMAGING IN CARDIAC INFECTIONS

PET imaging has been used for cancer diagnosis and staging and to detect infection in orthopaedic prostheses. In cardiology, it is used to evaluate myocardial viability, ischemia and to identify infection associated with vascular grafts, CIED and prosthetic valves.

With the combination of radionuclide imaging to CT scan (hybrid technology), nuclear imaging has provided significant supplementary information in patients with suspected IE. Two radionuclide imaging techniques are presently used in the diagnosis of CIED infection and PVE: (1) radiolabelled WBC SPECT/CT using either ^{111}In-oxine or ^{99m}Tc-hexamethylpropyleneamine oxime (HMPAO); and (2) ^{18}F-FDG PET/CT.

WBC SPECT/CT imaging uses autologous radio-

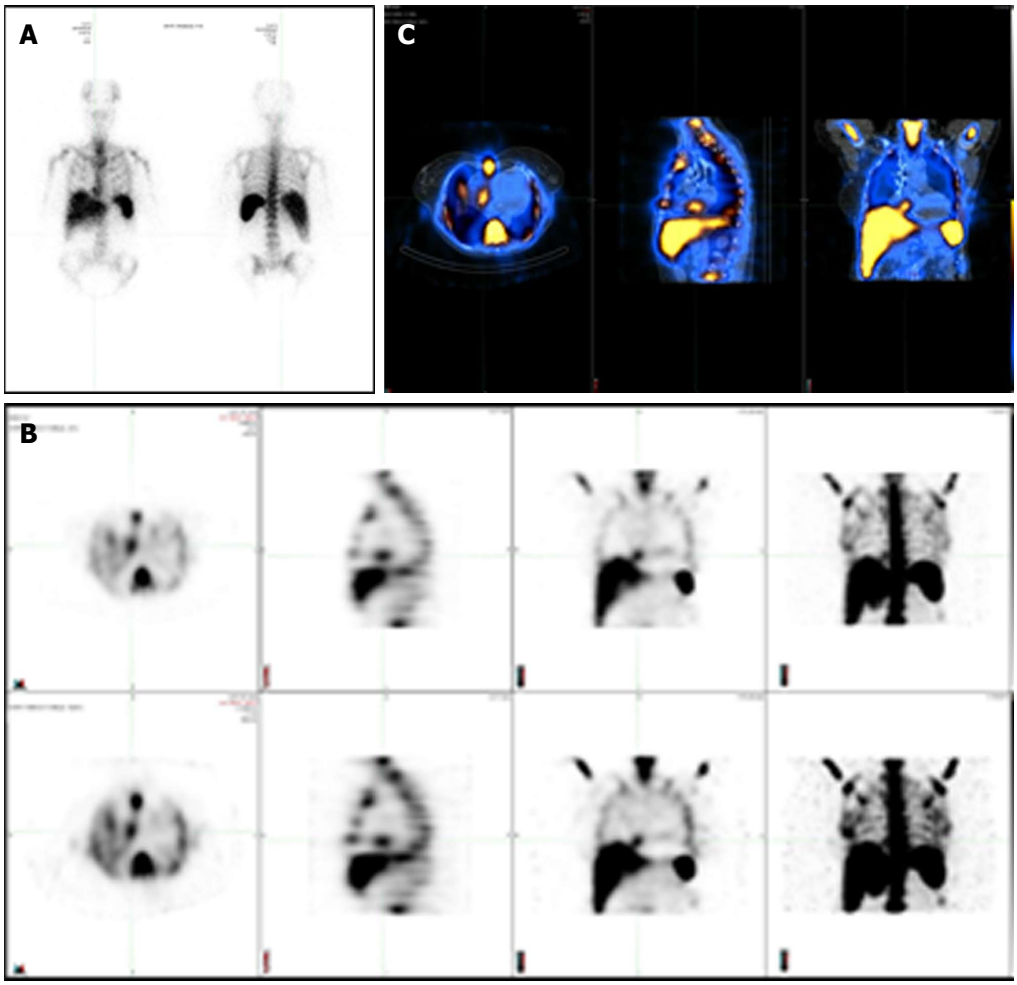

Figure 1 Different modalities in cardiac nuclear imaging. A: Planar scintigraphy with a single two-dimensional image; B: Single photon emission computed tomography (SPECT) displayed as transverse, sagittal, coronal and MIP attenuation corrected (top row) and uncorrected images (bottom row); C: Hybrid SPECT/CT with precisely registered CT image.

labelled leukocytes (^{111}In-oxine or ^{99m}Tc-HMPAO) that are injected intravenously back to the patient to look for infection in the body by imaging gamma rays. The accumulation of radiolabelled leukocytes is time-dependent between initial and late images. Planar images are obtained from different angulations with subsequent SPECT acquisition, 3D reconstruction and fusion with low-dose CT for further anatomical localization and attenuation correction. Figure 1 shows the differences between planar scintigraphy, conventional SPECT imaging and hybrid SPECT/CT. The sensitivity of this test depends on neutrophil granulocytes accumulation and is higher during acute infection. Studies have shown that cells participating in infection and inflammation, mainly neutrophils and macrophages, are able to express a great amount of glucose transporters, mainly GLUT1 or GLUT3 as well as hexokinase activity[10-14]. WBC SPECT/CT using ^{99m}Tc-HMPAO is performed 4 h following injection of radiolabelled leukocytes, although images at 24 h are possible but with loss of some image quality, whereas WBC SPECT/CT using ^{111}In-oxine allows imaging up to 72 h with potentially better sensitivity (typically performed at 4, 24 and sometimes 48 h). This is based on the half-life of each radioactive isotope, being 6 h for ^{99m}Tc and 67 h for ^{111}In. WBC SPECT/CT allows a higher specificity for the identification of active infection. However, leukocytes radiolabelling is more time-consuming. It also associated with manipulation of blood products.

^{18}F-FDG PET/CT is a well-known non-invasive imaging technique that allows 3D calculation of metabolic activity within the body obtained from the emission of positrons subsequent to the disintegration of a radioactive compound. ^{18}F-FDG is a glucose analogue, which is incorporated and retained within cells with a high metabolic activity, such as inflammatory cells. It is usually performed approximately 1 h after the injection of ^{18}F-FDG. This tracer is actively incorporated by leukocytes, macrophages and CD4$^+$ T-lymphocytes located at areas of infection *via* glucose transporters, primarily GLUT 1 and GLUT3, which are insulin sensitive and present in the myocardium[12-14]. Inside the cells, ^{18}F-FDG is phosphorylated and remains intracellular without further transformation.

Each technique has advantages and weaknesses for the identification of active infection in cases of

Table 1 Advantages and limitations of ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography and white blood cell single-photon emission computed tomography/computed tomography for the diagnosis of device infection and prosthetic valve endocarditis

Advantages	Limitations
^{18}F-FDG PET/CT	
Excellent spatial resolution	Moderate radiation exposure (8-30 mSv depending on the study performed)
Short acquisition time	Not available in several centers
High sensitivity for the detection of hypermetabolic activity	Physiological uptake of ^{18}F-FDG in the myocardium might prevent adequate detection of cardiac infection
Detection of peripheral events	Recent surgery may demonstrate residual inflammatory changes without evidence of infection
Detection of other sources of fever or bacteremia in patients with CIED	Possible uptakes can be found in active thrombi, cardiac tumours or metastasis, and foreign body reactions
Detection of CIED infection and PVE in cases of a negative TEE	Possible false-negative test in patients with small vegetations or prolonged antibiotic therapy
	Less useful for infectious brain embolisms because of high glucose metabolism in the brain
WBC SPECT/CT	
High specificity for the presence of active infection	Time-consuming
	It involves blood products handling
	Cases of false-negative study seen with Candida and Enterococcus infection

CIED: Cardiovascular implantable electronic device; ^{18}F-FDG PET/CT: 18F-fluorodeoxyglucose positron emission tomography/computed tomography; PVE: Prosthetic valve endocarditis; TEE: Transesophageal echocardiography; WBC SPECT/CT: Radiolabelled white blood cell single-photon emission computed tomography/computed tomography.

presumed PVE (Table 1). ^{18}F-FDG PET/CT has the convenience of a shorter procedure time and a high sensitivity for the identification of hypermetabolic areas. It also has an excellent spatial resolution. However, it does not discriminate enough between infection and inflammation, mainly in the first few months postoperatively. Also, evaluation of ^{18}F-FDG uptakes around cardiac valves can be more difficult if residual physiological myocardial uptake is present. For this reason, it is recommended to prepare the patient with the Atkins diet, which is a low-carbohydrate diet[15]. It is also suggested injecting a heparin bolus before administration of ^{18}F-FDG. Unfractionated heparin increases plasma free fatty acids *via* activation of lipoprotein and hepatic lipases[16]. This can lead to a reduction in glucose consumption within the normal myocardium

Technical aspects

In the literature, there are significant variations in the ^{18}F-FDG PET/CT protocols used. Normally, ^{18}F-FDG PET/CT is performed after a fasting period of 8 to 12 h. Eating foods rich in fat but very low in carbohydrates the evening prior to the exam is suggested in order to decrease the physiological uptake of ^{18}F-FDG within the myocardium[17]. Patients should avoid bread, cereals, pasta, potatoes, rice, beans, fruit juice, chewing gum and drinking alcohol. Unfractionated heparin (50 IU/kg) can also be administered intravenously 15 min prior to ^{18}F-FDG injection in an attempt to reduce more the physiological uptake. PET imaging is usually performed 1 h after the injection of 4-5 MBq/kg of ^{18}F-FDG. Simultaneously, a whole-body low-dose CT without intravenous contrast is carried out for correction of attenuation and anatomic localization. The capillary glucose is measured, and patients receive an insulin injection if the fasting glucose is above 7.7 mmol/L or 140 mg/dL. The analysis is then performed using dedicated softwares. Both attenuation-corrected and non-attenuation-corrected images are reviewed in order to recognize potential artefacts that could be related to close proximity of objects of high density, such as device generator or prosthesis. A visual analysis is first performed to identify sites of hypermetabolic or abnormal ^{18}F-FDG uptakes in close proximity to prosthetic valves and device generator/leads with further confirmation in the uncorrected images. In patients with CIED, focal uptake can be further classified based on the location (pocket infection, lead infection or both). Then, semi-quantitative analyses are done to measure the maximal standardized uptake value (SUV_{max}). However, it is important to recognize that these values have to be used with caution, since they can be falsely elevated due to the attenuation correction when measured in close proximity to a metallic object. For this reason, a semi-quantitative count ratio on non-attenuation-corrected images is likely superior to SUV_{max} (compared to an organ of reference, *i.e.*, lung, mediastinum or liver parenchyma). In addition, whole-body acquisition allows for the detection of silent embolic events and extracardiac abnormal uptakes.

Autologous radiolabelled WBC scintigraphy with ^{111}In-oxine was introduced in the mid-1970s. Over the years, it has been mainly substituted by ^{99m}Tc-HMPAO, which has more advantageous physical characteristics, cost, availability, and lower radiation burden[18]. ^{99m}Tc has a shorter imaging time because of a half-life of 6 h compared to 67 h for Indium. However, Indium is often preferred for the detection of CIED infection and PVE since it allows acquisitions over a longer period of time (up to 72 h).

There are several methods for labelling WBC, but the main principles and technique are similar. Around 40-60 mL of venous blood is taken from the patient and then combined to 10 mL of acid-citrate-dextrose anticoagulant solution. This syringe is then put in an upright position for 1 to 2 h to facilitate erythrocyte sedimentation by gravity. After erythrocytes have been removed, blood centrifugation is then performed to separate leukocytes from platelets. HMPAO is labelled with ^{99m}Tc and incubated for 15 min with leukocytes. The routine dose of ^{111}In labelled leukocytes is 10-20 MBq (0.3-0.5 mCi) while the quantity of ^{99m}Tc-HMPAO labelled

leukocytes is 185-370 MBq (5-10 mCi). Radiolabelled leukocytes are separated from HMPAO by centrifugation. The majority of labelled leukocytes are neutrophils. For this reason, the procedure is mainly useful for identification of a neutrophil-mediated process, such as a bacterial infection. A labelling efficiency of at least 40% should be achieved. Radiolabelled leukocytes are tested by the trypan blue exclusion test for viability. The cells are then resuspended in plasma before reinjection into the patient. For ^{99m}Tc-HMPAO labelled leukocytes, the scintigraphy is performed 4 and 24 h (delayed images) after injection, and sometimes 48 h or rarely 72 h for ^{111}In labelled leukocytes. Images are acquired using a SPECT/CT system. Scintigraphy is considered positive when an area of labelled WBC uptake superior to background activity is identified in the involved area and when the signal increases over time.

DEVICE INFECTION

CIED infection is associated with significant morbidity and mortality. Device infection prevalence is increasing in parallel with broader indications for ICD implantation and cardiac resynchronization, the presence of more comorbidities, and the growing number of implants in the world[19]. It is known however that the infection burden increases more than the increase in device implantations. This is probably related to more comorbidities and change in pathogens[20]. Cardiac device infections can present as a superficial or deep generator pocket infection or cardiac-device-related IE with involvement of the leads and/or extension to cardiac valves. It should be initially suspected in patients with CIED who consult for unexplained fever. Deep pocket infection and/or lead infection require complete system extraction. However, superficial infection not in contact with the device can be treated with antibiotic therapy alone. The diagnosis is sometimes quite obvious in the presence of significant pocket redness or pus, bacteremia or lead vegetation on TEE. Unfortunately, several cases are more complicated to assess. Since device and lead extraction can be associated with significant morbidity (major complications = 1.5%-2%) and mortality (0.8%) even in an experienced center, a definite diagnosis is important[21]. On the other hand, CIED infection can be overestimated with echocardiography since non-infectious accretions can be found in up to 21% by TTE and 28% by TEE in CIED patients without infection[22]. These patients can have fever or bacteremia for another reason. Thus, another form of imaging is proposed before proceeding to extraction/surgery.

Studies using ^{18}F-FDG PET/CT

The first report of cardiac infection detected by ^{18}F-FDG PET was published in 2006[23]. Afterwards, 2 small pilot studies were published on device infection and ^{18}F-FDG PET/CT. Bensimhon *et al*[24] evaluated the diagnostic value of ^{18}F-FDG PET/CT in 21 patients with presumed device infection, which were compared to 14 patients without infection. ^{18}F-FDG PET/CT had a sensitivity and specificity of 80% and 100%, respectively for diagnosis of infection. Patients with false negative studies for lead infection had received antibiotics for a longer period of time prior to the ^{18}F-FDG PET/CT (20 d *vs* 3.2 d; $P < 0.01$). The sensitivity was lower for the diagnosis of lead infection (60% compared to 100% for pocket infection). Ploux *et al*[25] investigated the role of ^{18}F-FDG PET/CT in 10 patients with CIED and fever of unknown origin. These patients were compared to a control group of 40 patients. ^{18}F-FDG PET/CT showed increased ^{18}F-FDG uptakes along the leads in 6 out 10 patients who had initial comprehensive negative investigation. Subsequently, these patients had complete extraction of the implanted material and lead cultures were positive on all 6 patients. This showed the promising value of ^{18}F-FDG PET/CT in difficult CIED cases.

In 2012, our group evaluated the usefulness of ^{18}F-FDG PET/CT for the identification of CIED infection[26]. We compared 3 groups: 42 patients with suspected CIED infection, 12 patients with recent device implantation (between 4 and 8 wk postoperatively) but no clinical signs of infection, and 12 patients with devices implanted for more than 6 mo and also no device infection. We showed an excellent correlation between sites of ^{18}F-FDG uptakes on ^{18}F-FDG PET/CT and clinical findings on TEE or at the time of extraction. ^{18}F-FDG PET/CT using a qualitative visual score had a sensitivity and specificity for diagnosis of CIED infection of 89% and 86%, respectively. We also demonstrated that ^{18}F-FDG PET/CT could identify patients with superficial infection without direct involvement of the generator or leads that could be treated only with antibiotics. Negative ^{18}F-FDG PET/CT identified a group of patients that had an excellent outcome without device extraction. Finally, we were able to identify a semi-quantitative ratio between the maximal uptake and normal lung parenchyma uptake, which was useful in differentiating between CIED infection and residual normal post-operative changes; a ratio of 1.5 had the best combination of sensitivity and specificity. Based on this information, we suggested an algorithm using ^{18}F-FDG PET/CT for the evaluation of CIED infection (Figure 2). An important clinical aspect of ^{18}F-FDG PET/CT is its high negative predictive value.

Since, Cautela *et al*[27] demonstrated that ^{18}F-FDG PET/CT had a high accuracy for the diagnosis of skin and pocket CIED infection (sensitivity 86.7% and specificity 100%), but a lower sensitivity of only 30.8% and a specificity of 62.5% for lead or cardiac involvement. Many patients with a false-negative test were already on antibiotics. The size of the vegetations might also have influenced the results. It cannot be excluded that some patients with lead extraction had a non-infectious cause for the vegetations seen on the lead. Finally, a possible limitation of this study is suboptimal patient preparation in order to partially explain the lower sensitivity observed for lead or cardiac involvement. It is of the utmost importance to make

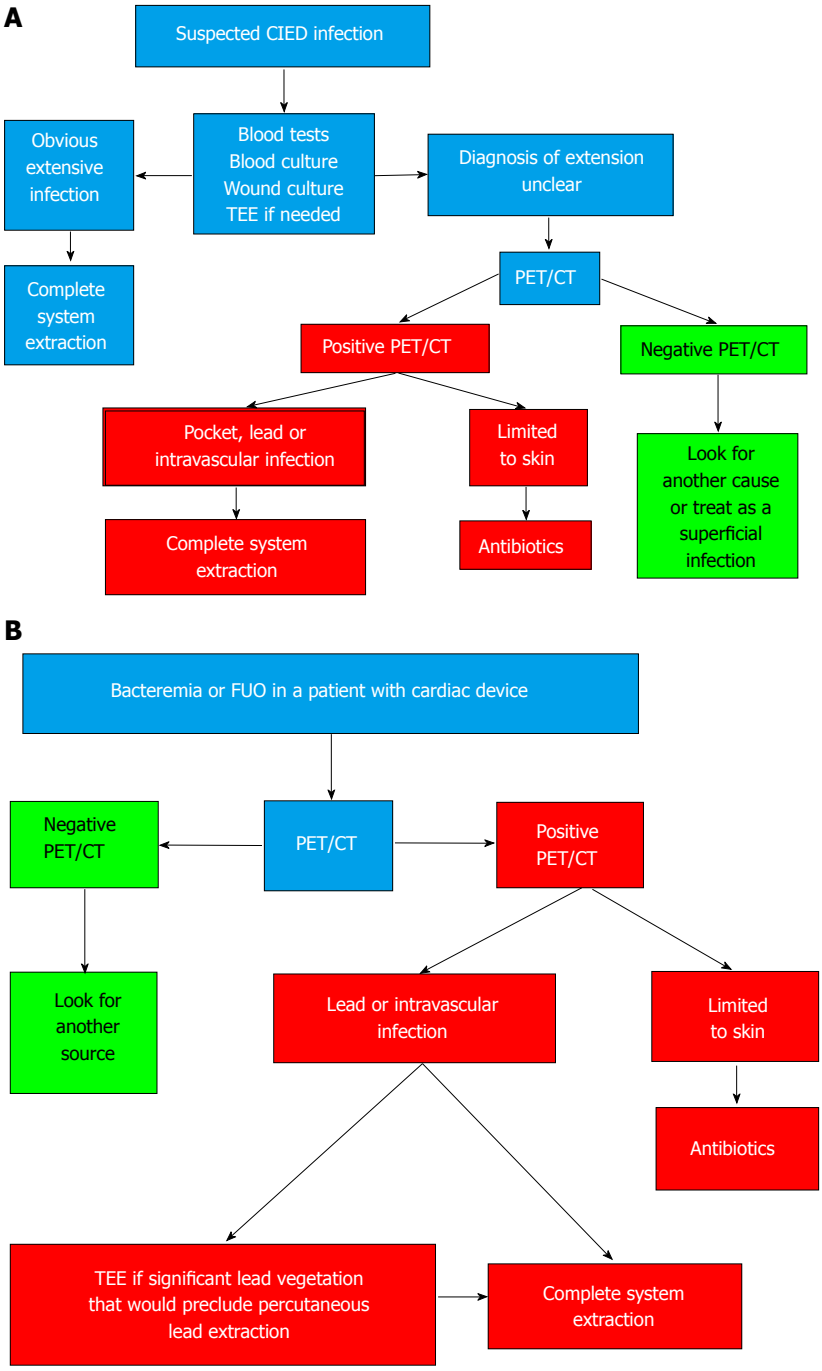

Figure 2 Proposed algorithms incorporating ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography in the evaluation and management of patients with possible device infection. A: Initial CIED infection suspicion; B: Patients with cardiac device and bacteremia or fever of unknown origin (FUO) (Reprinted from Sarrazin JF, Philippon F, Tessier M, Guimond J, Molin F, Champagne J, Nault I, Blier L, Nadeau M, Charbonneau L, Trottier M, O'Hara G. Usefulness of fluorine-18 positron emission tomography/computed tomography for identification of cardiovascular implantable electronic device infections. *J Am Coll Cardiol* 2012; 59: 1616-1625, with permission from Elsevier). CIED: Cardiovascular implantable electronic device; PET/CT: Positron emission tomography/computed tomography; TEE: Transesophageal echocardiography.

sure that physiologic myocardial uptake is suppressed to be able to realize an optimal evaluation. Ideally, every patient should be prepared with the Atkins diet and receive a heparin bolus before ^{18}F-FDG injection. Ahmed *et al*[28] demonstrated that ^{18}F-FDG PET/CT had a high diagnostic accuracy for the detection of patient with pocket infection that eventually required extraction. They find that the optimal semi-quantitative ratio cut-off value for the early identification of patients with pocket infection was > 2.0, giving a sensitivity of 97% and a specificity of 98%.

Figure 3 shows a positive ^{18}F-FDG PET/CT in a patient with a deep pocket infection, while Figure 4 shows another positive ^{18}F-FDG PET/CT but in a patient with a lead infection. Note how the physiologic myocardial uptake is well suppressed in this case.

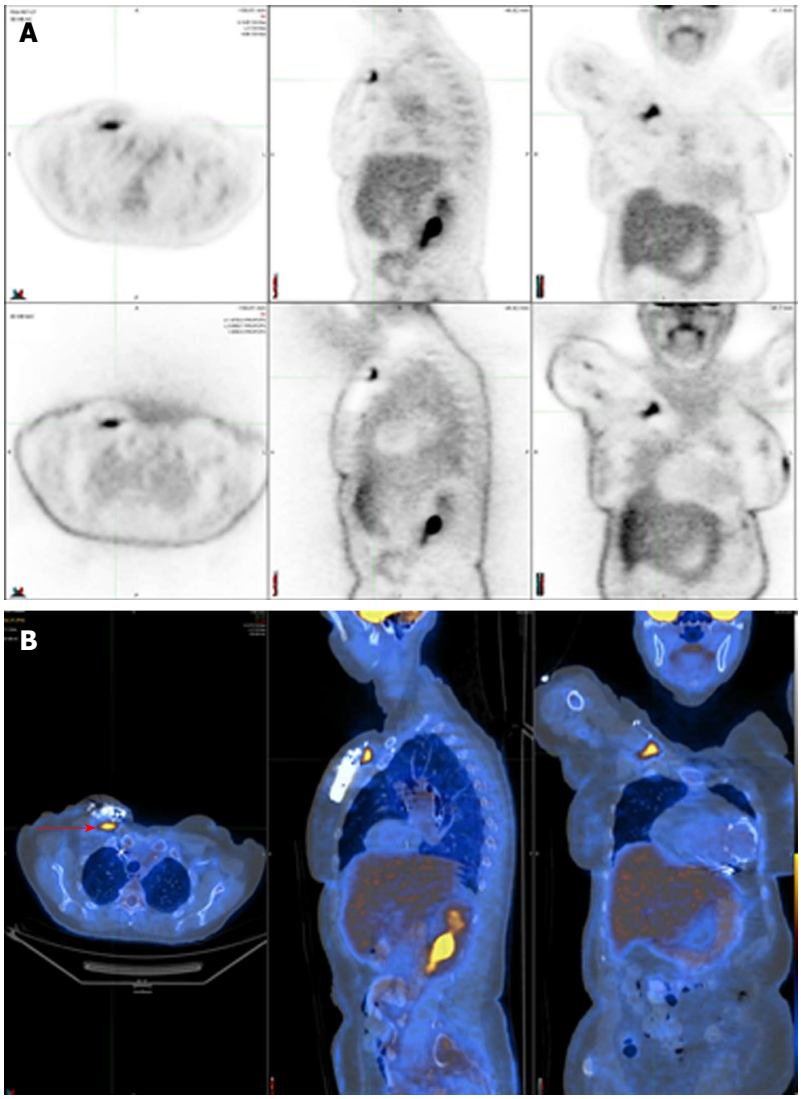

Figure 3 Positive ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography in a patient with a deep pocket infection shown by focal ^{18}F-fluorodeoxyglucose uptake just underneath the generator (red arrow). A: SPECT displayed as transverse, sagittal, and coronal attenuation corrected (top row) and uncorrected images (bottom row); B: Hybrid SPECT/CT displayed as transverse, sagittal, and coronal images. SPECT/CT: Single-photon emission computed tomography/computed tomography.

Studies using WBC SPECT/CT

The diagnostic accuracy of radiolabelled WBC scintigraphy was evaluated by Erba *et al*[29]. They obtained a sensitivity of 94% for both detection and localization of CIED infection. Two cases of false-negative scans were seen in patients with Candida and Enterococcus infection. No false-positive studies were seen, confirming the high specificity of this technique. They demonstrated the superiority of SPECT/CT over planar and SPECT alone imaging.

Based on these studies, ^{18}F-FDG PET/CT and WBC SPECT/CT might play an additional role in the diagnosis of CIED infection, but data were judged not sufficient at the moment to be incorporated into the diagnostic criteria of IE involving pacemaker or defibrillator leads in the latest European guidelines[1]. Overall, ^{18}F-FDG PET/CT seems to have an excellent sensitivity for the diagnosis of pocket infection, but a lower sensitivity in the context of lead infection.

PROSTHETIC VALVE INFECTION

Early diagnosis of PVE is also challenging. PVE is a severe form of IE and accounts for 10%-30% of all cases of IE. The diagnosis is often more difficult than in native valve endocarditis. Since the initial echocardiography is often normal or inconclusive in PVE, other imaging techniques are sometimes necessary. The use of ^{18}F-FDG PET/CT in patients with PVE has evolved as a useful tool.

Studies using ^{18}F-FDG PET/CT

Case reports have demonstrated the possible benefits of ^{18}F-FDG PET/CT in the diagnosis of prosthetic valves[30]. Saby *et al*[31] demonstrated the incremental benefit of using abnormal ^{18}F-FDG uptake as a major criterion for the modified Duke criteria in the detection of PVE. They have shown that ^{18}F-FDG PET/CT significantly increases the sensitivity of IE diagnosis from 70% to 97% (P = 0.008) on admission. They determined that ^{18}F-FDG PET/CT had an adequate diagnostic value when abnormal ^{18}F-FDG uptake is found near the prosthetic valve. They also showed that abnormal ^{18}F-FDG uptake could be seen prior to detection of valvular damage by echocardiography in multiple patients, which emphasizes the benefit of ^{18}F-FDG PET/CT to identify

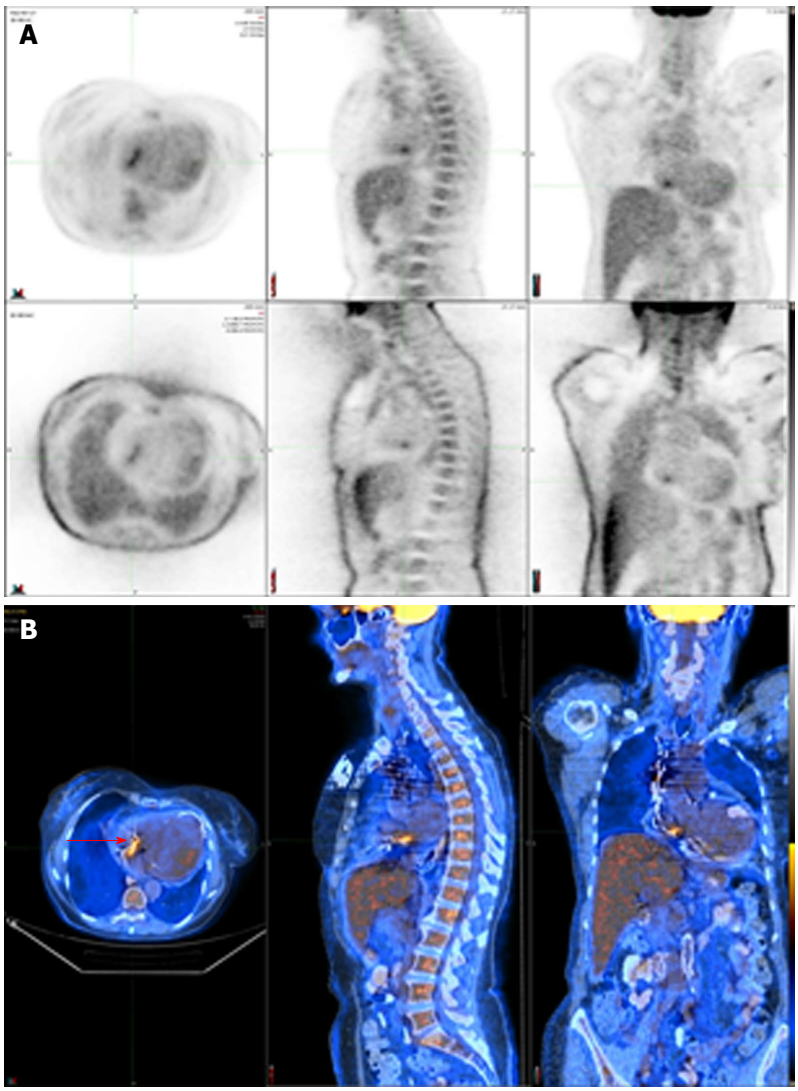

Figure 4 Positive ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography in a patient with a lead infection (red arrow). A: SPECT displayed as transverse, sagittal, and coronal attenuation corrected (top row) and uncorrected images (bottom row); B: Hybrid SPECT/CT displayed as transverse, sagittal, and coronal images. SPECT/CT: Single-photon emission computed tomography/computed tomography.

active infection before important damage has occurred.

Rouzet *et al*[32] evaluated the ability of ^{18}F-FDG PET/CT and radiolabelled WBC imaging to diagnose PVE in 39 patients with presumed PVE but inconclusive echocardiography findings. ^{18}F-FDG PET/CT had a higher sensitivity (93% *vs* 64%) but leukocyte scintigraphy had a higher specificity (100% *vs* 71%). Since it has a higher specificity for the detection of IE, it could be used in cases of equivocal ^{18}F-FDG PET/CT or within the initial two months after heart valve surgery[32].

^{18}F-FDG PET/CT can reduce the rate of misdiagnosed IE and help in the detection of peripheral events, including silent vascular phenomenon. ^{18}F-FDG PET/CT can identify lesions of clinical importance not detected by conventional work-up in one out of seven IE patients[33]. It also improves the sensitivity of the modified Duke criteria in the most difficult situations. When endocarditis on a prosthetic valve is suspected, abnormal uptake around the site of insertion identified by ^{18}F-FDG PET/CT (but more than 3 mo after prosthesis implantation) or radiolabelled WBC SPECT/CT could be considered a major diagnostic criterion. Results of ^{18}F-FDG PET/CT should always be examined together with the other conventional diagnostic tools (clinical, microbiological and echocardiographic data). In addition, ^{18}F-FDG PET/CT can be considered to monitor response to antibiotic therapy.

Studies using WBC SPECT/CT

Erba *et al*[34] assessed in another study the value of ^{99m}Tc-HMPAO leukocyte scintigraphy in 131 patients with suspected endocarditis. In these patients, 51 had a confirmed diagnosis of IE and 35 had PVE (69%). Scintigraphy had a sensitivity of 90% and a specificity of 100%. No false-positive cases were seen, including patients evaluated for IE during the first two months after their surgery. However, false-negative studies were seen with Candida and Enterococcus endocarditis. It also identified cases of septic embolism. The test could be useful in patients with a high suspicion of IE but inconclusive TEE, in differentiating between infective and sterile vegetations identified with echocardiography, when other tests are contradictory, and to exclude valve involvement in patients with sepsis and prosthetic valve. In another study, Hyafil *et al*[35] looked at the role of radiolabelled leukocyte imaging in patients with

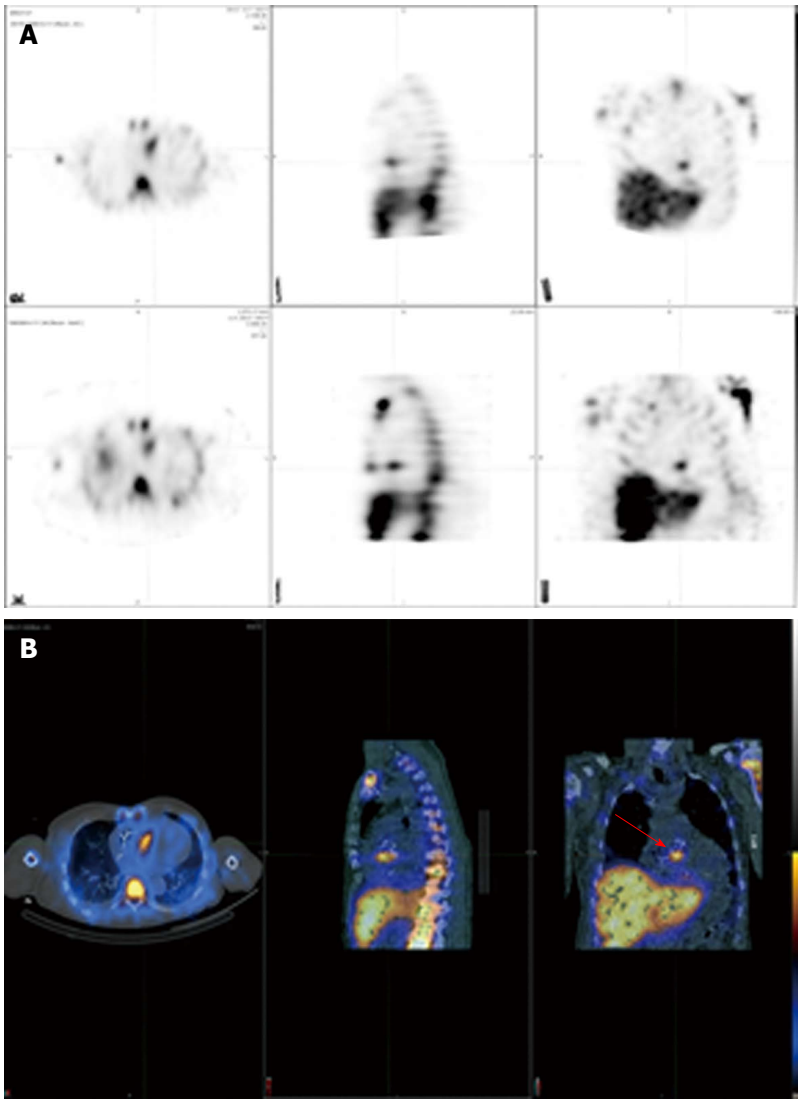

Figure 5 Positive ^{111}In white blood cell single-photon emission computed tomography/computed tomography in a patient with endocarditis following an aortic valve replacement (red arrow). A: SPECT displayed as transverse, sagittal, and coronal attenuation corrected (top row) and uncorrected images (bottom row); B: Hybrid SPECT/CT displayed as transverse, sagittal, and coronal images. SPECT/CT: Single-photon emission computed tomography/computed tomography.

presumed PVE and unconvincing echocardiography. They showed an excellent positive predictive value of intense signal with WBC scintigraphy for the presence of an abscess. Also, a negative scan predicted the absence of recurrent endocarditis in medically treated patients. Downsides of radiolabelled leukocyte scintigraphy are the necessity of blood handling, a longer procedure time, and a somewhat lower spatial resolution in contrast to ^{18}F-FDG PET/CT.

Figure 5 shows a positive ^{111}In WBC SPECT/CT in a patient with endocarditis following an aortic valve replacement.

Table 2 shows the sensitivity and specificity of both ^{18}F-FDG PET/CT and WBC SPECT/CT in the diagnosis of CIED infection and PVE.

LIMITATIONS

Despite its benefits, ^{18}F-FDG PET/CT can have false-positive and false-negative results. Postoperative inflammatory changes can lead to non-specific ^{18}F-FDG uptakes during the first several weeks after surgery, mainly following cardiac surgery or device implantation. Abnormal ^{18}F-FDG uptake could also be caused by BioGlue surgical adhesive, a combination of bovine serum albumin and glutaraldehyde, used to seal the aortic root graft at time of surgery[36]. In addition, possible uptakes can be found in active thrombi, cardiac tumours or metastasis, post-surgical inflammation, and foreign body reactions like vascular grafts. At the other end of the spectrum, ^{18}F-FDG PET/CT might be negative in patients with lower inflammation or when the test is performed after a long period of antibiotic therapy. The validity of ^{18}F-FDG PET/CT in the context of slowly evolving infections is still unknown. Because of the high glucose metabolism in the brain, ^{18}F-FDG PET/CT might not be the best test in order to detect infectious embolisms to the brain. However, an advantage of ^{18}F-FDG PET/CT is the possibility to identify non-infectious causes of fever or underlying neoplasm. As opposed to echocardiography, cardiac nuclear imaging does not evaluate hemodynamic conditions associated with IE, such as valvular regurgitation, cardiac output, pulmonary arterial pressure and ventricular function. Another important issue remains that ^{18}F-FDG PET/CT is less accessible than WBC SPECT/CT. The study quality

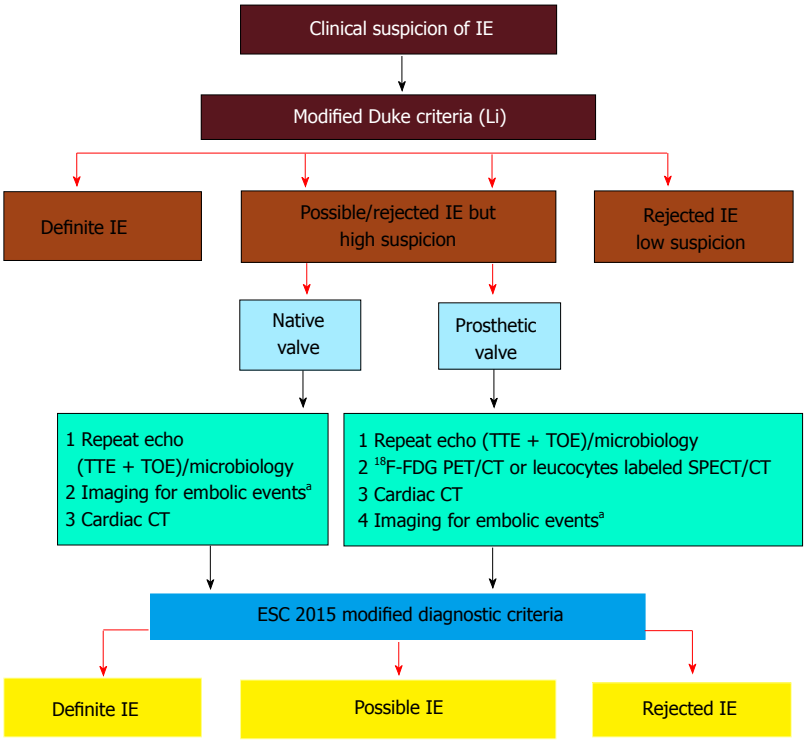

Figure 6 European Society of Cardiology 2015 algorithm for diagnosis of infective endocarditis. Reprinted from Habib G, Lancelloti P, Antunes MJ, Bongiorni MG, Casalta JP, Del Zotti F, Dulgheru R, El Khoury G, Erba PA, Iung B, Miro JM, Mulder BJ, Plonska-Gosciniak E, Price S, Roos-Hesselink J, Snygg-Martin U, Thuny F, Tornos Mas P, Vilacosta I, Zamorano JL; Document Reviewers, Erol Ç, Nihoyannopoulos P, Aboyans V, Agewall S, Athanassopoulos G, Aytekin S, Benzer W, Bueno H, Broekhuizen L, Carerj S, Cosyns B, De Backer J, De Bonis M, Dimopoulos K, Donal E, Drexel H, Flachskampf FA, Hall R, Halvorsen S, Hoen B, Kirchhof P, Lainscak M, Leite-Moreira AF, Lip GY, Mestres CA, Piepoli MF, Punjabi PP, Rapezzi C, Rosenhek R, Siebens K, Tamargo J, Walker DM. 2015 ESC Guidelines for the management of infective endocarditis: The Task Force for the Management of Infective Endocarditis of the European Society of Cardiology (ESC). Endorsed by: European Association for Cardio-Thoracic Surgery, the European Association of Nuclear Medicine. *Eur Heart J* 2015; 36: 3075-3128. Reprinted by permission of Oxford University Press (UK)© European Society of Cardiology, www.escardio.org/". This image/content is not covered by the terms of the Creative Commons license of this publication. For permission to reuse, please contact the rights holder). [a]May include cerebral MRI, whole body CT, and/or PET/CT; CT: Computed tomography; FDG: Fluorodeoxyglucose IE: Infective endocarditis; PET: Positron emission tomography; SPECT: Single-photon emission computed tomography; TTE: Transthoracic echocardiography; ^{18}F-FDG PET/CT: ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography.

could be improved by using respiratory and ECG gated techniques. This could minimize imaging artefacts, although it is technically more challenging and time-consuming. Cardiac nuclear imaging is a source of radiation. Administration of approximately 200 MBq of ^{18}F-FDG for a PET study represents an effective dose between 3 and 4 mSv, which is similar to a low-dose CT. Then the total dose for a PET/CT would be approximately 7.5 mSv[37]. A follow-up study to monitor response to antibiotic therapy would increase radiation exposure. However, an initial PET scan combined to a low-dose CT and followed by a subsequent study would be equivalent to a percutaneous coronary intervention or an atrial fibrillation ablation procedure (approximately 15 mSv)[38].

GUIDELINES

The ESC guidelines for the management of infectious endocarditis were updated in 2015[1]. The Task Force added ^{18}F-FDG PET/CT or radiolabelled WBC SPECT/CT as a new major criterion if abnormal FDG uptakes are found around the area of prosthetic valve implantation in patients with a prosthesis implanted for more than 3 mo[1]. Nuclear imaging has also been incorporated in the new algorithm for the diagnosis of IE when the diagnosis is still possible or has been dismissed but when a high index of suspicion is still present (Figure 6). However, despite data for the key role of ^{18}F-FDG PET/CT in the diagnosis of CIED infection, actual studies were judged insufficient to incorporate the results of ^{18}F-FDG PET/CT at this time as a diagnostic criterion for device infection. For the moment, ^{18}F-FDG PET/CT or radiolabelled leukocyte scintigraphy have a class IIb level of evidence C indication as an additional tool in patients with suspected CIED infection, positive blood cultures and negative echocardiography[1]. Also, the AHA scientific statement on IE judged that more clinical trials are still required to better clarify the utility of ^{18}F-FDG PET/CT for the diagnosis and management of endocarditis[9]. Since most studies on cardiac radionuclide imaging have been published in the past 5 years, the use of ^{18}F-FDG PET/CT in device infection was not discussed in the 2010 AHA scientific statement on CIED infections and their management[21].

Based on the recent ESC guidelines and previous studies, cardiac nuclear imaging could be considered in the following circumstances (Table 3): (1) accepted

Table 2 Sensibility and specificity of ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography and white blood cell single-photon emission computed tomography/computed tomography for both prosthetic valve endocarditis and cardiac device infection

	Test	Sensibility (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)	Accuracy (%)
Prosthetic valve endocarditis						
Saby *et al*[31]	PET/CT	73	80	85	67	76
Rouzet *et al*[32]	PET/CT	93	71	68	94	80
	WBC	64	100	100	81	86
Erba *et al*[34]	WBC	90	100	100	94	N/A
Cardiovascular implantable electronic device infection						
Bensimhon *et al*[24]	PET/CT	80	100	100	84.6	N/A
	Pocket	100	100	100	100	N/A
	Lead	60	100	100	73	N/A
Ploux *et al*[25]	PET/CT	100	93	N/A	N/A	N/A
Sarrazin *et al*[26]	PET/CT	88.6	85.7	N/A	N/A	N/A
Cautela *et al*[27]	PET/CT					
	Pocket	86.7	100	N/A	N/A	N/A
	Lead	30.8	62.5	N/A	N/A	N/A
Ahmed *et al*[28]	PET/CT					
	Pocket	97	98	N/A	N/A	N/A
Erba *et al*[29]	WBC	93.7	100	100	93.9	96.8

N/A: Not available; PET/CT: Positron emission tomography/computed tomography; WBC: White blood cell.

indication[1]: Possible or rejected IE diagnosis based on the modified Duke criteria, but persistent high clinical suspicion of infection in patients with a prosthetic valve; and (2) potential indications: Unclear diagnosis of CIED infection; Evaluation of the extent of infection when the results would affect the management of the patient, for example differentiation between superficial and deep pocket infection where device and lead extraction is recommended; Bacteremia with organisms not commonly a source of IE or fever of unknown origin in patients with CIED; High clinical suspicion of IE but negative TEE and/or negative blood cultures; Search for embolic events when it would affect the management of the patient; Monitoring the success of antibiotic therapy in medically treated patients.

FUTURE STUDIES

So far, available data on the diagnosis of CIED infection and PVE with either ^{18}F-FDG PET/CT or WBC SPECT/CT come from small studies and limited number of patients. Larger studies would be useful to confirm the preliminary data suggesting the additional benefit of cardiac nuclear imaging. Despite encouraging results, some questions need to be answered. Is the use of ^{18}F-FDG PET/CT cost-effective? Also, what is the consequence of prolonged antibiotic therapy prior to ^{18}F-FDG PET/CT? There is also a need for standardization of the imaging techniques available since the imaging and data acquisition protocols are sometimes different from one center to another. There is still a need for further prospective studies in this field of research before ^{18}F-FDG PET/CT should be systematically performed for the diagnosis of IE or used as a first line investigation. At the moment, it should be restricted to difficult cases of suspected CIED infection or PVE.

Table 3 Indications for the use of cardiac nuclear imaging in the context of cardiovascular implantable electronic device infection and prosthetic valve endocarditis

Accepted indication
Possible or rejected IE, but high suspicion of infection in patients with prosthetic valve
Potential indications
Unclear diagnosis of CIED infection
Evaluation of the extent of infection
Bacteremia or fever of unknown origin in patients with CIED
Cases with high clinical suspicion of IE but negative TEE and/or negative blood cultures
Search for embolic events
Monitoring the success of antibiotic therapy

CIED: Cardiovascular implantable electronic device; IE: Infective endocarditis; TEE: Transesophageal echocardiography.

CONCLUSION

^{18}F-FDG PET/CT appears to be a very promising imaging technique for the diagnosis of device infection and prosthetic valve endocarditis. Based on recent publications, there is growing evidence that cardiac nuclear imaging can play a key role in the diagnosis and management of patients with suspected CIED infections and PVE. This is now reflected in the most recent published guidelines. Although echocardiography remains an important initial test in the evaluation of these patients, ^{18}F-FDG PET/CT and WBC SPECT/CT have clearly demonstrated their usefulness, mainly in difficult cases. Larger prospective studies will help to confirm the benefits of ^{18}F-FDG PET/CT and clarify its role in the different algorithms of device and valve infections.

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ORIGINAL ARTICLE

Retrospective Study

Depression risk in patients with coronary heart disease in Germany

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Abstract

AIM

To determine the prevalence of depression and its risk factors among patients with coronary heart disease (CHD) treated in German primary care practices.

METHODS

Longitudinal data from nationwide general practices in Germany (n = 1072) were analyzed. Individuals initially diagnosed with CHD (2009-2013) were identified, and 59992 patients were included and matched (1:1) to 59992 controls. The primary outcome measure was an initial diagnosis of depression within five years after the index date among patients with and without CHD. Cox proportional hazards models were used to adjust for confounders.

RESULTS

Mean age was equal to 68.0 years (SD = 11.3). A total of 55.9% of patients were men. After a five-year follow-up, 21.8% of the CHD group and 14.2% of the control group were diagnosed with depression (P < 0.001). In the multivariate regression model, CHD was a strong risk factor for developing depression (HR =

1.54, 95%CI: 1.49-1.59, $P < 0.001$). Prior depressive episodes, dementia, and eight other chronic conditions were associated with a higher risk of developing depression. Interestingly, older patients and women were also more likely to be diagnosed with depression compared with younger patients and men, respectively.

CONCLUSION

The risk of depression is significantly increased among patients with CHD compared with patients without CHD treated in primary care practices in Germany. CHD patients should be routinely screened for depression to ensure improved treatment and management.

Key words: Coronary heart disease; Depression; Primary care; Risk factors; Quality of life

Core tip: This is a retrospective study to determine the prevalence of depression and its risk factors among patients with coronary heart disease (CHD) treated in German primary care practices. Fifty-nine thousand nine hundred and ninety-two patients with CHD from German primary care practices were included and matched to 59992 controls. After a five-year follow-up, 21.8% of the CHD group and 14.2% of the control group were diagnosed with depression. In the multivariate regression model, CHD was a strong risk factor for developing depression.

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INTRODUCTION

Coronary heart disease (CHD), as one of the cardiovascular diseases (CVDs), is a leading chronic medical condition worldwide, with a large number of affected patients[1,2]. CHD is characterized by the manifestation of atherosclerosis in coronary arteries, that is, narrowed coronary arteries and reduced perfusion of the heart. This can lead to a myocardial infarction[3,4]. CVD and CHD are major causes of death around the world[1], particularly in Germany, where CVD was responsible for 338056 deaths in 2014 (38.9% of the total number of deaths)[5]. In this context, the CHD-related mortality rate was approximately 20%, with a total of 69890 deaths in 2014[6].

Approximately 6 million people are affected by CHD in Germany[7]. Due to improvements in various therapies, mortality rates have decreased worldwide. Nevertheless, the prevalence of CHD is increasing, partly due to the demographic aging of the population, increased prevalence of cardiovascular risk factors, and patients' improved survival after a cardiovascular event[2]. While the lifetime prevalence of CHD among German women remained unchanged at approximately 7% between 2003 and 2012, it increased from 8% in 2003 to 10% in 2010 among German men[8].

It is known that the risk of depression is significantly increased among individuals with chronic diseases (*e.g.,* CHD), as they exhibit 2-3 times higher rates than the general population[9,10]. Depression significantly worsens the health state of patients with chronic diseases[11]. Overall, depression adversely affects the course, complications, and management of CHD[10,12]. Furthermore, depression in patients with CHD contributes to poor functional and cardiovascular outcomes, poor quality of life, and increased mortality[13-16].

Depression is frequently observed in patients with CHD[14]. Previous studies showed that up to 30% of patients with CHD suffer from depression[17]. Most published studies examined hospital patients or were based on a small number of patients[18]. Thus, little is known about the prevalence of depression among outpatients with CHD[14]. Because no relevant German data exist, the goal of this study was to estimate the prevalence and the risk factors of depression among CHD patients treated in primary care practices in Germany.

MATERIALS AND METHODS

Database

The Disease Analyzer database (IMS HEALTH) compiles drug prescriptions, diagnoses, and basic medical and demographic data obtained directly and in anonymous format from computer systems used by general practitioners[19]. IMS has monitored diagnoses (ICD-10), prescriptions (Anatomical Therapeutic Chemical (ATC) Classification System), and the quality of reported data according to a number of criteria (*e.g.,* completeness of documentation, linkage between diagnoses and prescriptions). In Germany, the sampling methods used to select physicians' practices were appropriate for obtaining a representative database of primary care practices[19]. The statistics regarding prescriptions for several drugs were very similar to data available in pharmaceutical prescription reports[19]. The age groups suffering from given diagnoses in the Disease Analyzer were also consistent with those in corresponding disease registries[19].

Study population

This study included patients between 40 and 90 years of age who were being treated in 1072 primary care practices and who received an initial CHD diagnosis (ICD 10: I25) during the index period (January 2009 to December 2013). Follow-up lasted a maximum of five years and ended in October 2015. Patients were excluded if they were diagnosed with depression

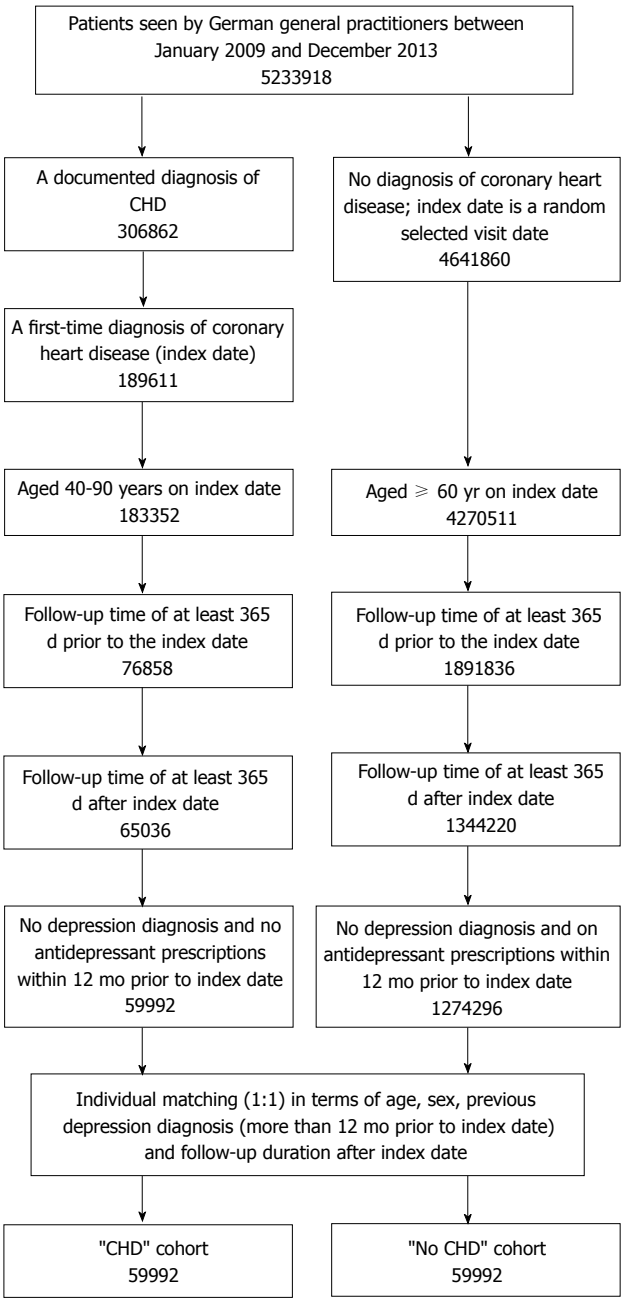

Figure 1 Selection of study patients. CHD: Coronary heart disease.

(ICD-10: F32, F33) or received any antidepressant prescription (ATC: N06A) within 12 mo prior to CHD diagnosis (index date). A total of 59992 CHD patients remained after these exclusion criteria were applied. Finally, 59992 controls without CHD, depression diagnosis or antidepressant prescriptions within 12 mo prior to index date (any randomly selected visit date) were chosen and matched (1:1) to CHD cases based on age, sex, past depression diagnosis (more than 12 mo prior to index date), and follow-up duration after the index date (Figure 1).

Study outcome

The primary outcome was the diagnosis of depression recorded in the database between the index date and the end of follow-up. Depression diagnoses were based on primary care documentation.

Table 1 Characteristics of coronary heart disease patients and matched controls treated in primary care practices in Germany

Variables	CHD group	Control group	*P* value
n	59992	59992	
Age (yr)	68.0 (11.3)	68.0 (11.3)	1
Aged ⩽ 60 (%)	26.7	26.7	1
Aged 61-70 (%)	26.5	26.5	1
Aged 71-80 (%)	32.6	32.6	1
Aged > 80 (%)	14.3	14.3	1
Males (%)	55.9	55.9	1
Follow-up time (yr)	3.6 (1.5)	3.6 (1.5)	1
Past depression diagnosis (> 12 mo prior to index date)	11.1	11.1	1
Co-diagnosis (%)			
Diabetes	35.9	23.4	< 0.001
Hypertension	78.7	59.4	< 0.001
Myocardial infarction	11.8	0.6	< 0.001
Cardiac arrhythmias	25.7	14.3	< 0.001
Heart failure	18.4	7.4	< 0.001
Stroke	9.2	5.6	< 0.001
Cancer	11.9	11.1	< 0.001
Dementia	4.9	4.5	< 0.001
Osteoarthritis	31.4	27.6	< 0.001
Osteoporosis	10.3	8.4	< 0.001

CHD: Coronary heart disease.

Independent variables

Demographic data included age and gender. Other chronic conditions that could be associated with depression risk were determined based on primary care diagnoses and included as confounders: Diabetes mellitus (E10-14), hypertension (I10), dementia (F01, F03, G30), stroke (F63, F64, G45), heart failure (I10), myocardial infarction (I21-23), cardiac arrhythmias (I46-I49), osteoporosis (M80, M81), cancer (C00-C98), and osteoarthritis (M15-19).

Statistical analysis

Descriptive statistics were obtained, and differences in patients' characteristics (CHD *vs* controls) were assessed using Wilcoxon tests for paired samples or McNemar's tests. Analyses of depression-free survival were carried out using Kaplan-Meier curves and log-rank tests. Cox proportional hazards models (dependent variable: Depression) were used to adjust for confounders. $P < 0.05$ was considered statistically significant. The analyses were carried out using SAS version 9.3.

RESULTS

Patient characteristics are displayed in Table 1. A total of 119984 patients were included in the CHD and control groups. Mean age was equal to 68.0 years (SD = 11.3 years), and 55.9% of the patients were men. The proportion of patients with a prior depression

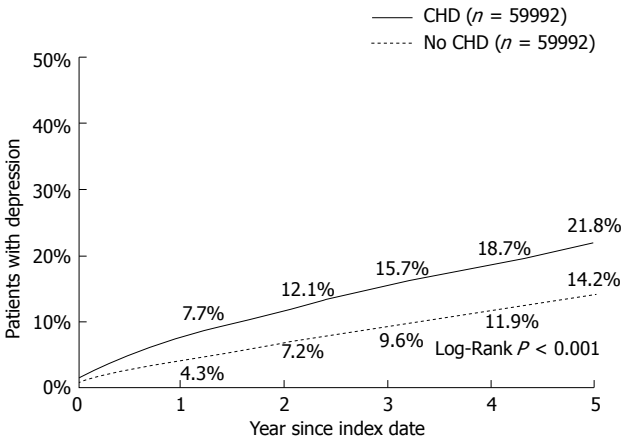

Figure 2 Kaplan-Meier curves for time to depression diagnosis in coronary heart disease patients and matched controls. CHD: Coronary heart disease.

diagnosis (> 12 mo prior to the index date) was 11.1% in both groups. All chronic conditions (*i.e.*, diabetes, hypertension, myocardial infarction, cardiac arrhythmias, heart failure, stroke, cancer, dementia, osteoarthritis and osteoporosis) occurred more frequently in the CHD group than in the control group (P < 0.001).

Kaplan-Meier curves for time to depression diagnosis in the CHD and control groups are displayed in Figure 2. Overall, 7.7% of CHD patients and 4.3% of matched controls had developed depression after one year of follow-up (P < 0.001). After a five-year follow-up period, 21.8% of the CHD group and 14.2% of the control group were diagnosed with depression (P < 0.001).

The results of the multivariate Cox regression model for depression diagnosis in CHD patients and matched controls are illustrated in Table 2. CHD was a strong risk factor for the development of depression (HR = 1.54, 95%CI: 1.49-1.59, P < 0.001). Prior depressive episodes also increased the risk of renewed depression diagnosis (HR = 3.44; 95%CI: 3.32-3.56, P < 0.001). Patients in the age group ⩽ 60 had a higher risk of depression compared with patients aged 61-70 years (HR = 1.50, 95%CI: 1.44-1.57, P < 0.001). Patients in the age groups 71-80 and > 80 years were also more likely to be diagnosed with depression than patients aged 61-70 years (HR = 1.08 (95%CI: 1.04-1.13) and 1.16 (95%CI: 1.10-1.23), respectively, both P < 0.001). Furthermore, other chronic co-diagnoses increased the risk of depression (P < 0.001). By contrast, men had a lower risk of being depressed than women (HR = 0.67; 95%CI: 0.65-0.69).

Table 2 Multivariate Cox regression model for depression diagnosis in coronary heart disease patients and matched controls chemotherapy

Variables	Hazard ratio (95%CI)	*P* value
CHD	1.54 (1.49-1.59)	< 0.001
Past depression diagnosis	3.44 (3.32-3.56)	< 0.001
Aged ⩽ 60 *vs* 61-70	1.50 (1.44-1.57)	< 0.001
Aged 71-80 *vs* 61-70	1.08 (1.04-1.13)	< 0.001
Aged > 80 *vs* 61-70	1.16 (1.10-1.23)	< 0.001
Male gender	0.67 (0.65-0.69)	< 0.001
Dementia	1.24 (1.17-1.31)	< 0.001
Stroke	1.22 (1.16-1.28)	< 0.001
Cancer	1.19 (1.14-1.24)	< 0.001
Osteoporosis	1.18 (1.13-1.24)	< 0.001
Heart failure	1.17 (1.12-1.22)	< 0.001
Osteoarthritis	1.15 (1.11-1.19)	< 0.001
Hypertension	1.10 (1.06-1.14)	< 0.001
Cardiac arrhythmias	1.08 (1.04-1.12)	< 0.001
Diabetes	1.06 (1.03-1.10)	< 0.001

CHD: Coronary heart disease.

DISCUSSION

In this retrospective study of 119984 patients treated in primary care practices in Germany, we showed that CHD was associated with an increased risk of developing depression. Moreover, prior depressive episodes and co-diagnoses such as dementia, stroke, cancer, osteoporosis, heart failure, osteoarthritis, hypertension, cardiac arrhythmias, and diabetes were also risk factors for this psychiatric disorder. Individuals aged 60 years or younger and individuals aged over 70 years were more likely to develop depression compared with patients aged 61-70 years. Finally, men were at a lower risk of being diagnosed with depression than women.

CHD is a chronic disease that has an important impact on patients' physical and psychological aspects of life. Indeed, patients affected by CHD are more likely to become depressed than those without CHD. Several studies estimated that depression affects between 17.2% and 30.6% of CHD patients[20-23] but only approximately 7% of the general population[17]. More recently, Ren *et al*[18] performed a meta-analysis on the prevalence of depression among CHD patients in hospital and community settings. In the 23 hospital-based studies (the total number of patients equalled 5236), the prevalence of depression ranged from 22.8% to 84.0%, with 0.5% to 25.44% categorized as severe forms[18]. In the four community-based studies (the total number of patients equalled 1353), depression prevalence ranged from 34.6% to 45.0%, with 3.1%-6.9% classified as major depressive disorders[18]. This meta-analysis clearly indicates that although hospital and community settings have a similar total number of patients, more hospital-based than community-based studies have been conducted and results differ between the two settings. Thus, because the findings of hospital-based studies cannot be extrapolated to the community population, new studies must be conducted outside the hospital setting. In line with previous data, we found that after five years of follow-up, 21.8% of CHD patients were depressed, whereas only 14.2% of controls exhibited this psychiatric condition. This important result underlines the fact that CHD increases the odds that patients treated in general

practices in Germany develop depression.

Interestingly, the relationship between depression and CHD is bidirectional; thus, depression is also a risk factor for CHD[17]. In 2010, Taylor *et al*[24] showed that CHD risk, which was similar at baseline to that of the general population, increased within the first two years following the diagnosis of major depressive disorders. The main hypothesis proposed to explain the bidirectional relationship between CHD and depression asserts that they share common risk factors. First, stress is known to increase the odds of developing these two diseases[24,25]. Indeed, stress has a major impact on the cardiovascular system and on psychological aspects of individuals' life and thus increases the occurrence of both disorders. Importantly, beyond the influence of stress, behavioral disorders can also lead to CHD and depression. In fact, such psychiatric preconditions are often associated with a loss of interest in daily tasks (*i.e.,* eating or engaging in physical activity)[17], which may indirectly lead to depression and disrupt the body's energetic balance. Finally, several authors suggested that CHD and depression share common genetic mechanisms that are involved in inflammation pathways and oxidative stress[17]. For example, the length of leukocyte telomeres is negatively associated with major depressive disorders and coronary artery disease[26,27].

In this study, we found that prior depressive episodes, dementia, stroke, cancer, osteoporosis, heart failure, osteoarthritis, hypertension, cardiac arrhythmias, and diabetes were additional risk factors for depression. Most of these diseases are chronic conditions that may reduce affected patients' quality of life. Of note, the strongest predictor was past depressive episodes (HR = 3.44; 95%CI: 3.32-3.56). In fact, depression is a highly recurrent disorder that is difficult for physicians to treat and manage[28]. Our data also showed that men were at a lower risk of developing this psychiatric disorder than women. In 2005, Perez *et al*[29] conducted a study of 345 patients with acute coronary syndrome and found that women were more likely to be diagnosed with depression than men (OR = 2.40, 95%CI: 1.44-4.00)[29]. Although several authors hypothesized that there are important gender differences in hormones, genes, and brain structures, our discovery may be explained by artefacts because women tend to be more emotional and are more inclined to seek medical help than men. Finally, we found that individuals aged 60 years or younger and those aged over 70 years have a higher risk of developing depression than patients aged 61-70 years. Although this finding is new and surprising, one hypothesis maintains that individuals aged 61-70 years receive optimal treatment and management. Because younger patients are less likely to develop chronic diseases, medical follow-up is difficult and they may be at higher risk of developing depression. However, very elderly patients are less compliant and may not follow the treatment prescribed by their general practitioner.

This study had several limitations. The database contained no valid information on biological markers associated with CHD. Furthermore, no detailed documentation concerning the diagnosis of depression, namely, the severity of depression, was available. Data on socioeconomic status and lifestyle-related risk factors were also unavailable. Each patient was observed retrospectively in only one practice. If a patient visited a different doctor - which is common in Germany - the visit was not documented.

In conclusion, this study showed that CHD patients were at a higher risk of developing depression than patients without CHD. Interestingly, prior depressive episodes, dementia, stroke, cancer, osteoporosis, heart failure, osteoarthritis, hypertension, cardiac arrhythmias, and diabetes were additional risk factors for this psychiatric condition. Finally, we found that individuals aged 60 years or younger and those aged over 70 years have a higher risk of developing depression than patients aged 61-70 years. Further investigations are needed to gain a better understanding of the association between depression and CHD in general practices in Germany.

COMMENTS

Background

Coronary heart disease (CHD) is a leading chronic medical condition worldwide, with a large number of affected patients. CHD is characterized by the manifestation of atherosclerosis in coronary arteries, that is, narrowed coronary arteries and reduced perfusion of the heart. This can lead to a myocardial infarction. CHD is one of the causes of death around the world. It is known that the risk of depression is significantly increased among individuals with chronic diseases. Overall, depression adversely affects the course, complications, and management of CHD.

Research frontiers

Thus, little is known about the prevalence of depression among outpatients with CHD. Because no relevant German data exist, the goal of this study was to estimate the prevalence and the risk factors of depression among CHD patients treated in primary care practices in Germany.

Innovations and breakthroughs

In this study, analyses were performed based on 119984 patients treated in primary care practices in Germany. At first, this is the first study using such large patient numbers; at second, the study cohort includes both high-risk patients and patients without CHD diagnosis.

Applications

This study showed that CHD patients were at a much higher risk of developing depression than patients without CHD, especially patients who additionally have further chronic co-diagnoses. Physicians who care for CHD patients should consider identification and treatment of depression a clinical practice.

Terminology

CHD: Coronary heart disease; ICD: International classification of disease.

Peer-review

The authors did a retrospective analysis on a German cohort of 119984 patients to examine the association between CHD and the development of depression. Strength of this study lies in the great sample size, and it is a community-based study. In this study, the author determines the prevalence of depression and its risk factors in patients with coronary heart disease. They found that CHD was a

strong risk factor for depression development in German population.

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ORIGINAL ARTICLE

Observational Study

Characterization of optimal resting tension in human pulmonary arteries

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Author contributions: Hussain A was the principal investigator and was responsible for the design and conduct of the study; Hussain A was responsible for the acquisition, analysis and interpretation of the data and initial draft of the manuscript; Bennett RT, Chaudhry MA, Qadri SS, Cowen M, Morice AH and Loubani M supervised the study and critically reviewed the article.

Institutional review board statement: The study was reviewed and approved by the Local Research Ethics Committee and local research and development department.

Informed consent statement: All patients were consulted and consented for resected lung tissue to be studied for our research prior to their operation at the time of their consent for surgery.

Conflict-of-interest statement: There are no conflicts of interest to report.

Data sharing statement: No additional data are available.

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Abstract

AIM

To determine the optimum resting tension (ORT) for in vitro human pulmonary artery (PA) ring preparations.

METHODS

Pulmonary arteries were dissected from disease free sections of the resected lung in the operating theatre and tissue samples were directly sent to the laboratory in Krebs-Henseleit solution (Krebs). The pulmonary arteries were then cut into 2 mm long rings. PA rings were mounted in 25 mL organ baths or 8 mL myograph chambers containing Krebs compound (37 ℃, bubbled with 21% O_2: 5% CO_2) to measure changes in isometric tension. The resting tension was set at 1-gram force (gf) with vessels being left static to equilibrate for duration of one hour. Baseline contractile reactions to 40 mmol/L KCl were obtained from a resting tension of 1 gf. Contractile reactions to 40 mmol/L KCl were then obtained from stepwise increases in resting tension (1.2, 1.4, 1.6, 1.8 and 2.0 gf).

RESULTS

Twenty PA rings of internal diameter between 2-4 mm

were prepared from 4 patients. In human PA rings incrementing the tension during rest stance by 0.6 gf, up to 1.6 gf significantly augmented the 40 mmol/L KCl stimulated tension. Further enhancement of active tension by 0.4 gf, up to 2.0 gf mitigate the 40 mmol/L KCl stimulated reaction. Both Myograph and the organ bath demonstrated identical conclusions, supporting that the radial optimal resting tension for human PA ring was 1.61 g.

CONCLUSION

The radial optimal resting tension in our experiment is 1.61 gf (15.78 mN) for human PA rings.

Key words: Pulmonary hypertension; Pulmonary artery; Optimal resting tension; Pulmonary artery rings; Human

Core tip: Pulmonary artery (PA) vasoconstriction is an important physiological process to regulate blood flow in the lungs but it also manifests in pathological conditions. Different models have been implemented to assess the baseline molecular and cellular functions of pulmonary ailments. However, a great deal of the research was undertaken on animals with little similarity to human tissue. Isolation of human PA and measurement of pulmonary vascular tension are vital to understand the pathophysiology of human pulmonary vessels. The objective behind this research is to assess the underlying resting tension for undertaking studies of the PA rings in humans.

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INTRODUCTION

The vascular wall is constituted by three sections or layers; the tunica intima, tunica media, and tunica externa, also otherwise known as the internal, middle and outer layer, respectively[1]. Endothelial cells are located in the intima and play an important role in regulating vascular operations through reacting to neurotransmitters, hormones and vasoactive elements[2]. The endothelium and smooth muscle are the vital components for maintenance of arterial tone and blood pressure directive. The arteries main purpose is to deliver the blood to the organs with high pulse pressure. Arteries are generally classified into conducting arteries, conduit arteries (macrovasculature) and resistance arteries (microvasculature) sourced on size, anatomical position and functionality[3]. Conducting arteries are the largest in size and rich in elastic tissues which support the vessels to expand and recoil to accommodate high changes in blood pressure. The aorta, pulmonary artery (PA) and carotid arteries are the main examples of conducting arteries[4]. Conduit arteries, *e.g.*, femoral, radial and brachial arteries are the subdivisions of conducting arteries, and their role is regulating the flow of blood to particular organs and sections of the body[5]. Conduit arteries advance more through separating into resistance arteries that mainly consist of smooth muscles and are highly innervated by sympathetic nerves. Resistance vessels regulate the blood flow to tissues through constricting or dilating as reaction to sympathetic simulation or dissimulation[6].

Hypoxic pulmonary vasoconstriction (HPV) is a fundamental physiological mechanism to redirect the blood from poorly to better-aerated areas of lungs to optimize the ventilation perfusion matching[7]. Persistent hypoxia leads to increased pulmonary vascular opposition and right ventricular afterload that leads to hypoxic pulmonary hypertension[8]. HPV initially thought to be caused by alveolar hypoxia by means of local lung mechanism but recent advances suggest that PA smooth muscle cells constitute both the sensor and the transducer of the hypoxic signal as well as its contractile effector[9]. A series of experiments performed to explain the phenomenon on macroscopic and microscopic level has been reported although the underlying mechanism is not clear[10-12]. However, vast majority of experiments performed in animals with little data available from humans. Experiments performed on animals are generally inapplicable on humans so we need to adapt new methodologies for use in human to understand the human disease biology.

The objective of this research is assessing the tension in human PA to facilitate future experiments and also to provide a methodology of isolation of PA and their use in studies in the form of arterial rings.

MATERIALS AND METHODS

All patients undergoing a lung lobectomy by a Consultant Cardiothoracic Surgeon at Castle Hill Hospital were consented for resected lung tissue to be included in this study prior to their operation at the time of their consent for surgery. Patients under the age of 18 and who cannot give informed consent were excluded from the study. Local research ethics committee and local research and development department approval was obtained for the use of human tissue for this study.

Isolation of PA rings

Tissue samples were collected from patients undergoing surgical lung resection for cancer and immediately moved to the laboratory in Krebs-Henseleit solution (consisting of 113.8 mmol/L NaCl, 4.7 mmol/L KCl, 1.2 mmol/L $MgSO_4$, 25 mmol/L $NaHCO_3$, 1.2 mmol/L KH_2PO_4, 11.4 mmol/L glucose, and 2.4 mmol/L $CaCl_2$ dissolved in distilled water). Pulmonary arteries were

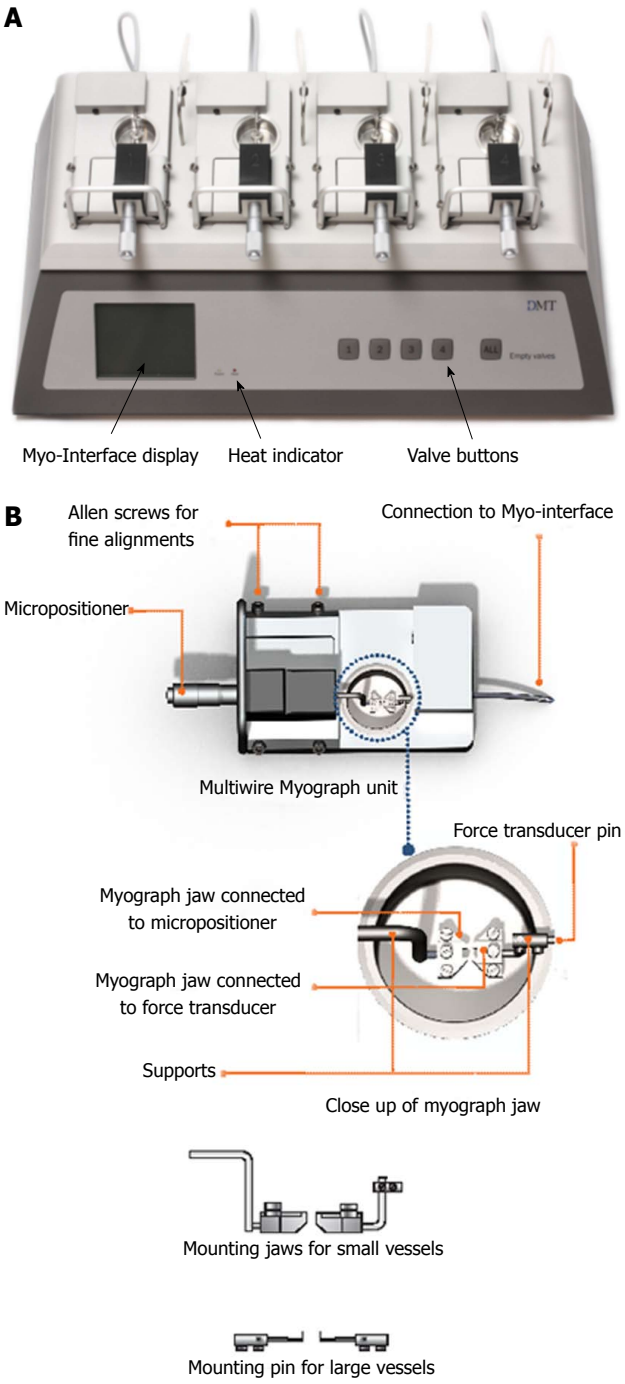

Figure 1 Multiwire Myograph System (DMT 620 M) (A) and Multiwire Myograph Unit (B).

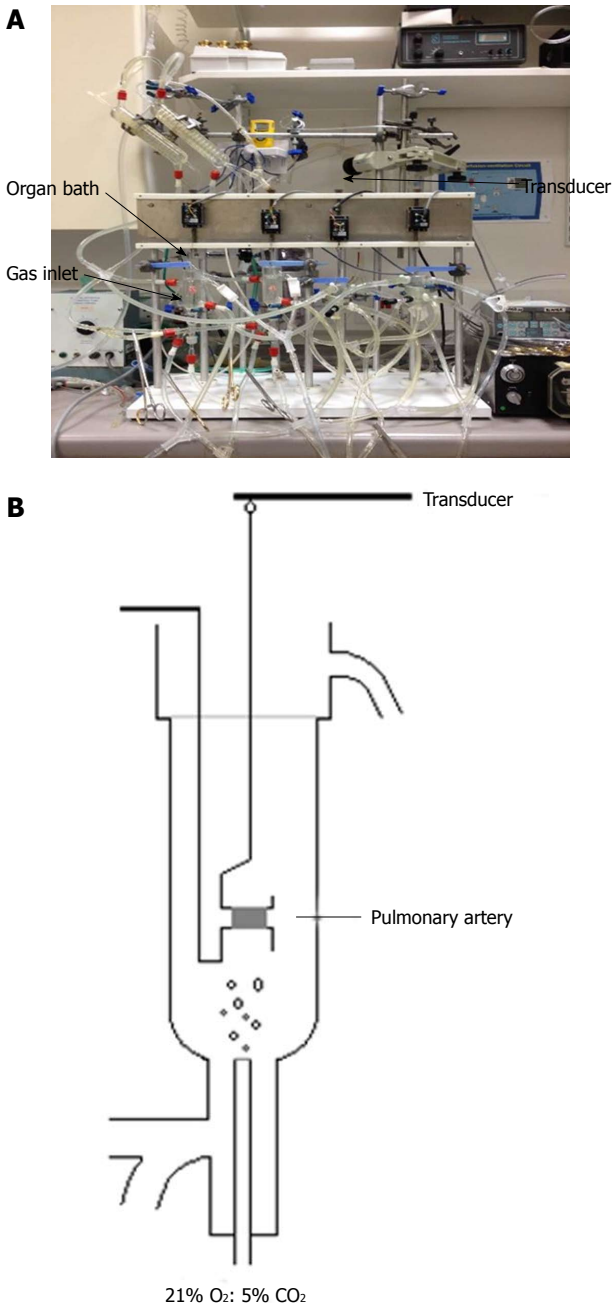

Figure 2 Radnotti (A) and Schematic (B) Organ Bath system.

dissected from disease free areas of lung resection and after careful removal of adipose and connective tissues cut into 2 mm long rings. The Internal diameter of vessels ranged between 2-4 mm.

Mounting of PA rings

A multiwire myograph system (DMT 620M) and an organ bath system (Radnotti) were used for mounting of PA rings and measurement of ORT. The Multi wire myograph system consists of 4 individual myograph units. Each unit is created with aluminum and has a centralized placement of 8 mL stainless steel chamber (Figure 1A). Pins to support the tissue were placed within the chamber, one end being connected to a force transducer whilst the other connected with a micrometer. PA rings were mounted between the pins. All units were subject to administered gas inflow and suction. Connections for vacuum and gassing, as well as heating are provided in the myograph interface, allowing for all chambers to be smoothly maintained under physiological settings (37 ℃, and bubbled with 21% O_2: 5% CO_2) (Figure 1B). The myograph system was connected to a PC *via* an amplifier (Power Lab 8/35, AD Instruments) for continuous measurement of isometric tension using data acquisition software (Lab

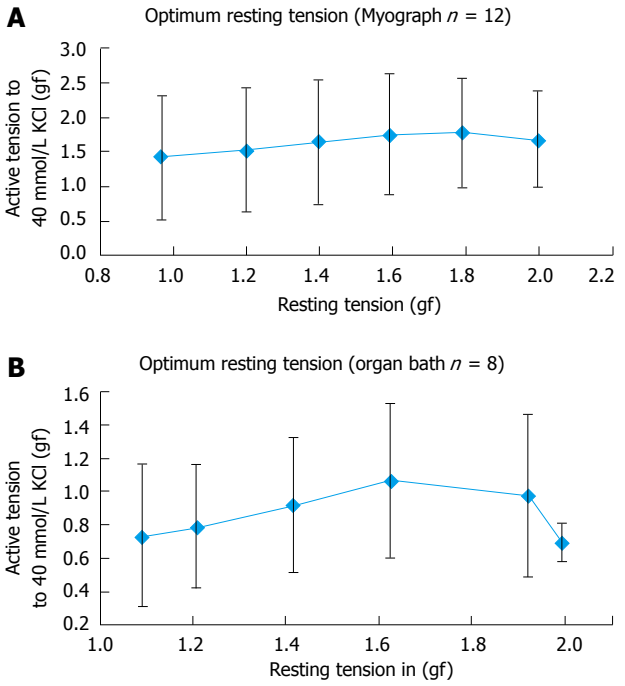

Figure 3 Measurement of Optimal Resting Tension using Multi-wire Myograph (A) and Organ Bath system (B). A: Total 12 PA rings from four patients were used to perform the experiment. Increasing the resting tension from 1.0 gf to 1.6 gf significantly augmented the 40 mmol/L KCl induced active tension. Increasing the active tension from 1.6 to 2.0 gf initially plateaued off than decreased the 40 mmol/L KCl induced response; B: Total 8 PA rings from four patients were used to perform the experiment. Increasing the resting tension from 1.0 to 1.6 gf significantly augmented the 40 mmol/L KCl induced active tension. Increasing the active tension from 1.6 to 2.0 gf either decreased the 40 mmol/L KCl induced response.

Chart Pro Version 8.0).

The organ bath system consists of 4 organ baths connected to a gas inlet where gas mixtures can be bubbled through (Figure 2A). Surrounding each bath is a heat exchanger that recreated the physiological temperatures of the human body. Each organ bath contained Krebs's solution and the PA rings were mounted between two hooks. One hook was fixed and the other connected with a force transducer (Harvard UF1), which was linked to a PC for continuous measurement of isometric tension (Figure 2B).

Determination of optimal resting tension

After mounting of PA rings the resting tension was set at 1 gf and the vessels left to equilibrate under 21% O_2: 5% CO_2 at 37 ℃ for 60 min. When a stable resting tension was achieved the vessels were contracted to 40 mmol/L KCl by direct addition to the organ bath. The maximum contraction to KCl was recorded when the contractile response reached a plateau. Active tension was calculated as maximum tension at plateau (gf) - resting tension (gf). Vessels were then washed for 30 min by rapidly replacing the Krebs solution in the chambers with fresh solution three times every five minutes. When a stable resting tension was achieved a repeat reaction with 40 mmol/L KCl was obtained and the vessels again washed before obtaining a third

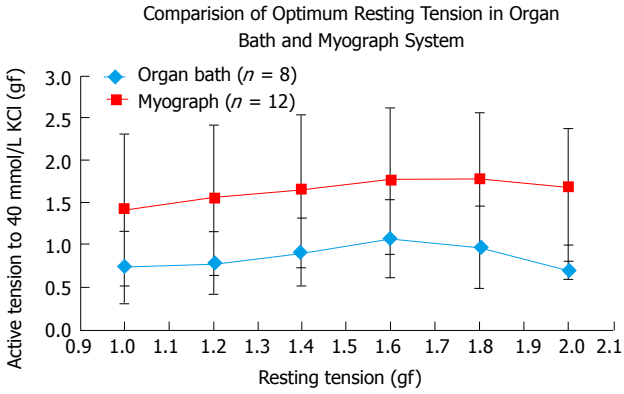

Figure 4 Comparison of Optimal Resting Tension measurement in Organ Bath and Myograph system. Total 20 PA rings from four patients were used to perform the experiment. Increasing the resting tension from 1.0 to 1.6 gf significantly augmented the 40 mmol/L KCl induced active tension. Increasing the active tension from 1.6 to 2.0 gf either decreased or plateaued off the 40 mmol/L KCl induced response. Both organ bath and myograph shows similar result and confirmed that radial optimal resting tension for human pulmonary artery ring was 1.61 g.

reaction to 40 mmol/L KCl for the purpose of confirming reproducibility in the response. When a reproducible response was obtained the maximum contraction to 40 mmol/L KCl had been established from increasing resting tensions of 1.2, 1.4, 1.6, 1.8 and 2.0 gf with the vessels being washed for 30 min between responses.

At the end of each experiment the integrity of endothelium was confirmed by the addition of 1 umol/L acetylcholine. Rings that did not contract to KCl were excluded from the study.

Chemicals and reagents

Five percent of carbon dioxide/balance air (10 lt cylinders) was sourced from BOC Limited. All reagents were obtained from Fischer Scientific and acetylcholine from Sigma Aldrich.

Statistical analysis

Data are presented as mean ± SD and n represents the number of PA rings used.

RESULTS

Twenty PA rings (internal diameter 2-4 mm) were obtained from 4 patients. Results showed that in human PA rings increasing the basal tension from 1.0 to 1.6 gf significantly augmented the 40 mmol/L KCl induced active tension. Increasing the active tension from 1.6 to 2.0 g mitigate the 40 mmol/L KCl induced response (Figure 3). The myograph and organ bath demonstrated identical conclusions (Figure 4), confirming that the most efficient resting tension for human PA rings is 1.61 gf (Figure 5).

DISCUSSION

The pulmonary circulation carries deoxygenated blood from right section of heart towards lungs, under which

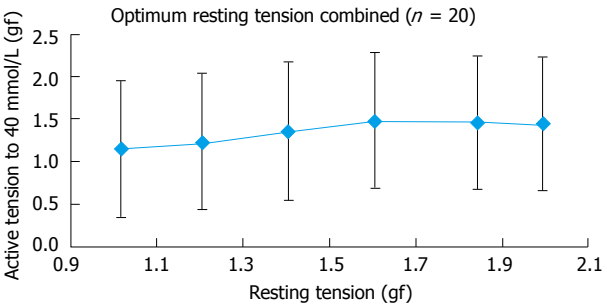

Figure 5 Combined result of optimal resting tension measurement. Total 20 PA rings from four patients were used to perform the experiment. Increasing the active tension from 1.6 to 2.0 gf decreased the 40 mmol/L KCl induced response. The radial optimal resting tension for human pulmonary artery ring measured was 1.61 g. PA: Pulmonary artery.

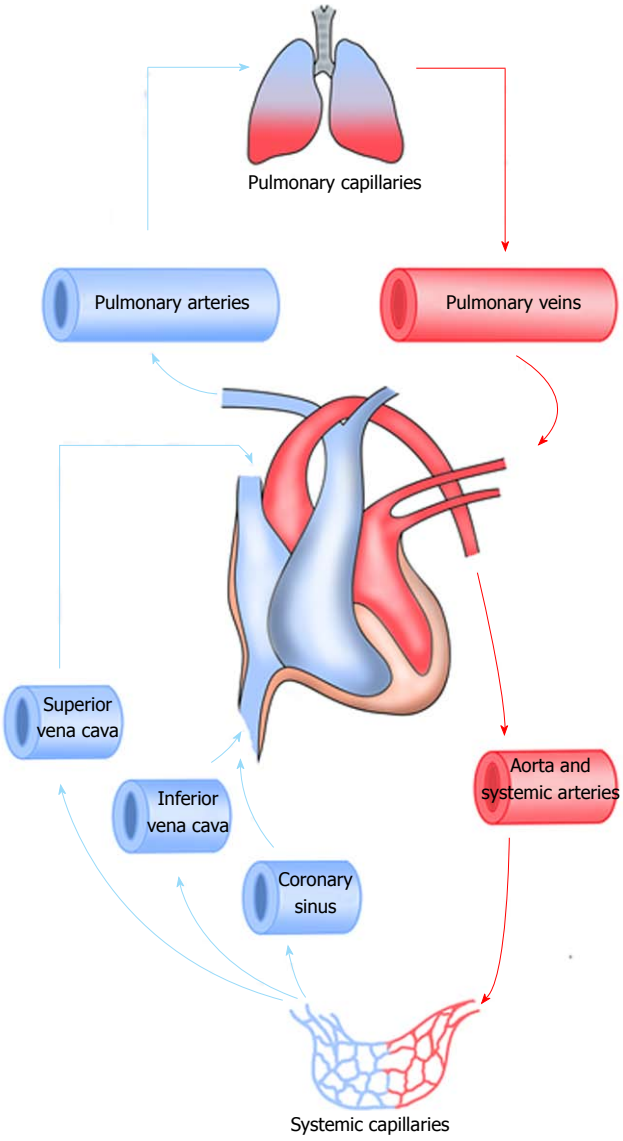

Figure 6 Schematic representation of pulmonary circulation.

it is subject to oxygenation while carbon dioxide is filtered, thereafter returning the clean blood onto the left section of the heart prepared for dissemination[13] (Figure 6). The pulmonary circulation is in series and reliant not only on the systemic blood flowing to right section of the heart, rather also the outflow from the left section[14]. Therefore, in case of an increment under the left atrium pressure or increase in afterload like in aortic stenosis, greater pressure will be observed in the PA[15]. PA vasoconstriction is an important physiological process to regulate blood flow in lungs but it also results in pathologies. Various models are utilized for assessing the baseline molecular and cellular functions of lung ailments, particularly pulmonary vascular affliction. However, a great deal of researches is undertaken on animals with little similarity to humans. Few centers have the luxury to utilize human tissue to study this phenomenon. Isolation of human PA and measurement of pulmonary vascular tension are vital to understand the pathophysiology of human pulmonary vessels. The objective behind this research is to assess the optimal resting tension for undertaking studies on human PA rings.

COMMENTS

Background

Pulmonary artery (PA) vasoconstriction is an important physiological process to regulate blood flow in the lungs but it also manifests in pathological conditions. Isolation of human PA and measurement of pulmonary vascular tension are vital to understand the human pulmonary vessels disease especially pulmonary hypertension.

Research frontiers

Further research is required to confirm the conclusion of this research, and also to evaluate if whether the optimum tension varies between various sizes of pulmonary arteries.

Innovations and breakthroughs

The authors yields the base optimal resting tension (ORT) for conducting studies on human PA rings and the ORT measured was 1.61 gf (15.78 mN) for vessels with internal diameter ranged between 2-4 mm.

Applications

This study provides a baseline ORT to facilitate future experiments on human PA rings and also provide a methodology of isolation of PA and their use in studies in the form of arterial rings.

Terminology

Pulmonary hypertension is a hemodynamic state elaborated by defined by a resting mean PA pressure at or above 25 mmHg.

Peer-review

It is a valuable paper for physiology and pathology pulmonary arteries. The system will provide a basic for further research about pulmonary arteries and its-related diseases.

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Remote electrocardiograph monitoring using a novel adhesive strip sensor: A pilot study

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Abstract

The increase in health care costs is not sustainable and has heightened the need for innovative low cost effective strategies for delivering patient care. Remote monitoring holds great promise for preventing or shortening duration of hospitalization even while improving quality of care. We therefore conducted a proof of concept study to examine the quality of electrocardiograph (ECG) recordings obtained remotely and to test its potential utility in detecting harmful rhythms such as atrial fibrillation. We tested a novel adhesive strip ECG monitor and assessed the ECG quality in ambulatory individuals. 2630 ECG strips were analyzed and classified as: Sinus, atrial fibrillation (AF), indeterminate, or other. Four readers independently rated ECG quality: 0: Noise; 1: QRS complexes seen, but P-wave indeterminate; 2: QRS complexes seen, P-waves seen but poor quality; and 3: Clean QRS complexes and P-waves. The combined average rating was: Noise 12%; R-R, no P-wave 10%; R-R, no PR interval 18%; and R-R with PR interval 60% (if Sinus). If minimum diagnostic quality was a score of 1, 88% of strips were diagnostic. There was moderate to high agreement regarding quality (weighted Kappa statistic values; 0.58 to 0.76) and high level of agreement regarding ECG diagnosis (ICC = 0.93). A highly variable RR interval (HRV $\geq$ 7) predicted AF (AUC = 0.87). The

monitor acquires and transmits diagnostic high quality ECG data and permits characterization of AF.

Key words: Remote; Electrocardiograph; Monitoring; Atrial fibrillation; Novel; Sensor

Core tip: The findings of this pilot study confirm that a remote monitoring system using a novel adhesive strip electrocardiograph (ECG) sensor can acquire and transmit diagnostic high quality ECG data over a period of 3 d when worn by elderly subjects leading active independent lives. Automated determination of heart rate variability permitted reliable characterization of ECG strips with atrial fibrillation. These data have implications for long term continuous monitoring for development of atrial fibrillation in independent elderly patients.

Bruce CJ, Ladewig DJ, Somers VK, Bennet KE, Burrichter S, Scott CG, Olson LJ, Friedman PA. Remote electrocardiograph monitoring using a novel adhesive strip sensor: A pilot study. *World J Cardiol* 2016; 8(10): 559-565 Available from: URL: http://www.wjgnet.com/1949-8462/full/v8/i10/559.htm DOI: http://dx.doi.org/10.4330/wjc.v8.i10.559

REMOTE ELECTROCARDIOGRAPH MONITORING USING A NOVEL ADHESIVE STRIP SENSOR: A PILOT STUDY

Due to increased longevity, people are facing an increasing prevalence of chronic disease that threatens their ability to live independently and has led to rapidly escalating healthcare costs. It is imperative that new, effective, economical and efficient methods to prevent and manage chronic disease are developed. Cardiovascular disease accounts for a significant burden of chronic illness, often manifesting as heart failure, and arrhythmias such as atrial fibrillation (AF) are commonly observed[1-4]. These arrhythmias may be difficult to detect, often initially presenting as decompensation of heart failure or stroke. Remote monitoring of physiologic measures such as the ECG and heart rate may provide an important option for early detection of cardiovascular compromise and arrhythmias[5]. Limitations of current monitoring systems include a large body burden and inconvenience in use, latency in transmission of physiologic information, enormous volumes of data for analysis consuming human resources, and significant false alarms generated by artifact, requiring human oversight[6-8].

We have developed a personal monitoring system capable of interfacing with additional low profile, unobtrusive, on-body and off-body sensors to provide real-time and cumulative data to a health care provider at any internet or cellular network enabled location. The system records ECG, respiration (*via* bioimpedance measurement), and physical activity using a 3-axis accelerometer. The system also has embedded algorithms that provide a self-diagnostic reliability index to qualify the value of the data, permitting reviewers to discard noisy signals, thus facilitating generation of alerts with greater specificity. In this pilot study, we sought to test the monitoring system in healthy volunteers residing in an independent living center, to determine whether the system satisfactorily acquires, stores, and displays ECG information of diagnostic quality in ambulatory, free-living individuals.

LITERATURE AND RESEARCH

We prospectively enrolled 10 healthy volunteers from residents of the Mayo Clinic Charter House, an assisted living center near the Mayo Clinic Rochester downtown campus. To be eligible, participants had to live in apartments with appropriate cellular network coverage. Subjects with implanted cardiac defibrillators or pacemakers were excluded.

After enrollment, a study coordinator provided each participant with a data hub that consisted of a SmartPhone preloaded with custom monitoring software (Google Nexus, HTC Corporation, Taipei, Taiwan), a charger for the SmartPhone, as well as two fully charged monitoring units and adhesive snap strips (Figure 1, BodyGuardian, Preventice Inc., Minneapolis, MN, described further below). A study coordinator instructed the subject on applying the adhesive strip sensor to the chest, methods for ensuring good signal quality, and how to ask for assistance if required.

Each subject was asked to use the system for 3 consecutive days. Supervised maneuvers, such as lying supine, sitting, standing, and walking were performed once per day, each day for 3 d, at which time the various signals were recorded. At the end of each 24-h period, the Study Coordinator exchanged the unit for a newly charged unit.

The study was approved by the Institutional Review Board. Since the system was not FDA approved at the time of the study, no clinical decisions or management changes were made based on data obtained during the trial.

REMOTE MONITORING SYSTEM

The remote health management system connects personal health sensors with secure mobile communication devices. The monitor front-end is composed of an electronic unit; an adhesive patch with attached electrodes and snaps for a rechargeable module. The rechargeable module measures 59 mm × 50 mm and houses the sensors, battery and wireless transmitter (Figure 2). It is detachable from the electrode snap strips to permit showering. The module is able to measure heart rate (HR), ECG, respiratory rate, and activity level.

Figure 1 Remote monitoring system. Top left: The rechargeable module is attached to the adhesive SnapStrip. The SnapStrip is positioned vertically over the sternum. Top right: The cellphone serves as (1) a wireless communication hub with the cloud and (2) as a user interface. Bottom: Recorded physiologic data including ECG and heart rate are presented on an iPAD for analysis and review. ECG: Electrocardiograph.

The ECG is recorded *via* the two inner electrodes (the distance between the inner electrodes is 70 mm and the distance between the outer electrodes is 104 mm). The electrode pads measure 10 mm diameter and have a signal sampling rate of 256 Hz with 12 bit resolution. Respirations are measured by injection of a low voltage charge from one pair of electrode contacts and measuring the change in voltage over a fixed distance on the other pair of electrode contacts (current amplitude: 100 μA, current frequency: 50 kHz, sampling frequency: 32 Hz). A three dimensional accelerometer acquires samples at 50 Hz and the signal is algorithmically processed to determine physical activity. Physiologic information is communicated to a remote server using a mobile phone as the communication hub. The mobile phone displays data acquisition, battery level and data transmission to the subject.

During normal operation, the system collects physiologic data and stores it in its on-board memory. The data are transmitted to the smart phone data hub at programmable intervals (nominally 60 min). In the absence of proximity to the data hub, data are stored on the rechargeable module attached to the adhesive strip until the next communication attempt. Data are automatically transmitted from the smart phone hub to a secure, HIPAA compliant server database.

Utilizing clinical algorithms, the system is capable of automated decision making based upon integration of data and can provide immediate feedback to the subject. The solution is a multi-tiered mobile health platform (Figure 3). The stored data are presented for review *via* a web-based interface, or using custom software on an iPad (Apple Computer, Cupertino, CA).

SELECTION OF ECG STRIPS FOR ANALYSIS

Each hour, a randomly selected two-minute ECG strip was automatically recorded and transmitted for the purposes of this study. Users could also manually activate a recording using the smart phone data hub interface.

ANALYSIS OF ECG QUALITY

Each of the ECG strips was read by 4 independent, experienced readers for ECG signal quality and rhythm interpretability. The readers were ECG technicians working in a 24-h continuous telemetry unit, and were blinded to clinical information and other readers' interpretations. Each reader independently rated the ECG quality using an ordinal scoring system: 0 Noise, cannot reliably determine QRS complexes 1 QRS complexes reliably seen and R-R intervals determined, but atrial activity indeterminate due to baseline noise 2, QRS intervals reliably recorded, and atrial activity seen but of poor quality, and PR interval not reliably seen 3, clean signal, with reliable assessment of QRS intervals, and PR intervals (when present). Quality scores were compared between each pair of readers and a weighted Kappa statistic was calculated assuming an ordinal outcome. In addition, in order to compare quality scores from all 4 readers, an intra-class correlation coefficient was calculated as a measure of agreement across all 4 raters.

ANALYSIS OF HEART RATE VARIABILITY

The system reports an average HR. The HR is derived by detecting the R wave component of the QRS complex for both normal and premature ventricular complexes (PVCs). The system calculates the interval between R waves (R-R interval) and processes this information to derive an average HR value every 10 s. The system also calculates heart rate variability (HRV). HRV is a value derived from the variance of the ECG R-to-R intervals based on a 10-s time interval. It is sensitive to both normal beats and PVCs. An event is triggered when the number of heart beats per minute varies by more than the HRV threshold. For example, if the threshold is set

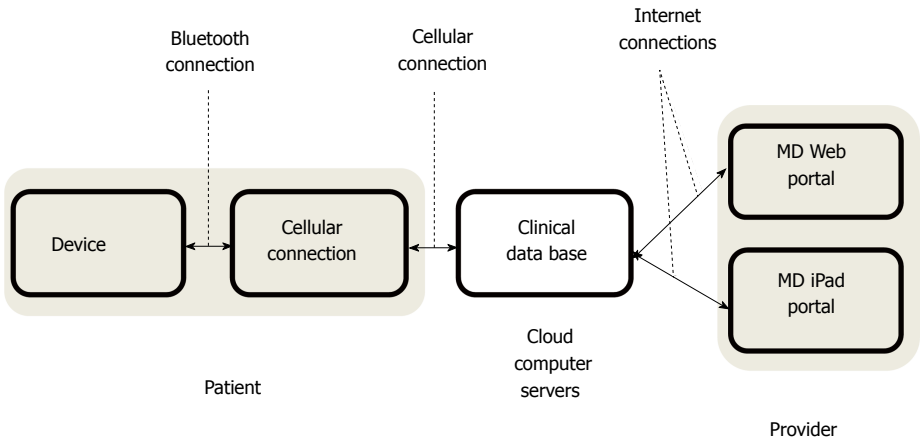

Figure 2 Remote monitoring system architecture.

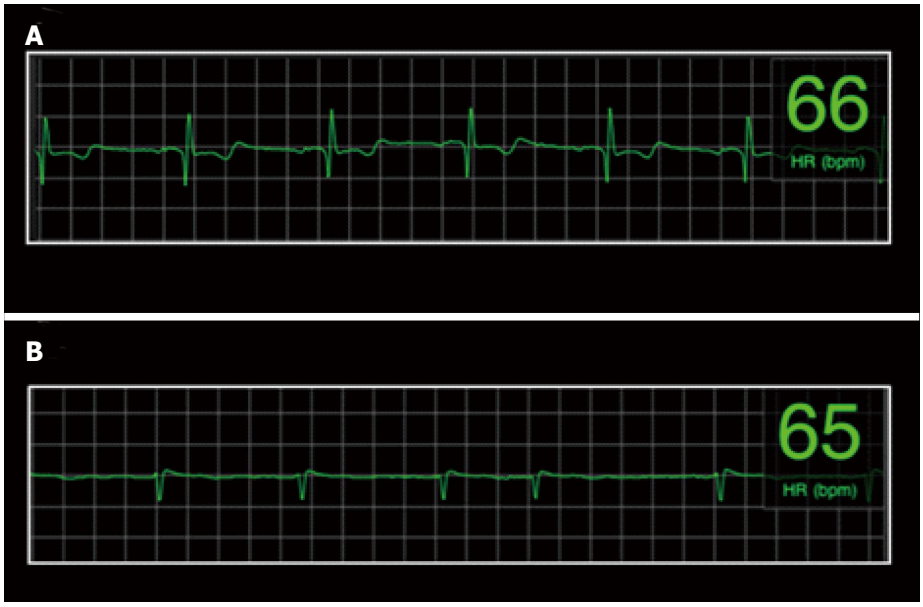

Figure 3 Representative examples of electrocardiograph strips. A: This strip demonstrates sinus rhythm. All 4 raters scored this strip as having high quality (score 3); B: This strip demonstrates atrial fibrillation. Although the raters quality score ranged from 1 through 3, the irregularly irregular RR interval and absence of discernible P waves present in this Electrocardiograph signal is diagnostic for atrial fibrillation.

to 30-bpm, a HR that varies from the average by more than 5 beats in a 10 s interval triggers an HRV event. Use of the HRV threshold to trigger an event helps to identify ECG tracings that may require physician review as they are more likely to indicate arrhythmia, based on dropped beats or irregular rhythm or increased heart rate. Logistic regression analysis was used to examine the association of HRV with the outcome of AF. A Receiver Operator Characteristic curve and concordance statistic (AUC) was used to illustrate the sensitivity and specificity of HRV.

RESULTS OF STUDY

Ten healthy volunteers were recruited to the study (4 men, average age 79.5 years (range 74 to 92 years). All 10 subjects wore the device for 72 h. Data from all 10 subjects were stored and were available for analysis for the 72-h duration the device was used.

Assessment of ECG quality

Data for 2630 ECG 2-min strips were available for analysis. Rhythm was classified by each of the 4 readers as sinus, AF, indeterminate or other (Table 1). There was moderate agreement in rhythm classification between pairs of readers (median Kappa = 0.65). In particular, variability was noted in the percentages of strips rated by each reader as sinus (48%-70%) while the percentages of those rated as AF was comparable across readers (11%-15%). Quality scores were compared between each pair of readers. There was a moderate to high level of concordance between readers (weighted Kappa statistic values ranged from 0.58 to 0.76). There was also a very high level of agreement across the 4 readers (ICC = 0.93).

The combined average rating of ECG quality based

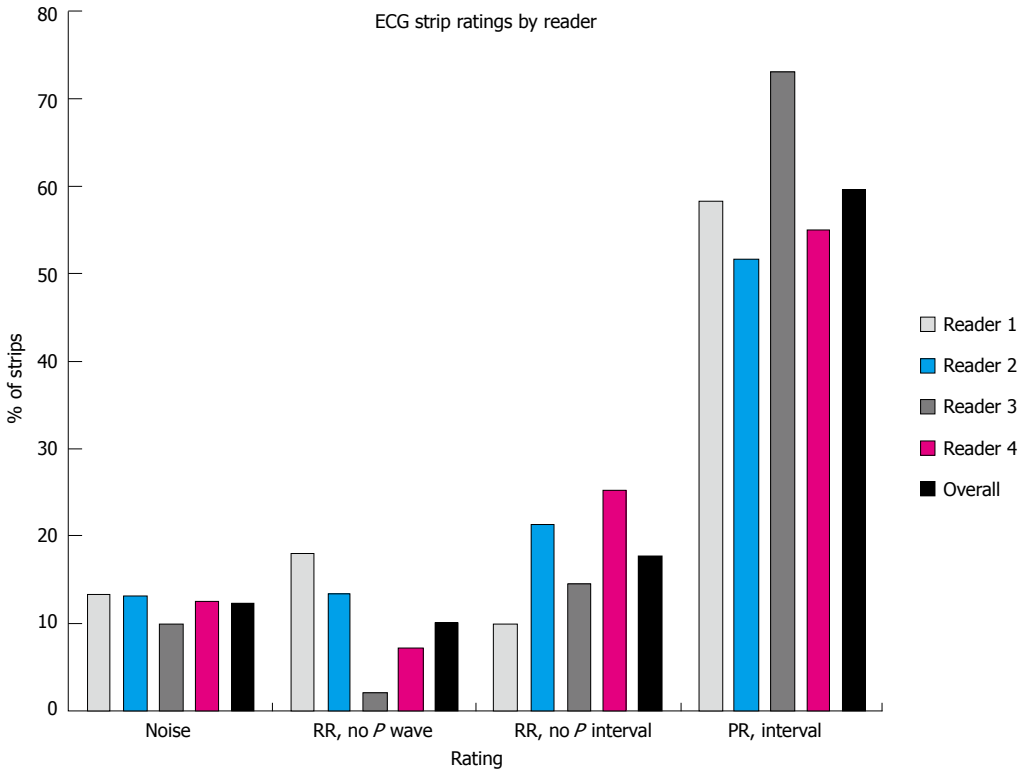

Figure 4 Electrocardiograph strip ratings by reader. Average combined and individual assessments of electrocardiograph quality based on 4 independent experienced raters. The vertical axis represents the percentage of strips rated within each category for each reader. ECG: Electrocardiograph.

Table 1 Electrocardiograph rhythm classification by reader

Rhythm	Reader 1 *n* (%)	Reader 2 *n* (%)	Reader 3 *n* (%)	Reader 4 *n* (%)
Sinus	1790 (68%)	1247 (48%)	1833 (70%)	1366 (52%)
AF	292 (11%)	384 (15%)	294 (11%)	334 (13%)
Indeterminate	457 (17%)	974 (37%)	497 (19%)	773 (29%)
Other	88 (3%)	4 (0.1%)	3 (0.1%)	154 (6%)

AF: Atrial fibrillation.

on the 4 independent raters was: No RR-noise 12%, RR-no P-wave 10%, RR-no PR interval 18%, PR interval 60% (if in sinus rhythm). Thus, if a minimum diagnostic quality was determination of an RR interval, 88% of strips were sufficiently diagnostic to provide a determination of HR, and a minority of strips was considered noise related to artifact (12%). Examples of ECG strips and the combined and individual assessments of ECG quality are presented in Figures 3 and 4.

One of the 10 subjects had persistent AF. In order to preliminarily assess the utility of HRV for identifying AF, and because of the variability in ECG classification variability, analysis was performed on those strips that were found to be in agreement across all 4 readers as either sinus rhythm (n = 889) or AF (n = 252). HRV scores were found to be significantly different between those classified as Sinus Rhythm (mean = 10.0, SD = 2.4) and those classified as AF (mean = 4.7, SD = 5.9), $P < 0.001$. Based on this finding, we defined images with a variability score of 7 or greater as highly variable. Ninety-seven percent of the strips with HRV $\geqslant$ 7 were classified as AF. This variable was also entered into a logistic regression model for predicting AF. The univariate area under the curve (AUC) for a highly variable RR interval (HRV $\geqslant$ 7) in predicting AF was 0.87 (Figure 5). Using HRV $\geqslant$ 7, sensitivity was calculated to be 97% (95%CI: 94-99) while specificity was 77% (74-80), positive predictive value was 54% (49-59) and negative predictive value was 99% (98-99).

DISCUSSION

The findings of this pilot study demonstrate for the first time the ability of this low body burden, unobtrusive, wireless remote monitoring system to acquire and transmit high diagnostic quality ECG data when worn by elderly subjects leading active independent lives, outside of a hospital environment. Artifact in ambulatory 24/7 ECG recordings results in erroneous arrhythmia classification that may significantly and adversely affect diagnostic accuracy and hence quality of care. These artifacts result from myopotentials (most commonly from the pectoralis muscles), galvanic skin currents, and less commonly electromagnetic interference. These issues are particularly prevalent in ambulatory settings and Band-Aid style sensors with only two electrodes are particularly at risk. Thus, it is reassuring that most of the ECG recordings using this system provided clinically diagnostic information, free from artifact. Furthermore, although the study was not designed to assess arrhythmia detection, serendipitously, one subject had persistent atrial fibrillation. Analysis of segments using the HRV

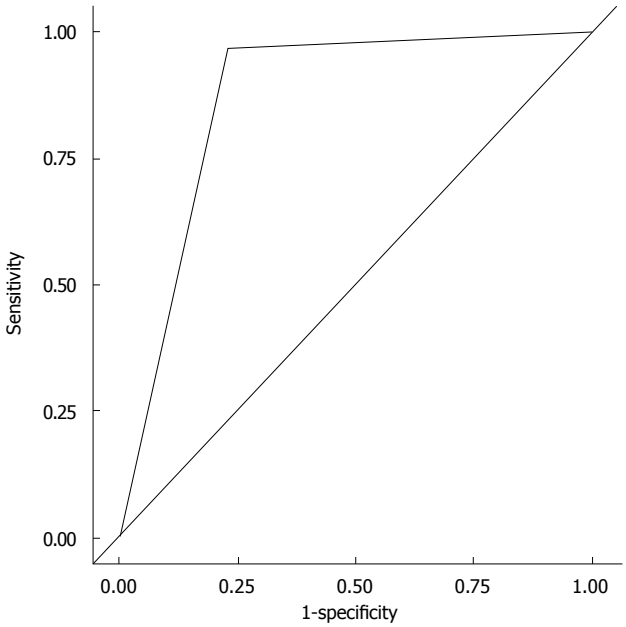

Figure 5 Receiver operator characteristic curve for atrial fibrillation using heart rate variability ⩾ 7.

algorithm permitted differentiation of ECG strips with AF from SR.

Determining reliable high quality ECG recordings is important in ambulatory monitoring systems to ensure appropriate diagnosis. It is also important to be able to characterize poor quality ECG data or noise (artifact) so that these data can be ignored. This is particularly important when large amounts of data are being recorded over prolonged periods, when frequent false alarms generate both user and healthcare provider "alarm" fatigue rendering the system cumbersome, and consequently adversely affecting effectiveness, adherence and prescription. The monitor system is capable of acquiring high quality ECG recordings using an unobtrusive adhesive electrode sensor in an ambulatory setting.

HRV as defined by this system may be useful for detection of arrhythmias such as atrial fibrillation. Indeed, in this study, one subject had AF. When excessive HRV was noted, ECG data strips from the patient could be reliably determined. This observation could be potentially useful in detecting AF, particularly if new AF develops in an individual who was previously in sinus rhythm (when HRV would be low). High HRV may be seen with arrhythmias other than AF, such as frequent PVC's.

LIMITATIONS

This study has limitations that may constrain broad generalization of our findings. The subjects enrolled in this study were elderly residents of an assisted living facility ranging in age from 72 years to 92 years. They are thus not representative of other population groups who may be younger, more active or less healthy. Furthermore, although there were large amounts of data for analysis, the subject sample size was small. The study design requirement for visual confirmation of rhythm and ECG quality rather than relying on automated algorithms made it necessary to limit the number of subjects studied. In mitigation, more than 2600 rhythm strips from the 10 subjects were visually inspected by study investigators to ascertain cardiac rhythm, which was labor and time-intensive. To prove the clinical utility of this approach in the future will require studies with larger numbers of subjects, which will only be practical with systems capable of automated rhythm identification in order to enable scalability. Additionally, very few patients experienced an arrhythmia (atrial fibrillation), and patients with other arrhythmias were not included. However, this was a pilot study directed toward evaluating the ergonomics, tolerability, and effectiveness of continuous EKG monitoring, and to determine whether the quality of the EKG recording could be preserved over extended periods.

CONCLUSION

The findings of this pilot study confirm that a remote monitoring system using a novel adhesive strip ECG sensor can acquire and transmit diagnostic high quality ECG data over a period of 3 d when worn by elderly subjects leading active independent lives. Automated determination of heart rate variability permitted reliable characterization of ECG strips with AF.

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MINIREVIEWS

Thoracic ultrasound: A complementary diagnostic tool in cardiology

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Abstract

Clinical assessment and workup of patients referred to cardiologists may need an extension to chest disease. This requires more in-depth examination of respiratory co-morbidities due to uncertainty or severity of the clinical presentation. The filter and integration of ecg and echocardiographic information, addressing to the clues of right ventricular impairment, pulmonary embolism and pulmonary hypertension, and other less frequent conditions, such as congenital, inherited and systemic disease, usually allow more timely diagnosis and therapeutic choice. The concurrent use of thoracic ultrasound (TUS) is important, because, despite the evidence of the strict links between cardiac and respiratory medicine, heart and chest US imaging approaches are still separated. Actually, available expertise, knowledge, skills and training and equipment's suitability are not equally fitting for heart or lung examination and not always already accessible in the same room or facility. Echocardiography is useful for study and monitoring of several respiratory conditions and even detection, so that this is nowadays an established functional complementary tool in pulmonary fibrosis and diffuse interstitial disease diagnosis and monitoring. Extending the approach of the cardiologist to lung and pleura will allow the achievement of information on pleural effusion, even minimal, lung consolidation and pneumothorax. Electrocardiography, pulse oximetry and US equipment are the friendly extension of the physical examination, if their use relies on adequate knowledge and training and on appropriate setting of efficient and working machines. Lacking these premises, overshadowing or misleading artefacts may impair the usefulness of TUS as an imaging procedure.

Key words: Thoracic ultrasound; Echocardiography; Congestive heart failure; Pneumonia; Pleural effusion; Cancer; Pneumothorax; Clinical risk management

Core tip: Thoracic ultrasound (TUS) is an imaging tool, well developed but not uniformly used, which provides information on pleura, lung and heart disease; TUS is a procedure that deserves greater dissemination, since quite neglected by cardiologists, pneumologists and even radiologists in the current practice; small

pleural effusions (useful for monitoring congestive heart failure), lung consolidation (particularly relevant in pneumonia) and pneumothorax, even with different reliability, may be detected; adequate training, avoiding overshadowing or misleading artefacts, is needed and must be integrated within curricula.

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OVERVIEW

This brief overview is essentially medical-centred, in a dual sense: (1) it regards the clinical approach (obviously patient-centred in its scope and ethics) that is, and must be, driven by an individual medical doctor with the most comprehensive as possible skills and expertise; and (2) it regards the clinical innovation and research, which raised and raise from the observation and reasoning of single clinicians; the dissemination of skills, practice, recommendation and guidelines must have the support of the best available clinical evidences, with the feature of appropriateness, sustainability and cost-benefit for the patient and the community.

This is particularly true for a procedure, such as thoracic ultrasound (TUS), basic, if not elementary, quite neglected by the cardiologist. This despite TUS was early concurrently practised with echocardiography[1] and, subsequently, limitedly used by internists, radiologists and in paediatrics[2-9].

The requirement that TUS shares with echocardiography[10] are remarkable. The effort of a good quality imaging, the reproducibility of the procedure by different operators and equipments and the criteria of the indications[9] can be summarized in two sentences: (1) the use of TUS for initial diagnosis is recommended when there is a change in the patient's clinical status, likely related to pulmonary function; and (2) when new data from a TUS would result in the physician changing the patient's care.

There is an established agreement for these criteria in cardiological patients for their use in echocardiography[9,10]. Moreover, alike echocardiography, TUS is not recommended as routine testing equally when the patient has no modification in clinical status or when a physician is unlikely to change care for the patient based on the results of testing: These are both two strongly advised points against the use of echocardiography as a routine testing, which are suitable to be transferred also to TUS[9].

Differently from echocardiography, TUS is almost exclusively an imaging tool, without any "functional" application comparable to M- B- and Doppler Echocardiography, no accurate and reproducible dynamic measures, no translational relevance in the description and interpretation of mechanisms of disease[11].

Nonetheless, the knowledge of these limitations and the use of the few direct information provided by TUS are a substantial add-on to the clinical strategy of the cardiologist[12], also in emergency[13-15].

RATIONALE AND KEY POINTS

The customized rules of a journal presentation are: What, who, why, when, where, how.

What

Clinical assessment and workup of patients referred to cardiologists is a task often more comprehensive and not only focused on the heart since it is extended to chest disease. This approach may require more in-depth examination of respiratory co-morbidities due to uncertainty or severity of the clinical presentation.

Who

The cardiologist, facing respiratory associated symptoms and co-morbidities, can usually detect and manage the clinical presentation by physical examination, a thoroughly collected story, and using the current non-invasive procedures at the hands. The cardiologist's view is of paramount relevance for the clinical reasoning and action of the other specialists. The adjunct of TUS examination is an excellent companion to the other knowledge, procedures and skills.

Why

According to uncertainty or severity of the clinical presentation, the referral to radiologist and to pneumologist is an assignment that is more appropriate if explicitly addressed with objective information, which exclusively can produce evident cost-benefit advantages[16,17]. Some investigation implicitly aims to a clinical risk management analysis with subsequent recommendations. Actually, TUS can be an excellent risk-reducing tool by increasing: (1) diagnostic certainty; (2) shortening time to definitive therapy; and (3) decreasing complications from blind procedures that carry an inherent level of complications. The background and the backbone of it all is an efficient network of timely, coordinated and experienced professionals, and the analysis of obstacles and structural barriers that may take place or that are interposed[17,18].

When

The contribution of the cardiologist in the diagnosis and management of respiratory disease must be well timed. Apart the obvious clinical judgement, the expert task of filtering ecg and echocardiographic information, addressing to the clues of right ventricular impairment, pulmonary embolism and pulmonary hypertension, and other less frequent conditions, including congenital, inherited and systemic disease, is an help for timely diagnosis and therapeutic choice. Even with limited indications, the concurrent use of TUS by the cardiologist

is important in this regard.

Where

Despite the evidence of the strict links between cardiac and respiratory medicine, the two ultrasound imaging approaches to heart and chest are still separated. This is due to different skills of physicians, to the different preference of patients in the choice of type of referrals and even due to the suitability of equipments and probes, which are not equally fitting for heart or lung examination and not always already available in the same room or facility.

How

Several respiratory conditions are currently studied and monitored, when not preliminary detected, by echocardiography, which is nowadays an established tool in the workup of pulmonary fibrosis and diffuse interstitial disease. As a further step, the ultrasound (US) approach of the cardiologist should be extended to lung and pleura, achieving simple and straightforward information suitable of articulation within the clinical cardiology frame. Electrocardiography, pulse oximetry and US equipment are the friendly technological extension of the physical examination, if their use is based on adequate knowledge and training of the professionals, on appropriate setting of tools which must be efficient and well working. If these premises lack, overshadowing or misleading artefacts can ensue: Overall, the procedure must be affordable, reliable and comfortable for both the patient and the well-trained doctor[18-20].

CHEST ULTRASOUND: THE THORAX, THE LUNG, THE HEART

Many clinical subsets increasingly use chest ultrasound, *i.e.,* TUS procedures. This is due to the greater availability of portable point-of-care US equipment, suitable also at the patient's bedside, in the ward, in the emergency and intensive care unit, in outpatient clinics and even at home of the patients themselves.

TUS procedure allows the view of the most superficial parts of the chest: The thorax "wall", the pleura, which may be a virtual space or a real fluid-filled space in pleural effusion, or may be a mass-occupied space in many cancers, and the lung itself[9]. Some part of the lung, where not overshadowed by ribs or other bones, such as scapula, is therefore clearly visible only if "consolidated". This happens in atelectasis, pneumonia and cancer, provided that the mass or nodule strictly adheres close to pleura, becoming accessible to micro-invasive procedures[21-23]. There is no TUS established criterion for differentiating the nature of lung consolidation. Physical interaction of the ultrasonic beam at the tissue/air interface strongly influences or frankly impairs transthoracic US imaging, so that TUS cannot detect any mass or nodule, behind more superficial and even small portion of aerated lung, often even clearly defined by radiological procedures.

The heart is one of the organ visible by ultrasound in the thorax - by echocardiography - and, as it is well known, also for this reason the worst enemy of its imaging is the air, the pulmonary air; as a consequence, any cardiologist focuses on the detection of the acoustical windows for achieving and recording useful and better images and videos. Actually, in children and in thin persons, high frequency (6-10 MHz) linear or convex probes[9] enhance the view of the chest wall and of the pleura-lung abnormalities. This is possible because, and only if the structures we are attempting to see are just below our transducers. The yield of a sector or phased array probe is usually more limited; the only notable exception is the detection, also by sector probes, of pleural fluid, which sometimes may be well visible even anteriorly, sometimes not well differentiated by a pericardial effusion requiring a complete lateral and posterior chest assessment by TUS[24]. More easily and with a greater sensibility for small amounts of fluid is the view through a window in the lateral and posterior part of the chest, better with the patient upright or sitting[9].

A LONG STORY: PIONEERS AND CURRENT USERS

TUS is a complementary tool also in cardiology[25-30], along its main use for more specific pleura and lung disease[31-34]. Nonetheless, TUS pioneering and practice began in late 60's. Then, the most important B-mode studies concurrently, in the same centre in United States, demonstrated the usefulness of TUS, along with the assessment of mitral and tricuspid valve disease[35,36], for the diagnosis of lung consolidation, envisaging an help even in pulmonary embolism[37]. In early 70's, with the improved quality and greater availability of the US equipments, the use of TUS as an allied support of cardiologists performing echocardiography was recognized and practised. Our practice was done, regretfully, without delivering relevant cardiology publications on this topic, which was considered a parallel but minor informative practice. Thereafter, in late 80's in France[5], the TUS procedure was optimally developed by pneumologists, as it was in Germany[6-8], and in Italy[3] defining appropriately the criteria of pneumothorax and of lung consolidation. The clinical research and practice of TUS in cardiology in late 90's in Japan, demonstrated the usefulness of detecting and monitoring pleura effusions[25-28,30], an achievement that others subsequently confirmed[29] enhancing the dissemination of knowledge and interest for TUS in Cardiology. The use in pediatric and newborn intensive care facilities was[2,4] and still is[17,38,39] greatly developed with the contribution of pediatric radiologists. The main barriers to the dissemination of an appropriate TUS practice are the limited availability of clinical application studies within cardiology and pneumology departments, the lack of TUS curricula inside those residency pro-

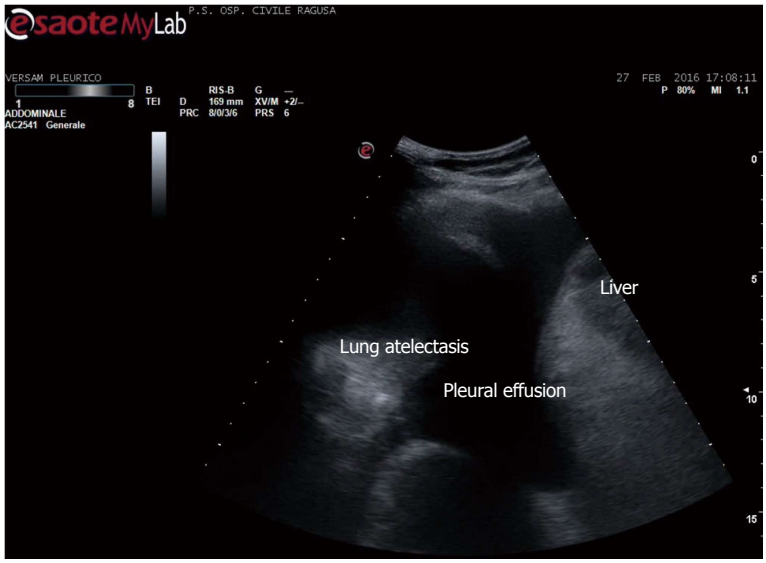

Figure 1 Pleural effusion.

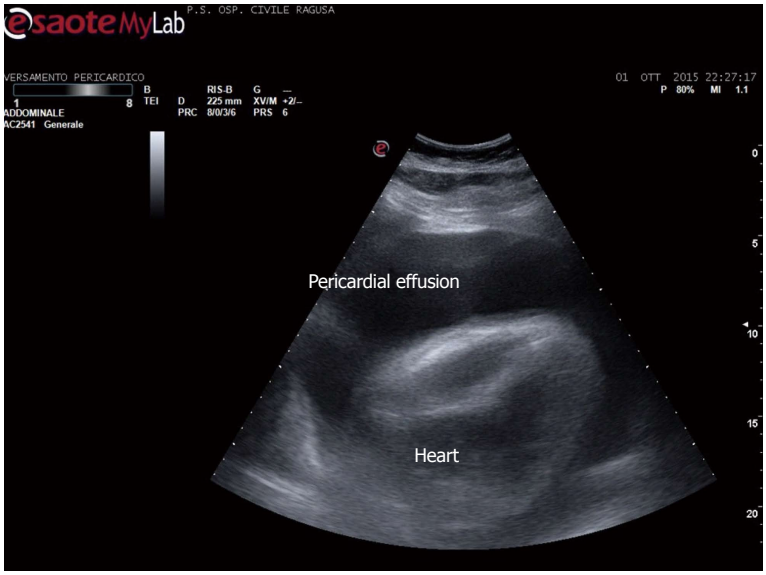

Figure 2 Pericardial and pleural effusion.

grams[18-20] and the small attention devoted to research and publications in this field by cardiologists.

THE PROCEDURE: NEEDS, FACILITIES, COLLABORATION AND INDICATIONS

There are good reasons for which a cardiologist should seek for the contribution of TUS, and they stems from the referral for a clinical consultation that usually includes echocardiography.

Apart the itemization of the main indications and conditions in which TUS can be of help for the diagnosis and workup of patients, which is below detailed, the focus of the cardiologist performing TUS is clinically-driven by the two more important concurrent conditions: (1) pleural effusion (Figure 1), which is observed even better by video-clip and may be associated with pericardial effusion (Figure 2); (2) lung consolidation (Figure 3) which may be due to pneumonia, as in this case, but which needs a further radiological work-up if there is the suspicion of cancer or lung atelectasis; (3) the appearance of B-lines is a very generic clue (Figure 4), particularly because their count is at best impractical and imprecise, as it is obvious looking at any videoclip; (4) differently, the dynamic view of the disappearance of pleura sliding (Figure 5) is a very specific sign, unless it is observed in the apical part of the lung, where it can be often undetectable for anatomical reasons; however, detection of the absence of pleura sliding is not a very usual need to search for a cardiologists.

The cardiologist can perform TUS procedure, after an appropriate training and with the adequate probe implementation of the US equipment, executing an articulated heart-lung US approach.

A list of the main findings attainable by TUS: (1) small or huge pleural effusions. These can be associated with pericardial effusion, and can be isolated pleural fluid effusions, unilateral, bilateral or, as less frequently happens, loculated. If loculated, effusions

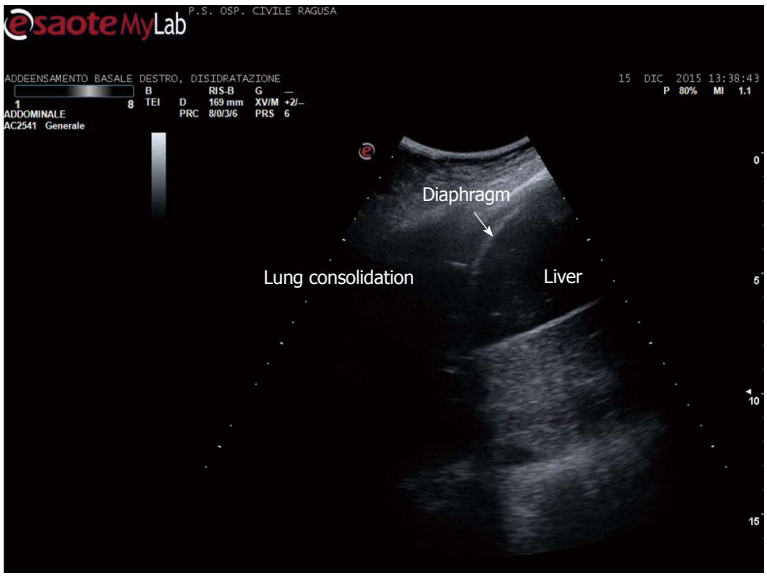

Figure 3 Lung consolidation. Community acquired pneumonia in an adult.

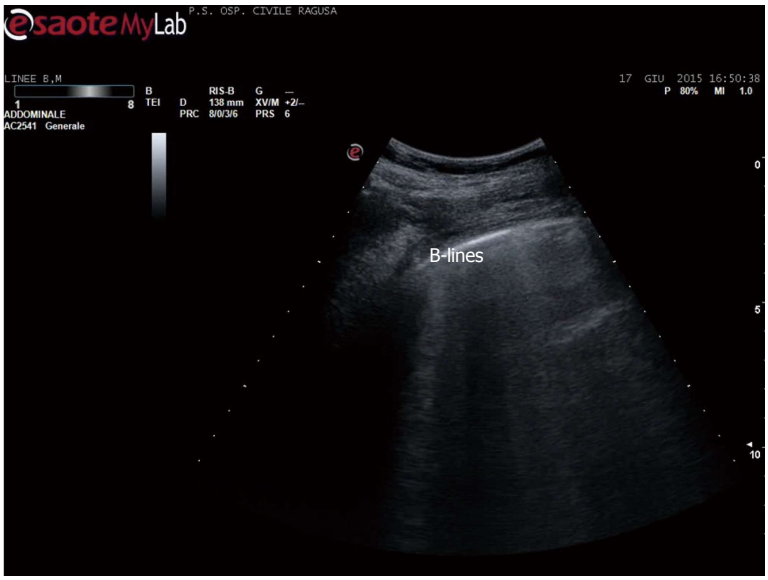

Figure 4 B-lines in acute heart failure. B-lines count is a dynamic observation, essentially qualitative, since the number changes continuously - from 3 to 6 or more - in case of numerous b-lines. Identical artefacts are detectable in other conditions, including pulmonary fibrosis and dyspnoea due to other causes, including BPCO.

may be not detected in the lower part of the chest, but only at the level where the fluid is actually restricted. The sensibility of linear *vs* phased array probes is greater (100% *vs* 91%) for uncovering pleural effusions; both are more sensible in comparison with chest X-rays[24]; (2) the recognition of pleural effusion is a frequent occurrence in echocardiography out-patient consultations, and follows referrals for dyspnea, due to congestive heart failure and/or respiratory failure; valvular or congenital heart disease; ischemic or primary myocardial heart disease; cancer disease, primitive or metastatic; other conditions.

These last miscellanea should be considered a particularly relevant group, since the detection of not previously suspected pleural-pericardial effusion can be the first evidence of otherwise still non-identified disease, or a clue of greater severity of an already diagnosed disease.

We see in the current practice pleural effusions, often previously undetected, in: Hypothyroidism; rheumatic and auto-immune disease; malnutrition, due to dietary insufficient intake, to intestinal disease (such as coeliac disease) and to liver disease; nephrosis.

The small, quick diagnostic step of the cardiologist can open the road for a more effective diagnosis and treatment of several patients in these cases.

A journey of a thousand miles starts under one's feet (Lao-Tzu)

The detection and monitoring of pleural effusion was the object of very careful studies, which demonstrated the usefulness of the detection and of the monitoring of pleural effusion in congestive heart failure patients throughout the time-course of management outcome[25-29] and along ecg changes[30].

Pleura-lung consolidation

This is a more detailed imaging diagnosis, non-specific and not suitable for reliably identifying the cause. It can address to subpleural pneumonia areas[31], pleural

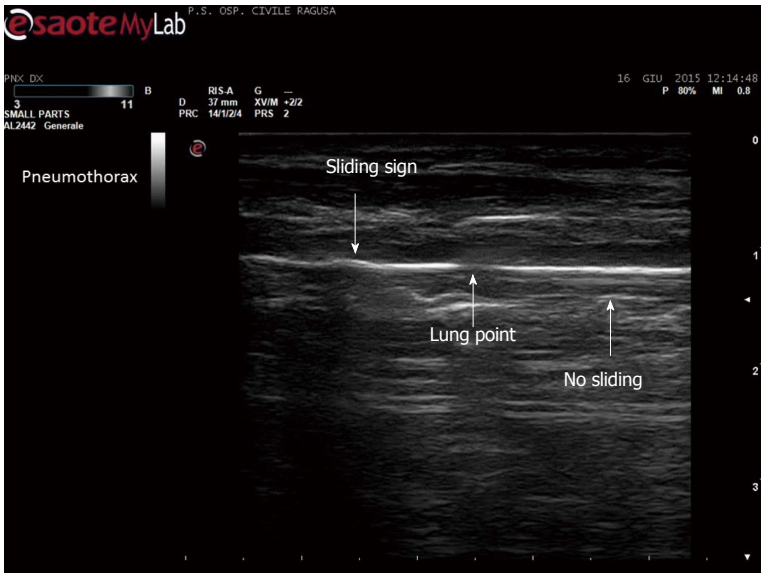

Figure 5 Disappearance of pleural sliding, better demonstrated by video. Which is here showed as a drop in the continuity of the line, not moving side by side (by courtesy of Giuseppe Molino, MD, MCAU Ospedale Civile di Ragusa, Italy).

and/or subpleural nodes[32], atelectasis[33] and loculated-organized pleural effusions[34], without a definite differentiation[9].

This type of report needs a very systematic chest examination, which should not be, usually, a part of the cardiological US procedure, requires more appropriate probes (linear or convex), and a great level of suspicion, apart the skills and a lasting expertise.

Nonetheless, there are several good reason for performing this type of TUS examination, in selected patients, along the echocardiographic examination, when a consolidation is suspected[35-37], if the cardiologist has achieved a reasonable level of skills, expertise and training: (1) newborn and children with fever, even without overt severe respiratory distress[38,39]. In these small patients, the chest X-ray is usually postponed after having achieved the physical examination evidence of pulmonary involvement and, in the recent years, after some evidence at physical examination of TUS subpleural consolidation, particularly if associated with small pleural effusion; (2) adults with respiratory symptoms, with or without fever, particularly in the outbreaks of community pneumonia[40]. Both situations can be associated with previous or active endocarditis, so that this diagnostic step can be useful for completing the elements of the clinical reasoning of the cardiologist; (3) adults with evidence of small pleural effusion without a definite suspicion of pulmonary infection and with the possibility of lung cancer. This is a special case, usually behind the actual skills and expertise of any US professional. Nonetheless, if positive, TUS could hasten the prescription of more efficient imaging (CT or NMR); and (4) pleural line thickening. This is a minor but relevant clue, detected in several diffuse pulmonary interstitial disease[41] and in conditions such as asbestosis[21,42,43]. This can be an early sign of involvement or of worsening of an already known disease, and can help in the decisional tree for the prescription of a radiological examination - CT.

TUS clues of pneumothorax: This is an important application, even without specific criteria, useful in emergency, for the diagnosis of spontaneous or traumatic/post-procedural pneumothorax, particularly in conditions of limited medical resources. TUS diagnosis relies on the sign of the absence of sliding on the pleural view[44,45] and to other less specific signs[9]. With the considerable exception of unavailability of adequate roentgenologic facilities, the TUS diagnosis is a preliminary step to the urgent definition and demonstration - usually by CT - of the chest condition, amenable to the choice of the most appropriate management[46,47].

ABSENCE OF TUS IMAGING

The ring-down artefacts in patients with dyspnea

In patients with severe dyspnea, whatever the cause (pulmonary oedema, congestive heart failure with or without orthopnea, pulmonary fibrosis, and other conditions), the so-called B-lines artifacts[48-53], which prevents the vision of lungs with the remarkable exception of pleural effusion, may overshadow an adequate imaging. Indeed, the clinical reliability of B-lines count is a doubtful stand-alone criterion, particularly because "in patients with a moderate to high pretest probability for acute pulmonary oedema, an US study showing B-lines can be used mainly to strengthen an emergency physician's working diagnosis of acute pulmonary oedema. In patients with a low pretest probability for acute pulmonary oedema, a negative US study can almost exclude the possibility of acute pulmonary oedema"[54]. These are the conclusion of the most accurate metanalysis on this topic, which substantially asserts that the only information provided by the B-lines artifacts is that one already available on clinical basis. Moreover, over-reliance on such tools could undermine quick clinical decisions in emergency

scenarios[55]. Acute severe dyspnea due to causes other than pulmonary oedema, including exacerbation of chronic obstructive pulmonary disease and pulmonary fibrosis, presents with the same B-line profile as acute pulmonary oedema. It is therefore obvious that in a clinical scenario of severe dyspnea, preliminary diagnosis by history and clinical examination takes precedence, and, in fact, it is almost all that the physician and the patient need for effective intervention. Finally yet importantly, the fact that the number and evidence of B-lines is greater according to the age of the patients[56], not to the body size[57], more than to other factors raises further doubts on a realistic use of this criterion for "universal" clinical purposes, as sometimes claimed.

Indeed, the reference tool in acute pulmonary oedema is auscultation, and the level on the chest - basal, middle, and apical - where wet sounds are heard[9]. Most source articles dealing with the B-lines approach do not mention such features and do not mention in the reports the extension of lung involvement. Furthermore, those articles also fail to inform us of the ultrasound time course of the observed pulmonary oedema cases, from the onset to improvement or recovery, or to the worsening of the clinical situation. This is a crucial point. Differently, usefulness of reduction of TUS pleural effusion with clinical improvement is a very well demonstrated and practised approach since several years[9,24-28]. Nonetheless, the reduction of artefacts grossly runs in parallel with the improvement of dyspnea, whatever is the prominent cause, allowing a grossly graded US detection of pleura-lung abnormalities, if any. The prominent role even in emergency of echocardiography over TUS is, also nowadays[58], when still necessary, confirmed again[15]. Unfortunately, TUS does not provide a substantial adjunctive contribution for the diagnosis of pulmonary embolism[59], as hopeful[37].

TUS guidance for intervention procedure

This is probably the most important application of TUS, useful for diagnostic of nodules by fine needle aspirate biopsy, for diagnosis and drainage treatment of pleural-pericardial effusions and, rarely, of cysts, for the guidance toward chest vessels[60] and, in special cases, toward the diaphragm[61]. The role of the cardiologist in these very specific actions is almost null; nonetheless, a trans-thoracic approach of pericardial effusions[62], instead of sub-xiphoid as currently usual, is safe and in some case - abdominal surgery or trauma - the best suited. The use of probes with a central hole - convex or linear - is particularly useful because these probes allow a greater precision in the guidance and in the visual tracing of the needle toward its target[9,16,21,22,63]. The percentage of complications is minimal or absent.

The cardiologist: The culture and the methodology

After its beginning and development in the cardiology and in the radiology units, TUS was quite relegated, if not neglected. It was used mainly in contexts of limited resources, when there was the need of quick diagnosis and, in a very privileged niche, in the laboratories of interventional diagnostic ultrasound, for performing highly focused and precise lung, nodes and pleural biopsies or therapeutical procedures.

The culture of the cardiologists and of the radiologists has the key traits of addressing quality and conformity to the morphology of the US images, of investigating using unambiguous criteria of comparisons between measurements (invasive, non-invasive, anatomic) and of achieving not redundant, not time wasting and not potentially misleading information. With these criteria in mind, the contribution of TUS, apparently limited to a couple of items and information, is, in the hands of the cardiologist performing echocardiography, a valuable add-on for ruling-in or ruling-out pleural effusions. Overall, the cardiologist may detect isolated lung consolidations, possible pneumonia or other masses, and pleural line thickening, as a possible clue of interstitial lung disease. The available information, particularly in point of care ultrasound, suffers from several limitations which were optimally addressed somewhere else: The concept of a focused examination implies that one is addressing binary questions (*e.g.,* does the patient have cholecystitis or not?). In practice, many diagnoses require the assessment of a variety of imaging findings of varying subtlety and often deal in probabilities rather than binary assessments. Lastly, in order to assess the quality and validity of point-of-care ultrasonography and to permit its correlation with other imaging methods, it is essential that images be documented, ideally on the same picture archiving and communication system used for other imaging[64]. It should be strongly considered that "it is not time to mandate training in the performance of lung ultrasound without proving that ultrasound can reliably make an accurate diagnosis"[65]; moreover, "formal training incorporating ultrasound in adequate curricula is crucial for physicians, avoiding simplistic numeric rules, since medicine is not arithmetic"[66]. The trends of contemporary practice and research address to precision, but also to sustainability within a framework of predictive, preventive and personalized medicine and an affordable implementation of clinical risk assessment and management planning[67-70]. TUS is a significant complementary aspect of this strategy, which can be integrated and articulated within the daily work of the cardiologist.

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MINIREVIEWS

Physical activity in primary and secondary prevention of cardiovascular disease: Overview updated

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Abstract

Although the observed progress in the cardiovascular disease treatment, the incidence of new and recurrent coronary artery disease remains elevated and constitutes the leading cause of death in the developed countries. Three-quarters of deaths due to cardiovascular diseases could be prevented with adequate changes in lifestyle, including increased daily physical activity. New evidence confirms that there is an inverse dose-response relationship between physical activity and cardiovascular disease and mortality risk. However, participation in moderate to vigorous physical activity may not fully attenuate the independent effect of sedentary activities on increased risk for cardiovascular diseases. Physical activity also plays an important role in secondary prevention of cardiovascular diseases by reducing the impact of the disease, slowing its progress and preventing recurrence. Nonetheless, most of eligible cardiovascular patients still do not benefit from secondary prevention/cardiac rehabilitation programs. The present review draws attention to the importance of physical activity in the primary and secondary prevention of cardiovascular diseases. It also addresses the mechanisms by which physical activity and regular exercise can improve cardiovascular health and reduce the burden of the disease.

Key words: Physical activity; Primary prevention; Secondary prevention; Cardiovascular disease; Health care evaluation mechanisms

Core tip: This review describes the benefits of physical activity in primary and secondary prevention of cardiovascular disease. Physical inactivity is related to high blood cholesterol and accumulation of visceral fat, accompanied by low-grade vascular inflammation, which in turn is associated with insulin resistance and atherosclerosis leading to the development of coronary artery disease. In contrast, physical activity decreases vascular inflammation, and improves endothelial function and coronary circulation, preventing myocardial ischemia. Health professionals and policy makers in public health should align strategies to increase participation in physical activity.

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INTRODUCTION

Notable progresses have been observed in the treatment of cardiovascular disease. Hence, cardiovascular mortality faced a progressive decline in the past two decades. Despite these progresses, incidence of new and recurrent coronary artery disease (CAD) remains elevated[1] and constitutes the leading cause of death in the developed countries[2]. This is expected to increase health care costs, increase work disability and reduce quality of life[3].

Development of cardiovascular diseases is associated with lifestyle behaviours, such as smoking, unhealthy diet, physical inactivity[4] and sedentary behaviour[5]. Physical inactivity is defined as not meeting 150 min weekly practice of moderate physical activity or 75 min of vigorous physical activity. Regardless of the physical activity recommendations, the accumulation of sedentary behaviour, characterized by a series of activities with low energy expenditure ($\leqslant$ 1.5 metabolic equivalents, *e.g.*, watching television, using the computer, playing video game or riding in a car) throughout the day seems to increase the risk of degenerative chronic diseases and death risk[5]. Over three-quarters of deaths due to cardiovascular diseases could be prevented with adequate changes in lifestyle[4]. Indeed, the adoption of healthy life habits such as increasing physical activity and decreasing sedentary behaviours are able to decrease the risk of type 2 diabetes, stroke, cardiac events and cardiovascular disease[5] improving the quality of life and decreasing risk of death[6]. Several studies have addressed the importance of increasing physical activity levels as a public health intervention[7]. However, even though it is an important factor in primary and secondary prevention[8], the levels of compliance with the physical activity recommendations are still far from desirable[9]. Therefore, enhancing physical activity is still considered a challenge to public health.

The present review draws attention to the importance of physical activity in the primary and secondary prevention of cardiovascular diseases. It also addresses the mechanisms by which physical activity and regular exercise can improve cardiovascular health and reduce the burden of the disease.

PHYSICAL (IN)ACTIVITY AND SEDENTARY BEHAVIOURS

Physical inactivity is the fourth leading risk factor for non-communicable diseases[10]. It is independently responsible for 12.2% of the global burden of acute myocardial infarction[7] as well as 6% of deaths that occur worldwide[9]. Due to its elevated prevalence, physical inactivity is responsible for almost as many deaths as smoking[11,12]. It is estimated to cause 5.3 million deaths worldwide[13] and to increase the risk of diabetes, obesity and several types of cancer[14]. An inactive lifestyle leads to increased blood cholesterol levels and the accumulation of visceral fat; this is accompanied by an innate and adaptive immunological response at cellular and tissue levels leading to a persistent low-grade vascular inflammation, which is a key regulatory mechanism in the pathogenesis of atherosclerosis[15]. The development of atherosclerosis leads to CAD, which becomes evident when it causes thrombosis, angina pectoris and/or myocardial infarction. Inactivity is also associated with low cardiorespiratory fitness, worse mental health and poor quality of life[16].

Time spent in sedentary activities is also associated with an increased risk of cardiovascular diseases and all-cause mortality[17]. Time spent in sedentary activities and mortality show a dose-response relationship, which means that the risk of mortality increases across greater amounts of time spent in sedentary activities, such as sitting or watching TV[18]. In adults who reported daily sitting time in almost none of the time, one fourth of the time, half of the time, three fourths of the time and almost all the time, the adjusted hazard ratios for cardiovascular mortality were 1.00, 1.01, 1.22, 1.47 and 1.54 ($P < 0.0001$)[18]. It should be noted that the association between sedentary behaviours and mortality is independent of participation in moderate to vigorous leisure-time physical activity[18]. In a recent study, Matthews *et al*[19] showed that excessive amounts of TV viewing (more than 7 h/d *vs* less than 1 h/d) are associated with an increased risk of all-cause and cardiovascular disease mortality, even among adults who reported high levels of moderate to vigorous physical activity (more than 7 h per week). The results of INTERHEART study published recently also demonstrated that subjects who owned both a car and a TV were at higher risk of myocardial infarction (multivariable-adjusted OR = 1.27, 95%CI: 1.05-1.54) compared with those who owned neither[20]. Together,

these data suggest that participation in moderate to vigorous physical activity may not be enough to fully attenuate the independent effect of sedentary activities on increased risk for cardiovascular diseases.

PHYSICAL ACTIVITY IN PRIMARY PREVENTION OF CARDIOVASCULAR DISEASES

It has long been demonstrated that physical activity decreases the likelihood of someone developing CAD and to suffer from its consequences[21]. Seminal studies demonstrated that active conductors were protected against CAD compared with inactive bus drivers[22]. These observations were replicated in active postmen compared with inactive telephonists, indicating that people with active occupations were less likely to have adverse events due to CAD[23]. Several studies extended these findings, and showed that physical activity has a graded inverse association with the risk of coronary events[24,25]. Walking is associated with decreased risk of coronary events, with women walking three or more hours per week at a brisk pace having about 35% lower risk of coronary events than those who walk infrequently[25].

Studies conducted in old aged individuals confirmed that physical activity also reduces significantly mortality risk in elderly people without pre-existent cardiovascular disease[26]. Inactive people who become active later in life have also lower risk of cardiovascular events compared with those who remain sedentary[25]. The relation of changes in physical activity and mortality were also seen in men with pre-existent cardiovascular disease[27]. The magnitude of risk reduction is similar as quit smoking[28]. This shows the importance of adopting active lifestyle behaviours, even if initiated during middle or late adulthood during leisure time, as increased leisure time physical activity reduces the risk of cardiovascular events, such as myocardial infarction[20].

In healthy individuals, some of the benefits that physical activity exerts on the prevention of cardiovascular diseases are attributed to positive modifications on traditional risk factors[29]. Maintaining or improving physical activity prevents weight gains and the development of hypertension, hypercholesterolemia, metabolic syndrome, and diabetes, all of which are important cardiovascular risk factors[30,31]. Indeed, physical activity prevents the development of hypertension in normotensive individuals, but it also reduces blood pressure in hypertensive patients[32,33]. In addition, physical activity is associated with better blood cholesterol levels as well as decreased prevalence of obesity and type-Ⅱ diabetes, all of which contribute to the development of vascular inflammation and atherosclerosis[34]. Many studies have also demonstrated that physical activity reduces blood concentrations of several inflammatory biomarkers such as C-reactive protein, lipoprotein-associated phospholipase A2, cytokines interleukin (IL)-1β, IL-6 and tumor necrosis factor-α, many of which have been recognized as important players in the initiation and development of atherosclerosis[35,36].

On the other hand, it was also shown that physical activity might prevent cardiovascular diseases independently of its potential benefit on other cardiovascular risk factors, including obesity, hypertension and diabetes. This could be related with the increase in physical fitness, which also prevents the burden of the cardiovascular diseases independently of the level of physical activity someone performs[37,38]. Improved physical fitness also attenuates the risk of developing hypertension, increased cholesterol and metabolic syndrome[30], suggesting that both physical activity and physical fitness are independent protective elements of cardiovascular events. A summary of the benefits of physical activity in primary prevention is presented in Table 1.

PHYSICAL ACTIVITY AND CARDIOVASCULAR RISK: INVERSE DOSE-RESPONSE RELATIONSHIP

Whether physical activity is associated with the reduced risk of cardiovascular events is beyond question. The issue that countless researchers have been trying to solve is how much physical activity is needed for reducing the risk of cardiovascular diseases.

Landmark studies showed that death rates declined steadily as energy expended on physical activities increased from less than 500 to 3500 kcal/wk[39]. Death rates were one quarter to one third lower in men expending 2000 or more kcal during exercise per week compared with less active men[39]. The inverse dose-response relationship between physical activity and all-cause mortality was confirmed in recent studies and seems to be stronger in women than in men[40,41]. Individuals who exercise for 90 min/wk have a three year longer life expectancy than inactive people[41]. Every additional 15 min of exercise per day promotes a further 4% risk reduction in all cause-mortality[41]. Moreover, recent meta-analysis of previous studies showed that individuals who engage in the equivalent of 150 min per week of moderate intensity leisure time physical activity have 15% to 20% lower risk of developing CAD than those who undertake no leisure time physical activity[42,43]. Those who perform the equivalent of 300 min/wk of moderate physical activity have even greater risk reduction of coronary artery disease. It is important to note that even persons who did 75 min of moderate intensity physical activity per week had reduced risk of cardiovascular disease, lending credence to the notion that some physical activity is better than none and that additional benefits occur with more physical activity[42].

On the other hand, vigorous physical activity leads to lower incidence of CAD and greater reductions in

Table 1 Summary of the benefits of physical activity in primary prevention

Physical activity in primary prevention	
Prevents	**Improves**
Diseases development associated with cardiovascular disease (hypertension, diabetes and metabolic syndrome)	Physical activity levels and physical fitness (cardiorespiratory fitness and skeletal muscle strength)
Obesity	Prevents weight gains, and improves blood cholesterol profile towards increased HDL blood levels and lower LDL blood levels
Type 2 diabetes	Glycemic control, and improves insulin sensitivity in type 2 diabetics
Hypertension	Prevents the development of hypertension in normotensive individuals, and reduces blood pressure in hypertensive patients
Vascular inflammation and atherosclerosis	Reduces blood concentrations of several inflammatory biomarkers such as C-reactive protein, lipoprotein-associated phospholipase A2, cytokines IL-1β, IL-6 and TNF-α

TNF: Tumor necrosis factor; HDL: High density cholesterol; LDL: Low density cholesterol; IL: Interleukin.

all-cause mortality[44,45]. However, not all studies have controlled for exercise volume, advising caution in the interpretation of these results. These results are consistent with the recent recommendations suggesting that healthy adults should perform at least 150 min of moderate intensity aerobic exercise (40%-60% of heart rate reserve) or 75 min of vigorous intensity physical activity (60%-85% of heart rate reserve) per week or through the equivalent combination of moderate and vigorous-intensity physical activities[46]. Very recently, pooled data from population-based prospective cohorts in the United States and Europe, including a total of 661137 men and women, with a median follow-up of 14.2 years, showed that risk of mortality was 20% lower among individuals performing less than the recommended minimum of leisure time physical activity [HR = 0.80 (95%CI: 0.78-0.82)], with this inverse association growing stronger among those reporting 1 to 2 times [HR = 0.69 (95%CI: 0.67-0.70)] or 2 to 3 times the recommended minimum [HR = 0.63 (95%CI: 0.62-0.65)] leisure time physical activity[47]. Interestingly the association appears to reach a threshold among persons performing higher levels of physical activity, suggesting that inactive individuals may benefit from modest amounts of physical activity in terms of reducing mortality while high levels of physical activity does not confer increased risk of mortality[47]. Additionally, maximum longevity benefit seems to be associated with meeting the recommended guidelines for moderate to vigorous physical activity[47]. Health benefits are also achieved when sedentary behaviours are replaced by light intensity physical activity (< 40% of heart rate reserve) and moderate to vigorous activities are held constant[48]. Reducing sedentary activities should be pursued by everyone independent of the amount and intensity of physical activity one achieves per week, as sitting time or time spent watching television is independently associated with greater incidence of cardiovascular risk factors, cardiovascular disease and cardiac mortality[18,49].

PHYSICAL ACTIVITY IN SECONDARY PREVENTION OF CARDIOVASCULAR DISEASES

Physical activity also plays an important role in secondary prevention of cardiovascular diseases by reducing the impact of the disease, slowing its progress and preventing recurrence. Nonetheless, it is difficult to ascertain the role of leisure time physical activity alone in secondary prevention, as most studies have not discerned the effects of structured exercise training alone or incorporated in comprehensive cardiac rehabilitation programs from those induced by leisure time physical activity alone. In patients following myocardial infarction, participation in an 8-wk exercise-based cardiac rehabilitation programme was found to improve leisure-time physical activity levels consistent with health-related benefits[50]. Interestingly, at baseline, only half of the subjects were compliant with physical activity recommendations (52%), but at the end of the intervention, 76% of the exercise group and 44% of controls complied with physical activity recommendations[50]. Likewise, a home-based cardiac rehabilitation program, composed by education and counselling intervention for 12 wk, regarding physical activity and cardiovascular risk factor management, showed an increase in physical activity index and time spent in moderate to vigorous physical activity during the intervention period with no changes in the control group[51].

Despite the well-known benefits of physical activity and exercise training, most of eligible cardiovascular patients do not benefit from cardiac rehabilitation programs[52], and these patients are more likely to taking less exercise[53]. Exercise levels may even decrease after the diagnosis of heart disease. The least active subjects are more likely to be older, male, obese and present symptoms during common activities such as short distance walking[53].

Participation in cardiac rehabilitation programs has been associated with decreased mortality and recurrent myocardial infarction, with compliant patients showing greater risk reduction when compared to patients with less attendance to exercise training sessions[54,55]. A recent meta-analysis including patients who have had myocardial infarction, coronary artery bypass graft, percutaneous transluminal coronary angioplasty, angina pectoris or CAD defined by angiography confirmed that exercise-based cardiac rehabilitation programs are effective in reducing total and cardiovascular mortality (in medium and long term) and hospital admissions (in

shorter term) but not the risk of myocardial infarction and revascularization[56]. Even though smoking cessation and nutritional counselling can also contribute for these positive outcomes, exercise training has an independent effect in the prevention of cardiovascular death[57]. Exercise-based cardiac rehabilitation programs promote an increase in cardiorespiratory fitness, a strong predictor of all-cause mortality, but also increase leisure time physical activity levels[51]. Hambrecht *et al*[58] demonstrated that estimated energy expenditure during leisure time physical activity is correlated with changes in coronary stenosis diameter independent of attendance in formal exercise interventions. Energy expenditure was lower in patients with progression of coronary atherosclerosis, higher in patients with no change, and highest in patients with regression of coronary stenosis diameter. High workloads were needed (about 1500 kcal/wk) to halt progression of coronary atherosclerosis, and regression of atherosclerosis was observed only in patients expending an average of 2200 kcal/wk in leisure time physical activity, corresponding to approximately 4 to 6 h of moderate intensity physical activity per week. A summary of the benefits of physical activity in secondary prevention is presented in Table 2.

Table 2 Summary of the cardiovascular protection mechanisms induced by physical activity in secondary prevention

Physical activity in secondary prevention	
Decreases	**Increases**
Resting heart rate	Heart rate reserve
Resting systolic blood pressure	Diastolic function
Myocardial oxygen demand	Coronary circulation
Risk of myocardial ischemia	Myocardial perfusion
Sympathetic tone	Parasympathetic activity
Arterial Stiffness	Endothelial function
Low-grade vascular inflammation (levels of pro-inflammatory cytokines)	Nitric oxide bioavailability and circulating levels of endothelial progenitor cells
Expression of reactive oxygen species	Expression and activity of anti-oxidant enzymes
Resting levels of plasminogen activator inhibitor type 1	Resting levels of tissue plasminogen activator activity
Platelet adhesion and aggregation	

CARDIOVASCULAR PROTECTION MECHANISMS INDUCED BY PHYSICAL ACTIVITY IN SECONDARY PREVENTION

It is well established that physical activity lowers resting heart rate and systolic blood pressure and increases heart rate reserve in patients with heart disease[59,60], thereby decreasing myocardial oxygen demands and preventing myocardial ischemia for a given absolute exercise intensity[61]. This may stem from a restored function of the autonomic nervous system towards lower sympathetic tone and enhanced parasympathetic activity[60,62]. In addition, aerobic physical activity improves myocardial perfusion in CAD patients, as a result of improved endothelial function, enhanced coronary circulation and vasomotor responses to vasoactive substances[63].

Aerobic physical activity seems to improve endothelial function in response to increases in blood flow-mediated shear stress, stimulating the endothelial production of nitric oxide and preventing its degradation by reactive oxygen species[64]. In addition, physical activity mitigates vascular inflammation while it improves anti-oxidant defences, also contributing for improving endothelial dysfunction[64-66]. Physical activity also promotes the mobilization of endothelial progenitor cells into the circulation to maintain endothelial integrity and stimulate vascular regeneration and endothelial repair[67,68].

Arterial stiffness has also been shown to decline in active individuals[69], as well as in CAD patients after cardiac rehabilitation[70,71], changes that may reduce aortic systolic blood pressure and cardiac afterload, increasing coronary perfusion and preventing myocardial ischemia as a result. A recent randomized controlled trial did not find significant changes between groups in arterial stiffness after an 8-wk exercise training program in post-myocardial infarction patients under optimized medication; however, when excluding those patients who did not attend, at least 80% of the exercise sessions, the authors found a significant reduction in arterial stiffness when compared to the control group[72].

In addition, a sedentary lifestyle during healthy aging is associated with decreased left ventricular compliance, leading to diminished diastolic performance, while prolonged, sustained endurance training seems to preserve ventricular compliance with aging[73] and to enhance diastolic function in heart failure patients[74,75]. Moderate to vigorous physical activity may also offer protection against cardiac events by inducing short-term transient ischemia, conferring a window of protection against an ischemic insult of longer duration, a phenomenon known as cardiac preconditioning[76,77]. It has been demonstrated in patients with old myocardial pectoris or angina pectoris that a single bout of physical exercise is capable of reducing exercise-induced ST-segment depression[78]. Prevention of coronary events may also stem from antithrombotic effects, even though evidence supporting an association between regular physical activity and decreased risk of thrombus formation and plaque rupture is scarce[79].

Acute strenuous physical activity seems to be associated to increased platelet adhesiveness and aggregation, increased thrombin formation and increased activity of several coagulation factors[80,81]. Nonetheless, regular moderate physical activity has been shown to blunt platelet adhesion and aggregation in healthy sedentary individuals[82] and heart failure patients[83]. Blood coagulation prospect after plaque rupture appears to diminish with regular physical activity, with studies finding lower plasma levels of several haemostatic factors in active individuals and women with CAD[84,85]. Inverse dose-response association between physical

activity and circulating levels of fibrinogen has been reported[86] and regular aerobic exercise seems to increase resting tissue plasminogen activator activity and to reduce plasminogen activator inhibitor type 1 in older adults[87,88].

SUMMARY

Physical inactivity is one of the four leading risk factors of non-communicable diseases, in particular those related with cardiovascular diseases such as acute coronary syndromes, stroke and heart failure. Despite this evident association, prevalence of physical inactivity is still elevated worldwide, being directly responsible for almost one tenth of premature death from non-communicable diseases. Even though physical activity has been shown to play an important role in primary and secondary prevention of cardiovascular diseases and major cardiovascular events, regular participation in physical activity is still below the necessary threshold to improve cardiorespiratory fitness and confer cardiac protection in many subjects. Reducing sedentary behaviours and performing less than the recommended minimum leisure time physical activity may be sufficient to reduce mortality, but meeting the recommended guidelines of moderate- or vigorous-intensity physical activities and reducing sedentary behaviours is associated with higher health benefits. Therefore, health professionals and policy makers in public health should align strategies to increase participation in physical activity, especially among those who show less interest or availability to engage in regular physical activity.

FUTURE PERSPECTIVES

The above-mentioned results are promising and provide good perspectives for the future.

Over the last decades the standard of living and physical activity profile performed throughout the day has been changing in societies around the world in parallel to the high death rates caused by CAD. Recent studies have addressed the time spent in sedentary behaviours as a risk factor for CAD, regardless of the amount and intensity of physical activity done. Taking these data into consideration, future studies should addresses both the causes and effects of both sedentary behaviour and physical inactivity in bodily adaptations and its relations with the development of cardiovascular disease.

It is also suggested that future studies evaluate the relationship between different covariates that may influence the effects of physical activity, such as age, sex, ethnicity, educational and/or socioeconomic status, and occupational and leisure-time contexts, in order to identify more assertively public health intervention strategies so that physical activity and exercise programs can be optimized for reducing the number of deaths caused by cardiovascular complications.

Although substantial evidence exists demonstrating the benefits of exercise training, referral to and participation in cardiac rehabilitation programs is still less than half among all eligible patients with cardiovascular diseases. Thus, more research is needed to identify common barriers to participation in physical activity programs, not only in the general population but also in special populations and minorities, and to understand how such barriers can be broken down to increase participation in physical activity.

Thus, we believe that such strategies could have important beneficial effects on the reduction of deaths caused by cardiovascular disease from the primary and secondary prevention.

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ORIGINAL ARTICLE

Basic Study

Impaired norepinephrine regulation of monocyte inflammatory cytokine balance in heart failure

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Abstract

AIM

To evaluate the effect of norepinephrine on inflammatory cytokine expression in *ex vivo* human monocytes and monocytic THP-1 cells.

METHODS

For human monocyte studies, cells were isolated from 12 chronic heart failure (HF) (66 ± 12 years, New York Heart Association functional class III-IV, left ventricular ejection fraction 22% ± 9%) and 14 healthy subjects (66 ± 12 years). Monocytes (1×10^6/mL) were incubated with lipopolysaccharide (LPS) 100 ng/mL, LPS + norepinephrine (NE) 10^{-6} mol/L or neither (control) for 4 h. Tumor necrosis factor-alpha (TNFα) and interleukin-10 (IL-10) production were determined by ELISA. Relative contribution of α- and β-adrenergic receptor subtypes on immunomodulatory activity of NE was assessed in LPS-stimulated THP-1 cells incubated with NE, the α-selective agonist phenylephrine (PE), and the β-selective agonist isoproterenol (IPN). NE-pretreated THP-1 cells were also co-incubated with the β-selective antagonist propranolol (PROP), α2-selective antagonist yohimbine (YOH) or the α1-selective antagonist prazosin (PRAZ).

RESULTS

Basal TNFα concentrations were higher in HF *vs* healthy

subjects (6.3 ± 3.3 pg/mL *vs* 2.5 ± 2.6 pg/mL, *P* = 0.004). Norepinephrine's effect on TNFα production was reduced in HF (-41% ± 17% HF *vs* -57% ± 9% healthy, *P* = 0.01), and proportionately with NYHA FC. Increases in IL-10 production by NE was also attenuated in HF (16% ± 18% HF *vs* 38% ± 23% healthy, *P* = 0.012). In THP-1 cells, NE and IPN, but not PE, induced a dose-dependent suppression of TNFα. Co-incubation with NE and antagonists revealed a dose-dependent inhibition of the NE suppression of TNFα by PROP, but not by YOH or PRAZ. Dose-dependent increases in IL-10 production were seen with NE and IPN, but not with PE. This effect was also antagonized by PROP but not by YOH or PRAZ. Pretreatment of cells with IPN attenuated the effects of NE and IPN, but did not induce a response to PE.

CONCLUSION

NE regulation of monocyte inflammatory cytokine production may be reduced in moderate-severe HF, and may be mediated through β-adrenergic receptors.

Key words: Monocytes; Cytokines; Heart failure; Inflammation

Core tip: In evaluating the relationship between sympathetic activation and inflammatory cytokine production in heart failure, we demonstrated that norepinephrine (NE) has reduced ability to suppress the production of the proinflammatory cytokine tumor necrosis factor-alpha, and increase anti-inflammatory interleukin-10, in human isolated monocytes from heart failure compared to healthy subjects. It appears to be mediated through beta-adrenergic, and not alpha-adrenergic, receptors based on monocytic THP-1 cells dose-response experiments. This suggests that the diminished immunomodulatory activity of NE in heart failure is primarily due to altered beta-adrenergic receptor function, and may represent an immunologic mechanism for the positive effects of beta-adrenergic blocking agents.

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INTRODUCTION

The importance of inflammatory cytokines to the pathophysiology of heart failure (HF) has been recognized for many years[1]. Much of the focus has been on proinflammatory tumor necrosis factor-alpha (TNFα) which has been shown to be cardiodepressant, contributes to exercise intolerance, and modulates apoptosis, oxidative stress and endothelial dysfunction[2,3]. Interleukin-10 (IL-10) antagonizes the inflammatory effects of TNFα. Both TNFα and IL-10 plasma levels are elevated in HF patients, although the increase in IL-10 is proportionately less, supporting the notion of a proinflammatory state[4].

Pro- and anti-inflammatory cytokine production is regulated by the adrenergic nervous system. Previous studies have demonstrated that β_2-, but not β_1-, receptor agonists attenuate TNFα expression, while increasing anti-inflammatory IL-10 production[5,6]. Conversely, $\alpha_{1,2}$-adrenergic stimulation results in increased expression of TNFα and reduction in IL-10[7]. Under normal physiologic conditions, norepinephrine, an α- and β-agonist, reduces TNFα and enhances IL-10 expression in monocytes exposed to lipopolysaccharide (LPS) and other stimuli[8]. However, in HF a paradox exists as both catecholamines and TNFα are elevated, which suggests that this negative feedback mechanism may be impaired. The mechanism for the diminished immunomodulatory response to norepinephrine in HF is also unknown but could occur secondary to the altered adrenergic expression and function known to exist in the failing heart.

The study purpose was to evaluate whether attenuation of TNFα production and augmentation of IL-10 production by the adrenergic agonist norepinephrine is altered in chronic HF compared to healthy, age-matched controls utilizing the model of LPS-stimulated monocytes. In addition, preliminary experiments were undertaken to determine the relative contribution of α- and β-adrenergic receptor subtypes on the immunomodulatory activity of norepinephrine in monocytic THP-1 cells.

MATERIALS AND METHODS

Isolated human monocytes

HF subjects were recruited from the cardiology clinics and the University Hospital at the University of Nebraska Medical Center. Subjects, male or female, were eligible for inclusion if they had: Clinical HF (LVEF < 40% on 2D-ECHO or MUGA within last 3 mo), New York Heart Association Functional Class (NYHA FC) III-IV HF, and were over 30 years of age. Exclusion criteria included: Primary restrictive or valvular HF, acute viral illness or bacterial infection, history of autoimmune disease, concurrent therapy with systemic norepinephrine, known anemia (Hgb < 10 mg/dL) or other contraindication to giving blood. Healthy subjects over the age of 30 were recruited from the University of Nebraska Medical Center through a posting on the university Intranet. All human subjects gave informed consent for their participation. The protocol was approved by the Institutional Review Board of the university.

Monocyte isolation was performed following a standard Nycodenz protocol[9], from 12 HF [age 66 ± 12 years old, New York Heart Association Functional Class (NYHA FC) 6 III, 6 IV, mean left ventricular ejection fraction 20% ± 10%] and 14 healthy subjects (age 66 ± 12 years). Aliquoted (1 x 10^6/mL) monocytes were

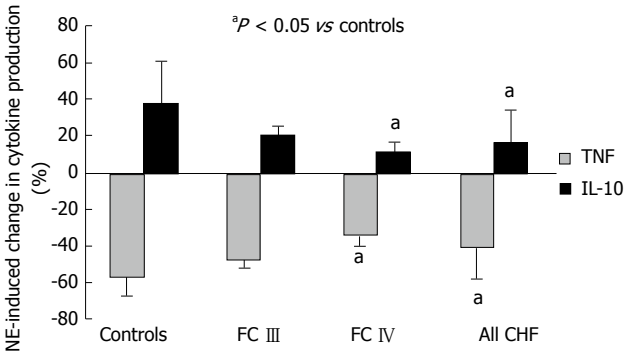

Figure 1 Comparative change in lipopolysaccharide-induced tumor necrosis factor-alpha and interleukin-10 production in monocytes induced by norepinephrine between heart failure patients and normal controls. Results expressed as mean ± SD. FC: Functional classification.

incubated with LPS 100 ng/mL, LPS + norepinephrine 10^{-6} mol/L or neither (negative control) for 4 h (all reagents from Sigma Chemical Co., Westbury, NY). Previous work demonstrated maximal stimulation of cytokines using the specified reagent concentrations and incubation time. TNFα and IL-10 production were determined by assaying the supernatant using commercially available enzyme-linked immunoassay (ELISA) kits (R and D Systems, Minneapolis, MN).

THP-1 cells

THP-1 cells were cultured and assayed in a supplemented RPMI media (ATCC, Manassas, VA). Cells were aliquoted into 1 × 10^6 cells/mL samples for experiments. Dose-response curves were determined for TNFα and IL-10 production in LPS-stimulated (100 ng/mL) THP-1 cell samples incubated with norepinephrine (10^{-5} to 10^{-10} mol/L), the α-selective agonist phenylephrine (PE) (10^{-6} to 10^{-10} mol/L) and the β-selective agonist isoproterenol (IPN) (10^{-5} to 10^{-10} mol/L). LPS-stimulated THP-1 cells were also co-incubated with a fixed concentration of norepinephrine 10^{-6} mol/L, which provided maximal effect in agonist experiments, and the β-selective antagonist propranolol (PROP) (10^{-5} to 10^{-10} mol/L), α2-selective antagonist yohimbine (YOH) (10^{-6} to 10^{-10} mol/L) or the α1-selective antagonist prazosin (PRAZ) (10^{-6} to 10^{-10} mol/L), for generation of dose-response curves. TNFα and IL-10 production was assessed as described above. Samples were assayed in duplicate.

Statistical analysis

To control for inherent inter-subject differences in constitutive production of cytokines, changes in TNFα and IL-10 concentrations are expressed as percent reduction by norepinephrine + LPS compared to LPS only for each sample. Comparison of percent reduction in TNFα and IL-10 concentrations from isolated monocytes of controls and HF subjects was performed by an independent two sample *t* test. Significance was set at $P < 0.05$. Results are reported as mean ± SD. Comparative effects on cytokine production in THP-1 cells between the different α- and β-adrenergic reagents was assessed *via* visual inspection of the dose-response curves as this was a preliminary study. The statistical methods of this study were reviewed by Mimi Lou, MS (biostatistician) from the University of Southern California School of Pharmacy.

Table 1 Patient characteristics

%	Heart failure (*n* = 12)	Healthy subjects (*n* = 14)	*P* value
Age (yr)	66 ± 12	66 ± 12	0.994
Male	67	36	0.238
Caucasian ethnicity	92	100	0.462
LVEF	22 ± 9		
Diabetes	33	0	0.033
CAD	50	0	0.004
Hypertension	25	29	1.000
Medications			
Beta-blocker	50	0	
ACE inhibitor or ARB	75	7	
Loop diuretic	100	0	
ARA	42	0	
Hydralazine/isosorbide dinitrate	8	0	
Amiodarone	50	0	
Digoxin	50	0	

ACE: Angiotensin converting enzyme inhibitor; ARA: Aldosterone receptor blocker; ARB: Angiotensin receptor blocker; CAD: Coronary artery disease; LVEF: Left ventricular ejection fraction.

RESULTS

Isolated human monocytes

Study subject characteristics are described in Table 1. Basal TNFα concentrations (supernatant) were higher in HF than healthy subjects (6.3 ± 3.3 pg/mL *vs* 2.5 ± 2.6 pg/mL, $P = 0.004$). Norepinephrine reduction of TNFα production was significantly reduced in monocytes from HF subjects (-41% ± 17% HF *vs* -57% ± 9% healthy, $P = 0.01$). Norepinephrine-induced increases in monocyte IL-10 production was also reduced in HF (16% ± 18% HF *vs* 38% ± 23% healthy, $P = 0.012$). The diminished response to norepinephrine appeared related to severity of HF, with a greater diminution for both TNFα and IL-10 in NYHA FC Ⅳ *vs* NYHA FC Ⅲ and controls (Figure 1). A signal for reduced IL-10 response in patients with left ventricular ejection fractions ≤ 20% when compared to those with left ventricular ejection fractions > 20% (7% ± 12 *vs* 25% ± 20%, $P = 0.07$) was also present. There were no differences in cytokine response based on the presence or absence of beta-blocker (BB) therapy (TNFα: -37% ± 17% no BB *vs* -46% ± 17% BB, $P = 0.9$; IL-10: 11% ± 13% no BB *vs* 20% ± 22% BB, $P = 0.3$), or HF etiology (TNFα: -41% ± 17% ischemic *vs* -42% ± 18% non-ischemic, $P = 0.7$; IL-10: 20% ± 19% ischemic *vs* 8% ± 15% non-ischemic, $P = 0.5$).

THP-1 cells

Norepinephrine and IPN, but not PE, induced a concentration-dependent suppression of TNFα production

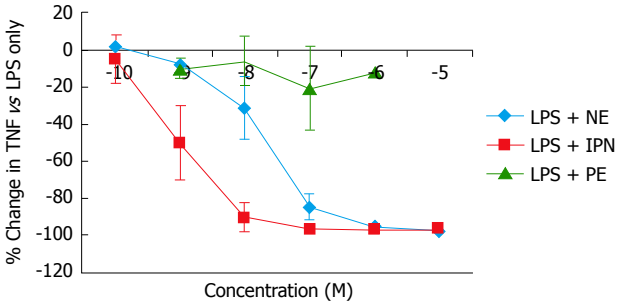

Figure 2 Concentration-dependent changes in lipopolysaccharide-induced tumor necrosis factor-alpha production in monocytic THP-1 cells induced by the α-adrenergic agonist phenylephrine and the β-adrenergic agonist isoproterenol. Results expressed as mean ± SD. LPS: Lipopolysaccharide; NE: Norepinephrine; IPN: Isoproterenol; PE: Phenylephrine.

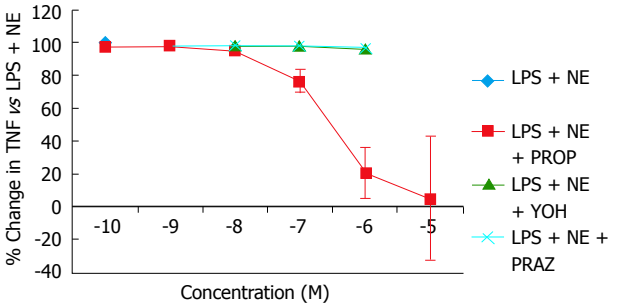

Figure 3 Concentration-dependent changes in norepinephrine attenuation of lipopolysaccharide-induced tumor necrosis factor-alpha production in monocytic THP-1 cells blocked by the α1-adrenergic antagonist prazosin, the α2-adrenergic antagonist yohimbine, and the β-adrenergic antagonist propranolol. Results expressed as mean ± SD. LPS: Lipopolysaccharide; NE: Norepinephrine; PE: Phenylephrine; PROP: Propranolol; YOH: Yohimbine; PRAZ: Prazosin.

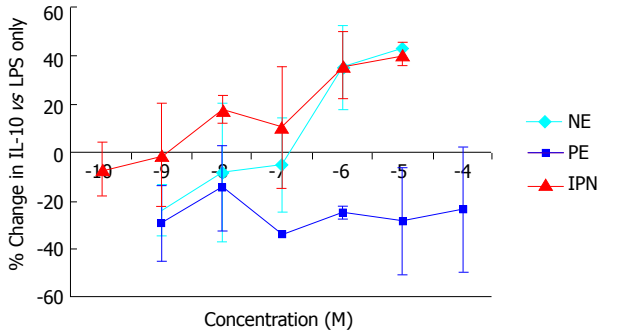

Figure 4 Concentration-dependent changes in interleukin-10 production in THP-1 cells induced by the α-adrenergic agonist phenylephrine and the β-adrenergic agonist isoproterenol. Results expressed as mean ± SD. NE: Norepinephrine; IPN: Isoproterenol; PE: Phenylephrine; LPS: Lipopolysaccharide; IL: Interleukin.

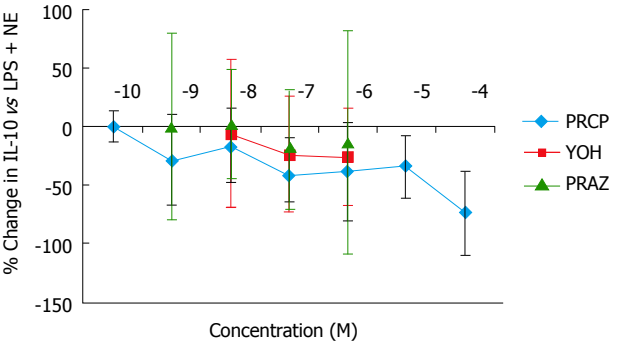

Figure 5 Concentration-dependent changes in norepinephrine attenuation of interleukin-10 production in THP-1 cells blocked by the α1-adrenergic antagonist prazosin, the α2-adrenergic antagonist yohimbine, and the β-adrenergic antagonist propranolol. Results expressed as mean ± SD. LPS: Lipopolysaccharide; NE: Norepinephrine; PE: Phenylephrine; PROP: Propranolol; YOH: Yohimbine; PRAZ: Prazosin.

in cultured monocytic THP-1 cells. Equivalent maximal suppression was achieved with norepinephrine 10^{-6} mol/L or IPN 10^{-7} mol/L (Figure 2). Co-incubation of THP-1 cells with LPS, norepinephrine and selective adrenergic receptor antagonists revealed a concentration-dependent inhibition of the norepinephrine suppression of TNFα by PROP, but not by YOH or PRAZ. Maximal blockade of norepinephrine's effects was obtained at PROP 10^{-5} mol/L (Figure 3). Concentration-dependent increases in IL-10 production were seen with norepinephrine and IPN, but not with PE (Figure 4). This effect was also antagonized by PROP but not by YOH or PRAZ (Figure 5). Pretreatment of cells with IPN (10^{-7} mol/L) for 4 h attenuated the effects of norepinephrine and IPN, but pretreatment did not induce a response to PE (data not shown).

DISCUSSION

Our preliminary findings suggest norepinephrine's ability to regulate monocyte inflammatory cytokine production may be reduced in moderate to severe HF. The ability of norepinephrine to exert an overall anti-inflammatory effect on the balance of production of TNFα and IL-10 appears to be reduced in proportion to disease severity, as indicated by the a greater diminution of the induced cytokine response in monocytes isolated from NYHA functional class Ⅳ as compared to functional class Ⅲ patients and controls. This is the first report demonstrating monocyte TNFα/IL-10 responsiveness to norepinephrine is diminished in HF and provides a novel mechanism to explain increased production of TNFα in HF. Our results are consistent with a study demonstrating a reduced inhibitory effect of norepinephrine on TNFα production assessed in whole blood of HF patients[10]. Our results also agree with other studies demonstrating basal monocytic inflammatory cytokine production is upregulated in chronic HF[11,12].

In addition, based on our experiments in monocytic THP-1 cells, norepinephrine's immunomodulatory effect in monocytes is likely secondary to activation of β-adrenergic receptors, with no or little involvement of α-adrenergic receptors. This was evidenced by the concentration-dependent reduction of TNFα and augmentation of IL-10 production by norepinephrine and isoproterenol, but not by phenylephrine. The effect of norepinephrine could also be antagonized by β-receptor blockade with propranolol, whereas α_1 and α_2-blocking agents had no effect. This is consistent with other

investigations and provides a plausible mechanism for the diminished cytokine response to norepinephrine observed in HF[13-16]. Altered β-adrenergic receptor function and expression have been well characterized in the failing heart[17,18]. Beta1-adrenergic receptor density and function is reduced in the failing heart, while beta-2-adrenergic receptor expression remains essentially unchanged[19]. This shift in importance towards the beta-2-adrenergic receptor would suggest immunomodulatory response to catecholamines would be preserved, however, other pathophysiologic alterations may still occur that change or limit their functionality[20,21]. In addition, norepinephrine is known to have low affinity for beta2-adrenergic receptors, but showed similar maximal effects comparable to isoproterenol[22,23]. Therefore, whether the observed immunomodulatory response to norepinephrine is mediated solely through beta2-adrenergic receptors requires confirmation.

The study has important limitations. The human monocyte experiment sample size is small. Unfortunately we did not have an adequate number of human monocytes to evaluate adrenoreceptor expression between HF and healthy subjects which would strengthen these preliminary findings as THP-1 are a monocytic cell-line but may not be identical to human monocytes. We also did not examine the isolated effects of the receptor antagonists propranolol, yohimbine and prazosin as we are not aware of literature suggesting a direct effect on inflammatory cytokine production, only modulation in a proinflammatory model[6,7,13,14,24-27]. As such, the results of this study are preliminary and should be interpreted as hypothesis generating. Further studies are required to determine whether monocyte production of other cytokines exhibit a similar reduction in response to catecholamine stimulation in HF, to fully characterize the mechanism for the observed impaired catecholamine-cytokine response, and to devise pharmacologic strategies to normalize cytokine responsiveness to the adrenergic nervous system.

ACKNOWLEDGMENTS

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COMMENTS

Background

Inflammation has been recognized as a major contributing factor to the pathophysiology of heart failure (HF) with reduced ejection fraction (HFrEF) for many years. However, attempts to improve the prognosis of HFrEF patients by targeting proinflammatory cytokines have failed largely in part to an incomplete understanding of the mechanisms which contribute to the initiation and perpetuation of their expression. Pro- and anti-inflammatory cytokine production is regulated by the adrenergic nervous system. Under normal physiologic conditions, norepinephrine, an α- and β-agonist, reduces tumor necrosis factor-alpha (TNFα) and enhances interleukin-10 expression in monocytes exposed to lipopolysaccharide and other stimuli. However, in HFrEF a paradox exists as both catecholamines and TNFα are elevated, which suggests that this negative feedback mechanism may be impaired.

Research frontiers

HF is recognized as a proinflammatory syndrome, and that inflammatory pathways likely contribute to the decline in cardiac function. However, the mechanisms for initiation or persistence of the proinflammatory balance are poorly described and remain an area of active investigation. Clinical trials of agents targeting proinflammatory cytokines have failed to improve long term prognosis of HF patients. A major explanation for the failures is an incomplete understanding of mechanisms underlying the proinflammatory state.

Innovations and breakthroughs

Although it has been described that catecholamines reduce proinflammatory cytokine production, this is the first study to demonstrate that attenuation of monocyte inflammatory cytokine production by norepinephrine is reduced in cells isolated from HF patients compared to healthy individuals.

Applications

The findings are mainly descriptive but may represent a novel pathway for the proinflammatory state in patients with HF. If alterations in β-adrenergic receptor function is a mechanism for the diminished counter-regulatory response to norepinephrine in HF, some of the benefit of beta-adrenergic receptor blockers in HF may be due to immunomodulatory or anti-inflammatory effects. These preliminary findings need confirmation in future studies.

Peer-review

The manuscript is interesting because it adds new information concerning mechanisms underlying this proinflammatory state.

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ORIGINAL ARTICLE

Retrospective Study

Left ventricular false tendons and electrocardiogram repolarization abnormalities in healthy young subjects

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Author contributions: All authors contributed equally to this work; Lazarevic Z collected and analyzed the data and drafted the manuscript; Lazarevic Z and Borrione P designed and supervised the study; Ciminelli E, Quaranta F, Sperandii F, Guerra E, Pigozzi F and Borrione P revised the manuscript for important intellectual content; all the authors have read and approved the final version to be published.

Institutional review board statement: This study retrospectively and anonymously analyzed clinical data routinely collected during the pre-participation screening of competitive athletes. For this reason, ethics committee approval was not required.

Informed consent statement: Subjects were not required to give informed consent for the study since the analysis used anonymous clinical data.

Conflict-of-interest statement: There are no financial or other relationships that might lead to a conflict of interest in this study.

Data sharing statement: No additional data are available.

Manuscript source: Invited manuscript

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Abstract

AIM

To describe echocardiographically left ventricular false tendon characteristics and the correlation with ventricular repolarization abnormalities in young athletes.

METHODS

Three hundred and sixteen healthy young athletes from different sport disciplines were evaluated from 2009 to 2011 during routine screening for agonistic sports eligibility. All subjects, as part of standard pre-participation screening medical evaluation, underwent a basal and post step test 12-lead electrocardiogram (ECG). The athletes with abnormal T-wave flattening and/or inversion were considered for an echocardiogram evaluation and an incremental maximal exercise test on a cycle ergometer. Arterial blood pressure and heart rate, during and after exercise, were also measured.

RESULTS

Twenty-one of the 316 subjects (6.9%) showed false tendons in the left ventricle. The majority of false

tendons (52.38%) were localized between the middle segments of the inferior septum and the lateral wall, 19.06% between the distal segments of the septum and the lateral wall, in 5 subjects between the middle segments of the anterior and inferior walls, and in one subject between the middle segments of the anterior septum and the posterior wall. ECG abnormalities, represented by alterations of ventricular repolarization, were found in 11 subjects (52.38%), 90% of these anomalies were T wave abnormalities from V1 to V3. These anomalies disappeared with an increasing heart rate following the three minute step test as well as during the execution of the maximal exercise.

CONCLUSION

Left ventricular false tendons are frequently localized between the middle segments of the inferior septum and the lateral wall and are statistically associated with ventricular repolarization abnormalities.

Key words: Repolarization anomalies; T wave inversion; Young athletes; False chordae tendineae; Echocardiography

Core tip: Ventricular repolarization abnormalities of subjects with false tendons were most frequently inverted T waves from V1 to V3. In this study, statistically significant associations between the presence of false tendons in the left ventricle and ventricular repolarization abnormalities in young healthy athletes were found. Furthermore, this study provides useful information for sports physicians when basic electrocardiogram abnormalities of ventricular repolarization are considered.

Lazarevic Z, Ciminelli E, Quaranta F, Sperandii F, Guerra E, Pigozzi F, Borrione P. Left ventricular false tendons and electrocardiogram repolarization abnormalities in healthy young subjects. *World J Cardiol* 2016; 8(10): 590-595 Available from: URL: http://www.wjgnet.com/1949-8462/full/v8/i10/590.htm DOI: http://dx.doi.org/10.4330/wjc.v8.i10.590

INTRODUCTION

"False tendons" are fibrous, fibrous-muscle or muscle structures, variable in length and thickness, found in the left ventricular cavity, generally located between the free wall of the left ventricle or a papillary muscle and the interventricular septum, without connection to the mitral valves[1-3]. Turner first described the false tendons in the left ventricle (LVFT) in 1893 but the functional significance of these structures is still unclear[4].

The left ventricular false tendons are easily identifiable with bi-dimensional echocardiography. They are usually found in about 50% of autoptical examinations[5-8], most frequently in males[4,9]. The prevalence of false tendons in the left ventricle appears to be higher in young athletes than in the general population (6.9% *vs* 0.5% to 4.6%)[7]. This difference can be attributed to an increased use of echocardiography in young athletes. However, a young athlete often has excellent acoustic windows, physiological bradycardia and enlargement of the ventricular cavity, which permit better identification of all structures inside the ventricular cavity and in particular, the trabeculae or fibrous-muscle structures, stretched between the walls of the ventricle[10].

The primary characteristic of the false tendons to be emphasized is their tension or laxity inside the left ventricular cavity during the cardiac cycle. More frequently, false tendons are stretched in diastole and are flaccid in systole (from 71.4% to 86% of cases); in some cases they are in tension for the entire cardiac cycle (10.6%-15.4%), while in rare cases they remain flaccid for the entire cycle (1.2%-2.8%).

This type of information is very useful since the stretching of these ventricular structures can play an important role in the genesis of electrocardiographic abnormalities or real arrhythmias. This mechanical phenomenon is also the basis of the genesis of a murmur that can be appreciated on auscultation in some subjects with false tendons[1,11]. Generally, LVFTs have been considered a normal variation but in some cases, they may be related to cardiac pre-excitation, ventricular arrhythmias, dilation of the left ventricle, congenital and/or acquired heart diseases and some repolarization abnormalities on resting electrocardiograms (ECGs), including negative or biphasic T waves in precordial leads as well as early repolarization[12].

A literature review highlighted that most of the studies regarding LVFT were performed on a general population and documented a correlation with arrhythmias and structural cardiac disease, while only a few and dated investigations described the correlation with ventricular repolarization abnormalities[13] and no studies were conducted on healthy young athletes.

The purpose of this study was to describe the echocardiographic characteristics of LVFTs and their correlation with the abnormal ventricular ECG repolarization findings in a group of healthy young athletes.

MATERIALS AND METHODS

The study population was composed of 316 subjects (162 males and 154 females) with a mean age of 22.3 ± 4 years, consecutively evaluated from March 2009 to November 2011. All subjects were healthy and engaged in different agonistic sports disciplines (athletics, swimming, gymnastics, basketball, football and volleyball) for a total of approximately 15-20 h a week for about 8 mo a year.

All tested athletes had a negative medical family history and a normal baseline medical examination. In most cases (71%), auscultation sounds with the characteristics of a Still's murmur could be heard.

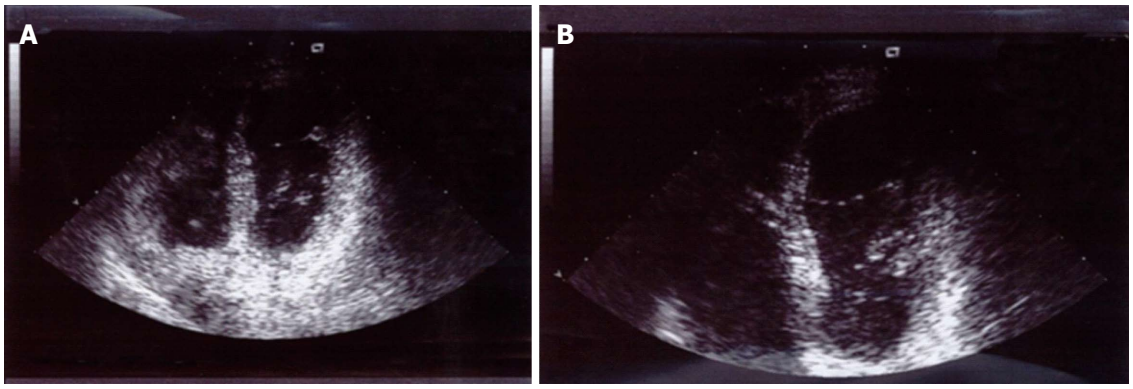

Figure 1 Left ventricular false tendon between the middle segments of the inferior septum and the lateral wall during the cardiac stolic (A) and diastolic (B) cycle.

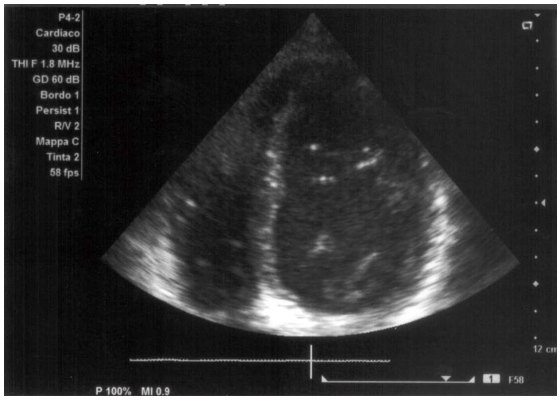

Figure 2 Double false tendon stretched between the lateral wall and inferior septum.

Each subject underwent: (1) a 12 lead ECG at rest and after a step test performed by the electrocardiographic device ESAOTE 421 ArchiMed-Esaote Biomedica. T wave flattening and the presence of T-wave inversion > 2 mm in one or more leads were considered for further investigations; (2) echocardiogram with bi-dimensional and color-Doppler evaluation using the instrument Terason T-3000 MORTARA. The echocardiographic diagnosis of false tendons in the left ventricle was based on the finding of a linear echogenic tendon, which crosses the left ventricular cavity, connecting different sites of the ventricular endocardium, and not correlated to the mitral valve apparatus. The false tendon size, thickness, pattern inside the left ventricular cavity, points of connection and tension or laxity during the cardiac cycle were evaluated; and (3) maximal exercise test on a cycle ergometer using the device Ergoline Ergometrics 800S and ECG monitoring device *via* CardiO2 MedGraphics, according to a protocol that included a 2 min warm-up at 20 W and subsequent increases of load for 40 W every 2 min, with active and passive recovery duration of 5 min. Values of systemic blood pressure and heart rate, during and after exercise were measured. Any cardiorespiratory symptoms and/or electrocardiographic changes during the execution of the test were noted.

Statistical analysis

Variables were reported by counts and percentages. When appropriate, comparisons were performed using a χ^2 test or Fisher's exact test. To evaluate the association between the variable of interest and the determinant, the odds ratio and 95% confidence interval (Cornfield's method) were calculated. All the tests were considered statistically significant for P values < 0.05. The analyses were conducted with STATA v.11.

RESULTS

Twenty one of the 316 subjects (6.9%), 12 males and 9 females with a mean age of 22 ± 2 years, showed false tendons in the left ventricle.

The majority of false tendons were localized between the middle segments of the inferior septum and the lateral wall (52.38%) (Figures 1 and 2), between the distal segments of the septum and the lateral wall (19.06%), between the middle segments of the anterior and inferior walls (23.8%), and between the middle segments of the anterior septum and the posterior wall (4.76%) (Table 1).

ECG abnormalities represented by alterations of ventricular repolarization were found in 11 subjects (52.38%).

The anomalies of the phase of ventricular repolarization observed in these cases were almost always characterized by the presence of inverted T waves from V1 to V3 (9 of 11 cases with abnormalities of the ventricular repolarization phase, 81%) (Figure 3).

Only one case had diphasic T waves from V1 to V3 and an inverted T wave in DIII and aVF. In this study, 90% of the anomalies of ventricular repolarization were abnormalities of the T wave from V1 to V3.

These anomalies disappeared with an increasing heart rate following three minutes of the step test as well as during the execution of the maximal exercise (Figure 4).

The association between false tendons in the left

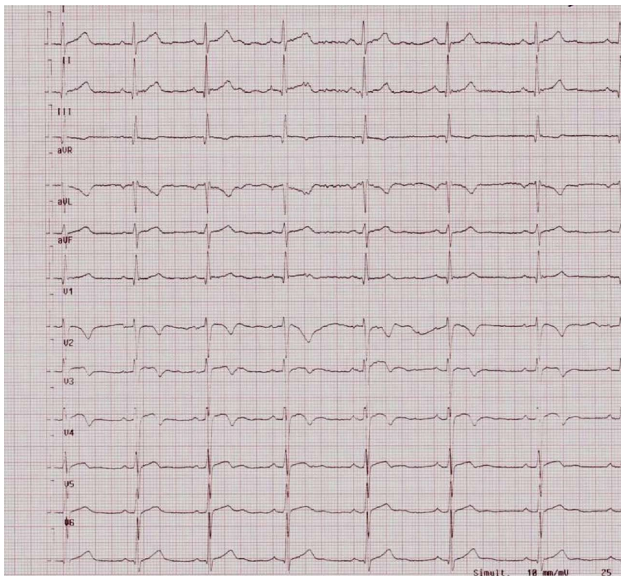

Figure 3 Ventricular repolarization anomalies in precordial leads V1-V4: Inverted T waves from V1 to V3 and flat T waves in D3.

ventricle and the abnormal ventricular repolarization phase showed an odds ratio of 11 (95%CI: 3.4-35.6, $P < 0.0001$).

The insertion sites of false tendons most often associated with abnormalities of the ventricular repolarization were in the middle segments of the inferior septum and the lateral wall (63.6%) and the distal segments of the septum and the lateral wall (30%). However, in this case, the Fisher's exact test did not demonstrate statistical significance ($P = 0.712$).

DISCUSSION

This study showed the presence of a statistically significant association between false tendons in the left ventricle and ventricular repolarization abnormalities. However, the odds ratio value is too high (a value of 11 with confidence interval width ranging from 3.4 to 3.5) due to the low number of subjects.

The false tendons were located more frequently (in over 63% of cases) between the middle segments of the interventricular septum and the lateral wall and presented a greater thickness when compared to normal tendons (> 2 mm). In 30% of cases, the false tendons stretched between the distal segments of the interventricular septum and the lateral wall.

The repolarization abnormalities were almost of the same type. Indeed, 90% of the subjects with a false tendon and an abnormal ventricular repolarization phase presented with alterations in T waves (more often reversed and symmetrical, sometimes diphasic) from V1 to V3.

The association between abnormalities of ventricular repolarization and false tendons in the left ventricle was described by Sutton *et al*[14] who presented three case reports regarding three patients in apparently good health with a false tendon in the left ventricle and inverted T waves in the precordial leads.

Table 1 Type of false tendon and altered ventricular repolarization

Anatomic site of false tendon	N° (%)	Altered ventricular repolarization N° (%)
Middle segment inferior septum - lateral wall	11 (52.38)	7 (63.6%)
Distal segment inferior septum - lateral wall	4 (19.06)	2 (50%)
Middle segment posterior wall - anterior septum	1 (4.76)	0 (0%)
Middle segment inferior wall - anterior wall	5 (23.8)	2 (40%)
Description of altered ventricular repolarization	Frequency	%
Flat T wave in DII, aVF, inverted T wave in DIII	10	47.6
Biphasic T wave in DII, DIII and aVF after incremental max exercise test	1	4.8
Biphasic T wave in V2 and V3, normalize after incremental max exercise test	1	4.8
Inverted T wave from V1 to V3 normalizes after incremental max exercise test	6	28.6
Inverted asymmetric T wave from V1 to V3 normalizes after incremental max exercise test	1	4.8
Inverted symmetric T wave from V1 to V3, that reduces but does not normalize after incremental max exercise test	1	4.8
Flat T wave in DIII and inverted from V1 to V3 normalizes after incremental max exercise test	1	4.8

Sutton *et al*[14] also noted an "electro-anatomical" correlation between false tendons and ECG abnormalities as well as the absence of modifications after a long follow-up of 13 years in his study. Other authors also identified the presence of Purkinje fibres within the false tendons; this information could explain the onset of arrhythmias associated with the presence of left ventricular false tendons. Some authors investigating the possible link between false tendons and ECG abnormalities identified 71 subjects with a false tendon and studied the possible presence of arrhythmias, such as ventricular extrasystole. The authors concluded that the false tendon can contribute to the etiology of arrhythmias such as ventricular extrasystole, but they did not describe abnormalities of the ventricular repolarization phase[15,16].

The statistically significant association between the presence of false tendons in the left ventricle and abnormal ventricular repolarization phase could have several explanations. The presence of a false tendon in the left ventricle would increase, although minimally, myocardial active mass, typical of the athlete's heart[10]. This increase in myocardial mass could activate a prolongation of the depolarization and eventually lead to T wave inversion. An alternative hypothesis considers purely mechanical aspects: the false tendon and its site of anatomical implantation (mainly medium-distal segments of the inferior septum and lateral wall) may exert mechanical traction

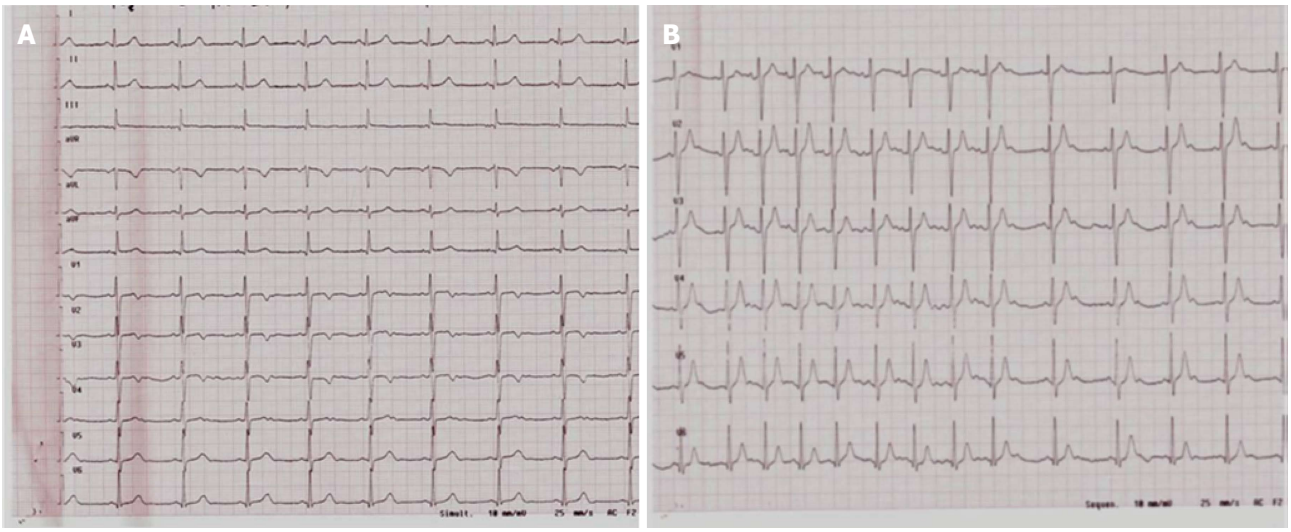

Figure 4 Ventricular repolarization anomalies at rest (A) and normalization after the incremental maximal exercise test on a cycle ergometer (B).

sufficient to alter repolarization.

Finally, the fibro-muscular false tendon contains elements of the cardiac conduction system, often providing the explanation for electrocardiographic abnormalities that might be associated with these structures[4].

In clinical practice, abnormal T-wave flattening and/or inversion can be detected in different physiological and pathological conditions[17]. When considering young and healthy subjects, T-wave flattening and/or inversion were found with variable frequency, from 0.5% to 19%, and in high-level athletes they have been described as clinically negative in 60%-80%[18]. The behavior of ventricular repolarization abnormalities during the incremental maximal exercise test on a cycle ergometer has fundamental importance. This test has significant diagnostic and prognostic importance. Usually, the normalization of T waves during a maximal exercise test on an ergometer suggests their benign nature, although in some cases organic diseases of the heart cannot be excluded[19] .

The results of this study showed a statistically significant association between the presence of false tendons in the left ventricle and ventricular repolarization abnormalities in a population of young healthy subjects engaged in competitive sports. The type of false tendon most frequently associated with ventricular repolarization abnormalities was identified in the middle-distal segments of the inferior interventricular septum and the lateral wall. Ventricular repolarization abnormalities of subjects with false tendons were all of the same type, indeed, the electrocardiogram showed inverted T waves from V1 to V3. These anomalies also regressed with the increase in heart rate during the physical exercise or incremental maximal exercise test on a cycle ergometer. A common electrocardiographic pattern can be described in athletes with a false left ventricular tendon. In fact, the ventricular repolarization abnormalities in the electrocardiogram in these individuals were similar and showed the same behavior under stress. The limitations of our study are related to the low number of participants and the lack of long term follow-up to evaluate eventual modifications.

In conclusion, the present study showed a statistically significant association between the presence of false tendons in the left ventricle and ventricular repolarization abnormalities in a population of young healthy subjects engaged in competitive sports.

The type of false tendon most frequently associated with ventricular repolarization abnormalities was identified among the middle-distal segments of the inferior interventricular septum and the lateral wall. Nonetheless, the results of this study may provide useful information for sports physicians when basic ECG abnormalities of ventricular repolarization are found.

COMMENTS

Background

False tendons are fibrous, fibrous-muscle or muscle structures, variable in length and thickness, found in the left ventricular cavity, generally located between the free wall of the left ventricle or a papillary muscle and the interventricular septum, without connection to the mitral valves. In 1893, Turner first described the false tendons in the left ventricle (LVFT) but the functional significance of these structures is still unclear. The left ventricular false tendons are easily identifiable with bi-dimensional echocardiography. They are usually found in 50% of autoptical examinations, mostly in males. Generally, LVFTs have been considered a normal variation but in some cases could be related to cardiac pre-excitation, ventricular arrhythmias, dilation of the left ventricle, congenital and/or acquired heart disease and some repolarization abnormalities on a resting electrocardiogram (ECG), including negative or diphasic T waves in precordial leads as well as early repolarization. Only a few studies have investigated the correlation between LVFTs and ventricular repolarization abnormalities and to our knowledge, no studies have been carried out on healthy young athletes. In this study they evaluated and described the echocardiographic characteristics of LVFTs and their correlation with the abnormal ventricular ECG repolarization findings in a group of healthy young athletes.

Research frontiers

The results of this study clarified the functional significance of left false tendons, adding useful information for the interpretation of abnormal ventricular ECG

repolarization findings during the pre-participation screening of healthy athletes.

Innovations and breakthroughs

The present study describes a statistically significant association between the presence of false tendons in the left ventricle and ventricular repolarization abnormalities for the first time. This finding certainly provides useful information for sports medicine physicians for the interpretation of ECG abnormalities found in otherwise healthy athletes during the pre-participation screening evaluation.

Applications

This study provides useful information for sports physicians about sport eligibility evaluation for athletes when basic ECG abnormalities of ventricular repolarization are found.

Terminology

LVFTs: Fibrous, fibrous-muscle or muscle structures generally located between the free wall of the left ventricle or a papillary muscle and the interventricular septum, without connection to the mitral valves; ECG: Electrocardiogram; VRA: Ventricular repolarization abnormalities.

Peer-review

This is an interesting study that is well written and uses appropriate methods. It was suggested that another image demonstrating the LV false tendon should be provided as this is a key aspect of the study and should be better illustrated.

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ORIGINAL ARTICLE

Retrospective Study

Congenital coronary artery fistulas complicated with pulmonary hypertension: Analysis of 211 cases

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Author contributions: Said SAM has solely contributed to conception, design, drafting and final approval of the manuscript.

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Data sharing statement: Technical appendix, statistical code, and dataset available from the corresponding author at salah.said@gmail.com.

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Abstract

AIM

To compare the behavior of pulmonary hypertension (PHT) associated with coronary artery fistulas (CAFs) between the Asian and Caucasian subjects.

METHODS

CAFs may be complicated with PHT secondary to left-to-right shunt. Literature review limited to the English language. A total of 211 reviewed patients were collected. Of those, 111 were of Asian and 100 were of Caucasian ethnic origin. The mean age of the Asian and the Caucasian groups of patients were 48.9 (range 19-83) and 49.9 years (range 16-85), respectively. In both groups, right heart catheterization was the most commonly (95%) used method for determining pulmonary artery pressure.

RESULTS

From all of the reviewed subjects, PHT was found in 49 patients (23%), of which 15 were Asian and 34 were Caucasian. In 75% of PHT subjects, mild to moderate PHT was reported and 76% of the fistulas had a vascular mode of termination. Treatment was surgical in 61%, followed by percutaneous therapeutic embolization (27%) and finally conservative medical management in 12% of PHT subjects. PHT was associated with a slight female gender predominance. The majority demonstrated mild to moderate PHT. PHT was reported more frequent in the Caucasian compared with the Asian ethnicity group. The majority of fistulas in patients with PHT had a vascular mode of termination. The results of this review are intended to be indicative and require cautious interpretation.

CONCLUSION

The likelihood for a CAF patient to develop PHT is presented when possessing the following features, with a Caucasian female having a fistula with a vascular mode of termination.

Key words: Congenital coronary artery fistulas; Congenital anomaly; Pulmonary hypertension; Asian population; Caucasian population

Core tip: Congenital coronary artery fistulas (CAFs) are infrequent but hemodynamically important anomalies which may evolve a myriad of complications, such as myocardial infarction, congestive heart failure, infective endocarditis, aneurysm, rupture, pericardial effusion, arrhythmias and sudden death. In addition, secondary pulmonary hypertension (PHT) may complicate the course of CAFs. Moreover, when monitoring CAF patients, the clinicians responsible for the management of patients with congenital CAFs should be aware of the development of PHT during the course of the disease.

Said SAM. Congenital coronary artery fistulas complicated with pulmonary hypertension: Analysis of 211 cases. *World J Cardiol* 2016; 8(10): 596-605 Available from: URL: http://www.wjgnet.com/1949-8462/full/v8/i10/596.htm DOI: http://dx.doi.org/10.4330/wjc.v8.i10.596

INTRODUCTION

Congenital coronary artery fistulas (CAFs) are uncommon anomalies. Most CAFs are small and hemodynamically inconsequential with a negligible shunt. However, some can be sizeable and lead to shunting of blood from the coronary circulation to low-pressure pulmonary vascular bed, resulting in pulmonary hypertension (PHT)[1]. CAFs may be associated with normal[2-4] pulmonary artery pressure (PAP) in unilateral[5-8] or bilateral[9,10] fistulas, or may sometimes be accompanied with elevated PAP[11-14]. Rarely, in octogenarians with bilateral CAFs, PAP may remain normal[15].

The hemodynamic consequences of CAFs varies, depending on their magnitude and the cardiac chamber or vascular site involved. Fistulas terminating into the right heart chambers may produce left-to-right shunt and volume overload of the pulmonary circulation, whereas fistulas to the left heart side cause left ventricular volume overload.

In a literature review, 211 subjects were included and a comparison was made between the Asian (*n* = 111) and Caucasian (*n* = 100) subjects regarding the behavior of PAP associated with CAFs.

MATERIALS AND METHODS

The data source was based on an extensive literature review of the English literature in the PubMed database regarding congenital CAFs and PAP. The search was conducted using the terms "congenital coronary artery fistulas" and "pulmonary artery pressure". Inclusion of a paper occurred when full data on PAP either using right heart catheterization (RHC) (direct measurement) or Doppler echocardiography [calculation of estimated PAP based on tricuspid regurgitation (TR) peak velocity] were provided.

This retrieval resulted in a collection of 133 papers which included 49 of Asian (*n* = 111 patients) and 84 of Caucasian (*n* = 100 patients) reports. Three were excluded because of duplication. Reference lists from selected papers were manually searched for potentially relevant publications. Whenever available, the most recent data were included. Another seven papers were therefore added, meaning that the final retrieval result was 137 papers. Congenital multiple micro-fistulas were not included and patients with acquired fistulas were excluded.

Definition of PHT[16-18]

Invasive method: PHT is defined as the systolic PAP (sPAP) or mean PAP, exceeding 35 mmHg or 25 mmHg, respectively. Furthermore, the mean PAP rises above 30 mmHg with exercise, occurring secondary to either a pulmonary or a cardiac disorder[16].

Non-invasive method: In accordance with the European Society of Cardiology criteria for detecting the presence of PHT, based on the TR peak velocity and Doppler-calculated sPAP at rest (assuming a normal right atrial pressure of 5 mmHg), additional echocardiographic variables suggestive of PHT were used to determine the sPAP[19,20]. PHT was defined by an estimate of right ventricular systolic pressure of greater than 40 mmHg. sPAP is estimated using TR jet velocity based on the simplified Bernoulli's equation [4 × (TRV)^2 + RA pressure][19,21,22] (TRV: TR velocity; RA: Right atrium). PHT was classified into three categories: Mild (40-49 mmHg), moderate (50-59 mmHg) and severe (> 59 mmHg).

Statistical analysis

Values were expressed as means, averages, and percentages.

RESULTS

Total group

A total of 211 (M: 87 = 41% and F: 124 = 59%) reviewed patients were collected from the world literature. The mean age was 49.4 years (range 16-85). The reported method of assessment of PAP was RHC (*n* = 201, Caucasian *n* = 94 and Asian *n* = 107) and Doppler echocardiography (*n* = 10, Caucasian *n* = 6 and Asian *n* = 4) in 95% and 5% of the subjects, respectively. The congenital CAFs were unilateral in 118 (56%), bilateral in 87 (41%) and multilateral in 6 (3%) of the subjects. The CAFs arose from the right (133/268 = 49.6%) and left (135/268 = 50.4%) coronary artery, respectively. The mode of termination was either vascular (90/211 =

Table 1 Reviewed Asian (*n* = 111) and Caucasian (*n* = 100) group of patients

	Total reviewed subjects	Asian group	Caucasian group
n	211	111 (53%)	100 (47%)
Gender	F 124 (59%)	F 63 (57%)	F 61 (61%)
	M 87 (41%)	M 48 (43%)	M 39 (39%)
Mean age (range)[1], yr	49.4 (16-85)	48.9 (19-83)	49.9 (16-85)
CAF characteristics			
Unilateral	118 (56%)	42 (38%)	76 (76%)
Bilateral	87 (41%)	63 (57%)	24 (24%)
Multilateral	6 (3%)	6 (5%)	-
Mode of termination			
CVFs	90 (43%)	43 (39%)	47 (47%)
CCFs	121 (57%)	68 (61%)	53 (53%)
RHC	201 (95%)	107 (96%)	94 (94%)
sPAP/RVSP	10 (5%)	4 (4%)	6 (6%)
Management			
CMM	38	20	18
PTE[2]	29	9 (8%)	20 (20%)
SL	124 (59%)	82 (74%)	42 (42%)
WW	2	-	2
Death	2	-	2
Not mentioned	16	-	16

[1]Subjects (*n* = 41) from ref. [35] were not included in calculation of mean age (*n* = 170, 70 Asian and 100 Caucasian). [2]In one patient, PTE failed followed by SL treatment (ref. [147]) and another treated with hybrid procedures (ref. [133]). CAF: Coronary artery fistula; CCFs: Coronary-cameral fistulas; CVFs: Coronary-vascular fistulas; CMM: Conservative medical management; F: Female; M: Male; PTE: Percutaneous therapeutic embolization; RHC: Right heart catheterization; SL: Surgical ligation; sPAP: Systolic pulmonary artery pressure; RVSP: Right ventricular systolic pressure.

43%) or cameral (121/211 = 57%) (Table 1).

Among the applied therapeutic modalities, surgical ligation (SL) was performed in 124 (59%), conservative medical management (CMM) in 38 (18%), percutaneous therapeutic embolization (PTE) in 29 (13%) and watchful waiting in 2 (1%). There were 2 mortalities (1%) and treatment options were not mentioned in 16 (8%) of the subjects. Among the whole group, 23% (49/211) were found to have elevated PAP.

Asian population: n = 111

The reviewed patients of Asian ethnicity [*n* = 111, Male *n* = 48 (43%) and Female *n* = 63 (57%)] had a mean age of 48.9 years (range 19-83).

Between 1986 and 2014, papers published describing Asian population with congenital CAFS and reported data on PAP were included: from 1986-1993[23-28], 1994-1999[29-33], 2001-2004[34-39], 2005[40-42], 2006[43-49], 2007[50-55], 2009-2011[56-61] and 2012-2014[62-69]. PAP was measured by RHC in 107 and by Doppler echocardiography in 4.

Ninety-six subjects (86%) had normal PAP. Among the CAFs, 42 were unilateral (38%), 63 bilateral (57%) and 6 multilateral (5%). The treatment modalities were SL [82 = (74%)], CMM [20 = (18%)] and PTE [9 = (8%)]. No watchful waiting strategy was conducted and death did not occur in any of the subjects.

Table 2 Asian and Caucasian group of patients (*n* = 49) with pulmonary hypertension

	Total group	Asian group	Caucasian group
n	49	15 (31%)	34 (69%)
Age[1]	56 (16-80)	54.4 (24-77)	56.8 (16-80)
Gender	F 34 (69%)	F 12 (80%)	F 22 (65%)
	M 15 (31%)	M 3 (20%)	M 12(35%)
CAF			
Unilateral	37 (76%)	9 (60%)	28 (82%)
Bilateral	12 (24%)	6 (40%)	6 (18%)
PHT			
Mild	26 (53%)	8/15 (53%)	18/34 (53%)
Moderate	11 (22%)	2/15 (13%)	9/34 (26%)
Severe	12 (25%)	5/15 (33%)	7/34 (21%)
Mean PAP (mmHg)	35.6 (range 26-60)	36.9 (range 27-49)	34.3 (range 26-60)
Mean Qp:Qs ratio	1.9 (range 1.13-2.75)	1.9 (range 1.13-2.75)	1.9 (range 1.3-2.7)
RHC	43 (88%)	13 (87%)	30 (88%)
Doppler (sPAP)	6 (12%)	2 (13%)	4 (12%)
CAF characteristics			
Origin	R 8, L 30, bilateral 11	R 2, L 8, bilateral 5	R 6, L 22, bilateral 6
Termination	RH side 45 LH side 4	RH side 13 LH side 2	RH side 32 LH side 2
Mode of termination			
CVFs	37 (76%)	9/15 (60%)	28/34 (82%)
CCFs	12 (24%)	6/15 (40%)	6/34 (18%)
Associated disorders	17/49 (35%)	5/15 (33%)	12/34 (35%)
Management			
SL	30 (61%)	9	21
PTE	13 (27%)	4	9[2]
CMM	6 (12%)	2	4

[1]Subjects from ref. [35] were not included in calculation of mean age. Mean age was calculated from 170 (70 Asian and 100 Caucasian) subjects. [2]One PTE failed (from ref. [147]) followed by SL treatment and another treated with hybrid procedures (from ref. [133]). CAF: Coronary artery fistula; CCFs: Coronary-cameral fistulas; CVFs: Coronary-vascular fistulas; CMM: Conservative medical management; F: Female; R: Right coronary artery; L: Left coronary artery; LH: Left heart side; M: Male; PAP: Pulmonary artery pressure; PHT: Pulmonary hypertension; PTE: Percutaneous therapeutic embolization; RH: Right heart side; RHC: Right heart catheterization; SL: Surgical ligation; sPAP: Systolic pulmonary artery pressure.

PHT was found in 15 Asian (14%) (M, *n* = 3; F, *n* = 12) subjects with a mean age 54.4 years (range 24-77). Among the 15 subjects, mild, moderate and severe PHT was detected in 8, 2 and 5, respectively.

Caucasian population: n = 100

The mean age (*n* = 100, Male 39 and Female 61) was 49.9 years (range 18-85). Published papers on Caucasian population regarding CAFs and PAP between 1955 and 2014 were included for evaluation: 1955-1961[70-75], 1964-1967[5,76-78], 1971-1976[2,79-82], 1981-1989[11,83-85], 1990-1991[3,6,10,86,87], 1992-1994[88-92], 1995-1997[4,9,31,93-95], 2000-2002[12,13,96-101], 2003-2004[102-106], 2005-2006[7,15,107-113], 2007-2009[14,114-124], 2010-2012[8,125-130], and 2013-2014[131-134]. PAP was evaluated by RHC in 94% (*n* = 94) and in 6 by Doppler echocardiography method. The CAFs were unilateral in 76 (76%) and bilateral in 24 (24%) of the subjects. No multilateral fistulas were

reported. Sixty-six subjects (66%) had normal PAP.

Treatment modalities included SL (42), PTE (20), CMM (18), and watchful waiting (2), and were not mentioned in 16 cases. There were 2 mortalities (2). PHT was found in 34 subjects (34%) [M: *n* = 12 (35%) and F: *n* = 22 (65%)], with a mean age of 56.8 years (range 16-80).

PHT population: n = 49

PHT was found in 49 patients (49/211 = 23%), with a mean age of 56 years (range 16-80). There were 34 females (69%) and 15 males (31%), with 15 Asian (mean age 54.4, range 24-77 years) and 34 (mean age 56.8, range 16-80 years) of Caucasian patients. The fistulas were unilateral in 37 (76%) and bilateral in 12 (24%) of the subjects. Measurement of PAP was achieved by RHC in 43 subjects (13 Asian and 30 Caucasian) and by Doppler echocardiography in 6 (2 Asian and 4 Caucasian) subjects. Mild, moderate and severe PHT was reported in 26 (53%), 11 (23%) and 12 (24%) subjects, respectively (Table 2).

The following features were detected among PHT group of patients: A female predominance (34/49 = 69%), unilateral origin (37/49 = 76%) from the left coronary artery (30/49 = 61%) and termination into the right heart side (45/49 = 92%) were the major findings of the PHT group of patients.

The percentage of unilateral and CVFs was higher in the Caucasian group (82% and 82%) compared to the Asian group (60% and 60%), respectively (Table 3).

DISCUSSION

CAFs may remain silent, co-existing with longevity for years and emerging as a coincidental finding during non-invasive or invasive[135] investigation for the analysis of suspected cardiac disorder.

CAFs are an uncommon congenital anomaly which may be associated with several complications (Table 4). These complications may have coronary vascular, pericardial or myocardial origin. Furthermore, they may have a valvular source or may originate from an atrial or ventricular arrhythmic substrate. Such complications may include myocardial infarction (MI) (4%)[136,137], congestive heart failure (20%)[136], infective endocarditis (reported in 4%-12% in different series)[81,136], atrial[138] and ventricular[139] arrhythmias, aneurysm (reported in 20% of cases)[96,140], rarely ruptured aneurysm with hemopericardium[141] and unruptured aneurysm[139,142], pericardial effusion[143], syncope[142,144] and sudden death[145]. It has been postulated that fistula-related complications increase with age[136]. Secondary PHT is an infrequent complication of congenital CAFs. As early as 1955, Davison reported PHT in patients with CAFs[70].

Most CAFs are small and hemodynamically inconsequential with a negligible left-to-right shunt. However, some can be sizeable and lead to shunting of blood from the coronary circulation to low-pressure pulmonary vascular bed, resulting in PHT[1].

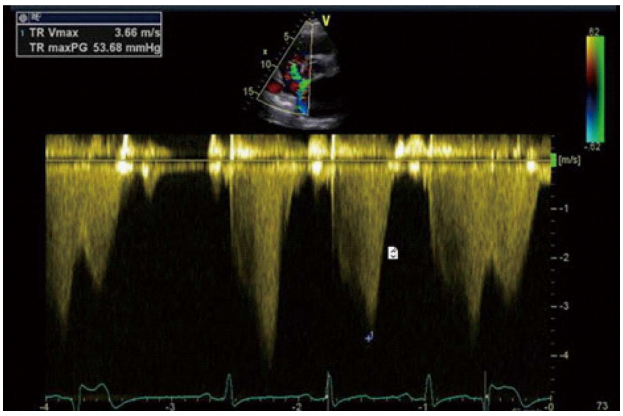

Figure 1 Continuous wave Doppler demonstrating blood flow velocity (3.66 m/c) across the tricuspid valve.

In congenital CAFs, although PHT may occur when sizeable left-to-right shunt exists; in the current review, the mean Qp:Qs was modest, with moderate magnitude 1.9:1.0.

It has been stated that severe PHT is not frequently observed in isolated CAFs[87]. Mild to moderate PHT[5] has sporadically been reported in unilateral[39,45,107,124,146,147] and bilateral fistulas[42,103,112,118]. Indeed, in the current literature review, only 25% were found to have severe PHT, with the majority (75%) having mild or moderate PHT. No reports of multilateral CAFs associated with PHT were found. It is noteworthy that CAFs may be associated with longevity[96] and PHT has been reported in septuagenarians[11] and octogenarians[107].

Although PAP can be measured on Doppler echocardiography, the gold standard for diagnosis is RHC. In the current review, 95% were direct calculation of PAP using RHC and only 5% as an estimate of right ventricular systolic pressure by Doppler echocardiography using TR jet velocity based on the simplified Bernoulli's equation (Figure 1). It is widely accepted that pulmonary artery systolic pressure (sPAP) can be considered normal until 40 mmHg in the elderly and obese subjects. Moreover, tricuspid regurgitant jet velocity is a parameter that has been widely applied to estimate sPAP[22].

In comparison with the Caucasian group of patients (65%) with PHT, female gender accounted for 80% in the Asian group and was almost equally associated (35% *vs* 33%) with concomitant congenital and acquired coronary and valvular heart defects.

In the total group of patients (*n* = 49) with PHT, female gender accounted for (69%), unilateral fistulas was present in (76%) and mild to moderate PHT (75%) was predominant. RHC was performed in 88% of patients and in 12% Doppler echocardiography was used for estimation of the sPAP. Coronary vascular fistulas as a mode of termination were found in the overwhelming majority (76%) of patients. SL was performed in 61% of

Table 3 Mode of termination coronary-vascular fistulas *vs* coronary-cameral fistulas in the pulmonary hypertension (*n* = 49) and all reviewed (*n* = 211) subjects

	CVFs	CCFs	Mean age and range (yr)
Total *n* = 211	90/211 (43%)	121/211(57%)	38.3 (26-67)
Asian 15/111 (14%)	9/15 (60%)	6/15 (40%)	39.7 (27-67)
Caucasian 34/100 (34%)	28/34 (82%)	6/34 (18%)	36.8 (26-60)

CCFs: Coronary-cameral fistulas; CVFs: Coronary-vascular fistulas.

patients with PHT.

In the present review of all 49 subjects, possible common features of CAFs associated with PHT were unilateral fistula (37/49 = 76%) originating from the left coronary artery (30/49 = 61%) with a vascular termination (76%) into the right heart side (45/49 = 92%). These findings have to be investigated in a future international survey or prospective study.

A significant difference was noted in the percentages of coronary-cameral fistulas between Asian (40%) and Caucasian (18%) groups of patients with PHT. There was no difference in associated cardiac defects, congenital or acquired, in both the Asian and Caucasian groups (33% and 35%, respectively).

Limitations of the study

Among the Asian population reported by Cheung *et al*[35] in 2001, among the 41 subjects, there were children included in their study. The time span for data collection spread from 1955 to 2014 due to period collection bias.

Publication bias, only subjects with abnormal findings are accepted for publication. Although the data were of high quality and were collected from the world literature, the results of this review are intended to be indicative and require cautious interpretation.

It is clear that more research and studies are warranted for the identification and registration of congenital CAFs associated with PHT; the cause seems to be more multi-factorial (gender, fistula origin and outflow) and dependent on the fistula characteristics itself. We are encouraged to initiate an international survey on CAFs (Euro-CAF.care).

In conclusion, among the whole population, 23% were found to have elevated PAP. In the Asian group of patients 14% demonstrated PHT compared to 34% among the Caucasian group. Among the patients (*n* = 49) with PHT, 69% were female. The majority of fistulas (76%) in patients (*n* = 49) with PHT were of CVFs type in contrast to CCFs who accounted for 24% of subjects. The likelihood for a CAF patient to develop PHT is presented when possessing the following features, with a Caucasian female having a fistula with a vascular mode of termination. The findings of this review need to be confirmed in a larger multicenter international registry, preferably with a longer follow-up.

Table 4 Possible complications of coronary artery fistulas

Complication	Features
Cardiovascular	Myocardial infarction, stroke, aneurysm, rupture
Infectious	Bacterial endocarditis, septic pulmonary and septic renal embolism
Valvular	Incompetence, dysfunction, perforation
Pericardial	Hemopericardium, pericardial effusion, tamponade
Myocardial	Congestive heart failure
Arrhythmic	Supraventricular arrhythmias, ventricular arrhythmias and sudden death

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COMMENTS

Background

Congenital coronary artery fistulas (CAFs) are uncommon anomalies. Most CAFs are small and hemodynamically inconsequential with a negligible shunt. However, some can be sizeable and lead to shunting of blood from the coronary circulation to low-pressure pulmonary vascular bed, resulting in pulmonary hypertension (PHT).

Research frontiers

CAFs may be associated with normal pulmonary artery pressure (PAP) in unilateral or bilateral fistulas, or may sometimes be accompanied with elevated PAP. Rarely, in octogenarians with bilateral CAFs, PAP may remain normal.

Innovations and breakthroughs

The likelihood for a CAF patient to develop PHT is presented when possessing the following features, with a Caucasian female having a fistula with a vascular mode of termination.

Applications

The findings of this review need to be confirmed in a larger multicenter international registry, preferably with a longer follow-up.

Peer-review

This paper is interesting review concerning association PAH and CAF. Therefore, this article should be published.

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ORIGINAL ARTICLE

Clinical Trials Study

Optimal C-arm angulation during transcatheter aortic valve replacement: Accuracy of a rotational C-arm computed tomography based three dimensional heart model

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Abstract

AIM

To investigate the accuracy of a rotational C-arm CT-based 3D heart model to predict an optimal C-arm configuration during transcatheter aortic valve replacement (TAVR).

METHODS

Rotational C-arm CT (RCT) under rapid ventricular pacing was performed in 57 consecutive patients with severe aortic stenosis as part of the pre-procedural cardiac catheterization. With prototype software each RCT data set was segmented using a 3D heart model. From that the line of perpendicularity curve was obtained that generates a perpendicular view of the aortic annulus according to the right-cusp rule. To evaluate the accuracy of a model-based overlay we compared model- and expert-derived aortic root diameters.

RESULTS

For all 57 patients in the RCT cohort diameter measurements were obtained from two independent operators and were compared to the model-based measurements. The inter-observer variability was measured to be in the range of 0°-12.96° of angular C-arm displacement for two independent operators. The model-to-operator agreement was 0°-13.82°. The model-based and expert measurements of aortic root diameters evaluated at the aortic annulus (r = 0.79, P < 0.01), the aortic sinus (r = 0.93, P < 0.01) and the sino-tubular junction (r = 0.92, P < 0.01) correlated on a high level and the Bland-Altman analysis showed good agreement. The interobserver measurements did not show a significant bias.

CONCLUSION

Automatic segmentation of the aortic root using an anatomical model can accurately predict an optimal C-arm configuration, potentially simplifying current clinical workflows before and during TAVR.

Key words: Aortic stenosis; Imaging modalities; Degenerative valve disease; Transcatheter aortic valve replacement

Core tip: We were able to demonstrate the accuracy of a rotational C-arm CT (RCT) based 3D heart model to predict an optimal C-arm configuration and to provide anatomical context information during transcatheter aortic valve replacement (TAVR). Established and upcoming complex cardiac interventions require detailed anatomical information for procedure planning and intraprocedural guidance. According to our experience, RCT can be smoothly integrated into the clinical workflow, providing three-dimensional information of the relevant anatomical structures in the catheterization lab prior and as part of the TAVR intervention.

Veulemans V, Mollus S, Saalbach A, Pietsch M, Hellhammer K, Zeus T, Westenfeld R, Weese J, Kelm M, Balzer J. Optimal C-arm angulation during transcatheter aortic valve replacement: Accuracy of a rotational C-arm computed tomography based three dimensional heart model. *World J Cardiol* 2016; 8(10): 606-614 Available from: URL: http://www.wjgnet.com/1949-8462/full/v8/i10/606.htm DOI: http://dx.doi.org/10.4330/wjc.v8.i10.606

INTRODUCTION

Transcatheter aortic valve replacement (TAVR) is an established treatment option for patients ineligible for surgery that suffer from severe aortic stenosis[1,2]. Optimal positioning of the prosthetic valve during the intervention in the catheter laboratory is crucial for procedural success. Malpositioning may lead to valve embolization, coronary ostial obstruction, perivalvular regurgitation, or conduction disturbances[3]. Optimal and safe device deployment is best accomplished by generating a specific fluoroscopic view perpendicular to the annulus plane, also known as the line of perpendicularity (LP)[4]. To achieve this specific fluoroscopic view during the TAVR procedure, several angiograms in different angulations of the C-arm are necessary, causing a considerable amount of nephrotoxic contrast agent and radiation for the patient and the operator[5]. Therefore, an accurate definition of the aortic annulus and the LP is desirable before the procedure is performed. Today, MSCT is the preferred modality for TAVR planning and intervention guidance, providing information about anatomic conditions as well as the opportunity to reformat the reconstruction in any 3D orientation[6,7].

Different imaging techniques have been established to define the LP optimal fluoroscopic view during the preprocedural screening of patients. For angiography and MSCT[7-10] different software solutions for optimal view planning and their clinical benefits have been proposed. Automated view planning along the LP has shown to improve the quality of implantation, may speed up workflow and may reduce the need for low-dose aortograms[5]. Rotational C-arm computed tomography (RCT)-based view planning has proven to be of equal quality as MSCT-based techniques[10-12]. But current studies purely rely on non-quantitative evaluations and systematic validation of software-based methods is lacking.

In this study we therefore sought to (1) evaluate the accuracy of a RCT based 3D heart model for segmentation of the aortic root to predict an optimal C-arm configuration that generates a perpendicular view of the aortic annulus during TAVR and (2) investigate whether the accuracy of a RCT-specific model is suitable for intervention guidance, comparing the dimensions of an automatically derived overlay with manual reference measurements.

MATERIALS AND METHODS

Study population

Retrospectively, 57 consecutive patients (30 male, mean age 80.9 years) with symptomatic severe aortic stenosis that underwent cardiac catheterization with RCT prior to planned TAVR or surgical aortic valve replacement (SAVR) procedure have been selected. Patients with insufficient RCT image quality, *e.g.,* due to incomplete RVP (n = 2), delayed contrast timing (n

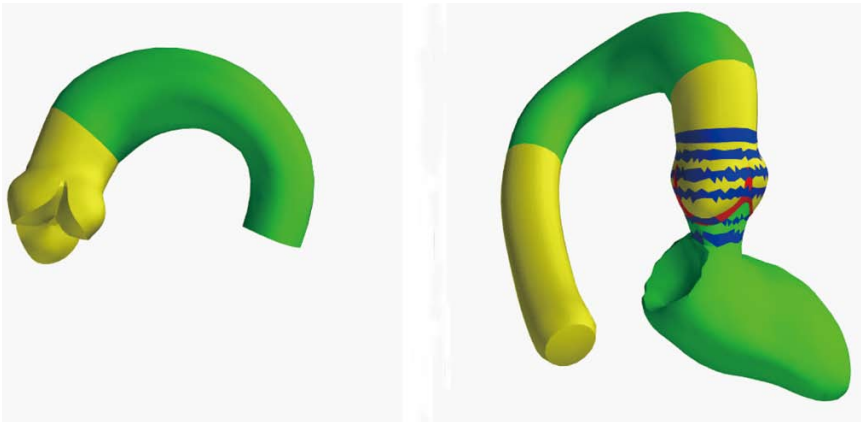

Figure 1 Mesh topology of the rotational C-arm computed tomography model for transcatheter aortic valve replacement (left), extended topology model with rings for diameter measurements (blue), prolonged descending aorta and left ventricle.

= 2), massive artefacts by ICD (n = 2) were excluded beforehand. All patients gave written consent and the study was approved by the local ethics committee (Study No. 4080, international registration NCT01805739).

RCT acquisition

RCT was performed as part of the pre-implant diagnostic coronary angiography study[13]. The C-arm of the Cathlab system (Allura FD 20, 30 cm flat panel detector, XperCT option, Philips Healthcare, Andover, MA, United States) was rotated over an angular range of 210° with a sweep duration of 5.2 s and a frame-rate of 60 frames/s around the patient. To mitigate motion the acquisition was conducted during inspiratory breath hold and under RVP. Contrast medium (Accupaque 350, Bracco Imaging, Konstanz, Germany) was diluted 1:1 with saline to a total volume of 0.8 mL/kg patient's weight (50-80 mL) and administered with a flow rate of 14 mL/s. The contrast agent was injected *via* a pigtail catheter either supravalvular into the ascending aorta aortic root or subvalvular into the left ventricular cavity. The rotational sweep data was reconstructed with standard product settings to a volume of size 256 × 256 × 198 with an isotropic resolution of 0.98 mm³. Since the RCT acquisitions were performed during RVP the exact cardiac phase cannot be specified.

Expert-based data analysis

To assess the operator-variability and the accuracy of software-based optimal C-arm configurations, reference views were defined by a medical expert. Three-dimensional reconstructions of the RCT were visualized as multi-planar reformats with proprietary prototype software. Two blinded operators, experienced in the analysis of cardiac cross sectional imaging, used standard volume interaction techniques to manually define a view perpendicular to the aortic valve plane with respect to a reference viewport. From this optimal view, a LP curve was automatically derived using the mathematical definitions below and the result was presented to the user. Based on the LP curve and a volume rendering of the original RCT data set, the operators defined an optimal C-arm configuration in terms of rotation and angulation following the right-cusp rule[14].

Furthermore the RCT data sets were studied with vendor-independent image processing software (Osirix MD Ver. 4.0, pixmeo, Geneva, Switzerland). Two independent, blinded observers performed aortic root diameter measurements in multiplanar reformatted RCT data sets at the level of the aortic annulus, the aortic sinus and the sino-tubular junction (STJ). These are supposed to be representative for the shape and dimension of the aortic root anatomy to be overlaid to the fluoroscopic data stream for intervention guidance[13].

Model-based data analysis

For automatic view planning and intervention guidance in RCT, a model-based segmentation technique was employed[15]. Unlike other segmentation techniques, model-based segmentation integrates information about the typical shape of the target anatomy, its variability and appearance in the adaptation process, and has been successfully employed in a broad range of medical image processing applications[16-18]. To tailor the shape model to the image characteristics of RCT the model was trained on the 57 patients of the RCT cohort whereby the validation was set-up in a leave-N-out manner so that training and test set never coincided. The shape model covers the 3D outline of the aortic valve, the supravalvular part of the aorta, the aortic arch, a list of anatomical landmarks and rings encoded on the mesh model that enable geometrical measurements relevant for the TAVR application (Figure 1). For clinical validation each RCT data set was segmented with our prototype software using the 3D heart model. The aorta, the aortic valve and the left ventricle (if visible in the RCT data set) as well as the nadir landmarks of the three aortic valve cusps were extracted. From that, the LP curve was obtained and an optimal view that aligns the nadir landmarks according to the right-cusp rule was computed.

To compute the accuracy of the model-based overlay for intervention guidance we assume that the shape and the dimensions of the aortic root can be roughly

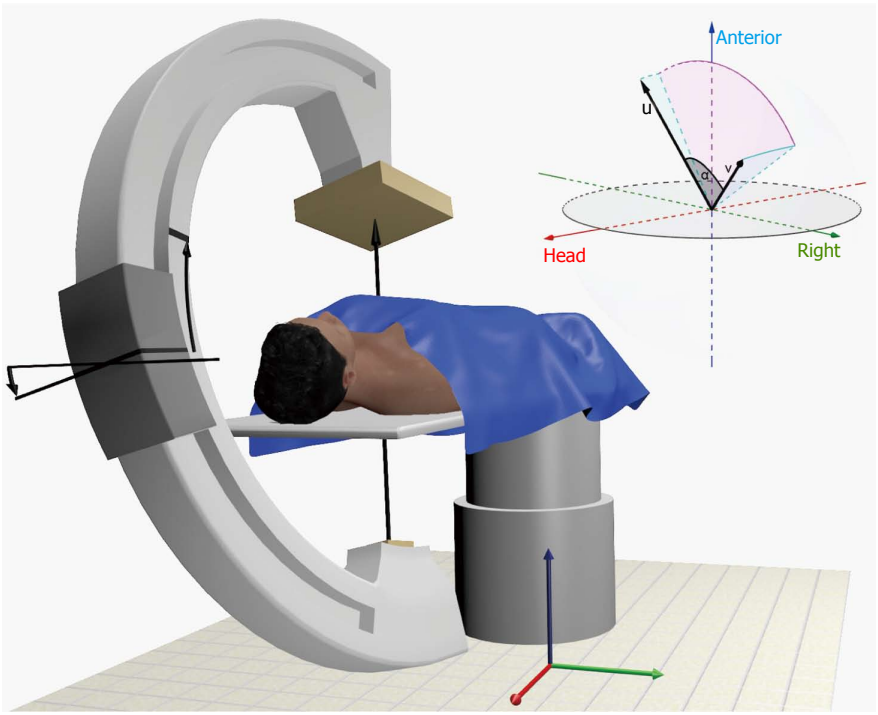

Figure 2 Definition of C-arm coordinate system and illustration of angular displacement between two position vectors each representing a C-arm projection view.

represented by a set of diameter measurements. These diameter measurements use the rings encoded on the segmentation model and are defined in accordance with the recommendations of the manufacturers of the TAVR devices. For the diameter of the annulus a circular cross-section model is fit to the segmentation result. The measurement of the bulbus width and the diameter of the STJ rely on an elliptical cross-section model.

Mathematical calculations and statistical analysis

The computation of the LP curve and the error computations require several geometrical definitions. Prerequisite is a Cartesian coordinate system which is defined in analogy to the work of Wollschläger *et al*[19]. The origin of the coordinate system coincides with the isocenter of the C-arm system. As in Figure 2 indicated, the C-arm can be angulated along the x-axis in cranial and caudal direction of the supine patient and is able to rotate along the y-axis in LAO and RAO direction. The z-axis is defined in dorsal-ventral patient orientation. One pair of rotation and angulation denoted as (ϕ,θ) can be represented by a vector in the C-arm coordinate system $v\_(\phi,\theta) = (x, y, z)$ where $x = \sin(\theta)$, $y = \sin(\phi)\cdot\cos(\theta)$, $z = \cos(\phi)\cdot\sin(\theta)$. Each combination of rotation and angulation spans a virtual half-sphere around the patient. In this half-sphere the LP curve is represented as trace of C-arm rotation and angulation combinations. Each respective view along this trace is orthogonal to the axial plane of the patient's aortic valve which can be defined by the unit vector $v\_AV = (x\_AV, y\_AV, z\_AV)$. To compute the LP curve we seek for a given C-arm rotation θ the C-arm angulations ϕ so that the vectors $v\_(\phi,\theta)$ and v_AV are perpendicular. This can be expressed as inner product of two vectors which is set to zero $v\_(\phi,\theta)\cdot v\_AV = 0$.

To evaluate the inter-observer variability and the agreement between model-based and expert-defined optimal views we compute the angular deviation (AD) between the respective position vectors v_model and v_expert in the spherical C-arm coordinate system which can be expressed as $\alpha = \text{acos}(v\_model \times v\_expert)$. In analogy to the work of the Tzikas-group[8], we compute the mean absolute difference and the standard deviation of the angular deviations between the position vectors given by the operators and the RCT model for all patients. However, this form of statistical analysis is error-prone, since it assumes the normal distribution of the random samples. But the angulation and rotation parameters are dependent on each other and further numerical restrictions (such as pole of acos-function near the optimal vector configuration) have to be considered. Thus, we propose to use a more advanced method of error calculation well-known from other research fields[20]. Therefore we apply Monte-Carlo methods to compute the cumulative distribution function of the angular deviations and use the value at 95% confidence level for the error calculation.

The Bland-Altman method was used for the assessment of the bias and standard deviations between model-based and expert-based aortic root measurements in RCT at 95% level of agreement (LoA). In addition, the Pearson correlation coefficient r was computed and t statistics were used to test the hypothesis of no correlation considering a significance level of $p < 0.01$. All statistical calculations were performed using Matlab Statistics Toolbox™ (MathWorks, Inc, Natick,

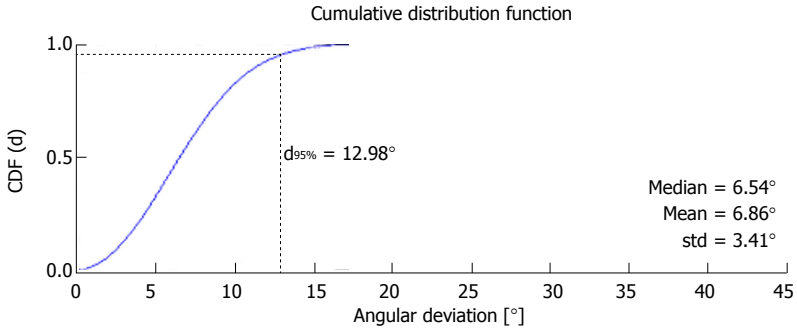

Figure 3 Interobserver variability of rotational C-arm computed tomography-based view planning. Using Monte-Carlo methods the cumulative distribution function of the angular deviation between two operator-defined C-arm configurations was computed; from this distribution function the expected angular deviation is derived to be the value of the distribution function at 95% confidence level.

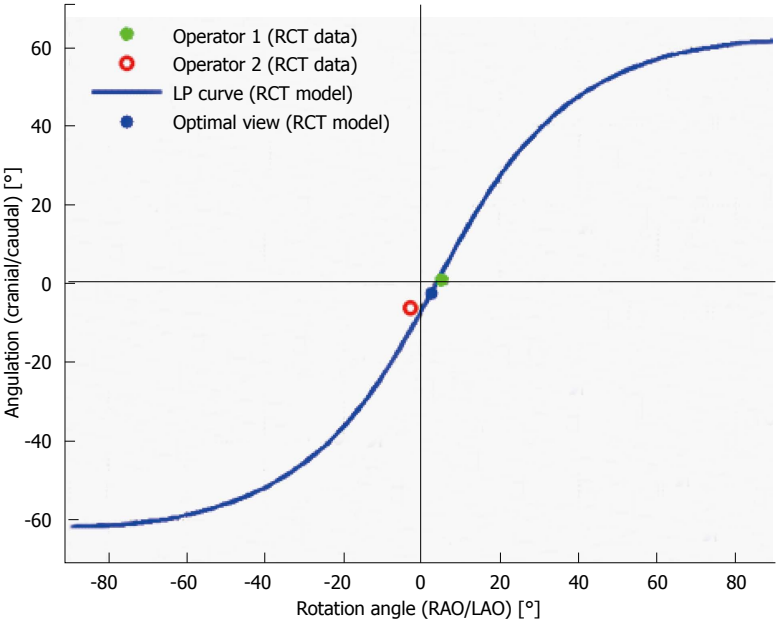

Figure 4 Line of perpendicularity curve for the aortic valve annulus of a sample patient. The solid line represents the line of perpendicularity curve derived from the RCT model; optimal views following the right-cusp rule are given for two operators and the RCT model. RCT: Rotational C-arm computed tomography.

Table 1 Operator variability and model-operator agreement of rotational C-arm computed tomography-based view planning data

n = 57	Average AD (ND)	Average AD (MC)
Operator 1 *vs* operator 2	7.05° ± 3.06°	12.96°
RCT model *vs* both operators	6.84° ± 3.78°	13.82°
RCT model *vs* operator 1	7.14° ± 4.12°	14.37°

To measure the error between two sample C-arm views the angular deviations (AD) are computed and evaluated assuming normal distribution (ND) of the samples and using Monte Carlo (MC) methods. RCT: Rotational C-arm computed tomography.

Massachusetts, United States).

RESULTS

Model-based view planning in RCT

For optimal view planning 57 patients with RCT were evaluated. To assess the inter-observer variability the angular deviations between two expert-defined views in the RCT patient cohort were computed. Assuming normal distribution of the angular deviations, the inter-observer variability was measured to be 7.05° ± 3.06° and thus, in the same range as reported in the work of Tzikas *et al*[8]. Using Monte Carlo methods an interobserver variability between 0° and 12.96° was obtained (compare Table 1 and Figure 3). Furthermore we compared the view planning results of our prototype software with the expert definitions. The model-operator agreement jointly computed for both operators was 6.84° ± 3.78° assuming normal distribution and 0°-13.82° for the Monte Carlo method and thus, on a similar level as the inter-observer variability. A sample LP curve and the respective optimal views of two operators and the prototype software are given in Figure 4.

Model-based intervention guidance

To evaluate the accuracy of RCT-based overlays to interventional data, the dimension of the aortic root at the level of the aortic annulus, the sinus and the

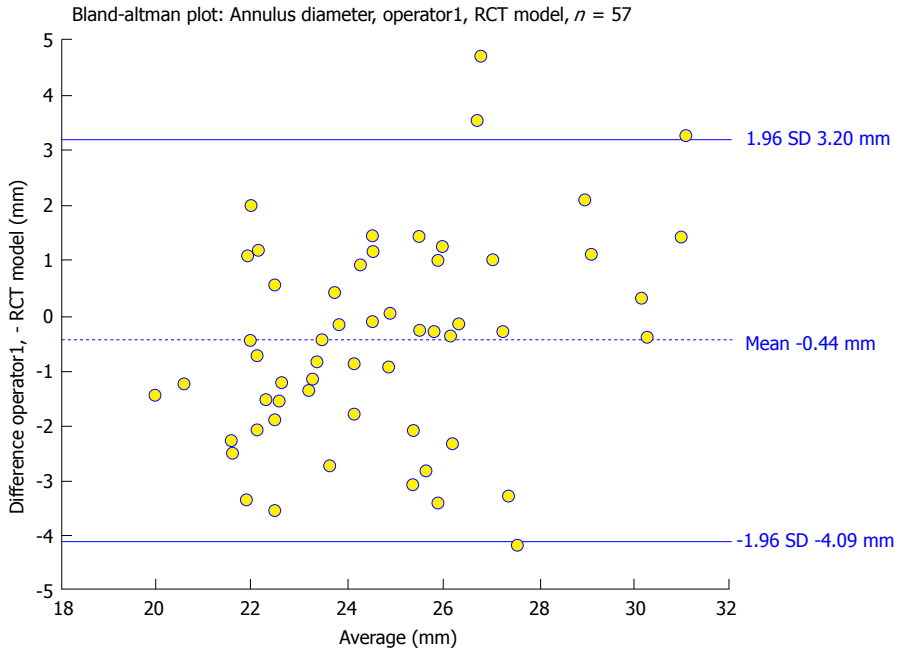

Figure 5 Bland-Altman plot relating aortic annulus diameter measurements done by a medical expert to rotational C-arm computed tomography-model-based measurements. RCT: Rotational C-arm computed tomography.

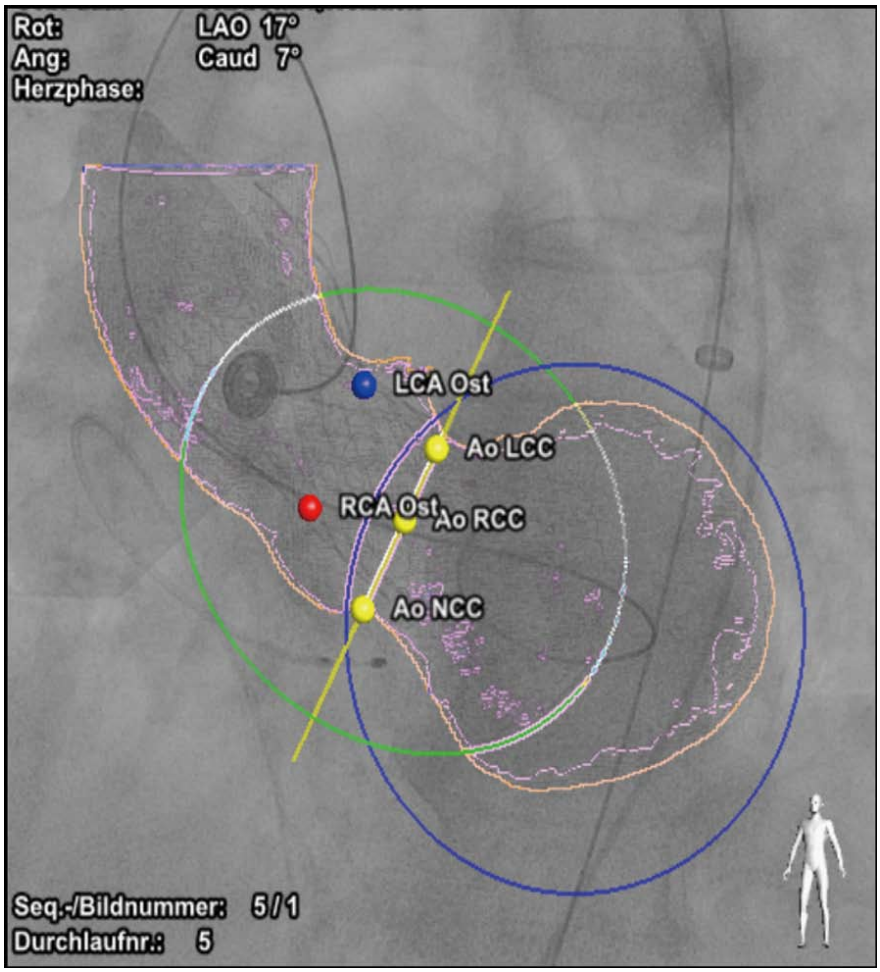

Figure 6 Model-based view planning and interventional overlay with Philips HeartNavigator software.

Table 2 Model-operator agreement for rotational C-arm computed tomography-based diameter measurements

n = 57	Annulus			Sinus			STJ		
	Bias	LoA	*r*	Bias	LoA	*r*	Bias	LoA	*r*
Operator *vs* operator 1	0.32	-3.17-3.81	0.81	-0.45	-3.61-2.71	0.91	-0.59	-3.29-2.10	0.92
RCT model *vs* operator 1	-0.44	-4.09-3.20	0.79	1.05	-1.64-3.75	0.93	-1.53	-4.21-1.15	0.92
RCT model *vs* operator 2	-0.76	-3.75-2.23	0.81	1.51	-0.61-3.62	0.96	-0.94	-3.41-1.53	0.93

To assess bias and deviation of measurements the Bland-Altman analysis is used; in addition the Pearson correlation coefficient is computed to evaluate the inter-measurement agreement considering a significance level of $P < 0.01$. RCT: Rotational C-arm computed tomography; LoA: Limits of agreement (Bland-Altman analysis).

STJ was studied. For all 57 patients in the RCT cohort diameter measurements were obtained from two independent operators and were compared to the model-based measurements. For the aortic annulus the Bland-Altman analysis showed no trend for under- or over-estimation comparing the model-based segmentation results with the expert measurements (mean difference for model *vs* operator 1: -0.44 mm, LoA: -4.09 mm to 3.2 mm). The correlation was significant ($r = 0.79$). A sample Bland-Altman plot is given in Figure 5. For the aortic sinus width and STJ diameter measurements the scatter and the limits of agreement were slightly smaller and the correlation levels higher as listed in Table 2. The Bland-Altman analysis for the aortic sinus diameter shows a good agreement between model-based and medical expert measurements with a bias of 1.05 mm using RCT and limits of agreement that range from -1.64 mm to 3.75 mm for operator 1. Correlations between expert and model-based measurements varied between 0.93 and 0.96. The results of the STJ diameter measurements show a slight bias of -1.53 mm and the limits of agreement were -4.21 mm to 1.15 mm for operator 1. Model-based and expert measurements correlated on a high level (operator 1: $r = 0.92$; operator 2: $r = 0.93$). The interobserver measurements did not show a significant bias. Scatter and correlation levels were for all studied parameters in the same range as the model-operator measurements.

DISCUSSION

Model-based view planning in RCT

Different imaging techniques have been established to define the optimal fluoroscopic view and to optimize valve deployment during TAVR. Standard to define a perpendicular view of the aortic valve is the repeated acquisition of aortographies from different projection angles. During recent years several software solutions for automatic view planning mainly on the basis of MSCT have been developed and have demonstrated high accuracy and many clinical benefits[5].

However, the collection of a MSCT data set for TAVR view planning involves extra logistics for the clinic and additional burden and hazards for the patient. Rotational C-arm CT has proven to be a useful imaging technique for many clinical applications[21] but is less established in the context of TAVR. The image quality of C-arm CT is generally limited by the acquisition quality and thus model-based view planning are dependent on accurate contrast agent bolus timing and on sufficient rapid pacing protocols. According to our clinical experience we believe that with more widespread use and maturity in future, rotational C-arm based imaging can play a more significant role in the TAVR workflow in combination with software-based view planning support.

In this study we evaluated the accuracy of automated view planning with RCT. We could show that our novel prototype software estimates optimal views on the basis of RCT data with good accuracy and that the interobserver variability and model-operator agreement are in the same range. Although different contrast agent injection protocols (aortic root injection *vs* left-ventricular injection) were part of the RCT validation cohort the model-based view planning in RCT has proven to be robust.

RCT-based intervention guidance

The current standard for intervention guidance during TAVR is plain fluoroscopy. In recent years software such as the HeartNavigator software (Philips Healthcare, Andover, MA, United States; compare Figure 6) that segments a three-dimensional MSCT data set to create a patient-specific model of the heart and overlays this to the interventional image stream has been developed. In this study we examined the accuracy of RCT-based overlays that are automatically generated from model-based segmentation. We found that our RCT-based techniques are able to accurately reflect the dimension of the aortic valve annulus and the aortic root. Bias and variations of model-based measurements *vs* the experts' references were in the same range as the operator variability. Thus, RCT modeling can potentially provide accurate anatomical overlays to interventional data to support the TAVR intervention as current software solutions already do for MSCT.

In conclusion, established and upcoming complex cardiac interventions such as TAVR require detailed information regarding heart and vessel anatomy for procedure planning and intra-procedural guidance. According to our experience, rotational C-arm CT can be smoothly integrated into the clinical workflow, providing three-dimensional information of the relevant anatomical structures in the catheterization lab prior and as part of

the TAVR intervention.

Limitations

This study was based on retrospective data and reflects solely the experience at our center. The RCT data was acquired during TAVR/SAVR procedure planning several days in advance to the procedure. The data in this study were based on a relatively small sample size to show the clinical feasibility. Possible clinical benefits have to be investigated in prospective studies with more standardized protocols and a more powerful sample size. Future studies should prove feasibility and accuracy of RCT acquisition as initial step during TAVR procedure which may increase accuracy of view planning and intervention guidance further due to fewer patient position changes. In addition, RCT-based calcium visualization and quantification has to be studied.

COMMENTS

Background

Optimal positioning of the prosthetic valve is crucial for procedural success of Transcatheter aortic valve replacement (TAVR). Optimal and safe device deployment is best accomplished by generating a specific fluoroscopic view perpendicular to the annulus plane, also known as the line of perpendicularity (LP). To achieve this specific fluoroscopic view during the TAVR procedure, several angiograms in different angulations of the C-arm are necessary, causing a considerable amount of nephrotoxic contrast agent and radiation for the patient and the operator. Different imaging techniques have been established to define the LP optimal fluoroscopic view during the preprocedural screening of patients. Multi-slice computed tomography (MSCT) is the preferred modality and "gold-standard" for TAVR planning and intervention guidance. For angiography and MSCT different software solutions for optimal view planning and their clinical benefits have been proposed. Automated view planning along the LP has shown to improve the quality of implantation, may speed up workflow and may reduce the need for low-dose aortograms. Rotational C-arm CT (RCT)-based view planning has proven to be of equal quality as MSCT-based techniques.

Research frontiers

Current studies purely rely on non-quantitative evaluations and a systematic validation of software-based methods is lacking. RCT has proven to be a useful imaging technique for many clinical applications but is less established in the context of TAVR. According to the achieved clinical experience a more widespread use of RCT-based imaging could play a more significant role in the TAVR workflow in combination with software-based view planning support in the future.

Innovations and breakthroughs

This study is the first which combines the evaluation concerning the accuracy of a RCT- based 3D heart model for segmentation of the aortic root and prediction of the LP and its suitability for intervention guidance. The authors could show that their novel prototype software estimates optimal views on the basis of RCT data and that the model-based view planning in RCT has proven to be robust.

Applications

According to the authors' results, RCT can be smoothly integrated into the clinical workflow, providing three-dimensional information of the relevant anatomical structures in the catheterization lab prior and as part of the TAVR intervention.

Terminology

RCT is an imaging diagnostic tool to predict an optimal C-arm configuration during TAVR. RCT was performed as part of the pre-implant diagnostic coronary angiography study. To mitigate motion the acquisition was conducted during inspiratory breath hold and under rapid ventricular pacing. With prototype software each RCT data set was segmented using a 3D heart model. From that the LP curve was obtained that generates a perpendicular view of the aortic annulus according to the right-cusp rule. To evaluate the accuracy of a model-based overlay we compared model- and expert-derived aortic root diameters.

Peer-review

The authors are congratulated with their meticulous work on the use of rotational C-arm 3D heart model for prediction of an optimal C-arm configuration to be used before and during the procedure of transcatheter aortic valve replacement.

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ORIGINAL ARTICLE

Randomized Controlled Trial

Randomized controlled trial of remote ischemic preconditioning and atrial fibrillation in patients undergoing cardiac surgery

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Abstract

AIM

To study whether remote ischemic preconditioning (RIPC) has an impact on clinical outcomes, such as post-operative atrial fibrillation (POAF).

METHODS

This was a prospective, single-center, single-blinded,

randomized controlled study. One hundred and two patients were randomized to receive RIPC (3 cycles of 5 min ischemia and 5 min reperfusion in the upper arm after induction of anesthesia) or no RIPC (control). Primary outcome was POAF lasting for five minutes or longer during the first seven days after surgery. Secondary outcomes included length of hospital stay, incidence of inpatient mortality, myocardial infarction, and stroke.

RESULTS

POAF occurred at a rate of 54% in the RIPC group and 41.2% in the control group (P = 0.23). No statistically significant differences were noted in secondary outcomes between the two groups.

CONCLUSION

This is the first study in the United States to suggest that RIPC does not reduce POAF in patients with elective or urgent cardiac surgery. There were no differences in adverse effects in either group. Further studies are required to assess the relationship between RIPC and POAF.

Key words: Chronic ischemic heart disease; Cardiac surgery; Coronary artery disease; Other treatment; Remote ischemic preconditioning; Post-operative atrial fibrillation

Core tip: This is the first study in the United States to suggest that remote ischemic preconditioning does not reduce post-operative atrial fibrillation in patients with elective or urgent cardiac surgery.

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INTRODUCTION

Post-operative atrial fibrillation (POAF) is the most common arrhythmia after coronary artery bypass grafting (CABG)[1]. Despite improvement in medical therapy, surgical technique, and anesthesia, POAF occurs in 25%-40% of patients undergoing CABG and valve surgery[1-4]. POAF remains challenging to prevent, treat, or cure[5], and contributes to increased short and long term mortality[6,7], stroke[8], an increase in length of hospital stay[9], intensive care unit readmission, and treatment costs[10]. Some factors associated with POAF include a patient's preoperative status, age, and preexisting electrocardiogram abnormalities[11]. Intra-operative stress also plays a key role, due to occurrence of reperfusion, inflammation, oxidative stress, and/or hemostasis[12-14]. Most POAF episodes occur within the first 6 d following cardiac surgery, with the peak incidence on the second or third post-operative day, coinciding with the peak of systemic inflammation caused by surgery and with atrial stretch[8].

Remote ischemic preconditioning (RIPC) is one strategy that has shown a myocardial protective effect during CABG and heart valve surgery[15-17]. It was first described in 1986 in a dog model, where RIPC provided a protective effect on the myocardium that was later subjected to a sustained bout of ischemia[18]. RIPC was shown to reduce the incidence of ischemic reperfusion ventricular arrhythmias[19]. There is evidence that RIPC can preserve mitochondrial function and influences myocardial microRNA expression of the right atrium, potentially decreasing the incidence POAF after CABG surgery[20,21]. In addition, the efficacy of preconditioning to reduce myocardial injury in cardiac surgery and percutaneous coronary interventions has also been demonstrated[22].

There is growing evidence that AF is associated with increased inflammation[23,24], and Jannati *et al*[25], demonstrated that myocardial ischemic preconditioning by aortic cross-clamping in patients undergoing CABG reduced the incidence of POAF.

Currently, there is no optimal preconditioning protocol or tool being utilized during cardiac surgery and aortic cross-clamping may increase the risk of embolic stroke, particularly in elderly patients[26]. We conducted a randomized clinical trial to assess if RIPC can reduce POAF after CABG, with or without concomitant valve surgery or valve surgery alone.

MATERIALS AND METHODS

Study design

This study was a prospective, single-center, single-blinded, randomized controlled trial. The trial was registered with www.clinicaltrials.gov (NCT01500369).

Patient population

Patients who were undergoing non-emergent cardiac surgery were screened and recruited from the cardiac surgical service.

Eligibility

Eligible patients were adults greater than 18 years old who were referred for elective or urgent CABG, with or without valve surgery, or valve surgery alone between April 2011 and October 2013.

Exclusion criteria included any preoperative rhythm detected other than a sinus rhythm, a history of AF, New York Heart Association Ⅳ congestive heart failure, cardiogenic shock, emergent CABG and/or valve surgery, bleeding diathesis, patients taking K(+) ATPase channel blockers (sulphonylureas), and women of child-

bearing age. Patients were contacted by the primary investigator or a cardiology fellow to explain the study and obtain consent. This occurred during the 24-h period after undergoing cardiac catheterization (urgent care patients) or during a pre-op office visit (elective surgery patients). Patients who were interested gave written informed consent. Trial approval was obtained from the Institutional Review Board and the study is registered at http://www.clinicaltrials.gov; identifier NCT01500369. Upon consent, participants were randomized during the pre-operative period to either the treatment or control group.

Blinding

Patient blinding: Patients were randomly assigned to a treatment strategy (RIPC/no RIPC) in the operative room during the 45-min pre-operation period. Randomization occurred after patients were anesthetized; thus, patients were unaware of their treatment assignment.

Physician blinding: Since randomization and the RIPC procedure were conducted preoperatively, we expect that the surgeons were unaware of patient treatment assignment, and an effort was made to prevent surgeon knowledge of which group was selected.

Randomization process

The randomization schedule was developed by the institution's statistical core facility and patients were randomized according to a computer-generated randomization procedure. Patients were randomized using blocks in sizes 4 and 6, administered in a random fashion.

Consecutively-numbered envelopes were created and populated with a patient identification and the treatment assignment, based on the random block. The envelopes were kept in a locked cabinet. When an eligible patient was identified, consented, and moved to the pre-operative area, the staff member would select the next envelope in the consecutive list and give it to the research nurse. The research nurse would open the envelope and proceed as indicated on the enclosed form.

Study procedures

For all study participants, anesthesia was induced with intravenous propofol (0.5-2 mg/kg), midazolam (0.04-0.05 mg/kg), fentanyl (1-5 μg/kg), and rocuronium (0.6-1 mg/kg), and maintained with isoflurane. On-pump surgical revascularization was achieved through a median sternotomy. The internal thoracic arteries, radial arteries, and saphenous veins were used as grafts. Heparin was administered to achieve an activated clotting time longer than 400 s. Standard non-pulsatile cardiopulmonary bypass with a membrane oxygenator was used with an ascending-aortic and two-stage venous cannulation. During cardiopulmonary bypass, moderate hemodilution with a hematocrit of approximately 25% and mild systemic hypothermia (32 ℃) were maintained. Retrograde warm blood cardioplegia was used for all distal anastomoses. Proximal anastomoses were constructed with partial side clamping of the ascending aorta. Bypass graft flow was assessed with an ultrasonic transit time-flow measurement probe. After reperfusion and weaning from cardiopulmonary bypass, protamine was administered for heparin reversal. For hemodynamic support, inotropes and/or vasopressors were infused as required.

RIPC, for those in the study arm, took place after induction of anesthesia and prior to skin incision during which time the patient was prepped, draped, and prepared for surgery using the following protocol.

Treatment group: Patients in the treatment group received 3 sequential sphygmomanometer cuff inflations on their right upper arm after induction of anesthesia in the operating room. The cuff was inflated to 200 mmHg for five minutes each occasion, with a period of five minutes deflation between inflations. The entire RIPC phase lasted 30 min.

Control group: Patients in the control group had the sphygmomanometer cuff placed on their right upper arm, but the cuff was not inflated. Similar to patients in the treatment group, patients in the control group had to undergo the same 30 min delay before the initiation of a skin incision.

Outcome events

Primary outcome: The primary outcome was POAF lasting for five minutes or longer during the first seven days after surgery. This outcome was assessed by using patient's hospital records as well as the Society of Thoracic Surgery (STS) database which records outcomes up until 30 d after surgery.

Secondary outcomes: Secondary outcomes such as length of hospital stay, inpatient death, myocardial infarction (MI), and stroke were recorded during the study follow-up period. Additionally, using the STS definitions for perioperative outcomes (Table 1), the 30-d death, MI, stroke, and readmission were obtained from the institutional STS database.

Adverse outcomes: Adverse events were documented after the initiation of the protocol.

Statistical analysis

Treatment and control groups were compared on baseline characteristics to identify whether randomization was successful. Continuous variables were compared using 2-sample *t* tests or the non-parametric equivalent (Wilcoxon rank-sum test), while categorical variables were compared using Pearson χ^2 or Fisher's exact test. For dichotomous outcomes, logistic regression was used to adjust for group imbalances, when necessary. To examine whether treatment assignment influenced

Table 1 Society of thoracic surgery definitions for peri-operative outcomes

Outcomes	Definition
Stroke	If the patient had a central neurological deficit persisting postoperatively for > 72 h
Peri-operative MI	0-24 h post-operative: The CK-MB (or CK if MB not available) must be greater than or equal to 5 times the upper limit of normal, with or without new Q waves present in two or more contiguous ECG leads No symptoms required > 24 h post-operative: Indicate the presence of a peri-operative MI (> 24 h post-op) as documented by at least one of the following criteria: (1) Evolutionary ST-segment elevations (2) Development of new Q-waves in two or more contiguous ECG leads (3) New or presumably new LBBB pattern on the ECG (4) The CK-MB (or CK if MB not available) must be greater than or equal to 3 times the upper limit of normal

MI: Myocardial infarction; ECG: Electrocardiogram.

Table 2 Baseline characteristics between control group and remote ischemic preconditioning group

Characteristic	Control (n = 51)	RIPC (n = 51)	P
Demographics			
Mean age (± SD)	68.9 (± 9.8)	69.4 (± 9.9)	0.77
Male % (n)	62.8 (32)	76.5 (39)	0.20
Caucasian % (n)	88.2 (45)	90.2 (46)	1.00
Mean BMI (± SD)	30.4 (± 7.6)	28.4 (± 5.2)	0.13
Co-morbidities			
Diabetes mellitus % (n)	39.2 (20)	62.7 (32)	0.029
Hypertension % (n)	84.3 (43)	82.4 (42)	1.00
Dyslipidemia % (n)	90.2 (46)	90.2 (46)	1.00
Heart failure % (n)	21.6 (11)	23.5 (12)	1.00
Atrial fibrillation % (n)	0.0 (0)	0.0 (0)	NA
AICD % (n)	0.0 (0)	2.0 (1)	1.00
CVA % (n)	3.9 (2)	5.9 (3)	1.00
TIA % (n)	2.0 (1)	7.8 (4)	0.36
PAD % (n)	9.8 (5)	21.6 (11)	0.17
CKD % (n)	23.5 (12)	23.5 (12)	1.00
Dialysis % (n)	2.0 (1)	2.0 (1)	1.00
Mean creatinine (± SD)	1.2 (± 1.1)	1.2 (± 0.7)	0.89
COPD % (n)	5.9 (3)	0.0 (0)	0.24
Tobacco use % (n)	17.6 (9)	27.5 (14)	0.34

AICD: Automatic implantable cardioverter-defibrillator; BMI: Body mass index; COPD: Chronic obstructive pulmonary disease; CKD: Chronic kidney disease; CVA: Cerebrovascular accident; TIA: Transient ischemic attack; PAD: Peripheral arterial disease; RIPC: Remote ischemic preconditioning.

time to first occurrence of POAF, a log-rank test of the Kaplan-Meier survival functions was conducted.

RESULTS

A total of 102 patients were randomized between April 2011 and September 2013 (Figure 1). Sixty-nine point nine percent of the patients were males and 89% were Caucasian (Table 2). The mean age of patients in the RIPC and control group was 69.4 and 68.9 years, respectively. With the exception of diabetes mellitus, the two groups were balanced with respect to baseline characteristics. Study groups were also well balanced with respect to medication use including beta blocker and HMG-CoA reductase inhibitors (statins). 46% of the patients presented with acute coronary syndrome and 23.5% presented with stable angina and were well matched (Table 3).

POAF occurred at the rate of 54.0% in the RIPC group and 41.2% in the control group (P = 0.23). Expressed as a difference in proportions, the percent of patients experiencing POAF was 12.8% higher in the RIPC group compared with the usual care group (95%CI: -6.5%-32.1%). Although the presence of diabetes was significantly higher in the RIPC group, it was not associated with any outcome, and consequently, adjusting for diabetes in logistic regression models did not materially change the univariable results.

No post-operative MIs occurred in the RIPC group while 3.9% did in the control group, although this difference was not statistically significant (P = 0.50) (Table 4). There were only two deaths and two strokes for the entire study group and both occurred in the RIPC group. The 30-d readmission rates demonstrated no statistically significant difference between the two groups. The length of stay, left ventricular ejection fraction, and cross-clamp time demonstrated no significant difference between the control and RIPC groups.

The event rate for POAF, based on Kaplan-Meier analysis, was not significantly different between the RIPC and control group (P = 0.13) (Figure 2). No adverse events related to RIPC occurred.

DISCUSSION

In our study that assessed the effect of RIPC on clinical outcomes in patients undergoing elective or urgent cardiac surgery, we found that RIPC did not reduce POAF. In addition, there were no statistically significant differences in secondary outcomes, including post-operative MI and stroke and no adverse events were reported with RIPC.

The Effect of Remote Ischemic Preconditioning on Clinical Outcomes in CABG Surgery (ERICCA) study randomized 1216 patients who underwent CABG to RIPC *vs* control and demonstrated that at one year there was no statistically significant difference in the primary clinical outcome (cardiovascular clinical death, MI, stroke and coronary revascularization)[27]; no data regarding POAF were provided. Previous studies to date have largely evaluated the impact of RIPC on surrogate markers of clinical outcomes. RIPC has been evaluated in patients undergoing percutaneous coronary intervention to reduce myocardial injury[28], reduce contrast-induced nephropathy[29], and myocardial salvage in

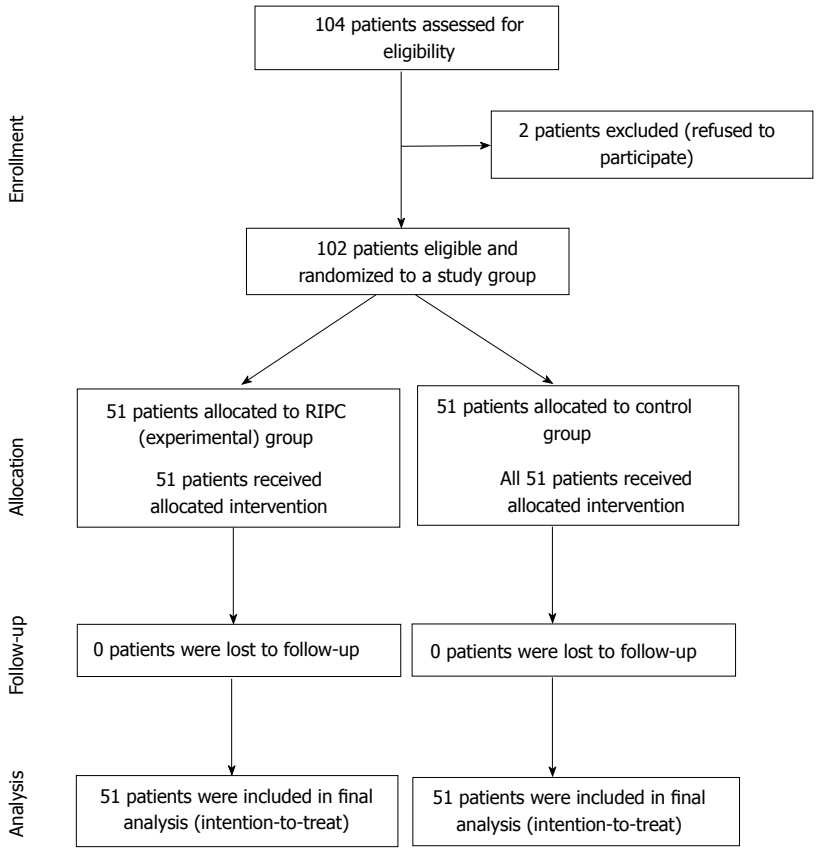

Figure 1 Randomization and follow up of patients. RIPC: Remote ischemic preconditioning.

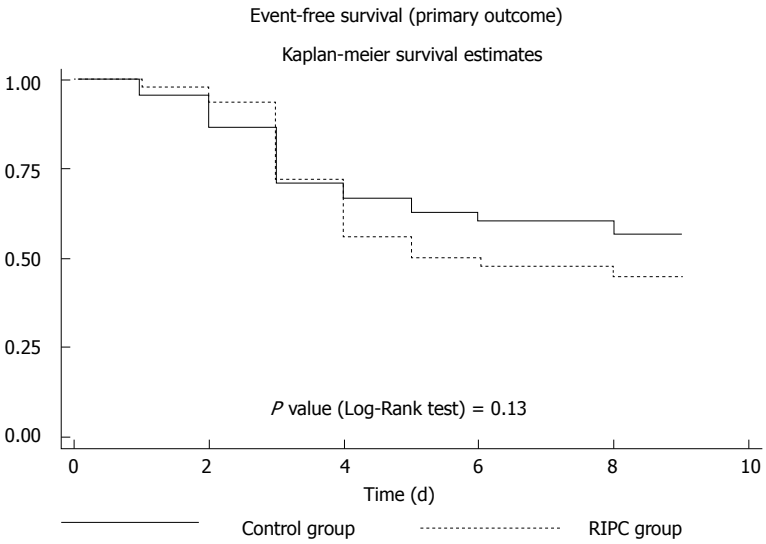

Figure 2 Kaplan-Meier estimates of the probability of remaining free from post-operative atrial fibrillation, according to study group. RIPC: Remote ischemic preconditioning.

ST-segment elevation MI[30]. Specifically, in patients undergoing cardiac surgery, RIPC has been known to decrease myocardial injury measured by cardiac troponin release[31,32]. At the same time, several other trials have failed to show improvement in surrogate outcomes with the implementation of RIPC[33,34], and this can be attributed to variable protocols, medications, surgical, and anesthetic regimens. It is also difficult to draw any conclusions regarding clinical outcomes from these studies as they were included only as secondary outcomes, often under-powered and had varying definitions of clinical outcomes[35]. Thus, no trials have been published demonstrating that RIPC significantly reduced clinical endpoints in patients undergoing cardiac surgery[36].

The rate of POAF in our study was higher than

Table 3 Baseline medications and clinical presentation in the control group and remote ischemic preconditioning group

Characteristic	Control (n = 51)	RIPC (n = 51)	P
Medications % (n)			
Alpha blockers	7.8 (4)	2.0 (1)	0.36
Beta blockers	78.4 (40)	80.4 (41)	1.00
ACE-inhibitors	37.3 (19)	41.2 (21)	0.84
Aspirin	90.2 (46)	90.2 (46)	1.00
Statins	84.3 (43)	86.3 (44)	1.00
Clinical presentation % (n)			
Stable angina	23.5 (12)	23.5 (12)	1.00
Unstable angina	25.5 (13)	25.5 (13)	1.00
Positive stress test	27.5 (14)	25.5 (13)	1.00
Non-STEMI	19.6 (10)	17.6 (9)	1.00
STEMI	0.0 (0)	2.0 (1)	1.00
Valve without CAD	17.6 (9)	27.5 (14)	0.34

ACE: Angiotensin converting enzyme; CAD: Coronary artery disease; RIPC: Remote ischemic preconditioning; STEMI: ST-elevation myocardial infarction.

Table 4 Clinical outcomes in the control group *vs* remote ischemic preconditioning group

Characteristic	Control (n = 51)	RIPC (n = 51)	P
Primary endpoint			
POAF % (n)	41.2 (21)	54.0 (27)	0.23
Secondary endpoints			
Other arrhythmia % (n)	13.7 (7)	11.8 (6)	1.00
MI % (n)	3.9 (2)	0.0 (0)	0.50
Stroke % (n)	0.0 (0)	3.9 (2)	0.24
Mean EF (± SD)	53.1 (± 14.8)	50.5 (± 16.9)	0.43
Bleeding % (n)	21.6 (11)	28.0 (14)	0.50
Mean cross-clamp time (± SD)	88.7 (± 44.8)	93.0 (± 38.5)	0.61
In-hospital mortality % (n)	0 (0)	3.9 (2)	0.50
30-d mortality (after discharge) % (n)	0 (0)	0 (0)	1.0
30-d readmission % (n)	11.8 (6)	16.3 (8)	0.57
Mean LOS (± SD)	13.7 (± 7.8)	14.0 (± 7.7)	0.87

EF: Ejection fraction; LOS: Length of stay; MI: Myocardial infarction; POAF: Post-operative atrial fibrillation; RIPC: Remote ischemic preconditioning; STEMI: ST-elevation myocardial infarction.

expected in both groups, which could be related to the small sample size and the presenting co-morbidities. Additionally, the absolute numbers of secondary outcomes recorded were quite small and therefore, are only exploratory at this stage. The unreliability of studies with small study samples is well-known[37,38]. Even if significant results had emerged from our study, regardless of direction of effect, we would caution against the over-interpretation of results, since small studies often produce large effects that frequently defy replication[39]. To our knowledge, this is the first study undertaken in the United States to assess the relationship of RIPC with POAF. Although this small study found no significant association of RIPC with clinical outcomes, it serves as an addition to the sparse literature on RIPC and clinical outcomes and would be of value when additional small studies are published. Meta-analyses of randomized controlled studies could yield a more accurate estimation of the true relationship between RIPC and POAF by combining patients and increasing sample power.

There were several limitations to our study that may have contributed to it not resulting in a positive finding. First, the study was halted prematurely, due to the lack of financial support to continue recruitment, which led to a study with less power than intended. However, given a control POAF rate of 50% (as seen in this population), the study still had 70% power to detect a 25% percentage points difference. Second, there was a significantly higher percentage of patients with diabetes mellitus in the RIPC arm, which may have masked the beneficial effect of RIPC[40]. However, this is unlikely to have significantly confounded the results as there was no change in the relationship of RIPC with outcomes even after adjustment using logistic regression analysis. Third, there is some recent evidence that patients given propofol may not gain protection from RIPC[41,42], possibly related to its structure being similar to that of phenol-based radical scavengers. This study was started prior to the publication of the study by Kottenberg *et al*[41], and in our study, propofol was used for the induction of anesthesia, not for maintenance. As with the majority of RIPC studies[35], we performed 3 cycles of RIPC, and in future trials it may be necessary to perform more than 3 cycles of blood pressure cuff inflation to provide clinical benefit. A final limitation is that warm cardioplegia has demonstrated a reduction in myocardial injury as compared to cold cardioplegia with similar clinical events[43,44]. Given that all our patients received warm cardioplegia, this could have masked the benefit of RIPC.

Despite the fact that the results of this study suggest that there is no beneficial effect of RIPC on reducing POAF, RIPC still holds promise in improving clinical outcomes, based on "proof-of-concept" studies using cardiac biomarkers as primary endpoints[31,45,46] and, due to the fact it is a simple, safe, non-invasive, and inexpensive intervention. Although it has been challenging to identify which groups of patients benefit from RIPC, further evaluation of RIPC to decrease post-operative events with carefully planned and funded studies with adequate power is warranted. Additionally, meta-analysis of small randomized controlled studies may also be useful in studying the relationship of RIPC and clinical outcomes, including POAF.

COMMENTS

Background

Remote ischemic preconditioning (RIPC) has been demonstrated to reduce perioperative myocardial injury following cardiac surgery (coronary artery bypass, with or without valve surgery).

Research frontiers

It is unknown whether it has an impact on clinical outcomes, such as post-operative atrial fibrillation, peri-operative myocardial infarction and stroke.

Innovations and breakthroughs

This is the first study in the United States evaluating these clinical outcomes following the use of RIPC with cardiac surgery.

Applications

Although this study did not suggest a clinically significant benefit with the use of RIPC, future meta-analyses of small randomized controlled studies may be useful in studying its relationship with clinical outcomes.

Terminology

RIPC is a strategy in which brief episodes of non-lethal ischemia and reperfusion are applied to the arm or leg in order to achieve myocardial protection from ischemic events.

Peer-review

This is an interesting manuscript about the effect of (PIPC on clinical outcomes such as post-operative atrial fibrillation (POAF), myocardial infarction, stroke, and mortality in 102 patients undergoing cardiac surgery. The data demonstrated that PIPC did not reduce POAF. In addition, there were no significant differences in post-operative myocardial infarction, stroke, and mortality between RIPC group and control group. Therefore, the authors have suggested that further evaluations of RIPC are required to decrease post-operative events.

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WJC covers topics concerning arrhythmia, heart failure, vascular disease, stroke, hypertension, prevention and epidemiology, dyslipidemia and metabolic disorders, cardiac imaging, pediatrics, nursing, and health promotion. Priority publication will be given to articles concerning diagnosis and treatment of cardiology diseases. The following aspects are covered: Clinical diagnosis, laboratory diagnosis, differential diagnosis, imaging tests, pathological diagnosis, molecular biological diagnosis, immunological diagnosis, genetic diagnosis, functional diagnostics, and physical diagnosis; and comprehensive therapy, drug therapy, surgical therapy, interventional treatment, minimally invasive therapy, and robot-assisted therapy.

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REVIEW

Physiology of *in-situ* arterial revascularization in coronary artery bypass grafting: Preoperative, intraoperative and postoperative factors and influences

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Author contributions: This manuscript was prepared and written by Ferguson Jr TB.

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Abstract

Surgical revascularization with coronary artery bypass grafting (CABG) has become established as the most effective interventional therapy for patients with moderately severe and severe stable ischemic heart disease (SIHD). This recommendation is based on traditional 5-year outcomes of mortality and avoidance of myocardial infarction leading to reintervention and/or cardiac death. However, these results are confounded in that they challenge the traditional CABG surgical tenets of completeness of anatomic revascularization, the impact of arterial revascularization on late survival, and the lesser impact of secondary prevention following CABG on late outcomes. Moreover, the emergence of physiologic-based revascularization with percutaneous cardiovascular intervention as an alternative strategy for revascularization in SIHD raises the question of whether there are similar physiologic effects in CABG. Finally, the ongoing ISCHEMIA trial is specifically addressing the importance of the physiology of moderate or severe ischemia in optimizing therapeutic interventions in SIHD. So it is time to address the role that physiology plays in surgical revascularization. The long-standing anatomic framework for surgical revascularization is no longer sufficient to explain the mechanisms for short-term and long-term outcomes in CABG. Novel intraoperative imaging technologies have generated important new data on the physiologic blood flow and myocardial perfusion responses to revascularization on an individual graft and global basis. Long-standing assumptions about technical issues such as competitive flow are brought into question by real-time visualization of the physiology of revascularization. Our underestimation of the impact of Guideline Directed Medical Therapy, or Optimal Medical Therapy, on the physiology of preoperative SIHD, and the full impact of secondary prevention on post-intervention SIHD, must be better understood. In this review, these issues are addressed through the perspective of multi-arterial revascularization in CABG, which is emerging (after 30 years) as the "standard of care" for CABG. In fact, it is the physiology of these arterial grafts that is the mechanism for their impact

on long-term outcomes in CABG. Moreover, a better understanding of all of these preoperative, intraoperative and postoperative components of the physiology of revascularization that will generate the next, more granular body of knowledge about CABG, and enable surgeons to design and execute a better surgical revascularization procedure for patients in the future.

Key words: Coronary artery bypass grafting; Arterial revascularization; Myocardial perfusion; Surgical outcomes; Intraoperative imaging

Core tip: This review examines the emerging understanding of physiology in revascularization from the preoperative, intraoperative and postoperative perspectives. The particular importance of physiology in arterial revascularization, which is becoming the standard of care, is discussed using novel intraoperative imaging data results. These imaging data objectively confirm certain physiologically-determined outcomes, and highlight inadequacies in a number of long-standing assumptions about surgical revascularization with coronary artery bypass grafting.

Ferguson Jr TB. Physiology of *in-situ* arterial revascularization in coronary artery bypass grafting: Preoperative, intraoperative and postoperative factors and influences. *World J Cardiol* 2016; 8(11): 623-637 Available from: URL: http://www.wjgnet.com/1949-8462/full/v8/i11/623.htm DOI: http://dx.doi.org/10.4330/wjc.v8.i11.623

INTRODUCTION

Arterial revascularization, and in particular complete arterial revascularization, is a current emerging trend in surgical revascularization with coronary artery bypass grafting (CABG). This Review examines the physiologic aspects of arterial revascularization in light of its documented clinical outcomes benefits (Table 1).

ARTERIAL REVASCULARIZATION IN CABG

Since its inception in the 1960s, the history of CABG has included incremental developments to improve outcomes[1]. Among these, the use of *in situ* internal mammary artery (IMA) grafting has been documented to have the most profound beneficial effect[2,3]. Placed to the left anterior descending coronary artery (LAD), this intervention is perhaps the most singularly effective in all of ischemic heart disease[4,5]. Multiple studies have documented excellent short-term angiographic results, superior long-term patency *vs* other conduits, and a direct impact on long-term survival in observational studies[6,7]. Interestingly, this benefit appears to have its maximal impact 10-20 years post-surgery, after most non-arterial conduits have lost their efficacy[8].

Surgical groups with a long-standing interest in multi-arterial grafting have hypothesized about the mechanism(s) for this incremental benefit on survival, based on their excellent observational studies[9-11]. With improvement in techniques such as skeletonization[12], the use of bilateral arterial grafting is being advocated as the new "standard" of care[13,14]. This despite the additional work product and time required for this surgical approach, because of it's association with significantly better long-term outcomes[15].

The standard explanation for these improved outcomes is the substantial long-term anatomic patency of arterial grafts, both early and late[16]. While this certainly is a factor, the complete mechanism is more complicated. Indeed, as our understanding of the physiologic substrates for stable ischemic heart disease (SIHD) and acute coronary syndrome (ACS) have evolved, it is clear that physiologic factors are as if not more important than anatomic factors, which have for years formed the based of technical surgical revascularization design and execution.

Thus the premise of this review is that the true impact of multi-arterial *in situ* grafting in CABG results from its impact on the physiology of myocardial revascularization in that patient.

PREOPERATIVE FACTORS AND INFLUENCES

The revascularization strategy that is CABG today should be very different from previous iterations, in order to take advantage of: (1) concomitant developments in ischemic heart disease therapies and their physiologic impact on SIHD and ACS; and (2) the changes in the patient population of those patients coming to surgery, and the changes in the myocardial pathophysiologic substrate in these new patients. Truly innovative improvements in surgical revascularization must address these physiologic and pathophysiologic substrate issues in order to be successful.

Nowhere has this been more evident than in the emergence of optimal medical therapy (OMT), or guideline-directed medical therapy (GDMT), in SIHD[17]. From an afterthought 10-15 years ago, GDMT has emerged as an initial mainstay of therapy for SIHD patients outside the scope of ACS, where emergent intervention can be life-saving[18]. The impact of GDMT on clinical survival outcomes was documented in the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) and trial substudies in patients with mild to moderate ischemia[19-22]. These findings are not without controversy, however[23,24], with particular attention to their impact on early inter-

Table 1 Factors and influences in arterial revascularization

Arterial revascularization in CABG
Emerging "standard of care" for CABG
Years of data to document benefits, but slow to adopt
Both based on long term survival outcomes
Mechanisms for increased survival based on traditional anatomic construct for surgical revascularization
Better long-term graft patency
Preoperative factors and influences
Effectiveness of GDMT - physiologic modulation of underlying ischemia
Extent of disease
Collateral development
Influence on myocardium
Impact on subsequent revascularization
ISCHEMIA trial
Equipoise issue
Implications for revascularization
Same physiologic principles impacting PCI must also impact CABG
Difference in anatomic extent of disease
Surgical revascularization not dependent on completeness of (anatomic) revascularization
Intraoperative factors and influences
Dynamic nature of *in situ* arterial grafts
Competitive flow in arterial grafts (*vs* vein grafts)
Incomplete revascularization *vs* appropriate incomplete revascularization
FFR-based revascularization
Postoperative factors and influences
Secondary prevention measures in CAD
DAPT
Secondary prevention efforts following CABG

CABG: Coronary artery bypass grafting; GDMT: Guideline directed medical therapy; PCI: Percutaneous cardiovascular intervention; DAPT: Dual anti-platelet therapy; FFR: Fractional flow reserve; ISCHEMIA: International Study of Comparative Health Effectiveness with Medical and Invasive Approaches.

vention revascularization strategies, mostly for percutaneous coronary intervention (PCI) but also for CABG[17]. The COURAGE population had predominantly mild ischemia symptoms and objective findings, and early PCI in these patients demonstrated no benefit in terms of the primary outcome of death from any cause and non-fatal myocardial infarction (MI)[19].

The importance of preoperative ASA, beta-blockers and statins on CABG surgical outcomes have all been examined as well. Preoperative beta-blockade was documented to positively impact on CABG outcomes in 2002[25], with incorporation into the National Quality Forum Quality Measures for CABG Surgery and the ACCF/AHA Guidelines for CABG[26]. A decade later, this benefit was re-examined in a more contemporary patient population, and no longer found to be a statistically significant influence on survival[27]. Rather than indicating the loss of effectiveness of beta-blocker therapy in CABG patients however, or that the initial studies were flawed, these findings almost certainly reflect the change in the underlying physiologic substrate of patients coming for contemporary CABG[28,29].

In patients with SIHD, GDMT is necessary because it prevents MI and death. The mechanism for the effectiveness of GDMT is the beneficial modulation of the underlying physiologic substrates of hypoperfusion/ischemia, atherosclerosis, myocardial contractility and relaxation, and microvascular and macrovascular myocardial blood flow[30]. Obviously, these same factors greatly influence CABG patients as well.

The impact of GDMT with and without early revascularization in patients with moderate to severe ischemia is currently being tested in the International Study of Comparative Health Effectiveness with Medical and Invasive Approaches (ISCHEMIA) trial, (NCT01471522). The aim of the ISCHEMIA trial is to determine whether an initial invasive strategy of cardiac catheterization and optimal revascularization (with PCI or CABG, as determined by the local heart team) plus OMT will reduce the primary composite endpoint of cardiovascular death or nonfatal MI in SIHD with moderate or severe ischemia and medically controllable or absent symptoms, as compared with an initial conservative strategy of OMT alone, with catheterization reserved for failure of OMT (Figure 1). The major secondary endpoint is angina-related QoL. Other important secondary endpoints are health resource utilization, costs and cost effectiveness. The ISCHEMIA study thus aims to address limitations of previous strategy trials by: (1) enrolling patients before catheterization, so that anatomically high-risk patients are not excluded; (2) enrolling a higher-risk patients are not excluded; (3) minimizing crossovers; (4) using contemporary DES and physiologically-guided decision-making [fractional flow reserve analysis (FFR)] to achieve complete ischemic (rather than anatomic) revascularization; and (5) being adequately powered to demonstrate whether routine revascularization reduces cardiovascular death or nonfatal MI in patients with SIHD and at least moderate ischemia. The results of the ISCHEMIA trial will have important implications regarding global guidelines for performance and reimbursement of revascularization procedures in patients with SIHD.

One additional preoperative pathophysiologic substrate that impacts surgical revascularization today much more than before involves the substantial development of the myocardial collateral circulation as a result of the heart's response to MI or even transient myocardial ischemia[31,32]. According to the STS database, approximately 40% of patients revascularized with CABG have a documented prior MI, with many more lacking that documentation or with a history of multiple episodes of ischemia preoperatively. Thus patients coming to surgery today have much more extensive collateralization than in the past. These collaterals have been directly linked to long-term survival in IHD patients, and recently their importance in patients with diabetic microvascular disease has been established[33,34].

In surgical revascularization with CABG, particularly in patients with extensive anatomic and functional disease, these collaterals impact the effectiveness of each individual bypass graft, depending upon the regional myocardial perfusion substrate supplied by that

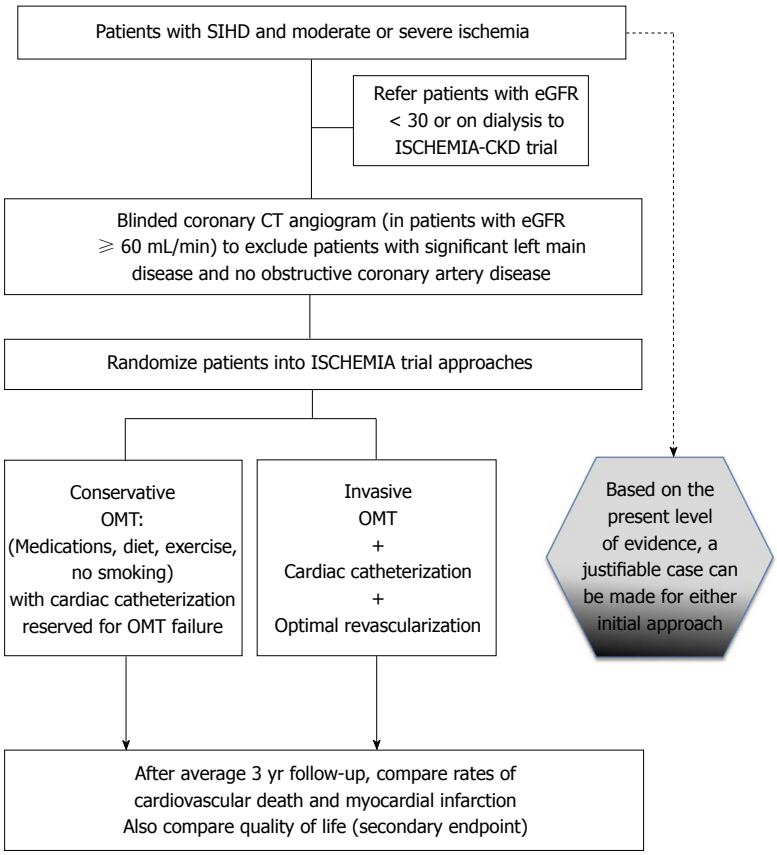

Figure 1 International Study of Comparative Health Effectiveness with Medical and Invasive Approaches (NCT01471522) trial design. After Stone *et al*[17]. CCTA may not be performed with estimated glomerular filtration rate < 60 mL/min. Participants in whom CCTA show significant left main disease (⩾ 50% stenosis) or no obstructive disease are excluded. CCTA results are otherwise kept blinded. ISCHEMIA: International study of comparative health effectiveness with medical and invasive approaches; CCTA: Coronary computed tomographic angiography; eGFR: Estimated glomerular filtration rate; OMT: Optimal medical therapy = guideline-directed medical therapy; SIHD: Stable ischemic heart disease.

graft and the surrounding adjacent substrates[35-37].

Several randomized trial post-hoc analyses have produced data to support the importance of this patho-physiologic substrate in contemporary CABG patients. The Project of *Ex-Vivo* Vein Graft Engineering *via* Transfection IV (PREVENT IV) documented 12-18 mo angiographic follow-up and 5-year clinical outcomes[38]. Vein graft failure in patients on follow-up angiogram was common (43%); in these patients followed for 4 years, clinical outcomes were associated with repeat revascularization, but not with death and/or MI[39]. These data suggest that the myocardium supplied by these occluded vein grafts had enough other blood flow [from the native target vessel epicardial coronary artery (TVECA) and/or collateral flow] so as not to influence the major outcomes of death and MI. In the SYNergy between PCI with TAXus and cardiac surgery (SYNTAX) trial, (ClinicalTrials.gov number NCT00114972)[40] the better outcomes seen in the surgical arm occurred despite a > 40% incomplete revascularization rate at CABG by SYNTAX anatomic criteria[41,42]. Head *et al*[43] documented that incomplete revascularization was associated with adverse outcomes in the PCI cohort but not the CABG cohort. This outcome is impacted by the higher incidence of preoperative MI in the CABG group, and by the greater extent of anatomic disease impacting the underlying myocardial pathophysiologic substrate in these patients. While the revascularization was as complete as technically possible, incompleteness by anatomic criteria alone was likely ameliorated by this dynamic collateral exchange of perfusion in these contemporary surgical revascularization patients.

INTRAOPERATIVE FACTORS AND INFLUENCES

The patient-level benefits of arterial grafting are clear, as IMA grafting to the LAD has been the standard of care for three decades. Despite the overwhelming body of evidence that multi-arterial grafting yields even further benefit for patients, including long-term survival, and freedom from MI, and that bilateral IMA grafting can be safely performed in elderly diabetic patients[44,45], transitioning of the standard of care to this new technical solution has been difficult[11]. Multi-arterial grafting represents a substantial change in the approach and work product of a CABG procedure for the surgeon[9,46]. Therefore, a more thorough understanding of the mechanisms underlying the benefits of multi-arterial grafting is important.

Most randomized trials involving CABG with protocol-specified angiographic follow-up have documented 1 year patency rates for *in-situ* IMA grafts between 95% and 100% at 12-18 mo, with grafting thresholds for angiographic stenoses of 70% or greater[47-50]. The 5% early attrition rate is widely thought to be due to technical errors at surgery[51,52].

Late graft failure following IMA grafting is much more complex in terms of etiology. The "competitive

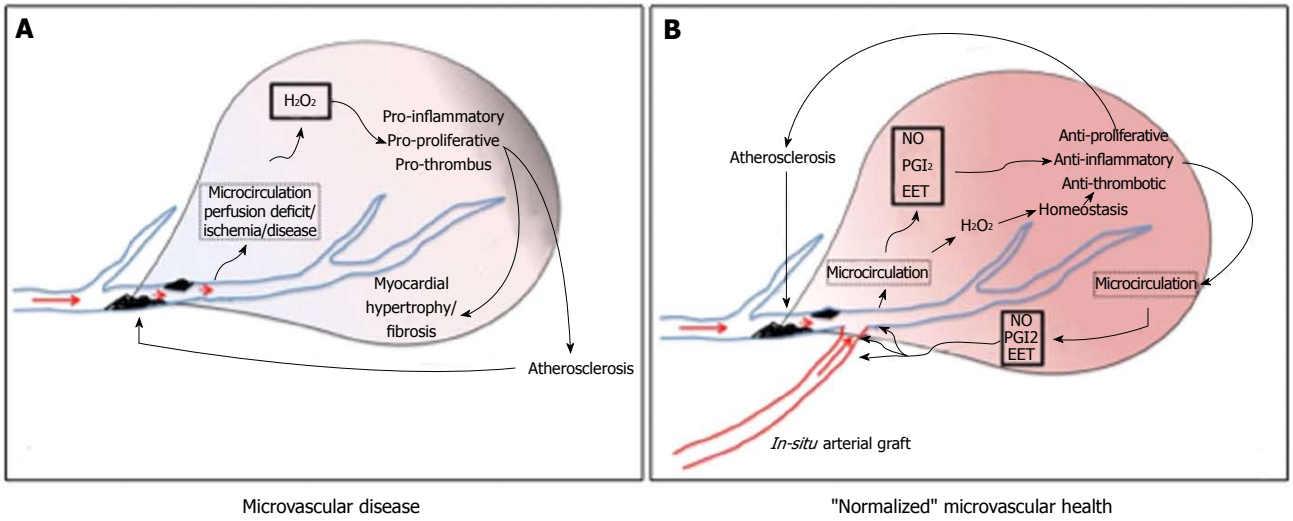

Figure 2 From Ferguson *et al*[37], with adaptation from Gutterman *et al*[62]. In a healthy heart, arteriolar endothelium produces NO, prostacyclin (PGI2, and EETs) as well as low levels of hydrogen peroxide, which support a quiescent non proliferative state. With the onset of disease (A), flow through the microvasculature releases hydrogen peroxide, creating a proinflammatory environment throughout the organ, potentially leading to hypertrophy, fibrosis, and atherosclerosis. In B, with bypass grafting of ischemic myocardium, the microvascular health of the myocardium is "normalized". NO: Nitric oxide; PGI2: Prostacyclin; EET: Epoxyeicosatrienoic acids.

flow" from moderately stenosed native TVECA has been posited as a major cause for late *in situ* IMA graft failure. This is in contradistinction to causes for vein graft failures[53]. Additional causes of late arterial graft failure include factors typically attributed to other conduit failures, such as poor run-off of the distal native coronary circulation, thrombogenic factors, and size mis-match might be factors as well[50]. More recently, computer flow dynamic modeling studies have clarified the role of wall shear stress (WSS) on local hemodynamics, where atheroma are inhibited or retarded under conditions of high shear stress but predisposed to occur under conditions of low shear stress[54-56]. Despite the clinical studies associating intermediate coronary stenoses with increased IMA graft failure, Shimizu *et al*[57] demonstrated that the shear stress of the *in situ* IMA is maintained despite the flow volume being reduced by flow competition. Ding *et al*[58] used computerized flow dynamic modeling to study competitive flow in an IMA-LAD graft model. In this study, they correlated the Time-Averaged WSS and the oscillatory shear index (OSI) with TVECA percent stenosis, and found that TAWSS dropped when the stenosis was < 75%; concomitantly, the OSI distribution increased below 75% stenosis, where high OSI predisposes to endothelial dysfunction and atherogenesis[59], while maintained WSS is responsible for normal endothelial function and endogenous vasodilator production such as nitric oxide (NO).

Further complicating this story is the fact that two myocardial factors influence WSS in TVECAs and arterial conduits as well: Myocardial ischemia resulting from a physiologically significant proximal coronary stenosis increases WSS at the anastomosis and in the vessels, and this increased WSS stimulates the development of collateral circulation through arteriogenesis[60,61]. The influence of myocardial vasculature WSS on conduit and TVECA shear stresses has not been well-characterized.

The reasons for improved long-term patency *vs* other conduits for grafting have been discussed at length in the surgical literature. These include the *in situ* nature of the conduit, endothelial production of endogenous vasodilators NO, prostacyclin (PGI_2) and epoxyeicosatrienoic acids (EETs) to dilate the conduit and protect against the development of atherosclerotic disease in the vessel, better diameter matching between the graft and the TVECA, the absence of atherosclerotic disease and disease progression, and others. In a recent article, Gutterman *et al*[62] characterized the differences between microvascular health and microvascular disease. Figure 2 adapts this concept to the CABG setting, including pre-grafting ischemia (Figure 2A) and post-grafting regional myocardial status (Figure 2B). In "normalized" microvascular health (such as a non-diseased IMA graft in a CABG patient), atherostasis is achieved by predominant endothelial production of these vasodilators (NO, PGI_2 and EET), with anti-proliferative, anti-inflammatory, and anti-thrombotic effects. In disease (such as SIHD), microcirculatory production of reactive oxygen species (H_2O_2) maintains dilation but at the expense of pro-inflammatory, pro-proliferative, and pro-thrombotic responses that contribute to atherosclerosis in TVECAs and hypertrophy and fibrosis in the myocardium. In arteries from healthy subjects, normal WSS activates production of NO to stimulate dilation and vascular homeostasis. Abnormal WSS, vascular stress or the presence of coronary artery disease stimulates the pathological basal level of oxidants and initiates a switch in the mediator of flow-induced dilation from NO to H_2O_2; dilation is maintained (for a time) but at the expense of vascular inflammation and its consequences[62].

Among these, specific relevance to CABG is the

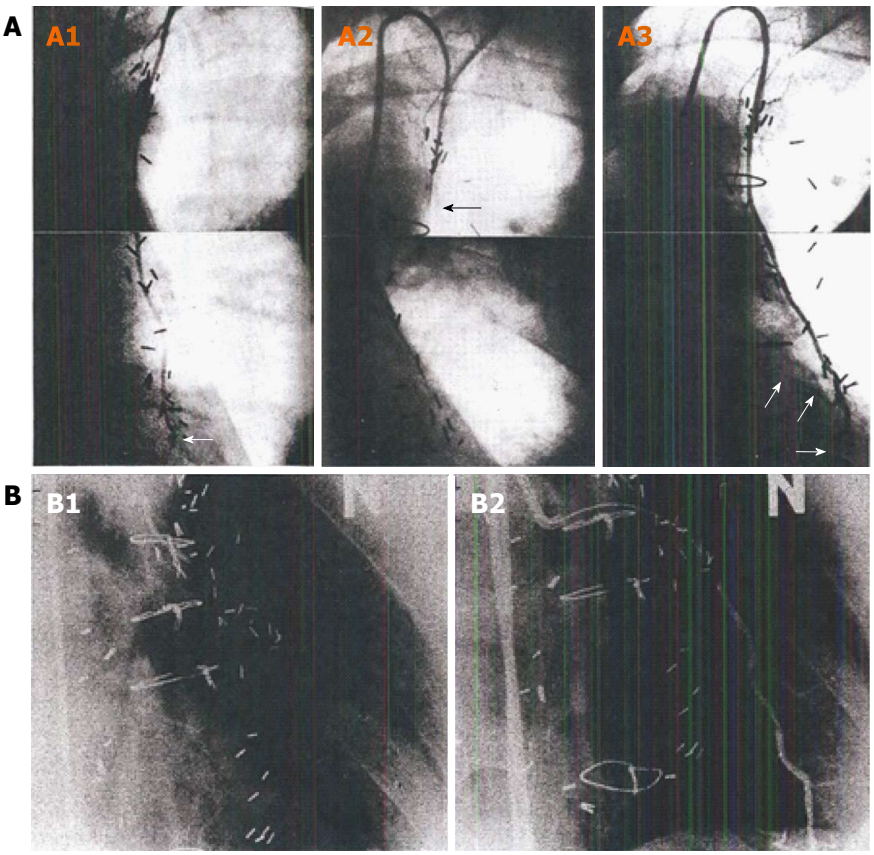

Figure 3 Composite of string sign data. Angiographic documentation of the development of a "string-sign" IMA graft. A: Data from Dincer *et al*[98]. A1: Composite still images from angiogram of IMA-LAD graft at 8 d postop. White arrow show anastomotic site; A2: Composite still images from an angiogram at 1-year postop. Black arrow identifies "string-sign" IMA conduit with little if any distal flow; A3: Composite still images from angiogram at 5 years postop, documenting a widely patent IMA-LAD graft. The three white arrows outline the native TVECA LAD proximal and distal to the anastomosis. There is no angiographic evidence of atherosclerotic disease in the IMA, and no anastomotic evidence of narrowing; B: Data from Kitamura *et al*[99]. Images that clearly illustrate the physiology of arterial conduits. B1: A stringlike LIMA with no-flow into the LAD. Because of the limitations of conventional angiography, flow down the TVECA LAD cannot be simultaneously visualized, but was patent with good antegrade flow; B2: Repeat LIMA arteriography now showing anatomical patency of the graft, as a result of temporary occlusion of the recipient LAD with a percutaneous transluminal coronary angioplasty balloon. The acute influence of anterior wall hypoperfusion immediately translated into resumed functionality of the LIMA graft, documenting the coupling of physiologic IMA flow to the distal regional myocardial physiologic status. IMA: Internal mammary artery; LAD: Left anterior descending coronary artery; TVECA: Target vessel epicardial coronary artery.

endogenous production of vasodilators is believed to be the most important[59,63]. The powerful influence of these physiologic processes has been documented in studies illustrating serial angiographic follow-up after *in situ* IMA grafting. Hartman *et al*[64] and Akasaka *et al*[65] both documented progression from a normal-sized *in situ* conduit, to a string sign several years later, and finally to a supra-normal conduit, as the native coronary circulation and non-arterial bypass grafts developed progressive disease (Figure 3). It is clear from the above discussion that this string sign is not the product of irreversible microvascular disease from vascular inflammation. Rather, it must be an exogenously-stimulated normal endothelial response that can change over time.

In fact, many studies have documented that there is a predictable physiologic response in size and conduit flow in normal *in-situ* arterial grafts not compromised by technical errors over time. In their studies, Shimizu *et al*[57] and Akasaka *et al*[66] hypothesized that competitive flow between the TVECA and the *in situ* graft created the angiographic string sign - a technically angiographically patent graft, where conduit flow was minimal, but which could respond over time by increasing diameter and decreasing flow velocity, improving flow capacity, due to endothelial response triggers.

We now understand more clearly the role that the distal myocardium plays in influencing IMA conduit flow. Our near-infrared fluorescence (NIRF) imaging studies at the time of off-pump beating heart coronary artery bypass (OPCAB) quantified the change in regional myocardial perfusion, if any, associated with anatomically patent bypass grafting, including IMA, vein, and radial arterial grafts (Figure 4). Overall, in 80% of anatomic grafts to arteries with a minimum 70% proximal stenosis, there was a real-time increase in quantified regional perfusion when supplied by the TVECA and the graft conduit, *vs* the TVECA alone[35,37,67]. We believe this perfusion increase was dependent on the physiologic status of the distal myocardium in terms of tissue oxygen and blood flow demand. In the same way, this myocardial status impacts the dynamic flow

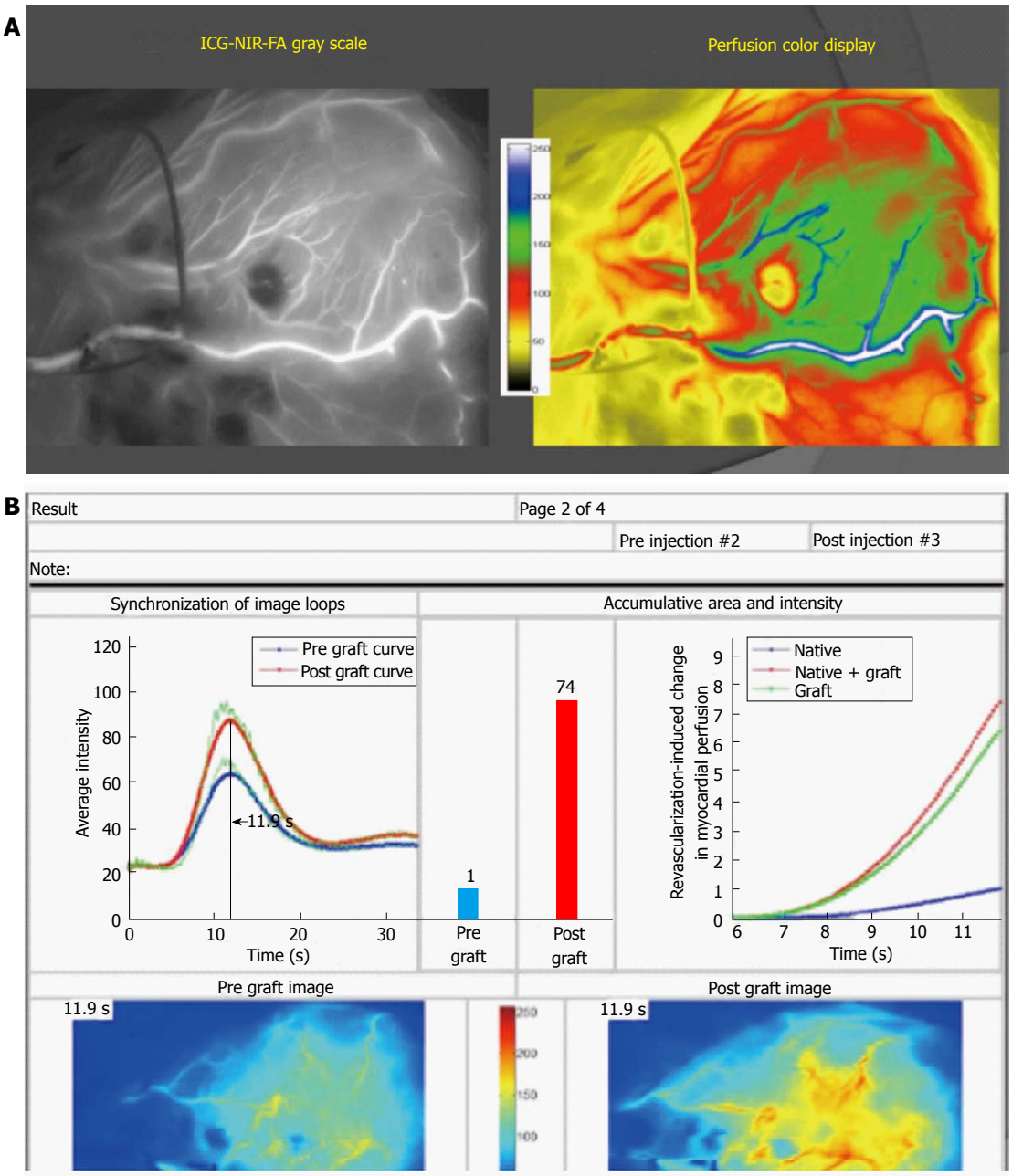

Figure 4 SPY near-infrared imaging of the physiology of revascularization and quantification of the change in regional myocardial perfusion as a result of bypass grafting. A: Near-infrared frame from 34-s video of IMA graft to LAD in 256 grey scale (left panel) and more intuitive color scale (see color bar) to differentiate perfusion differences to the myocardium. The video shows the dynamic arterial and microvascular blood flow interaction between the native TVECA flow and the IMA graft flow in real-time and under true physiologic conditions; B: The Complex Angiography and Perfusion Analysis platform result from and IMA to LAD graft in a patient with prior anterior MI and regional myocardial ischemia preoperatively. The right upper panel quantitatively compares pre-bypass TVECA regional myocardial perfusion (blue line and bar) with post-bypass combination of TVECA + IMA perfusion (red line and bar). The green line in the graph is the relative contribution to perfusion of the IMA graft flow. The two bottom images are synchronized with respect to timing, as shown by the marker on the upper left graph. This patient with anterior ischemia had a 7-fold increase in perfusion to the anterior regional myocardium as a result of IMA grafting. In addition, the proximal LAD in this patient was 100% occluded, and the pre-grafting TVECA perfusion was entirely from flow through lateral and inferior collaterals. IMA: Internal mammary artery; LAD: Left anterior descending coronary artery; TVECA: Target vessel epicardial coronary artery.

characteristics of the *in situ* arterial conduits. Beginning with a technically adequate patent IMA graft, the functionality of the proximal TVECA stenosis (beyond anatomic severity alone) will influence subsequent IMA graft behavior. Early on, the perfusion status of the myocardium impacts early WSS and flow[57]. The pressure drop across the stenosis, if functionally significant, increase shear stress in the myocardial collateral vessels; both ischemia and increased shear stress promote the development of collateralization in the myocardium[60]. In the TVECA, the diminution of flow decreases WSS. If myocardial ischemia is relieved by the combined IMA/TVECA flow, then TVECA WSS is normalized, and the IMA graft accommodates flow

velocity and flow capacity according to its contribution to myocardial demand relief[66]. If the proximal stenosis in the TVECA is not functionally significant, such as described by Ding *et al*[58], then time-averaged WSS of the graft falls, and OSI increases, contributing to the development of a string sign configuration angiographically. This IMA conduit, under new conditions of ischemia, can physiologically respond accordingly to meet this perfusion demand deficit[64]. Over time, as the native TVECA and graft disease progressed, the IMA conduit was driven to supply more and more blood flow to that regional myocardium, resulting in significant vasodilation of the *in situ* conduit. Importantly, this *in situ* conduit likely is supplying blood flow to other regions of the heart as well, given the extent of angiographic disease at this later stage and the assumed presence of extensive collaterals.

From a physiologic perspective, this dynamic nature of *in situ* IMA grafts, coupled to the functional status of the TVECA regional myocardium in a heart with extensive coronary disease and significant collateralization, is a likely physiologic-based explanation for the long-term clinical outcomes benefit from IMA grafting.

Competitive flow is the term used to describe flow interaction between the graft conduit and the TVECA, presumed to occur to a greater extent as the angiographic stenosis in the TVECA lessens. Thus it is presumed that there is more competitive flow to a TVECA with a 50% proximal stenosis than a 70% proximal stenosis. Glineur has reported that this situation of arterial graft competitive flow occurs when conductance (the ability of fluid to transmit through materials) of the graft closely matches that of the native circulation, and is mainly dependent on stenosis severity and on graft diameter and length[68]. However, because intraoperative conventional coronary angiography has not been widely available, and because coronary angiography *per se* does not represent true physiologic conditions, our knowledge about competitive flow in arterial grafts is limited. Moreover, since the behavior of these grafts changes over time, documentation of competitive flow at the time the bypass is created would be useful for understanding its true physiologic impact[69].

Pagni *et al*[70,71] performed a series of animal studies assessing the flow patterns in the graft conduit (IMA and/or vein grafts) and the unobstructed native TVECA. These studies documented four characteristic flow phases during systole and diastole associated with actual competitive flow between the IMA conduit and the TVECA in this experimental setting, without a proximal stenosis (fully competitive flow): In phases 1 and 2, during diastole, there is antegrade flow in both the TVECA and the arterial graft. In early systole, there is antegrade flow in the TVECA but retrograde flow in the distal arterial graft, which reverses in late systole, where there is retrograde flow in the TVECA and antegrade flow in the arterial conduit[70].

The actual flow patterns that occur with more significant proximal stenoses and more severe distal disease are less understood. Gould *et al*[72] demonstrated the relationship between coronary flow reserve (CFR) and isolated coronary stenoses, where CFR was maintained until the stenosis reached 70% or greater. With diffuse anatomic disease, however, this relationship degrades, and "critical" coronary flow reduction becomes prognostic[73]. Ding's simulated competitive flow results in models of the IMA-LAD anastomosis are similar to Gould and Pagni, with a dependency on the degree of proximal stenosis[58]. Using angiographic characteristics, however, Berger[50] concluded that minimal competitive flow occurs until the proximal stenoses is greater than 70% angiographically.

Our extensive studies of bypass grafting in off-pump CABG, where the actual physiology of blood flow in grafts and perfusion to the myocardium has been studied in over 1000 patients on a per graft basis, documented exactly this same reversal of flow pattern as Pagni in angiographically widely-patent IMA grafts to the LAD[67]. However, all these TVECAs (LAD or circumflex marginal branches) had a minimum of 70% proximal stenoses by preoperative angiography (Figure 5). The real-time intraoperative imaging technique was NIRF angiography (SPY, Novadaq Technologies, Toronto, Ontario, CA), coupled with the Complex Angiography and Perfusion Analysis analysis platform developed and patented in our Imaging Laboratory[35]. Importantly, this technology in OPCAB images blood flow and perfusion simultaneously in the TVECAs and graft conduits, and where there are physiologic conditions of coronary flow, coronary pressure, and myocardial functional performance[36].

These clinical studies uncovered two important factors. First, competitive flow was not ever documented angiographically in non-arterial conduits to TVECAs, regardless of the degree of TVECA proximal stenosis, similar to Glineur's data[68]. Presumably, at the time of surgery, the flow down vein grafts free of technical problems is so dominant that even with intermediate (40%-70%) stenosis in the TVECA, competitive flow doesn't occur. Second, in a sub-study of *in situ* IMA conduits to TVECAs with a 70% or greater proximal stenosis on the L side of the heart (LAD, circumflex marginal branches), a total of 23% of IMA grafts did not improve regional myocardial perfusion. That is, the post *vs* pre quantified distal regional myocardial perfusion (Figure 4) didn't increase, despite a widely patent anastomosis angiographically and the absence of any clinical signs of incomplete relief of regional hypoperfusion/ischemia, or hemodynamic instability[67]. Examination of the real-time image sequences from these 23% *in situ* IMA grafts documented that > 80% had NIRF angiography documented competitive flow by these Pagni criteria.

These objective, imaging-based data document that competitive flow in arterial grafts does occur with

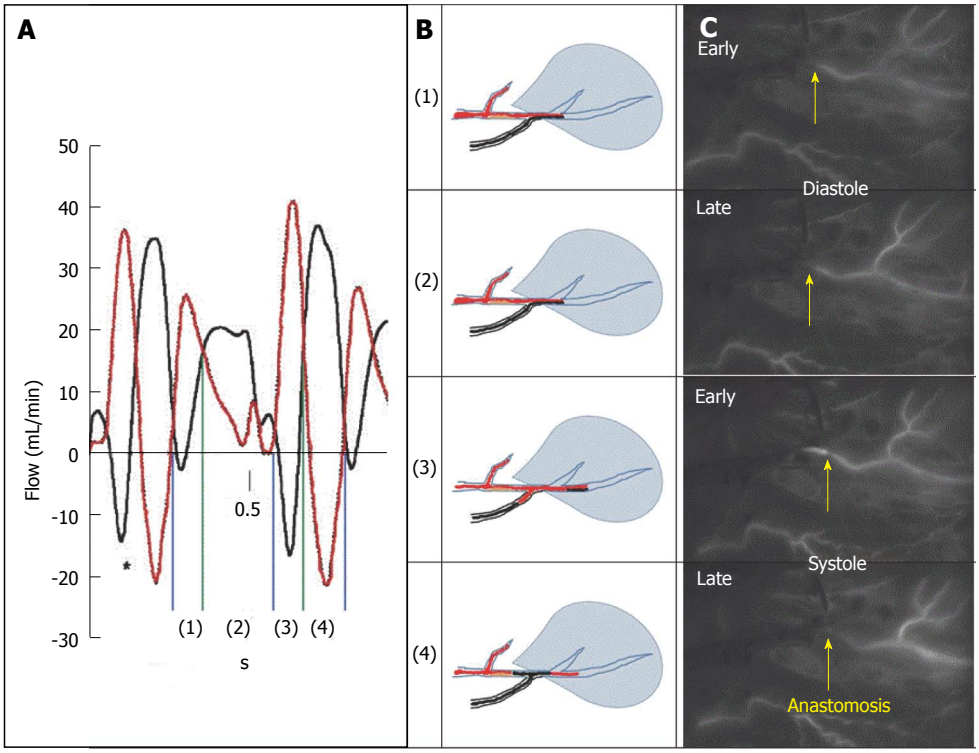

Figure 5 Intraoperative real-time documentation of competitive flow in arterial internal mammary artery-left anterior descending coronary anastomosis with > 70% stenosis. Competitive flow documented in *in situ* arterial graft to TVECA with > 70% proximal stenosis. A: Dynamic flow data from Pagni *et al*[71] illustrating flow in IMA (red) and LAD (black) in an experimental model of competitive flow where the LAD has no proximal stenosis (maximal competitive flow). In phases 1 and 2, during diastole, there is antegrade flow in both the TVECA and the arterial graft. In early systole, there is antegrade flow in the TVECA but retrograde flow in the distal arterial graft, which reverses in late systole, where there is retrograde flow in the TVECA and antegrade flow in the arterial conduit; B: Diagrammatically the IMA-LAD interaction at the anastomosis in this patient; C: Four still frames taken from the 34-s video of this bypass graft using near-infrared imaging technology (SPY, Novadaq Technologies, Toronto, Ontario, CA). The arrow indicates the site of the anastomosis. The four frames are in temporal sequence but not consecutive frames; they are selected at the four diagram points indicated at the middle panel. Each diagram point is taken from the appropriate time-point within each of the four intervals (early diastole, late diastole, early systole, late diastole). This real-time intraoperative imaging shows identical flow patterns as demonstrated in the Pagni experimental model, despite the proximal > 70% stenosis. IMA: Internal mammary artery; LAD: Left anterior descending coronary artery; TVECA: Target vessel epicardial coronary artery.

proximal stenoses of 70% or greater severity at a much higher frequency that presumed based on indirect data as reported[74,75]. These data also strongly support the concept that the flow interaction between the *in situ* conduit and the TVECA is in fact less influenced by the proximal stenosis severity (anatomy) and more influenced by the physiologic status of the distal regional myocardium in terms of perfusion deficit and regional myocardial ischemia. As discussed above, based on these physiologic factors the arterial conduits will adapt to meet these demands over time and to the degree possible[66,69]. Nordgaard *et al*[76] demonstrated in an experimental model that WSS and OSI of an IMA graft was affected by the degree of competitive flow, where high competitive flow produced unfavorable WSS conditions consistent with endothelial dysfunction and subsequent graft narrowing and failure. However, the severity of competitive flow was based on percent proximal stenosis, and did not account for the functionality status of the stenosis.

These intraoperative imaging findings, in fact, are supported by the critically important developments over the past decade in PCI revascularization, based on the numerous studies with FFR and instantaneous wave free (iFR) studies[77-82]. In the FFR *vs* Angiography for Multivessel Evaluation (FAME) (ClinicalTrials.gov, No. NCT00267774) 1 study, 20% of angiographic stenoses between 70% and 90% were determined to be non-functional stenoses, consistent with our OPCAB studies[77]. Moreover, as presented by Stone *et al*[17], the physiologic status of the myocardium in patients with SIHD, and the ability of OMT to influence that status, creates equipoise in determining a conservative *vs* interventional therapeutic approach to patients, even with documented moderate-to-severe ischemia prior to therapy initiation. Importantly, in this context PCI and CABG are considered alternative forms of revascularization intervention determined by current RCT data from the head-to-head SYNTAX[42] and Future Revascularization Evaluation in patients with Diabetes mellitus: Optimal management of Multivessel disease (FREEDOM) (ClinicalTrials.gov number NCT00086450) trials[83]. However, the fact that they are alternative revascularization strategies means that the physiologic substrate for that intervention is equivalent, from a physiologic perspective. Our data strongly support the

importance of physiology in determining short-term and long-term outcomes from surgical revascularization, in parallel to this experience in percutaneous revascularization[36]. In addition, others have described the current potential role of FFR-guided CABG, further emphasizing the emerging importance of physiology in revascularization[84].

In addition, recent data from SYNTAX examining the causes of death following PCI *vs* CABG in complex CAD emphasized the importance of the physiological impact of revascularization on the myocardial substrate in complex CAD[85]. CABG was associated with a significantly reduced rate of MI-related death, indicating that the anatomically-incomplete but functionally complete CABG revascularization provided sustained global perfusion and protection from subsequent ischemic events (*e.g.*, MI), in part because of the collateralization associated with more extensive severity of CAD.

Importantly, the emerging call for multi-arterial revascularization to become the "standard of care" for contemporary CABG fits tightly into this strategy. Because of the findings outlined here, the concept of "complete anatomic revascularization" must be revised into "reasonable incomplete revascularization"[86,87]. A multi-arterial strategy may be initially thought to limit the number of potential grafts, producing incomplete revascularization, at least from an anatomic perspective. However, recognizing the importance of physiology in surgical revascularization, including the functional nature of the proximal stenoses, physiologic status of the distal regional myocardium *vs* assumed competitive flow, understood dynamic nature of the *in situ* arterial conduit, and the existence of collateral flow in the myocardial substrate being operated upon, allows for more specific design of a revascularization strategy using arterial conduits that will remain beneficial over the long-term.

POSTOPERATIVE FACTORS AND INFLUENCES

The current results, based on clinical outcomes, from CABG intervention in patients with moderate and severe SIHD by anatomic criteria are excellent, and clearly are preferable to OMT and PCI interventions in the correct patient population[88]. Overall, however, the 25-plus year decline in risk-adjusted 30-d mortality for CABG, despite the concomitant increase in predicted operative risk, has plateaued over the past 5 years (STS database) at approximately 2%. This plateau is so distinct from the prior trend that it is appropriate to query why this might be the case[89]. Is 2% "as low at is feasible", given the current population coming to CABG? Is the relative impact of collecting and sharing clinical outcomes data on continuous quality improvement efforts lessened at this level of high-performance? Or is risk-adjusted mortality as a benchmark for quality no longer effective at this high-performance level[45]?

An alternative perspective is that current standard outcomes are not granular enough to drive further quality improvements, as has been demonstrated previously with the infrastructure of the STS National Database[90,91]. Other metrics, in addition to existing ones, are needed to further drive clinical improvements in outcomes. It may well be that these physiologic aspects of revascularization (preoperative, intraoperative and postoperative), along with intraoperative documentation of technical quality and the absence of surgeon error represent the new metrics needed to drive quality improvement in the future.

One area where the impact of quality improvement interventions remains to demonstrate its effectiveness is in the area of secondary prevention of SIHD following CABG. Based on then-contemporary data from other areas of cardiovascular medicine therapy, we documented in the largest randomized clinical trial of continuous quality improvement to date the effectiveness of dissemination of information, local quality improvements and the infrastructure of a national database the increased adoption of secondary prevention measures [ASA, beta-blocker, statin, and ACE inhibitor therapy (in appropriate patients)] following CABG[91]. This study covered a time interval that was relatively early in the statin era, and while the adoption at > 400 surgical centers across the United States increased for each measure and the composite of all measures, the adoption of post-operative statin therapy was the most dramatic.

Since the Achilles' heel of CABG has been the late development of atherosclerotic disease in vein graft conduits (in patients operated upon 15-50 years ago)[53], the full effect of this postoperative statin intervention still remains to be evaluated. Importantly, the benefits of statin therapy in non-surgical patients with SIHD are incontrovertible[92]. However, if the anti-atherosclerotic effects of statins in CABG mirror the effects in other settings of IHD, this intervention should impact long-term outcomes by retarding the development of disease progression in CABG patients[93]. Other pleiotropic effects of statins have been advocated as beneficial in CABG patients as well[26,92].

In an important recent study, however, room for improvement and justification for that improvement was highlighted. Iqbal *et al*[94] studied the use of OMT in patients with complex coronary disease undergoing revascularization in SYNTAX, and addressed the long-term significance of these use patterns. OMT was defined as the combination of at least one antiplatelet drug, statin, beta-blocker and angiotensin-converting enzyme inhibitor/angiotensin receptor blocker. OMT was underused in all revascularization patients, especially in the CABG group. In five-year outcomes analyses, OMT was an independent predictor of survival, including mortality and the composite end-point of death/MI/stroke. The treatment effect with OMT (36% relative reduction over 5 years) was greater than the treatment effect of the revascularization strategy (26% relative

reduction in mortality with CABG *vs* PCI over 5 years). All components of OMT were important for reducing adverse outcomes in both revascularization strategies. Clearly, contemporary cardiac surgery must continue to aggressively incorporate this life-sustaining physiologic intervention in post-CABG patients, no only for the first six weeks but work with all cardiovascular providers to make sure this intervention is sustained indefinitely following CABG[17].

One area of continuous evolution in secondary prevention is the utilization of dual anti-platelet therapy (DAPT) following CABG, and in particular in the approximately 18% of CABG cases performed using the OPCAB technique. The AHA/ACC/STS recently updated the guidelines for Secondary Prevention Following CABG, in particular with reference to DAPT. At the same time, the Guidelines on duration of DAPT in patients with Coronary Artery Disease has been updated as well[95]. The recent introduction of other new anti-platelet agents may result in the emergence of an improved DAPT strategy. Thus this post-operative secondary prevention arena following CABG will continue to evolve, as the full impact of statin therapy and DAPT therapy becomes evident. Again, the effects of these agents in modifying the physiology of atherosclerosis and platelet actions drives new potential improvements in clinical outcomes in CABG[95].

The STS has recently published Clinical Practice Guidelines on Arterial Conduits for Coronary Artery Bypass Grafting[96]. This excellent, technically and anatomically focused Guideline recommending that use of arterial grafts (specific targets, number, and type) should be a part of the discussion of the heart team in determining the optimal approach for each patient. This physiologic discussion provides in part the underlying scientific support for that recommendation.

Finally, this emerging granularity of the physiologic circumstances and effects of revascularization in CABG promises to have a similar impact as FFR/iFR have had on PCI intervention: The generation and incorporation of an entire body of new knowledge, which has benefitted both revascularization strategies. Thus far, these data presented here have produced a new definition for the goal of CABG, namely, to relentlessly restore blood supply, by both anatomic and physiologic criteria, to all areas of myocardium possible for the longest interval of time possible. "What we don't know" represents the future[97].

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MINIREVIEWS

Mechanisms and clinical significance of early recurrences of atrial arrhythmias after catheter ablation for atrial fibrillation

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Abstract

Early recurrence of atrial arrhythmias (ERAA) after ablation is common and strongly predicts late recurrences and ablation failure. However, since arrhythmia may eventually resolve in up to half of patients with ERAA, guidelines do not recommend immediate reintervention for ERAA episodes occurring during a 3-mo post-ablation blanking period. Certain clinical demographic, electrophysiologic, procedural, and ERAA-related characteristics may predict a higher likelihood of long-term ablation failure. In this review, we aim to discuss potential mechanisms of ERAA, and to summarize the clinical significance, prognostic implications, and treatment options for ERAA.

Key words: Atrial fibrillation; Recurrence; Catheter ablation; Pulmonary vein isolation

Core tip: There have been several studies examining the predictors of early recurrences of atrial arrhythmias (ERAA) during the blanking period after atrial fibrillation (AF) ablation and the predictive value of such early recurrences on late recurrences. In this review, we summarize the mechanisms and predictors, clinical significance, prognostic implications, and treatment options of ERAA after AF ablation.

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INTRODUCTION

Catheter ablation is an effective treatment option for patients with symptomatic atrial fibrillation (AF). The

cornerstone of AF ablation involves pulmonary vein isolation (PVI). Early recurrences of atrial arrhythmia (ERAA) are frequent in the post-ablation period, and may occur as either AF or organized atrial tachycardia (OAT), and in some instances may resolve over time without requiring repeat intervention. These early recurrences are thought to be related to post-ablation inflammation, edema, and healing. As such, the consensus guideline statements have recommended employing a 3-mo "blanking period" after AF ablation during which AF or OAT recurrences should not be considered as ablation failure[1]. In this review, we will define and discuss the implications of ERAA, as well as summarize the literature with regards to methods to prevent and treat ERAA.

BLANKING PERIODS AND EARLY RECURRENCES

The use of a blanking period has been employed under the assumption that not all ERAA episodes results in late recurrences. The 2012 HRS/EHRA/ECAS expert consensus statement recommends the use of a 3-mo blanking period after ablation, during which time ERAA episodes not be classified as treatment failure. However, the authors of the guideline statement do state that the use of a shorter blanking period (< 3 mo) is acceptable as long as it is pre-specified and described in the study methods[1]. In line with the consensus statement, most operators tend to avoid repeat ablation for ERAA occurring within the blanking period unless patients are extremely symptomatic with recurrences which are refractory to antiarrhythmic drugs (AADs) and repeated cardioversions.

Variable blanking periods have been utilized across published studies, ranging anywhere from 72 h up to 3 mo post-ablation[2]. While the HRS/EHRA/ECAS consensus statement selected 3 mo as the blanking period of choice, the optimal blanking period to maximize the sensitivity and specificity of prognostic implication of ERAA- and therefore the optimal cutoff interval during which early re-ablation should be avoided, remains poorly studied.

DETECTION OF ERAA IN THE BLANKING PERIOD

Methods of monitoring used to detect ERAA episodes have varied between studies. There is a wide range of intensiveness with regards to duration and strategy of monitoring, and detection of ERAA is dependent on type of monitoring post-ablation. The least intensive monitoring strategies involve symptom-driven 12-lead electrocardiogram, and 24-h or 48-h Holter monitoring ordered only when patients endorse symptoms of palpitations or notice an abnormal pulse. More intensive strategies which studies have utilized include handheld symptom-driven rhythm monitor applications, 30-d transtelephonic monitors, and auto-triggered external and implantable subcutaneous loop recorders. Landmark trials in patients with cryptogenic stroke have demonstrated that more intensive rhythm monitoring for longer durations using transtelephonic monitoring devices (*i.e.*, CardioNet, Malvern, PA; LifeWatch, Rosemont, IL; Medicomp, Melbourne, FL) or implantable cardiac monitors (*i.e.*, Reveal XT and Reveal LINQ; Medtronic, Minneapolis, MN) may increase the likelihood of detecting asymptomatic AF[3,4]. However, since most operators tend to avoid early reablation for paroxysmal recurrences of asymptomatic ERAA during the blanking period, the optimal method of post-ablation monitoring (or whether any monitoring is necessary at all, for that matter) remains controversial.

FREQUENCY OF ERAA

In a pooled analysis by Andrade *et al*[2], the incidence of ERAA after radiofrequency catheter ablation across multiple studies utilizing a 3-mo blanking period ranged from 16%-67% with a mean pooled estimate of approximately 38%. The incidence of ERAA is highest immediately post-ablation and tends to decrease over time throughout the blanking period[5,6]. Rates of ERAA appear to be similar after ablation with radiofrequency or cryoablation, although there may be differences in the predictive value of inflammatory responses on the incidence of ERAA post-ablation between techniques.

For example, in the multicenter Sustained Treatment of Paroxysmal Atrial Fibrillation trial, which randomized patients with paroxysmal AF to medical therapy *vs* PVI with cryoballoon ablation, 51% of patients treated with cryoablation experienced ERAA within the first 3 months post-ablation, and those with ERAA (*vs* without ERAA) were significantly more likely to experience late recurrence (55.6% *vs* 12.7%; $P < 0.001$)[7].

Ciconte *et al*[8] studied 100 patients with persistent AF treated with PVI using second-generation cryoballoon *vs* radiofrequency ablation and found that the rates of both ERAA (51.9% *vs* 48.1%; $P = 1.0$) and late recurrence (47.6% *vs* 52%; $P = 0.84$) were similar between ablation technologies. Among all patients, ERAA in their study predicted late recurrence with a hazard ratio of 6.31 (CI: 3.37-11.83, $P < 0.01$).

In a nonrandomized fashion, Miyazaki *et al*[9] prospectively examined 82 consecutive patients with paroxysmal AF treated with PVI using either radiofrequency ablation *vs* cryoablation with the second generation cryoballoon. While the peak hs-CRP level was similar between ablation techniques, the level of hs-CRP 2 days post-ablation predicted development of ERAA in those treated with radiofrequency (HR = 1.7; 95%CI: 1.01-2.87; $P = 0.048$) but not cryoablation, suggesting that degree of inflammatory marker response may have a stronger predictive value for ERAA after radiofrequency compared with cryoablation.

Table 1 Characteristics which are predictive of the development of early recurrences of atrial arrhythmias after atrial fibrillation ablation

Clinical characteristics
Older age[5]
Male gender[7]
Hypertension[5]
Structural heart disease[10,20]
Longer AF duration[5]
Nonparoxysmal AF type[5]
CHA2DS2-VASc, R2CHADS2 scores[11]
Imaging characteristics
Left atrial size/volume[5]
Right atrial size/volume[12]
Left ventricular size/volume[13]
Left ventricular systolic dysfunction[14]
Left ventricular diastolic dysfunction[15]
Left atrial epicardial adipose tissue[16]
Ablation procedural characteristics
Incomplete PVI[13,20]
AF inducibility[21]
Multiple AF foci[10]
LA free wall AF foci[10]
Lack of AF termination during procedure[22]
Lack of SVC isolation[5]
Inflammatory markers
Higher body temperature post-ablation[17]
C-reactive protein[17]
Homocysteine[18]
Increased LA roof thickness with delayed enhancement MRI 24 h post-ablation[19]

Table modified from Andrade *et al*[2]. AF: Atrial fibrillation; PVI: Pulmonary vein isolation; MRI: Magnetic resonance imaging.

PREDICTORS OF ERAA

Prior studies have identified clinical and demographic characteristics, arrhythmia characteristics, electrocardiographic and echocardiographic characteristics, and AF ablation procedural and post-procedural characteristics which are predict the development of ERAA after ablation, several of which we have listed in Table 1[2,5,7,10-22].

MECHANISMS AND PATHOPHYSIOLOGY OF ERAA

The incidence and clinical significance of ERAA after surgical MAZE is strikingly similar to that of catheter ablation. Approximately 50%-60% of patients develop in-hospital ERAA after MAZE, and those with ERAA have a higher rate of late recurrence (30%) *vs* those whose hospital course is not complicated by ERAA (5%-10%)[23,24].

The mechanism of ERAA after catheter ablation probably differs from that of late recurrences, and is likely dependent on the initial ablation strategy. In patients with paroxysmal AF treated with limited ablation strategies focused primarily on achieving PVI, we have found that late recurrence is usually due to chronic reconnection of previously isolated PVs. In patients with persistent AF treated with empiric linear ablation or those who undergo more extensive substrate-based ablation, gaps in lines may predispose to the development of late macroreentrant OATs. ERAA within the first 7 d post ablation occurs in the setting of an intensely inflammatory milieu. As such, it is difficult to differentiate in the early post-ablation period whether ERAA results from transient post-ablation inflammation (which is likely to resolve without the need for repeat ablation) *vs* chronic PV reconnection. Furthermore, using a rigorous trigger induction protocol, we have identified that non-PV triggers of AF may exist in 11% of patients presenting for AF ablation[25]. Thus the persistence of non-PV triggers due to inadequate identification and elimination of non-PV triggers during the initial ablation procedure can allow for both ERAA and late recurrences to occur.

Lim *et al*[26] measured the blood concentration of several inflammatory markers (hs-CRP, Troponin T, CK-MB, fibrinogen, and D-dimer) before ablation, and serially at different time periods (1, 2, 3, 7 d, and 1 mo) after ablation and correlated the degree of inflammatory marker elevation with AF recurrence documented at different time points post-ablation. They found that the degree of elevation of hs-CRP, troponin-T, and fibrinogen predicted ERAA within 3 d post-ablation, but not at 3 or 6 mo.

Das *et al*[27] examined the association between timing of ERAA with the likelihood of PV reconnection at repeat electrophysiology study in 40 patients with nonparoxysmal AF treated with PVI. After the index ablation procedure, all 40 patients were brought back for electrophysiology study regardless of whether they had recurrence post-ablation. The operator was blinded to the presence and timing of ERAA, and all PVs were assessed for reconnection using a circular mapping catheter. All identified sites of reconnection were related to reisolate PVs, regardless of the presence or absence of ERAA. In total, 17 (42%) of the patients had ERAA within the first 2 months after ablation, preceding the repeat electrophysiology study. The authors found that ERAA occurring within the second month was strongly associated with PV reconnection, and also strongly predicted "extensive reconnection" of $\geqslant$ 2 PVs. Contrarily, ERAA limited to the first month post-ablation had no association with PV reconnection. The results of the study suggested that ERAA within the first month was more likely to be related to transient factors such as inflammation, temporary autonomic imbalances, and the time-course of lesion formation, while ERAA occurring after the first month was more likely to represent ablation failure and PV reconnection[28].

Ablation strategies

The initial ablation strategy may affect the prognostic implications of ERAA. With approaches which involve more extensive substrate-based ablation, ERAA is more likely to be related to edema and inflammation, and accordingly may be more likely to resolve with

time. Meanwhile, ERAA in patients treated with less extensive ablation approaches mainly (*i.e.*, targeting PV and non-PV triggers, for example), may be more likely to represent PV reconnection or inadequate trigger elimination. Since these triggers are unlikely to resolve spontaneously without intervention over time, eventual reablation may be necessary for these patients to achieve freedom from AF.

Post-hoc analysis of data from the Substrate and Trigger Ablation for Reduction of Atrial Fibrillation trial [which compared PVI alone, ablation of complex fractional atrial electrograms (CFAE) alone, and PVI plus CFAE] showed that patients treated with PVI alone who experienced ERAA (*vs* those without ERAA) had significantly higher rates of late recurrence[29]. Interestingly, the predictive value of ERAA on late recurrence was not as strong among those treated with CFAE or PVI plus CFAE. This suggests that substrate-based approaches involving extensive ablation may cause higher incidence of AF related to acute reversible changes post-ablation.

We at our institution employ a strategy aimed at elimination of PV and non-PV triggers. In our experience, patients with recurrent AF after ablation who present for repeat ablation nearly always have PV reconnection and/or non-PV triggers[30]. Non-PV triggers which were not targeted during the initial ablation may manifest as PACs during the ERAA period post-ablation, and may predict late AF recurrence. Gang *et al*[31] examined 7-d Holter monitors in 124 patients six months post-PVI (3 mo after the blanking period had ended) and found that frequent premature atrial complexes (PACs) strongly predicted late AF recurrence. Patients who developed late recurrence had a median of 248 PACs per day compared *vs* those without late recurrence (77 PACs per day). Based on receiver operating characteristic curve analysis, the authors calculated that the presence of $\geqslant$ 142 PACs/d predicted late AF recurrence with a hazard ratio of 2.84 (95%CI: 1.26-6.43; P = 0.01). While their study did not examine the predictive value of PACs during the ERAA blanking period, one could hypothesize that atrial ectopy originating from PV and non-PV foci manifesting as PACs during the blanking period might represented inadequately targeted triggers or partial PV reconnection.

ERAA CHARACTERISTICS WHICH PREDICT LATE RECURRENCE

The occurrence of ERAA after ablation is well known to be a strong independent predictor of late recurrence and long-term ablation failure. In the pooled analysis of several studies by Andrade *et al*[2], there was a 53.7% late recurrence rate among patients with ERAA compared *vs* only 6.9% in patients without ERAA. Several studies have examined whether certain types of ERAA (AF *vs* OAT or atrial flutter) are more predictive of late ablation success. While some authors have suggested success rates after repeat ablation in patients who recur as OAT (*vs* AF) after their initial ablation attempt, it remains unclear whether OAT in the ERAA period is more or less predictive of late ablation failure[32].

Nalliah *et al*[33] examined 119 consecutive patients with paroxysmal or persistent AF who underwent ablation with PVI and additional ablation (50% underwent mitral isthmus linear ablation, and 18% had additional CFAE ablation) to determine the impact of AF and OAT occurring within the blanking period. Patients were not closely monitored for asymptomatic AF during the blanking period, but ERAA as AF was detected in 28% and OAT in 25% within the 3 mo blanking period. Overall, early AF predicted late AF (HR = 3.53; 95%CI: 1.72-7.29; P = 0.001) and early OAT predicted late OAT (HR = 5.62; 95%CI: 2.88-10.95; P < 0.0001). Interestingly, early AF did not predict late OAT, and early OAT did not predict late AF. The authors also found that AF and OAT occurring in the third month of the blanking period had different predictive values for late recurrence: AF in the third month predicted late AF, although OAT in the third month did not predict late OAT.

We do not routinely do empiric linear ablation at our institution, and the majority of patients experiencing ERAA after ablation have AF only (71%; *vs* 5% with early OAT only and 24% with both early AF/OAT)[28]. In our experience, we have found no differences in the likelihood to develop late recurrences based on ERAA type (AF *vs* OAT) (P = 0.92). Since we employ a limited ablation strategy limited to antral PVI and targeting of non-PV triggers, it is possible that in patients treated with more extensive substrate-based ablation approaches involving linear or CFAE ablation, the presence of ERAA as OAT may suggest the presence of gaps in the ablation lines or incomplete CFAE ablation, resulting in late OAT, frequently necessitating repeat ablation.

The predictive value of ERAA appears to be dependent on both frequency and timing of ERAA within the blanking period. We have shown that in patients treated with a limited ablation strategy focused on PVI and elimination of non-PV triggers, the predictive value of ERAA episodes during the first 6 weeks post-ablation is quite variable based on these factors[28]. In our study, we divided the 6-wk blanking period into three separate intervals (Early: weeks 1-2; Intermediate: weeks 3-4; and Late: weeks 5-6), and found that patients with ERAA in a single interval (OR = 3.2, 95%CI: 1.7-5.8 *vs* no ERAA) are significantly less likely to have late recurrence within 1 year *vs* those with ERAA spanning over multiple intervals (OR = 14.6, 95%CI: 7.3-29.6).

Mugnai *et al*[34] have shown similar prognosis of late ERAA within the blanking period after ablation for paroxysmal AF using second-generation cryoballoon ablation instead of radiofrequency energy. In their study of 331 consecutive patients treated with cryoballoon ablation, all patients with ERAA occurring in the second half of the 3-mo blanking period experienced subse-

quent recurrences after the blanking period- suggesting that ERAA occurring later within the blanking period are more predictive of ablation failure[34].

Willems *et al*[35] recently reported the results of a predefined secondary analysis of the prospective, randomized Adenosine Following Pulmonary Vein Isolation to Target Dormant Conduction Elimination trial where the authors analyzed the significance of ERAA at different times throughout the 3-mo blanking period in predicting late recurrences. They divided ERAA which occurred during month 1, 2, and 3 of the blanking period and found that the 1-year ablation success rate was significantly higher among patients without ERAA (77.2% 1-year freedom from AF), while success rates decreased as ERAA occurred later within the blanking period: 62.6% ERAA in month 1, 36.4% in month 2, and 7.8% in month 3 ($P < 0.0001$), with HR = 1.84 for month 1, 4.45 for month 2, 9.64 for month 3. The authors identified a blanking period of 50 d to yield the greatest discriminatory potential by reviewer operating characteristic analysis, and given the dismal (> 90%) late recurrence rates among patients with ERAA during month 3, the results of this study question whether the 3-mo blanking period should be revised.

PREVENTION OF ERAA

AADs

A number of studies have demonstrated that the use of AADs after ablation reduces the incidence of ERAA and reduces hospitalizations and cardioversions during the blanking period. However, meta-analyses have shown that long-term ablation success remains unaffected by early AAD use[36-38]. This would suggest that AADs might mask the early indicators of failed ablation, which may be allowed to manifest only once AADs are withdrawn. While this may indeed decrease hospitalization rates and healthcare expenditure, it may also simply be delaying the recognition of ablation failure.

The Antiarrhythmics After Ablation of Atrial Fibrillation (5A Study) Randomized 110 patients with PAF to AAD (propafenone, flecainide, sotalol, or dofetilide) *vs* no AAD after AF ablation[39]. Those in the AAD group were less likely to have sustained AF recurrence (> 24 h), AF-related hospital admission, cardioversion, AAD adjustment or drug intolerance (19% *vs* 42%; $P = 0.005$ for primary composite endpoint) six-week post ablation.

The Efficacy of Antiarrhythmic Drugs Short-Term Use After Catheter Ablation for Atrial fibrillation trial was a multicenter prospective randomized controlled trial which compared the use of AADs for 90 d post ablation *vs* control in patients after catheter ablation for paroxysmal AF[40]. The authors aimed to examine whether prevention of ERAA with AADs would promote LA remodeling and therefore improve long-term ablation success. They enrolled 2038 patients (1016 randomized to AADs, 1022 control) and the primary endpoint was AF recurrence (lasting > 30), need for repeat ablation, hospitalization, or use of class Ⅰ or Ⅲ AAD at 1 year. They found that although those in the AAD group were more likely to be free from AF during the 90-d treatment period (59% *vs* 52%; HR = 0.84, 95%CI: 0.73-0.96; $P = 0.01$), there was no difference in any of the primary outcome measures at 1 year post-ablation.

The recurrence of arrhythmia following short-term oral AMIOdarone after CATheter ablation for atrial fibrillation trial was a two-center double-blind, randomized placebo-controlled trial which randomized 212 patients with paroxysmal or persistent AF treated with AF ablation to 8 wk of oral amiodarone *vs* placebo following catheter ablation[41]. The authors aimed to determine whether temporary amiodarone use post-ablation would decrease both early and late recurrences. Patients in the amiodarone group had significantly lower rates of ERAA within the blanking period (34% *vs* 53%; $P = 0.006$) but there was no difference in rates of late recurrence at 6 mo between groups (39% *vs* 48%; $P = 0.18$). Additionally, AF-related hospitalization (RR = 0.43, 95%CI: 0.23-0.77, $P = 0.006$) and the need for cardioversion (RR = 0.36, 95%CI: 0.20-0.62, $P = 0.0004$) within the blanking period was significantly reduced in those treated with short-term amiodarone-driven mainly by those with persistent AF, as demonstrated in a subgroup analysis.

Anti-inflammatory agents: Corticosteroids and colchicine

The pro-inflammatory milieu in the immediate post-ablation period is thought to contribute to the development of ERAA, thus many investigators have examined the utility of anti-inflammatory agents to prevent inflammation-induced ERAA. The two major pharmacologic anti-inflammatory agents which have been studied include corticosteroids and colchicine.

Studies examining the use of steroids post-ablation to reduce ERAA have produced conflicting results. Koyama *et al*[42] randomized 125 patients with PAF to steroids (2 mg/kg IV hydrocortisone given immediately post-procedure, followed by 0.5 mg/kg per day oral prednisone for 3 d) *vs* placebo and found that patients randomized to treatment with corticosteroids were less likely to have ERAA within 3 d (7% *vs* 31%), but had similar rates of ERAA between days 4-30. Kim *et al*[43] randomized 138 patients to treatment with steroids *vs* control after ablation. Patients randomized to steroids in their study were treated with intravenous methylprednisolone (0.5 mg/kg per dose) for 2 d followed by 12 mg of oral methylprednisolone for 4 d. Those treated with steroids had a lower rate of ERAA in the 3 mo blanking period (23.4% *vs* 48.6%, $P = 0.003$) but there was no difference in late recurrence rate up to 24 mo ($P = 0.918$). In their multivariate model, the use of steroids was independently associated with lower rate of ERAA (OR = 0.45; 95%CI: 0.25-0.83, $P = 0.01$).

The anti-inflammatory agent colchicine has also been tested as an antiarrhythmic agent to prevent ERAA after AF ablation. In a double-blind fashion, Deftereos

et al[44] randomized 80 patients with paroxysmal AF to colchicine (0.5 mg twice daily for 3 mo) *vs* placebo after AF ablation (antral PVI and left atrial isthmus ablation). Patients randomized to the colchicine arm had lower levels of inflammatory markers post-ablation (C-reactive protein and IL-6) compared with placebo, and were less likely to experience ERAA within the 3-mo blanking period (16% *vs* 33.5%; OR = 0.38; 95%CI: 0.18-0.8) *vs* placebo. In a larger subsequent study, Deftereos *et al*[45] found that patients randomized to colchicine for 3 mo post-ablation had a significantly lower single-procedure late AF recurrence rate after a median follow-up duration 15 mo (31.1% *vs* 49.5%; OR = 0.46; 95%CI: 0.26-0.81). Colchicine is a relatively benign medication (with its major side-effect being gastrointestinal upset), and the results of these preliminary studies are certainly promising. However, future, larger prospective studies are required to confirm the benefit of colchicine after ablation before it can be widely accepted.

TREATMENT OF ERAA

Timing of cardioversion

In patients experiencing ERAA after AF ablation, early cardioversion might improve long-term ablation success. Restoration of sinus rhythm may prevent AF-induced progression of adverse LA remodeling, thus facilitating maintenance of sinus rhythm. Chilukuri *et al*[46] examined timing to cardioversion (before *vs* after the 3-mo blanking period) in patients with nonparoxysmal AF treated with ablation and reported an extremely low (16%) rate of long-term ablation success in patients treated with early cardioversion for persistent AF/OAT during the blanking period, although the rate of long-term freedom from AF was even more dismal (8%) among those who underwent late cardioversion after the blanking period. Baman *et al*[47] examined the effect of the timing of cardioversion after ERAA in 93 patients treated with antral PVI for AF. They found that time to cardioversion was inversely correlated with long-term freedom from AF off AAD: Those who were cardioverted within 30 d (*vs* those cardioverted after 30 d) of ERAA were more likely to remain in sinus rhythm over the remainder of the study duration (OR = 22.5, 95%CI: 4.87-103.88, $P < 0.0001$). Additionally, time between ERAA and cardioversion was the only independent predictor of sinus rhythm maintenance in their multivariate model.

At our institution we aim to restore sinus rhythm as soon as possible in patients with ERAA since we believe that maintenance of sinus rhythm allows for favorable structural, electrical, and mechanical remodeling of the atria and may maximize the likelihood of achieving long-term ablation success. However, it remains to be determined whether the benefits of this approach are similar between paroxysmal and non-paroxysmal types of AF.

Early reablation

The optimal timing for repeat ablation in patients with ERAA remains unknown. As discussed throughout this review, a number of factors including arrhythmia characteristics, patient characteristics, ablation procedural characteristics, and recurrence characteristics play a role in predicting long-term ablation success. The goal is to identify patients in whom ERAA is not just due to transient post-ablation factors, and in whom ablation early in the recurrence course may be more likely to result in long-term ablation success. In a study by Lellouche *et al*[14], of 302 patients with persistent and paroxysmal AF, they reported their experience of 302 patients with persistent and paroxysmal AF, 151 patients had ERAA, 61 of whom were treated with very early reablation (within 1 mo of the index ablation). They found that patients who underwent early reablation had a significantly lower rate of late recurrences (51% *vs* 91%; $P < 0.0001$), although they required more total procedures over the entire follow-up period (2.5 ± 0.7 *vs* 2.2 ± 0.6; $P = 0.02$). Additionally, Andrade *et al*[7] found that patients with ERAA after cryoablation in the STOP AF trial who underwent early reablation during the blanking period were significantly less likely to have late recurrences out to 1 year follow-up (33% *vs* 56% late recurrence rate; HR = 0.04, 95%CI: 0.01-0.32; $P = 0.002$). While their results suggest that early reablation within the blanking period for ERAA after cryoablation improves long-term ablation success, the authors acknowledge that it is possible that reablation may not have been necessary in all patients since it is possible that ERAA may have resolved spontaneously in some.

Recently, Yanagisawa *et al*[48] performed a retrospective analysis examining outcomes after early reablation during the first 3 months post-ablation in 66 patients with ERAA. Compared to 66 propensity-matched controls who did not undergo early reablation, the patients treated with early reablation had a significantly lower rate of late recurrence (64% *vs* 44%; $P = 0.023$), but required more additional procedures (0.4 *vs* 1.2 procedures; $P = 0.001$). Interestingly, the benefit of early reablation for ERAA was limited to those with paroxysmal AF (37% *vs* 66% late recurrence rate for early reablation *vs* no early reablation; $P = 0.008$), while there was no significant benefit to early reablation in those with persistent AF (56% *vs* 60%; $P = 0.77$). Furthermore, 36% of those with ERAA who did not undergo early reablation had no further recurrences in after the 3-mo blanking period.

We have recently shown that in patients with non-paroxysmal AF treated with a limited ablation strategy of antral PVI and targeting of non-PV triggers, patients who recur as paroxysmal (rather than persistent) AF type are more likely to experience long-term ablation success[49]. We believe that patients with persistent or longstanding persistent AF who experience paroxysmal-type ERAA after ablation may represent a subgroup of patients in whom early reablation (even during the blanking period)

can improve long-term ablation success. Transformation of nonparoxysmal AF to paroxysmal AF may represent favorable alteration of the underlying substrate, and we hypothesize that early intervention before AF is allowed to become persistent again (and cause adverse LA electrical and structural remodeling) might result in improved outcomes.

CONCLUSION

Early recurrences of atrial arrhythmia are common in the post-ablation period, and detection of ERAA is dependent on the monitoring strategy. Although ERAA clearly predicts late AF recurrences, some patients with ERAA do not develop late recurrence and thus the guidelines recommend a 3-mo blanking period during which recurrences should not be considered as ablation failure. However, ERAA episodes which occur later within the blanking period (particularly after the first 2 weeks) as well as multiple ERAA occurrences appear to be strongly predictive of late recurrence. Thus, the optimal blanking period during which ERAA events may be benign remains unclear. While pharmacologic agents such as AADs and corticosteroids reduce the incidence of ERAA, they do not improve long-term ablation success. Colchicine is a promising medication which has been shown in isolated studies to decrease both early and late recurrences but larger prospective studies are necessary to validate this effect. Whether reablation should be performed in patients experiencing ERAA remains undetermined. Further studies are necessary to elucidate the optimal timing for reablation based on patient and ERAA characteristics to maximize long-term ablation success.

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ORIGINAL ARTICLE

Retrospective Cohort Study

Clinical characteristics and prognostic impact of atrial fibrillation in patients with chronic heart failure

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Author contributions: All authors substantially contributed to this paper; in particular Gigli L, Ameri P and Canepa M conceived and designed the analysis, interpreted the results and drafted the manuscript; Secco G, De Blasi G, Miceli R, Lorenzoni A and Torre F contributed to data acquisition and to the interpretation of results; all authors participated in drafting the article and revised it critically for important intellectual content, read and approved the final manuscript.

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Data sharing statement: Statistical code and dataset are available from the corresponding author at his email address. All data are anonymized and there is no risk of patients' identification.

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Abstract

AIM

To assess the prevalence, clinical characteristics and independent prognostic impact of atrial fibrillation (AF) in chronic heart failure (CHF) patients, and the potential protective effect of disease-modifying medications, particularly beta-blockers (BB).

METHODS

We retrospectively reviewed the charts of patients referred to our center since January 2004, and collected all clinical information available at their first visit. We assessed mortality to the end of June 2015. We compared patients with and without AF, and assessed the association between AF and all-cause mortality by

multivariate Cox regression and Kaplan-Meyer analysis, particularly accounting for ongoing treatment with BB.

RESULTS

A total of 903 patients were evaluated (mean age 68 ± 12 years, 73% male). Prevalence of AF was 19%, ranging from 10% to 28% in patients ⩽ 60 and ⩾ 77 years, respectively. Besides the older age, patients with AF had more symptoms (New York Heart Association II-III 60% *vs* 44%), lower prevalence of dyslipidemia (23% *vs* 37%), coronary artery disease (28% *vs* 52%) and left bundle branch block (9% *vs* 16%). On the contrary, they more frequently presented with an idiopathic etiology (50% *vs* 24%), a history of valve surgery (13% *vs* 4%) and received overall more devices implantation (31% *vs* 21%). The use of disease-modifying medications (*i.e.*, BB and ACE inhibitors/angiotensin receptor blockers) was lower in patients with AF (72% *vs* 80% and 71% *vs* 79%, respectively), who on the contrary were more frequently treated with symptomatic and antiarrhythmic drugs including diuretics (87% *vs* 69%) and digoxin (51% *vs* 11%). At a mean follow-up of about 5 years, all-cause mortality was significantly higher in patients with AF as compared to those in sinus rhythm (SR) (45% *vs* 34%, *P* value < 0.05 for all previous comparisons). However, in a multivariate analysis including the main significant predictors of all-cause mortality, the univariate relationship between AF and death (HR = 1.49, 95%CI: 1.15-1.92) became not statistically significant (HR = 0.98, 95%CI: 0.73-1.32). Nonetheless, patients with AF not receiving BB treatment were found to have the worst prognosis, followed by patients with SR not receiving BB therapy and patients with AF receiving BB therapy, who both had similarly worse survival when compared to patients with SR receiving BB therapy.

CONCLUSION

AF was highly prevalent and associated with older age, worse clinical presentation and underutilization of disease-modifying medications such as BB in a population of elderly patients with CHF. AF had no independent impact on mortality, but the underutilization of BB in this group of patients was associated to a worse long-term prognosis.

Key words: Atrial fibrillation; Chronic heart failure; Beta-blockers; Digoxin; Prognosis

Core tip: In this retrospective analysis atrial fibrillation (AF) was diagnosed in 1 out of 5 patients with chronic heart failure. The arrhythmia was associated with older age, worse clinical presentation and underutilization of disease-modifying medications, particularly beta-blockers (BB) and ACE inhibitors/angiotensin receptor blockers. At a mean follow-up of about 5 years, mortality was significantly higher in patients with AF, and patients with AF not receiving BB treatment were found to have the worst prognosis. However, in a multivariate analysis including main significant predictors of all-cause mortality, such as age, gender, blood pressure, coronary artery disease, comorbidities and medications, the univariate relationship between AF and death became not statistically significant.

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INTRODUCTION

Atrial fibrillation (AF) is the most common arrhythmia and frequently coexists with chronic heart failure (CHF)[1]. It is commonly held that CHF decompensated by a transient AF episode has better prognosis than CHF with permanent AF[2]. However, the real prognostic impact of permanent AF in patients with CHF remains poorly understood[3-6] and a matter of current debate[7,8]. Conflicting data also exist on medical treatment of CHF patients with AF, particularly in the elderly. Indeed, although beta-blockers (BB) are a corner-stone therapy of CHF, their value when AF coexists has recently been questioned[9]. Thus, the aim of this study was to investigate the prevalence, clinical characteristics and prognostic impact of permanent AF in a cohort of unselected CHF patients referred to a single tertiary outpatient clinic. In particular, we assessed whether a diagnosis of permanent AF was independently associated with increased all-cause mortality, and whether this association was influenced by medical therapy with BB.

MATERIALS AND METHODS

Study population

The study population was drawn from a tertiary CHF outpatient clinic; all patients with a diagnosis of CHF, New York Heart Association (NYHA) functional class between I and III and a readable rest ECG were considered eligible. Data were retrospectively collected by reviewing all available complete records of the first visit at the clinic between January 1st 2004 and May 31st 2015. A total of 941 unique patients were originally included; 23 patients were subsequently excluded because they did not have a readable ECG, and another 10 patients because the heart rhythm was not clearly definable due to pacemaker stimulation. Mortality was ascertained by consulting hospital and administrative databases and death registers. Follow-up was censored at June 30, 2015; survival status was not retrievable

in five patients, leaving a final study sample of 903 patients.

All patients signed an informed consent allowing the utilization of their anonymized clinical information for medical research purposes, as approved by the local Institutional Review Board.

Variables of interest

Permanent AF (subsequently indicated solely as AF) was defined as a documented history of AF that had persisted for more than 6 mo and was confirmed by a surface ECG at first visit. A diagnosis of coronary artery disease (CAD) was ascertained by coronary angiography, and patients without any luminal stenosis > 50% were considered without CAD. Information regarding previous percutaneous and/or surgical revascularization and previous valve surgery was also routinely collected. The remaining patients with other CHF etiology (including hypertensive cardiac disease, valve disease, tachycardiomyopathy, idiopathic cardiomyopathy) were all incorporated in a single group. Implanted devices were divided as follows: Mono/bicameral pacemakers (PM), biventricular pacemakers (CRT-D/CRT-P) and implantable-cardioverter defibrillators (ICD). Hypertension was defined by a blood pressure $\geqslant$ 140/90 and/or the use of antihypertensive medications. Diabetes mellitus was defined by history of diabetes mellitus and/or a random plasma glucose $\geqslant$ 200 mg/dL and/or fasting plasma glucose $\geqslant$ 126 mg/dL and/or an HbA1c $\geqslant$ 7% and/or use of antidiabetic treatments. Dyslipidemia was defined by history of high cholesterol levels and/or a total cholesterol $\geqslant$ 200 mg/dL. Present or former smoking was ascertained by medical interview, and patients who had smoked > 100 cigarettes/year were considered as smoker. Cancer history was defined by a previous or current malignancy, regardless of disease status at the time of medical interview. A clinical diagnosis of chronic obstructive pulmonary disease (COPD) was made during the visit based on the presence of a history of COPD, and/or signs and/or symptoms suggestive of COPD including chronic productive cough, chronic wheezing, emphysema or bronchitis.

Lab tests completed within 3 mo from the study visit were considered to identify anemia (hemoglobin levels < 13.5 g/dL in male and < 12.5 g/dL in female patients) and chronic kidney disease (CKD: Estimated glomerular filtration rate < 60 mL/min per 1.73 m^2 as calculated from creatinine using the CKD-EPI formula).

The following variables were collected from a basal 12-lead standard ECG: Heart rhythm, heart rate, and presence of a right or left bundle branch block. Left ventricular ejection fraction (LVEF) was derived from a transthoracic echocardiogram obtained within 3 mo from the first visit, and patients with a LVEF > 45% were considered as having a preserved LVEF.

Information regarding ongoing medications was ascertained for each patient, and included CHF-modifying drugs [*i.e.*, BB, ACE inhibitors and/or angiotensin receptor antagonists (ACEi/ARB) and aldosterone antagonists], diuretics (both loop diuretics and thiazides), other blood pressure lowering drugs (such as calcium channel blockers and alpha blockers), digoxin, amiodarone, lipid-lowering drugs (*i.e.*, statins) antiplatelet drugs (including aspirin, clopidogrel and - for very few patients - ticagrelor), and anticoagulants (*i.e.*, warfarin and very few patients with direct factor X or thrombin inhibitors).

Statistical analysis

Continuous variables were expressed as mean ± standard deviation (SD), and categorical variables as percentages. Characteristics of patients with AF *vs* sinus rhythm (SR) were compared using student's *t* test and χ^2 test as appropriate. To define univariate predictors of all-cause mortality, we compared characteristics of dead *vs* alive patients at the end of follow-up. Univariate and multivariate predictors of mortality were also investigated by Cox regression analysis. Variables with a *P* value < 0.10 in univariate analysis were selected based on clinical and statistical criteria (*i.e.*, to ease the interpretation of the analysis and to avoid multicollinearity) and introduced into a multivariate model. A backward elimination of variables with a *P* value > 0.05 was performed to obtain the final multivariate reduced model. Kaplan-Meyer curves were obtained for all-cause mortality in patients with AF *vs* SR, and also based on the use of BB medications. All analyses were performed using SAS for Windows (version 9.2; SAS Institute Inc, Cary, NC). The statistical review of the manuscript was performed by a biomedical statistician.

RESULTS

Study population

From January 2004 to May 2015, a total of 903 patients were evaluated who satisfied our inclusion criteria (mean age 68 ± 12 years, 73% male). Prevalence of AF was 19%, ranging from 10% to 28% in patients $\leqslant$ 60 and $\geqslant$ 77 years of age, respectively (*P* < 0.0001). Characteristics of study population by the presence of AF or SR are summarized in Table 1. Patients with AF were significantly more symptomatic in comparison to patients with SR (NYHA class Ⅱ-Ⅲ 60% *vs* 44%). CAD was less common in patients with AF than in those with SR (28% *vs* 52%), as were previous coronary revascularization (21% *vs* 37%) and dyslipidemia (23% *vs* 37%). By contrast, a non-ischemic etiology was more frequent in the AF group (50% *vs* 24%), as well as a history of previous valve surgery (13% *vs* 4%). Patients with AF received overall more devices implantation (31% *vs* 21%). ECG data showed a lower prevalence of left bundle branch block (9% *vs* 16%) and a higher mean heart rate (80 ± 19 *vs* 70 ± 13) in patients with AF. Patients with AF were more frequently diagnosed with CHF with preserved LVEF (29% *vs* 21%).

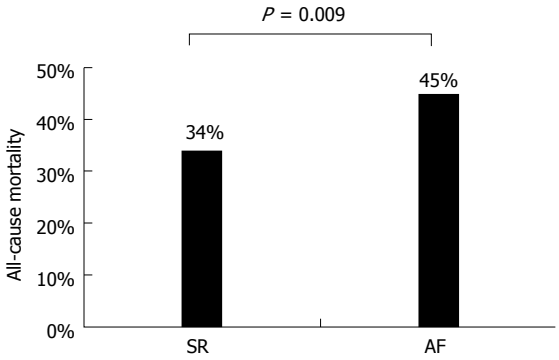

Figure 1 All-cause mortality in patients with atrial fibrillation and in patients with sinus rhythm. SR: Sinus rhythm; AF: Atrial fibrillation.

Treatment differences in patients with AF

When AF was present, there was a significant lower percentage of treatment with disease-modifying medications, including BB (72% *vs* 80%) and ACEi/ARB (51% *vs* 66%), as well as a less frequent use of calcium channel blockers (6% *vs* 13%), statins (28% *vs* 49%), amiodarone (6% *vs* 13%) and antithrombotic treatment (19% *vs* 63%). On the contrary, treatment with diuretics (87% *vs* 69%), aldosterone blockers (46% *vs* 37%), digoxin (87% *vs* 69%) and oral anticoagulants (82% *vs* 16%) was lower in patients with SR (Table 1).

Mortality in the study population

At a mean follow-up of 59 ± 40 mo (range 1 to 137 mo), all-cause mortality was significantly higher in patients with AF as compared to those in SR (45% *vs* 34%, Figure 1). Patients with AF were more likely to die during the course of our extended follow-up (Figure 2). Table 2 shows univariate associations of variables listed in Table 1 with all-cause mortality. At univariate analysis, patients who died had more frequently a diagnosis of AF than those who survived (23% *vs* 16%), were significantly older at baseline (71 ± 10 years *vs* 66 ± 12 years), had lower systolic and diastolic blood pressure (127 ± 19 mmHg *vs* 130 ± 19 mmHg, 72 ± 10 mmHg *vs* 76 ± 10 mmHg, respectively) and had more often NYHA class II-III (60% *vs* 40%), idiopathic etiology of CHF (32% *vs* 26%), implantable devices (29% *vs* 19%), PM stimulation (14% *vs* 9%) and a history of ventricular tachycardia (7% *vs* 4%). Moreover, diabetes mellitus (32% *vs* 24%), cancer history (14% *vs* 8%), COPD (18% *vs* 10%), chronic anemia (11% *vs* 8%), CKD (10% *vs* 6%), and use of diuretics (82% *vs* 67%), digoxin (26% *vs* 14%) or aldosterone blockers (45% *vs* 35%) was more frequent in the group of patients who died at follow-up. On the contrary, variables associated with survival were the presence of dyslipidemia (27% *vs* 39%), a preserved LVEF (19% *vs* 24%), and the use of BB (72% *vs* 82%) and ACEi/ARB (75% *vs* 79%) (Table 2).

In a multivariate analysis including the main significant predictors of all-cause mortality, the univariate relationship between AF and death (HR = 1.49, 95%CI: 1.15-1.92) became not statistically significant (HR =

Table 1 Characteristics of study population by presence of atrial fibrillation or sinus rhythm at baseline

	Atrial fibrillation (*n* = 173)	Sinus rhythm (*n* = 730)	*P* value
Demographics and physical examination			
Age (yr)	72 ± 11	66 ± 12	< 0.0001
Age ⩾ 65 yr (%)	81	60	< 0.0001
Male gender (%)	70	73	0.42
SBP (mmHg)	127 ± 18	130 ± 19	0.10
DBP (mmHg)	74 ± 10	75 ± 10	0.47
NYHA II-III (%)	60	44	0.0002
Aetiology			
CAD (%)	28	52	< 0.0001
Previous CABG/PCI (%)	21	37	< 0.0001
Without CAD (%)	22	24	0.58
Others/idiopathic (%)	50	24	< 0.0001
Valve surgery (%)	13	4	< 0.0001
Device			
Any PM (%)	30	19	0.001
CRT-P/CRT-D (%)	10	7	0.14
ICD (%)	11	16	0.07
Any device (%)	31	21	0.005
History of VT (%)	2	5	0.06
Risk factors			
Hypertension (%)	61	60	0.81
Diabetes mellitus (%)	24	28	0.39
Dyslipidaemia (%)	23	37	0.0004
Ever smoke (%)	27	41	0.0010
Comorbidities			
Cancer history (%)	12	10	0.47
COPD (%)	14	13	0.55
Anaemia (%)	6	10	0.11
CKD (eGFR < 60) (%)	7	8	0.57
ECG			
Heart rate (bpm)	80 ± 19	70 ± 13	< 0.0001
PM stimulation (%)	24	8	< 0.0001
Right bundle branch block (%)	7	5	0.65
Left bundle branch block (%)	9	16	0.01
Echocardiogram			
Preserved LVEF (> 45%) (%)	29	21	0.022
LVEF (%)	38 ± 14	35 ± 12	0.05
Medications			
Beta-blockers (%)	72	80	0.01
ACEi/ARB (%)	71	79	0.02
Beta-blockers and ACEi/ARB (%)	51	66	0.0003
Aldosterone blockers (%)	46	37	0.02
Diuretics (%)	87	69	< 0.0001
Calcium channel blockers (%)	6	13	0.01
Alfa-blockers (%)	6	8	0.55
Digoxin (%)	51	11	< 0.0001
Statin (%)	28	49	< 0.0001
Amiodarone (%)	6	13	0.01
Antithrombotic treatment (%)	19	63	< 0.0001
OAT (%)	82	16	< 0.0001
DAPT (%)	2	16	< 0.0001
OAT and antithrombotic (%)	8	2	0.0006
Antithrombotic only (%)	11	61	< 0.0001

SBP: Systolic blood pressure; DBP: Diastolic blood pressure; NYHA: New York Heart Association; CAD: Coronary artery disease; CABG: Coronary artery bypass grafting; PCI: Percutaneous coronary intervention; PM: Pacemaker; CRT-P/D: Cardiac resynchronization therapy pacing/defibrillator; ICD: Internal cardioverter defibrillator; VT: Ventricular tachycardia; COPD: Chronic obstructive pulmonary disease; CKD: Chronic kidney disease; eGFR: Estimated glomerular filtration rate (obtained by CKD-EPI formula); LVEF: Left ventricular ejection fraction; ACEi: ACE inhibitors; ARB: Angiotensin receptor blockers; OAT: Oral anticoagulant treatment; DAPT: Dual anti-platelet therapy.

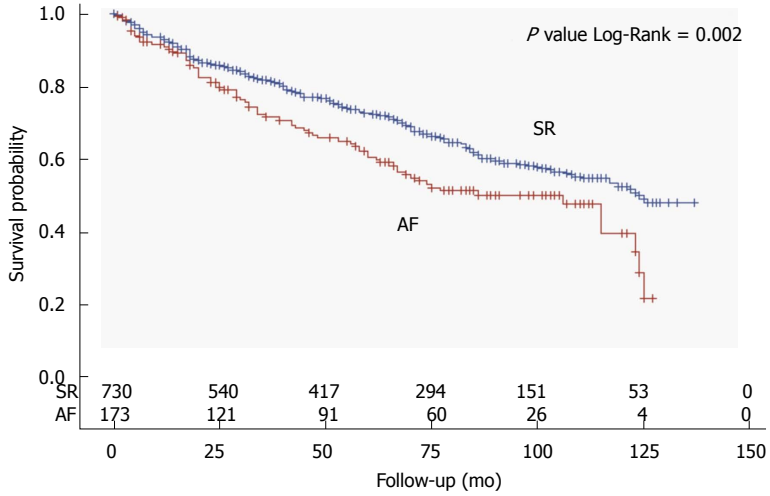

Figure 2 Kaplan-Meier curves of overall survival according to the presence of atrial fibrillation or sinus rhythm. SR: Sinus rhythm; AF: Atrial fibrillation.

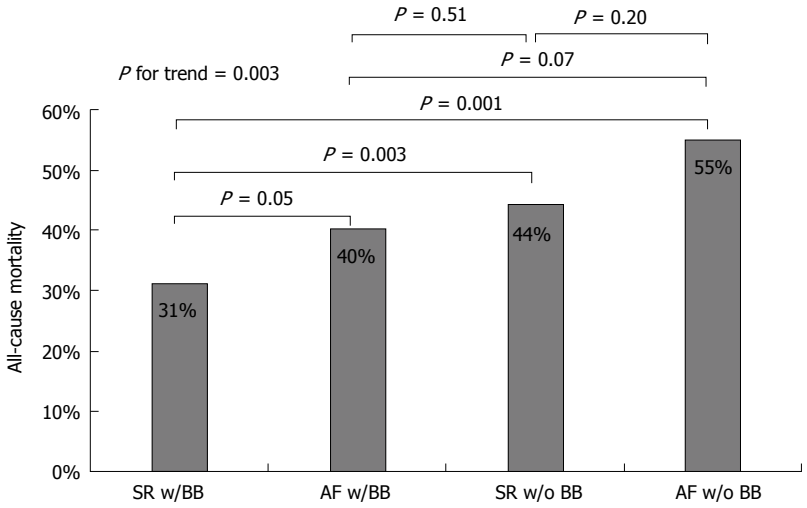

Figure 3 All-cause mortality in patients with atrial fibrillation as compared to patients with sinus rhythm based on the use of beta-blocker medications. SR: Sinus rhythm; AF: Atrial fibrillation; BB: Beta-blocker.

0.98, 95%CI: 0.73-1.32, Table 3). In the final reduced multivariate model, independent predictors at baseline of all-cause mortality were the following: Older age, male gender, lower systolic blood pressure, NYHA class II-III, presence of CAD at coronary angiography, presence of an implanted device, diagnosis of diabetes mellitus, COPD or anemia, history of cancer, non-use of ACEi/ARB and statins, and use of diuretics and digoxin (Table 3).

Mortality differences by BB medications

All-cause mortality was studied also through a comparison between patients with SR and patients with AF based on the presence or absence of BB treatment. Patients with AF not receiving BB treatment were found to have the worst prognosis, followed by patients with SR not receiving BB therapy and patients with AF receiving BB therapy, who both had similarly worse survival when compared to patients with SR receiving BB therapy (Figure 3). During the course of follow-up, patients with AF not receiving BB treatment had the worst prognosis, followed by patients with SR not receiving BB therapy together with patients with AF receiving BB therapy, and finally patients with SR receiving BB therapy (Figure 4).

DISCUSSION

Overall, our data demonstrates that in ambulatory patients with CHF, the presence of permanent AF is associated with worse clinical presentation, underuse of disease-modifying medications including BB, and possibly worse prognosis. After accounting for confounders, we found no independent association between AF and all-cause mortality; nonetheless, we found a significantly worse prognosis in AF patients with CHF not receiving BB treatment.

Patients with AF in our study population were older and had a higher NYHA functional class at presentation, in agreement with other data reported in the litera-

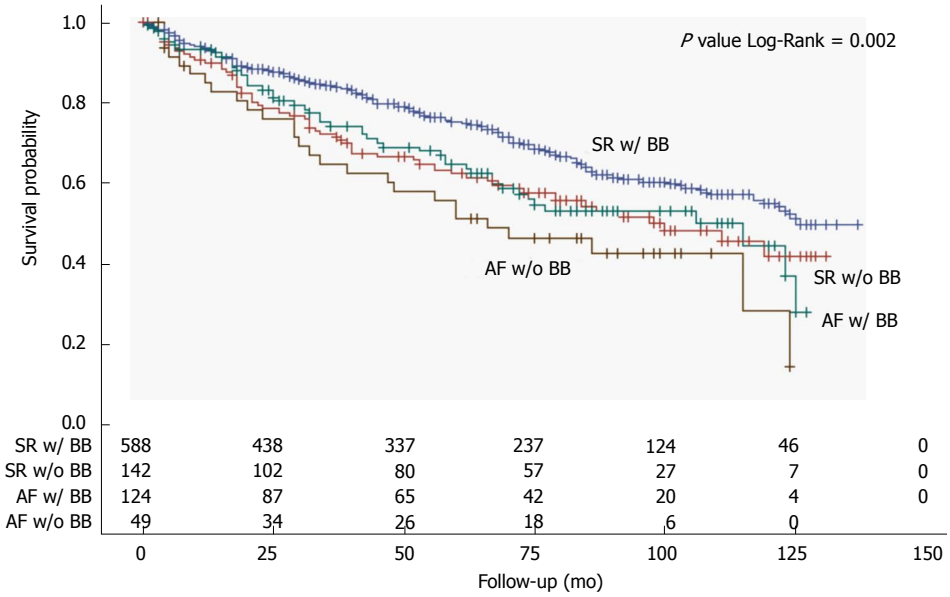

Figure 4 Kaplan-Meier curves of overall survival according to the presence of atrial fibrillation or sinus rhythm and the use of beta-blocker medications. SR: Sinus rhythm; AF: Atrial fibrillation; BB: Beta-blocker.

Table 2 Characteristics of study population by survival or death

	Death (n = 324)	Alive (n = 579)	P value	HR (95%CI)	P value
Atrial fibrillation (%)	23	16	0.0085	1.48 (1.14-1.92)	0.0028
Demographics and physical examination					
Age (yr)	71 ± 10	66 ± 12	< 0.0001	1.05 (1.04-1.06)	< 0.0001
Male gender (%)	25	29	< 0.0001	2.4 (1.85-3.07)	< 0.0001
SBP (mmHg, 10)	127 ± 19	130 ± 19	0.0238	0.93 (0.88-0.99)	0.0228
DBP (mmHg, 10)	72 ± 10	76 ± 10	< 0.0001	0.76 (0.67-0.85)	< 0.0001
NYHA II-III (%)	60	40	< 0.0001	1.7 (1.35-2.10)	< 0.0001
Aetiology					
CAD (%)	51	46	0.18		
Previous CABG/PCI (%)	33	35	0.57		
Without CAD (%)	17	27	0.0002	0.53 (0.4-0.71)	< 0.0001
Others/idiopathic	32	26	0.049	1.29 (1.02-1.63)	0.0302
Valve surgery (%)	5	6	0.57		
Device					
Any PM (%)	28	17	0.0003	1.64 (1.29-2.1)	< 0.0001
CRT-P/CRT-D (%)	8	7	0.32		
ICD (%)	20	13	0.0027	1.45 (1.1-1.9)	0.0074
Any device (%)	29	19	0.0006	1.57 (1.23-2.00)	0.0002
History of VT (%)	7	4	0.0258	1.53 (1.01-2.32)	0.0439
Risk factors					
Hypertension (%)	58	61	0.2619		
Diabetes mellitus (%)	32	24	0.0053	1.72 (1.36-2.17)	< 0.0001
Dyslipidaemia (%)	27	39	0.0003	0.68 (0.53-0.87)	0.0023
Ever smoke (%)	32	41	0.0055	0.92 (0.72-1.16)	0.4668
Comorbidities					
Cancer history (%)	14	8	0.0044	1.89 (1.37-2.60)	< 0.0001
COPD (%)	18	10	0.0006	1.84 (1.4-2.40)	< 0.0001
Anaemia (%)	11	8	0.0521	2.22 (1.57-3.13)	< 0.0001
CKD (eGFR < 60) (%)	10	6	0.0551	2.807 (1.85-4.25)	< 0.0001
ECG					
Heart rate (bpm, 10)	72 ± 15	70 ± 15	0.1026	1.06 (0.99-1.14)	0.0805
PM stimulation (%)	14	9	0.0438	1.56 (1.14-2.14)	0.0057
Right bundle branch block (%)	7	5	0.0866	1.38 (0.9-2.1)	0.1321
Left bundle branch block (%)	12	16	0.0761	0.75 (0.53-1.05)	0.0958
Echocardiogram					
Preserved LVEF (> 45%) (%)	19	24	0.0560	0.74 (0.56-0.98)	0.0345
LVEF (%)	34 ± 12	36 ± 11	0.0015	0.98 (0.97-0.99)	0.0008
Medications					
Beta-blockers (%)	72	82	0.0003	0.67 (0.53-0.85)	0.0012
ACEi/ARB (%)	75	79	0.0994	0.69 (0.53-0.88)	0.0032

Beta-blockers and ACEi/ARB (%)	32	68	0.003	0.66 (0.53-0.83)	0.0002
Aldosterone blockers (%)	45	35	0.0033	1.57 (1.26-1.95)	< 0.0001
Diuretics (%)	82	67	< 0.0001	2.50 (1.87-3.31)	< 0.0001
Calcium channel blockers (%)	14	11	0.1588		
Alfa-blockers (%)	8	7	0.8049		
Digoxin (%)	26	14	< 0.0001	1.60 (1.25-2.05)	0.0002
Statin (%)	39	48	0.0088	0.80 (0.64-1.00)	0.0513
Amiodarone (%)	12	12	0.8421		
Antithrombotic treatment (%)	56	54	0.5669		
OAT (%)	31	27	0.2374		
DAPT (%)	10	15	0.0282	0.89 (0.62-1.29)	0.5394
OAT and antithrombotic (%)	3	4	0.4946		
Antithrombotic only (%)	53	50	0.4149		

SBP: Systolic blood pressure; DBP: Diastolic blood pressure; NYHA: New York Heart Association; CAD: Coronary artery disease; CABG: Coronary artery bypass grafting; PCI: Percutaneous coronary intervention; PM: Pacemaker; CRT-P/D: Cardiac resynchronization therapy pacing/defibrillator; ICD: Internal cardioverter defibrillator; VT: Ventricular tachycardia; COPD: Chronic obstructive pulmonary disease; CKD: Chronic kidney disease; eGFR: Estimated glomerular filtration rate (obtained by CKD-EPI formula); LVEF: Left ventricular ejection fraction; ACEi: ACE inhibitors; ARB: Angiotensin receptor blockers; OAT: Oral anticoagulant treatment; DAPT: Dual anti-platelet therapy.

Table 3 Univariate and multivariate predictors of all-cause mortality

	Univariate		Multivariate full		Multivariate reduced	
	HR (95%CI)	*P* value	HR (95%CI)	*P* value	HR (95%CI)	*P* value
Atrial fibrillation	1.48 (1.14-1.92)	0.0028	0.98 (0.73-1.32)	0.8896		
Age (1 yr)	1.05 (1.04-1.06)	< 0.0001	1.04 (1.03-1.05)	< 0.0001	1.04 (1.03-1.05)	< 0.0001
Male gender	2.4 (1.85-3.07)	< 0.0001	1.45 (1.11-1.90)	0.0068	1.48 (1.13-1.93)	0.0045
SBP (10 mmHg)	0.93 (0.88-0.99)	0.0228	0.92 (0.86-0.98)	0.0084	0.91 (0.86-0.97)	0.0057
NYHA II-III	1.70 (1.35-2.10)	< 0.0001	1.3 (1.03-1.65)	0.0265	1.32 (1.05-1.66)	0.0195
Without CAD	0.53 (0.4-0.71)	< 0.0001	0.61 (0.44-0.84)	0.0023	0.58 (0.43-0.80)	0.0008
Any device	1.57 (1.23-2.00)	0.0002	1.65 (1.19-2.29)	0.0028	1.57 (1.23-2.02)	0.0004
Dyslipidaemia	0.68 (0.53-0.87)	0.002	0.8 (0.60-1.06)	0.1151		
Diabetes mellitus	1.72 (1.36-2.17)	< 0.0001	1.63 (1.27-2.08)	0.0001	1.59 (1.25-2.04)	0.0002
Cancer history	1.89 (1.37-2.60)	< 0.0001	1.82 (1.31-2.54)	0.0004	1.84 (1.33-2.56)	0.0003
COPD	1.84 (1.4-2.4)	< 0.0001	1.33 (0.98-1.80)	0.0707	1.38 (1.02-1.86)	0.0359
Anaemia	2.22 (1.57-3.13)	< 0.0001	1.82 (1.23-2.69)	0.0027	1.95 (1.37-2.79)	0.0002
CKD (eGFR < 60)	2.81 (1.85-4.25)	< 0.0001	1.42 (0.87-2.29)	0.1577		
Preserved LVEF (> 45%)	0.74 (0.56-0.98)	0.034	0.91 (0.68-1.22)	0.5369		
PM stimulation	1.56 (1.14-2.14)	0.006	0.91 (0.59-1.40)	0.6561		
Beta-blockers	0.67 (0.53-0.85)	0.001	0.83 (0.64-1.09)	0.1903		
ACEi/ARB	0.69 (0.53-0.88)	0.003	0.77 (0.59-1.01)	0.0634	0.73 (0.56-0.94)	0.0169
Aldosterone blockers	1.57 (1.26-1.95)	< 0.0001	1.11 (0.86-1.43)	0.429		
Diuretics	2.5 (1.87-3.31)	< 0.0001	1.51 (1.09-2.10)	0.0134	1.58 (1.17-2.15)	0.0031
Digoxin	1.6 (1.25-2.05)	0.0002	1.29 (0.97-1.73)	0.0807	1.31 (1.00-1.72)	0.0482
Statin	0.8 (0.64-1.00)	0.051	0.8 (0.60-1.05)	0.1108	0.71 (0.55-0.90)	0.0057

Any device included any pacemaker or internal-cardioverter defibrillator. SBP: Systolic blood pressure; NYHA: New York Heart Association; CAD: Coronary artery disease; COPD: Chronic obstructive pulmonary disease; CKD: Chronic kidney disease; eGFR: Estimated glomerular filtration rate by CKD-EPI formula; LVEF: Left ventricular ejection fraction; PM: Pacemaker; ACEi: ACE inhibitors; ARB: Angiotensin receptor blocker.

ture[10,11]. The presence of AF was also associated with an increased use of symptomatic medications, such as diuretics and digoxin, and a less frequent use of CHF-modifying medications, such as BB and ACEi/ARB. In addition, CAD was less represented among AF patients, whereas the prevalence of valve disease and non-cardiovascular comorbidities was greater in this group of patients, who interestingly also had a higher mean LVEF and more frequently a preserved LVEF (here LVEF > 45%). Recent literature emphasizes the stronger correlation of AF with CHF with preserved LVEF as compared to reduced LVEF[12], though this association was rather weak in our population, possibly because it mainly included CHF patients with reduced LVEF. CHF patients with AF are usually characterized by the presence of multiple comorbidities, and it is still unknown whether the adverse outcomes associated with AF are related to the arrhythmia itself, or to the burden of comorbidities associated with this diagnosis[8].

Contrasting findings have been published regarding a potential independent contribution of AF to increased mortality in patients with CHF. Some studies found AF to be an independent predictor of worse outcomes[13,14] whereas others found no independent association after accounting for confounders[4-6]. Two meta-analyses reported a 30%-40% increased risk of mortality when CHF is associated with a diagnosis of AF[7,8], irrespective of LVEF. In our study population, the coexistence of CHF and permanent AF resulted in a worse outcome, as shown by the Kaplan-Meyer survival curve in

Figure 2. However, after adjusting for other significant predictors (including older age, male sex, systolic blood pressure, NYHA class Ⅱ-Ⅲ, ischemic etiology, pacemaker implanted, diabetes mellitus, history of cancer, COPD, anemia), AF did not show an independent impact on overall mortality (Table 3). This finding is in accordance with the abovementioned analyses from the COMET[5] and the V-HeFT study[4]. Advanced age and CHF severity have been shown to largely explain the association between AF and mortality in CHF patients, and this was also true in our study population, in which beyond age and NYHA functional class, we demonstrated a significant and independent contribution of non-cardiovascular comorbidities to mortality, including COPD, anemia and a history of cancer.

Although the use of BB in the setting of CHF has recently been disputed[9], we observed the worst prognosis in AF patients not receiving BB medications, while patients with AF receiving BB presented a significant survival benefit similar to those with SR not receiving BB but still lower than those with SR receiving BB treatment (Figures 3 and 4). It is still uncertain whether BB therapy reduces morbidity and mortality in patients with AF, but a class IA indication is given for these medications in patients with CHF and AF to control ventricular rate[15]. Our present results support this recommendation and point against the underuse of BB medications that is generally observed in CHF with AF as compared to those with SR[9].

The contribution of treatment with digoxin to the worse outcome in patients with CHF and AF is a matter of current debate[16]. We observed that digoxin was used in half of our patients with AF, and in only 1 out of 10 patients with SR. These percentages refer to the use of digoxin at first study visit, which happened some years ago starting in 2004, and probably do not reflect the current use of this medication in our clinical practice. Trends in the use of digoxin for AF have been steadily decreasing in the recent years, at least in the American population[17], and this drug has class IIa/B recommendations for rate control treatment of AF in most recent European[15] and American[18] HF guidelines. This is because of an overall neutral effect of this drug on mortality[19], and some observational studies showing an independent association with increased mortality[20]. Accordingly, its utilization was a strong and independent predictor of mortality at multivariate analysis in our retrospective analysis (Table 3).

The presence of implantable devices was associated with increased mortality in our final multivariate model. This finding appears counterintuitive at first, but may have different explanations. In particular, the presence of a device may be representative of a sicker CHF patient, for which the implantation of a device is generally indicated. In addition, when we distinguished patients with only pacing devices from patients with a resynchronizing device (either CRT-P or CRT-D) and patients with an ICD, only patients with a pacing device and an ICD implanted showed a statistically significant worse prognosis (Table 2). Treatment of LV dyssychrony with CRT device is expected to improve EF and symptoms over time, which in turn has a major positive impact on outcomes, including survival[15]. This is also at least partially reflected by the positive prognostic association of the presence of a left bundle branch block that we found in our study population (Table 2), which is likely indicative of the effect of CRT in patients that were implanted with a resynchronizing device after the first study visit at our clinic.

In contrast to what would be expected, dyslipidemia was associated with a reduction of mortality. In the setting of CHF, the presence of low cholesterol levels is known to identify patients with more advanced cardiac disease (*i.e.*, with sarcopenia and possibly cachexia), and low concentrations of low-density lipoproteins have been associated with worse prognosis[15]. Patients with advanced cardiac disease are also less likely to receive lipid-lowering medications such as statins, for which the indication in CHF patients without active CAD is lacking[15]. Thus, the presence of dyslipidemia and the use of statins in our CHF population of advanced age probably indicate a healthier patient, which explain the associations of both these variables with a better prognosis.

Our analysis has several limitations that should be acknowledged. First, this is a retrospective analysis, thus our findings can only be interpreted with the intrinsic limits of this methodology. Second, cardiac rhythm was defined at first study visit, and we cannot exclude subsequent rhythm modifications. Third, we assessed mortality from all causes and could not obtain clear information specifically on cardiovascular and non-cardiovascular mortality. Because a history of cancer was a significant predictor of increased mortality, in an attempt to remove deaths due to malignancy, we performed sensitivity analysis excluding patients with a positive history of cancer. This analysis included 812 patients, of whom 659 with SR (81%) and 153 with AF (19%), and a total of 279 deaths out of the original 324. In this subsample, final results of independent predictors of mortality were substantially unchanged (data not shown). Finally, due to the low number of patients with preserved LVEF, we could not explore the interaction between LVEF and AF on mortality.

Our retrospective cohort study investigating a real-world population of elderly ambulatory CHF patients confirmed the association of AF with older age and worse clinical presentation previously reported in the literature. It further highlighted how a diagnosis of AF also led to an underutilization of disease-modifying medications such as BB and ACEi/ARBs, and to a more frequent use of symptomatic and antiarrhythmic drugs, particularly diuretics and digoxin, which in turn were independently associated with worse prognosis. In multivariate analysis, AF had no independent impact on all-cause mortality, which nonetheless was found to be the highest in AF patients not receiving BB medications. Further prospective randomized studies are needed

investigating the independent prognostic impact of BB treatment in CHF with AF.

COMMENTS

Background

Atrial fibrillation (AF) frequently coexists with chronic heart failure (CHF). Conflicting data exist on the prevalence, clinical characteristics and medical treatment of HF patients with AF, particularly in the elderly. The independent prognostic impact of AF in these patients also remains unknown, as well as the potential protective effect of disease-modifying medications, particularly beta-blockers (BB).

Research frontiers

The independent prognostic impact of AF in patients with CHF is a current matter of debate, and many have argued that this association is solely explained by other conditions associated to this arrhythmia, particularly comorbidities and underuse of disease-modifying medications.

Innovations and breakthroughs

This analysis confirmed the relevant clinical impact of AF in patients with CHF, although like other previous studies in the literature found no independent prognostic impact of this arrhythmia on overall mortality at long-term follow-up after accounting for several important confounders which are frequently found in these elderly CHF patients.

Applications

The study findings highlight the underuse of disease-modifying medications in CHF patients with coexisting AF, particularly BB. This is a matter of current debate in the clinical arena, with international guidelines giving a strong recommendation for the use of BB as a first-line treatment to control ventricular rate in euvolemic patients with New York Heart Association class I-III CHF. Efforts need to be done in order to increase the appropriate use of these medications in CHF with AF in the real world.

Peer-review

This interesting study by Gigli *et al* examined the impact of AF on outcomes in patients with CHF. The authors conclude that AF did not have an independent impact on mortality, but BB use appeared to affect this relationship.

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ORIGINAL ARTICLE

Observational Study

Riata silicone defibrillation lead with normal electrical measures at routine ambulatory check: The role of high-voltage shock testing

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Abstract

AIM

To describe our experience with shock testing for the evaluation of patients with Riata™ leads.

METHODS

Among 51 patients with normal baseline electrical parameters, 20 died during follow-up. Of the remaining 31 patients, 15 underwent the test: In 10 cases a defibrillation testing with ventricular fibrillation (VF) induction and in 5 cases a R-wave-synchronized shock (> 20 J, without inducing VF). The test was performed under sedation with Midazolam.

RESULTS

Twelve patients (80%) had a normal behavior during shock testing: In 8 cases induced VF was correctly detected and treated; in 4 cases of R-wave-synchronized shock electrical parameters remained stable and normal. Three patients (20%) failed the test. One patient with externalized conductors showed a sudden drop of high-voltage impedance (< 10 Ohm) after a 25 J R-wave-synchronized shock. Two other patients with externalized conductors, undergoing defibrillation testing, showed a short-circuit during shock delivery and the implantable cardioverter defibrillator was unable to interrupt VF.

CONCLUSION

In Riata™ leads the delivery of a low current during

routine measurement of high-voltage impedance may not reveal a small short circuit, that can only be evident by attempting to deliver a true shock, either for spontaneous arrhythmias or in the context of a shock testing.

Key words: Implantable cardioverter defibrillator; Lead failure; Defibrillation testing; Riata™ lead; Externalized conductors

Core tip: The management of Riata™ defibrillator leads is complex and optimal treatment is often carried out on individual basis. These leads are prone to a unique failure mechanism: The conductors can externalize through the silicone insulation ("inside-out" abrasion) and appear outside the lead body leading to electrical failure. The potential role of high-voltage shock testing for these leads has been poorly studied, only sparse reports being available. In Riata™ leads the delivery of a low current during routine measurement of high-voltage impedance may not reveal a small short circuit, that can only be evident by attempting to deliver a true shock, either for spontaneous arrhythmias or in the context of a shock testing. Defibrillation testing (or alternatively synchronized shock) should be considered an important tool to check Riata™ integrity.

De Maria E, Borghi A, Bonetti L, Fontana PL, Cappelli S. Riata silicone defibrillation lead with normal electrical measures at routine ambulatory check: The role of high-voltage shock testing. *World J Cardiol* 2016; 8(11): 657-666 Available from: URL: http://www.wjgnet.com/1949-8462/full/v8/i11/657.htm DOI: http://dx.doi.org/10.4330/wjc.v8.i11.657

INTRODUCTION

The Riata™ St. Jude Medical family of implantable cardioverter defibrillator (ICD) silicone leads underwent class I recall by the Food and Drug Administration in December 2011. These leads are prone to a unique failure mechanism: The conductor cables can externalize through the silicone insulation ("inside-out" abrasion) and appear outside the lead body[1]. The prevalence of externalized conductors (EC) is lower in 7Fr compared to 8Fr leads (9.3% *vs* 24.2%)[2]. The rate of electrical failure can be > 6% per year[3] and it is not always associated with EC[2,4,5]. However, a meta-analysis of 23 observational studies showed that the presence of EC increased the risk of electrical failure by more than 6-fold[6].

The management of patients with Riata™ leads is complex and optimal treatment is often carried out on individual basis. The most important factors to consider are: presence of electrical abnormalities; presence and degree of EC; patient's characteristics. When EC is discovered in absence of electrical abnormalities an "opportunistic" approach is suggested based on patient's risk profile and lead's characteristics[4,5]. The Food and Drug Administration, the manufacturer and many scientific societies do not recommend preemptive routine replacement/removal of externalized functional leads. Riata lead extraction is difficult (especially with EC) so it is not a first choice when the lead seems to function normally[5,7]. However essential questions arise: Will the system defibrillate the heart? Can we rely on a lead with normal electrical parameters even when EC is not evident?

In this paper we retrospectively describe our experience with high-voltage (HV) shock testing for the evaluation of Riata™ leads with normal baseline electrical parameters, with and without EC. We also review current scientific evidence and potential role of HV shock testing (full defibrillation testing or commanded R-wave-synchronized shock).

MATERIALS AND METHODS

Overview of Riata leads in our center

From 2003 to 2010 we implanted 60 Riata™ silicone leads: 51 8Fr (85%), 57 dual-coil (95%). Starting from 2012 we initiated a follow-up program according to manufacturer and Italian Arrhythmological Society (AIAC) recommendations, with fluoroscopic evaluation in three orthogonal views (PA: Postero-anterior; LAO/RAO: Left and right anterior oblique - 40°) at least once a year. Externalized conductors were found in 22% of cases (same percentage in 8Fr and 7Fr). Electrical abnormalities were found in 9 patients (15%): Two failed defibrillation testing (DFT) (two patients described afterward), electrical noise by non-physiological signals (n = 3), significant increase in pacing threshold (n = 2), decrease in R-wave amplitude (n = 1), drop of HV impedance after shock (n = 1). Notably in 3-out-9 cases electrical dysfunction occurred in absence of externalization (electrical noise in two cases, increase in pacing threshold in the other). Electrical abnormalities without EC occurred all with 8Fr dual-coil leads. All patients with electrical dysfunction were advised to have the lead extracted or replaced. Patients with normal electrical parameters (with or without EC) were evaluated in our ambulatory every 3-6 mo.

Defibrillation testing and R-wave-synchronized shock testing

Among 51 patients without baseline electrical dysfunction, 20 died during the follow-up period (3 cases of sudden unexplained death, before 2010, not further investigated). From 2014 we started to consider a HV shock testing in selected cases: At the time of generator replacement, in high risk patients or high risk leads (Table 1). Of the remaining 31 patients with normal baseline electrical parameters, 15 underwent the test: In 10 cases a DFT [ventricular fibrillation (VF) induction with shock-on-T or DC Fibber™] and in 5 cases a R-wave-synchronized shock (> 20 J,

Table 1 Potential role of high-voltage shock testing for the management of Riata™ leads with normal baseline electrical measures

At the time of generator replacement
All cases, with and without externalization, except if contraindications
Independently of generator replacement (case-by-case evaluation)
High risk patient: Recent/prior appropriate ICD shocks; secondary prevention; pacemaker dependency; young age
High risk lead: Externalization, especially if worsening over time; minimal change in electrical parameters not sufficient to define malfunction; 8Fr dual coil leads (?); 1570-1580-1590 families (?)
When to perform: Within 6-12 mo of an effective shock?
How often: Each 6-12 mo?
Contraindication or excessive risk with ventricular fibrillation induction
Commanded synchronized HV shock (preferably > 20 J)

ICD: Implantable cardioverter defibrillator; HV: High-voltage.

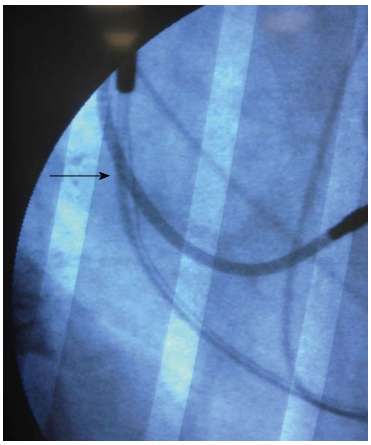

Figure 1 Cable externalization in patient 1.

without inducing VF). The decision to perform R-wave-synchronized shock instead of classical DFT was based on patient risk profile (high risk of complications from VF induction). The remaining 16 patients were non tested, at the time of manuscript draft, due to different clinical reasons: Patient's refusal (n° 1), low risk patients or low risk leads (n° 6), severe comorbidities/very old age (n° 9). The shock test was performed under sedation with Midazolam in all cases. In patients with atrial fibrillation or flutter the test was performed only if optimal anticoagulation could be confirmed. All patients gave their consent and the study was approved by the Institutional Board of our Department.

RESULTS

Twelve patients (80% of those undergoing the test, 7 with EC) had a normal behavior during the shock: In 8 cases of DFT (5 with EC), with VF induction, the arrhythmia was correctly detected and treated; in 4 cases of R-wave-synchronized shock (2 with EC) electrical parameters (in particular HV impedance) remained normal and stable. At 6 mo follow-up none of these patients died or experienced electrical failure of the lead.

Three patients (20%) failed the test. One patient with EC had a sudden drop of HV impedance (< 10 Ohm) after a 25J R-wave-synchronized shock, so a new defibrillation lead was implanted without complications. Two other patients with EC, undergoing DFT, showed a short-circuit during shock delivery and the ICD was unable to interrupt VF (they were externally defibrillated).

Among the 16 patients who were *not* tested 4 died of non-cardiac causes (cancer), 4 died of end-stage heart failure, 8 continued to have their lead functional (at 6 mo follow-up). The two cases with failed DFT are described in details hereinafter.

Case 1

A 75-year-old man with ischemic dilated cardiomyopathy had received a St Jude Medical biventricular defibrillator in 2009 for primary prevention (Promote™ RF 3213). Defibrillation lead was a 7Fr Riata™ ST 7000, dual-coil, active fixation. At the time of implant, a defibrillation testing had been successfully performed. During routine scheduled device interrogations electrical parameters had always been stable and normal. In accordance with AIAC recommendations we performed a complete fluoroscopic evaluation in three views each 6 mo. In 2013 we discovered an initial, mild conductors' externalization, type 1-2 according to Parvathanemi's fluoroscopic grading score[8], near the proximal coil. In 2014 the externalization worsened, becoming a type 3 (> 1 cm length extrusion, Figure 1) with extension toward ventricular coil; nevertheless, electrical parameters remained normal and stable. At this point we decided to check system integrity performing a defibrillation testing: Under sedation VF was induced with a shock-on-T; the arrhythmia was correctly sensed and detected but two consecutive internal shocks (20 and 36 J) were unsuccessful (Figures 2 and 3); an external 200J biphasic shock promptly restored sinus rhythm (arrow, Figure 3). Post-shock ICD interrogation revealed very low HV impedance during shock delivery (< 10 Ohms) and warning messages on programmer screen: "Problem with HV electrodes", "High current drainage during HV therapy". Further analysis showed truncated ineffective shocks, likely due to device protection circuitry after recording HV impedance < 10 Ohms. The patient underwent uneventful lead extraction; notably, at visual inspection, there was no sign of abrasion or externalization between the lead and the ICD can. Unfortunately, neither the extracted lead (seriously damaged during the procedure) nor the generator were sent to the manufacturer for further analysis.

Case 2

A 64-year-old man with ischemic dilated cardiomyopathy had received a St Jude Medical single-chamber defibrillator in 2008 for primary prevention (Epic™

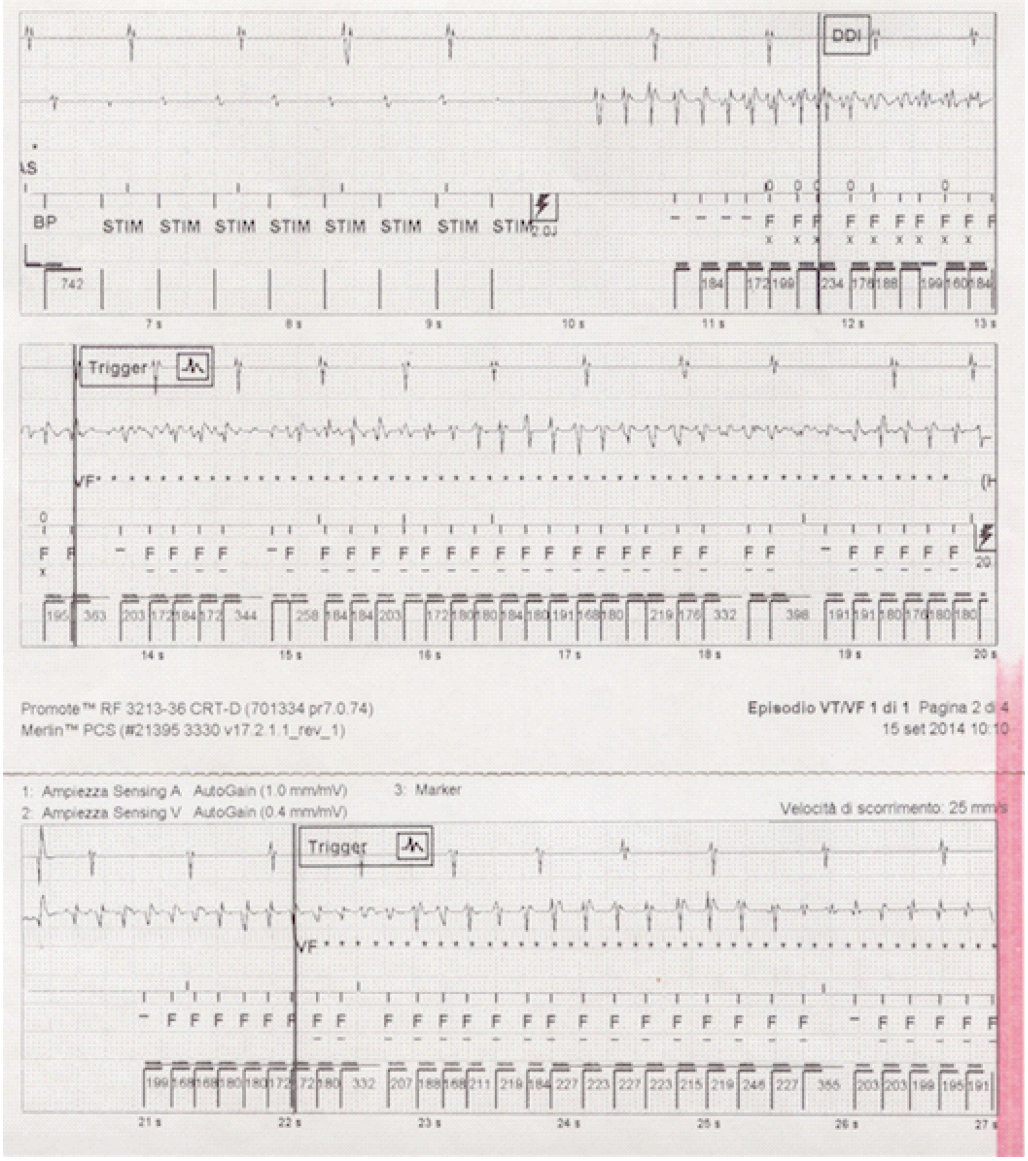

Figure 2 Patient 1: Induction of ventricular fibrillation with shock-on-T and failed defibrillation at 20 J.

VR197). Defibrillation lead was an 8Fr Riata™ 1571, dual-coil, passive fixation. At the time of implant, a defibrillation testing had been successfully performed. During routine device interrogations, electrical parameters of the lead had always been stable and normal. Notably in Epic™ family HV impedance cannot be measured automatically with a painless sub-threshold test, but requires a true shock at 12 Volts (< 0.1 J) synchronized with the QRS complex. In 2014 the patient was hospitalized for elective pulse generator change. At this time fluoroscopy showed conductors externalization, type 2 according to Parvathaneni *et al*[8]'s grading score, near the ventricular coil (Figure 4). For this reason, we decided to perform a defibrillation testing before the generator replacement, even if we could expect a prolonged charging time (battery charge time about 20"). Under sedation VF was induced with DC Fibber™, that delivers a single, direct current pulse through HV electrodes. A very "bad" VF was induced (Figure 5) with very low and fragmentated QRS complexes; however the arrhythmia was correctly sensed and detected. After a long charge time (> 28") a 30J shock was delivered but it did not interrupt VF. So an external 200J biphasic shock was promptly delivered, with resumption of sinus rhythm only after the third attempt. Post-shock ICD interrogation revealed no detectable HV impedance during shock delivery and warning messages on programmer screen: "HV impedance not detectable", "High current drainage during HV therapy", "Charge time limit reached", "Delivered shock truncated at 12 ms". As impedance was not detectable during the defibrillation testing, we decided to check it with a "routine" HV lead impedance (HVLI) test, the same test performed during routine ambulatory interrogation. Figure 6 shows what happened: Soon after the delivery of 12 V (arrow, Figure 6) VF restarted and again we promptly delivered external 200 J biphasic shock, and again sinus rhythm was restored

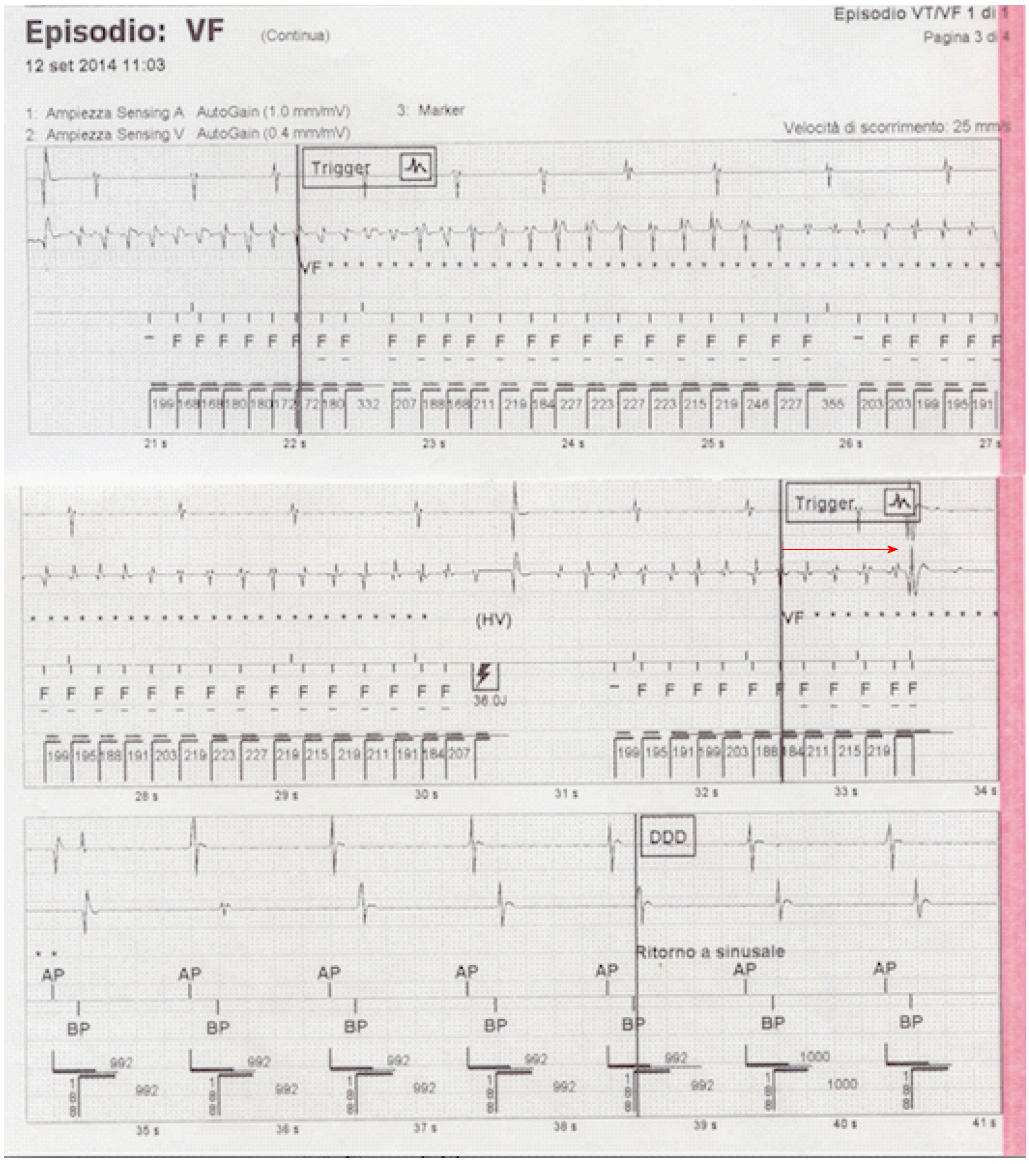

Figure 3 Patient 1: Failed defibrillation at 36 J; external 200 J biphasic shock promptly restored sinus rhythm (arrow).

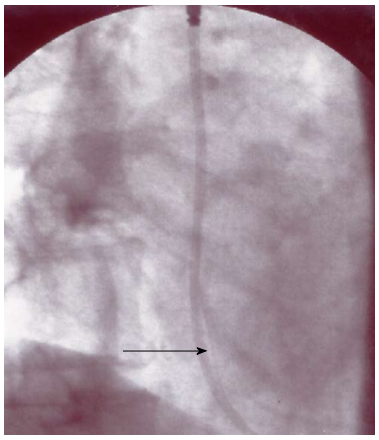

Figure 4 Cable externalization in patient 2.

only after the third attempt. During manual external defibrillation the ICD tried to deliver its own shock at 30 J that was ineffective: Post-shock interrogation showed a truncated shock with HV impedance < 10 Ohms. Luckily the patient recovered well after this "arrhythmic storm" and he subsequently underwent an uneventful lead extraction. At visual inspection there was no sign of abrasion or externalization between the lead and the ICD can. Unfortunately, also in this case, neither the extracted lead nor the generator were sent to the manufacturer.

DISCUSSION

Structural and electrical failure in Riata™ leads

Riata™ and Riata ST™ leads have a multilumen construction that includes paired HV and pace-sense cables (anode-ring) covered with 1.5 mL of ethylenetetrafluoroethylene (ETFE) and strung through individual lumens that run the length of the silicone body; the central pace-sense coil (cathode-tip), with stylet lumen encased, is further wrapped in a tube of polytetrafluoroethylene. The body of lead is insulated

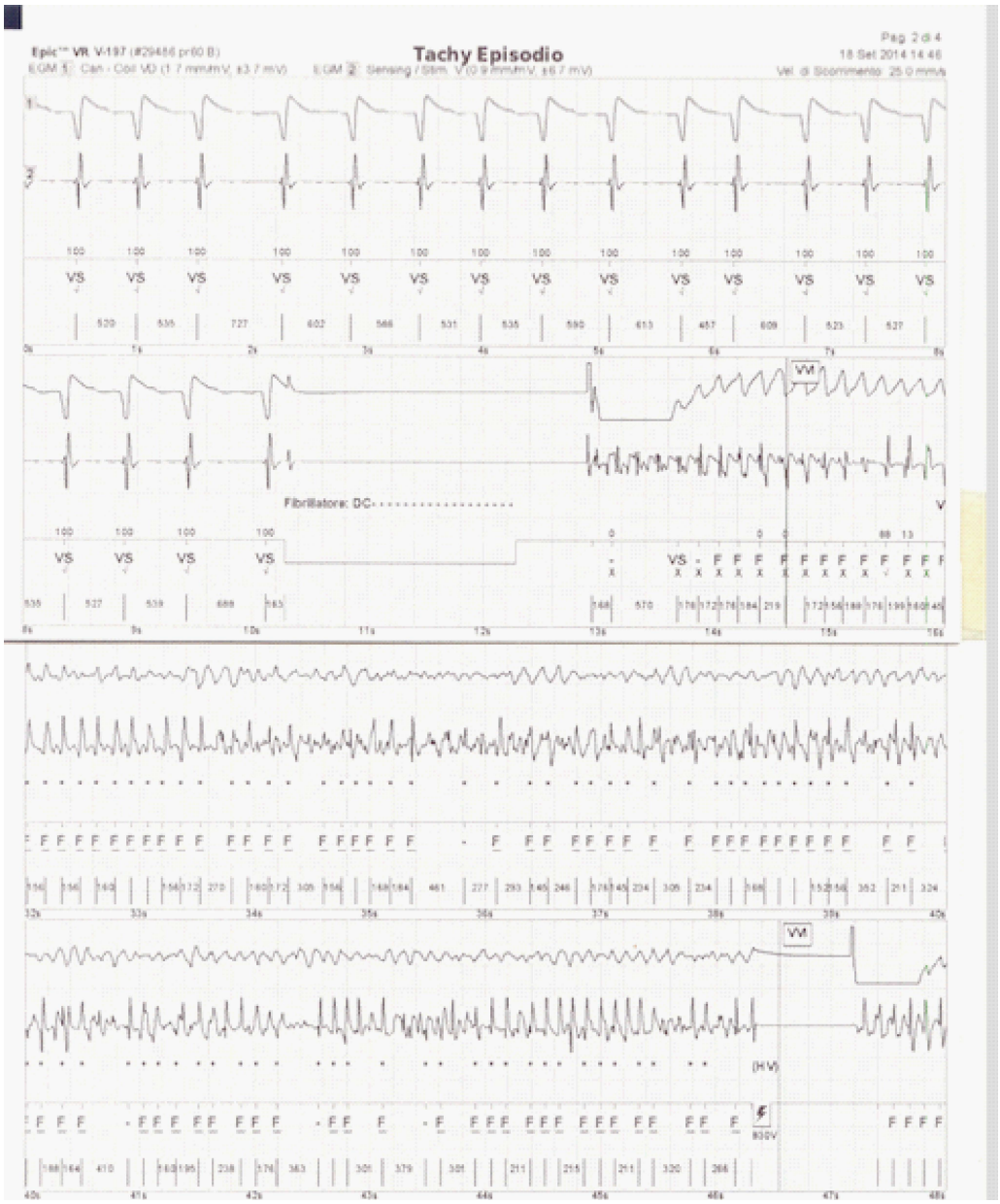

Figure 5 Patient 2: Induction of ventricular fibrillation with DC Fibber™ and failed defibrillation at 30 J.

with pure silicone rubber that has an increased risk of abrasion[1,6]. The anatomy of these leads accounts for the mechanism of externalization caused by the movement of the redundant cables within their lumen ("inside-out" abrasion). 8Fr single-coil leads are more prone to externalization: This can be explained by the design with two lumens directly opposed to one another, whereas dual-coil and ST models have three lumens equally spaced around the central coil, which reduces tension[9]. Importantly, in about 25% of cases (especially dual-coil), externalization is not evident on fluoroscopy because "inside-out" abrasion occurs underneath the shocking coils.

The risk for the patients is mainly linked to electrical failure[1,6] ranging from 1.3%[2] to 17.3%[10]. In our experience electrical abnormalities were found in 15% of patients, the majority with 8Fr leads. Increased pacing threshold appears earlier, while impedance changes occur later; overall noise and sensing issues are the most common electrical dysfunctions[1,5]. Short circuits and failure to defibrillate are rare but potentially lethal complications: It is disturbing that such shorts can occur without any other previous electrical abnormality, sometimes being the first and only sign of failure, also in absence of externalization[1,5-7].

In our two patients the cause of the short circuits cannot be explained with certainty, as the leads were not sent to manufacturer for further analysis. It is possible that the short took place in correspondence to the externalized cables, but "inside-out" abrasion underneath a shocking coil could not be excluded. An insulation break under a shocking coil can cause friction and abrasion of ETFE, with bare cables coming in contact with the HV conductors: The shock can

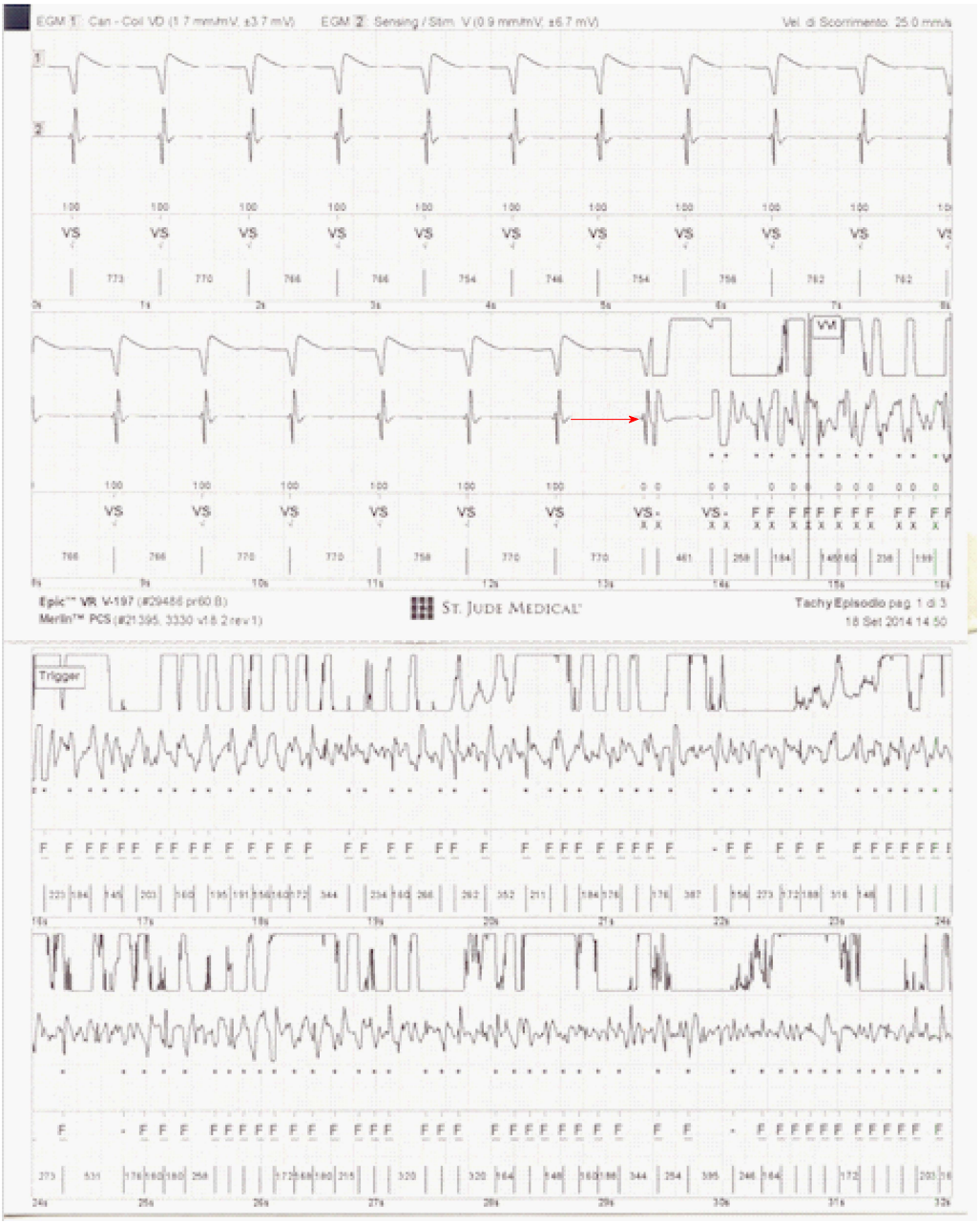

Figure 6 Patient 2: Ventricular fibrillation unintentionally re-induced after high-voltage impedance test with a synchronized 12 V shock (arrow).

be shorted, melting the cable and the coil, and fails to defibrillate[7]. In more than 65% of cases multiple insulation defects are present on each single lead[1]. Moreover, in 15%-22% of electrical failures the abrasion occurs between the lead and the can in the pocket or as a consequence of "outside-in" abrasion (contact with another lead or anatomic structures)[1,5]. In our patients "lead-to-can" abrasion could be reasonably excluded as there was no sign of abrasion/externalization between the lead and the can at a careful visual inspection.

"Lead-to-can", "outside-in" abrasion and ETFE disruption underneath shocking coils are the mechanisms that explain electrical failures and shorts in leads without visible externalization.

In the Multicenter Riata Evaluation Study[2], in Hauser's experience[5] and in another work[10] the prevalence of electrical dysfunction was not associated with EC. In our Center 37% of electrical failures occurred without EC, all in 8Fr dual-coil leads.

Some other studies have shown that leads with EC were more prone to electrical dysfunction, in particular lower R waves[4,6,11]. A recent prospective observational study showed[12] that the incidence of new electrical dysfunction was 6.4% at 12 mo and was associated with EC. Also in Danish experience EC was associated with a higher risk of electrical abnormalities[13]. Finally, Zeitler *et al*[6] in a recent meta-analysis of 23 observational studies, showed that the presence of EC was associated with a more than 6-fold increase in the rate of electrical failure compared to no EC.

Role of defibrillation or HV shock testing

When EC is evident, or when other mechanisms expose the cables, the lead may still function normally because HV and pace-sense ring cables are covered with ETFE, which serves as a second insulation. However, if ETFE abrades, electrical short circuits can occur during shock delivery with potential catastrophic consequences[1,5]. The delivery of a low current during routine measurement of HV impedance may not reveal a small short circuit, that can only be evident by attempting to deliver a true shock for spontaneous arrhythmias or in the context of a HV defibrillation testing[1,2]. Moreover HVLI test, during routine ambulatory evaluation, is not without risk: In our patient n° 2 VF was unintentionally re-induced during HV impedance test with a synchronized 12 Volts shock. This disturbing phenomenon had already been described by Hauser *et al*[5]: A patient, with an 8Fr dual-coil 1581 model, died from VF induced by HVLI test and not terminated by the ICD.

Given this very complex background the clinical decision regarding patients with Riata™ leads is troubling, particularly when managing "apparently" functional leads. Routine follow up (including home monitoring, programming additional far-field and noise reversion electrograms, tightening HV lead impedance limits) may be insufficient to detect such failure[5].

The potential role of defibrillation testing in the management of Riata™ is currently unclear and has been poorly studied; only sparse reports are available in literature[14-19]. Some authors advocate it at time of pulse generator change[1,4,6,7] but patients at high risk could benefit from the test even before that time.

Leong *et al*[14] was the first to describe a case of failure to deliver an appropriate shock by a 8Fr dual-coil 1570 Riata™ (implanted 8 years before) during a DFT performed after generator replacement; lead measurements were normal and stable, in absence of EC. The lead was not extracted but product analysis report of the generator indicated structural damage by a short circuit in the lead, while lead connection with the header box appeared normal.

Subsequently, Doshi *et al*[15] described an 8Fr dual-coil 1580 Riata™, with known externalization but no prior electrical abnormality, which was unable to deliver HV shock to interrupt VF at DFT after ICD replacement. After the failed shock HV impedance dropped to < 10 Ohms. The lead was extracted and its analysis revealed that the short in the HV circuit occurred underneath the caval coil.

In the report by Webber *et al*[16] another failure to defibrillate induced VF was described, again at the time of battery depletion. The lead was an 8Fr dual-coil 1580 Riata™, implanted 8 years before, without signs of malfunction (no externalization) but with decreasing R wave amplitude over time. Induced VF was correctly sensed and detected, the device charged 36 J but delivered 0.6 J first and 0 J at second attempt; post-shock impedance was < 20 Ohms. The lead was not extracted and the generator not analyzed by the manufacturer, but the normal appearance of the insulation in the lead segment looped beneath the generator suggested a short circuit within the intravascular/intracardiac body of the lead.

Shah *et al*[17] presented a case of failure to deliver effective shock during DFT by an 8Fr dual-coil 1581 lead, implanted 8 years before, with moderate EC and prior normal electrical parameters. This failure was discovered incidentally while the device was attempting to deliver an inappropriate shock for a supraventricular tachycardia; shock delivery was truncated and HV impedance dropped to < 10 Ohms. The subsequent DFT failed to interrupt VF. The patient refused extraction and a new lead was implanted; careful visual inspection of the proximal part of the lead did not reveal any insulation defect in the pocket.

Lakshmanadoss *et al*[18] described two cases of failed DFT at time of generator replacement: Both leads were 1581 models, a dual-coil and a single-coil (implanted 5 years before). The two leads displayed normal baseline electrical parameters in absence of externalization. In both cases delivery of shock was aborted due to loss of HV impedance and short circuit. The leads were explanted and the first was analyzed by the manufacturer: Superior vena cava coil and HV cable-to-ventricular coil were melted, confirming a short circuit due to an internal insulation defect not apparent on fluoroscopy.

Shen *et al*[19] described their experience with externalized leads and normal baseline electrical measures. Fifteen-out-23 patients with EC received a recent HV shock: 2 patients for spontaneous ventricular arrhythmias, 5 during scheduled defibrillation testing, 8 during an elective synchronized HV shock. Only one patient (6%) demonstrated post-shock electrical failure. An important finding from this study is that system integrity was checked with a commanded HV synchronized shock, without inducing VF, in 8-out-15 patients.

It is intriguing that, in these reports, the leads were all (except one) dual-coil models 1570-1580-1581. Moreover, in four cases there was no sign of externalization on fluoroscopy[14,16,18]. Our two patients had a 1571-8Fr and a 7000ST-7Fr, both dual-coil, both with EC. Are dual-coil leads more prone to short circuits and electrical failure in general? Numbers are small so we have no definitive answers, but the hypothesis is plausible given the failure mechanisms described above. Also in Hauser's experience[1,5] the vast majority of shorts occurred in dual-coil models, independently of EC. In the meta-analysis by Zeitler *et al*[6] rates of both EC and electrical failure were higher in dual-coil *vs* single-coil leads. However, Valk *et al*[20] found that electrical failure of single-coil was 17%, compared to 7% for dual-coil models, but they did not address short circuit in particular.

Externalized conductors are only the "tip of the iceberg" of the "Riata history". The association between

EC and electrical failure is still controversial but it is clear that these leads have a proclivity to failure. When an overt electrical dysfunction is present the lead has to be replaced or removed, independently of EC. When the lead seems to function normally (routine ambulatory check) management should be individualized and the factors to consider are: Presence/absence of externalization; lead's characteristics (model, implant duration, degree of externalization and its worsening over time); patient's high risk profile (secondary prevention, pacemaker dependency, recent/prior ICD intervention, young age, long life expectancy). Due to the failure mechanisms and the possibility of a short circuit, defibrillation testing should be considered as an important tool to check Riata™ integrity. Based on our experience and literature review, we believe that all patients with an electrically intact Riata™ lead should undergo such test at least at the time of generator replacement. If induction of VF is contraindicated, or too risky for the patient, an alternative "stress test" for the lead could be a commanded synchronized HV shock (preferably > 20 J) with a lower risk of inducing VF[21,22]. Some patients at high risk should be advised to undergo a HV shock testing even before the time of generator change. For example, if a patient has received a recent/prior effective shock for spontaneous arrhythmias a DFT should be considered within 6-12 mo: The reason is that when the ETFE is only partially abraded, a first shock may defibrillate but subsequent shocks may fail if the remaining ETFE breaks thereafter. HV shock testing should be advised also for "high risk leads": Presence of externalization (especially if worsening over time); minimal changes in electrical parameters (impedance changes < 25%, intermittent non-sustained noise from non-physiological signals); some models (8Fr, dual coil, 1570-1580-1590 families). Many questions remain unanswered: Are dual-coil leads more prone to shorts and electrical dysfunction? When and how often to perform a HV shock test? Is long-term outcome of patients undergoing the test better than non-tested patients? Future studies are needed to define the best strategy for the management of Riata™ leads with normal baseline electrical parameters, with and without EC[23]. Table 1 summarizes potential indications for HV shock testing in this setting.

The main limitations of our study are the small sample size, the retrospective nature, the empirical selection of patients for HV shock test. Moreover, neither the extracted leads nor the generators were sent to the manufacturer for further analysis.

COMMENTS

Background

The management of the recalled Riata™ defibrillator leads is complex and optimal treatment is often carried out on individual basis.

Research frontiers

The potential role of high-voltage shock testing for management of Riata™ defibrillator leads has been poorly studied, only sparse reports being available in literature. The research hotspot is to evaluate how shock testing can impact on patient outcome.

Innovations and breakthroughs

In Riata™ leads the delivery of a low current during routine measurement of high-voltage impedance may not reveal a small short circuit, that can only be evident by attempting to deliver a true shock, either for spontaneous arrhythmias or in the context of a shock testing.

Applications

Defibrillation testing (or alternatively synchronized shock) should be considered an important tool to check Riata™ integrity.

Terminology

Riata™ defibrillator leads are prone to a unique failure mechanism: The conductors can externalize through the silicone insulation ("inside-out" abrasion) and appear outside the lead body leading to electrical failure. Routine electrical measures may miss small short circuits. Defibrillation testing consists in inducing ventricular fibrillation (VF) and waiting for the implantable cardioverter defibrillator to defibrillate it. R-wave-synchronized shock is a less invasive testing that delivers a high-voltage shock to check the system, but does not induce VF.

Peer-review

This interesting article is a comprehensive discussion about management of Riata defibrillator lead. It is a very important study, about an important issue for which there is much heterogeneity in management.

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ORIGINAL ARTICLE

Observational Study

Increased levels of circulating platelet-derived microparticles in psoriasis: Possible implications for the associated cardiovascular risk

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Institutional review board statement: The study was reviewed and approved by the Attikon University Hospital Institutional Review Board, conducted in compliance with the Declaration of Helsinki.

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Abstract

AIM

To evaluate platelet activation markers in psoriasis patients, compared to controls, and investigate their association with the inflammatory burden of psoriasis.

METHODS

Forty psoriatic patients without cardiovascular disease,

and 12 healthy controls were subjected to measurement of baseline platelet CD62P, CD63 and CD42b expression, platelet-leukocyte complexes, *i.e.*, platelet-monocyte complexes (PMC), platelet-neutrophil complexes (PNC) and platelet-lymphocyte complexes, and concentrations of platelet-derived microparticles (PMPs) using flow cytometry. Both larger-size (0.5-0.9 μm) and smaller-size (< 0.5 μm) PMPs were determined. Serum interleukin (IL)-12 and IL-17 levels were also measured by enzyme-linked immunosorbent assay. The severity of psoriasis was evaluated by the Psoriasis Area Severity Index (PASI).

RESULTS

PMP concentrations were significantly higher in psoriasis patients than controls [mean ± standard error of mean (SEM): 22 ± 5/μL *vs* 11 ± 6/μL; $P = 0.018$), for both smaller-size (10 ± 2/μL *vs* 4 ± 2/μL; $P = 0.033$) and larger-size (12 ± 3/μL *vs* 6 ± 4/μL; $P = 0.014$) PMPs. Platelet CD62P, CD63 and CD42b expression and circulating PMC and PNC were similar between the two groups. Lower circulating PLC were observed in psoriasis patients compared to controls (mean ± SEM: 16% ± 3% *vs* 23% ± 6%; $P = 0.047$). Larger-size PMPs were related with IL-12 levels ($P < 0.001$) and smaller-size PMPs with both IL-12 and IL-17 levels ($P < 0.001$). Total PMPs also correlated with IL-12 ($P < 0.001$). CD63 expression was positively correlated with both IL-12 and IL-17 ($P < 0.05$). Increased PASI score was associated with increased levels of larger-size PMPs ($r = 0.45$; $P = 0.011$) and increased CD63 expression ($r = 0.47$; $P < 0.01$).

CONCLUSION

PMPs, known to be predictive of cardiovascular outcomes, are increased in psoriasis patients, and associated with high inflammatory disease burden. Enhanced platelet activation may be the missing link leading to cardiovascular events in psoriatic patients.

Key words: Psoriasis; Atherosclerosis; Inflammation; Platelet activation; Platelet-derived microparticles

Core tip: Psoriasis is associated with increased risk of cardiovascular disease. The pathogenic mechanisms shared by the two diseases seem to converge onto "inflammation" phenomenon. Platelets have a potent role in inflammation. Herein we evaluated platelet activation in psoriasis patients compared to healthy controls, and investigated a potential association between platelet activation markers and the inflammatory burden of psoriasis, the latter assessed by serum levels of pivotal pro-inflammatory cytokines implicated in psoriasis. We conclude that the association between psoriasis and atherosclerosis may be related to excessive platelet-derived microparticles (PMPs) formation. The size class of PMPs was taken into consideration in our study.

Papadavid E, Diamanti K, Spathis A, Varoudi M, Andreadou I, Gravanis K, Theodoropoulos K, Karakitsos P, Lekakis J, Rigopoulos D, Ikonomidis I. Increased levels of circulating platelet-derived microparticles in psoriasis: Possible implications for the associated cardiovascular risk. *World J Cardiol* 2016; 8(11): 667-675 Available from: URL: http://www.wjgnet.com/1949-8462/full/v8/i11/667.htm DOI: http://dx.doi.org/10.4330/wjc.v8.i11.667

INTRODUCTION

Psoriasis is now considered as an immune-mediated inflammatory disease of the skin affecting about 3% of the adult general population[1]. Although primarily a cutaneous disease, recent research implicates its association with systemic inflammation resulting in increased risk for atherosclerosis and subsequent cardiovascular disease (CVD)[2,3]. The detailed pathophysiological mechanisms which lead psoriasis patients to atherosclerosis remain unclear; however the common inflammatory milieu the two diseases share is of rising significance[3,4].

Hemostasis-maintaining platelets also have relevant functions in inflammation, with recent evidence showing that thrombosis and inflammation are in fact two intrinsically linked processes[5]. Pathomechanisms of psoriasis involve platelet activation, as reported by several investigators so far[6-9]. Increased platelet activation is also implicated in atherosclerotic plaque formation and plaque destabilization[10,11]. Activation of platelets is associated with their degranulation and the subsequent surface expression of antigens, such as CD62P (P-selectin) and CD63, the decreased surface expression of CD42b (GPIb alpha)[12], and the formation of platelet-leukocyte complexes[13]. In addition, the so-called platelet-derived microparticles (PMPs)[14] constitute a marker of platelet activation which, in recent years, has gained emerging importance. PMPs are membrane vesicles of a diameter of 0.1 to 1 μm generated from activated platelets in an exocytotic budding process. They display procoagulant and atherosclerotic properties, being reported to possess 50- to 100-fold higher specific procoagulant activity than activated platelets themselves[15]. PMPs are involved in inflammatory diseases[16], as well as in atherosclerosis and CVD[17,18]. Besides platelet activation, the chronic inflammatory burden of psoriatic patients may also be the trigger for the development of CVD, with interleukin (IL)-12 and IL-17 implicated in the pathogenesis of both diseases[19-21]. Interestingly, IL-17 has recently been shown to facilitate platelet aggregation[22].

Five studies so far have shown elevated PMPs in psoriasis patients[7,8,23-25], two of them methodologically limited in PMP detection by using ELISA-based assays[7,24]. PMPs were also shown, albeit not always[8,23,25], to correlate with the activity of psoriasis, as assessed by the Psoriasis Area Severity Index (PASI) score[7,24]. However,

a possible association of platelet activation with cytokines identified as key players in psoriasis has not yet been examined, to the best of our knowledge. Therefore, the purpose of this investigation was to evaluate platelet activation markers in patients with psoriasis without overt cardiovascular complications, compared to healthy controls, by means of flow cytometry, and to determine the relationship between marker levels and the pro-inflammatory cytokine profile of psoriasis, as this was assessed by IL-12 and IL-17 levels.

MATERIALS AND METHODS

Study population

This hospital-based cross-sectional study was carried out in 40 patients with psoriasis without coronary artery disease (CAD), and 12 participants selected as healthy controls with age, sex, atherosclerotic risk factors (hypertension, hyperlipidemia, current smoking) and use of anti-hypertensive or lipid-lowering medication, similar to those of the patients with psoriasis (Table 1). Eligible patients were given a diagnosis of plaque psoriasis for at least 6 mo. None of them had received relevant topical medications during the two weeks prior to the study and prior systemic therapy, if any, was interrupted for adequate wash-out period. Exclusion criteria for patients with psoriasis and healthy donors included disorders or drugs affecting platelet activity or likely to influence the outcome of the study, namely obstructive CAD (as defined by the absence of clinical history, angina, and reversible myocardial ischemia during a treadmill test and stress echocardiography), chronic inflammatory disease, psoriatic arthritis, familial hyperlipidemia, diabetes mellitus, moderate or severe valvular heart disease, primary cardiomyopathies, chronic renal failure, malignancies and the use of anti-platelet drugs and systemic steroids. All patients underwent exercise treadmill test and/or stress echocardiography as well as carotid and peripheral artery ultrasonography before blood sampling to exclude the presence of clinical significant CVD. Psoriasis patients were recruited from the inpatients' section and the outpatients' clinics of the Department of Dermatology and Venereology of our hospital, while controls were selected from visitors and hospital staff. Written informed consent was obtained from all participants before enrollment in the study. This study was conducted according to the Declaration of Helsinki principles, and was approved by the medical ethical committee of Athens University.

Blood collection

To avoid artificial platelet activation during collection of samples, blood was taken from the antecubital vein through a 21G needle following light application of a tourniquet; the first 2 mL of blood were discarded to avoid procedurally-induced platelet activation. Subsequently, 4 mL of blood were collected in plastic tubes without anticoagulant for assay of serum IL-12 and IL-17. Finally, 4.5 mL of whole blood were drawn into Vacutainer tubes containing 3.2% sodium citrate stock solution (1:9 volume) and mixed immediately, avoiding frothing during the procedure, for the estimation of platelet activation markers by means of flow cytometry within 45 min after blood collection. All patients and controls had ceased antihypertensive treatment and statins 48 h before blood sampling.

Table 1 Clinical characteristics of the study population

Variable	Psoriasis (n = 40)	Controls (n = 12)	P value
Age, yr	51 ± 12	49 ± 13	0.8
Sex (male) (%)	25 (63)	7 (58)	0.8
PASI score	11 ± 7	-	-
Risk factors (%)			
Hypertension	14 (35)	4 (33)	0.9
Hyperlipidemia	14 (35)	4 (33)	0.9
Current smoking	19 (48)	5 (42)	0.8
Medications (%)			
Anti-hypertensives	13 (33)	4 (33)	0.9
Statins	16 (40)	5 (42)	0.9

Flow cytometry

We examined platelet activation state using several markers because it is recognized that platelet activation is a complex process and measuring the classical degranulation markers alone may limit the ability to detect platelet activation under all circumstances.

Platelet surface markers: Platelet membrane glycoproteins (GPs) expression was measured from whole blood. Five microliter of blood diluted to 100 μL with PBS per tube were incubated with CD36-PE and FITC labeled monoclonal antibodies against platelet markers that may be expressed in the basal state (CD41, CD42b, CD61) and markers that may be expressed upon activation (CD62P, CD63) (Biolegend, United States) for 10 min at room temperature. One milliliter of PBS was added and samples were analyzed *via* flow cytometry. Gating was performed using a forward/side scatter (FSC/SSC) dot plot. Expression levels were measured for low FSC/SSC with CD36 positivity using the percentage of platelets with fluorescence over the cutoff set by running 4 samples from control patients (Figure 1A).

PMPs: The technique used for PMP quantification was adapted from a previously described method[26,27]. Plasma was separated from whole blood by centrifugation at 1500 *g* for 15 min. Recovered plasma was centrifuged for 2 min at 13000 *g*. Microparticles were labeled using FITC-conjugated Annexin V and PE-conjugated CD41 (Biolegend, United States). Fluorescent-conjugated isotype antibodies were used as controls and a suitable set of beads (Megamix, Biocytex, France) containing three types of beads with a defined size (0.5, 0.9 and 3 μm diameter) was used to identify microparticles *via* FSC/SSC and determine two PMP-size regions (0.5-0.9 μm and < 0.5 μm PMPs). Samples were diluted to 1 mL using binding buffer and analyzed

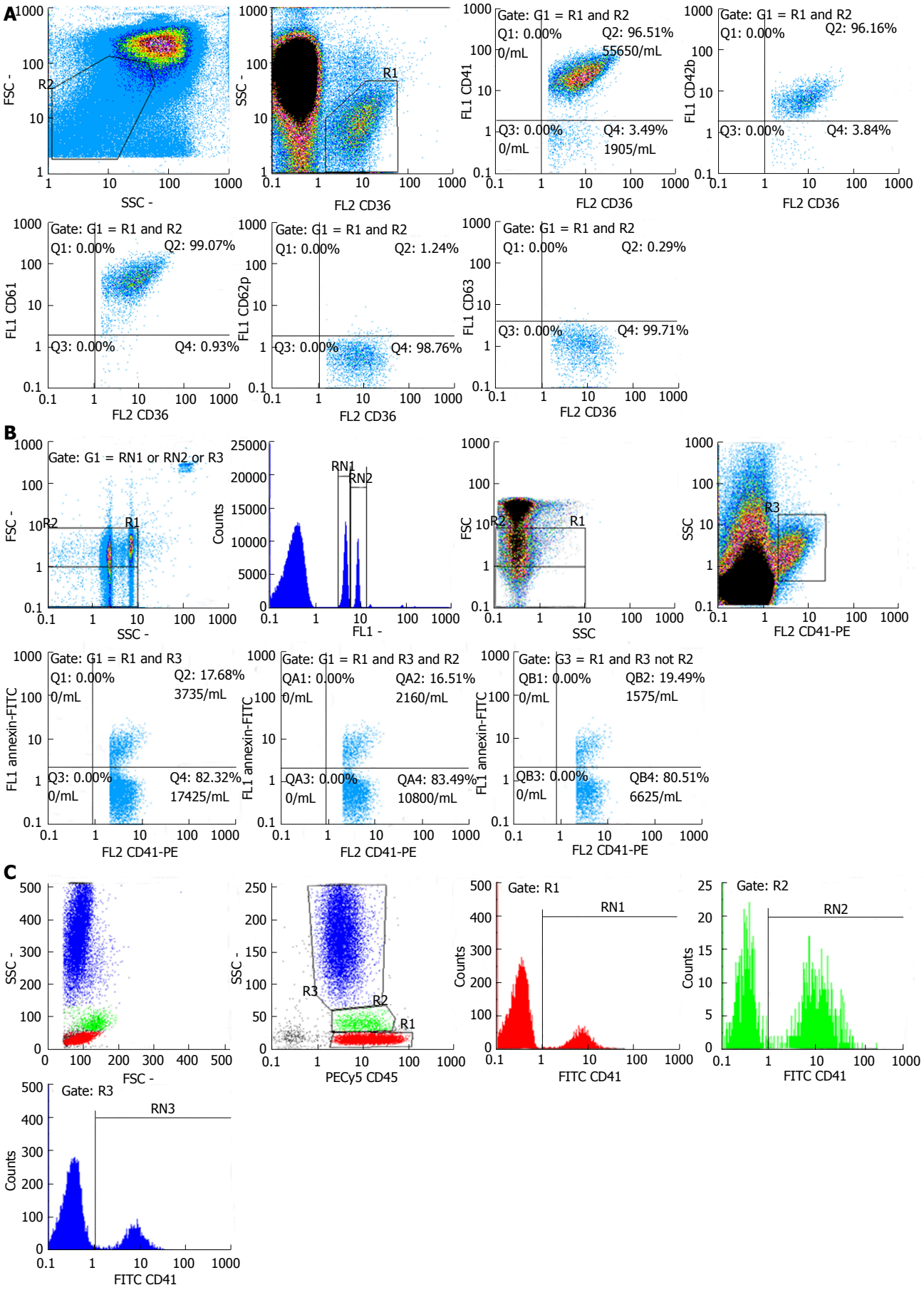

Figure 1 Flow cytometric analysis of platelet membrane glycoproteins, platelet-derived microparticles and platelet-leukocyte aggregates. A: Flow cytometric analysis of membrane-bound glycoproteins. Analysis of each GP was performed on particles of FSC/SSC of platelets (R2) expressing CD36 (R1); B: Beads for gating of microparticles of 0.5 μm (left population), 0.9 μm (right population) and 3 μm (upper right population). Same gating strategy was used to identify PMPs of 0-0.5 μm (R1 and R3 not R2), 0.5-0.9 μm (R1 and R2 and R3) or PMPs in general (R1 and R3); C: Platelet-leukocyte aggregates calculated for lymphocytes (red), monocytes (green) and granulocytes (blue).

using absolute counting, when available, on a Partec Cyflow (Partec, Munster, Germany) *via* volumetric count. PMPs were identified as dual-positive Annexin V-FITC/CD41-PE events in the microparticle region and count/μL was calculated *via* multiplying the count/mL of the cytometer with the dilution factor of 50 divided by 1000 (Figure 1B).

Platelet-leukocyte complexes: In order to analyze platelet-monocyte complexes (PMC), platelet-neutrophil complexes (PNC) and platelet-lymphocyte complexes (PLC), 100 μL of whole blood, 20 μL of FITC-conjugated anti-CD41 (or negative control antibody) and 20 μL of PECy5-conjugated anti-CD45 (Biolegend, United States) were added into each tube, gently mixed, and incubated in dark, at room temperature for 15 min. Erythrocyte lysis was performed using 2 mL of Quicklysis solution (Cytogons, Spain). Samples were analyzed on a Partec Cyflow Space (Partec, Munster, Germany) within 30 min. Leukocyte populations were gated on a SSC/CD45-PECy5 dot plot and aggregates for each population were calculated as the percentage of monocytes, neutrophils and lymphocytes which were CD41-positive (Figure 1C).

Soluble IL-12 and IL-17

IL-12 was measured in serum using a commercially available kit (Human IL-12 p70 Quantikine HS ELISA Kit; R and D Systems, Minneapolis, United States). This assay detects values as low as 0.5 pg/mL. IL-17 serum levels were also measured by high-sensitivity immunoassay (Human IL-17A High Sensitivity ELISA; eBioscience, Vienna, Austria). The lower limit of detection of the assay was 0.01 pg/mL.

Statistical analysis

The independent-samples *t* test was performed to determine the significance level for differences between patient and control groups. Data were expressed as mean ± standard error of mean (SEM). Correlation testing (using Spearman rank correlation coefficient) was performed to assess the strength of relationships between multiple variables. A probability value of < 0.05 was taken to be statistically significant. Statistical Package for Social Sciences version 22.0 (IBM, Chicago, IL) was used for the analysis.

RESULTS

Baseline characteristics of the study population

We did not observe any significant difference in baseline characteristics between the two groups (Table 1).

Markers of platelet activation

Activation-dependent surface change: No significant difference was observed in CD62P, CD63 or CD42b expression between the two study groups. Mean ± SEM for the fraction of platelets expressing CD62P and CD63 in psoriasis patients and controls were 7 ± 2 *vs* 6 ± 3; $P = 0.748$ and 5 ± 2 *vs* 3 ± 2; $P = 0.791$, respectively. Mean ± SEM for the fractions of platelets with reduced expression of CD42b was 8 ± 2 *vs* 10 ± 7; $P = 0.397$ for psoriasis patients and controls, respectively (Table 2).

PMPs: PMP concentrations were markedly higher in psoriasis patients compared to controls (mean ± SEM: 22 ± 5/μL *vs* 11 ± 6/μL; $P = 0.018$). When considering PMP size, both smaller-size (mean ± SEM: 10 ± 2/μL *vs* 4 ± 2/μL; $P = 0.033$) and larger-size (12 ± 3/μL *vs* 6 ± 4/μL; $P = 0.014$) PMPs were higher in patients compared to healthy subjects (Table 2).

Platelet-leukocyte complexes: There was no significant difference in the percentage of circulating neutrophils or monocytes in whole blood which formed complexes with platelets between the two groups (mean ± SEM for PMC and PNC in psoriasis patients and controls respectively were 38% ± 4% and 27% ± 3% *vs* 33% ± 6% and 29% ± 5%; $P = 0.723$ and $P = 0.775$, respectively). However, significantly lower circulating PLC were observed in psoriasis patients (mean ± SEM: 16% ± 3% *vs* 23% ± 6%; $P = 0.047$) (Table 2).

Relationship between platelet activation marker levels and the inflammatory burden of psoriasis

A significant correlation was established between larger-size PMPs and IL-12 levels ($r = 0.55$; $P < 0.001$) and between smaller-size PMPs and levels of both IL-12 and IL-17 ($r = 0.58$ and $r = 0.49$ respectively; $P < 0.001$). Total PMPs also correlated with IL-12 levels ($r = 0.56$; $P < 0.001$). CD63 expression correlated well with levels of both IL-12 and IL-17 ($r = 0.46$; $P = 0.011$ and $r = 0.43$; $P = 0.015$, respectively). Increased PASI score was associated with increased levels of larger-size PMPs ($r = 0.45$; $P = 0.011$) and increased CD63 expression ($r = 0.47$; $P < 0.01$). Circulating PLC were found to be negatively correlated with PMPs ($r = -0.44$; $P = 0.002$), both with smaller-size ($r = -0.28$; $P = 0.048$) and larger-size ($r = -0.4$; $P = 0.005$) PMPs.

DISCUSSION

The exact mechanism of predisposition to CVD in psoriasis *per se* has not been fully elucidated so far. However, several lines of evidence highlight the potent role inflammation plays. Indeed, psoriasis patients, in addition to chronic skin inflammation, display a higher prevalence of CVD risk factors and metabolic syndrome components[28] which lead to systemic inflammation, and therefore atherosclerosis, CVD and myocardial infarction[2,3]. Platelets have an important role in increasing inflammation, and pathogenetic mechanisms of both psoriasis and atherosclerosis may involve platelet activation[6-11,23-25]. The present study demonstrated that circulating platelets are in a state of activation in patients with psoriasis without clinically evident CVD compared to healthy subjects, as shown by a significant increase in circulating PMPs. It reinforces previous findings of

Table 2 Markers of platelet activation and inflammatory markers in the study population

Marker	Psoriasis (n = 40)	Controls (n = 12)	P value
CD42b negative platelets (%)	8 ± 2	10 ± 7	0.397
CD62P positive platelets (%)	7 ± 2	6 ± 3	0.748
CD63 positive platelets (%)	5 ± 2	3 ± 2	0.791
Total AV+/CD41+ PMPs[1]	22 ± 5	11 ± 6	0.018[3]
< 0.5 μm AV+/CD41+ PMPs[1]	10 ± 2	4 ± 2	0.033[3]
0.5-0.9 μm AV+/CD41+ PMPs[1]	12 ± 3	6 ± 4	0.014[3]
Platelet-lymphocyte complexes (%)	16 ± 3	23 ± 6	0.047[3]
Platelet-monocyte complexes (%)	38 ± 4	33 ± 6	0.723
Platelet-neutrophil complexes (%)	27 ± 3	29 ± 5	0.775
IL-12[2]	19 ± 0.5	2 ± 0.3	< 0.001[3]
IL-17[2]	3 ± 0.4	0 ± 0.1	< 0.001[3]

Results are expressed as the mean number ± standard error of mean. [1]Results are expressed in microparticles per plasma microlitre; [2]Results are expressed in pg/mL; [3]Values are statistically significant. AV: Annexin V; PMPs: Platelet-derived microparticles; IL: Interleukin.

elevated circulating PMP levels in psoriasis patients[7,8,23-25] and adds to those findings by demonstrating for the first time, to the best of our knowledge, a positive relationship between PMP concentrations and high inflammatory psoriasis burden, as this was assessed by IL-12 and IL-17 levels, suggesting a close association between PMPs and psoriasis activity. It is also the first study to report a higher level of larger-size PMPs, in addition to small-size ones, in psoriasis patients. It is now accepted that PMPs are separated into four size classes with different active components and different functional effects on platelets and endothelial cells[29], and therefore, elucidation of the size class(es) involved in psoriasis can help clarify PMP involvement in the disease and the mechanisms implicated in exertion of their effects. Pelletier *et al*[8] had previously showed that only small-size PMPs are increased in psoriasis. The discrepancy with our results may be related to the different working definition of blood-derived PMPs in the two studies, based on the prerequisite or not of Annexin V (a phospholipid-binding protein that binds to exposed phosphatidylserine on the surface of activated platelets) binding. Annexin V positive PMPs are documented to elicit pro-coagulant activity, in contrast to little or no such activity possessed by Annexin V negative PMPs[30].

PMPs are involved in CAD by binding to the endothelium, submatrix of the vascular wall and leukocytes, thereby facilitating thrombus propagation[17,18,31]. They are also known to cause endothelial dysfunction[32]. In the setting of psoriasis *per se*, PMPs may well contribute to leukocyte recruitment in psoriatic skin lesions, given their known ability to increase leukocyte adhesion to the endothelium and to promote leukocyte activation by modulating leukocyte-leukocyte and leukocyte-endothelial cell interactions[5]. Taken together, elevated levels of PMPs observed in psoriasis patients may be the contributory factor to development of atherosclerosis and the increased cardiovascular risk in those patients by triggering a cascade of events.

In the present study, PMPs proved to be the most "sensitive" index of platelet activation, whereas the classical platelet activation markers CD62P, CD63 and CD42b were not altered. To our knowledge, CD63 or CD42b expression in psoriasis had not been investigated so far. In contrast to our CD62P results, three previous studies have shown enhanced CD62P surface expression in psoriasis[6,9,33]. One other study was in concordance with our findings[34]. Although P-selectin has been considered by many the "gold standard" marker of platelet activation, it was shown that degranulated, P-selectin-positive platelets rapidly lose surface P-selectin to the plasma pool *in vivo*[35,36]. Therefore, platelets may circulate in an increased state of activation but express normal levels of CD62P. In fact, it has been proposed that CD62P is a more reliable tool for monitoring platelet function at acute but not chronic stimulus of platelets[37]. The majority of our patients did not have a flare of their disease at the time of our study. Regarding platelet-leukocyte complexes as a marker of platelet activation, there is only one previous study measuring PMC and PNC in psoriasis[34], also not managing to highlight a significant increase. There is no report in the literature concerning PLC in psoriasis, to the best of our knowledge. In the setting of CVD, it has been suggested that the formation of PMC is related to the development of atherosclerotic complications being a sensitive marker of platelet activation[38]. Contrary to our expectations for increased PLC in psoriasis pointing to platelet activation, lower PLC were measured in the bloodstream of our psoriasis patients compared to healthy controls. Our finding could be attributed to the adhesion of PLC in the inflamed skin microvasculature, on asymptomatic atherosclerotic lesions or both. Therefore, decreased blood concentration could merely reflect increased sequestration of the generated platelet-lymphocyte aggregates on the vessel wall. With regard to this, it has already been shown *in vivo* that increased leukocyte rolling in murine skin and subsequent extravasation is due to the aggregate formation of platelets with mononuclear leukocytes[6]. Interestingly, a negative correlation was established in our study between PMP levels and circulating PLC.

Chronic inflammatory skin diseases and atherosclerosis share common pathogenic features in which pro-inflammatory cytokines play an important role[3,4,39]. In the inflammatory microenvironment present in psoriasis, IL-12 and IL-17 are of crucial importance[19]. This is underlined by the fact that the biologic agents ustekinumab and secukinumab are targeted against IL-12 and IL-17, respectively. IL-12 leads to the differentiation of type 1 T helper (Th1) lymphocytes, whereas IL-17A and IL-17F, secreted by type 17 T helper (Th17) cells, activate keratinocytes and induce the production of antimicrobial peptides. Notably, recent interest has focused particularly on IL-17-producing Th17 cells[40]. This cell type is specialized in immunosurveillance of epithelium, and it also secretes

IL-22, a key cytokine linking adaptive immune effectors and epithelial dysregulation in psoriasis. Amelioration of epidermal hyperplasia during successful anti-TNF treatment is associated with reduced Th17 responses. Based on the current knowledge, it appears that Th17 cells are responsible for many of the inflammatory and autoimmune responses once attributed to Th1 lymphocytes. Apart from their implication in psoriasis pathogenesis, IL-12 and IL-17 are also involved in the development of atherosclerosis[20,21,41]. In this viewpoint, IL-12 and IL-17 release into the circulation by cell populations in inflamed psoriatic skin could exert harmful atherosclerotic effects. Taken the aforementioned data into consideration, the association of platelet activation markers, namely PMPs and CD63, with the levels of pro-inflammatory cytokines IL-12 and IL-17, demonstrated in our study, comes as no surprise. Interestingly, it has been recently shown that IL-17A can promote platelet function in patients with acute coronary syndrome *via* activating platelets ERK2 signaling pathway and may provide a novel target for antiplatelet therapies in CAD[22]. On the basis of the ability of IL-17A to promote platelet function, the view that inflammation and platelet activation perpetuate each other and cascade to the development of atherosclerosis is reinforced.

Features of psoriasis pathogenesis, including chronic inflammation and the proven platelet activation, may contribute to atherosclerotic risk in psoriasis. Our study has shown increased levels of PMPs, a marker of platelet activation, in psoriasis patients without overt CVD compared to healthy controls. This difference has been demonstrated for the first time in both smaller-size and larger-size PMPs. As PMPs express procoagulant phospatidylserine activities, facilitate thrombus propagation and provoke endothelial cell damage, elevated PMP levels could provide one of the missing links leading to increased cardiovascular risk in psoriasis. Furthermore, PMPs were higher in those patients with high inflammatory disease burden, as this was assessed by IL-12 and IL-17 levels, as well as in those patients with high PASI score, suggesting a close association between PMPs and psoriasis activity. Given the ability of IL-17A to promote platelet function, this finding is in favor of the view that inflammation and platelet activation may perpetuate each other and cascade to the development of atherosclerosis. Finally, we identified the presence of lower PLC in the bloodstream of psoriasis patients which could be attributed to their adhesion in the inflamed skin microvasculature, on asymptomatic atherosclerotic lesions or both. PLC levels negatively correlated with PMP levels. The clinical relevance of our findings, however, remains still disputed. While there is ample *in vitro* evidence of the potential downstream biological effects of microparticles (*e.g.*, promotion of coagulation, regulation of inflammation, vascular damage)[42], many of which are known to be important in atherogenesis, *in vivo* data in patients with psoriasis are lacking. In this setting, PMP generation could merely represent an epiphenomenon related to the inflammation of psoriasis with little *in vivo* biological activity. Future studies are needed to address whether PMPs are simply biomarkers of inflammatory disease or have a role in psoriasis pathophysiology leading to accelerated atherosclerosis.

The small number of controls and the absence of age/sex matching between patients and controls should be acknowledged as study limitations.

In conclusion, PMPs, known to be predictive of cardiovascular outcomes, are increased in psoriasis patients, and associated with high inflammatory disease burden. Enhanced platelet activation may be the missing link leading to cardiovascular events in psoriatic patients.

COMMENTS

Background

Psoriasis is a common immune-mediated inflammatory disease of the skin. Although primarily a cutaneous disease, recent research implicates its association with systemic inflammation resulting in increased risk for atherosclerosis and subsequent cardiovascular disease (CVD). Platelets have an important role in inflammation. Pathogenic mechanisms of both psoriasis and atherosclerosis seem to involve platelet activation.

Research frontiers

Enhanced platelet activation in psoriasis patients has already been established, but a potential association between platelet activation markers and the inflammatory burden of psoriasis has not yet been examined.

Innovations and breakthroughs

The present study demonstrated increased platelet activation in patients with psoriasis without clinically evident CVD compared to healthy controls, as shown by a significant increase in circulating platelet-derived microparticles (PMPs), a platelet activation marker which is known to be predictive of cardiovascular outcomes. It reinforces previous findings of elevated circulating PMP levels in psoriasis patients and adds to those findings by demonstrating for the first time, to the best of our knowledge, a positive relationship between PMP concentrations and levels of cytokines identified as key players in psoriasis, namely interleukin (IL)-12 and IL-17, suggesting a close association between PMPs and high inflammatory disease burden. Given the ability of IL-17A to promote platelet function, this finding is in favor of the view that inflammation and platelet activation may perpetuate each other culminating in the development of atherosclerosis. Furthermore, this is the first study, to the best of our knowledge, to report a higher level of larger-size PMPs, additionally to small-size ones, in psoriasis patients. It is now accepted that PMPs are separated into four size classes with different active components and different functional effects on platelets and endothelial cells, and therefore, elucidation of the size class(es) involved in psoriasis can help clarify PMP involvement in the disease and the mechanisms implicated in exertion of their effects. Taken together, the study concludes that the association between psoriasis and atherosclerosis may be related to excessive PMP formation.

Applications

Enhanced platelet activation may be the missing link leading to cardiovascular events in psoriatic patients. Future studies are needed to address the *in vivo* biological activity of PMPs contributing to CVD in patients with psoriasis, as well as the potential role of anti-platelet medications in psoriasis in the context of reducing both psoriasis activity and atherosclerotic risk.

Terminology

PMPs constitute a marker of platelet activation which, in tecent years, has gained emerging importance. PMPs are membrane vesicles of a diameter of 0.1 to 1 μm generated from activated platelets in an exocytotic budding process.

They display procoagulant and atherosclerotic properties, being reported to possess 50- to 100-fold higher specific procoagulant activity than activated platelets themselves.

Peer-review

Interesting and very relevant study regarding the level of markers of platelet activation in psoriasis.

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ORIGINAL ARTICLE

Prospective Study

Outcomes and long-term survival of coronary artery surgery: The controversial role of opium as risk marker

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Abstract

AIM

To study survival in isolated coronary artery bypass graft (CABG) patients and to evaluate the impact of preoperative chronic opium consumption on long-term outcome.

METHODS

Cohort of 566 isolated CABG patients as Tehran Heart Center cardiac output measurement was conducted. Daily evaluation until discharge as well as 4- and 12-mo and 6.5-year follow-up information for survival status were fulfilled for all patients. Long-term 6.5-year overall and opium-stratified survival, adjusted survival curves based on opium consumption as well as possible predictors of all-cause mortality using multiple cox regression were determined by statistical analysis.

RESULTS

Six point five-year overall survival was 91.8%; 86.6% in opium consumers and 92.7% in non-opium consumers (P = 0.035). Patients with positive history of opium consumption significantly tended to have lower ejection fraction (EF), higher creatinine level and higher prevalence of myocardial infarction. Multiple predictors of all-cause mortality included age, body mass index, EF, diabetes mellitus and cerebrovascular accident. The hazard ratio (HR) of 2.09 for the risk of mortality in opium addicted patients with a borderline P value (P = 0.052) was calculated in this model. Further adjustment with stratification based on smoking and opium addiction reduced the HR to 1.20 (P = 0.355).

CONCLUSION

Simultaneous impact of smoking as a confounding variable in most of the patients prevents from definitive judgment on the role of opium as an independent contributing factor in worse long-term survival of CABG patients in addition to advanced age, low EF, diabetes mellitus and cerebrovascular accident. Meanwhile, our findings do not confirm any cardio protective role for opium to improve outcome in coronary patients with the history of smoking. Further studies are needed to clarify pure effect of opium and warrant the aforementioned findings.

Key words: Coronary artery bypass; Outcomes; Survival analysis; Opium; Hazards models

Core tip: A significant percentage of coronary artery disease patients undergo cardiac surgery so defining outcome predictors is essential for risk calculation and is necessary for estimation of resource utilization and provision of services. Employing global knowledge on this issue is not justified without adjustment for regional specifications and needs. This study aimed at clarifying the role of opium addiction in predicting long-term mortality of coronary artery bypass graft surgery in addition to advanced age, low ejection fraction, diabetes mellitus and cerebrovascular accident.

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INTRODUCTION

Growing number of patients undergoing coronary artery bypass graft (CABG) surgery all over the world[1], justifies studying on possible predicting factors of clinical outcomes such as short and long-term survival. There are published reports of some predictive factors responsible for short-term mortality such as advanced age, previous history of cardiac surgery and myocardial infarction, non-cardiac comorbidities, New York Heart Association functional class (FC) III or IV and serum creatinine (Cr) level[2,3]. Also some additional factors have been suggested for intermediate-term mortality including left ventricular ejection fraction (EF) and history of percutaneous coronary stenting[2,4]. Similarly, long-term survival could be influenced by diabetes mellitus[5], hypoalbuminemia[6], female gender, smoking, cardiogenic shock[7] and severe preoperative renal dysfunction[3,8].

Coronary artery disease (CAD) has a high prevalence in Iranian population, affecting 22.2% of men and 37.5% of women[9]. In addition, opium is the major abused substance in Iran[10] and the prevalence of opium addiction is believed to be higher in CAD patients undergoing revascularization[11]. The predictive role of opium in short-term outcomes of patients undergoing CABG is controversial. Some investigations have suggested cardiac protective role for opium during ischemic events[12,13]. In a propensity-matched study, Sadeghian *et al*[14] found no association between opium dependence and post CABG in-hospital complications. On the other hand, in Safaii *et al*[15]'s study, six months post-CABG readmission was significantly more frequent in opium users. However, there are few evidences to clarify the definite relationship between chronic opium abuse and long-term survival in cardiac surgery patients.

So not only there is limited knowledge regarding the adverse impact of opium consumption on long-term survival of CABG patients, but also the available studies on short-term outcomes have shown controversial results. Therefore in this study we aimed to assess the impact of chronic opium consumption on long-term survival of patients who underwent isolated CABG in a cardiac tertiary center.

MATERIALS AND METHODS

Patients and methods

In the present cohort study (Tehran Heart Center Cardiac Output Measurement)[16], 566 consecutive CAD patients who underwent isolated CABG during six months (April 2006-September 2006) at THC, a high-volume specialized heart tertiary care center, were identified and after signing the informed consent were entered the study. Exclusion criteria were concomitant replacement or repair of heart valve, ventricular aneurism resection or any surgeries other than CABG.

Data collection

Patients' demographic characteristics including age, gender, weight, waist circumference, body mass index (BMI) as well as their initial laboratory measurements were recorded in previously defined data sheets and were completed from THC surgery database[17] in case of

missing information. Family and drug history, associated comorbidities, habitual habits, FC and left ventricular EF were also among documented variables. Regular daily consumption of opium along with fulfilling DSM-IV-TR criteria for opium dependence was considered for opium addiction[11,18].

EuroSCORE was also calculated for all study population and were categorized as low risk (0-2), medium risk (3-5), high risk (6-8) and very high risk (≥ 9) based on what has been previously reported in literature[19,20].

Follow-up

CABG Patients were followed at 4 and 12 mo following the operation through the organized regular visits at CABG follow-up clinic or by telephone interviews. Meanwhile, any outpatient or inpatient services thereafter are recorded precisely in patients' electronic medical file at our institution by the initial unique code. But for the specific purpose of our study in evaluation of long-term survival, we contacted patients by telephone to attend at hospital to be followed 7 years after the cardiac surgery. The precise date of patients' attendance was recorded.

In these long-term follow-up sessions, all patients were investigated for survival status. FC and EF along with further laboratory assessments were also assessed. For non-responders, mortality tracking as well as the exact time and to somehow the etiology of death was noted through telephone interviews with patients' relatives or by checking up the online registration of deaths. For surviving non-responders, the last attendance at THC for receiving any services was considered as the last time of follow-up. The latter group was defined as incomplete follow-up.

Statistical analysis

Continuous variables were presented as mean and standard deviation (SD) or median with 25^{th} and 75^{th} percentiles, and were compared between two groups of opium usage using independent samples *t* or Mann-Whitney *U* test. Categorical variables were expressed as frequency and percentage and were compared between aforementioned groups applying χ^2 or Fisher's exact test. Survival probabilities were estimated using Kaplan-Meier method and their 95%CI were calculated through log-transformed method. The univariate effect of variables on long-term mortality was evaluated using Cox proportional hazards (PH) regression. All variables with *P* values less than 0.2 in the univariate analysis were candidate to enter the multivariable model. A backward stepwise Cox PH model, with removal and entry probabilities as 0.1 and 0.05 respectively, was applied to find the multiple predictors of long-term mortality. The PH assumption was checked through the χ^2 test of the correlation coefficient between transformed survival time and scaled Schoenfeld residuals. Those variables which simultaneously associated with opium usage and long-term mortality with *P* values less than 0.2 were detected as potential confounders. The effect of opium on long-term mortality adjusted for potential confounders was assessed using Cox PH model. All effects on long-term mortality were reported through hazards ratio (HR) with 95%CI. Softwares IBM SPSS statistics for windows version 22 (Armonk, NY: IBM Corp.) and STATA (StataCorp. 2013. Stata Statistical Software: Release 13. College Station, TX: StataCorp LP.) were used to conduct the analyses.

RESULTS

Based on findings, among 566 patients, 53 (9.4%) deaths occurred during the 6.5 years of follow-up among which 40.9% was cardiac and 59.1% was of non-cardiac cause. Median follow-up time for all of the study population was 78.7 mo (95%CI: 78.5-78.9). Median (25^{th}-75^{th} interquartile range) follow-up time of 235 patients with incomplete follow-up was 74.6 (25^{th}-75^{th}: 73.5-75.7) mo.

Patients' demographics characteristics and risk factors: Table 1 demonstrates patients' baseline demographic and clinical characteristics by survival status. According to univariate analysis, age, blood urea nitrogen and high-density lipoprotein levels were significantly lower and EF, albumin and triglyceride levels were significantly higher among survivors. Moreover, opium consumption, diabetes mellitus, cerebrovascular accident and peripheral vascular disease were significantly more frequent among the expired cases.

The frequency of moderate, high and very high risk EuroSCORE was significantly higher in non-survivors as compared to survivors. However, the number of diseased vessels and performed bypass grafts was similar between the both groups.

Table 2 shows patients' baseline demographic and clinical characteristics generally and based on opium consumption. Mean ± SD age of patients was 59.08 ± 8.9 years and 75.1% were men. History of opium consumption was present in 14.5%. Forty-one percent had diabetes mellitus and 3.9% had history of cerebrovascular accident. Body mass index and EF mean ± SD was 27.3 ± 4.08 kg/m^2 and 48.5% ± 10.3%, respectively. Functional class Ⅲ was documented in 14.7% of patients. Opium users were significantly more often men, younger, smoker and also alcohol consumer.

Patients with positive history of opium consumption also significantly tended to have lower EF (44.9 ± 9.4 *vs* 49.1 ± 10.3), higher Cr (1.3 ± 0.3 *vs* 1.2 ± 0.2) and higher prevalence of MI (71.6% *vs* 47.5%). On the other hand, the level of BMI and fasting blood sugar and prevalence of hyperlipidemia (HLP), hypertension were significantly lower in these patients.

Opium-stratified survival

Based on follow-up information, 6.5 years (78.7 mo) overall survival was 91.8% (95%CI: 89.5%-94.2%). When analyzed based on habitual history of opium consumption, 6.5-year (78.7 mo) overall survival was

Table 1 Basic demographic and clinical characteristics of patients, univariate analysis for overall survival using Cox regression

	Alive (n = 513)	Dead (n = 53)	Hazard ratio (95%CI)	P value
Age (yr)	58.5 ± 8.81	64.6 ± 8.27	1.08 (1.044-1.117)	< 0.001
Gender (male)	382 (74.5)	43 (81.1)	1.425 (0.716-2.837)	0.313
BMI (kg/m^2)	27.4 ± 4.04	26.5 ± 4.39	0.947 (0.881-1.019)	0.146
Waist circumference (cm)	101.3 ± 1.46	100.2 ± 2.95	0.962 (0.85-1.09)	0.543
FC				0.141
I	177 (34.6)	21 (39.6)		
II	263 (51.5)	20 (37.7)	0.701 (0.379-1.295)	0.256
III	71 (13.9)	12 (22.6)	1.433 (0.702-2.924)	0.323
EF (%)	49.1 ± 10.07	42.2 ± 11.07	0.94 (0.915-0.965)	< 0.001
FH	251 (49.1)	18 (34)	0.5 (0.282-0.887)	0.018
Smoking	183 (35.8)	20 (37.7)	0.954 (0.542-1.678)	0.870
Alcohol	66 (13.7)	5 (9.8)	0.523 (0.201-1.363)	0.185
Opium	69 (13.5)	13 (24.5)	1.939 (1.032-3.644)	0.040
DM	204 (39.9)	28 (52.8)	1.789 (1.033-3.097)	0.038
HLP	366 (71.6)	32 (60.4)	0.58 (0.334-1.008)	0.053
HTN	253 (49.5)	26 (49.1)	1.033 (0.602-1.774)	0.906
CVA	16 (3.1)	6 (11.3)	4.146 (1.761-9.76)	0.001
PVD	136 (26.6)	22 (41.5)	2.166 (1.246-3.766)	0.006
MI	254 (49.9)	32 (61.5)	1.61 (0.92-2.816)	0.095
Alb (g/dL)	4.6 ± 0.32	4.5 ± 0.39	0.351 (0.16-0.77)	0.009
FBS	96 (87-117)	98 (84-124)	1.004 (0.997-1.011)	0.266
BUN	38 (31-46)	40 (33-52)	1.035 (1.016-1.054)	< 0.001
Cr	1.2 ± 0.27	1.3 ± 0.26	2.009 (0.832-4.856)	0.121
Mg	1.9 ± 0.34	1.9 ± 0.39	1.15 (0.421-3.143)	0.785
HCT	42.3 ± 5.92	42.8 ± 3.82	1.013 (0.979-1.047)	0.462
TG	165 (115-210)	126 (97-173)	0.994 (0.990-0.999)	0.010
Chol	160 ± 44.86	166.3 ± 48.06	1.003 (0.997-1.008)	0.347
LP	23 (12-45)	28 (15-54)	1.006 (0.997-1.016)	0.191
CRP	5.75 (4.9-7)	6.35 (4.82-8.57)	1.001 (0.99-1.013)	0.814
LDL	82 (59-105)	86 (68-114)	1.003 (0.997-1.009)	0.280
HDL	40.3 ± 8.5	42.8 ± 9.37	1.031 (1-1.062)	0.049
No. of diseased vessel				0.473
1	19 (3.7)	2 (3.8)		
2	99 (19.4)	7 (13.2)	0.616 (0.127-2.976)	0.547
3	393 (76.9)	44 (83)	1.013 (0.245-4.191)	0.985
No. of grafts	3.7 ± 0.94	3.9 ± 1.02	1.234 (0.922-1.650)	0.158
Euro score				0.017
Low (0-2)	301 (58.9)	20 (37.7)		
Moderate (3-5)	171 (33.5)	25 (47.2)	2.089 (1.160-3.762)	0.014
High (6-8)	32 (6.3)	6 (11.3)	2.851 (1.143-7.110)	0.025
Very high (≥ 9)	7 (1.4)	2 (3.8)	4.479 (1.044-19.220)	0.044

Data are shown as mean ± SD, median (25th-75th percentiles) or number (%). BMI: Body mass index; FC: Functional class; EF: Ejection fraction; FH: Family history; DM: Diabetes mellitus; HLP: Hyperlipidemia; HTN: Hypertension; CVA: Cerebrovascular accident; PVD: Peripheral vascular disease; MI: Myocardial infarction; Alb: Albumin; FBS: Fasting blood sugar; BUN: Blood urea nitrogen; Cr: Creatinine; Mg: Magnesium; HCT: Hematocrit; TG: Triglyceride; Chol: Cholestrol; LP: Lipoprotein; CRP: C-reactive protein; LDL: Low density lipoprotein; HDL: High density lipoprotein.

found to be 86.6% (95%CI: 79.1%-94.7%) in opium users and 92.7% (95%CI: 90.3%-95.1%) in non-opium users.

After adjustments for confounding variables such as age, BMI, EF, diabetes, alcohol, HLP, MI, Cr, BUN and EuroSCORE, we found an evidence of predicting mortality for opium with a borderline P value (HR = 2.16; 95%CI: 0.96-4.84; P = 0.06) (Figure 1). As appears from curves, opium users have a trend to worse long-term survival as compared to non-opium consumers.

Multiple predictors of all-cause mortality

Multiple Cox regression for predictors of all-cause mortality is described in Table 3. As demonstrated, age, BMI, EF, diabetes mellitus and cerebrovascular accident remained the significant independent predictors of all-cause mortality. We found a trend of increasing risk of all-cause mortality by increasing age and functional class. A converse trend for all-cause mortality was noted by increasing BMI and EF. As shown, cerebrovascular accident had the greatest HR for mortality (HR = 3.45; 95%CI: 1.3-9.1, P = 0.013).

Smoking rate was not significantly different between survivors and non-survivors (Table 1). However, due to high coincidence of smoking and opium addiction (Table 2) we adjusted the results by adding the history of smoking to the list of predictors of long-term mortality which reduced the HR of opium for mortality from 2.09

Table 2 Baseline characteristics of patients base on opium consumption

	All patients (*n* = 566)	Opium + (*n* = 82)	Opium - (*n* = 484)	*P* value
Age (yr)	59.08 ± 8.9	55.9 ± 8.3	59.6 ± 8.9	< 0.001
Gender (male)	425 (75.1)	80 (97.6)	345 (71.3)	< 0.001
BMI (kg/m^2)	27.3 ± 4.08	25.7 ± 3.6	27.6 ± 4.08	< 0.001
Waist circumference (cm)	101.3 ± 11.3	100.3 ± 9.3	101.5 ± 11.6	0.514
FC				0.531
I	198 (35)	33 (40.2)	165 (34.2)	
II	283 (50)	39 (47.6)	244 (50.6)	
III	83 (14.7)	10 (12.2)	73 (15.1)	
EF (%)	48.5 ± 10.3	44.9 ± 9.4	49.1 ± 10.3	0.001
FH	269 (47.5)	44 (53.7)	225 (46.7)	0.242
Smoking	203 (35.9)	67 (81.7)	136 (28.2)	< 0.001
Alcohol	71 (12.5)	29 (37.7)	42 (9.2)	< 0.001
DM	232 (41)	26 (31.7)	206 (42.7)	0.061
HLP	398 (70.3)	48 (58.5)	350 (72.6)	0.010
HTN	279 (49.3)	30 (36.6)	249 (51.7)	0.012
CVA	22 (3.9)	4 (4.9)	18 (3.7)	0.545
PVD	158 (27.9)	21 (25.6)	137 (28.4)	0.600
MI	286 (50.5)	58 (71.6)	228 (47.5)	< 0.001
Alb (g/dL)	4.6 ± 0.3	4.5 ± 0.3	4.6 ± 0.3	0.200
FBS	96 (87-118)	92 (81-106)	97 (88-119)	0.011
BUN	38 (31-46)	35 (27-42)	39 (32-47)	0.004
Cr	1.2 ± 0.2	1.3 ± 0.3	1.2 ± 0.2	0.024
Mg	1.9 ± 0.3	1.8 ± 0.3	1.9 ± 0.3	0.314
HCT	42.3 ± 5.7	42.2 ± 3.6	42.4 ± 6.04	0.848
TG	159 (113-205)	150 (107-194)	162 (113-208)	0.353
Chol	157 (129-186)	156 (124-177)	157 (129-188)	0.167
LP	23 (12-46)	24 (9-44)	23 (13-47)	0.432
CRP	5.8 (4.9-7.2)	5.8 (4.8-7.1)	5.8 (4.9-7.2)	0.617
LDL	83 (60-106)	85 (60.7-100.5)	82.5 (60-110)	0.517
HDL	40.5 ± 8.6	39.4 ± 8.5	40.7 ± 8.6	0.205
No. of diseased vessel				0.733
1	21 (307)	2 (2.4)	19 (3.9)	
2	106 (18.7)	17 (20.7)	89 (18.5)	
3	437 (77.2)	63 (76.8)	374 (77.6)	
No. of grafts	4 (3-4)	4 (3-5)	4 (3-4)	0.400
Euro score				0.199
Low (0-2)	321 (56.7)	45 (54.9)	276 (57.3)	
Moderate (3-5)	196 (34.6)	26 (31.7)	170 (35.5)	
High (6-8)	38 (6.7)	10 (12.2)	28 (5.8)	
Very high (≥ 9)	9 (1.6)	1 (1.2)	8 (1.7)	

Data are shown as mean ± SD, median (25th-75th percentiles) or number (%). BMI: Body mass index; FC: Functional class; EF: Ejection fraction; FH: Family history; DM: Diabetes mellitus; HLP: Hyperlipidemia; HTN: Hypertension; CVA: Cerebrovascular accident; PVD: Peripheral vascular disease; MI: Myocardial infarction; Alb: Albumin; FBS: Fasting blood sugar; BUN: Blood urea nitrogen; Cr: Creatinine; Mg: Magnesium; HCT: Hematocrit; TG: Triglyceride; Chol: Cholesterol; LP: Lipoprotein; CRP: C-reactive protein; LDL: Low density lipoprotein; HDL: High density lipoprotein.

to 1.20 (95%CI: 0.819-1.745, *P* = 0.355) (Table 3).

Table 3 Multivariable model for all-cause mortality using Cox regression

	Hazard ratio (95%CI)	*P* value
Age (per 10 yr increase)	2.46 (1.64-3.70)	< 0.001
Opium	2.09 (0.99-4.39)	0.052
BMI	0.89 (0.82-0.96)	0.004
FC		0.653
II *vs* I	0.86 (0.44-1.66)	0.653
III *vs* II	2.18 (0.97-4.88)	0.057
EF (per 5% increase)	0.71 (0.62-0.81)	< 0.001
DM	2.97 (1.59-5.54)	0.001
CVA	3.45 (1.30-9.16)	0.013

BMI: Body mass index; FC: Functional class; EF: Ejection fraction; DM: Diabetes mellitus; CVA: Cerebrovascular accident.

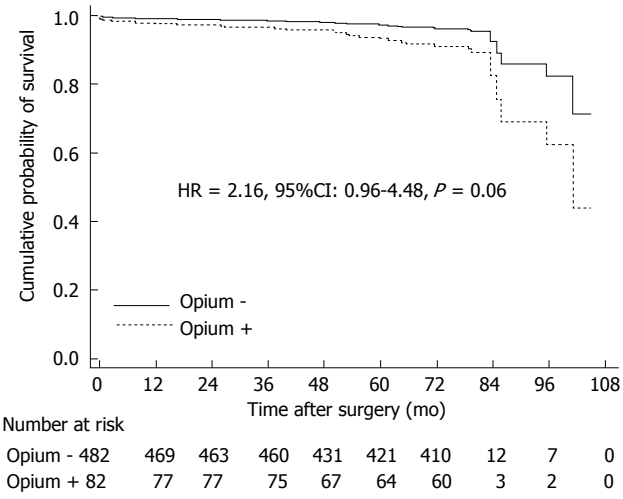

Figure 1 Adjusted survival curves based on opium consumption.

DISCUSSION

The current study represents the overall and opium-based stratified survival of patients undergoing CABG surgery who were followed-up for a median time of 78.7 mo. The prevalence of opium addiction was found to be 14.5% in our study. To our knowledge, studies are lacking to clarify the long-term effects of opium consumption on survival of patients undergoing CABG surgery. One of the notable points of our study was relatively long duration of follow-up.

Considering overall survival of patients undergoing CABG surgery, we found an overall survival of 91.8% in 6.5 years (78.7 mo). Five-year survival has been reported 72.1% in Yoo *et al*[21]'s study and Dunning *et al*[22] identified a ten-year survival of 66%. Meanwhile unadjusted 5 and 10-year survivals have been reported 83.8% and 65% in Filardo *et al*[1]'s research.

We identified that age, BMI, EF, diabetes mellitus and cerebrovascular accident could independently and significantly predict all-cause mortality of patients undergoing CABG surgery. Findings of Leavitt *et al*[5], Marcheix *et al*[23] and Barsness *et al*[24] support our results in terms of adverse effect of diabetes mellitus on long-term survival. Interestingly cerebrovascular accident had the greatest HR of 3.45 in predicting mortality by multiple Cox regression analysis suggesting that non-cardiac comorbidities may play an important role in patients' outcomes as well as unfavorable cardiac performance.

We found a significant HR of 0.89 for BMI in predicting overall mortality. Our results were in accordance with

those reported in Gruberg *et al*[25]'s work. They found that overweight or obese patients under CABG have significantly better survival outcomes at 3-year follow-up than those with normal BMI. The phenomenon obesity-mortality paradox which is generally accepted in short term outcome studies is described by better outcome in patients with higher BMI compared to the others. However, there is no consensus in long term investigations as Del Prete *et al*[26] noted that long-term survival was not significantly different between obese and non-obese patients after making adjustment model (HR = 1.2, *P* = 0.2). This is partially explained by increasing rate of complications due to major cardiovascular risk factors and substantial re stenosis in grafted coronary arteries by time[27,28]. Though we followed our patients for long period of time we found that BMI was still a predictor of mortality. Low mortality rate in our cohort compared to other studies with similar time intervals that reflect lower risks and complications in our patients could be an explanation. The other reason may be the finding of missed to follow up in a group of our patients which decreases the median time of overall follow-up.

Opium can potentially cause coronary atherosclerosis and increase cardiovascular mortality in different ways. Some metabolic changes by opium that could have deleterious effects on cardiovascular system include: Decreasing plasma testosterone and estrogen, and increasing plasma prolactin, increasing insulin resistance, increasing inflammation as well as oxidative stress, increasing fibrinogen and factor VII, and decreasing apolipoprotein A, increasing the release of nitric oxide and inhibiting production and release of hydrogen peroxide. Moreover, opium can decrease myocardial oxygenation from different ways that could extend infarct size and increase probability of death[29,30].

The role of opium in CAD remains controversial. Masoomi *et al*[13] showed that opium was an independent risk factor of CAD in non-smoker patients. But findings of Sadeghian *et al*[14]'s research on 4398 isolated CABG patients and opium dependence rate of 15.6%, found no relationship between post CABG in hospital complications and opium addiction. But on the other hand, in a study conducted by Safaii *et al*[15] on 6-mo outcomes of CABG patients, opium usage leaded to more readmission following CABG operation.

We found a HR of 2.1 for mortality in opium consumers as compared to patients who did not use opium with a borderline *P* value of 0.06. Since the rate of smoking is higher among opium-consumers, when we further adjusted the results by smoking, we observed that the role of smoking would be more prominent in predicting mortality so that HR for opium decreased to 1.2. Though our findings are not in favor of any protective role for opium in smoker cardiac patients, there is still no evidence to consider opium as a risk marker for long term survival in this group too.

The main problem with clarifying pure effect of opium on long term outcome in cardiac patients is high co incidence of smoking and opium addiction (Table 2). In deed there were only 15 patients who were opium users and non-smokers in our cohort. We need to perform further investigation to clarify pure effect of opium, because ignoring the adverse effects of opium and attributing any poor clinical outcomes to the smoking alone would be potentially associated with worse consequences.

There are other obstacles to detect the effects of opium on outcome in coronary patients that has been discussed elsewhere[30,31]. Briefly there are variations in self-reported dosage, route of usage, and purity of consumed opium. The other important issue probably would be the reason for beginning opium consumption: recreational or for pain relief[29,30].

In conclusion, in the present study, we found advanced age, low EF, DM and CVA as predictors for long term mortality. However, due to the simultaneous impact of smoking as a confounding variable neither the cardio protective role of opium in ischemic phase suggested in some studies nor its role as a predictor for long-term survival of CABG patients could be justified. Further large sample size studies are needed to clarify pure opium role and verify the aforementioned findings.

COMMENTS

Background

Cardiovascular diseases especially coronary artery disease have been known causes of morbidity and mortality all over the world. Though most of predictive factors of outcome in coronary artery bypass surgery are common among different countries, there are ethnic, environmental, and psychosocial specifications that necessitate separate studies on predictors of outcome in different parts of the world. Opium consumption is a controversial topic with regard to its impact on coronary artery disease outcome. Current literature is not conclusive about short term mortality and there is paucity of data on the role of opium as a risk marker for long term survival after coronary artery bypass surgery.

Research frontiers

A large cohort in normal population revealed that opium consumption has been associated with increased all cause and cardiovascular mortality. Some studies are focused on the pattern of obesity impact on outcome in cardiovascular disease. Finding a mixed group of factors including risk markers and a panel of biomarkers with the highest level of outcome prediction is currently an important research topic.

Innovations and breakthroughs

It is always possible to mix up the role of opium consumption with the known risk of cigarette smoking. This study showed that opium has no protective role in smoker cardiac patients. However, there is still lack of evidence to consider opium as a risk marker for long term outcome in cardiac surgical patients.

Applications

This study showed that advanced age, low ejection fraction, lower body mass index, diabetes mellitus, and cerebrovascular accident (CVA) are predictors for long term mortality. High hazard ratio for CVA put an emphasis on the importance of this non cardiac factor in predicting mortality.

Peer-review

This is an interesting manuscript about the effects of opium consumption on all-

cause mortality in patients undergoing coronary artery bypass graft surgery.

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CASE REPORT

Pulmonary vein thrombosis in a patient with polycythemia vera

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Abstract

Pulmonary vein thrombosis (PVT) is a rarely encountered disease entity with varied clinical presentations. It is usually associated with lung carcinoma, lung surgeries and as a complication of the radiofrequency catheter ablation procedure for atrial fibrillation. Its clinical manifestations can vary from mild hemoptysis to lung infarction with hemodynamic compromise. A 76-year-old male presented with a 2-d history of pleuritic left sided chest pain. His past medical history included polycythemia vera, atrial fibrillation, coronary artery disease, pulmonary embolism and pulmonary hypertension. Chest radiograph was normal, troponins were normal and the 12-lead electrocardiogram did not show any ischemic changes. A computerized tomography pulmonary angiogram revealed a filling defect in the left lower lobe pulmonary vein. He was treated with subcutaneous enoxaparin and his symptoms improved. This case highlights a rare etiology of chest pain and the first reported case of the association of polycythemia vera and pulmonary vein thrombosis. A high index of suspicion is required for appropriate diagnostic work up. PVT can mimic pulmonary embolism. The diagnostic work up and treatment strategies depend on acuity of presentation.

Key words: Pulmonary veins; Polycythemia rubra vera; Thrombosis/etiology; Thrombosis/radiography

Core tip: Pulmonary vein thrombosis (PVT) is a rare but potentially life-threatening disease entity. Its signs and symptoms are often non-specific and it can be difficult to diagnose unless there is a high index of clinical suspicion. Misdiagnosis can lead to grave consequences. We describe a case of PVT in the setting of polycythemia vera. The patient had presented with symptoms of pleuritic chest pain and the workup revealed a thrombus in the left inferior pulmonary vein. This association of polycythemia vera with PVT has not

been reported in the literature previously. The PVT is a less known disease process and with this manuscript, we would like to briefly review its causes, presentation and treatment options.

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INTRODUCTION

Pulmonary vein thrombosis (PVT) is a rare but potentially life threatening condition. Lung circulation has rich venous collaterals; however certain medical conditions can cause obstruction to the pulmonary veins[1]. The various etiologies for the pulmonary vein thrombosis can be broadly categorized as post lung surgery, from primary or secondary tumors of lung, cardiac causes and miscellaneous causes[2-8]. The clinical diagnosis of the PVT is difficult as its signs and symptoms can be vague and nonspecific. It can either present acutely in the form of dyspnea, pleuritic chest pain and hemoptysis or as progressive lung fibrosis and chronic pulmonary edema[9]. Several different imaging modalities have been used in diagnosing PVT including computerized tomography angiography (CTA), transesophageal echocardiography (TEE) and magnetic resonance imaging (MRI)[8-13]. PVT is managed with anticoagulation but treatments can differ depending on the various etiologies and clinical status on presentation. We are presenting a case of pulmonary vein thrombosis in a patient with polycythemia vera which is the first reported case in literature of this unique association.

CASE REPORT

A 76-year-old male presented with a two day history of the severe left sided chest pain. The chest pain was sudden onset, unrelated to exertion but worsened with inspiration. His past medical history included polycythemia vera, coronary artery disease, pulmonary hypertension, pulmonary embolism, diastolic heart failure and permanent atrial fibrillation. He had JAK2 proven polycythemia vera and had required intermittent phlebotomy in the past. He was on chronic thromboprophylaxis with aspirin. He was on chronic anticoagulation with warfarin due to his history of pulmonary embolism. He was admitted with the suspicion for acute coronary syndrome. His troponins remained within normal limits and there were no significant electrocardiogram (ECG) changes. His ECG revealed an ejection fraction of 55% with grade 2 diastolic dysfunction and elevated pulmonary artery pressures. His labs were within normal limits other than hemoglobin of 12.9 g/dL and elevated white blood cell count of 17400. INR on arrival was 2.1. He underwent a CT angiography with suspicion for pulmonary embolism. CTA revealed a left inferior pulmonary vein thrombosis with extension into the left atrium (Figure 1) along with left lower lobe consolidation. He was immediately started on therapeutic dosage of low molecular weight heparin and antibiotics for the presumed bacterial pneumonia. His symptoms improved on the treatment and he was discharged with subcutaneous low molecular weight heparin. A follow up CT angiogram a few weeks later showed the resolution of his pulmonary vein thrombosis (Figure 2).

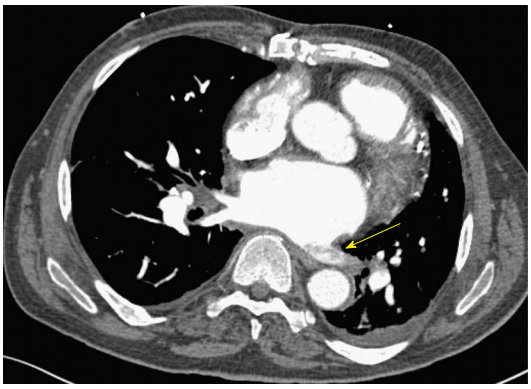

Figure 1 Computerized tomography angiography showing the pulmonary vein thrombosis of the left lower pulmonary vein. A yellow arrow marks the position of the thrombus.

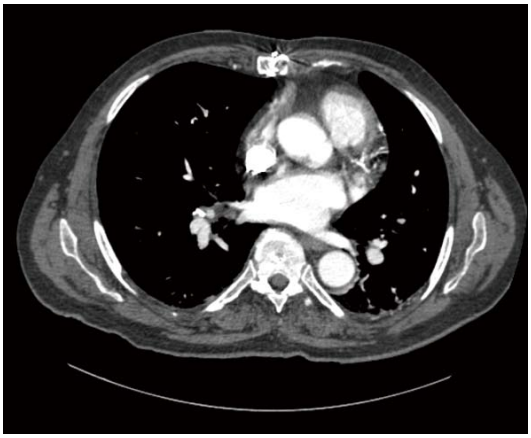

Figure 2 A follow up computerized tomographic angiogram showing the resolution of pulmonary vein thrombosis in the left lower pulmonary vein.

DISCUSSION

Etiologies

Pulmonary vein thrombosis is the most distal source of the upstream arterial thrombi. It is most common etiologies include lung surgeries either in the form of lung transplantation and lobectomies[2,3]. Other etiologies associated with PVT are lung cancers and sclerosing mediastinitis[5,6]. PVT has been associated with atrial myxomas and after radio frequency catheter ablation[7,8] (Figure 3).

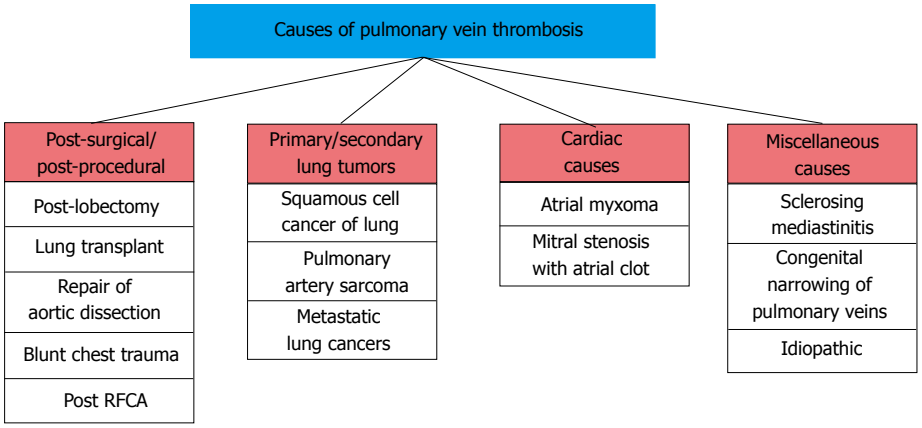

Figure 3 Flowchart describing the various causes of pulmonary vein thrombosis. RFCA: Radio frequency catheter ablation.

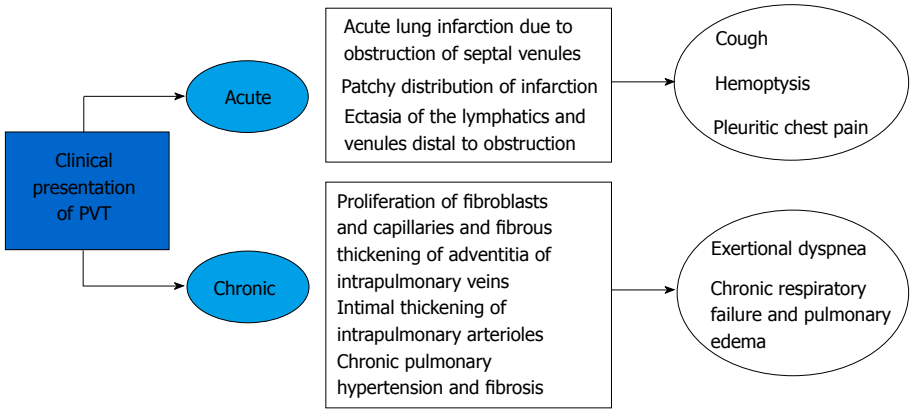

Figure 4 A flow diagram of the two different clinical presentation of pulmonary vein thrombosis. PVT: Pulmonary vein thrombosis.

Clinical presentations

The clinical presentation of the PVT can vary depending on the number of veins involved, extent of occlusion, adequacy of the venous collaterals and degree of lymphatic obstruction (Figure 3). Historically the pulmonary vein thrombosis presentation is associated with a triad of cough, dyspnea and hemoptysis[1]. The clinical presentations can be broadly divided into acute lung infarction pattern with cough, chest pain and pleuritic chest pain or in an insidious symptom pattern with progressive pulmonary fibrosis and pulmonary edema[1,9]. Patients with chronic PVT are prone to recurrent bouts of respiratory infection. In advanced disease with involvement of more than one pulmonary vein, patients can have frequent episodes of pulmonary edema progressing to intractable heart failure[1].

Pathophysiology

Before understanding the pathophysiology of the pulmonary vein thrombosis it is important to know that both pulmonary and bronchial circulation drain into the left atrium through the pulmonary veins. Any obstruction to this flow can lead to dilation of the bronchial and pulmonary veins. The pathophysiology of the symptoms can be very similar to mitral valve stenosis, *i.e.*, increase in pulmonary venous pressure and compensatory pulmonary arterial vasoconstriction leading to increase in right ventricular end diastolic pressures. In an animal study Wyatt *et al*[11] had demonstrated sequential changes in the canine lungs after the ligation of pulmonary veins which comprised of congestion, serum extravasation and alveolar hemorrhage leading to lobar consolidation.

Diagnosis

It is a challenge to establish the diagnosis of the PVT syndrome unless there is a strong clinical suspicion. Several diagnostic modalities can help in making the diagnosis including chest X-ray, CTA[6,7,9], TEE[5,12] or MRI[10] (Figure 4 and Table 1). Chest X-ray may reveal no finding or nonspecific air space disease or opacities[2]. Modified CT angiography that is utilized to identify pulmonary artery embolus can also detect the pulmonary vein thrombosis. ECG gated MRI is the least invasive modality to demonstrate the pulmonary vein embolus extending to left atrium. MRI imaging can also differentiate the bland thrombus from a tumor thrombus[10]. Pulmonary angiography is not commonly used to diagnose PVT due the increased risks from the procedure as well as contrast exposure. A normal

Table 1 Diagnostic modalities used in the diagnosis of pulmonary vein thrombosis with the findings and drawbacks

Type of modality	Findings	Drawbacks
Chest X-ray	Increased vascular marking, increased hilar size Consolidation, atelectasis Mitral configuration of pulmonary conus (extensive PVT)	Nonspecific in the setting of coexistent infections Variable findings
CT angiography/multidetector CT	Longer delays of contrast clearance on the venous phase Filling defect in pulmonary veins	Requires IV contrast Artifact from heart motion, dense contrast, poorly opacified blood can leads the PVT undetected
TEE	Can detect the thrombus when it extends to the left atrium Echo dense thrombus occluding the pulmonary veins	Invasive, requires sedation Can't detect the distal PVT
MRI	Least invasive methods Can differentiate blood clot from tumorous clot	Expensive Needs cooperative patients with stable cardiac rhythm
Pulmonary angiography	Failure to enhance the vein lumen A partial filling defect surrounded by normal contrast	Invasive and requires the contrast exposure Possibility of injury to the pulmonary artery, cardiac perforation, cardiac arrest

PVT: Pulmonary vein thrombosis; CT: Computerized tomography; TEE: Transesophageal echocardiography; MRI: Magnetic resonance imaging.

arterial phase and delayed or absent venous filling during the pulmonary angiogram can demonstrate a pulmonary vein thrombosis[1].

Complications

The PVT can become a source of arterial thromboembolic disease. Because of the high flow in pulmonary venous circulation small fragments of the platelets and fibrinous material can constantly break off from the thrombus. Garcia *et al*[12] described a case of bilateral femoral arterial occlusion in a patient of PVT. It can lead to pulmonary infraction and pulmonary gangrene[1] during the acute occlusive phase and in chronic phases it can cause progressive pulmonary fibrosis[9]. There are case reports about PVT complicating old myocardial ischemia[13].

Treatments

There is no clear consensus regarding the treatment of the PVT. The choice of therapy depends on the clinical status of the patient and the etiology of PVT. In case of pulmonary infraction requiring urgent intervention, surgical treatments in the form of embolectomy or lung resection might be indicated[2,14]. Appropriate use of the anticoagulation in the absence of hemorrhage can prevent clot progression and embolization. In patients where any carcinoma is involved, the use low molecular weight heparin is advisable. In the past, antibiotics were used for treating PVT[11,14]. But the role of antibiotics in the absence of infection is questionable. The use and duration of the Warfarin for PVT has not been evaluated in studies. In patients with PV, the risk of thrombosis directly correlates with hematocrit, and frequent phlebotomies to maintain this at < 45% in males and < 42% females remains the cornerstone of therapy for all patients groups. The venous thrombotic events are managed in standard fashion with parenteral heparin followed by oral anticoagulation with warfarin. The patients should be followed closely with strict monitoring of the INRs and platelet counts as the patients are at increased risk for bleeding too. Systemic anticoagulation might not be sufficient and these patients should get concomitant myelosuppressive therapy preferable with hydroxyurea as well as phlebotomies. In a study done by De Stefano *et al*[15] cytoreductive therapy reduced the incidence of rethrombosis by 50% especially in patients who presented with acute coronary syndrome. The use of systemic anticoagulation (after venous thromboembolism) as well as antiplatelet therapy (after cerebrovascular accidents as well as venous thromboembolism) improved the protective effect. It is recommended to use the cytoreductive chemotherapies in addition to phlebotomies in high risk patients (age > 60 years and previous thrombotic events)[16].

In our patient pulmonary venous thrombosis occurred while he was on both aspirin and warfarin with a therapeutic INR of 2.1. It was considered to be warfarin failure and his anticoagulation was changed to subcutaneous enoxaparin while continuing low dose aspirin.

In summary, we want to describe a case of pulmonary venous thrombosis in a patient with polycythemia vera. The clinical signs and symptoms of PVT can mimic pulmonary arterial embolism, acute coronary syndrome or pulmonary infections. Early recognition is imperative as PVT can lead to numerous complications including arterial thromboembolic disease. Anticoagulation can be chosen as first line therapy if there are no contraindications. Choice of anticoagulant agent can be tailored based on the clinical picture and patient comorbidities. In our case the patient developed thrombosis despite being on warfarin and was discharged on low molecular weight heparin. Cytoreductive therapies reduce the recurrence of the thrombotic events and should be considered in all high risk patients. Further studies and experience is needed to make the correct decision about the type and duration of anticoagulation in patients with PVT.

COMMENTS

Case characteristics

This is a unique case describing a rare presentation of polycythemia vera as a thrombotic event in pulmonary veins.

Clinical diagnosis
The patient presented with a left sided chest pain and the computerized pulmonary angiogram revealed a thrombus in the left lower pulmonary vein.

Differential diagnosis
Coronary artery disease, pulmonary embolism and pneumonia.

Laboratory diagnosis
The INR on arrival was 2.1, white cell count of 17400 and computerized tomographic angiogram revealed a thrombus on the left lower pulmonary vein.

Imaging diagnosis
A filling defect on the venous phase of the computerized pulmonary angiogram which diagnosed a thrombosis of the left lower pulmonary vein.

Treatment
Patient was started on low molecular weight heparin. He was on warfarin and had a therapeutic INR when he presented with the pulmonary vein thrombosis. A computerized tomography angiography done few weeks later showed resolution of the thrombus.

Related reports
Pulmonary vein thrombosis is an uncommonly encountered disease entity with various clinical presentations. It can lead to serious complications including lung infarction and hemodynamic instability. Although polycythemia vera presents with thrombosis at unusual sites but the association of pulmonary vein thrombosis with polycythemia vera has not been described in the literature so far.

Term explanation
Computerized tomographic pulmonary angiography is a common modalities utilized to rule out acute pulmonary embolism. It utilizes infusion of an iodinated contrast to look at the pulmonary vasculature.

Experiences and lessons
The timely diagnosis of pulmonary vein thrombosis could be difficult and requires high index of suspicion. It should be considered an etiology for the clinical presentations with chest pain and dyspnea in people at high risk for thrombotic events.

Peer-review
A well described case of pulmonary vein thrombosis presenting as left sided chest pain. In the discussion authors have delineated the spectrum of clinical presentation and treatment options in detail. The type and duration of anticoagulants use for the pulmonary vein thrombosis has not been studied in clinical trials so far.

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EDITORIAL

Interaction of hyperlipidemia and reactive oxygen species: Insights from the lipid-raft platform

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Abstract

Reactive oxygen species (ROS) and oxidative stress are closely associated with the development of atherosclerosis, and the most important regulator of ROS production in endothelial cells is NADPH oxidase. Activation of NADPH oxidase requires the assembly of multiple subunits into lipid rafts, which include specific lipid components, including free cholesterol and specific proteins. Disorders of lipid metabolism such as hyperlipidemia affect the cellular lipid components included in rafts, resulting in modification of cellular reactions that produce ROS. In the similar manner, several pathways associating ROS production are affected by the presence of lipid disorder through raft compartments. In this manuscript, we review the pathophysiological implications of hyperlipidemia and lipid rafts in the production of ROS.

Key words: Lipid raft; Hyperlipidemia; Free cholesterol; Reactive oxygen species; NADPH oxidase

Core tip: Lipid raft is a membrane microdomain in which specific combinations of lipid components such as free cholesterol and proteins function to mediate and amplify a variety of cellular signals. The platform has a significant impact on the cellular reactions such as the production of reactive oxygen species, however, there are limited articles on the clinical relevance of this platform. Lipid disorder, such as hyperlipidemia, is one that significantly affects the platform, with the modification of associating cell functions in various ways. We focused on the effect derived from this platform in hyperlipidemia in this manuscript.

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REACTIVE OXYGEN AND VASCULAR INJURY

Reactive oxygen species (ROS) and oxidative stress are considered key mediators of atherosclerosis[1]. ROS are involved in the progression of endothelial-cell dysfunction, which is accompanied by inactivation of endothelial nitric oxide synthase (eNOS) and decrease of nitric oxide (NO) levels[2]. Oxidative stress results from overproduction of ROS, failure of host antioxidant defense, or both. The effects of ROS-associated signal pathways have a meaningful impact on cellular function in endothelial cells. The most important modulator of ROS in endothelial cells is NADPH oxidase[3], and ROS metabolism is constantly modified by the surrounding environment. Pathological conditions associated with hyperlipidemia may be derived from these pathways of ROS, and the suppression of ROS may block the progression of those pathology[4].

RAFT PLATFORMS AS A REGULATOR OF ROS

Lipid rafts or membrane rafts are membrane microdomains in which specific combinations of lipid components and proteins function to mediate and amplify a variety of cellular signals[5]. Rafts are dynamic assemblies of cholesterol and lipids with saturated acyl chains, such as sphingolipids and glycosphingolipids in the exoplasmic leaflet of the membrane bilayer; and cholesterol in the inner leaflet. Intracellular reactions that produce ROS in endothelial cells can occur in lipid rafts, as a plasma membrane-associated NADPH oxidase complex exists within that compartment[6]. Clustering of lipid rafts in the cell membrane of endothelial cells causes the aggregation and activation of NADPH oxidase, thereby forming a redox signaling platform[7].

Raft structure and composition differ in various pathological states. Extracellular free cholesterol can be directly incorporated into the plasma membrane, leading to increase in cellular cholesterol levels[8]. Fang *et al*[9] showed that hypercholesterolemia increased the level of cellular free cholesterol approximately two-to four-fold in vascular endothelial cells[8]. The presence of very low-density lipoprotein (LDL) can cause a 50%-100% increase in total-cell unesterified cholesterol[10]. Indeed, endothelial cells are more likely to accumulate free rather than esterified cholesterol due to low ratio of hydrolysis to esterification. As a result, an increase in free cholesterol in endothelial cells causes a change in plasma membrane cholesterol content and may contribute to alterations in membrane function[11]. Similarly, hypercholesterolemia is also reported to alter the composition of lipid rafts and affect cell function in smooth muscle cells[12].

These pathological modifications of raft components affect ROS production. For example, a reduction of free cholesterol in rafts attenuates ROS production, leading to the suppression of ROS-associated downstream pathways[13]. By contrast, increase of plasma membrane free cholesterol leads to the modification of associated reactions that enhance ROS production[9]. Other conditions are known to affect the lipid components of rafts. For instance, aging has been associated with changes in sphingolipid and cholesterol, leading to the production of long-chain ceramides in plasma membrane[14] and the resulting enhancement of membrane-associated oxidative stress contributes to the progression of Alzheimer disease.

Not only lipid content of rafts but also specific proteins influence the behavior of associated reactions. Caveolin is an essential protein component of caveolae, which are unique raft compartments in the plasma membrane of endothelial cells[15]. Caveolin interacts with both lipids and lipid anchors on the raft proteins, and it functions as a scaffolding protein to organize and concentrate specific lipids and lipid-modified signaling molecules within the rafts[12,16]. In the presence of hypercholesterolemia, caveolin binding to eNOS is enhanced, leading to eNOS inactivation[17]. The resulting decrease in NO production has a significant impact on ROS metabolism. Hypercholesterolemia thus affects the production of ROS by a caveolin-associated pathway. Lobysheva *et al*[18] demonstrated that Caveolin-1 modulated the ROS behavior by regulating the balance of eNOS-derived NO. An increase in caveolin and eNOS interactions that occur with hyperlipidemia, may act to decrease NO production and promote endothelial dysfunction and atherosclerotic lesion formation[17].

The spatial compartmentation of eNOS in the raft compartment also has a significant impact of the behavior of ROS, in especially the cross-talk between NO and ROS. Under normal conditions, eNOS is associated with cholesterol-enriched caveolae in endothelial cells, where its activity can be closely regulated. However, in hyperlipidemia, lipoprotein particles modulate the activity and subcellular distribution of eNOS[19]. Incubation of endothelial cells with LDL, particularly oxidized LDL (ox-LDL), causes an increase in the binding of eNOS to CD36, which attenuates its activity and causes displacement of the protein from endothelial caveolae. In addition, the spatial interaction between eNOS and NADPH oxidase determines net NO and ROS production because the NO produced adjacent to NADPH oxidase is scavenged by the ROS[20]. Therefore, the pathological condition affects localization of ROS-associated molecules, resulting a change in the output from these pathways.

Rafts can also be platforms that enhance the production of reactive nitrogen. Yang *et al*[21] reported that TNF-α enhanced ROS production within these membrane compartments concomitant with recruitment of the p47phox regulatory subunit of NADPH oxidase

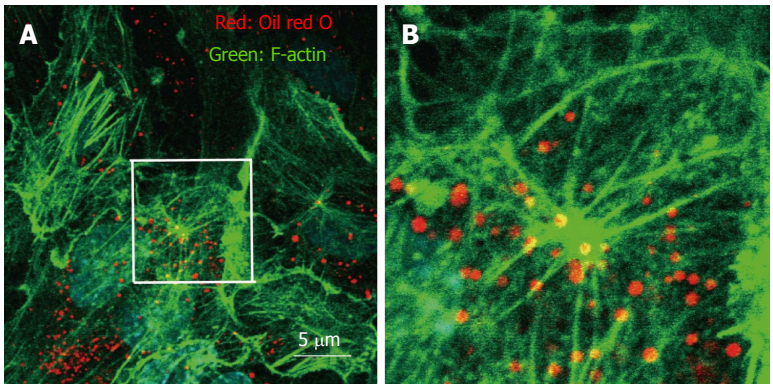

Figure 1 Immunohistochemistry of actin, and visualization of vesicle structures after free cholesterol loading and angiotensin Ⅱ in cultured human aortic endothelial cells. The cells were loaded by cholesterol-saturated methyl-b-cyclodextrin (Sigma, St. Louis, MO) (Chol/MBCD) and angiotensin Ⅱ (Wako, Tokyo, Japan) (200 nmol/L). Following treatment, cell were fixed, and stained using Alexa 546-conjugated phalloidin (Invitrogen, Carlsbad, CA) for visualization of F-actin and oil red O for visualization of vesicle structure. Oil red O-positive vesicles formed, and moved along the F-actin filament in the setting of actin remodeling induced by angiotensin Ⅱ. B is a magnified view of the white square in A.

subunit domains. In addition, TNF-α induced activation and phosphorylation of eNOS present in plasma membrane raft compartments. The dual activation of superoxide-generating and NO-generating systems within the same membrane domains provided a spatially favorable environment for formation of peroxynitrite.

Conversely, raft compartments are also susceptible to the oxidative reactions, resulting the oxidation of lipid components and modifying the associating reactions. For instance, 7-ketocholesterol, one oxidized form of cholesterol, was reported to deplete cholesterol from the raft domains and disrupt it[22,23]. However, the exact results of membrane injury by oxidized lipids are uncertain and are beyond the scope of this manuscript.

RAFT CONDITIONS AND ASSOCIATED REACTIONS

The association of rafts and the actin cytoskeletal network has been reported to affect the endocytic pathway. For instance, when the vacuolating cytotoxin (VacA), a major virulence factor of *Helicobacter pylori*, was continuously associated with raft compartments it was routed to early endosome antigen 1-sorting endosomes and then sorted to late endosomes[24]. We previously reported that intracellular vesicle structures in endothelial cells act as a raft-like domains that move along the actin cytoskeleton network (Figure 1)[13].

The most common raft protein, caveolin, can also be found in these endocytic pathways, such as late endosomes and lysosomes. Once it is ubiquitinated, it is transferred into intraluminal vesicles in endosomes for degradation using the endosomal sorting complex required for transport machinery[25]. During this translocation, caveolin is also recruited by accessory membrane compartments that affect its interactions with other intracellular compartments. Changes in lipid raft-based membrane compartmentation can involve movement of key molecules that modify intracellular dynamics. ROS production is one of the activities affected by the translocation of raft compartments. Indeed, NADPH oxidase-dependent ROS production in endosomes is seen as a proinflammatory immune response. Li *et al*[26] have demonstrated that interleukin-1β (IL-1β) stimulation promotes endocytosis of the IL-1β receptor (IL-1R1), leading to NADPH oxidase-dependent ROS production in early endosomes and subsequent redox-dependent activation of transcription factor NF-κB.

Previous reports demonstrated that visfatin activated lysosomal acid sphingomyelinase (ASM), the formation of raft redox signaling platforms, and consequent local oxidative stress[27]. Lysosome-associated molecular trafficking and the resulting ceramide accumulation in the cell membrane may mediate the assembly of NADPH oxidase subunits and their activation in response to adipokine visfatin in coronary artery endothelial cells, thereby producing endothelial dysfunction in the coronary vasculature.

In addition to intercellular vesicle structures, extracellular vesicle structures have been reported to associate with raft components[28]. Characterization of human B-cell-derived exosomes showed an abundance of membrane raft-associated lipids, including cholesterol and sphingomyelin[29]. Indeed, we found that modification of raft lipid components affected changes of molecules in vesicle structures (unpublished data). In addition, endothelial microparticles induced by angiotensin Ⅱ through the NADPH oxidase pathway, have been shown to associate with lipid raft[30]. These findings suggest that cholesterol metabolism affects the behavior of extracellular vesicles that can have an effect on pathological conditions. However, the physiological and pathological role of extracellular vesicles had not yet been elucidated. Further study of the mechanisms underlying the relationships of raft compartments and the extracellular vesicles produced by endothelial cells is warranted.

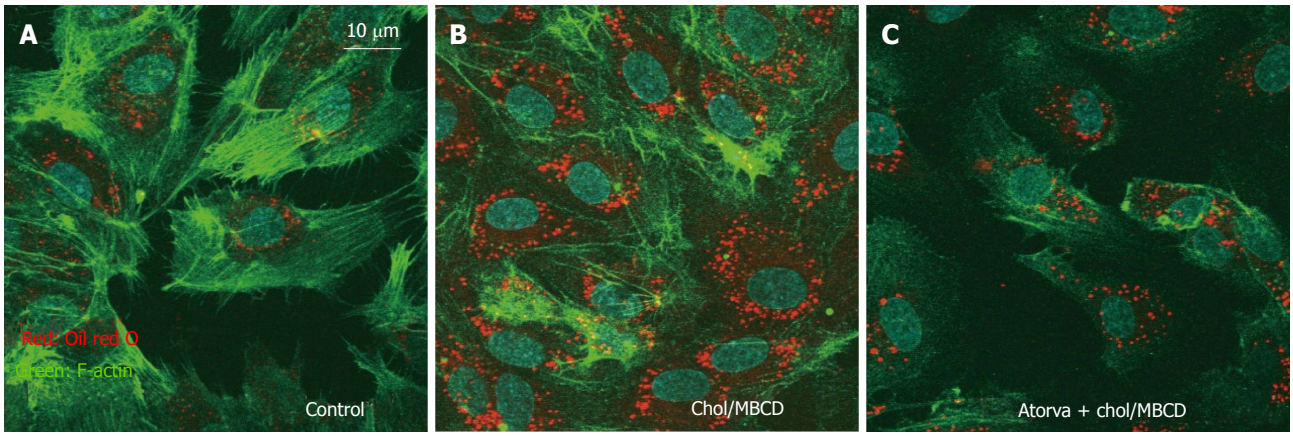

Figure 2 Immunohistochemistry of actin and visualization of vesicle structures after free cholesterol loading and atorvastatin pretreatment in cultured human aortic endothelial cells. The cells were loaded by cholesterol-saturated methyl-b-cyclodextrin (Chol/MBCD) with and without atorvastatin (10 μmol/L) pretreatment. Atorvastatin (Pfizer, New York, NY) pretreatment (C) significantly suppressed formation of vesicles induced by free cholesterol loading, as shown by oil red O as compared with Chol/MBCD loading alone (B); A: Control.

EFFECT OF STATINS ON RAFT COMPLEXES

Statins, inhibitors of HMG-CoA reductase, block cholesterol biosynthesis by inhibiting the mevalonate pathway, thereby producing a dramatic reduction in circulating LDL-cholesterol. Statins also exhibit non-cholesterol-lowering activities, including inhibition of inflammatory responses by immune cells such as macrophages and lymphocytes[31]. Statins also affect intracellular cholesterol pharmacokinetics, leading to other pleiotropic effects.

By interacting with the raft compartment, statins have been reported to inhibit the formation of raft redox signaling platforms and to decrease production of oxidized LDL in endothelial cells stimulated by a proatherogenic factor[32]. The inhibitory effect of statins on raft-redox signaling is associated with their vascular protective effects. Ponce *et al*[33] demonstrated that small reductions of intracellular cholesterol levels by simvastatin were associated with reduction in neuronal excitotoxity. The mechanism was found to be related to the translocation of NMDA receptors from raft compartment[33]. Other groups have found that statins inhibit OxLDL-induced ASM translocation and ceramide production in human aortic endothelial cells[34]. Previous studies have shown that lysosomal trafficking and translocation of ASM into membrane rafts results in ceramide production, membrane raft clustering, and formation of ceramide-enriched macrodomains[27]. Statins inhibit this ceramide formation, leading to the protection of endothelial function.

Raft cholesterol content affects cell function and changes in raft cholesterol content in response to statins have been shown to impact cell function. Zhuang *et al*[35] demonstrated that simvastatin lowered raft cholesterol content, leading to inhibition of Akt/PKB pathway signaling and induction of apoptosis in caveolin-negative and phosphatase and tensin homolog-negative LNCaP prostate cancer cells. On the other hand, cholesterol elevation also promoted tumor growth, increased phosphorylation of Akt, and decreased apoptosis in the xenografts.

We also observed that free cholesterol loading-induced vesicle structures were significantly suppressed by statin pretreatment (Figure 2). Intracellular vesicle structure was considered an intracellular raft platform, and statin affected the behavior of these platforms. As a result, the activity of platforms where key ROS-producing molecules are assembled may be decreased, with reduction of intracellular oxidative stress[13]. However, there had been little reports about the clinical effects of raft modifying agents other than statin. Further studies investigating about it is warranted.

CONCLUSION

This review described how ROS production is affected by the modification of lipid raft compartments in hyperlipidemia. The concept of lipid rafts may stimulate the development of novel therapeutic strategies for hyperlipidemia-associated pathologies. However, there had been little reports that demonstrated the clinical implication and importance of lipid raft compartments in lipid disorder. Further studies investigating about the associations between raft compartment and pathologic changes are needed.

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FRONTIER

To ventricular assist devices or not: When is implantation of a ventricular assist device appropriate in advanced ambulatory heart failure?

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Abstract

Advanced heart failure has been traditionally treated *via* either heart transplantation, continuous inotropes, consideration for hospice and more recently *via* left ventricular assist devices (LVAD). Heart transplantation has been limited by organ availability and the futility of other options has thrust LVAD therapy into the mainstream of therapy for end stage heart failure. Improvements in technology and survival combined with improvements in the quality of life have made LVADs a viable option for many patients suffering from heart failure. The question of when to implant these devices in those patients with advanced, yet still ambulatory heart failure remains a controversial topic. We discuss the current state of LVAD therapy and the risk *vs* benefit of these devices in the treatment of heart failure.

Key words: Left ventricular assist device; Mechanical circulatory support; Heart failure; Cardiomyopathy; Diastolic dysfunction

Core tip: Heart failure remains the most common diagnosis in patients discharged from the hospital. In its most advanced stages, it bears a grim prognosis and there are only a limited number of treatments that can truly change the course of the disease. Advancements in left ventricular assist device technology have enticed

clinicians to expand their role in earlier ambulatory, but advanced heart failure. Here, we describe the current equilibrium between early implantation and risks of the current technology.

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INTRODUCTION

Approximately 5.7 million people in the United States have heart failure (HF) and more than half of those who develop heart failure die within five years of the diagnosis[1]. As the population ages, the incidence of HF is expected to concurrently increase highlighting the importance of a continuation of need for developing more effective therapies. In the current spectrum of options, heart transplantation remains the gold standard for those with advanced heart failure[2]. The limitation of organ availability and unpredictability of rapidly advancing multi-system organ deterioration in patients with advanced heart failure have contributed to the rapid rise of left ventricular assist device (LVAD) implantation.

Since their first inception, there have been marked improvements in LVAD technology making them now a reliable therapeutic option for patients with advanced heart failure. There have been over 15000 mechanical circulatory support devices implanted since 2006 in the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) registry[3]. In addition to improvements in technology, better understanding of patient selection, peri-operative management strategies, and long term management have led to reduced complications with improvements in survival and quality of life in HF patients[4].

Despite tremendous advancements, however, there remain important limitations to LVADs. Gastrointestinal bleeding, infections, thromboembolic events such as stroke, pump thrombosis and right heart failure remain barriers to earlier use of this therapy. Even with these improved clinical outcomes and significant decreases in size of LVADs, many patients and clinicians still view them as bulky machines associated with significant morbidity, mortality and need for life-long hospitalization. Patients with advanced disease who have not quite reached "end-stage heart failure" present lower surgical risk with less end organ dysfunction, better functional capacity, and enhanced capacity to rehabilitate from major surgery. Many experts contend that these "less sick" ambulatory advanced heart failure patients could benefit from earlier LVAD implantation, but in clinical practice this has yet to commonly occur.

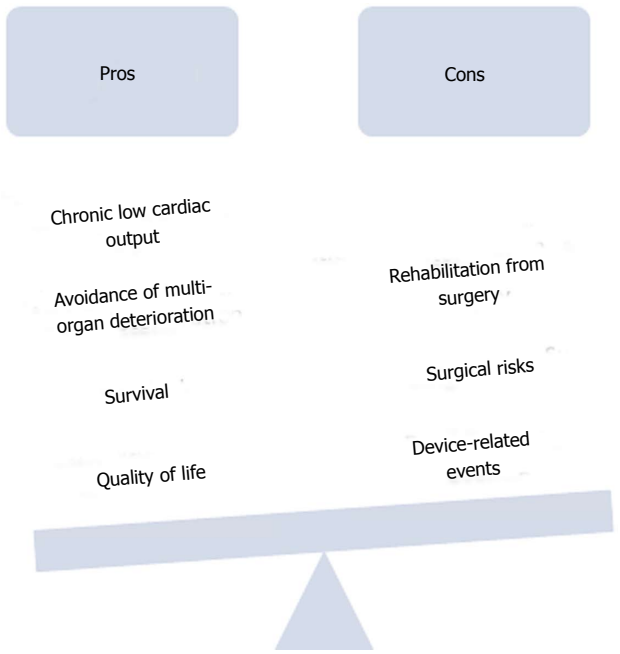

Figure 1 Factors determining timing of left ventricular assist devices implantation. Factors for earlier implantation of left ventricular assist devices are increased survival and quality of life, avoidance of multi-organ deterioration and chronic low cardiac output while factors against earlier implantation are device-related events, surgical risks, and rehabilitation from surgery.

(Cite intermacs report and can find other opinion pieces about early implantation).

This paper aims to review the current advantages and disadvantages of LVAD implantation in patients with advanced, ambulatory heart failure and discuss the pertinent issues in establishing an equilibrium between early surgical and/or device-related risks and benefits of quality and/or quantity of life with earlier implantation (Figure 1).

QUALITY OF LIFE

When asked about their decision to pursue optimal medical management over LVAD, patients stated reasons such as "they didn't like the idea of a major device implantation surgery", "they are worried about the possible complication", and they don't think an LVAD will improve quality of life and survival[5]. Moreover, many patients are never referred for advanced mechanical support due to inadequate understanding of LVAD outcomes by their medical providers and unavailability of the technology locally. However, one-year survival with the current pump technology is near 80%, which is markedly higher compared to the original data that established LVADs as a form of heart failure therapy[3]. To parallel the great advancements in LVAD therapy, it seems natural that the number of patients offered this therapy will continue to increase to the more than 10% of the HF population that will progress to advanced heart failure.

Even with tremendous improvements in survival and device related adverse events over the past

decade, considerable debate persists regarding the optimal timing of LVAD implantation. The benefits of LVAD implantation in inotrope dependent patients and those in cardiogenic shock are generally accepted. However, for patients with advanced heart failure who have not yet progressed to inotrope dependency the decision is more challenging. A single effective model for risk stratification is currently lacking for this large, heterogeneous, group. Traditionally patients have been classified according to the New York Heart Association (NYHA) functional classification, but this system is somewhat subjective and limited by significant inter-reporter variability[6]. While current FDA approval exists for LVAD implantation in NYHA class IIIB and class IV patients, the vast majority (81%) of LVADs are implanted in those identified as class IV on chronic inotropic therapy or in cardiogenic shock[5]. Implantation of LVADs has led to improved symptom burden and quality of life in those with advanced heart failure. In the HeartMate II destination therapy trial, 80% of patients who received a continuous flow LVAD went from NYHA class III or IV to NYHA class I or II. Furthermore, these patients also had a significant increase in a 6-min walk distance by 1 year[7].

SURVIVAL

As previously stated, the one-year survival with the current pump technology is near 80%[5]. The greatest risk for mortality following LVAD implantation falls during the early post-operative period and reaches a low by 3 mo following the procedure[8]. When analyzing factors that are related to survival following LVAD implantation, the 7th INTERMACS Annual Report found that patients with an INTERMACs profile of 2-3, and thus less severe disease, have better survival than those with an INTERMACS profile 1[5]. However, while INTERMACS levels 1-3 have been associated with lower survival rates 3 years post-LVAD implantation when compared to levels 4-7, no graded mortality risk has been demonstrated to help further discriminate the potential benefit between levels 4-7, which could be associated with the subjectivity of assignment in these levels[9]. Per Shah *et al*[8], other factors that have a great impact on LVAD perioperative mortality include age, female sex, prior stroke, mechanical ventilation, LVAD for destination therapy, hepatic or renal dysfunction, right ventricular dysfunction, and prior or concurrent cardiac surgery.

Risk assessments

To better characterize patients' risk to benefit profiles for LVAD implantation, multiple risk assessments have been developed. Unfortunately, few consistent predictors have been identified across models and currently no single model effectively triages potential LVAD patients. In general, however, the predictors that have been recognized in different models are markers of end-organ dysfunction secondary to heart failure or other significant comorbidities, such as age[9,10]. Patients that are "sicker", as reflected by a more acute INTERMACS profile, are also known to have worse outcomes. Moreover, regardless of INTERMACS profile, mortality increases with increasing age at the time of implantation[3]. With this in mind, there is support for considering LVAD implantation earlier in the disease course theoretically leading to lower operative risk and fewer post-operative complications.

In continuing to lower the morbidity and mortality associated with LVADs the balance of patient risk to benefit for LVAD implantation may suggest sooner application of this technology.

Adverse events

Though LVAD implantation can result in significant improvements in morbidity and mortality, their use is associated with complications including infection, stroke, pump thrombosis, gastrointestinal bleeding, and right ventricular failure. Infection occurs in about 20% of patients following implantation and may present as sepsis or a driveline infection. Infection additionally may predispose to pump thrombosis[11]. Pump thrombosis occurs at an annual incidence of 6%-12%, although the exact incidence varies based on device type and anticoagulation regimen employed. One thing for certain; however, is that pump thrombosis is associated with an increase in neurologic events as well as a higher rate of mortality. Cerebrovascular complications occur with an annual incidence of greater than 6%[8]. Furthermore, 30% of patients have major bleeding in the first month, and then following one month, bleeding occurs at a rate of 8%-23% by one year. Overall, 55% of patients will be rehospitalized for any cause[11].

Bleeding

Bleeding, in particular gastrointestinal bleeding, is associated with significant morbidity after LVAD implantation. The cause of increased bleeding is multifactorial and can be attributed to chronic anticoagulation, acquired von Willebrand syndrome, and chronic low pulse pressure leading to increased risk for angiodysplasia. Therefore, screening patients for angiodysplasia and von Willebrand syndrome prior to implantation may allow for preemptive treatment of these conditions to help avoid complications postoperatively[12]. With further understanding of the pathogenesis of bleeding post implantation and research on the prevention and appropriate management, its hopeful the risk of bleeding will decrease to support the earlier implantation of LVADs.

Pump thrombosis

As stated before, Pump thrombosis occurs at an annual incidence of 6%-12% raising awareness that LVAD therapy is not without inherent risks[8]. The lack of equipoise in many physicians' minds of

benefit *vs* risk of LVAD for NYHA Class Ⅲ patients that were highlighted by pump thrombosis led to early termination of the Registry Evaluation of Vital Information for VADs in Ambulatory Life (REVIVE-IT) trial. The PREVENT (Prevention of Heartmate Ⅱ Pump Thrombosis through Clinical Management) study was designed to analyze the impact of clinical practices developed to decrease the risk of Heartmate Ⅱ pump thrombosis. The study followed the "PREVENT protocol" which were recommendations on LVAD implantation, anticoagulation and antiplatelet protocols, and pump management. Preliminary results have been positive and show that the protocol is associated with lower rates of thrombosis without increased incidence in bleeding complications[13].

Furthermore, in the case that pump exchange must occur, the morbidity and mortality of the exchange has decreased. Soleimani *et al*[14] found that off-pump minimally invasive exchange of the Heartmate Ⅱ can be safely accomplished with low morbidity and mortality, resulting in excellent outcomes. Therefore, will evolving clinical guidelines improving the risk of pump thrombosis and minimizing the risk of adverse events in addition to the decreased morbidity and mortality of pump exchange, this supports the shift to earlier implantation of LVADs.

Right ventricle failure

In particular, the risk of right heart failure following LVAD implantation has been extremely difficult to predict. With improved left ventricular decompression, pulmonary congestion should decrease resulting in decreased afterload for the right ventricle. However, increased cardiac output from LVAD support will result in increased right ventricle preload. Also, leftward shift of the interventricular septum shift and change in motion after LVAD implantation may impair the right ventricle contractility, leading to right ventricle dysfunction, and ultimately right heart failure[15]. Right ventricular failure is likewise often the last manifestation of advanced heart failure. There are no durable treatment options currently available for right ventricular failure emphasizing the need to prevent it in LVAD patients, and identify those who may be at increased risk of developing it with extended time with an LVAD.

A study by Santambrogio *et al*[16] showed that early right heart failure will develop in about 25% of patients receiving LVAD support. Furthermore, Argiriou *et al*[15] noted that female sex, existence of pre-operative circulatory failure, presence of end-organ dysfunction, severe right ventricle systolic dysfunction, and presence of pulmonary vascular disease are all pre-operative risk factors for early right heart failure. However, there are limitations to all these risk factor stratification models as has been pointed out by Lampert *et al*[17] that most of the risk scores were developed primarily in BTT patients with pulsatile devices, and so there is a need for further investigation. The report notes that echocardiography, hemodynamic parameters, and biomarkers including neutrophil gelatinase-associated lipocalin, blood urea nitrogen, aspartate aminotransferase and serum creatinine could be of use in predicting pre-operative risk of early right heart failure.

While much has been studied about early right heart failure following LVAD implantation, less is known about the development of late right ventricular failure, which is an important complication to consider when arguing to implant LVADs in patients earlier. As there is a question of whether late right heart failure is a distinct entity, or just undiagnosed early right heart failure, the risk factors are not as well established, although there is likely significant overlap with the risk factors of early right heart failure[17]. Takeda *et al*[18] found that late right heart failure occurred in about 11% of patients at a median of 99 d, with significant predictors including diabetes mellitus, body mass index greater than 29 kg/m^2, and BUN level greater than 41 mg/dL. These patients had significantly worse survival when compared to those who did not develop late right heart failure, but this could also be attributable to their increased incidence of comorbidities. Currently, treatment for late right heart failure is directed at the underlying causes and management of symptoms, however it is thought that optimization of pump speed, which will avoid excessive leftward septal shift and decrease excessive venous return, may help to avoid this late complication[17]. Further research on the effects of more frequent imaging and hemodynamic measurements in patients with LVADs could help develop appropriate post implantation management guidelines to best screen for and prevent late right heart failure. Additionally, avoiding early and aggressive titration of beta-blockers and use of inotropes to support right ventricular function and pulmonary vasodilators to decrease right ventricular afterload may also help[17].

Thus, if these risk factors could be further developed and taken into consideration when selecting patients for early implantation, the risk of late right heart failure could be minimized. With the shift to earlier implantation of LVADs, there is a clear need for continued research in the screening and management of late right heart failure to better care for patients who do receive LVADs earlier in their course of heart failure. However, the development of bi-ventricular failure in non-transplant eligible patients still warrants special consideration. Advancements in total artificial heart technology and a better understanding of right ventricular failure are needed to better care for these patients who do develop right ventricular failure.

Despite these adverse events, The 7th INTERMACS Annual Report demonstrated that with the improved technology of the continuous-flow pumps, there has been a dramatic decrease in the overall adverse event rate when pumps implanted between 2012 to 2014 are compared to pumps implanted between 2008 to

Table 1 Studies analyzing the early implantation of left ventricular assist devices

Study	Objective	Significant findings
ROADMAP	Compare outcomes of HeartMate Ⅱ implantation in destination therapy patients who are not dependent on inotropic support with those on optimal medical management	Early LVAD implantation associated with improved quality of life and more adverse events. Intent to treat analysis showed no survival benefit with early implantation
REVIVE-IT	Compare outcomes of HeartMate Ⅱ implantation in NYHA class Ⅲ patients not severe enough to qualify for transplant or permanent LVAD therapy with those on optimal medical management	Study discontinued due to difficulty recruiting from observed increase in pump thrombosis (enrolled 0/100 patients (randomized study), 0/2500 patients (screening registry)
MedaMACS	Characterize and report on patients with ambulatory advanced heart failure who have not receive an LVAD	Patients desire LVADs and LVAD shows survival benefit compared to medical management for INTERMACS 4 and 5

ROADMAP and REVIVE-IT both evaluated the impact of implanting LVADs earlier in the heart failure progression while MedaMACS created a registry of patients on optimal medical therapy without LVADs to parallel INTERMACS data, and allow for a comparison of patients with LVADs to patients on optimal medical therapy; REVIVE-IT: Registry Evaluation of Vital Information for VADs in Ambulatory Life; NYHA: New York Heart Association; MedaMACS: Medical Arm of the Interagency Registry for Mechanically Assisted Circulatory Support; LVAD: Left ventricular assist devices.

2011[5].

CURRENT TRIALS IN TIMING OF LVAD IMPLANTATION

Appropriate identification of patients with the best chance to benefit from therapy and lowest risk of complications is a perpetual focus of investigation for LVAD implantation. For example, Boyle *et al*[19] found that patients on inotropes before LVAD implantation trended toward a higher incidence of hemorrhagic stroke post-operatively. Boyle *et al*[19] also found that patients in INTERMACS 4-7 had significantly shorter length of stay following LVAD implantation and greater survival when compared to both INTERMACS 1, and 2/3 patients[20]. This suggests that selecting patients earlier on in the progression of heart failure, prior to dependence of inotropic therapy, would reduce the LVAD implantation post-operative risk of complications. Furthermore, studies are currently being conducted which directly show the benefit in both quality of life and survival with earlier LVAD implantation (Table 1, Figure 2).

Risk Assessment and Comparative Effectiveness of Left Ventricular Assist Device and Medical Management in Ambulatory Heart Failure Patients

The Risk Assessment and Comparative Effectiveness of Left Ventricular Assist Device and Medical Management in Ambulatory Heart Failure Patients (ROADMAP) Study attempted to evaluate the effects of LVAD implantation in less sick patients[5]. ROADMAP was a prospective, multi-center, nonrandomized observational study that evaluated outcomes of LVAD implantation in destination therapy patients who are not dependent on inotropic support (INTERMACS profiles 4-7). Currently, these patients make up roughly 20% of all implantations[5]. In ROADMAP, patients and their providers chose to continue on optimal medical therapy (OMM) or proceed with LVAD implantation. The primary composite end-point was survival on original therapy with increase in 6 min walk distance (6MWD) by at least 75 m. Significantly more patients in the LVAD cohort (n = 97) reached this endpoint than those on OMM (n = 103) (39% *vs* 21%). Furthermore, the LVAD group had greater improvements in self-reported quality of life and depression. Additionally, the LVAD group had 77% of patients change in their NYHA classifications to class Ⅱ or Ⅰ, while the OMM group only had 29% change to class Ⅱ, and none to class Ⅰ (Figure 3). This greater improvement in functional status was also supported by the improvements in the 6MWD, as LVAD patients had a significant increase while there was no significant change in the OMM cohort. The LVAD group also had a significantly greater 12-mo as-treated (event-free) survival (80% *vs* 63%). However, since delayed LVAD implantation counted as a "failure" in OMM patients, the intent-to-treat analysis showed no survival benefit with early LVAD implantation[5].

There were some adverse findings with early LVAD implantation. These patients had more frequent adverse events as compared to the OMM patients. LVAD patients' adverse events were primarily due to bleeding as opposed to the OMM patients' adverse events that were primarily due to worsening heart failure[5]. The ROADMAP results suggest that earlier LVAD implantation in select patients may provide significant benefit, but there remains no consensus on a singular way to identify these patients.

A significant limitation to the ROADMAP trial that prevents generalization of the results is the lack of randomization of patients between LVAD and OMM. At baseline, patients who elected to have an LVAD were sicker than those who elected to continue OMM. The LVAD group had more NYHA class Ⅳ patients (52% *vs* 25%), which is a group that is generally already thought to benefit from LVAD implantation. Moreover, the LVAD group in ROADMAP consisted of more INTERMACS profile 4 patients (65% *vs* 34%), had less beta-blocker use, and a lower predicted Seattle Heart Failure Model 12-mo survival. Also, the LVAD cohort was much less satisfied with their quality of life on average than the OMM group[5]. This could lessen the significance of the greater improvements in self-reported depression and quality of life. Despite these limitations, the LVAD group

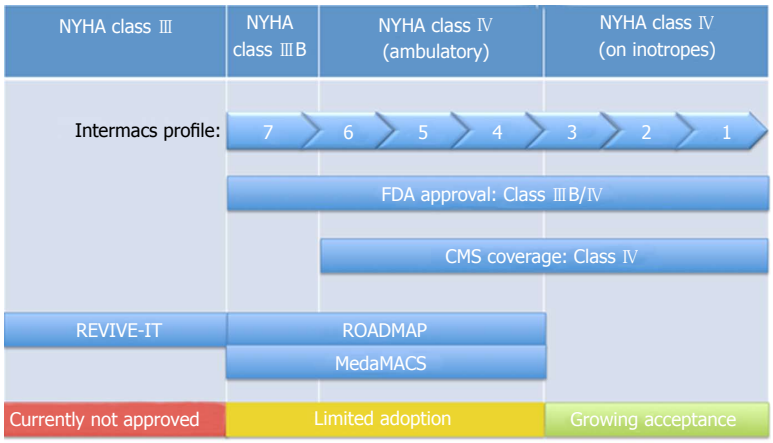

Figure 2 New York Heart Association classes considered for left ventricular assist devices implantation. Currently, FDA approval for LVAD implantation exists for NYHA Class ⅢB and Ⅳ, which encompasses all of the INERMACS profile levels. ROADMAP is evaluating LVAD implantation in patients of NYHA class Ⅲ and class Ⅳ (ambulatory), which has limited adoption in most clinical practices. MedaMACS looked at the same patient population as ROADMAP however focused on those patients without LVADs. REVIVE-IT was evaluating implantation in patients in NYHA class Ⅲ, which is not currently FDA approved. LVAD: Left ventricular assist devices; FDA: Food and Drug Administration; MedaMACS: Medical Arm of the Interagency Registry for Mechanically Assisted Circulatory Support; NYHA: New York Heart Association.

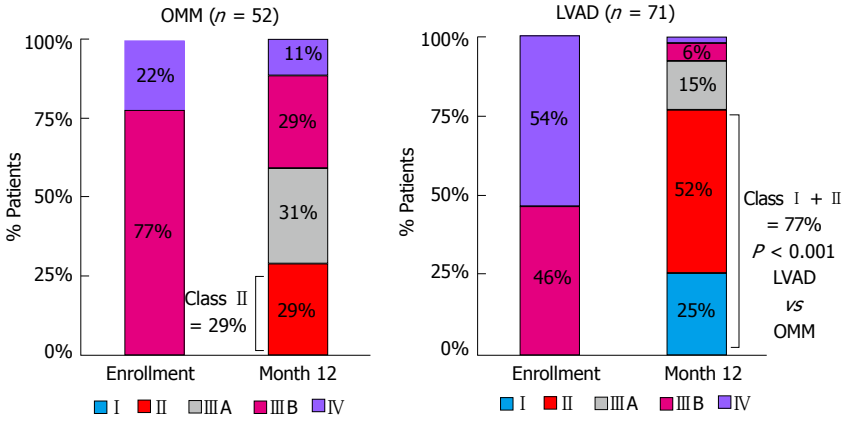

Figure 3 Comparison of baseline and 12-mo after enrollment from the ROADMAP study comparing left ventricular assist device implantation with optimal medical management. OMM: Optimal medical management; LVAD: Left ventricular assist device; Ⅰ-Ⅳ: New York Heart Association classification[5] (Reprinted with permission from *J Am Coll Cardiol*).

still showed much more functional improvement in both the 6 min walk test and NYHA classification.

Medical Arm of the Mechanically Associated Circulatory Support

The Medical Arm of the Mechanically Associated Circulatory Support (MedaMACS) project is an ongoing cross-sectional, observational study following patients with ambulatory advanced heart failure (INTERMACS profile 4-7) that aims to characterize and report on the medical outcomes of those patients who have not yet received an LVAD (include citation). In the MedaMACS screening pilot study, a majority (56%) of patients reported they would "definitely" or "probably" want an LVAD given the alternative was their current symptomatic state. Interestingly, 93% of these patients were at a low or intermediate implant risk based on the HeartMate Ⅱ Risk Score. Furthermore, many patients were willing to consider LVAD surgery despite expectation of a long survival with OMM suggesting that more than HF mortality influences preference for mechanical support[21]. This suggests that patients value the improved quality of life made possible by LVADs and may be willing to take on the risk of adverse events associated with them. Hence an argument can be made for LVAD implantation in the ambulatory heart failure patient by individualized patient desire.

In terms of survival, MEDAMACS showed a one-year survival for patients on medical management of 78% in INTERMACS level 6/7, 67% in INTERMACS level 5, and 39% in INTERMACS level 4[8]. Therefore, when compared to the 80% one-year survival after LVAD implantation, this data would suggest an increase in survival for patients in INTERMACS level 4/5 who undergo LVAD implantation and further supports a shift towards earlier implantation of LVADs and an expansion in their utilization.

REVIVE-IT

The REVIVE–IT study, like the ROADMAP study, also

planned to test the theory that patients with less advanced heart failure will benefit in both survival and quality of life with LVAD implantation as opposed to optimal medical management. This trial however was to analyze LVAD implantation in moderate NYHA class Ⅲ patients with marked limitation of physical activity and LVEF of 35% or less[22]. However, this study was discontinued as it met great challenges with recruiting patients due to the observed increase from 2.2% at 3 mo post-implantation to 8.4% in pump thrombosis in the pump used in the study discovered by Starling *et al*[23]. Therefore, in combination with the perceived increased risk of thrombosis, a renewed hesitancy for wider adoption of LVAD technology grew. As some were already risk aware in patients with NYHA class Ⅳ/INTERMACS profile 4-6 patients, it became clear that routine consideration of patients for NYHA Class Ⅲ/INTERMACS profile 7 were too far out of reach. However, it is clear that controversy persists as, the ROADMAP study has shown the benefits of earlier implantation with regards to quality of life and once again shifting the equilibrium towards early implantation.

CONCLUSION

When considering the earlier implantation of LVADs, its critical for one to account for the extended amount of time these patients will have using the LVADs and how that will impact the potential for adverse events. The increased chance of adverse events will need to be weighed against the increase in quantity and quality of life.

Although LVADs are currently being used to improve quality and quantity of life for those in NYHA class Ⅳ end-stage heart failure, there is anticipation that a much larger group of patients may benefit from this potentially life-saving therapy. Although we are not quite there yet, we are moving towards a balance where the improvement of quality and quantity of life outweigh the risks of adverse events for patients who aren't quite yet at NYHA class Ⅳ end-stage heart failure. Patients who are implanted earlier may experience much greater benefits with lower risks of complication than those currently being treated. Earlier implantation of LVADs, prior to the onset of end organ dysfunction, may have benefits when compared to optimal medical management and could be considered as an alternative for less advanced heart failure patients, who do not have risk factors for adverse events. In continuing to reduce the morbidity and long-term risks of LVAD implantation, LVADs will likely be used earlier in the treatment of advanced heart failure as the technology progresses. In fact the next generation of devices, the HeartMate Ⅲ (St. Jude Medical, St. Paul, MN) and the MVAD (HeartWare International Inc, Framingham, MA) have been developed with this very goal in mind – to push the boundaries of reducing surgical morbidity and long-term reduction of device related adverse events. With continued research in the early implantation of LVADs we can better identify what to expect with extended time on LVAD support. Additionally, with continued research on incidence, management and prevention of adverse events, we can better select patients for early implantation and be more prepared in the case that adverse events occur. As we continue to learn from trials such as the ROADMAP trial and the MedaMACS registry, we hope to clarify the delicate balance between implantation of devices in patients who are too sick to benefit from the therapy and those who are too well to undergo the morbidity of the procedure.

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REVIEW

Hematological disorders and pulmonary hypertension

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Abstract

Pulmonary hypertension (PH), a serious disorder with a high morbidity and mortality rate, is known to occur in a number of unrelated systemic diseases. Several hematological disorders such as sickle cell disease, thalassemia and myeloproliferative diseases develop PH which worsens the prognosis. Associated oxidant injury and vascular inflammation cause endothelial damage and dysfunction. Pulmonary vascular endothelial damage/dysfunction is an early event in PH resulting in the loss of vascular reactivity, activation of proliferative and antiapoptotic pathways leading to vascular remodeling, elevated pulmonary artery pressure, right ventricular hypertrophy and premature death. Hemolysis observed in hematological disorders leads to free hemoglobin which rapidly scavenges nitric oxide (NO), limiting its bioavailability, and leading to endothelial dysfunction. In addition, hemolysis releases arginase into the circulation which converts L-arginine to ornithine, thus bypassing NO production. Furthermore, treatments for hematological disorders such as immunosuppressive therapy, splenectomy, bone marrow transplantation, and radiation have been shown to contribute to the development of PH. Recent studies have shown deregulated iron homeostasis in patients with cardiopulmonary diseases including pulmonary arterial hypertension (PAH). Several studies have reported low iron levels in patients with idiopathic PAH, and iron deficiency is an important risk factor. This article reviews PH associated with hematological disorders and its mechanism; and iron homeostasis and its relevance to PH.

Key words: Anemia; Hemolysis; Iron homeostasis; Myelofibrosis; Pulmonary hypertension

Core tip: Oxidant injury, inflammation, impaired nitric oxide bioavailability and coagulopathy that

occur in hematological diseases lead to endothelial dysfunction and thrombo-embolism with subsequent development of pulmonary hypertension (PH). In addition, treatment used for these disorders such as immunosuppressive drugs, splenectomy, bone marrow transplantation and radiation therapy are also known to cause endothelial damage and thrombo-embolism leading to PH. Furthermore, there is a causal relationship between vascular and hematopoietic systems. Patients with chronic myeloproliferative diseases are at a risk of developing PH; and the occurrence of myelofibrosis contributing to impaired hematopoiesis is not uncommon in PH.

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INTRODUCTION

Pulmonary hypertension (PH) is a devastating sequela of a number of diverse systemic diseases including cardiopulmonary, autoimmune, inflammatory and myeloproliferative diseases, drug toxicity, acquired immunodeficiency syndrome, portal hypertension, and hemolytic anemia. Based on the clinical diagnosis, PH is classified into 5 major groups, which was updated in 2013[1]. Group 1 is labeled pulmonary arterial hypertension (PAH). Included in this group are idiopathic and heritable PAH, PAH associated with human immunodeficiency viral infection, schistosomiasis, congenital heart defect, connective tissue diseases, portal hypertension and drug-induced PAH. In the current updated classification, PH associated with hematological disorders, myeloproliferative diseases and splenectomy has been moved to Group 5. Pulmonary veno-occlusive disease (PVOD)/pulmonary capillary hemangioma and persistent PH of the newborn are in Group 1 as subcategories (1′ and 1″ respectively). Group 2 comprises PH associated with congenital and acquired left heart diseases, Group 3 includes PH due to lung diseases and/or hypoxia, Group 4 includes chronic thromboembolic pulmonary hypertension (CTEPH). PH associated with hematological disorders, myeloproliferative diseases, splenectomy and a number of miscellaneous systemic and metabolic disorders are included in group 5. PH is defined as a mean pulmonary artery (PA) pressure of $\geqslant$ 25 mmHg at rest as measured by cardiac catheterization. Right heart catheterization is considered the gold standard for the diagnosis of PH. Echocardiography is a useful noninvasive tool to estimate right ventricular systolic pressure (in the absence of right heart obstruction) for screening and monitoring the patients with PH[2].

Pulmonary vascular endothelial injury/disruption is considered to be an important initiating factor in the development of PH. The severity, the extent and the site of endothelial damage may determine the type of PH and the irreversibility of the disease. Endothelial cells (EC), a non-thrombogenic monocellular layer function as an interface between the circulating blood and the underlying tissue. EC produce vasorelaxants such as nitric oxide (NO), prostacyclin, and endothelium-derived hyperpolarizing factor. In addition, EC inhibit cell proliferation, and participate in inflammation, thrombosis, barrier function, cell cycle and apoptosis; EC control vascular tone and structure, maintain homeostasis, thus, participate in vascular pathobiology. NO, generated from L-arginine by catalytic activity of endothelial NO synthase (eNOS) in vascular EC is a short-lived free radical; it stimulates soluble guanylate cyclase that catalyzes guanosine triphosphate to cyclic guanosine monophopshate (cGMP). Increase in cGMP results in a decrease in Ca^{2+} levels that mediates NO functions including vascular relaxation[3]. eNOS is localized in special cellular domains in EC including Golgi bodies and plasmalemmal caveolae, and is tightly regulated by a variety of transcriptional, post-transcriptional and post-translational mechanisms. The proteins that modulate the eNOS activity include caveolin-1, heat shock protein 90, cationic amino acid transporter 1 (arginine transporter), Ca^{2+}-calmodulin, and others. Caveolin-1 is a scaffolding protein of caveolae found on the plasma membrane of a variety of cells including EC, smooth muscle cells (SMC) and fibroblasts. Caveolin-1 interacts with transducing molecules in caveolae and maintains these molecules in an inhibitory state. It has a dynamic relationship with eNOS. In EC, caveolin-1 inhibits NO signaling by binding to eNOS. In response to various stimuli, eNOS is dissociated from caveolin-1, and generates NO. However, caveolin-1 is essential for agonist-induced eNOS activation[3,4]. In addition, the eNOS activity is controlled by endogenous circulating inhibitors; the most important being the L-arginine analog, asymmetric dimethylarginine (ADMA). ADMA inhibits eNOS-mediated production of NO from L-arginine. A large portion of circulating ADMA is metabolized by dimethylarginine dimethylaminohydrolase (DDAH) to L-citrulline and dimethylamine. DDAH is inhibited by oxidative stress, thereby leading to ADMA accumulation and resulting EC dysfunction[5]. Recent studies have shown that erythrocytes take up and store ADMA. Following lysis of erythrocytes, proteolysis of methylated proteins generate free ADMA which then can inhibit NO production leading to EC dysfunction, and contribute to vascular disease[6]. In a group of 34 healthy individuals (age 2 d-24 years), plasma levels of ADMA has been shown to decrease with age[7].

Hemolysis is a common occurrence in a number of hematological disorders. Released free hemoglobin (Hb) as a result of hemolysis reacts with NO and forms inactive nitrate and methemoglobin, thus leading to endothelial dysfunction. In addition, arginase 1 released

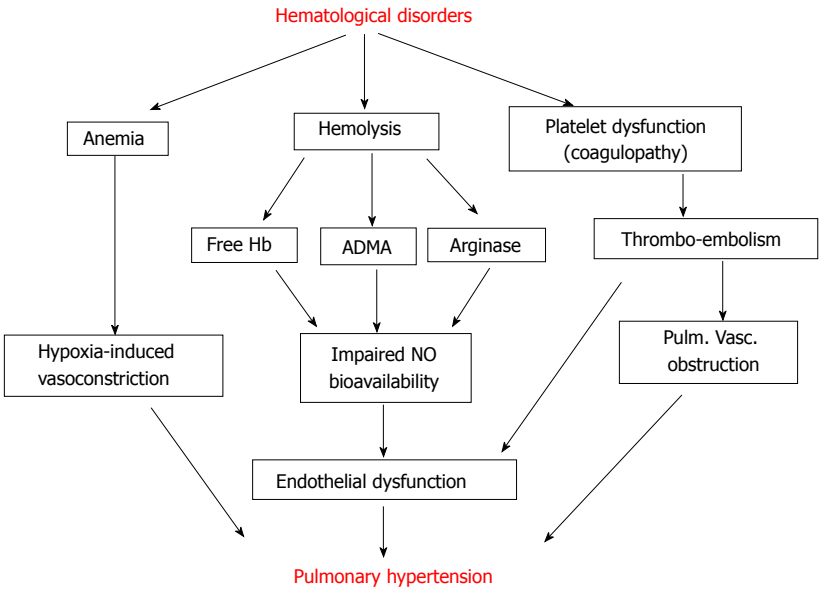

Figure 1 Various pathways of hematological disturbances leading to pulmonary hypertension. ADMA: Asymmetric dimethylarginine; Hb: Hemoglobin; NO: Nitric oxide; Pulm. Vasc.: Pulmonary vascular.

during hemolysis alters arginine metabolism, further reducing NO bioavailability[8,9]. Arginase 1 converts L-arginine to ornithine, a precursor of proline. Proline is an amino acid involved in collagen formation, lung fibrosis and SMC proliferation. Low arginine/ornithine ratio has been reported to be associated with high mortality. Under conditions of low arginine and tetrahydrobiopterin, eNOS is uncoupled generating reactive oxygen species[10]. These changes lead to pulmonary vascular remodeling and increased pressure. Furthermore, therapeutic measures used in patients with hemolytic disorders have been shown to be associated with PH[11]. Figure 1 depicts the alterations observed in hematological disorders that can lead to PH.

Iron is an essential trace element required for a number of biological processes including cellular response to hypoxia, cell proliferation, immune responses and mitochondrial function. It also has the ability to generate free radicals, which cause deleterious effects. Mitochondria use iron for heme synthesis and in iron-sulfur cluster biogenesis. Hepcidin expressed in the liver is thought to be a key regulator of iron homeostasis. Dietary iron is absorbed through the duodenal enterocytes and exported to circulation *via* ferroportin, an iron transporter. Increased levels of hepcidin degrade ferroportin, thus inhibit iron uptake; whereas low levels allow increased iron absorption. Hepcidin is upregulated by BMP6, and inflammatory cytokines including IL-6, IL-1β through JAK2/STAT3 pathway. It is downregulated by iron deficiency, erythropoiesis and hypoxia in order to increase iron levels. Major portion of iron is in erythroid marrow, and erythropoiesis is the major regulator of hepcidin. Erythropoiesis releases erythroferrone that in turn inhibits hepcidin transcription to increase iron absorption. Excess intracellular iron is stored by ferritin that prevents iron-mediated free radical formation[12-15]. Iron circulates bound to a glycoprotein, transferrin, which keeps it soluble; iron is delivered into cells through transferrin receptor (TfR1)[16]. Physiological iron saturation range for transferrin is 20%-45%. Less saturation is indicative of iron deficiency and saturation above 80% is associated with non-transferrin-bound iron which has toxic effect on the tissue[17]. Intracellular iron regulates TfR1 *via* iron responsive elements that are recognized by iron regulatory proteins (IRPs) which bind to iron responsive elements of TfR1, and prevent degradation when the intracellular iron levels are low. Increased cellular iron levels inactivate IRP1 resulting in degradation of TfR. Furthermore, IRP1 and IRP2 are required for mitochondrial iron supply and function[18,19]. Deregulation of iron homeostasis plays an important role in the pathophysiology of hematological disorders and several cardiovascular diseases including PAH. Deregulated iron metabolism can result in iron overload as seen in some of the hematological disorders leading to toxic effects, or to deficiency as seen in anemia. Several recent studies have reported low iron levels in patients with idiopathic PAH, that is considered to be an important risk factor[20].

HEMATOLOGICAL DISORDERS AND PH

Persistent pulmonary hypertension of the newborn associated with anemia

Persistent pulmonary hypertension of the newborn (PPHN) is the result of failure of cardiopulmonary transition at birth. It is associated with cardiovascular anomalies, meconium aspiration syndrome, lung hypoplasia, sepsis, respiratory distress syndrome, or it could be idiopathic. In addition, maternal factors such as diabetes, obesity, elective cesarean section; and maternal drug use such as aspirin, nonsteroidal inflammatory agents and serotonin reuptake inhibitors are known to be associated with PPHN. The incidence of PPHN is about 1.9 per 1000 live births, and the mortality is reported to be 10%. The major findings of PPHN are elevated pulmonary artery pressure, right to left shunt at the foramen ovale or at the ductus level, and

hypoxemia[21,22]. Recent studies have shown that PPHN can also be associated with severe neonatal anemia. However, anemia as a potential cause of PPHN is not well recognized. In a series of 12 infants, 7 were reported to have congenital dysrythropoietic anemia; and three with ε-γ-δ β-thalassemia, one with HbH disease and another one with Diamond-Blackfan anemia[23]. Another report described 3 siblings with dysrythropoietic anemia and PPHN. Two infants survived after blood transfusion, oxygen; and one infant in addition, had received inhaled NO[24]. Others have reported PPHN associated with anemia; one infant with fetal anemia associated with maternal trophoblastic tumor, two infants with fetal anemia due to massive feto-maternal hemorrhage and in the fourth case the reason for anemia was not known. All these infants had received blood transfusion for anemia[25,26]. In addition, neonates with twin-to-twin transfusion syndrome are at a risk of developing PPHN[27]. The reason for PPHN associated with anemia is not clear. Hypoxia secondary to low Hb level could be a contributing factor to PPHN. Interestingly, booster packed red blood cells (RBCs) transfusion has been shown to improve tissue oxygenation in premature infants[25,28]. The increase in plasma Hb levels following transfusion could be an additional factor contributing to high pulmonary artery pressure. Cell-free Hb scavenges NO, thus, leading to vasoconstriction and increased pulmonary artery pressure. Experimental studies have shown transient increase in pulmonary artery pressure following blood transfusion[29]. Furthermore, transfusion with aged stored blood results in increased cell free plasma Hb levels, higher levels of arginase, endothelial dysfunction and increased pulmonary artery pressure[30,31]. Recently, significant reduction in flow-mediated dilatation was reported in adult patients who received old blood (> 21 d) compared with the ones who received fresh blood (< 14 d old)[32]. Inhaled NO prevents the elevation of pulmonary artery pressure induced by aged blood transfusion[31,32]. The possibility of PPHN needs to be considered in the presence of severe anemia in newborns. In addition to blood transfusion, inhaled NO may be necessary to ameliorate PH.

Hemolytic disorders and PH

Hb disorders include sickle cells disease and thalassemia; and RBC membrane diseases include spherocytosis, stomatocytosis and paroxysmal nocturnal hemoglobinurea. PH is one of the leading causes of morbidity and mortality in patients with hemolytic disorders. Major causes of PH in hemolytic disorders are hemolysis, hypercoagulabilty and iron overload resulting from transfusions and splenectomy[9,33-35]. Recently, in a murine model of hemolysis, significant reduction in NO bioavailability due to free Hb was shown to be accompanied by platelet activation and the activation of coagulation pathway resulting in thrombosis, PH, right ventricular failure and death. Interestingly, treatment with sildenafil reduced the mortality rate[36]. Furthermore, Hb has been shown to interact with superoxide and hydrogen peroxide, thus increasing reactive oxygen species formation, lipid peroxidation, and increase inflammatory response. Interestingly, in an experimental model, treatment with haptoglobin, a Hb scavenger was shown to decrease oxidative and inflammatory response and attenuate PH[37]. Free Hb plays a significant role in the pathogenesis of PH in hemolytic disorders; therefore, treatment with Hb scavengers appears to be an attractive therapeutic option.

Sickle cell disease: Hb in patients with sickle cell disease (SCD) is structurally different; valine is substituted for glutamic acid in the 6th position of β-globulin subunit of Hb[38]. This mutation produces abnormal and insoluble HbS. The major genotypes of SCD are homozygous SS, heterozygous SC and S/β thalassemia. In the United States, 0.15% of African-Americans are homozygous for SCD, and 8% have sickle trait. SCD is characterized by anemia, severe pain, potentially life-threatening complications such as bacterial sepsis, splenic sequestration, acute chest syndrome, stroke, chronic organ damage resulting from chronic hemolysis and intermittent ischemia. Vasculopathy in SCD results in irreversible organ damage, a frequent cause of death beyond childhood. Recent studies have shown that chemically-induced RBC stiffness leads to increased pulmonary artery pressure and pulmonary vascular resistance[39]. Importantly, sickled RBCs are stiffer than controls[40], which may partly contribute to PH in SCD. Furthermore, RBCs from SCD patients have an abnormal tendency to adhere to vascular endothelium. This abnormal adhesion plays an important role in facilitating the trapping of sickle cells in post-capillary venules and causing vascular obstruction which is the underlying factor for the characteristic features of SCD such as painful vascular occlusive crises and acute chest syndrome. In addition, the sickle cell adherence to EC results in the activation of EC and a chronic state of inflammation. Endothelial activation is a critical component of the microvascular responses accompanying SCD resulting in inflammatory response, increased expression of cell adhesion molecules and reactive oxygen species, and altered vasomotor tone leading to vasculopathy including PH. Interestingly, hypoxia/reperfusion injury causes inflammatory response in sickle cell transgenic mice[41-43].

Morbidity and mortality in SCD are high, and PH is a serious complication in SCD. Sudden death in patients with SCD and PH is not uncommon[44,45]. In a small series of autopsy cases (12 patients), 75% of patients had right ventricular hypertrophy and 50% revealed large thrombus in pulmonary artery, and 40% exhibited pulmonary vascular remodeling. The mortality in patients with catheterization-confirmed PH is 50% within 2 years compared to 7% at 10 years in SCD patients without PH[46-49]. In adult population with SCD, echocardiography revealed high incidence of PH (27%) as assessed by a tricuspid regurgitation jet velocity

(TRJV) of > 2.5 m/s, however, the incidence was confirmed to be 6%-10% by cardiac catheterization, and > 50% of these patients had post-capillary PH[50-52]. A recent study showed increased TRJV in children to be associated with an increased PA pressure, increased cardiac output due to anemia and normal pulmonary vascular resistance[53]. The incidence of PH in patients with SCD, however, is relatively high (6%-10%), compared with the normal population (2.4-7.6 people/million per year). It is noteworthy that SCD patients with lower pulmonary artery pressure are at a higher risk compared with idiopathic PAH with equivalent pressure. Recent experimental studies in rodents reveal that it is the Hb-induced inflammation and to a lesser extent the Hb-induced oxidant injury leads to vascular injury[54]. Thus, RBC sickling, rheological abnormalities, hypoxemia, heme-induced oxidant injury and resulting inflammatory response leading to endothelial dysfunction play a major role in vasculopathy leading to vaso-occlusive disease including PH.

Thalassemia: Thalassemia diseases are an inherited Hb disorders associated with chronic anemia, impaired erythropoiesis and dysregulated iron metabolism; resulting from defective synthesis of α and β subunits of HbA. Absence or impaired production of α globulin results in β thalassemia and vice versa. PH is quite rare in α thalassemia. β thalassemia is characterized by impaired erythropoiesis and dysregulated iron metabolism. Two types of β thalassemia have been described; thalassemia major (TM) and thalassemia intermedia (TI). Patients at birth are asymptomatic because of the presence of HbF. Diagnosis of TM is usually made during infancy because of anemia. They require frequent transfusion and chelation therapy which have improved their survival. Furthermore, well transfused patients with TM are at a lower risk of developing PH. In contrast, the TI patients remain transfusion-independent for a longer period; the incidence of PH is higher in this group[34,55-57]. Pathophysiology of PH in thalassemia is similar to other hemoglobinopathies. Chronic hemolysis, iron overload, splenectomy, hypercoagulability, vascular inflammation and left ventricular dysfunction contribute to the pathogenesis of PH. Dysregulated arginine metabolism[58] and elevated levels of ADMA[59] have been reported in patients with β-thalassemia associated with PH. Higher incidence of PH was noted in patients with E/β-thalassemia who had more severe hemolysis and had had splenectomy; in addition, inflammatory markers were increased[60]. Increased non-transferrin bound iron and increased transferrin saturation indicative of iron overload increase the risk of cardiopulmonary damage[61]. Interestingly, in a mouse model of β thalassemia, transferrin treatment normalized labile plasma iron levels and RBC survival, and increased hepcidin expression[62]. In addition, increased hepcidin levels were accompanied by increased BMP2 expression in the liver and concomitant decrease in extracellular-signal related kinase (ERK) activation[63].

Compared to β thalassemia, SCD patients do not have iron overload. This difference is thought to be due to the presence of chronic inflammation in SCD which could block iron release from reticulo-endothelial system. In addition, unlike SCD, hepcidin levels are low in β thalassemia, which can further enhance iron absorption[64]. In β thalassemia, transfusion not only improves anemia but also suppresses erythropoiesis and increases hepcidin levels[65]. Globin chain imbalance leads to ineffective erythropoiesis, and erythroferrone suppresses hepcidin production during increased erythropoiesis, resulting in low hepcidin levels and increased iron absorption. In a mouse model of β-thalassemia, ablation of erythroferrone restored hepcidin expression and reduced iron accumulation without affecting anemia[66]. Furthermore, thalassemia carriers have been reported to have abnormal iron metabolism[67].

RBC membrane disorders: RBC membrane-associated abnormalities are found in inherited disorders such as spherocytosis and stomatocytosis. A defect in one or several proteins such as ankyrin, spectrin (α and β), band 3 has been reported. Paroxysmal nocturnal hemoglobinuria (PNH) is an acquired RBC membrane defect. RBCs play a role in regulating membrane properties to undergo reversible deformation while maintaining integrity. In addition, RBCs have a pivotal role in regulating cell volume homeostasis. Inability to regulate cell volume is a feature of hemoglobinopathies[68-70].

Hereditary spherocytosis (HS) is considered not to be associated with thrombo-embolic risk. In a recent study, 26 children who underwent splenectomy, no evidence of PH or coagulation defect was observed during a follow-up period of median 4.5 years[71]. In another study that included 36 patients with HS (28 with splenectomy and 8 without), no evidence of PH was found[72]. However, arterial and venous thrombo-embolic events in patients with HS have been observed after splenectomy[73]; and several cases of CTEPH have been reported in patients with HS several years after splenectomy[74-76]. In a review of 22 patients with CTEPH following splenectomy, 3 patients with HS had had splenectomy 17-35 years before the diagnosis of CTEPH was made[77].

In hereditary stomatocytosis, the RBC membrane shows a leak of univalent cations (Na^+ and K^+). Two clinical variants have been recognized; hydrocytosis (overhydrated) and xerocytosis (dehydrated). Stewart *et al*[78] described 11 patients with stomatocytosis after splenectomy. Most of them had thrombo-embolic episodes, and 3 of them developed PH. Other case reports have described PH in patients with stomatocytosis several years (approx 6-30 years) after splenectomy. One patient underwent successful pulmonary endarterectomy for CTEPH. He had undergone splenectomy as a child because of the family history of spherocytosis[79]. Another patient with dehydrated hereditary stomatocytosis underwent

splenectomy because of splenic infarct following air travel. Approximately 12 years later she developed CTEPH. Because of the worsening condition she underwent successful heart-lung transplantation[80]. The third case of stomatocytosis had splenectomy done for traumatic rupture of the spleen. About 6 years later he developed PH[81]. Splenectomy is not recommended for stomatocytosis, however, stomatocytosis is often mistaken for spherocytosis, and splenectomy is performed. At times it is difficult to distinguish RBC morphology; therefore, intracellular electrolyte measurements or flux studies may be required to make the correct diagnosis[78].

PNH is a progressive hemolytic disorder. It is an acquired clonal genetic deficiency of glycosylphosphatidylinositol-linked protein on the RBC surface that leads to complement-mediated hemolysis[35,82]. One case of PNH was diagnosed to have PH 5 years after splenectomy and associated chronic thromboembolism[83]. In one study, 41% patients with PNH and associated hemolysis (total 29 patients) had echocardiographic evidence of PH. Treatment with eculizumab reduced hemolysis[82,84]. In another study, 23 patients with PNH and hemolysis were examined before and after eculizumab therapy. Importantly, markers of endothelial dysfunction (sVCAM1, vWF) and coagulation activation were significantly reduced after eculizumab therapy[85].

Chronic myeloproliferative diseases and PH

Evidence is accumulating to suggest a link between PH and chronic myeloproliferative diseases (CMPD). CMPD originate in multipotent hematopoietic progenitor cells that are characterized by increases in one or more types of blood cells. CMPD include polycythemia vera, essential thrombocythemia, idiopathic myelofibrosis and chronic myeloid leukemia (CML)[86]. Dingli *et al*[87] examined 26 patients with CMPD and echocardiography based diagnosis of PH (estimated systolic pulmonary artery pressure 35-100 mmHg); 24 patients had symptoms related to PH and 4 had had splenectomy. The mortality rate among these patients was high. Another report[88] described 6 patients with myeloproliferative disease who developed PH (echocardiographic diagnosis, and in 4 confirmed with cardiac catheterization), and all had had splenectomy; 5 patients died within 1-6 mo of PH diagnosis. Lung histology in 3 patients revealed pulmonary myeloid metaplasia and fibrosis. A 72-year-old patient developed PH, right ventricular failure and thrombocytosis after splenectomy. The peripheral blood smear revealed megakaryoblasts. Interestingly, treatment with hydroxyurea not only decreased the platelet counts but also improved right heart failure. It was considered possible that megakaryocytes created obstruction in the pulmonary capillaries leading to PH[89]. In a group of 30 patients with a past history of thromboembolism, high incidence of valve disease (aortic and mitral valve with vegetation) was noted; 13% of patients had PH secondary to venous obstruction[90]. In another study, 46 patients with essential thrombocytosis were compared with 40 patients with reactive thrombocytosis secondary to anemia. In the essential thrombocytosis group, elevated platelet levels and 43% thrombo-embolic events were recorded; and 47.8% (22/46) had echocardiographic evidence of PH. In contrast, the reactive thrombocytosis secondary to anemia group did not have increased platelet levels, thrombo-embolic events or PH[91]. Garypidou *et al*[92] reported incidence of PH by echocardiography to be 41.7% in 24 patients with CMPD. In another report, among 103 patients with various CMPD, echocardiographic diagnosis of PH was made about 15 mo after the initial diagnosis of CMPD. The incidence of PH was found in less than 5%[93]. A 50 years old individual was diagnosed to have PH (confirmed by cardiac catheterization) 15 years after the diagnosis of latent myeloproliferative disorder and portal hypertension. Portal hypertension is a known complication of CMPD[94]. PVOD also has been reported in CMPD. A patient with myeloproliferative and myelodysplastic syndrome was treated with hydroxyurea for 4 years. Because of refractory thrombocythemia and hydroxyurea-induced neutropenia, anagrelide was started. Six weeks later, the patient was admitted with severe dyspnea at rest and was diagnosed to have PVOD[95]. Guilpain *et al*[96], reviewed 10 cases of CMPD (8 polycythemia vera and 2 essential thrombocythemia) and PH; 6 patients developed CTEPH and 4 patients had PAH. Importantly, CTEPH occurred early in the course of the disease and PAH occurred several years after the diagnosis of CMPD. All patients with PAH revealed myeloid metaplasia but none in the CTEPH group.

The patients with CMPD are at a risk of developing PH; and the occurrence of myelofibrosis in patients with PAH is not uncommon and is thought to contribute to impaired hematopoiesis. Popat *et al*[97] reported moderate to severe myelofibrosis in 14/17 patients with PAH. However, platelets and granulocytes in PAH patients were polyclonal unlike monoclonal cells that were found in patients with polycythemia vera and essential thrombocythemia. Erythropoietin facilitates erythroid lineage and proliferation. Erythropoietin has also been shown to induce tyrosine phosphorylation of JAK2 and to associate with it for biological activities including mitogenesis[98]. In a number of patients with CMPD, an acquired somatic *JAK2V617F* mutation has been observed, which confers a selective growth advantage. Interestingly, a small molecule inhibitor of JAK2 has been shown to attenuate myeloproliferative disease in a mouse model[99,100]. However, the patients with PAH (13 Familial PAH, 24 Idiopathic PAH, and 15 Associated PAH) and the controls did not reveal JAK2 mutation[101], nor was the JAK2 mutation noted in 19 patients with myelofibrosis secondary to PH[102]. Circulating $CD34^+CD133^+$ cells were higher in familial PAH compared with idiopathic PAH and the control subjects; interestingly, in non-affected family members, the $CD34^+CD133^+$ cell counts were comparable to

that observed in Familial PAH group[101]. Furthermore, patients with PAH and myelofibrosis have blood vessels morphologically similar to what is observed in myeloproliferative myelofibrosis such as, microvascular density, distended lumina and irregular branching. In addition, VEGF levels are much higher in patients with primary myelofibrosis compared with the controls; and even higher in patients with primary myelofibrosis associated with PH. However, in PH associated with myeloproliferative diseases, the levels of circulating endothelial progenitor cells and the bone marrow pericytes were lower[103,104]. Almost a century ago it was thought that EC and hematopoietic cells have a common progenitor, hemangioblasts. Furthermore, EC and hematopoietic cells affect each other[105], which may explain the increased incidence of PH in CMPD and myelofibrosis accompanying PH. Transplantation of bone marrow-derived $CD133^+$ cells from PAH patients into mice has been shown to result in endothelial injury, angioproliferative remodeling of pulmonary vasculature and right ventricular failure; $CD133^+$ cells from control subjects, however, had no effect[106]. Recent studies have shown that bone marrow cells from BMPR2 mutant mice when transplanted into control mice induce PH, whereas bone marrow cells from the control mice protect mutant mice from developing PH[107]. These results further support a causal relationship between vascular and hematopoietic systems.

Autoimmunity, PH and hematological disorders

Autoimmunity is a well-known underlying feature of hematological disorders as well as of PH. Autoimmune diseases such as systemic sclerosis, systemic lupus erythematosus (SLE), Sjogren's disease, and mixed connective tissue diseases are known to be associated with PH[108-110]. Loss of $CD4^+CD25^+$ cells, the T regulatory (Treg) cell population has been reported in several forms of PAH[110]. Furthermore, normal Treg function has been shown to limit the vascular injury and provide protection from developing PH[111]. In 132 patients with SLE, the incidence of PH was 12.9%. PH patients had longer duration of anemia; oxygen delivery was inversely related to PA pressure, indicating that tissue hypoxia may play a greater role in the lupus-associated PH[112]. Another patient with SLE and associated lupus anticoagulant and clotting disorder was described to have PH[113].

Autoimmunity is also important in thyroid diseases and thyroid disease-associated PH. Scicchitano *et al*[114] in a recent review article have discussed the prevalence of PH in hypothyroid state as well in hyperthyroid state. Interestingly, approximately half of the patients with PAH have been shown to have autoimmune thyroid disease[115]. Coagulation abnormalities associated with thyroiditis[116] may lead to chronic embolism and eventually CTEPH. Furthermore, thyroid hormone participates in EC proliferation and facilitates angiogenesis. Recent studies with an angio-proliferative model (Sugen + hypoxia) of PH have shown that thyrodectomy inhibits angioproliferation and reduces the expression of p-ERK1/2, integrin receptor $\alpha v\beta 3$, fibroblast growth factor (FGF) 2 and FGF receptor[117]. These results suggest that the status of thyroid function in PH is important and it may affect the progression of the disease adversely.

Evan's syndrome includes immune thrombocytopenia and associated autoimmune hemolytic anemia. Connor *et al*[118] reported 2 children with Evan's syndrome and associated PH; both with the evidence of perivascular lymphoid infiltration indicative of vasculitis. Both improved with steroid and rituximab treatment. The incidence of PH in Evans's syndrome, however, is not known. PH has also been reported in an adult patient with autoimmune hemolytic anemia who improved significantly on regular steroid therapy[119].

Therapy-associated PH

A number of alkylating agents including cyclophosphamide, bleomycin, mitomycin used for hematological diseases have been shown to lead to PVOD and PH[11,120]. Other therapeutic measures used for hematological disorders such as tyrosine kinase inhibitor dasatinib, interferon, splenectomy, bone marrow transplantation (BMT) and radiation also contribute to PH as discussed below.

Dasatinib: CML is caused by active BCR/ABL tyrosine kinase. Tyrosine kinase inhibitor, imatinib inhibits BCR/ABL and platelet-derived growth factor (PDGF), and has been used as a first line treatment for CML with good results. However about 29% of patients do not recover completely with imatinib, therefore, newer tyrosine kinase inhibitor, dasatinib is used as a second line treatment. Dasatinib inhibits Src kinase in addition to BCR/ABL and PDGF. Several case reports have appeared showing the development of precapillary PH after about 8-48 mo of dasatinib therapy[121-127]. In the French experience, the incidence of dasatinib-associated PH is 0.45%. The patients, however, did not recover fully after having been taken off dasatinib treatment. Interestingly, in the monocrotaline (MCT) and hypoxia-induced PH models, the pretreatment with dasatinib, unlike imatinib induced increased pulmonary artery pressure and increased inflammatory cells in the perivascular area. Furthermore, *in vitro* studies with human pulmonary EC, dasatinib induced apoptosis in a dose dependent manner through mitochondrial reactive oxygen species generation[128,129]. Interestingly a number of patients with dasatinib-induced PH is accompanied by pleural effusion (as high as 68%), which is not observed in classical PH. In most cases, discontinuing the medication appeared to have reversed PH; however, in a few cases prolonged PH therapy might be required[130]. Recent studies have shown that the inhibition of Src tyrosine kinase or dasatinib increases pulmonary artery pressure, and depolarizes PA SMC by altering potassium channels[131]. Thus, dasatinib-associated Src inhibition and the alterations in potassium channels may be

responsible for the increased vasoconstriction and PH. It is noteworthy that decreased expression of Src tyrosine kinase has been reported in the lungs of patients with PAH[132]. It is suggested that Src function may depend on the state of vascular SMC[133].

Interferon: Interferon (IFN) α and β are used for various hematological disorders, cancer and infection especially hepatitis C. Evidence is accumulating to suggest that IFN pathway may have a role in the pathobiology of PH. INF therapy has been shown to be complicated by vasculopathy. IFN therapy has been shown to lead to reversible PH and in some cases irreversible PH[134-136]. Infusion of IFN-α into sheep has been shown to elevate pulmonary artery pressure associated with increased expression of thromboxane B2, a stable byproduct of thromboxane A2, a vasoconstrictor; that is attenuated by a selective thromboxane A2 synthetase inhibitor, OKY-046[137]. Interestingly, a subgroup of patients treated with INF exhibit increased levels of endothelin-1 (ET-1), which is known to play an important role in PH. Recent studies have shown that IFN induces *ET1* gene and IFN-inducible protein IP10, a mediator of inflammation in vascular SMC; and the combination of IFN and TNF-α produce the highest amount of ET1. These cytokines have direct effect on ET1 transcription and also on increased translocation of NF-κB and STAT1[138]. Importantly, recent studies have shown increased levels of IP10 and ET1 in patients with PAH which correlated positively with serum brain natriuretic peptide and the status of the disease. These Authors have further shown increased type 1 IFN receptor (IFNR1) protein levels in the lungs of patients with PAH compared with the controls. Furthermore, IFNR1 knockout mice exhibit attenuated response to hypoxia[139]. These studies strongly indicate a role for IFN in the pathobiology of PAH.

Splenectomy: A number of patients who undergo splenectomy following trauma or for various hematological disorders develop PH, associated with histological changes in pulmonary arteries such as intimal fibrosis, plexiform lesions and thrombo-embolic lesions. The prevalence of PH in patients in the presence of asplenia is reported to be 11.5%[140]. In another study, 22 out of 257 patients with CTEPH (8.6%) had a prior history of splenectomy, compared with the positive history of splenectomy in 2.5% of idiopathic PAH patients and 0.4% in general population[77]. PH has been shown to occur several years after splenectomy for hereditary spherocytosis[74,75], stomatocytosis[78], thalassemia[141] and Hb Mainz hemolytic anemia[142]. Splenectomy is associated with deep vein thrombosis and un-resolving recurrent thrombosis eventually leading to CTEPH. Loss of spleen results in a loss of filtering function leading to abnormal circulating erythrocytes and the activation of coagulation. The activation of platelets enhances thrombin generation as well as cytokine activation. Human thrombi obtained after pulmonary endarterectomy revealed increased platelet-derived micro-particles and increased anionic phospholipids (phosphotidylserine, phosphotidylethanol and phosphotidylglycerine), reduced angiogenesis related gene expression, and reduced vascular canalization. These micro-particles are pro-coagulant. In addition, in a murine model of CTEPH, inhibition of angiogenesis was associated with delay in thrombus resolution[143,144]. In a rabbit model with splenic artery ligation, transfusion of sonicated blood resulted in platelet rich thrombi in pulmonary circulation; in contrast, transfusion of normal blood did not have any effect[145].

BMT: BMT is used for a number of blood disorders and cancer. Hepatic veno-occlusive disease is a well-established complication of BMT and cytotoxic drugs. In 1984, Troussard *et al*[146] were the first ones to report a child who developed PVOD a few years after having received BMT for a relapse of acute lymphoblastic leukemia. Since then, PVOD following BMT have been reported in several adults and children[147-152]. Hepatic veno-occlusive disease is a recognized complication of cytotoxic therapy used concomitantly with BMT. BMT in combination with cytotoxic drugs and radiation increases the chances of EC damage and PH. Another possibility that has been considered is that malignancy itself may cause PH[151]. Transplantation-associated thrombotic microangiopathy (TM-TMA), a known complication of BMT is caused by EC injury resulting in thrombin and fibrin deposition in microcirculation with ensuing organ damage. Jodele *et al*[153] have described 5 children who developed severe PH 71-205 d after having undergone hemopoietic stem cell transplantation. These children did have TM-TMA 56-101 d before the diagnosis of PH was made. PH can occur from a few months to several years after transplantation**.** In addition, PH without any evidence of PVOD was reported to occur in an adult almost a year after BMT[154]. A 5.25-year-old child underwent BMT after conditioning with cyclophosphamide and antithymocyte globulin; and he was treated with cyclosporine A and a short course of methotrexate to prevent graft-*vs*-host disease. Within a month of BMT, he developed respiratory distress, anemia and thrombocytopenia. Approximately 1.5 mo later, he was diagnosed to have microangiopathic changes. His condition, however, stabilized after cyclosporine A was discontinued and treatment with mycophenolate mofetil was started. About a year or so later he started to have vague respiratory symptoms which was subsequently diagnosed as severe PH[155]. These cases illustrate that PH can occur early or late after BMT. Cytotoxic drugs and radiation used to prepare the patient for BMT and to prevent graft-*vs*-host disease can contribute to EC damage leading to pulmonary vasculopathy. These patients need to be carefully monitored and PH should be considered a possibility when they present with

pulmonary symptoms.

Radiation injury: Lung radiation leads to pneumonitis, fibrosis and vascular injury. Thoracic or whole body radiation is used for several types of lung cancer; and at times radiation in combination with immunosuppressive drugs is used before BMT. PVOD and pulmonary insufficiency have been reported to occur several months to years following therapy for cancer that included chemotherapy and radiation therapy. Histopathological changes in the lungs comprised interstitial fibrosis, thromboemboli, veno-occlusive lesions, and medial hypertrophy of pulmonary arteries, consistent with PVOD[156,157]. In addition, a 14-year-old was reported to have developed PH after receiving radiation therapy during infancy following the surgical removal of neuroblastoma arising from the left of the thoracic spine. At cardiac catheterization significant PH was noted. In addition, the branches of left pulmonary artery were described as hypoplastic, and the pulmonary veins from the left lung were underdeveloped[158].

EC play a pivotal role in radiation-induced vascular injury. Irradiated EC from rectal adenocarcinoma have been shown to induce fibrogenic phenotype in vascular SMC, and increase proliferation and migration[159]. Furthermore, several experimental studies have shown radiation injury resulting in elevated pulmonary artery pressure, and structural remodeling of the small pulmonary arteries. In a sheep model, several weeks after the whole lung exposure to radiation resulted in abnormal vascular reactivity, PH and pulmonary vascular remodeling[160]. In a mouse model, low dose radiation resulted in EC injury, followed by rapid recovery. However, a higher dose resulted not only in EC injury, but also a delay in recovery followed by prolonged EC proliferation, fibroblast proliferation and collagen secretion indicative of significant vascular damage[161]. In a rat model, radiation injury induced pulmonary vascular EC damage followed by medial wall and adventitial thickening, neointima formation and obliteration of vessels similar to what is observed in PAH[162].

These studies underscore the fact that vascular EC are susceptible to radiation injury. The patients who receive radiation therapy with or without alkylating drugs are at a risk of developing PH. PH has been shown to occur several years after the cessation of therapy; therefore these patients need a long careful follow-up.

IRON HOMEOSTASIS AND PAH

Deregulation of iron homeostasis and resulting alterations in iron availability plays an important role in the pathogenesis of cardiovascular diseases including PH. Both iron deficiency and iron overload have deleterious effect on cardiovascular system. Iron deficiency has been shown to have an adverse effect on survival in patients with chronic heart failure[163]. Anemia in PH is associated with worse function and poor survival[164]. Iron deficiency is being recognized as an important factor in the prognosis of PAH. Low transferrin saturation, an indicator of iron deficiency has been reported in PAH patients, particularly the ones with BMPR2 mutation, but not in the CTEPH group. In this group of PAH patients, 72% of iron deficient patients had anemia, whereas only 4% in non-iron deficient patients[20]. In another study, iron deficiency was found in 43% of 70 patients with idiopathic PAH accompanied by low exercise capacity. However, anemia did not affect the exercise intolerance. Interestingly, 8 out of 18 patients did not respond to oral iron therapy[165]. Red cell distribution width (RDW), a biomarker of anemia has a better survival predictive value independent of NT-proBNP levels and 6 min walk distance. Increased RDW was accompanied by other indicators of iron deficiency such as decreased ferritin levels and low transferrin saturation. Patients with increased soluble TfR (sTfR) had higher mortality independent of WHO class or exercise capacity. sTfR levels are a sensitive marker of tissue iron availability, unaffected by inflammation. Interestingly, hepcidin levels were increased in PAH despite iron deficiency. Hepcidin which restricts iron absorption is stimulated by cytokines and BMP6; however, hepcidin levels did not correlate with IL-6 levels. Since a number of patients have BMPR2 mutation and loss of function, it is likely that increased BMP6 levels secondary to BMPR2 loss may increase hepcidin levels. Furthermore, erythropoietin levels are increased in idiopathic PAH despite the fact that these patients were not anemic. The hematocrit and Hb levels were not different compared with the controls. Erythropoietin is known to reduce hepcidin levels in order to increase iron uptake. Increased levels of hepcidin in the presence of increased erythropoietin indicates deregulated erythropoiesis in idiopathic PAH[166,167]. In 29 patients with idiopathic PAH, 46.2% of iron deficient patients belonged to NYHA functional class 3 or higher compared with 12.5% in non-iron deficient. There were no differences in the hematocrit or Hb levels between the two groups. The iron deficiency was related to the severity[168]. In addition, zinc protoporphyrin (ZnPP) levels, indicative of iron deficiency was significantly higher in patients with idiopathic PAH associated with increased RDW; however, ZnPP levels were not altered in "Associated" PAH. Iron containing protein is also required for mitochondrial electron transport and catalyzes reactions that form NO[169]. Intravenous iron therapy in patients with idiopathic PAH was well tolerated and it improved endurance capacity; however, it did not alter cardiac function[170]. Thus, iron deficiency seems to be a more important prognosticator compared with anemia.

Iron deficiency is common in patients with systemic sclerosis (SSc) associated with PH than in the non-PH group. PH was present in 27.8% of patients with SSc. Iron deficiency was associated with poor exercise tolerance and survival. Hepcidin levels were high in the SSc population, but did not correlate with IL-6

levels. Hb levels, however, were not altered. Soluble transferrin receptor (sTfR) levels in both groups were significantly increased associated with iron deficiency[171]. Interestingly, iron-depletion by desferrioxamine infusion in normal individuals resulted in higher systolic pulmonary artery pressure during 8 h hypoxia compared with the iron-repleted individuals. Thus, the alterations in iron availability affect the pulmonary vascular response to hypoxia. HIF is implicated in hypoxia; it is likely that increased iron potentiates HIF hydroxylation and its degradation[172]. Sufficient iron availability is required for adjustment to high-altitude hypoxia. There is a close connection between oxygen and iron homeostasis[173].

Recently it was reported that iron-deficient diet in rats resulted in elevated PA pressure, right ventricular hypertrophy, vascular remodeling, and increased expression of HIF1α, HIF2α, STAT3 activation and aerobic glycolysis, which could be reversed by iron therapy[174]. Furthermore, deletion of iron regulatory protein 1 (IRP1) in mice leads to PH and polycythemia that is exacerbated by low iron diet, resulting in increased HIF2α levels and ET1 in EC. Iron deficiency can stabilize HIF2α by diminishing activity of iron-dependent prolyl hydroxylases involved in HIF2α degradation[175]. In contrast, dietary iron restriction attenuated monocrotaline-induced PH, although, the serum iron concentration in MCT group was not different from the control group. However, the expression of TfR1 in pulmonary arteries was increased. Interestingly, TfR1 hetero-knockout mice showed attenuated hypoxia-induced PH, right ventricular hypertrophy and vascular remodeling[176,177]. Iron chelation has been shown to attenuate hypoxia-induced PH, pulmonary vascular remodeling and right ventricular hypertrophy in rats. In addition, carbonylation of proteins was increased in hypoxia-induced rats as well in the plasma of the patients with PAH indicative of oxidative stress[178]. Furthermore, PH in patients with idiopathic pulmonary fibrosis was shown to correlate with iron deposition in alveolar spaces[179]. These foregoing results show opposite effects of iron levels on pulmonary vasculature. Iron homeostasis is intricately balanced and maintained; any injury and/or stress can alter this balance resulting in iron overload or iron deficiency. Mitochondria play a pivotal role in energy and iron metabolism[180]. The opposing effects of iron levels observed in different forms of PH may depend on the level of non-transferrin-bound iron and on the status/health of mitochondria.

In summary, hemopoietin system, pulmonary vasculature and iron metabolism are intricately related. Hematological disorders affect pulmonary vasculature and PH can cause myelofibrosis. Deregulated iron homeostasis and resulting status and function of mitochondria in PH may have an important effect on prognosis.

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MINIREVIEWS

Cardiac biomarkers in pediatric heart disease: A state of art review

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Abstract

Every year there are more than 11000 hospitalizations related to heart failure in children resulting in significant morbidity and mortality. Over the last two decades, our understanding, diagnosis and management of pediatric heart failure is evolving but our ability to prognosticate outcomes in pediatric heart acute heart failure is extremely limited due to lack of data. In adult heart failure patients, the role of cardiac biomarkers has exponentially increased over the last two decades. Current guidelines for management of heart failure emphasize the role of cardiac biomarkers in diagnosis, management and prognostication of heart failure. It is also noteworthy that these biomarkers reflect important biological processes that also open up the possibility of therapeutic targets. There is however, a significant gap present in the pediatric population with regards to biomarkers in pediatric heart failure. Here, we seek to review available data regarding cardiac biomarkers in the pediatric population and also explore some of the emerging biomarkers from adult literature that may be pertinent to pediatric heart failure.

Key words: Pediatric heart failure; Biomarkers; Cardiac; Outcomes; Congenital heart disease

Core tip: Biomarkers such as BNP, ST2 are well established in adult heart failure. Emerging data supports the use of some of these biomarkers for diagnosis, monitoring and prognostication of pediatric heart disease. Continued research is needed to better understand these established and emerging biomarkers. Here, we review the available data regarding cardiac biomarkers in the pediatric population and also explore some of the emerging biomarkers from adult literature that may be pertinent to pediatric heart disease.

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INTRODUCTION

Pediatric acute heart failure is now being increasingly recognized as an important source of healthcare resource utilization with 11000 to 14000 heart failure related hospital admissions in the United States every year[1,2]. Additionally, pediatric heart failure is associated with significant morbidity and mortality. Over the last two decades, our understanding, diagnosis and management of pediatric heart failure is evolving. This is especially true with regards to acute heart failure. However, unlike adult heart failure, underlying mechanisms and etiology is responsible for pediatric heart failure are very heterogeneous from simple congenital heart defects, cardiomyopathies to complex palliated single ventricle patients. Similar to the underlying etiologies, management and outcomes in these groups of patients are also very variable. However, ability to prognosticate outcomes in pediatric heart acute heart failure is extremely limited due to lack of data.

In adult patients with heart failure both related to ischemic and non-ischemic cardiomyopathy, the role of cardiac biomarkers has exponentially increased over the last two decades.

Current American Heart Association guidelines for management of heart failure emphasize the role of cardiac biomarkers in diagnosis, management and prognostication of heart failure[3]. This is especially true for two biomarkers included in these guidelines *viz.* brain-type natriuretic peptide and suppression of tumorigenicity-2 (ST2)[3]. In addition to these there are several biomarkers being studied that have provided additive information beyond the well-established biomarkers. It is also noteworthy that these biomarkers reflect important biological processes that also open up the possibility of therapeutic targets.

There is however, a significant gap present with regards to biomarkers in pediatric heart failure. Here, we seek to review available data regarding cardiac biomarkers in the pediatric population and also explore some of the emerging biomarkers from adult literature that may be pertinent to pediatric heart failure.

B-TYPE NATRIURETIC PEPTIDE AND N-TERMINAL SEGMENT OF PRO-B-TYPE NATRIURETIC PEPTIDE

B-type natriuretic peptide (BNP) and the N-terminal segment of pro-BNP (NT-ProBNP) are used as essential parts of adult cardiologic evaluation. BNP belongs to a larger family of titrated peptides which have a paracrine role in the body. It is primarily secreted by cardiocytes in the form of pre-pro-peptides. These pro-peptides are synthesized within the endoplasmic reticulum of the cardiac cells where they're stored as specific atrial granules. These pre-pro-peptides have a constant basal rate of release and play an important regulatory function in maintenance of salt and water homeostasis. Various stimuli such as myocardial stretch or stress can lead to a very rapid increase in the secretion of these pre-pro-peptides. Once released it undergoes conversion into pro BNP which is cleaved by serine peptidases into the active moiety BNP and inactive moiety NT-proBNP. Outside of the heart, kidneys and blood vessels are the major target organs where natriuretic peptide receptors types A, B and C are present. Once receptor bound, BNP leads to increased diuresis, natriuresis and vasorelaxation. On the cardiac sites, BNP has significant anti-proliferative and anti-hypertrophic properties mediated by the same receptor[4]. Since its first description in 1970s by de Bold[5,6], natriuretic peptides have been extensively studied in various disease conditions both cardiac and non-cardiac. It is one of the most studied biomarker for heart failure. The cumulative data has led to the recognition of its value in diagnosis, management and prognosis of heart failure by the current AHA/ACC heart failure guidelines[3].

BNP and age

BNP and NT-ProBNP levels vary with age especially in the pediatric group. Immediately after birth, BNP and NT-ProBNP are elevated and then rapidly decrease after the first week of life. Reasons for this physiologic fluctuation in the levels are unclear at this point, but hypotheses include removal of the placenta and thereby significant redistribution of blood volume to the heart causing a volume overload and an increase in the afterload at the same time. Rapid increase in pulmonary blood flow with lung expansion further adds to the stimulus. Lastly, renal immaturity may contribute to decreased clearance of the BNP during the first week of life. As a result, the BNP (and NT-proBNP) levels are significantly elevated in newborns and drop rapidly over the first two weeks of life. The BNP concentrations due appear to hold steady until 12 years of age without any differences in gender. However, in the second decade of life, higher BNP levels were seen in girls than in boys. This parallels differences in the activity of the renin-angiotensin-aldosterone system, renin levels (higher in males) as well as the influence of gonadal hormones in the second decade of life[7-10]. BNP, along with the biomarkers reviewed here are also summarized in Table 1.

BNP and congenital heart disease

Before delving into the diagnostic value of BNP, it is important to note that BNP levels are strongly method dependent. This is because different assays that are used to measure BNP use different methods and have varying sensitivities and specificities. The various com-

Table 1 Overview of cardiac biomarkers and their physiologic actions

Name of biomarker	Mechanism of action	Primary effect	Available evidence
BNP/NT-ProBNP	Activates the intracellular Guanylyl cyclase-A moieties after binding to the NPR types A, B and C	Increases diuresis, natriuresis and vasorelaxation Anti-proliferative and anti-hypertrophic properties	[4]
ST2	After binding to its TL/IL-1 receptor like family, interacts with IL-33	Anti-proliferative and anti-hypertrophic properties	[3]
CTGF	Unknown	Deposition of extracellular matrix	[43]
h-FABP	Participate in the uptake, intracellular metabolism and transport of fatty acids	Modulation of cell growth and proliferation	[48]
Pro-adrenomedullin	Releasing nitric oxide from the endothelium Inhibit nicotinic agonist-induced catecholamine secretion and synthesis and nicotinic agonist-induced Na^+ and Ca^{2+} influx	Regulation of hormonal secretion Angiogenesis proliferation Vasodilation	[50]
GDF-15	Unknown	Deposition of extracellular matrix	[55]

ST2: Suppression of tumorigenicity-2; CTGF: Connective tissue growth factor; h-FABP: Serum heart-type fatty acid-binding protein; BNP: B-type natriuretic peptide; NT-ProBNP: N-terminal segment of pro-B-type natriuretic peptide; GDF: Growth differentiation factor.

ponents of pro-BNP cleavage impact measurements to varying degree depending on the method used. Hence, the reference ranges change according to which method was used.

BNP has utility in diagnosis of congenital heart disease (CHD) in newborns. Cantinotti *et al*[11] have shown that while there is a rapid decline in the BNP levels in normal newborns within the first few days of life, newborns with CHD maintain significantly elevated levels beyond 5 d of life. This was true across the spectrum of various congenital heart defects except those leading to volume or pressure overload on the right heart[11]. Maher *et al*[12] studied infants with left-sided obstructive lesions admitted to our center. Infants were divided into 2 groups: Group 1 was diagnosed with cardiogenic/circulatory shock at presentation, and group 2 consisted of infants with ductal-dependent systemic circulation without evidence of shock. In this group of total 122 patients, newborns with cardiogenic shock had a median BNP of 4100 pg/mL at presentation compared to a median BNP of 656 pg/mL ($P < 0.001$) for those without shock. A 100% of patients presenting with shock had significantly abnormal BNP values. They also report an incremental value of BNP such that every 100 units rise in BNP increased the odds of cardiogenic shock by 100 ($P < 0.001$)[13].

A study comparing new diagnosis of CHD in an emergency room setting evaluated the value of BNP compared to patients with diagnosis of respiratory distress due to primary respiratory illness or infection. This study found that in a cohort of critically sick patients with a heart disease, a mean BNP value of 3290 pg/mL was seen in patients with heart disease when compared to 17.4 pg/mL for the patients with respiratory illness or infection[13]. Koulouri *et al*[14] (2004) and Cohen *et al*[15] (2005) report similar findings that plasma BNP or NT-proBNP can differentiate between cardiac or pulmonary etiologies for patients presenting with respiratory distress.

Elevation of BNP/pro-B-type NP are seen due to long term exposure of right heart or left heart to volume and pressure overload. These elevations are especially seen with diseases that causes left ventricular volume overload when compared to right ventricular volume or pressure overload[16]. Furthermore, when comparing pediatric populations with complex CHD *vs* simple cardiac defects (ASD, VSD or PDA), on average, complex defects tend to have higher concentrations. Nir *et al*[9] (2004) showed that patients with higher pressure left to right shunts (VSD, PDA) have higher levels of NT-proBNP when compared to low pressure left to right shunts (ASD). BNP can be used to differentiate preemies with and without a patent ductus arteriosus (PDA) as well as potentially guide therapy. Attridge *et al*[17] showed that by using BNP, fewer doses of indomethacin were used for therapy of PDA. Of note, the pediatric heart can compensate better with pressure overload than volume overload and this can directly impact BNP secretion or level. A normal BNP reflects a compensated heart status but does not rule out heart disease.

BNP can assist in clinical decision making especially when identifying populations at high risks for outcomes after cardiac surgery. Various studies have shown that post-operative BNP, lack of decrease in BNP post-operatively were all strongly related to poor hemodynamics or adverse outcomes after a cardiac surgery[18,19]. Bobik *et al*[20] evaluated the value of NT-pro BNP in patients with atrioventricular septal defects (AVSD) preoperatively. They found that patients with complete AVSD had higher levels of BNP preoperatively compared to partial AVSD. Additionally, NT-proBNP levels predicted longer ICU length of stay, ventilator needs and inotropic support needs post-operatively[20].

For pediatric patients supported on mechanical support (ECMO), Huang *et al*[21] have suggested the utility of serial BNP monitoring before, during and after decannulation from ECMO. In their series, it was noteworthy that after coming off ECMO, BNP levels on the fourth day after removal of ECMO among the

survivors (median, 498 pg/mL) were significantly lower than those among non-survivors (median, 3900 pg/mL; $P = 0.017$)[21].

BNP and heart failure without structural heart disease

As mentioned above, majority of adults have heart failure (ischemic or non-ischemic) in the setting of structurally normal heart. In pediatric patients dilated cardiomyopathy is the most dominant etiology for heart failure[22]. Additional forms such as restrictive, hypertrophic cardiomyopathies are rare but important causes of genetic cardiomyopathies and heart failure. Amongst acquired causes, myocarditis followed by rheumatic heart disease in certain regions of the globe cause acute and chronic heart failure in children.

Although the overall incidence of these clinical conditions is relatively common, our understanding of BNP in these patients is not as robust. Mir *et al*[23] reported significantly higher NT-ProBNP levels in children with heart failure (from various etiologies) than health children. Ohuchi *et al*[24] showed that the BNP levels differentiated NYHA classes regardless of the underlying etiology. Law *et al*[25] in their study used two cutoff values to differentiate between a hemodynamically significant cardiologic process *vs* other disease process with a similar presentation. For neonates, a cutoff value of 170 pg/mL showed a sensitivity of 94% and a specificity of 73%. For the older age group, a cutoff value of 41 pg/mL produced a sensitivity of 87% and specificity of 70% to detect significant cardiovascular disease and related heart failure[25]. For patients presenting with acute heart failure in non-CHDs, our data (currently under review) indicated that mean BNP at presentation in this cohort is very elevated; mean of approximately 1700 pg/mL. In the outpatient setting for pediatric populations with chronic left ventricular systolic dysfunction, BNP values > 300 pg/mL have shown high sensitivity, specificity, positive and negative predictive value for the prediction of adverse cardiovascular events. Price *et al*[26] studied pediatric patients with chronic heart failure. They found that whole blood BNP concentrations were increased in patients who had a 90-d adverse cardiovascular event compared with those who did not (median, 735 pg/mL *vs* median, 37 pg/mL; $P < 0.001$). Patients with a BNP concentration > 300 pg/mL were at increased risk of death, hospitalization, or listing for cardiac transplantation (adjusted hazard ratio, 63.6; $P < 0.0001$)[26].

BNP and other diseases (post-chemotherapy, heart transplantation, Kawasaki disease, cardiac surgery)

BNP can be used to predict cardiac dysfunction in a myriad of conditions such as post-chemotherapy cancer patients, rejection from heart transplantation and Kawasaki disease. It is well known that anthracyclines exposure can lead to significant cardiac dysfunction. As such, serial measurement of BNP maybe of value to detect anthracycline induced cardiomyopathy. Studies have shown BNP to correlate with both early and late effects of anthracycline exposure, correlate well with echocardiographic findings as well as other makers of cardiac dysfunction[27].

Utility of BNP in patients with heart transplantation is being increasing explored. Lan *et al*[28] (2004 showed that BNP was elevated early on after heart transplantation however, falls exponentially early on and reached very low levels around 3 mo post-transplant. Lindblade *et al*[29] and Rossano *et al*[30] showed that BNP was significant elevated in acute rejection and had sensitivities of 96% with BNP > 100 pg/mL 1 year after transplantation. Sparks *et al*[31] have documented reduction in BNP over the first 3 mo and showed correlation it with hemodynamics. Overall, it appears that BNP correlates well with acute episodes of rejection, especially when accompanied by hemodynamic compromise.

Kawasaki disease is an acute febrile vasculitis process that may have cardiac manifestations such as myocarditis, pericarditis and coronary vasculitis leading to coronary ectasia and aneurysms. In one of the earlier studies to assess the utility of BNP in Kawasaki patients, Kurotobi *et al*[32] studied echocardiographic markers of diastolic function during acute phase of Kawasaki disease. They found that diastolic dysfunction occurs during the acute phase of the disease and BNP levels correlated well with the presence of significant diastolic dysfunction[32]. Similarly, Iwashima *et al*[33] have demonstrated the utility of BNP in identifying non-responders. They demonstrated that high level of NT-pro BNP in acute phase KD was associated with systemic inflammatory responses, elevated CRP, and increased vascular permeability. This level was particularly higher in immunoglobulin (IVIg) non-responders compared to responders (1689.3 ± 1168.8 pg/dL *vs* 844.4 ± 1276.3 pg/dL, $P < 0.001$)[33].

ST2

ST2 receptor is a member of toll like/IL-1 receptor family. It interacts with IL-33, a cytokine synthesized by cardiac fibroblasts leading to a cardioprotective stress-induced signaling that produces both antihypertrophic and antifibrotic cell signaling. ST2 is present in a membrane bound and soluble form. Soluble ST2 (sST2) may prevent the binding of IL-33 to a membrane-bound receptor version of ST2. The soluble ST2 has been shown to be of significant value in diagnosis and prognosis of heart failure. One of the key initial studies looked at myocyte stretch induced marked upregulation of myocardial *ST2* gene expression[34,35]. This was followed by multiple, large studies which have corroborated the importance of ST2 in heart failure. An analysis of the patients enrolled in the PRIDE study showed that elevated ST2 levels at presentation to the emergency room with dyspnea was a very strong predictor of death at one year. This was true for both patients with dyspnea as well as those with acute heart failure[36]. In a recent study, Parikh *et al*[37] studied population of

community-dwelling older individuals enrolled in the Cardiovascular Health Study. They found that soluble ST2 levels were significantly associated with incident heart failure, cardiovascular death and that greater ST2 level was continuously associated with increasing hazard for cardiovascular death[37]. Various studies have documented the incremental value of addition of ST2 to pre-existing predictive models of heart failure[37,38]. Accumulation of these data have led the ACC/AHA guidelines to recommend ST2 measurement for additive risk stratification in patients with acute or chronic ambulatory heart failure[3]. Normal concentration of ST2 in adults is less than 18 ng/mL, with a level greater than 35 ng/mL generally accepted as a predictor of morbidity and mortality.

Data regarding pediatric application of ST2 is extremely limited. Meeusen *et al*[39] evaluated healthy children between 2-17 years of age and measured their soluble ST2 levels using the Presage ST2 quantitative assay (Critical Diagnostics, San Diego, CA, United States). The median value for the entire cohort was 21 ng/mL (range: 6 to 122 ng/mL). They found that the ST2 levels normally increase with age, was slightly higher in males and that the central 95th percentile reference interval was 9-50 ng/mL[39].

Mathews *et al*[40] report analysis of patients with heart transplantation and small bowel transplantation and present relationship between soluble ST2 and episodes of rejection. ST2 levels are significantly elevated at the time of acute rejection (cellular and or antibody mediated) in pediatric heart transplant patients. During an episode of biopsy proven rejection, serum sST2 was elevated compared to rejection-free time points (1714 ± 329 pg/mL *vs* 546.5 ± 141.6 pg/mL; $P = 0.0002$). The authors found that, a level of > 600 pg/mL could discriminate time points of acute rejection and nonrejection [area under the curve (AUC) = 0.724 ± 0.053; $P = 0.0003$][40]. Additive value of ST2 as a marker for rejection needs to be validated.

In pediatric patients with idiopathic or primary pulmonary hypertension, Chida *et al*[41] studied the utility of ST2, BNP and other cardiac biomarkers. They report finding to statistically significant relationship between ST2 levels and functional class in these patients. Additionally, ST2 levels along with BNP levels were predictive of poor outcomes. On AUC analysis, a cutoff value of 11.1 ng/mL was identified for mortality prediction, with an AUC of 0.830. The authors conclude that ST2 and BNP levels correlate with clinical status and our predictive of outcome in pediatric patients with pulmonary hypertension[41].

To date, there has been only one published study looking at the utility of ST2 in pediatric heart failure. Hauser *et al*[42] evaluated 114 patients (and 89 controls) with heart failure due to various etiologies, analyzed for different biomarkers along with BNP for diagnostic utility. In this study, MR-proANP was the only novel biomarker that performed in a comparable manner to BNP as far as diagnostic utility was concern. ST 2 levels were not statistically different between controls and heart failure patients[42]. However, it is noteworthy that only 17/114 (15%) of patients with heart failure were in class Ⅲ or class Ⅳ heart failure. The rest of the patients were categorized as class Ⅰ or Ⅱ heart failure. It is therefore not surprising that majority of the levels were not different compared to the controls. Subgroup analysis of the 17 patients with class Ⅲ or class Ⅳ heart failure is not available. Our experience with a pilot group of 15 pediatric heart failure patients was more favorable. In our patients, the ST2 levels ranged from 14 to > 1000 ng/mL, with a mean of 229.7 ng/mL. BNP values ranged from 217 to 18216 pg/mL with a mean of 4179.5 pg/mL. There was a very strong and statistically significant correlation between ST2 and BNP levels in this cohort. We could not establish correlation between functional status or ventricular function (ejection fraction) and ST2 levels probably due to a small sample size (unpublished data).

This biomarker therefore warrants more studies in the pediatric heart failure population to establish its value in diagnosis and prognosis.

CONNECTIVE TISSUE GROWTH FACTOR /CCN2

In addition to the myocardial remodeling seen in heart failure, the role of extracellular matrix is being increasingly recognized. The ultrastructural changes in the extracellular matrix contribute towards both functional as well as structural changes that take place in acute and chronic heart failure. Enhanced collagenous deposition and fibrosis are some of the key changes in the extracellular matrix in CHF. Various mediators and matri-cellular proteins in the extracellular matrix are being increasingly looked at as biomarkers for heart failure. Connective tissue growth factor (CTGF) is one such matri-cellular protein that is involved in pathologic process of fibrosis in addition to other physiologic conditions such as endochondral ossification, vascular growth, cellular growth. Recently CTGF plasma levels have been investigated in patients with chronic and acute heart failure[43]. Koitabashi *et al*[44] studied CTGF levels along with other cardiac biomarkers as well as markers of fibrosis in 52 patients with chronic heart failure. In this study plasma CTGF levels were significantly elevated in patients with symptomatic heart failure and strongly correlated with plasma BNP, TGF beta, matrix metalloproteinase levels. Plasma CTGF levels also correlated with E/E' ratio[44].

Behnes *et al*[45] studied CTGF levels in 212 patients enrolled in the Mannheim NT-proBNP study including 66 patients with acute heart failure. This study showed that CTGF levels were significantly elevated (median 93.3 pg/mL) in patients with heart failure with reduced ejection fraction as well as in patients with acute heart failure (median 77.3 pg/mL) when compared to those with normal heart function (median 25.9 pg/mL). In

addition, CTGF significantly improved the diagnostic capacity of NT proBNP for acute heart failure. There is limited data in pediatric heart failure[45]. Li *et al*[46] studied CTGF and BNP levels in 61 children including 41 with heart failure. They report that CTGF levels were significantly increased in patients with heart failure and that the levels correlated with the severity of heart failure. Addition of CTGF levels to NT-proBNP levels also improved ability to diagnose heart failure in children[46]. The same group has also shown significant correlation of CTGF levels with pulmonary arterial hypertension associated with CHD in children[47].

SERUM HEART-TYPE FATTY ACID-BINDING PROTEIN

The serum heart-type fatty acid-binding protein (h-FABP) is an intracellular transport protein mainly involved in transport of fatty acids. When compared to skeletal muscle, it is highly expressed (about 10 ×) in cardiac muscle. H-FABP has a very strong specificity for diagnosing myocardial injury since it has a small size and so rapidly appears in the blood stream and no isotype mismatch between different types of FABP. Sun *et al*[48] showed both h-FABP and BNP concentrations have good correlation with the degree of heart failure in patients with CHF. In their study, they also evaluated the effects of therapy with carvedilol and found that initiation of carvedilol was associated with decrease in h-FABP and BNP levels. They concluded that h-FABP can be used as biomarkers to evaluate the severity of heart failure in children[48]. In a different study, the group has also demonstrated the utility of h-FABP as a marker of cardiac involvement in patients with Kawasaki disease[49].

PRO-ADRENOMEDULLIN

The adrenomedullin protein (ADM) is protein is cleaved to form adrenomedullin and proadrenomedullin (proADM). This protein has several functions including regulation of hormonal secretion, promotion of angiogenesis, antimicrobial activity and vasodilation. CHF is a complex multifactorial process and since there is neurohormonal activation playing quite an important role in HF, ADM can be implicated in this process. Gegenhuber *et al*[50] found that ADM was found to be elevated and comparable to BNP in patients with acute decompensated heart failure. They also found that high concentrations of ADM predicted 1-year all-cause mortality[50]. Furthermore, ADM may not only be used to evaluate the severity of HF but also a prognostic indicator of this syndrome. In a study by Khan *et al*[51] looking at the value of proADM in heart failure patients post-myocardial infarction, they found that proADM was an excellent predictor of mortality. Additionally, proADM provided further risk stratification in those patients who had NTproBNP levels above the median and therefore could be of additive value[51].

Due to the implication of fluid distribution and vasodilatory properties, this biomarker has been used to predict response to treatment in patients with postural orthostatic tachycardia syndrome (POTS). Zhang *et al*[52] have shown that the levels of midregion-proADM are elevated in patients with POTS and that midodrine responsive patients had higher levels compared to non-responders. ROC analysis showed that a cutoff value for MR-proADM of 61.5 pg/mL produced both high sensitivity (100%) and specificity (71.6%) in predicting the efficacy of midodrine hydrochloride therapy for treating POTS[52].

GROWTH DIFFERENTIATION FACTOR

Growth differentiation factor (GDF-15) is a member of the TGF-B cytokine family that is implicated in the stress response. Unlike h-FABP that is expressed by the myocardium, GDF-15 is not. However, GDF-15 expression is induced in the heart in response to inflammation, tissues injury, ischemia, pressure overload. It is known that GDF-15 is elevated in the setting of left ventricular overload but may also be in response to right ventricular pressure changes as seen in pulmonary embolism. Kempf *et al*[53] found that GDF-15 can provide prognostic information in patients with heart failure. They found that GDF-15 was significantly increased in these patients. They however, concluded that since GDF-15 is non-specific for cardiac myocytes and is involved in stress overload pathways, GDF-15 would need to be compared to specific cardiac makers to get a complete prognostic assessment[53,54]. Raedle-Hurst *et al*[55] found that GDF-15 levels are significantly associated with NYHA functional class and heart function of patients after completing the Fontan procedure for single ventricle. Since Fontan physiology is not a good model of pressure overload on the single ventricle, they found that NT-proBNP failed to be directly related to the echocardiographic measures of heart function. They concluded that GDF-15 is an early marker of decreased heart function in this cohort while NT-proBNP appear to be late markers when clinical heart failure is already present. They used a cutoff of > 613 pg/mL to suggest further cardiac evaluation may be indicated to assess for impaired ventricular function[55]. A recent meta-analysis has found that increased levels of GDF-15 were associated with increased mortality in patients with heart failure (HR of 1.86, 95%CI: 1.37-2.52), although cautions about heterogeneity in the studies as well as potential publication bias[56]. Overall, it appears that GDF-15 studies focused on specific pediatric patient populations (volume load, pressure load) may clarify its role in diagnosis and prognosis of pediatric heart failure.

CONCLUSION

As our understanding of the pathobiology of heart

disease evolves we continue to identify important biomarkers responsible for the same. These biomarkers are indicative of the cascade of events resulting in various forms of heart failure and heart disease. Elucidation of these processes is extremely important as they have the potential to identify new therapeutic targets. Specifically, biomarkers therefore play a vital role in diagnosis, management and prognosis of heart failure. Of all the biomarkers reviewed, BNP continues to be the dominant biomarker even in pediatric heart failure. Our understanding of the role of these novel biomarkers, some of which have already established a role in adult heart failure, will improve with further research. There is therefore an intermediate and an urgent need for undertaking biomarkers research in pediatric heart failure to enable us to improve care of these patients.

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MINIREVIEWS

Newer perspectives of coronary artery disease in young

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Abstract

Coronary artery disease (CAD) occurring in less than 45 years of age is termed as young CAD. Recent studies show a prevalence of 1.2% of CAD cases in this age group. Ethnic wise south Asians especially Indians are more vulnerable to have CAD in young age group with a prevalence of 5% to 10%. Conventional risk factors such as smoking, diabetes, hypertension, obesity and family history seems to be as important as in older CAD subjects. But the prevalence of these risk factors seems to vary in younger subjects. By far the most commonly associated risk factor is smoking in young CAD. Several genes associated with lipoprotein metabolism are now found to be associated with young CAD like cholesterol ester transfer protein (*CETP*) gene, hepatic lipase gene, lipoprotein lipase gene, *apo A1* gene, *apo E* gene and *apo B*. Biomarkers such as lipoprotein (a), fibrinogen, D-dimer, serum Wnt, gamma glutamyl transferase, vitamin D2 and osteocalcin are seems to be associated with premature CAD in some newer studies. In general CAD in young has better prognosis than older subjects. In terms of prognosis two risk factors obesity and current smoking are associated with poorer outcomes. Angiographic studies shows predominance of single vessel disease in young CAD patients. Like CAD in older person primary and secondary prevention plays an important role in prevention of new and further coronary events.

Key words: Young; Coronary artery disease; Risk factors; Epidemiological trends; Prognosis

Core tip: Coronary artery disease (CAD) in patients less than 45 years of age is termed young CAD. South Asians especially Indians are more vulnerable to have CAD in young age group. Although conventional risk factors, mainly smoking, are also important in young CAD but there are numerous other factors that are responsible for it. Several genes associated with lipoprotein metabolism are now found to be associated with young CAD. Gamma glutamyl transferase, vitamin D2 and osteocalcin seem to be associated with premature CAD in some studies. Angiographic studies shows predominance of single vessel disease in young CAD patients.

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INTRODUCTION

Coronary artery disease (CAD) occurring below the age of 45 years is termed as young CAD[1]. However various studies had considered the age limit varying from 35 years to 55 years in the spectrum of young CAD[2-10] (Table 1). This arena of cardiology has gained importance very recently due to increased prevalence in this age group over a last few decades, with varying risk factor profiles and difference in prognosis as well as longevity after an acute coronary episode. Recently, apart from the established biomarkers of CAD, many new markers, specifically associated with young CAD are discovered. The purpose of this review is to analyse the changing epidemiological trends, role of conventional and newer risk factors and prognosis of young CAD population.

TRENDS IN EPIDIMIOLOGICAL PROFILE

Coronary heart disease is the leading cause of morbidity and mortality, worldwide both in developing as well as developed countries, and is responsible for one third or more of all deaths in individuals greater than 35 years of age[11,12]. World Health Organisation has projected that burden due to CAD is going to increase globally from 47 million disability adjusted life years (DALYs) in 1990 to about 82 million DALYs in 2020. Many studies have demonstrated that young CAD contributes to 2% to 6% of all acute coronary events[13]. In the early 1980s, the Framingham study (FHS) reported a 10 year CAD incidence of 12.9 per 1000 in the age of 30 to 34 years and 5.2 per 1000 in the age group 35 to 44 years, in men and women respectively[14].

Studies have shown an increased prevalence of CAD in the subjects with family history of premature CAD, than in general population (35% *vs* 14%)[15]. The original as well as offspring cohort data of Framingham study, by National heart lung and blood institute (NHLBI's), from 1880 to 2003 revealed an annual incidence of cardiovascular disease of 3 per 1000 men between 35 to 44 years of age[16]. Centre of disease control prevalence data for the year 2010 revealed that prevalence of CAD in the age group of 18 to 44 years, 45 to 64 years and more than 65 years was 1.2%, 7.1% and 19.8% respectively[17]. Epidemiological data of United Kingdom published in the year 2000, reported a prevalence of 0.5% and 0.18% in men and women between 35 to 44 years respectively[1]. The prevalence of occult CAD in 112 asymptomatic young individuals, less than 40 years of age, was found to be 11% (9 had single vessel disease and 3 had double vessel disease) in a study done in Korea. The occult CAD in these individuals was defined by performing coronary CT angiography[18].

Table 1 Spectrum of terminology for young coronary artery disease

No.	Terminology	Age group studied	Ref.
1	Young CAD	Less than 45 yr	Ericsson *et al*[2]
2	Young CAD	Less than 40 yr	Konishi *et al*[3]
3	Young CAD	15-39 yr	Gupta *et al*[4]
4	Very young CAD	⩽ 35 yr	Christus *et al*[5]
5	Premature CAD	Men ⩽ 45 yr Female ⩽ 55 yr	van Loon *et al*[6]
6	Premature CAD	Less than 60 yr	Genest *et al*[7]
7	Premature CAD	Less than 45 yr	Pineda *et al*[8]
8	Precocious CAD	2 case reports of familial CAD of 29 and 31 yr	Norum *et al*[9]
9	Early onset CAD	Less than 45 yr	Iribarren *et al*[10]

CAD: Coronary artery disease.

The mean age of onset of CAD in Southeast Asians seems to be 53 years as compared to European figure of 63 years[19]. South Asians especially Indians are at greater risk of developing CAD at a young age (5% to 10%) when compared to other ethnic groups (approximately 1% to 2%)[20]. Reported prevalence of young CAD under the age of 40 years, in a study published from Indian subcontinent, in 1991 was 5% to 10%. This vulnerability of Indians to coronary events may be related to life style, environmental and genetic factors[20].

The median age of presentation of CAD in young women is higher when compared to men. Singapore myocardial infarction registry of CAD in group less than 65 years showed that men have 4 times greater risk of CAD than women[21]. In Asians 9.7% males and 4.4% females develop first episode of MI under 40 years of age[20].

RISK FACTORS PROFILE

Conventional risk factors (Table 2)

Prevalence of conventional risk factors like diabetes, hypertension, smoking, dyslipidemia and obesity accounts for about 85% to 90% of premature CAD patients[22]. Often young CAD patients have multiple coexisting risk factors contributing to the disease[23]. The most common risk factor associated with young CAD seems to be smoking. The prevalence of smoking in younger individuals less than 45 years of age, with CAD, was reported to be 60% to 90% as compared to 24% to 56% in subjects greater than 45 years[13,24]. Smoking in presence of additional risk factors like diabetes, hypertension and obesity predispose a young individual to increased risk of future acute coronary events[25].

The prevalence of diabetes and hypertension seems to higher in young patients with CAD than without CAD. The prevalence of hypertension is 25% in young

Table 2 List of conventional and newer risk factors in young coronary artery disease discussed in the review

Conventional risk factors	Newer risk factors
Age	Polymorphisms in *CETP* gene
Sex	Hepatic lipase gene
Hypertension	Lipoprotein lipase gene
Diabetes mellitus	C-reactive protein gene
Dyslipidaemia	*Apo A1* gene
Obesity	*Apo B* gene
Smoking	*Apo E* gene
Family history of premature CAD	*HIF1A* gene
	Factor 5 leiden
	MTHFR gene
	Methionine synthase gene
	Cocaine use
	Lipoprotein-a, Fibrinogen and D-dimer
	Decreased serum Wnt
	Increased gamma glutamyl transferase
	Raised vitamin D2 and D3
	Decreased osteocalcin
	Hypothyroidism
	Systemic lupus erythematosis
	Rheumatoid arthritis
	HIV patients on HAART
	Homocysteinemia
	Kawasaki disease in childhood,
	Patent foramen ovale
	Spontaneous coronary artery dissection

CETP: Cholesterol ester transfer protein; HAART: Highly active anti retroviral therapy; *MTHFR*: Methylene tetrahydrofolate reductase; *HIF1A*: Hypoxia inducible factor 1 alpha.

CAD as compared to 13% without CAD. Similarly, the incidence of diabetes and pre diabetes is 14.3% and 7.6% in young CAD as compared to only 5.4% and 4.3% in patients without CAD respectively[26]. However, prevalence of these risk factors is much higher in older individuals with CAD as compared to young CAD[27-29]. Various studies have demonstrated a recent increase in the prevalence of hypertension [8.86% (2001-2002) to 27.7% (2009-2010)] and dysglycemia [7.6% (2001-2002) to 36.15% (2009-2010)] in young CAD[30].

Although, dyslipidemia is an important risk factor for young CAD, there seems to be a little difference in prevalence of lipid abnormalities in younger and older patients. One study demonstrated a significantly increased level of LDL and total cholesterol in persons of CAD more than 55 years of age when compared with less than 55 years of age[27]. Conversely in an another study there is high prevalence of lipid abnormalities in young CAD when compared to older CAD group[28]. These differences in lipid parameters may due effect of dietary, genetic and environmental factors on lipid metabolism.

Obesity is a well established risk factor for CAD. There is little difference in the prevalence of obesity in young CAD when compared with older CAD patients[28]. Sagittal abdominal diameter to skin fold ratio seems to be a good indicator in predicting premature CAD, even better than body mass index (BMI) and waist circumference[31].

Family history of premature CAD is an important risk factor for young CAD. It stresses the role of genes in the aetiology of young CAD. Studies have shown that person with a positive family history of premature CAD tend to have severe coronary atherosclerosis and is a very strong predictor of future acute coronary event[32]. The atherosclerosis in coronary vessels, as revealed by increased plaque content is seen in individuals with a positive family history of premature CAD and increases the incidence of severe obstructive CAD[32]. One study revealed around 64% of young CAD patients had a positive family history[13].

The prevalence of conventional risk factors like hypertension (67%), dyslipidemia (67%), obesity (53%), smoking (42%), and diabetes (33%) is higher in women with a family history of CAD[33].

Other risk factors

There are numerous risk factors found to be associated with CAD in younger people. Some of the newer risk factors are discussed in the review. Polymorphisms in cholesterol ester transfer protein (*CETP*) gene, hepatic lipase gene, lipoprotein lipase gene, C-reactive protein gene, *apo A1* gene, *apo E* gene, *apo B*, hypoxia inducible factor 1 alpha gene, factor 5 leiden, Methylene tetrahydrofolate reductase (*MTHFR*) gene and methionine synthase gene have been associated with premature CAD[34-38].

Kuivenhoven *et al*[39] found a significant association between variation at the CETP locus and angiographic progression of coronary atherosclerosis in men with CHD.

The ApoE4 allele has been associated with CAD in several populations. ApoE2/E2 homozygous individuals are at risk for type Ⅲ hyperlipoproteinemia, which is associated with an increased risk for atherosclerosis[40,41].

Homozygosity for the *MTHFR C677T* mutation has been associated with elevated levels of homocysteine, and homocysteine levels have been associated with CAD risk[42,43].

Hepatic lipase (HL) is both a phospholipase and a triglyceride lipase and plays an important role in HDL metabolism and in the conversion of VLDL to LDL. Single nucleotide polymorphisms in the *HL* gene have been shown to associate with plasma lipid concentrations and increased CHD risk[44].

Hypercholesterolemia is the most common and treatable cause of heart disease. Familial Hypercholesterolemia (FH) results from mutations in the LDL receptor, *ApoB*, *PCSK9*, and *ApoE* genes. FH is characterized by isolated elevation of plasma low-density lipoprotein cholesterol and is associated with high risk of premature cardiovascular disease[45].

The prevalence of premature arcus senilis (16.1%), premature greying (34.9%) and premature balding (22.3%) have been found to be significantly increased in young CAD patients when compared to non CAD

subjects of same age[26,46]. Thus young CAD patients are associated with premature ageing as depicted by these markers. The arcus senilis is also a marker of familial hypercholesterolemia which in turn is a risk factor for premature CAD.

Cocaine use is also considered as a risk factor for CAD, it is associated with a number of cardiovascular diseases, including myocardial infarction, heart failure, cardiomyopathies, arrhythmias, aortic dissection, and endocarditis[47].

Young CAD patient shows an increased serum levels of lipoprotein-a, fibrinogen and D-dimer as compared to age matched controls[8]. Decreased serum Wnt, increased gamma glutamyl transferase, raised vitamin D2 and D3 and decreased levels of osteocalcin are found to be associated with premature CAD[48-50]. This association of CAD in young with high levels of vitamin D is in contradiction to the studies done in general population where deficiency of vitamin D is associated with adverse cardiovascular outcomes[51-53].

Diseases such as hypothyroidism, systemic lupus erythematosis, rheumatoid arthritis, HIV patients on highly active anti retroviral therapy (HAART) (especially with protease inhibitors), homocysteinaemia, kawasaki disease in childhood, patent foramen ovale (causing paradoxical embolism) and various other conditions are found to associated with accelerated atherosclerosis[54,55].

The mean age of presentation of spontaneous coronary artery dissection is 35-40 years, and is more common in females. The patients are divided into three groups: A peripartum, atherosclerotic and idiopathic group[56]. Dissection occurs in tunica intima of coronary arteries, the blood penetrates and results in intramural hematoma in tunica media, resulting in restriction in the size of lumen, reduction of blood flow and myocardial infarction[57].

PATHOPHYSIOLOGY OF CAD IN YOUNG

Conventional CAD accounts for about 80% of CAD in young adults. About 4% of heart attacks in young adults are due to congenital abnormalities of the coronary artery anatomy, about 5% due to blood clots that originate elsewhere and are carried to otherwise normal coronary arteries, and block the artery, in another 5%, various disorders of the blood clotting system increase the risk of clot formation. The remaining 6% of CAD in young adults is due to spasm or inflammation of the coronary arteries, radiation therapy for chest tumors, chest trauma, and abuse of cocaine, amphetamines, and other drugs. Coronary segments, with non-significant stenosis and non calcified plaque, shows positive remodeling that might be the cause of CAD in young individuals with normal coronary artery. Positive remodeling is related to plaque instability, suggesting it is more prone to rupture and erosion with subsequent coronary events. Lipid core plaques, in contrast to the severely calcified plaques, showed positive vascular remodeling, thus early plaques are more prone for CAD[58-60].

PROGNOSIS

Obesity and current smoking are the two important conventional risk factors associated with adverse outcomes in the form of increased mortality and future acute coronary events[3]. Mortality of CAD in people of China, less than 40 years of age, was 13.81/100000 in 2006 which increased to 19.07/100000 in 2009[61]. There is a widespread decrease in mortality due to CAD in older age group in the recent years but it not seen in CAD in younger age group[62]. The possible explanation that is proposed is increase in prevalence of risk factors such as diabetes, obesity and hypertension in younger age groups[62]. Mortality after an acute coronary event is two times higher in women than in men under 50 years of age[63,64]. The cause of increased incidence of adverse event in women with premature CAD is still unknown.

In patient with acute coronary event both percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG) are associated with excellent immediate survival (mortality of 0.8% *vs* 1.4% for PCI and CABG respectively at 30 d) as well as long term survival outcomes at end of 5 years[65]. But PCI seems to associated with lower rate of repeated acute coronary events and revascularisation procedures when compared to CABG at the end of 5 years (repeat myocardial infarction 89.9% *vs* 96.6% for PCI *vs* CABG)[66]. Mortality outcomes at 30 d and 3 years after an ST segment elevation myocardial infarction in 3601 patients with and without family history of premature CAD were compared in Harmonizing outcomes with revascularization and stents in acute myocardial infarction (HORIZONS-AMI) trial, which did not show any significant association of family history of premature CAD with mortality outcomes[67]. In patients with young CAD high C-reactive protein have been associated recurrence of future acute coronary event and raised fibrinogen levels seems to be associated with increased mortality[6]. Persons with positive family history of premature CAD and coronary artery calcium scores greater than 80th percentiles benefit from treatment with statins for primary prevention of acute coronary events[68].

Young CAD patients have higher rates of normal coronary vessels on angiography, mild luminal irregularities and increased prevalence of single vessel disease than older CAD patients[24]. In recent study from Nepal of young CAD less than 45 years angiography revealed 7.6% had normal or non critical disease, 6.1% had triple vessel disease, 36.9% had double vessel disease and 53.8% had single vessel disease[69].

Single vessel disease involving left anterior descending artery is much more common in young women when compared with young men with CAD[70,71]. The prevalence of normal coronary arteries in patients with young CAD is about 8% to 22% as reported in various studies[72-74] compared to 3% to 4% in general

CAD population[75]. The cause of this high prevalence of normal angiography in young CAD patients is still unclear. The probable reason could be the natural extra luminal progression of disease in the initial stages, as the vessel wall compensates to maintain unrestricted luminal blood flow[76]. An occlusive thrombus produced by the rupture of an angiographically "invisible" vulnerable plaque totally lysed after few hours or a long-lasting vasospasm leading to complete occlusion of a normal coronary artery or a combination of these two are the most likely mechanism of CAD in patient with normal coronaries[77].

CONCLUSION

The overall prevalence of CAD including the subset of young CAD is on decreasing trend but mortality of CAD doesn't seems to be decreasing when comparing to older CAD patients. In addition to conventional risk factors numerous other risk factors and genes play an important role in the causation of the disease. The prognosis of CAD in younger people is better than older people. Current smoking and obesity have major impact in long term mortality and morbidity. Young CAD patients with an acute coronary event undergoing PCI and CABG have an excellent immediate and long term survival rates.

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ORIGINAL ARTICLE

Retrospective Study

Comparison between the SAPIEN S3 and the SAPIEN XT transcatheter heart valves: A single-center experience

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Institutional review board statement: This study was reviewed and approved by the Ethics Committee of the Institut Cardiovasculaire Paris Sud.

Informed consent statement: Patients were not required to give informed consent to the study because the analysis used anonymous clinical data that were obtained after each patient agreed to treatment by written consent.

Conflict-of-interest statement: Dr. Thierry Lefèvre is a proctor for Edwards LifeSciences. All other authors report no conflict of interest regarding this manuscript.

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Abstract

AIM

To investigate the clinical outcomes of transcatheter aortic valve implantation (TAVI) with the SAPIEN 3 transcatheter heart valve (S3-THV) *vs* the SAPIEN XT valve (XT-THV).

METHODS

We retrospectively analyzed 507 patients that underwent TAVI with the XT-THV and 283 patients that received the S3-THV at our institution between March 2010 and December 2015.

RESULTS

Thirty-day mortality (3.5% *vs* 8.7%; OR = 0.44, *P* = 0.21) and 1-year mortality (25.7% *vs* 20.1%, *P* = 0.55) were similar in the S3-THV and the XT-THV groups. The rates of both major vascular complication and paravalvular regurgitation (PVR) > 1 were almost 4 times lower in the S3-THV group than the XT-THV group (major vascular complication: 2.8% *vs* 9.9%, *P* < 0.0001; PVR > 1: 2.4% *vs* 9.7%, *P* < 0.0001). However,

the rate of new pacemaker implantation was almost twice as high in the S3-THV group (17.3% *vs* 9.8%, *P* = 0.03). In the S3 group, independent predictors of new permanent pacemaker were pre-procedural RBBB (OR = 4.9; *P* = 0.001), pre-procedural PR duration (OR = 1.14, *P* = 0.05) and device lack of coaxiality (OR = 1.13; *P* = 0.05) during deployment.

CONCLUSION

The S3-THV is associated to lower rates of major vascular complications and PVR but higher rates of new pacemaker compared to the XT-THV. Sub-optimal visualization of the S3-THV in relation to the aortic valvular complex during deployment is a predictor of new permanent pacemaker.

Key words: SAPIEN-3 valve; Vascular complications; Permanent pacemaker; Lack of coaxiality; Paravalvular regurgitation

Core tip: The SAPIEN 3 transcatheter heart valve (S3-THV) is associated to lower rates of major vascular complications and PVR but higher rates of new pacemaker compared to the SAPIEN XT valve (XT-THV). Sub-optimal visualization of the S3-THV in relation to the aortic valvular complex during deployment is a predictor of new permanent pacemaker (PPM). Our findings highlight the increased importance to adequately visualize the S3-THV in relation to the aortic valvular complex during deployment, in order to improve device positioning and potentially mitigate new PPM requirements.

Sawaya FJ, Spaziano M, Lefèvre T, Roy A, Garot P, Hovasse T, Neylon A, Benamer H, Romano M, Unterseeh T, Morice MC, Chevalier B. Comparison between the SAPIEN S3 and the SAPIEN XT transcatheter heart valves: A single-center experience. *World J Cardiol* 2016; 8(12): 735-745 Available from: URL: http://www.wjgnet.com/1949-8462/full/v8/i12/735.htm DOI: http://dx.doi.org/10.4330/wjc.v8.i12.735

INTRODUCTION

Transcatheter aortic valve implantation (TAVI) has gained rapid acceptance for patients with severe aortic stenosis[1-4] and has recently been associated with excellent short-, mid- and long-term outcomes in patients at intermediate risk[5-7]. However, TAVI is still associated with a higher incidence of paravalvular regurgitation (PVR), permanent pacemaker implantation (PPM) and vascular complications[8-12] when compared to surgical aortic valve replacement. In order to justify the extension of the procedure to lower risk patients, these adverse outcomes have to be mitigated. The development of novel transcatheter heart valves (THVs) and further iterations of delivery systems and prostheses have contributed to the decrease in complications rates in TAVI[13]. One of the recent developments is the balloon-expandable Sapien 3 transcatheter heart valve (S3-THV; Edwards Lifesciences, Irvine, CA). It has been designed with a lower profile to be delivered in a 14 French sheath (for sizes 23 and 26 mm), and with an external sealing cuff. The lower profile should diminish vascular complications while the sealing cuff should diminish PVL[14,15].

Despite positive procedural and short-term outcomes in small single center series and registries, large reports comparing the S3-THV to its predecessor, the Sapien XT (XT-THV), are lacking[16,17]. Recent reports suggest an increased rate of new PPM implantation following TAVI with the S3-THV, compared to the XT-THV[16,17]. Whether procedural characteristics such as depth of implant are related to PPM implantation with this new device remains unclear[18].

The objective of this analysis was to retrospectively compares the procedural outcomes, 30-d clinical outcomes and one-year mortality of TAVI with the S3-THV *vs* the XT-THV in patients with symptomatic severe aortic stenosis in a single high-volume center. We also explored clinical and procedural predictors of new PPM in the S3-THV group.

MATERIALS AND METHODS

Patient population and procedure

To compare clinical outcomes of patients undergoing TAVI with the S3-THV to those undergoing TAVI with the XT-THV, we retrospectively identified all patients treated with TAVI at our institution with either device. Patients underwent TAVI by the transfemoral, transaortic or transapical approach according to previously described techniques[17].

A multidisciplinary heart team involving at least one interventional cardiologist and one cardiac surgeon discussed all cases and consensus was achieved regarding therapeutic strategy. All patients provided informed written consent for the procedure and data collection, and the local ethics committee approved the study.

Pre-procedural planning

All patients underwent TTE examination and native valve function was assessed according to the recommended guidelines[19]. In addition, pre-procedural MSCT evaluation including measurements of the aortic annulus and aortic root was systematically performed. Aortic annulus dimensions were measured according to standard procedures using dedicated software (Philips Brilliance 64-slice multidetector computed tomography scanner, Philips Healthcare, Best, the Netherlands). Valve prosthesis size was selected in accordance with the manufacturer's recommendations after taking into account other anatomic features such as the presence and location of calcification, eccentricity of the aortic

annulus and dimensions of the sinuses of Valsalva and sino-tubular junction in case of borderline sizing ranges. In addition to dimensions, annulus orientation was assessed with MSCT. Implantation projection was selected so that the aortic valve would be seen coaxially, with the three cusps aligned. Cardiac catheterization and femoral angiography were performed prior to the procedure to assess for concomitant coronary artery disease and vessel narrowing or tortuosity.

Study devices

The SXT-THV and the S3-THV designs have been described in detail previously[15,20]. Both consist of bovine pericardium sewn to a balloon-expandable cobalt-chromium tubular frame. The XT-THV was available in the 23, 26, and 29 mm sizes and was implanted with the use of the NovaFlex catheter, which employed an 18- or 19-F introducer sheaths. The S3-THV is available in the 23, 26, and 29 mm sizes. The device's height is about 15% greater than that of the XT-THV. It was implanted with the use of the lower-profile Commander delivery catheter, which employed 14- (sizes 23 and 26 mm) or 16-F (size 29 mm) expandable sheaths (eSheath, Edwards Lifesciences, Inc.). The S3-THV stent was designed with a frame geometry that provides greater radial force. The difference in cell geometry between the inflow and the outflow causes the valve frame to foreshorten more from the ventricular side. The device also includes an outer polyethylene terephthalate fabric seal designed to minimize PVR.

Study procedure

The techniques of SAPIEN XT and SAPIEN S3 valve implantation have been described in detail elsewhere[15,20]. In our center, all trans-femoral cases were performed under local anesthesia and conscious sedation in the catheterization laboratory. The selected femoral artery was "pre-closed" with two 6-Fr suture-mediated closure devices Perclose ProGlide(Abbott Laboratories, Abbot Park, Illinois). With a pigtail in the right coronary cusp, aortography was performed to correct, if necessary, the implantation projection provided by MSCT. Pre-dilatation was performed routinely in the XT-THV group, but only in cases of severe calcification in the S3-THV group. Device positioning was based on fluoroscopy using annular calcification as a landmark along with serial 12 to 15 mL supra-annular aortography to validate its position. The XT-THV was implanted by means of a 2-step inflation technique[21]. The S3-THV was deployed during one-slow inflation (5-10 s). Prosthesis position and function, and patency of the coronary ostia were evaluated by angiography and transthoracic echocardiography. Significant aortic regurgitation was treated by post-dilatation adding 1 to 3 cc of contrast in the balloon delivery system or second valve implantation if the valve was positioned too high or too low. Removal of the sheath was cautiously achieved with serial contralateral angiograms to detect ilio-femoral complications. In the absence of any conduction abnormality, the pacing lead was removed at the end of the procedure. Patients were monitored in the intensive care unit for at least 24 h after valve implantation. For the transapical and transaortic cases, the SXT-THV and S3-THV were deployed with the Ascendra and Certitude delivery systems, respectively. These cases were performed in a hybrid room.

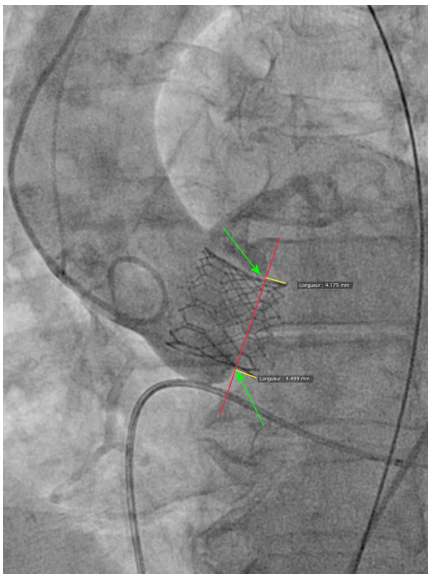

Figure 1 Depth of implant measurement. The arrows show the hinge points between the device and neighboring sinuses of Valsalva. Next, the red line is drawn from the septal to the non-septal hinge point. The yellow lines, drawn perpendicularly from the red line to the extremity of the device frame, represent depth on the septal side (left) and the non-septal side (right).

Data collection and study endpoints

Clinical and echocardiographic data at baseline and follow-up were collected by dedicated personnel and entered in a local database and a national registry (FRANCE-TAVI)[22]. Data from the ECG and MSCT prior to the intervention were retrospectively collected by the co-authors and entered into the local database. The co-authors also retrospectively collected implant depth and device coaxiality from procedure fluoroscopy.

The primary endpoint was 30-d mortality. Secondary endpoints consisted of 1-year mortality, stroke, myocardial infarction, annulus rupture, new PPM implantation, major vascular complication, PVR greater than mild, annulus rupture, acute kidney injury and post-procedural mean gradient. Endpoints were defined according to the VARC-2 criteria[23].

Implant depth and device coaxiality during implant measurement

We reviewed procedural fluoroscopy of all patients in the S3-THV group to measure valve implant depth. A post-implant aortic angiogram with the device coaxial was required for implant depth measurement. First, on a single still frame, the hinge points between the device and the sinus of Valsalva on the septal and non-septal

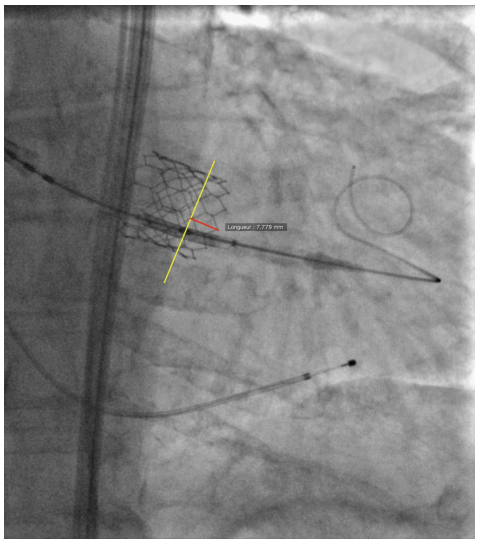

Figure 2 Device coaxiality measurement. On a still frame, immediately after deployment while still under rapid pacing, a line is drawn connecting neighboring valve struts on the ventricular side of the device (yellow line). Next, a perpendicular line is drawn from the yellow line to the tip of the strut that appears the deepest (red line). The length of this red line is recorded as device lack of coaxiality.

side were identified (Figure 1). Next, a line was drawn between both hinge points. The distances between this line and the bottom of the valve frame on both the septal and non-septal sides were then recorded as implant depth. Measurements were performed using the OsiriX sorftware, version 5.9.

In addition to depth, we also measured device lack of coaxiality during deployment. This was done on a single still frame at the end of valve deployment, while still under rapid pacing. The maximal perpendicular distance between the "front" and the "back" struts of the device was measured and recorded as device lack of coaxiality during deployment (Figure 2).

Statistical analysis

Continuous data are reported as mean ± SD, and categorical variables are reported as number of patients and percentages. Categorical data were compared using Fisher's exact test, and continuous data using Student's *t* test or Mann-Whitney's *U* test, as appropriate. Events are reported as counts of first occurrence per type of event. Event probabilities at 30 d were compared for patients treated with the XT-THV *vs* the S3-THV using logistic regression. Crude and adjusted odds ratios (with 95%CI) are reported. Odds ratios are adjusted for procedure date (to account for a potential learning effect of time) and for baseline characteristics with a univariate *P* value < 0.10 for each individual outcome. One-year survival data was fitted in a Cox proportional hazards model and the XT-THV and S3-THV groups were compared using an adjusted hazard ratio. No adjusted analyses were performed for outcomes with less than 15 events overall. Patients with previous pacemaker implantation were excluded from analyses pertaining to the outcome of new pacemaker requirement. A *P* value < 0.05 was considered significant for adjusted models. Statistical analyses were performed with SPSS version 23 (IBM Corp, Armonk, NY).

Table 1 Baseline characteristics

Variable	S3-THV (*n* = 283)	XT-THV (*n* = 507)	*P* value
Age	82.8 ± 7.1	83.5 ± 7.0	0.14
Female sex	137 (48.4)	275 (54.3)	0.12
STS-PROM, %	5.3 ± 3.5	6.4 ± 4.0	< 0.0001
Logistic EuroSCORE, %	15.7 ± 10.8	18.8 ± 11.5	< 0.0001
NYHA class 3 or 4	162 (59.1)	383 (75.8)	< 0.0001
History of syncope	1 (0.5)	10 (2.1)	0.19
Atrial arrhythmia (flutter or fibrillation)	80 (29.5)	135 (27.8)	0.67
Diabetes	71 (25.1)	124 (24.5)	0.86
Hypertension	161 (71.6)	344 (68.8)	0.49
Dyslipidemia	99 (44.0)	263 (52.6)	0.04
Active smoker	4 (1.4)	18 (3.6)	0.11
Previous PPM	35 (12.4)	60 (11.8)	0.91
Previous PCI	81 (29.3)	114 (22.9)	0.06
Previous CABG	25 (9.0)	51 (10.3)	0.62
Previous SAVR	2 (0.7)	7 (1.4)	0.50
Previous stroke	25 (8.8)	39 (7.7)	0.59
Peripheral vascular disease	56 (19.8)	143 (28.4)	0.01
eGFR, mL/min per 1.73 m^2	62.8 ± 24.6	61.4 ± 22.6	0.42
eGFR < 40 mL/min per 1.73 m^2	82 (16.2)	41 (14.5)	0.61
Dialysis	4 (1.5)	13 (2.6)	0.44
Chronic obstructive pulmonary disease	33 (11.7)	110 (21.9)	< 0.0001
Body mass index, kg/m^2	26.5 ± 5.1	26.3 ± 4.9	0.61
LVEF, %	54.9 ± 14.8	53.6 ± 14.2	0.24
LVEF < 30%	55 (11.1)	31 (11.4)	0.91
Mean aortic gradient, mmHg	46.7 ± 15.3	46.9 ± 15.3	0.92
AVA, cm^2	0.67 ± 0.17	0.65 ± 0.14	0.31
Pulmonary artery systolic pressure, mmHg	44.5 ± 13.0	46.5 ± 12.9	0.06
Pulmonary artery systolic pressure > 50 mmHg	64 (28.3)	123 (28.5)	1

Values are mean ± SD or *n* (%). AVA: Aortic valve area; CABG: Coronary artery bypass graft; eGFR: Glomerular filtration rate estimated by the MDRD formula; EuroSCORE: European System for Cardiac Operative Risk Evaluation; LVEF: Left ventricular ejection fraction; NYHA: New York Heart Association functional class; PPM: Permanent pacemaker; PCI: Percutaneous coronary intervention; SAVR: Surgical aortic valve replacement; STS-PROM: Society of Thoracic Surgeons Predicted Risk of Mortality; S3-THV: SAPIEN 3 transcatheter heart valve; XT-THV: SAPIEN XT transcatheter heart valve.

RESULTS

Between March 2010 and December 2015, 790 patients underwent TAVI with the XT-THV (*n* = 507) or the S3-THV (*n* = 283) in our center. The XT-THV was used from March 2010 to September 2014, after which the S3-THV was used routinely. Patients in the S3-THV group had lower STS scores than those in the XT-THV group (STS score: 5.3% ± 3.5% *vs* 6.4% ± 4.0% respectively, *P* < 0.0001) (Table 1). Patients in the S3-THV group were also less likely to be in NYHA functional class 3 or 4 (59.1% *vs* 75.8%, *P* < 0.0001), and less likely to have peripheral vascular disease (19.8% *vs* 28.4%, *P* =

Table 2 Procedural characteristics

Procedural characteristic	S3-THV (*n* = 283)	XT-THV (*n* = 507)	*P* value
Transfemoral approach	232 (82.6)	273 (53.8)	< 0.0001
Local anesthesia	232 (82.6)	271 (54.2)	< 0.0001
Predilatation	50 (17.7)	440 (86.8)	< 0.0001
Postdilatation	45 (15.9)	61 (12.0)	0.13
Implanted device size			< 0.0001
23 mm	111 (39.8)	127 (25.1)	
26 mm	101 (36.2)	270 (53.4)	
29 mm	67 (24.0)	109 (21.5)	
Valve area oversizing, %	11.5 ± 9.8	22.9 ± 11.2	< 0.0001
Device diameter/annulus diameter (area-derived)	1.05 ± 0.05	1.11 ± 0.05	< 0.0001
Need for seconde valve implantation	7 (2.5)	8 (1.6)	0.42
Annulus rupture	0 (0)	13 (2.6)	0.01
Conversion to SAVR	2 (0.7)	14 (2.8)	0.06
Contrast use (mL)	108.2 ± 42.7	131.6 ± 60.9	< 0.0001
Fluoroscopy time (min)	17.4 ± 9.9	16.5 ± 9.8	0.28

Values are mean ± SD or *n* (%). SAVR: Surgical aortic valve replacement; S3-THV: SAPIEN 3 transcatheter heart valve; XT-THV: SAPIEN XT transcatheter heart valve.

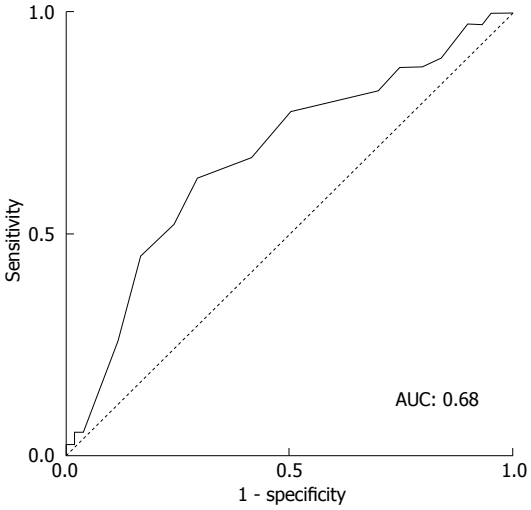

Figure 3 Receiver operating characteristic curve analysis of device diameter to annulus diameter ratio. ROC curve analysis of device diameter to annulus diameter ratio below the threshold of 1.03 increased the risk of post-dilatation or PVR > mild (area under the curve: 0.68). PVR: Paravalvular regurgitation; ROC: Receiver operating characteristic; AUC: Area under curve.

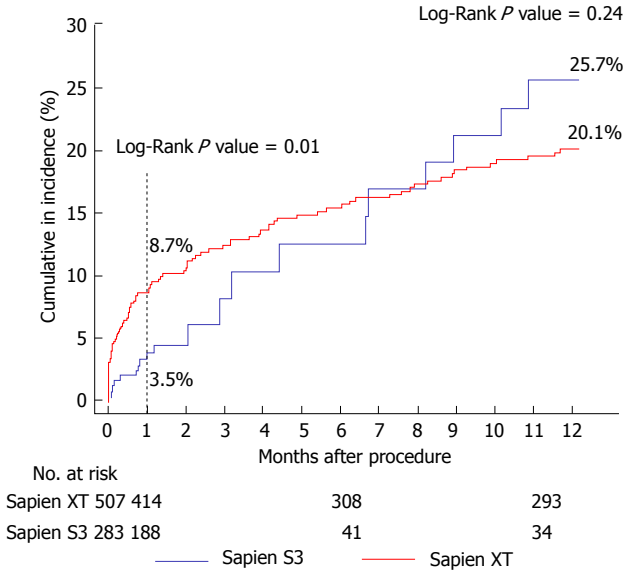

Figure 4 Cumulative incidence of all-cause mortality. Cumulative incidence (%) of all-cause 1-year mortality in the S3-THV group (blue line) and the XT-THV group (red line). S3-THV: SAPIEN 3 transcatheter heart valve; XT-THV: SAPIEN XT transcatheter heart valve.

0.01) or chronic obstructive pulmonary disease (11.7% *vs* 21.9%, *P* < 0.0001). Baseline echocardiographic characteristics were similar between groups.

The use of the transfemoral approach increased from 54% in XT-THV group to more than 80% in the S3-THV group (*P* < 0.0001) (Table 2).

Predilatation was performed routinely in the XT-THV group (86.8%), which was not the case in the S3-THV group (17.7%, *P* < 0001) (Table 2). In the S3-THV group, predilatation was reserved for patients with an extensively calcified aortic valve. The lower use of predilatation in the S3-THV group did not translate into significantly more post-dilatation (S3-THV: 15.9% *vs* XT-THV: 12.0%; *P* = 0.13). As per manufacturer recommendations, device diameter to annulus diameter (area-derived) ratio was reduced from 1.11 ± 0.05 (XT-THV) to 1.05 ± 0.05 (S3-THV; *P* < 0.0001). As a result of this reduced oversizing, smaller device sizes were used in the S3-THV group (*P* < 0.0001). However, according to ROC curve analysis, a device diameter to annulus diameter ratio below the threshold of 1.03 increased the risk of post-dilatation or PVR > mild (area under the curve: 0.68; Figure 3).

While fluoroscopy time was similar between groups, contrast use decreased by more than 15% in the S3-THV group compared to the XT-THV group (131.6 ± 60.9 mL *vs* 108.2 ± 42.7 mL; *P* < 0.0001).

Clinical outcomes

Thirty-day mortality was lower in the S3-THV group than the XT-THV group (3.5% *vs* 8.7%; univariate OR = 0.36; *P* = 0.01) (Figure 4 and Table 3). After adjustment for baseline characteristics, this difference was no longer statistically significant (adjusted OR = 0.44, *P* = 0.21). One-year mortality was also similar between groups (25.7% *vs* 20.1%, adjusted *P* =0.55) (Figure 4). In total, 20 deaths had occurred at 1 year in the S3-THV group. These are listed in Table 4 along with cause of death.

The rates of major vascular complication and PVR > 1 were both almost 4 times lower in the S3-THV group than the XT-THV group (major vascular complication: 2.8% *vs* 9.9%, adjusted *P* < 0.0001; PVL > 1: 2.4% *vs* 9.7%, adjusted *P* < 0.0001) (Figure 5). However, the rate of new pacemaker implantation was almost twice as high in the S3-THV group (17.3% *vs* 9.8%, adjusted *P* = 0.03) (Figure 5).

Acute kidney injury was 10 times lower in the S3-THV group than the XT-THV group (1.1% *vs* 13.6%,

Table 3 Thirty-day and 1-year outcomes

30-d outcomes	S3-THV (*n* =283)	XT-THV (*n* = 507)	Odds ratio (95%CI)	*P* value	Adjusted odds ratio (95%CI)	Adjusted *P* value
Death	8 (3.5)	42 (8.7)	0.36 (0.16-0.81)	0.01	0.44 (0.12-1.56)	0.21
Stroke	4 (1.4)	13 (2.8)	0.51 (0.16-1.58)	0.24	0.59 (0.08-4.33)	0.60
Myocardial infarction	0 (0)	2 (0.4)	0 (0-∞)	1		
New pacemaker implantation[1]	43 (17.3)	44 (9.8)	1.88 (1.19-2.97)	0.007	1.68 (1.05-2.69)	0.03
Major vascular complication	8 (2.8)	50 (9.9)	0.27 (0.13-0.57)	0.001	0.20 (0.09-0.44)	< 0.0001
Paravalvular regurgitation > mild	6 (2.4)	47 (9.7)	0.23 (0.10-0.55)	0.001	0.20 (0.08-0.47)	< 0.0001
Acute kidney injury	3 (1.1)	69 (13.6)	0.07 (0.02-0.22)	< 0.0001	0.12 (0.04-0.39)	< 0.0001
Mean gradient > 20 mmHg	7 (2.8)	6 (1.3)	2.48 (0.78-7.89)	0.13		
Mean gradient, mmHg	11.8 ± 5.8	10.0 ± 5.0		< 0.0001		
Total hospital length of stay, d [median (IQR)]	8 [5-13]	9 [7-14]		< 0.0001		
1-yr outcomes				*P* value	Adjusted hazard ratio (95%CI)	Adjusted *P* value
Death	20 (25.7)	87 (20.1)		0.24	0.86 (0.52-1.42)	0.55

Values are mean ± SD or *n* (%) unless specified otherwise. [1]Patients with previous permanent pacemaker were excluded from this analysis. No adjusted analyses were performed for outcomes with less than 15 events overall. IQR: Inter-quartile range; S3-THV: SAPIEN 3 transcatheter heart valve; XT-THV: SAPIEN XT transcatheter heart valve.

Table 4 Causes of death at 1 year in the SAPIEN 3 transcatheter heart valve group

Patient	Days to death	Cause of death
1	0	Dissection of ascending aorta
2	2	Left main compression/cardiogenic shock
3	3	Iliac rupture
4	5	Sudden cardiac death
5	10	Cardiogenic shock
6	22	Heart failure
7	24	Subdural hematoma
8	25	Unknown
9	31	Stroke
10	36	Acute renal failure
11	62	Unknown
12	87	Heart failure
13	96	Heart failure
14	133	Unknown
15	200	Sudden cardiac death
16	202	Cancer
17	247	Myocardial infarction
18	268	Septic shock
19	305	Chronic obstructive pulmonary disease acute exacerbation
20	326	Major stroke

P < 0.0001). There were no statistically significant differences between groups with respect to stroke, myocardial infarction and post-procedural mean gradient > 20 mmHg.

Predictors of new pacemaker implantation in the S3-THV group

Electrocardiographic and angiographic characteristics of patients in the S3-THV group that required a new PPM are displayed in Tables 5 and 6. Implantation depth in the S3-THV group was 5.1 ± 2.5 mm on the septal side (non-coronary cusp) and 5.2 ± 2.0 mm on the non-septal side (left coronary cusp). According to multivariate analysis, independent predictors of new permanent pacemaker implantation were pre-procedural

Table 5 Electrocardiographic and angiographic characteristics according to new permanent pacemaker requirement in the SAPIEN 3 transcatheter heart valve group

Variable	New PPM (*n* = 43)	No PPM (*n* = 201)	*P* value
Complete RBBB	12 (32.4)	17 (9.5)	0.001
Complete LBBB	0 (0)	14 (7.8)	0.14
Fascicular block	12 (32.4)	33 (18.4)	0.07
QRS duration, ms	108 ± 26	101 ± 23	0.1
PR duration, ms	196 ± 37	183 ± 30	0.04
Implant depth (septal), mm	5.3 ± 2.4	5.0 ± 2.6	0.67
Implant depth (non-septal), mm	4.9 ± 2.4	5.2 ± 1.9	0.64
Device lack of coaxiality during deployment, mm	4.0 ± 3.6	2.9 ± 2.5	0.06

Values are mean ± SD or *n* (%). LBBB: Left bundle branch block; RBBB: Right bundle branch block; PPM: Permanent pacemaker.

complete right bundle branch block (RBBB) (OR = 4.9; 95%CI: 1.88-12.95; *P* = 0.001), PR duration (OR = 1.14 per 10 ms increment; 95%CI: 1.00-1.29; *P* = 0.05) and device lack of coaxiality during deployment (OR = 1.13 per 1 mm increment; 95%CI: 1.00-1.29; *P* = 0.05). Device implantation depth was not a predictor of new pacemaker implantation in our series.

DISCUSSION

To our knowledge, this is one of the largest observational studies to date comparing the newer balloon-expandable S3-THV to the XT-THV in an all-comer population. The major findings are as follows: (1) the S3-THV is associated with similar adjusted 30-d and one-year mortality rates compared to the XT-THV; (2) the S3-THV is associated with 4-fold lower rates of both major vascular complications and PVR compared to the XT-THV; (3) the S3-THV is associated with twice the rate of new PPM implantation compared to the XT-THV; and (4) independent predictors of new pacemaker included

Table 6 Predictors of new pacemaker implantation in the S3 group

Parameter	Univariate analysis		Multivariate analysis		
	OR	*P* value	OR	95%CI	*P* value
Complete RBBB	4.6	< 0.001	4.9	1.88-12.95	0.001
Complete LBBB	1	1	-	-	-
Fascicular block	2.12	0.06	1.88	0.71-5.00	0.20
QRS duration (per 10 ms increment)	1.12	0.1	0.87	0.65-2.72	0.345
PR duration (per 10 ms increment)	1.14	0.05	1.14	1.00-1.29	0.05
Implant depth (septal, per 1 mm increment)	1.05	0.66	-	-	-
Implant depth (non-septal, per 1 mm increment)	0.94	0.63	-	-	-
Device lack of coaxiality during implant (per 1 mm increment)	1.13	0.07	1.13	1.00-1.29	0.049

LBBB: Left bundle branch block; RBBB: Right bundle branch block.

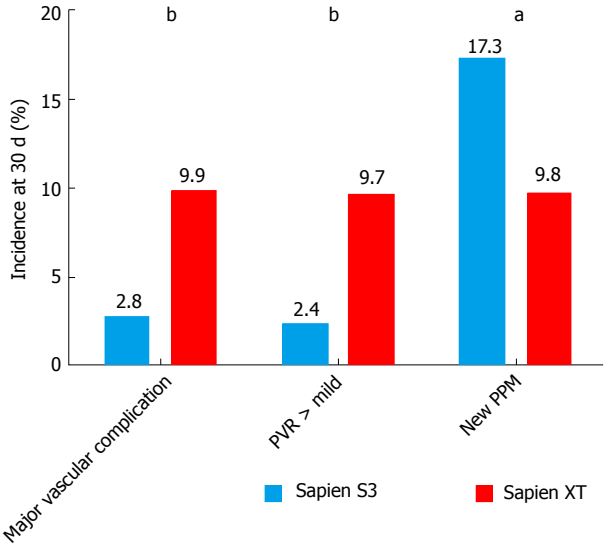

Figure 5 Incidence of major vascular complication, > mild para-valvular regurgitation and new permanent pacemaker. Thirty-day incidence (%) of major vascular complication, > mild PVR and new PPM in the S3-THV group (blue bars) and the XT-THV group (red bars). $^{a}P < 0.05$; $^{b}P < 0.0001$. XT-THV: SAPIEN XT transcatheter heart valve; PPM: Permanent pacemaker; PVR: Paravalvular regurgitation.

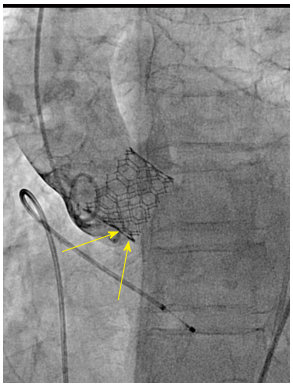

Figure 6 Example of difficult depth measurement. In this case, the projection has been modified after implant so the device appears coaxial. However, the annulus is no longer coaxial: Two aortic cusps are seen at different levels on the septal side (arrows), making difficult the localization of the hinge point and therefore the measurement depth of implant.

pre-procedural complete RBBB and PR duration, and lack of device coaxiality during implant.

Mortality

In a recent study, all-cause 30-d mortality rates were reported between 0% and 17.5%, with a pooled estimate rate of 5.7% for all second-generation THVs[24]. Reported 30-d mortality rates with the S3-THV ranges from 0.5% to 4.5%[16,17,25]. We report also a low 30-d mortality of 3.5% in the S3-THV cohort that was not statistically lower than the 8.7% rate of the XT-THV group after covariates adjustment. The low 30-d mortality speaks to the advancement of TAVI in regard to valve design improvement, increased operator experience, improved patient selection and procedural pre-planning, but also the lower baseline risk profile of TAVI patients.

Vascular complications

One of the shortcomings of TAVI is the association of major vascular complications with mortality[10]. Sheath size, severe ilio-femoral artery calcification, sheath external diameter to minimal femoral diameter artery ratio (≥ 1.05), early site experience and early operator experience, have all been previously associated with major vascular complications[13,26,27]. The S3-THV, with the lower profiles of its 14 and 16-F sheaths and the expanding properties of its E sheath, allows TAVI to be performed in patients with smaller arteries and for it to be safer in patients with larger arteries[28]. This is reflected in our series by the significant increase in proportion of transfemoral procedures. Three studies reported rates of major vascular complications of 4.5%, 5.2% and 3.6%, reflecting increased safety compared to the XT-THV[16,17,25]. We observed a similar rate of 2.9% in our S3-THV cohort, despite seeing the number operators performing TAVI increase from 4 to 9 between 2013 and 2015.

PVR

Patients with more than mild PVR have lower short- and long-term survival than those with trivial or mild PVR, making this an important echocardiographic outcome[29,30]. In the PARTNER trial, moderate or severe PVR was seen in 11.8% of patients implanted with the Edwards SAPIEN valve[31]. In the France 2 Registry,

Table 7 Summary of studies comparing the rate of permanent pacemaker between the S3 and XT device

PPM	S3	XT	*P* value	Predictor/comments
Binder *et al*[40] 2015 Circulation interventions	17%	13%	0.01	Predictors: Depth, RBBB
Binder *et al*[14] 2013 JACC interventions	13.3%			Excluded patient with LBBB, PR > 200 ms No predictors studied
Husser *et al*[25] 2015 JACC interventions	15.2%			Predictors not studied
Binder *et al*[40] 2015 EuroIntervention	20.7%			Predictor > 8 mm depth of implants
Nijhoff *et al*[17] 2015 Circulation interventions	9.8%	8.80%	0.94	High implants: 80/20 in aorta as mentioned by authors

it was reported in 12.2%[32]. We found similar rates of PVR in the XT-THV group. In contrast, the S3-THV group had four times less PVR. Our 2.4% > mild PVR rate in the S3-THV group is comparable to other reports that showed a PVR range between 0% and 3.8%[25,33]. The reduced rate of PVR can be explained by improved annular sealing by the external cuff. Whether the decreased PVR rate with the S3 device could translate into improved long-term outcomes should be evaluated in long-term registries.

Permanent pacemaker implantation

The need for new PPM implantation following TAVI may be correlated to prognosis[34-36]. As the S3-THV valve frame has greater height than the XT-THV, it may extend deeper into the LVOT after deployment[15,16]. Stent frame extension in the LVOT, *i.e.*, depth of implant, has been shown to be a predictor of PPM implantation[37].

Preliminary data on the S3-THV device from the pivotal SAPIEN 3 trial have shown an increased 30-d PPM implantation rate (13.3%), despite excluding patients with LBBB, RBBB and PR > 200 ms[38]. A study by Tarantini *et al*[16] also showed an increased rate of PPM (20.7%) with the S3-THV. This increased risk for PPM was driven by deep implantation of the S3-THV (valve implantation depth ⩾ 8 mm). Similarly, the Swiss registry showed an increased rate of PPM with the S3-THV of 17% compared to 11% with the XT-THV valve[16]. Our study showed similar results with a rate of 17.3% in S3-THV *vs* 9.8% in XT-THV (Table 7). As reported by others, independent predictors of new permanent pacemaker implantation in the S3-THV group included complete right bundle branch block and PR duration[25].

However, implant depth was not a predictor of new PPM in our study. Rather, lack of coaxiality of the device during its deployment was independently associated to new PPM. These findings may be explained by flaws in the way depth is estimated before the prosthesis is deployed, and by flaws in the way depth is measured after it is deployed.

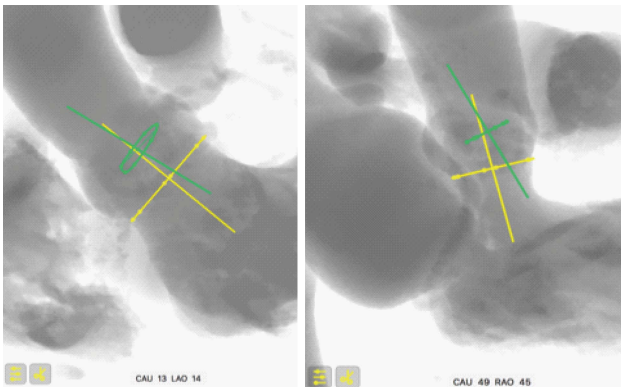

Figure 7 Coaxiality concept. In this example, the aortic annulus is drawn in yellow and the device is in green. Two different C-arm angulations of the same structures are shown. If the operator selects the angulation on the left for deployment, estimation of implant depth will be more difficult as one of the structures (the device) is not coaxial. Notice that in both angulations, the annulus (yellow) is coaxial.

Before the prosthesis is deployed, the aortic annulus is seen in a coaxial projection, with the three cusps aligned. This projection is determined from the MSCT and confirmed during the procedure by aortography. However, the device positioned in the annulus, before deployment, is not necessarily coaxial. This may be difficult to appreciate because, unlike the Corevalve, the XT-THV and the S3-THV do not have a ring at their extremity. This lack of device coaxiality before deployment can induce flaws in the estimation of depth due to parallax error[18,39]. In our experience, lack of device coaxiality induces underestimation of implant depth. In other words, the less coaxial the device, the higher it will look, and the more the operator will want to push it deeper. This increases the true depth of implant and therefore risk of conduction disturbance and new PPM.

After the prosthesis is deployed, measurement of depth of implant can also be flawed by parallax error. As previously described, the projection in which depth is measured is not the one in which the device was deployed. Indeed, after deployment, the device is not necessarily coaxial. The projection is therefore modified to obtain device coaxiality and this is when final aortography is performed and depth is measured. In this new projection, however, the aortic annulus is no longer coaxial[18,39]. An example of this is provided in Figure 6, where two cusps are seen at different levels on the septal side. Proper localization of the hinge point between the device and sinus of Valsalva, and therefore proper implant depth measurement, can be difficult in such circumstances and prone to parallax error. To adequately measure device implantation depth, future studies should rely on post-procedural MSCT. This would allow measurement of depth all around the annulus, and not only on the septal and non-septal sides. Alternatively, computer programs that allow the

operator to find the unique projection where both the device and the annulus are coaxial could be used. This would be the optimal projection to deploy the device, do the final aortography and measure depth.

The premise of this concept is that there is a slight angle between the un-deployed device and the aortic annulus. This is caused by patient anatomy and delivery catheter properties. As a result of this angle, even if the C-arm is perpendicular to the aortic annulus, it may not be perpendicular to the device. Figure 7 illustrates the coaxiality concept.

Limitations

This retrospective study reflects a single-center experience. Groups had significant baseline characteristics differences and adjustment for these may be incomplete or flawed by residual confounding. Although PVR was assessed by experienced echocardiographers and reported according to VARC-2 criteria, the absence of a central core lab may lead to some heterogeneity in assessment of this outcome. In addition, we did not analyze the timing of conduction disturbances. Indeed, one of the possible reasons for higher PPM in the S3-THV group may be a delayed inflammatory process caused by the skirt polymer, in addition to its immediate mechanical effect on the conduction system. To reflect contemporary practice of TAVI, we collected ECG data, depth and device coaxiality only in the S3-THV group. As it is difficult to measure device coaxiality before implant on a crimped valve, we used the device coaxiality at the end of deployment. Measurements were taken as the balloon was deflated and the patient still under rapid pacing so that measurements reflected pre-deployment status. In addition, device coaxiality measurements were only available for procedures done in the catheterization laboratory, thereby excluding patients with non-transfemoral access.

Conclusion

The third generation Edwards S3-THV is associated to improved outcomes with lower rates of major vascular complications and PVR but higher rates of new PPM compared to its predecessor, the XT-THV.

These results are encouraging in the endeavor to take TAVI to lower risk populations. Our findings highlight the increased importance to adequately visualize the S3-THV in relation to the aortic valvular complex during deployment, in order to improve device positioning and potentially mitigate new PPM requirements.

COMMENTS

Background

Since its introduction in 2002, transcatheter aortic valve implantation (TAVI) has evolved tremendously and is now standard of care for high risk and inoperable aortic stenosis patients. However, TAVI is still associated with a higher incidence of paravalvular regurgitation (PVR), permanent pacemaker (PPM) and vascular complications when compared to surgical aortic valve replacement. In order to justify the extension of the procedure to lower risk patients, these adverse outcomes have to be mitigated. The development of novel transcatheter heart valves and refinement of technical skills have contributed to the decrease in complications rates associated with TAVI.

Research frontiers

TAVI indication has now moved to intermediate and lower risk patients and it is crucial to continue careful evaluation of the newer generation devices aimed at improving patient outcomes. The study aimed to compare the different iterations between 2 valves on patient outcomes. New devices with lower profile and different designs have currently been introduced to further improve valve performance and efficacy.

Innovations and breakthroughs

TAVI is still associated with a higher incidence of PVR, PPM and vascular complications when compared to surgical aortic valve replacement. However, the third generation Edwards SAPIEN 3 transcatheter heart valve (S3-THV) the newest approved valve have improved TAVI outcomes by lowering complication rates and have recently been associated with improved outcomes compared to surgical aortic valve replacement in high risk patients. This breakthrough technology will without a doubt become the standard care of all patients in the near future with the continue improvement in device designs.

Applications

The third generation Edwards S3-THV is associated to improved outcomes with lower rates of major vascular complications and PVR but higher rates of new PPM compared to its predecessor, the SAPIEN XT transcatheter heart valve (XT-THV). These results are encouraging in the endeavor to take TAVI to lower risk populations. The authors' findings highlight the increased importance to adequately visualize the S3-THV in relation to the aortic valvular complex during deployment, in order to improve device positioning and potentially mitigate new PPM requirements. Dedicated software devices that can align the annulus and the prosthesis during deployment could help in coaxial implantation of the valve.

Terminology

TAVI: Transcatheter aortic valve implantation; PVR: Paravalvular regurgitation.

Peer-review

The paper is well written and offers a fairly large comparison of the performance of these 2 valves.

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