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REVIEW

Cardiac damage in athlete's heart: When the "supernormal" heart fails!

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Abstract

Intense exercise may cause heart remodeling to compensate increases in blood pressure or volume by increasing muscle mass. Cardiac changes do not involve only the left ventricle, but all heart chambers. Physiological cardiac modeling in athletes is associated with normal or enhanced cardiac function, but recent studies have documented decrements in left ventricular function during intense exercise and the release of cardiac markers of necrosis in athlete's blood of uncertain significance. Furthermore, cardiac remodeling may predispose athletes to heart disease and result in electrical remodeling, responsible for arrhythmias. Athlete's heart is a physiological condition and does not require a specific treatment. In some conditions, it is important to differentiate the physiological adaptations from pathological conditions, such as hypertrophic cardiomyopathy, arrhythmogenic dysplasia of the right ventricle, and non-compaction myocardium, for the greater risk of sudden cardiac death of these conditions. Moreover, some drugs and performance-enhancing drugs can cause structural alterations and arrhythmias, therefore, their use should be excluded.

Key words: Athlete's heart; Cardiac damage; Fibrosis; Intense exercise; Arrhythmogenic dysplasia of the right ventricle; Atrial fibrillation; Doping; Anabolic-androgenic steroids; Hypertrophic cardiomyopathy

Core tip: Athlete's heart is a physiological condition that in some cases can simulate pathological disease,

sometimes due to the use of doping drugs. Furthermore, exercise can induce atrial dilation and arrhythmias. Our objective is to analyze the current literature and to review the most important changes in the heart of athletes, from the different molecular pathways to the structural anomalies.

Carbone A, D'Andrea A, Riegler L, Scarafile R, Pezzullo E, Martone F, America R, Liccardo B, Galderisi M, Bossone E, Calabrò R. Cardiac damage in athlete's heart: When the "supernormal" heart fails! *World J Cardiol* 2017; 9(6): 470-480 Available from: URL: http://www.wjgnet.com/1949-8462/full/v9/i6/470.htm DOI: http://dx.doi.org/10.4330/wjc.v9.i6.470

INTRODUCTION

High-intensity exercise training leads to morphological, functional, and electrical remodeling of the heart, which are included in the "athlete's heart", characterized by increased left ventricular mass (LVM), cavity dimensions and wall thickness[1]. Athletes with left ventricular (LV) hypertrophy generally have normal cardiac function and normal systolic and diastolic function[2]. Athletes exhibit an improvement in myocardial diastolic indices and supernormal LV diastolic function[3]. Recent studies have documented decrements, especially in right ventricular (RV) function, during intense endurance exercise[4,5]. Actual evidence suggests that there may be some overlap between physiological and pathological conditions, such that a modest amount of fibrosis may be present in cardiac remodeling associated with lifelong endurance training and then acts as a substrate for arrhythmias[6].

Our objective is to describe the mechanisms of cardiac remodeling in athletes and to delineate the most important differences, from the molecular mechanisms to the structural changes, between athlete's heart and pathological conditions, taking into account the most important cardiomyopathy, arrhythmias and the abuse of performance-enhancing drugs.

PHYSIOLOGICAL *VS* PATHOLOGICAL CARDIAC HYPERTROPHY: FROM PHYSICAL PRINCIPLES TO MOLECULAR MECHANISMS

Cardiac hypertrophy is an adaptive response to the increased cardiac loading that normalizes wall stress, according to Laplace relationship (Figure 1). Unfortunately, long-term maladaptive remodeling of reactive hypertrophy in various cardiovascular diseases (*e.g.*, valvular heart disease, myocardial ischemia, coronary artery disease, hypertension, and cardiomyopathy) is associated with gradual ventricular dilation, due to loss of myocytes and cardiac fibrosis[7]. Physiological hypertrophy, such as athlete's heart, is typically not associated with myocyte death, although recent studies have shown myocardial damage during intense exercise and RV inflammation and fibrosis in long term endurance athletes[4,8]. The shift from compensated pathological hypertrophy to failure of myocardium includes cellular and molecular events, such as myocyte death, with three different mechanisms: Apoptosis, necrosis and autophagic cell death[9,10]. Cardiomyocyte replacement and myocardial fibrosis are representative of all types of pathological hypertrophy and proceed along with functional decompensation. To explain fibrosis and necrosis in athlete's heart, interesting is the "ischemic core" hypothesis: Hypertrophic cardiomyocyte becomes ischemic when his surface exceeds the distance across which oxygen can diffuse down its concentration gradient from adjacent capillaries, with contractile depression and cellular death[11]. Physiological hypertrophy is associated with a normal or increased number of myocardial capillaries, due to the activation of VEGF pathway[9]. Akt is a serine/threonine protein kinase responsible for the cellular growth in multiple cell types, which can be activated by exercise. Recent data suggest that Akt pathway might be implicated both in physiological and pathological cardiac growth. In animal models, myocardial expression of Akt pathway caused reversible hypertrophy after 2 wk of strenuous exercise, but an irreversible cardiomyopathy with decreased capillary density and fibrosis after 6 wk of intense training. It seems that myocardial angiogenesis is more intense in the acute phase of heart hypertrophy but insufficient in the advanced phase: Excessive "physiological" hypertrophy might be associated with poor angiogenesis and consequently with heart failure[12].

Autocrine and paracrine triggers are released in response to hemodynamic overload, and definite substances are preferentially released for pathological or physiological stimuli. Insulin like growth factor 1 (IGF1) is released in the course of postnatal development and during exercise training and is increased in swim-trained rats and in veteran athletes compared with controls[13], whereas elevated levels of angiotensin Ⅱ (Ang Ⅱ), catecholamine and endothelin-1 (ET-1) were observed in pathological hypertrophy and in heart failure subjects[14]. IGF1 promotes the PI3K-Akt molecular pathway to induce physiological cardiac hypertrophy, whilst the mitogen activated protein kinase (MAPK) pathway and calcineurin system are activated by Ang Ⅱ and ET-1 in pathological hypertrophy (Table 1)[15].

In conclusion, familial hypertrophic cardiomyopathy[16] is associated with sarcomeric protein mutations, such as cardiac troponin I or T, β-MHC, α-MHC, myosin light chain, α-tropomyosin, titin, and actin, with loss of contractile filaments and proteins of sarcomeric skeleton[17].

CARDIOMYOCYTE DAMAGE DURING INTENSE EXERCISE

After intense exercise, acute increases in troponin (cTn) and B-type natriuretic peptide have been detected in

Table 1 Differences in between physiological and pathological hypertrophy

Physiological hypertrophy	Pathological hypertrophy
Angiogenesis, release of VEGF	Perivascular fibrosis and inflammation
Activation of IGF-1 pathway (IGF-1- > PI3K- > Akt)	Activation of Angiotensin Ⅱ, Catecholamine and Endotelin-1
No fibrosis	MAPK and Calcineurin pathway
Normal gene expression	Fibrosis, myocyte necrosis and apoptosis
Proportional chamber enlargement	Cardiac dysfunction

The table summarizes the differences in the cellular and molecular pattern between physiological and pathological hypertrophy. VEGF: Vascular endothelial growth factor; IGF-1: Insulin like growth factor; PI3K: Phosphoinositide 3-kinase; MAPK: Mitogen-activated protein kinase.

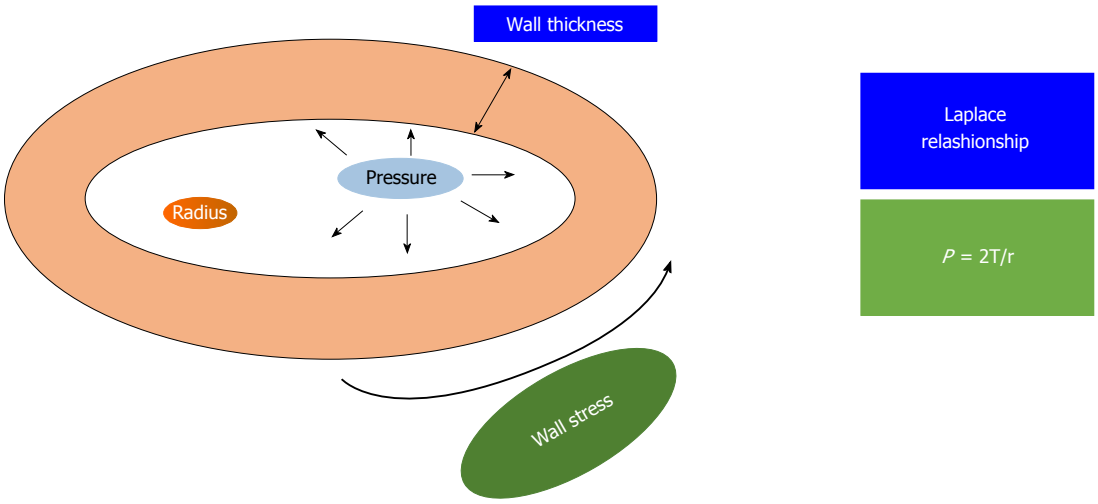

Figure 1 The figure shows the Laplace relationship: The pressure (P) generated in a sphere is directly proportional to the wall tension (T) and inversely related to the radius of the sphere (r).

athletes[18]. These are specific markers of myocyte injury and strain, but do not indicate a permanent injury. Potential mechanisms have been showed to elucidate cTn elevation after intense exercise, but actually, the elevation of cTn levels in healthy individuals cannot be explained by any of these theories[18]. It is possible that exercise induces an increase in myocardial sarcolemma permeability, due to mechanical stress on the cardiomyocytes and to increased production of oxidative radicals or altered acid base balance exercise, with passive diffusion of cTn from the intra- to extra-cellular compartment[18]. Cellular stretching might cause transient disruption of the myocardial plasma membrane and then, the release of cTn[19]. Furthermore, it can stimulate integrins, mediating the transport of entire cTn molecules out of viable cardiomyocytes[20]. Increased levels of cTn are more common in cycling or triathlon and depend on the exercise intensity[21].

Case reports have shown myocardial fibrosis and late gadolinium enhancement, associated with cTn elevation post-exercise, in a small number of veteran athletes, but the pathogenesis of these cases remains unclear[18].

EXERCISE-INDUCED MYOCARDIAL FIBROSIS

Despite the widely recognized benefits of regular physical activity, high-level exercise training may be associated with increased arrhythmia risk and even with sudden cardiac death[22].

The athlete's heart is a benign condition, representing a normal adaptation to chronic exercise, in which loss of myocytes and abnormal deposition of collagen do not usually occur[15]. Pathological hypertrophy is associated with apoptosis and necrosis; in this case, the loss of myocytes is replaced with excessive collagen deposition. Excessive collagen deposition increases the stiffness of the ventricles, with consequent impaired contraction and relaxation, electrical conduction system fibrosis and reduced capillary density, leading to myocardial ischemia and the transition from hypertrophy to failure[15]. Interestingly, recent studies have shown myocardial inflammation and fibrosis in animal models of long term, intensive exercise. Chen *et al*[23] forced rats to swim strenuously and found histological evidence of localized myocyte damage, myocardial necrosis and inflammatory infiltrates. Benito *et al*[24] instituted an intensive treadmill running protocol in rats and demonstrated an increase in atrial and ventricular inflammation and fibrosis and a greater risk of ventricular arrhythmias in the "marathon rats". Fibrosis and inflammatory infiltrates have been identified in well-trained athletes who underwent cardiac biopsy for high probability of identifying a cardiac pathology[25]. Histology offers the tangible evidence of fibrosis, but inflammatory infiltrates and fibrosis are

non-specific and their etiology can be supposed only by other clinical factors. Furthermore, cardiac biopsy is an invasive procedure with significant risks and it is not applicable in the absence of high suspicion of heart disease. An accurate, non-invasive surrogate tool for detecting fibrosis is cardiac magnetic resonance (CMR) imaging with gadolinium contrast. Gadolinium-based extracellular paramagnetic contrast agents concentrate in areas of fibrosis and thus can be used to characterize injured myocardium. Using gradient-echo inversion recovery imaging, fibrosis appears as bright signal, with a prolonged wash-out time for gadolinium [delayed gadolinium enhancement (DGE)], contrasting with the normal myocardium, which looks black[6]. Several studies have identified the presence of DGE in the heart of extensively trained veteran athletes. In most cases, the patches of DGE were very small and sited in the septum and in RV insertion points, regions subjected to local stretching during exercise[6]. More recently, La Gerche *et al*[4] have shown myocardial fibrosis by CMR and a reduction in RV systolic function in athletes with long-term exercise, suggesting that the heart has a limited capacity to tolerate the overload exercise. The patches of cardiac fibrosis may be the substrate for ventricular tachycardia and sudden death, in predisposed individuals[4]. Some authors have recently suggested a new entity, the so called Phidippides cardio-myopathy: Long term strenuous exercise can induce cardiac dilation and also activates resident macrophages, pericytes, and fibroblasts, resulting in the deposition of collagen and fibrosis[26,27]. CMR can also specifically detect intra-myocardial fibrofatty infiltration of the RV wall, typical of the arrhythmogenic right ventricular cardiomyopathy (ARVC), which often leads to ventricular arrhythmias and usually appears in young adulthood and affected asymptomatic or minimally symptomatic individuals[27]. In conclusion, it is possible that the RV is more susceptible to fatigue than the left ventricle after prolonged exercise. It needs more studies to identify a probable effect of exercise "dose" and their implication in the development of heart failure.

IS CARDIAC REMODELING IN ATHLETES ALWAYS BENIGN?

Cardiac adaptations to exercise not involve only the left ventricle, but all the heart chambers. Often these changes are absolutely physiological, but in some cases, they can predispose to pathological conditions, such as arrhythmias. Below, we report the main morpho-functional changes of the different cardiac structures in athletes and their implications in the pathogenesis of cardiovascular diseases.

ATHLETE'S ATRIA FUNCTION AND DYSFUNCTION

Atrial abnormalities can be present in athletes, such as a mild increase in atrial volume and diameter, and may be considered a physiological adaptation to exercise[28]. The pathophysiological mechanisms are not well defined. Studies in animal models have shown that, in rats, prolonged and vigorous exercise resulted in eccentric hypertrophy and diastolic dysfunction with atrial dilatation and fibrosis, especially in the atria and the right ventricle, and increased fibrotic mRNA compared with controls[24]. A recent meta-analysis of 7189 adult elite athletes have shown that exercise causes an increase in left atrium (LA) dimensions, compared with controls, evaluating both diameter and volume, corrected for body surface area. The endurance athletes reported the largest average LA diameters[29]. Since pre-adolescence, the long-term endurance exercise results in considerable bi-atrial remodeling and enlargement compared with sedentary subjects of the same age, with a preserved cardiac function[30,31]. LA enlargement could be considered part of athlete's heart, considering that the LA pressure rises during ventricular diastole more than in sedentary subjects, to maintain adequate filling whereas LV stiffness or pressure are increased[32]. On the other hand, there is evidence that the endurance exercise increases the risk of developing atrial fibrillation (AF) and atrial flutter in the middle age, in subjects without any clinical or echocardiographic signs of cardio-pulmonary pathologies or hypertension[33]. The mechanisms responsible for these arrhythmias might be: The major incidence of atrial ectopic beats in this population, as a consequence of physical activity; the influence of autonomic nervous systems, and in particular the vagal system, responsible for the "vagal AF"[34]; the atria dilatation, fibrosis, and inflammation induced by high exercise training and the atrial remodeling[33] (Table 2). In mice, exercise can induce TNFα-dependent activation of both NF-κB and p38MAPK, increasing inflammation and AF susceptibility[35].

Moreover, AF might be closely connected with oxidative cellular changes and redox imbalance in the atrium. The oxidative species, generated from cardiomyocytes in stress conditions such as strenuous exercise, can increase inflammation and activate downstream molecular pathways, promoting morphological and electrical modeling. Recently, Mont *et al*[36] have shown that loss of Nrf2, a gene with antioxidant function in the atria, could be associated with atrial hypertrophy and AF, suggesting that the preservation of the redox state is essential for the atrium health.

Finally, in athletes AF appears as some symptomatic and paroxysmal episodes that could become more frequent and progress to persistent AF. The GIRAFA study has showed that the crisis appears in the night or after the meal, related to an increased vagal tone[36].

Data about right atrial (RA) function in top level athletes are lacking. Previously, our group has delineated the upper limits of RV and RA dimensions in highly-trained athletes and showed that right heart dimensions were greater in elite endurance-trained athletes than in age- and ex-matched strength athletes and controls[37]. Then, D'Ascenzi *et al*[38] investigated the RA function and dimension in 100

Table 2 Pathological mechanisms of atrial fibrillation in long-term athletes

Pathological mechanism
Atrial ectopic beats
Vagal nervous system
Atrial fibrosis
Atrial dilatation
Myocardial injury
Inflammation
Redox imbalance

The table shows the most important mechanisms involved in atrial fibrillation exercise related.

top level athletes by standard echocardiography and 2D speckle tracking echocardiography and showed that RA area, volume, volume index, and inferior vena cava were significantly greater in athletes than in controls and the peak atrial longitudinal strain and peak atrial contraction strain values were lower in athletes than in controls. This strain reduction should not represent a real dysfunction, but only a physiological phenomenon, and can be included in the "athlete's heart"[38].

LV CHANGES IN EXERCISE RELATED AND PATHOLOGICAL CONDITIONS

In some highly-trained athletes, the LV wall thickness may be increased, mimicking a hypertrophic cardiomyopathy (HCM). The thickening is usually mild, but in some cases, it may be significant and creates difficulties to differentiate athlete's heart and hypertrophic cardiomyopathy, especially in the ambiguous "gray zone", when the wall thickness is of 13 to 15 mm (12 to 13 mm in women)[39]. This differential diagnosis is important, since most cases of sudden death in athletes are probably due to HCM[40]. Echocardiography plays an important role in the differential diagnosis: HCM is probable with LV end-diastolic cavity < 45 mm, evidence of pathogenic sarcomere mutation, family history of HCM, abnormal LV diastolic function, left atrial dilatation, and late gadolinium enhancement on contrast-enhanced CMR imaging. Usually athlete's heart is characterized by LV cavity enlargement (> 55 mm), peak VO_2 > 110% of expected, and thickness or mass decreases with short periods of detraining[41,42]. Pelliccia *et al*[43] have shown that LV wall thickness $\geqslant$ 13 mm is mostly present in elite rowers and cyclists, and the upper limit appeared to be 16 mm (Figure 2).

Other conditions that can cause cardiac hypertrophy include valve disease, hypertension and non-compaction myocardium. Despite the prevalence of hypertension is approximately 50% lower in athletes compared with the general population, it is also the most common cardiovascular condition in athletes. The pharmacological therapy can be difficult for the competition regulations and potential adverse effects[44]. It is important to diagnose this condition, because it is associated with an increased risk of developing heart failure. Recently, an elevated prevalence of LV noncompaction (LVNC) has been reported in athletes, phenotypically characterized by a more thick endocardial noncompact layer, increased trabeculations and deep recesses[45]. Caselli *et al*[46], in a recent study, have shown that in a large population of athletes, only a small subgroup presented LVNC. The increased trabeculations may represent a LV variant of athlete's heart without any clinical significance[46].

Figure 3 summarizes the different characteristics of physiological remodeling and pathological condition of LV.

EXERCISE-RELATED RIGHT VENTRICLE REMODELING

Strenuous and prolonged exercise can cause RV dysfunction, usually transient, with evidence of increased biomarkers of cardiac damage. On the other hand, repeated bouts of exercise can lead to RV structural remodeling and arrhythmias and can lead to a syndrome similar to familial ARVC, without an identifiable genetic predisposition[47,48]. ARVC is present in 4% to 22% of athletes with sudden cardiac death[49,50]. As mentioned above, the RV function may be more interested by intense endurance training, therefore the diagnostic criteria for ARVC should be nonspecific in athletes with electrocardiographic anomalies and biventricular dilation.

Marcus *et al*[51] in a multi-center study of 108 probands with ARVD/C showed that 34% were athletes. Vigorous or long term athletic exercise might facilitate the phenotypic expression of ARVC due to the repetitive stretch of the RV with an underlying genetic desmosomal protein anomaly[51].

Signs of RV dysfunction seem to include: Syncope; Q waves in precordial leads; augmented QRS duration; three abnormal signal averaged electrocardiography parameters; delayed gadolinium enhancement; RV ejection fraction < 45% or wall motion anomalies at CMRI; > 1000 ventricular extra-systoles (or > 500 non-RV outflow tract) per 24 h; ventricular tachyarrhythmia or abnormal blood pressure response during exercise (Table 3)[52,53]. RV cavity size is not significantly larger in ARVC patients compared with athletes, whereas RV outflow tract is larger in ARVC subjects than in athletes[53]. The thickened and high reflective moderator band, commonly considered typical of ARVC, are present also in athletes and could be due to RV dilatation[53] (Figure 4). Further studies regarding the differential diagnosis between ARVC and physiological remodeling in athletes are needed to create useful clinical diagnostic algorithms.

PERFORMANCE-ENHANCING DRUGS AND CARDIAC DAMAGE

Some banned athletic performance-enhancing drugs

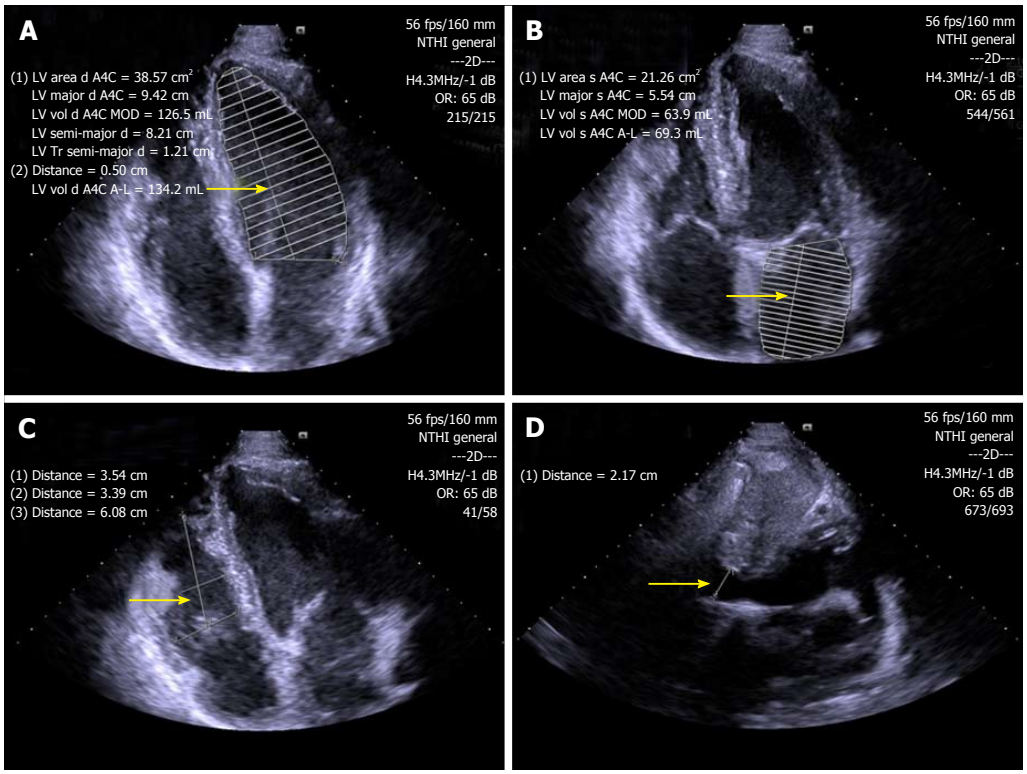

Figure 2 Standard B-mode echocardiography of endurance athlete showing enlargement of left ventricular (A), left atrial (B) and right ventricular (C) chambers, as well as inferior cavae vein dilatation (D) (arrows). LV: Left ventricular.

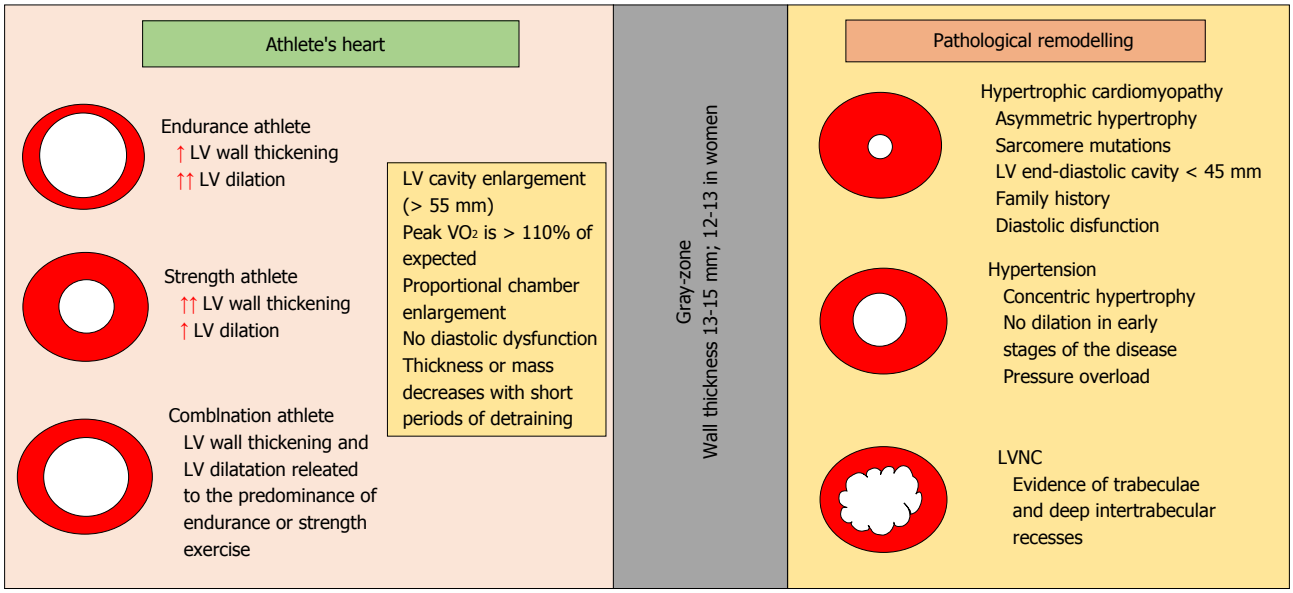

Figure 3 Different characteristics of physiological remodeling and pathological condition of the left ventricle. LV: Left ventricular; LVNC: LV noncompaction.

might have cardiac toxic effects, such as anabolic-androgenic steroids (AASs) and growth hormone (GH).

Healthy athletes abusing AASs may exhibit LV hypertrophy with both systolic and diastolic myocardial dysfunction and focal areas of DGE at CMR, with non-ischemic distribution[54] (Figure 5). AASs have direct toxicity on myocardial structures, with increased collagen deposition, fibrosis, and intimal hyperplasia of the intramural coronary vessels with chronic ischemic damage and microcirculation alterations. Moreover, testosterone might inhibit the extra-neuronal uptake of neuroamine and consequently result in vasospasm due to an abnormal vascular response to norepinephrine[55]. Post-mortem studies of athletes who used AASs have found infiltration of eosinophils into myocardial cells, as well as destruction of myofibrils. Endothelial dysfunction was

Table 3 Indicators of right ventricle pathology

Episodes of syncope
> 1000 ventricular extra-systoles (or > 500 non-RV outflow tract) per 24 h; ventricular tachyarrhythmias; Q waves in precordial leads; augmented QRS duration
⩾ 3 abnormal signal averaged electrocardiography parameters
Delayed gadolinium enhancement; RV ejection fraction < 45%, or wall motion abnormalities at CMRI; impaired RV strain imaging
Attenuated blood pressure response during exercise
Dilatation of RV outflow tract

The table shows the indicators of right ventricle pathology (ARVC *vs* athlete's heart). CMRI: Cardiac magnetic resonance imaging; RV: Right ventricle; ARVC: Arrhythmogenic right ventricular cardiomyopathy.

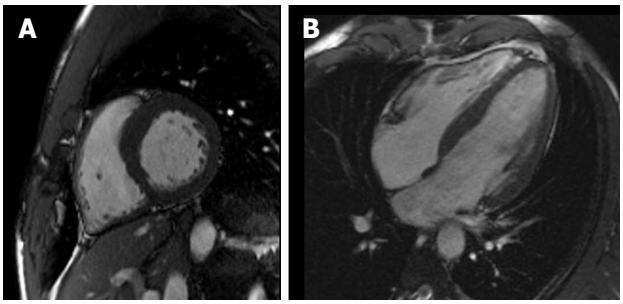

Figure 4 Cardiac magnetic resonance depicting in short-axis (A) and long-axis (B) view balanced biventricular enlargement in endurance athlete.

also observed[56].

GH abuse has tainted many sports, including baseball, cycling, and track and field, for promoting an increase in muscle mass, though its effects on physical performance are not completely supported by the literature[57]. GH promotes cellular growth by stimulating protein synthesis, inhibiting catabolism, and inducing IGF-1 production. At the molecular level, GH binds its receptor and induces subsequent expression of growth-promoting molecules[58]. GH, both in excess or in deficient states, is related to increased cardiovascular mortality. The excess, like in acromegaly or in doping, results in cardiac hypertrophy and an increase in collagen, fibrosis, and cellular infiltration. *In vivo* studies on healthy mice demonstrated that increased GH levels induce significant LV hypertrophy and an increase in concentric anterior and posterior wall thicknesses, LV diastolic diameters and volumes, and cardiac output[59]. Unfortunately, the majority of conclusions about GH abuse and its cardiac effects result from data regarding acromegaly and not from direct data, which are lacking.

Also, erythropoietin (EPO), which increases hematocrit levels and thus improves aerobics capacity, may lead to cardiac dysfunction, increasing blood viscosity and cardiac afterload, and predisposes to hypertension and thromboembolism. Experimental studies have shown hypertension, cardiac hypertrophy and fibrosis after administration of high doses of EPO[60].

Thyroxine is used, generally, by athletes to promote weight loss. Thyroid hormones (TH) play an important role in cardiac growth and might cause cardiac hypertrophy and also heart failure if they are in excess. High levels of TH might result in elevated heart rate, decreased total peripheral resistance, widened pulse pressure, blood volume expansion, increased LVM and cardiac output, with improved contractile function and hemodynamic parameters in the short term. Long-standing hyperthyroidism can lead to dilatation of cardiac chambers and heart failure. Interestingly, the diminished cardiac function is often reversible when euthyroidism is re-established[61]. Weltman *et al*[61] showed that hyperthyroid rodents had important cardiac hypertrophy and adverse cardiac remodeling with chamber dilatation, LV systolic and diastolic dysfunction, decreased relative wall thickness, and fibrosis[61]. Few data in the literature are about the cardiac consequences of the prolonged use of thyroxine treatment. Thyroxine treatment, in high doses which suppress serum thyrotropin to below normal, has been associated with LV hypertrophy (in the absence of significant changes in heart rate, stroke volume, blood pressure, and LV systolic function), but untreated thyrotoxicosis resulted in more pronounced cardiovascular changes than thyroxin treatment[62]. Furthers studies are necessary to evaluate the cardiovascular risk in patients treated with thyroxine.

Many other drugs are responsible for heart failure in athletes, such as corticotrophin, beta 2 agonists, amphetamines and cocaine. Often athletes use combinations of different banned drugs, resulting in additive effects on cardiac remodeling. Cardiac alterations may lead to arrhythmias, heart failure and sudden death. It is important to exclude the abuse of these drugs, when athletes with heart dysfunction come to our attention. Figure 6 shows a flow chart to differentiate athlete's heart from pathological conditions.

ENERGY DRINK CONSUMPTION AND HEMODYNAMIC EFFECTS

A growing number of case reports of cardiovascular adverse events associated with energy drinks (EDs) are present in the literature. The use of EDs is more common in young students and in athletes. The consumption of EDs negatively affects the hemodynamic system. Important changes in arterial pressure and heart rate may occur with the ingestion of only one can (355 mL drink volume). Furthermore, it seems that EDs may diminish cerebral blood velocity, increasing breathing frequency[63]. Caffeine and sugar appear to be the ingredients underlying hemodynamic impact of EDs. Taurine and vitamin B complex play a minor role[64]. Genetic polymorphisms in cytochrome P-450 enzymes and variations of adenosine receptors play a role in the different responses to the caffeine[65]. Caffeine improves athletic performance in rowing[66], swimming[67,68], soccer[69] and hockey[70]. On the other hand, EDs can cause many cardiovascular adverse

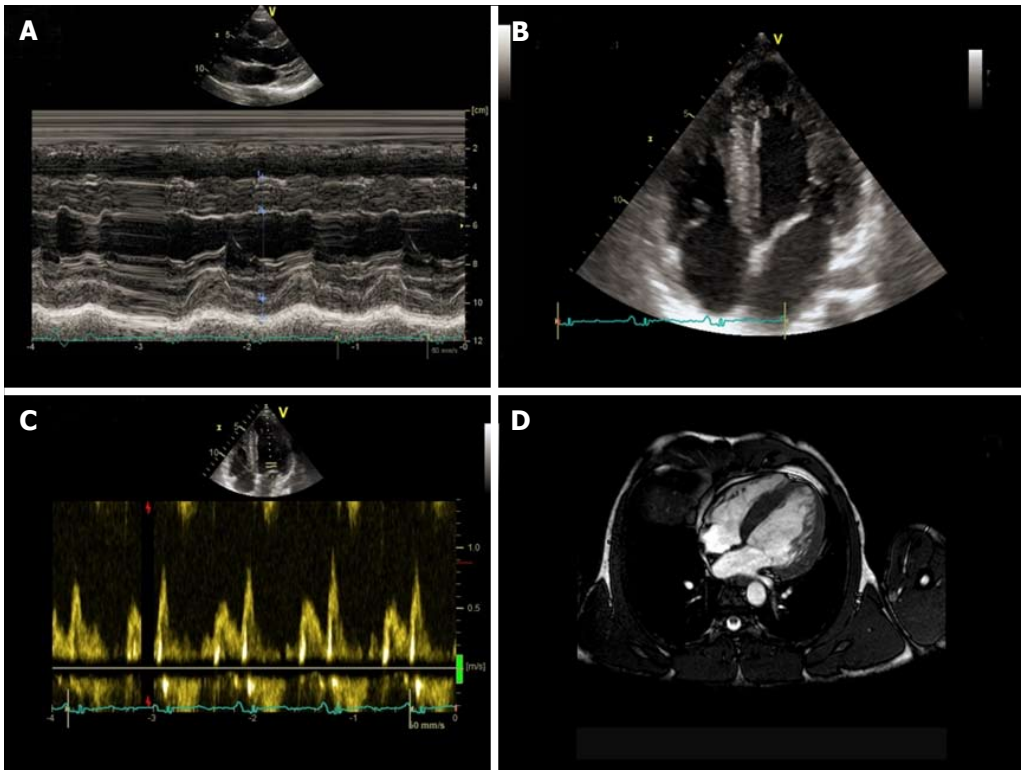

Figure 5 Non-invasive evaluation of power athlete abusing of steroids. Standard M-mode (A) and 4-chamber view B-mode (B) echocardiography, evidencing sever left ventricular hypertrophy, with diastolic dysfunction (C) underlined by Doppler transmitral flow pattern. Cardiac magnetic resonance confirmed severe left ventricular hypertrophy (D).

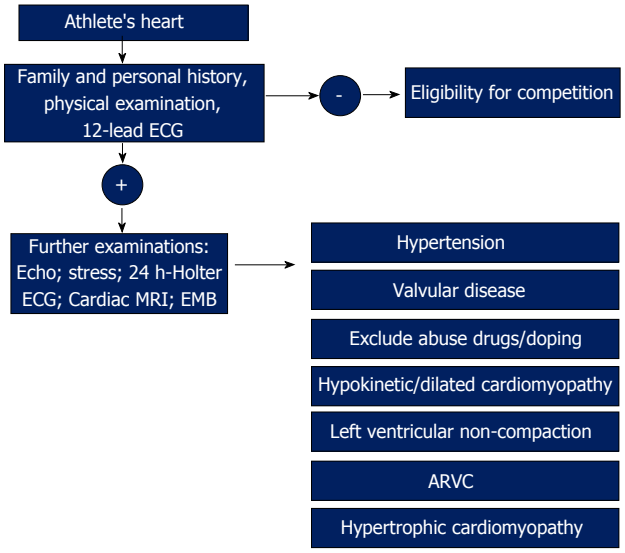

Figure 6 The management of athlete's heart. The figure shows an algorithm to distinguish athlete's heart from pathological conditions. ARVC: Arrhythmogenic right ventricular cardiomyopathy; ECG: Electrocardiograph; MRI: Magnetic resonance imaging.

effects (Table 4), such as hypertension, palpitations, ischemic stroke, epileptic seizure[71] and myocardial ischemia, with no additional trigger[72]. The possible mechanism is related to the caffeine interaction with the G-protein coupled receptors on the cardiomyocytes that leads to an increase in intracellular cyclic-AMP and calcium concentrations with chronotropic and inotropic

Table 4 Adverse effects of energy drinks

Adverse effect
Hypertension
Palpitations/arrhythmias (atrial fibrillation)
QTc prolongation
Myocardial ischemia
Ischemic stroke/Transient ischemic attack
Epileptic seizure
Anxiety, insomnia, irritability
Psychosis/Mania

The table shows the most common adverse effect of consumption of energy drinks.

effects[73]. Large studies regarding EDs and their effects on the cardiovascular system are necessary, especially for the widespread consumption of these substances in recent years.

CONCLUSION

The exact clinical significance and prognostic value of cardiac injury and fibrosis in athletes are unknown. Physiological remodeling is characterized by specific molecular activation and gene expression. More large studies are needed to gain a better understanding of these conditions and the pathological changes in the heart structure in athletes and to investigate the cardiac effects of performing-enhanced drugs and EDs in this population.

REFERENCES

1 **La Gerche A**, Taylor AJ, Prior DL. Athlete's heart: the potential for multimodality imaging to address the critical remaining questions. *JACC Cardiovasc Imaging* 2009; **2**: 350-363 [PMID: 19356581 DOI: 10.1016/j.jcmg.2008.12.011]

2 **Lazzeroni D**, Rimoldi O, Camici PG. From Left Ventricular Hypertrophy to Dysfunction and Failure. *Circ J* 2016; **80**: 555-564 [PMID: 26853555 DOI: 10.1253/circj.CJ-16-0062]

3 **D'Andrea A**, D'Andrea L, Caso P, Scherillo M, Zeppilli P, Calabrò R. The usefulness of Doppler myocardial imaging in the study of the athlete's heart and in the differential diagnosis between physiological and pathological ventricular hypertrophy. *Echocardiography* 2006; **23**: 149-157 [PMID: 16445736 DOI: 10.1111/j.1540-8175.2006.00186.x]

4 **La Gerche A**, Burns AT, Mooney DJ, Inder WJ, Taylor AJ, Bogaert J, Macisaac AI, Heidbüchel H, Prior DL. Exercise-induced right ventricular dysfunction and structural remodelling in endurance athletes. *Eur Heart J* 2012; **33**: 998-1006 [PMID: 22160404 DOI: 10.1093/eurheartj/ehr397]

5 **D'Andrea A**, La Gerche A, Golia E, Padalino R, Calabrò R, Russo MG, Bossone E. Physiologic and pathophysiologic changes in the right heart in highly trained athletes. *Herz* 2015; **40**: 369-378 [PMID: 25822292 DOI: 10.1007/s00059-015-4220-8]

6 **La Gerche A**. Can intense endurance exercise cause myocardial damage and fibrosis? *Curr Sports Med Rep* 2013; **12**: 63-69 [PMID: 23478555 DOI: 10.1249/JSR.0b013e318287488a]

7 **Diwan A**, Dorn GW. Decompensation of cardiac hypertrophy: cellular mechanisms and novel therapeutic targets. *Physiology* (Bethesda) 2007; **22**: 56-64 [PMID: 17289931 DOI: 10.1152/physiol.00033.2006]

8 **Galderisi M,** Cardim N, D'Andrea A, Bruder O, Cosyns B, Davin L, Donal E, Edvardsen T, Freitas A, Habib G, Kitsiou A, Plein S, Petersen SE, Popescu BA, Schroeder S, Burgstahler C, Lancellotti P. The multi-modality cardiac imaging approach to the Athlete's heart: an expert consensus of the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging* 2015; **16**: 353 [PMID: 25681828 DOI: 10.1093/ehjci/jeu323]

9 **Oka T**, Komuro I. Molecular mechanisms underlying the transition of cardiac hypertrophy to heart failure. *Circ J* 2008; **72** Suppl A: A13-A16 [PMID: 18772527 DOI: 10.1253/circj.CJ-08-0481]

10 **Nakai A**, Yamaguchi O, Takeda T, Higuchi Y, Hikoso S, Taniike M, Omiya S, Mizote I, Matsumura Y, Asahi M, Nishida K, Hori M, Mizushima N, Otsu K. The role of autophagy in cardiomyocytes in the basal state and in response to hemodynamic stress. *Nat Med* 2007; **13**: 619-624 [PMID: 17450150 DOI: 10.1038/nm1574]

11 **Vatner SF**. Reduced subendocardial myocardial perfusion as one mechanism for congestive heart failure. *Am J Cardiol* 1988; **62**: 94E-98E [PMID: 2970785 DOI: 10.1016/S0002-9149(88)80020-1]

12 **Shiojima I**, Sato K, Izumiya Y, Schiekofer S, Ito M, Liao R, Colucci WS, Walsh K. Disruption of coordinated cardiac hypertrophy and angiogenesis contributes to the transition to heart failure. *J Clin Invest* 2005; **115**: 2108-2118 [PMID: 16075055 DOI: 10.1172/JCI24682]

13 **Perrino C**, Naga Prasad SV, Mao L, Noma T, Yan Z, Kim HS, Smithies O, Rockman HA. Intermittent pressure overload triggers hypertrophy-independent cardiac dysfunction and vascular rarefaction. *J Clin Invest* 2006; **116**: 1547-1560 [PMID: 16741575 DOI: 10.1172/JCI25397]

14 **Neri Serneri GG**, Boddi M, Modesti PA, Cecioni I, Coppo M, Padeletti L, Michelucci A, Colella A, Galanti G. Increased cardiac sympathetic activity and insulin-like growth factor-I formation are associated with physiological hypertrophy in athletes. *Circ Res* 2001; **89**: 977-982 [PMID: 11717153 DOI: 10.1161/hh2301.100982]

15 **Bernardo BC**, Weeks KL, Pretorius L, McMullen JR. Molecular distinction between physiological and pathological cardiac hypertrophy: experimental findings and therapeutic strategies. *Pharmacol Ther* 2010; **128**: 191-227 [PMID: 20438756 DOI: 10.1016/j.pharmthera.2010.04.005]

16 **Elliott PM**, Anastasakis A, Borger MA, Borggrefe M, Cecchi F, Charron P, Hagege AA, Lafont A, Limongelli G, Mahrholdt H, McKenna WJ, Mogensen J, Nihoyannopoulos P, Nistri S, Pieper PG, Pieske B, Rapezzi C, Rutten FH, Tillmanns C, Watkins H. 2014 ESC Guidelines on diagnosis and management of hypertrophic cardiomyopathy: the Task Force for the Diagnosis and Management of Hypertrophic Cardiomyopathy of the European Society of Cardiology (ESC). *Eur Heart J* 2014; **35**: 2733-2779 [PMID: 25173338 DOI: 10.1093/eurheartj/ehu284]

17 **Morimoto S**. Sarcomeric proteins and inherited cardiomyopathies. *Cardiovasc Res* 2008; **77**: 659-666 [PMID: 18056765 DOI: 10.1093/cvr/cvm084]

18 **Shave R**, Baggish A, George K, Wood M, Scharhag J, Whyte G, Gaze D, Thompson PD. Exercise-induced cardiac troponin elevation: evidence, mechanisms, and implications. *J Am Coll Cardiol* 2010; **56**: 169-176 [PMID: 20620736 DOI: 10.1016/j.jacc.2010.03.037]

19 **Koller A**, Schobersberger W. Post-exercise release of cardiac troponins. *J Am Coll Cardiol* 2009; **53**: 1341; author reply 1341-1342 [PMID: 19358956 DOI: 10.1016/j.jacc.2008.12.046]

20 **Hessel MH**, Atsma DE, van der Valk EJ, Bax WH, Schalij MJ, van der Laarse A. Release of cardiac troponin I from viable cardiomyocytes is mediated by integrin stimulation. *Pflugers Arch* 2008; **455**: 979-986 [PMID: 17909848 DOI: 10.1007/s00424-007-0354-8]

21 **Shave R**, George KP, Atkinson G, Hart E, Middleton N, Whyte G, Gaze D, Collinson PO. Exercise-induced cardiac troponin T release: a meta-analysis. *Med Sci Sports Exerc* 2007; **39**: 2099-2106 [PMID: 18046180 DOI: 10.1249/mss.0b013e318153ff78]

22 **Siscovick DS**, Weiss NS, Fletcher RH, Lasky T. The incidence of primary cardiac arrest during vigorous exercise. *N Engl J Med* 1984; **311**: 874-877 [PMID: 6472399 DOI: 10.1056/NEJM198410043111402]

23 **Chen Y**, Serfass RC, Mackey-Bojack SM, Kelly KL, Titus JL, Apple FS. Cardiac troponin T alterations in myocardium and serum of rats after stressful, prolonged intense exercise. *J Appl Physiol* (1985) 2000; **88**: 1749-1755 [PMID: 10797139]

24 **Benito B**, Gay-Jordi G, Serrano-Mollar A, Guasch E, Shi Y, Tardif JC, Brugada J, Nattel S, Mont L. Cardiac arrhythmogenic remodeling in a rat model of long-term intensive exercise training. *Circulation* 2011; **123**: 13-22 [PMID: 21173356 DOI: 10.1161/CIRCULATIONAHA.110.938282]

25 **Dello Russo A**, Pieroni M, Santangeli P, Bartoletti S, Casella M, Pelargonio G, Smaldone C, Bianco M, Di Biase L, Bellocci F, Zeppilli P, Fiorentini C, Natale A, Tondo C. Concealed cardiomyopathies in competitive athletes with ventricular arrhythmias and an apparently normal heart: role of cardiac electroanatomical mapping and biopsy. *Heart Rhythm* 2011; **8**: 1915-1922 [PMID: 21782775 DOI: 10.1016/j.hrthm.2011.07.021]

26 **Trivax JE**, McCullough PA. Phidippides cardiomyopathy: a review and case illustration. *Clin Cardiol* 2012; **35**: 69-73 [PMID: 22222888 DOI: 10.1002/clc.20994]

27 **Limongelli G**, Rea A, Masarone D, Francalanci MP, Anastasakis A, Calabro' R, Giovanna RM, Bossone E, Elliott PM, Pacileo G. Right ventricular cardiomyopathies: a multidisciplinary approach to diagnosis. *Echocardiography* 2015; **32** Suppl 1: S75-S94 [PMID: 25234203 DOI: 10.1111/echo.12399]

28 **D'Andrea A**, Riegler L, Rucco MA, Cocchia R, Scarafile R, Salerno G, Martone F, Vriz O, Caso P, Calabrò R, Bossone E, Russo MG. Left atrial volume index in healthy subjects: clinical and echocardiographic correlates. *Echocardiography* 2013; **30**: 1001-1007 [PMID: 23594028 DOI: 10.1111/echo.12217]

29 **Iskandar A**, Mujtaba MT, Thompson PD. Left Atrium Size in Elite Athletes. *JACC Cardiovasc Imaging* 2015; **8**: 753-762 [PMID: 26093921 DOI: 10.1016/j.jcmg.2014.12.032]

30 **Rundqvist L**, Engvall J, Faresjö M, Carlsson E, Blomstrand P. Regular endurance training in adolescents impacts atrial and ventricular size and function. *Eur Heart J Cardiovasc Imaging* 2016 [PMID: 27406576 DOI: 10.1093/ehjci/jew150]

31 **D'Ascenzi F**, Solari M, Anselmi F, Maffei S, Focardi M, Bonifazi M, Mondillo S, Henein M. Atrial chamber remodelling in healthy pre-adolescent athletes engaged in endurance sports: A study with

a longitudinal design. The CHILD study. *Int J Cardiol* 2016; **223**: 325-330 [PMID: 27543703 DOI: 10.1016/j.ijcard.2016.08.231]
32 **D'Andrea A**, Bossone E, Radmilovic J, Riegler L, Pezzullo E, Scarafile R, Russo MG, Galderisi M, Calabrò R. Exercise-Induced Atrial Remodeling: The Forgotten Chamber. *Cardiol Clin* 2016; **34**: 557-565 [PMID: 27692224 DOI: 10.1016/j.ccl.2016.06.005]
33 **Calvo N**, Brugada J, Sitges M, Mont L. Atrial fibrillation and atrial flutter in athletes. *Br J Sports Med* 2012; **46** Suppl 1: i37-i43 [PMID: 23097477 DOI: 10.1136/bjsports-2012-091171]
34 **Wilhelm M**, Roten L, Tanner H, Wilhelm I, Schmid JP, Saner H. Atrial remodeling, autonomic tone, and lifetime training hours in nonelite athletes. *Am J Cardiol* 2011; **108**: 580-585 [PMID: 21658663 DOI: 10.1016/j.amjcard.2011.03.086]
35 **Aschar-Sobbi R**, Izaddoustdar F, Korogyi AS, Wang Q, Farman GP, Yang F, Yang W, Dorian D, Simpson JA, Tuomi JM, Jones DL, Nanthakumar K, Cox B, Wehrens XH, Dorian P, Backx PH. Increased atrial arrhythmia susceptibility induced by intense endurance exercise in mice requires TNFα. *Nat Commun* 2015; **6**: 6018 [PMID: 25598495 DOI: 10.1038/ncomms7018]
36 **Mont L**, Tamborero D, Elosua R, Molina I, Coll-Vinent B, Sitges M, Vidal B, Scalise A, Tejeira A, Berruezo A, Brugada J. Physical activity, height, and left atrial size are independent risk factors for lone atrial fibrillation in middle-aged healthy individuals. *Europace* 2008; **10**: 15-20 [PMID: 18178694 DOI: 10.1093/europace/eum263]
37 **D'Andrea A**, Riegler L, Golia E, Cocchia R, Scarafile R, Salerno G, Pezzullo E, Nunziata L, Citro R, Cuomo S, Caso P, Di Salvo G, Cittadini A, Russo MG, Calabrò R, Bossone E. Range of right heart measurements in top-level athletes: the training impact. *Int J Cardiol* 2013; **164**: 48-57 [PMID: 21737163 DOI: 10.1016/j.ijcard.2011.06.058]
38 **D'Ascenzi F**, Cameli M, Padeletti M, Lisi M, Zacà V, Natali B, Malandrino A, Alvino F, Morelli M, Vassallo GM, Meniconi C, Bonifazi M, Causarano A, Mondillo S. Characterization of right atrial function and dimension in top-level athletes: a speckle tracking study. *Int J Cardiovasc Imaging* 2013; **29**: 87-94 [PMID: 22588713 DOI: 10.1007/s10554-012-0063-z]
39 **Pelliccia A**, Maron MS, Maron BJ. Assessment of left ventricular hypertrophy in a trained athlete: differential diagnosis of physiologic athlete's heart from pathologic hypertrophy. *Prog Cardiovasc Dis* 2012; **54**: 387-396 [PMID: 22386289 DOI: 10.1016/j.pcad.2012.01.003]
40 **Maron BJ**. Sudden death in young athletes. *N Engl J Med* 2003; **349**: 1064-1075 [PMID: 12968091 DOI: 10.1056/NEJMra022783]
41 **Pelliccia A**, Maron BJ, De Luca R, Di Paolo FM, Spataro A, Culasso F. Remodeling of left ventricular hypertrophy in elite athletes after long-term deconditioning. *Circulation* 2002; **105**: 944-949 [PMID: 11864923 DOI: 10.1161/hc0802.104534]
42 **Caselli S**, Maron MS, Urbano-Moral JA, Pandian NG, Maron BJ, Pelliccia A. Differentiating left ventricular hypertrophy in athletes from that in patients with hypertrophic cardiomyopathy. *Am J Cardiol* 2014; **114**: 1383-1389 [PMID: 25217454 DOI: 10.1016/j.amjcard.2014.07.070]
43 **Pelliccia A**, Maron BJ, Spataro A, Proschan MA, Spirito P. The upper limit of physiologic cardiac hypertrophy in highly trained elite athletes. *N Engl J Med* 1991; **324**: 295-301 [PMID: 1824720 DOI: 10.1056/NEJM199101313240504]
44 **Ponikowski P**, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, Falk V, González-Juanatey JR, Harjola VP, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GM, Ruilope LM, Ruschitzka F, Rutten FH, van der Meer P. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur J Heart Fail* 2016; **18**: 891-975 [PMID: 27207191 DOI: 10.1002/ejhf.592]
45 **Jenni R**, Oechslin E, Schneider J, Attenhofer Jost C, Kaufmann PA. Echocardiographic and pathoanatomical characteristics of isolated left ventricular non-compaction: a step towards classification as a distinct cardiomyopathy. *Heart* 2001; **86**: 666-671 [PMID: 11711464]
46 **Caselli S**, Ferreira D, Kanawati E, Di Paolo F, Pisicchio C, Attenhofer Jost C, Spataro A, Jenni R, Pelliccia A. Prominent left ventricular trabeculations in competitive athletes: A proposal for risk stratification and management. *Int J Cardiol* 2016; **223**: 590-595 [PMID: 27561165 DOI: 10.1016/j.ijcard.2016.08.272]
47 **La Gerche A**, Claessen G. Is exercise good for the right ventricle? Concepts for health and disease. *Can J Cardiol* 2015; **31**: 502-508 [PMID: 25840099 DOI: 10.1016/j.cjca.2015.01.022]
48 **Corrado D**, Basso C, Rizzoli G, Schiavon M, Thiene G. Does sports activity enhance the risk of sudden death in adolescents and young adults? *J Am Coll Cardiol* 2003; **42**: 1959-1963 [PMID: 14662259]
49 **Maron BJ**, Doerer JJ, Haas TS, Tierney DM, Mueller FO. Sudden deaths in young competitive athletes: analysis of 1866 deaths in the United States, 1980-2006. *Circulation* 2009; **119**: 1085-1092 [PMID: 19221222 DOI: 10.1161/CIRCULATIONAHA.108.804617]
50 **Corrado D**, Leoni L, Link MS, Della Bella P, Gaita F, Curnis A, Salerno JU, Igidbashian D, Raviele A, Disertori M, Zanotto G, Verlato R, Vergara G, Delise P, Turrini P, Basso C, Naccarella F, Maddalena F, Estes NA, Buja G, Thiene G. Implantable cardioverter-defibrillator therapy for prevention of sudden death in patients with arrhythmogenic right ventricular cardiomyopathy/dysplasia. *Circulation* 2003; **108**: 3084-3091 [PMID: 14638546 DOI: 10.1016/j.jacc.2003.03.002]
51 **Marcus GM**, Glidden DV, Polonsky B, Zareba W, Smith LM, Cannom DS, Estes NA, Marcus F, Scheinman MM. Efficacy of antiarrhythmic drugs in arrhythmogenic right ventricular cardiomyopathy: a report from the North American ARVC Registry. *J Am Coll Cardiol* 2009; **54**: 609-615 [PMID: 19660690 DOI: 10.1016/j.jacc.2009.04.052]
52 **Zaidi A**, Sheikh N, Jongman JK, Gati S, Panoulas VF, Carr-White G, Papadakis M, Sharma R, Behr ER, Sharma S. Clinical Differentiation Between Physiological Remodeling and Arrhythmogenic Right Ventricular Cardiomyopathy in Athletes With Marked Electrocardiographic Repolarization Anomalies. *J Am Coll Cardiol* 2015; **65**: 2702-2711 [PMID: 26112193 DOI: 10.1016/j.jacc.2015.04.035]
53 **Bauce B**, Frigo G, Benini G, Michieli P, Basso C, Folino AF, Rigato I, Mazzotti E, Daliento L, Thiene G, Nava A. Differences and similarities between arrhythmogenic right ventricular cardiomyopathy and athlete's heart adaptations. *Br J Sports Med* 2010; **44**: 148-154 [PMID: 18603583 DOI: 10.1136/bjsm.2007.042853]
54 **D'Andrea A**, Limongelli G, Morello A, Mattera Iacono A, Russo MG, Bossone E, Calabrò R, Pacileo G. Anabolic-androgenic steroids and athlete's heart: When big is not beautiful....! *Int J Cardiol* 2016; **203**: 486-488 [PMID: 26547743 DOI: 10.1016/j.ijcard.2015.10.186]
55 **Montisci M**, El Mazloum R, Cecchetto G, Terranova C, Ferrara SD, Thiene G, Basso C. Anabolic androgenic steroids abuse and cardiac death in athletes: morphological and toxicological findings in four fatal cases. *Forensic Sci Int* 2012; **217**: e13-e18 [PMID: 22047750 DOI: 10.1016/j.forsciint.2011.10.032]
56 **Pope HG**, Wood RI, Rogol A, Nyberg F, Bowers L, Bhasin S. Adverse health consequences of performance-enhancing drugs: an Endocrine Society scientific statement. *Endocr Rev* 2014; **35**: 341-375 [PMID: 24423981 DOI: 10.1210/er.2013-1058]
57 **Liu H**, Bravata DM, Olkin I, Friedlander A, Liu V, Roberts B, Bendavid E, Saynina O, Salpeter SR, Garber AM, Hoffman AR. Systematic review: the effects of growth hormone on athletic performance. *Ann Intern Med* 2008; **148**: 747-758 [PMID: 18347346]
58 **Palmeiro CR**, Anand R, Dardi IK, Balasubramaniyam N, Schwarcz MD, Weiss IA. Growth hormone and the cardiovascular system. *Cardiol Rev* 2012; **20**: 197-207 [PMID: 22314142 DOI: 10.1097/CRD.0b013e318248a3e1]
59 **Cittadini A**, Strömer H, Katz SE, Clark R, Moses AC, Morgan JP, Douglas PS. Differential cardiac effects of growth hormone and insulin-like growth factor-1 in the rat. A combined in vivo and in vitro evaluation. *Circulation* 1996; **93**: 800-809 [PMID: 8641010 DOI: 10.1161/01.CIR.93.4.800]
60 **Noakes TD**. Tainted glory--doping and athletic performance. *N Engl J Med* 2004; **351**: 847-849 [PMID: 15329417 DOI: 10.1056/

NEJMp048208]
61 **Weltman NY**, Wang D, Redetzke RA, Gerdes AM. Longstanding hyperthyroidism is associated with normal or enhanced intrinsic cardiomyocyte function despite decline in global cardiac function. *PLoS One* 2012; **7**: e46655 [PMID: 23056390 DOI: 10.1371/journal.pone.0046655]
62 **Ching GW**, Franklyn JA, Stallard TJ, Daykin J, Sheppard MC, Gammage MD. Cardiac hypertrophy as a result of long-term thyroxine therapy and thyrotoxicosis. *Heart* 1996; **75**: 363-368 [PMID: 8705762]
63 **Grasser EK**, Yepuri G, Dulloo AG, Montani JP. Cardio- and cerebrovascular responses to the energy drink Red Bull in young adults: a randomized cross-over study. *Eur J Nutr* 2014; **53**: 1561-1571 [PMID: 24474552 DOI: 10.1007/s00394-014-0661-8]
64 **Miles-Chan JL**, Charrière N, Grasser EK, Montani JP, Dulloo AG. The blood pressure-elevating effect of Red Bull energy drink is mimicked by caffeine but through different hemodynamic pathways. *Physiol Rep* 2015; **3**: pii: e12290 [PMID: 25716925 DOI: 10.14814/phy2.12290]
65 **Yang A**, Palmer AA, de Wit H. Genetics of caffeine consumption and responses to caffeine. *Psychopharmacology* (Berl) 2010; **211**: 245-257 [PMID: 20532872 DOI: 10.1007/s00213-010-1900-1]
66 **Bruce CR**, Anderson ME, Fraser SF, Stepto NK, Klein R, Hopkins WG, Hawley JA. Enhancement of 2000-m rowing performance after caffeine ingestion. *Med Sci Sports Exerc* 2000; **32**: 1958-1963 [PMID: 11079528]
67 **MacIntosh BR**, Wright BM. Caffeine ingestion and performance of a 1,500-metre swim. *Can J Appl Physiol* 1995; **20**: 168-177 [PMID: 7640644]
68 **Collomp K**, Ahmaidi S, Chatard JC, Audran M, Préfaut C. Benefits of caffeine ingestion on sprint performance in trained and untrained swimmers. *Eur J Appl Physiol Occup Physiol* 1992; **64**: 377-380 [PMID: 1592065]
69 **Lara B**, Gonzalez-Millán C, Salinero JJ, Abian-Vicen J, Areces F, Barbero-Alvarez JC, Muñoz V, Portillo LJ, Gonzalez-Rave JM, Del Coso J. Caffeine-containing energy drink improves physical performance in female soccer players. *Amino Acids* 2014; **46**: 1385-1392 [PMID: 24615239 DOI: 10.1007/s00726-014-1709-z]
70 **Del Coso J**, Portillo J, Salinero JJ, Lara B, Abian-Vicen J, Areces F. Caffeinated Energy Drinks Improve High-Speed Running in Elite Field Hockey Players. *Int J Sport Nutr Exerc Metab* 2016; **26**: 26-32 [PMID: 26251550 DOI: 10.1123/ijsnem.2015-0128]
71 **Gray B**, Das K J, Semsarian C. Consumption of energy drinks: a new provocation test for primary arrhythmogenic diseases? *Int J Cardiol* 2012; **159**: 77-78 [PMID: 22704863 DOI: 10.1016/j.ijcard.2012.05.121]
72 **Sanchis-Gomar F**, Leischik R, Lippi G. Energy drinks: Increasing evidence of negative cardiovascular effects. *Int J Cardiol* 2016; **206**: 153 [PMID: 26797159 DOI: 10.1016/j.ijcard.2016.01.107]
73 **Higgins JP**, Tuttle TD, Higgins CL. Energy beverages: content and safety. *Mayo Clin Proc* 2010; **85**: 1033-1041 [PMID: 21037046 DOI: 10.4065/mcp.2010.0381]

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REVIEW

Assessment of aortic valve disease - a clinician oriented review

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Abstract

Aortic valve disease [aortic stenosis (AS) and aortic regurgitation (AR)] represents an important global health problem; when severe, aortic valve disease carries poor prognosis. For AS, aortic valve replacement, either surgical or interventional, may provide definite treatment in carefully selected patients. For AR, valve surgery (either replacement or - in selected cases - aortic valve repair) remains the gold standard of care. To properly identify those patients who are candidates for surgery, the clinician has to carefully assess the severity of valve disease with an understanding of the potential pitfalls involved in these assessments. This review focuses on the practical issues concerning the evaluation of patients with AS and AR from a general cardiologist's perspective. The most important issues regarding the documentation of the severity of AS and AR are summarized. More specific issues, such as the role of stress echocardiography, other imaging techniques and details regarding the treatment options (medical, surgical, or interventional), are mentioned briefly.

Key words: Echocardiography; Aortic stenosis; Aortic regurgitation; Treatment; Evaluation

Core tip: Aortic stenosis (AS) and aortic regurgitation (AR) represent important health problems world-wide. This review focuses on the practical issues concerning the evaluation of patients with AS and AR from a general cardiologist's perspective. The most important issues regarding the documentation of the severity of AS and AR are summarized, and potential pitfalls are highlighted. More specific issues, such as the role of stress echocardiography, other imaging techniques and details regarding the treatment options (medical, surgical, or interventional), are mentioned briefly.

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INTRODUCTION

Aortic valve disease [aortic stenosis (AS) and aortic regurgitation (AR)] represents an important global health problem. The data on the exact prevalence of AS and AR in the general population are lacking, but studies performed in Western populations estimate that 3% to 4% of the adult population suffers from moderate or severe aortic valve disease. The prevalence of AS and AR increases with age; it is estimated that 1% of persons aged < 55 years and 6% of persons aged > 75 years suffer from moderate or severe AS/AR[1,2].

This review focuses on the practical issues concerning the evaluation of patients with AS and AR from a general cardiologist's perspective. The most important issues regarding the documentation of the severity of AS and AR using echocardiography are summarized. More specific issues, such as the role of stress echocardiography, other imaging techniques and details regarding the treatment options (medical, surgical, or interventional), are mentioned briefly. For more detailed information on these topics, the reader is referred to several recent excellent reviews, mostly regarding AS[3-11].

AS

AS is defined as a narrowing of the surface area of the aortic orifice [aortic valve area (AVA)] below the normal value (approximately 3 cm^2). AS becomes significant [*i.e.*, determines a significant increase in left ventricular (LV) afterload] only after the AVA decreases by more than half. In general, the accepted criteria for the definition of severe AS is an AVA $\leqslant$ 1 cm^2 (or $\leqslant$ 0.6 cm^2/m^2 of body surface area). These cut-off values have been used in clinical studies but are patient-dependent and do not completely overlap with other indices that are also used to define severe AS (*e.g.*, transaortic pressure gradients - see below).

Etiology

In Western countries, AS has the following two major causes: Degenerative (calcific) and congenital. Calcific AS is predominant in the elderly population, shares common pathological features and is commonly associated with atherosclerosis. Congenital AS [> 90% represented by bicuspid aortic valve (BAV)] manifests clinically 10 to 20 years earlier than calcific AS. Contemporary data from 932 isolated aortic valves excised from adults aged 26 to 91 years between 1993 and 2004 suggest that 54% of these cases were congenital in origin[12].

AS is a slowly progressive disease. Almost 50 years ago, Ross and Braunwald highlighted that the appearance of symptoms marks a sharp decline in survival with nearly universal death within 5 years[13]. The types of symptoms are important, as follows: The mean survival after the appearance of angina was 5 years, 3 years after syncope and 2 years after the appearance of heart failure. When these data were published, the predominant etiology was rheumatic heart disease, and the mean patient age was 63 years old[14]. Thus, the contemporary application of these data is limited. Recent data suggest that the presence of AS is associated with a 68% increased risk of coronary events, a 27% increased risk of cerebrovascular events, and a 36% increased risk of mortality[15]. The data from the PARTNER study in elderly patients with severe calcific AS suggest an annual mortality of 50% with conservative treatment[16].

Evaluation of AS

The evaluation of patients with AS must define the following 2 issues: (1) identification of patients with severe AS; and (2) in patients with severe AS, identification of patients whose prognosis will be improved by aortic valve replacement (AVR) (surgical or interventional).

Identifying patients with severe AS: The clinical (presence of symptoms, grade $\geqslant$ 4/6 ejection murmur, and "tardus et parvus" peripheral pulse), electrocardiographical (left ventricular hypertrophy) or radiological (valve calcification) criteria for severity have high sensitivity but low specificity in identifying patients with severe AS. Therefore, objective assessment of AS severity is needed.

Historically, invasive direct measurement of transaortic pressure gradients was performed, and the aortic valve area was calculated using the Gorlin formula. This practice was abandoned because of the following important drawbacks: (1) invasively measured pressure gradients (mean transaortic pressure gradient and the difference between peak aortic pressure and peak LV systolic pressure) do not overlap with the Doppler estimation of transaortic pressure gradients. This is because Doppler echocardiography measures instantaneous velocities and through the use of Bernoulli equation estimates instantaneous pressure gradients, whereas peak LV pressure occurs before peak aortic pressure (the invasively measured peak-to-peak transaortic pressure difference is not instantaneous); and (2) the risk of atherosclerotic cerebral embolism during the transaortic passage of the pressure catheter may reach 20%[17]. Thus, today, objective assessment of AS severity almost completely relies on proper performance and interpretation of Doppler echocardiography.

The currently used criteria for the definition of severe AS by echocardiography are listed in Table 1[18]. These criteria have advantages and disadvantages.

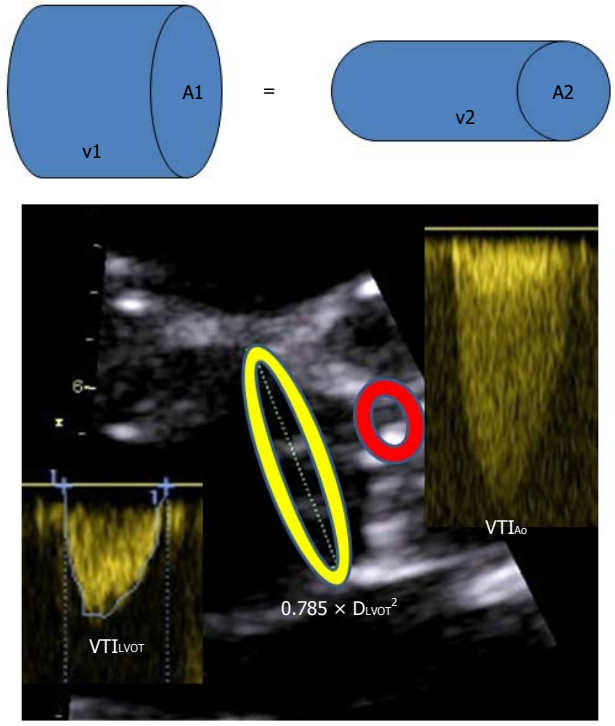
It is of critical importance that the echocardiographic evaluation of AS is based on correctly performed measurements, using an integrative approach, because the echocardiographic criteria for the definition of severe AS are not interchangeable, and the criteria based on pressure gradients and velocities are highly dependent on blood flow.

The most robust and reproducible estimation of AVA

Table 1 Echocardiographic criteria for the definition of severe aortic stenosis: Advantages and disadvantages[18]

Criteria	Severe AS	Advantages	Disadvantages
Aortic surface area	$\leqslant$ 1.0 cm^2	Measures effective AVA. However, this may also constitute a disadvantage because it does not measure anatomical AVA Less flow-dependent compared with other measurements	Very sensitive to measurement errors
Indexed AVA to body surface area	$\leqslant$ 0.6 cm^2/m^2	Useful for extreme heights/weights	Very sensitive to measurement errors
Mean transaortic pressure gradient	$\geqslant$ 40 mmHg		Flow-dependent Requires correct alignment of Doppler signal with the flow direction
Peak transaortic flow velocity	$\geqslant$ 4.0 m/s	Measures instantaneous velocity Best predictor of adverse events	Flow-dependent Requires correct alignment of Doppler signal with the flow direction
Ratio between peak transaortic flow velocity and peak LVOT velocity	$\leqslant$ 1/4	Good reproducibility (compared with AVA calculation)	Limited data on prognostic utility

AS: Aortic stenosis; AVA: Aortic valve area; LVOT: Left ventricular outflow tract.



$A_{LVOT} \times VTI_{LVOT} = AVA \times VTI_{Ao} \rightarrow AVA = A_{LVOT} \times VTI_{LVOT}/VTI_{Ao}$
where $A_{LVOT} = (\pi \times D_{LVOT}^2)/4 = 0.785 \times D_{LVOT}^2$

Figure 1 Relationship between flow, area and velocity. Calculation of the aortic valve area (AVA) based on the continuity equation. Flow (mL) equals the cross-sectional area (cm^2) of the vessel multiplied by the mean flow velocity through that cross-sectional area during a period of time [measured as velocity-time-integral, VTI (cm)]. The flow is constant throughout the length of the vessel without ramifications. Thus, at the aortic valve level, the flow below the valve (in the left ventricular outflow tract, LVOT) equals flow through the aortic valve. Therefore, the AVA equals the LVOT area multiplied by the mean flow velocity through the LVOT area during ejection [LVOT velocity-time-integral, VTI_{LVOT} (cm)] divided by the transaortic mean flow velocity during ejection [transaortic velocity-time-integral, VTI_{Ao} (cm)]. The LVOT area, given the theoretical circular shape of the LVOT, is calculated by measuring its internal diameter [D_{LVOT} (cm)]. A: Area; V: Velocity; D_{LVOT}: Left ventricular outflow tract diameter; VTI: Velocity-time-integral.

is based on the continuity equation (Figure 1).

To calculate the AVA, it is essential to perform correct measurements, especially for the left ventricular ejection tract diameter (D_{LVOT}) and velocities.

Any error in the measurements of D_{LVOT} will be squared when calculating AVA using the continuity equation. Thus, for a correct measurement of D_{LVOT}, the following technical requirements are suggested: (1) use of the "zoom" function on the echocardiograph to focus and enlarge the LVOT; (2) decrease the grey-scale gain towards the minimum; (3) D_{LVOT} measurement is performed from the inner anterior edge to the inner posterior edge of the LVOT in mid-systole ("inner-edge to inner-edge"), which is immediately under the aortic valve. The maximal visualized D_{LVOT} is considered, using an echocardiographic section that passes through the center of the LVOT and is not excentric because an excentric slice will underestimate the true maximal diameter. The measured D_{LVOT} should be compatible with the patient's height and weight. A D_{LVOT} < 16 mm is extremely rarely seen in adults and should raise suspicion of measurement errors[19].

It is important to realize that the true shape of the LVOT is not circular but oval; thus, echocardiographically determined AVA will always be an estimation and not a true measurement.

The correct measurement of transaortic velocities and gradients requires the use of the following multiple echo windows: Modified apical 5 chamber view towards the axilla; apical long axis view; 4th right intercostal space; and suprasternal window. Given these views, the following precautions should be applied: (1) the full envelope of the Doppler signal should be measured to avoid noise and/or aliasing; (2) measurements should not be made on post-extrasystolic beats; (3) correct measurement of the LVOT velocity-time-integral (VTI_{LVOT}) should be made. The sample area should be placed immediately under the aortic valve in the middle of the LVOT where the velocity is maximal. In this location, the signal should record the clear click of the aortic valve closure without the click of the aortic valve opening; and (4) for the correct assessment of AVA using the simplified Bernoulli equation (automatically given by the echocardiograph), the measured VTI_{LVOT} should be < 1.5 m/s. When the

VTI_{LVOT} is $\geq$ 1.5 m/s (*e.g.*, increased LVOT flow due to severe AR, *etc.*), the simplified Bernoulli equation cannot be used because it will overestimate the transaortic pressure gradient and AS severity based on the continuity equation and calculated AVA.

In conclusion, a correct and complete echocardiographic assessment of AS severity should report on the overall context of the cardiac pathology, LV volumes and LVEF, stroke volume (based on Doppler, not volumetric measurements), grade of calcification of the aortic valve (is it compatible with the measured severity?), associated abnormalities, estimation of pulmonary pressures, dimensions of right heart chamber, and estimation of right ventricular function.

The echocardiographic criteria for the definition of severe AS are not interchangeable. For example, a recent study on the correlation between mean transaortic pressure gradient and AVA in patients with AS and normal LVEF proved that for a mean pressure gradient of 40 mmHg, the corresponding AVA was 0.8 cm^2 and not 1 cm^2 as is the standard definition of severe AS[20]. Similarly, it is important to understand that a simple documentation of an AVA $\leq$ 0.8 cm^2 does not prove the presence of severe AS because AVA is calculated using pressure gradients that are highly dependent on flow. Thus, when the transaortic flow is low, any valve (including normal ones) will appear "stenotic" because the orifice will not be fully opened. It has been proven that at transaortic flow rates < 125 mL/s (corresponding to a cardiac output of approximately 3 L/min) the effective orifice area of any aortic valve, from mild anatomic AS to severe anatomic AS, will be $\leq$ 1 cm^2. Similarly, the mean transaortic pressure gradient will be $\leq$ 40 mmHg for any AS severity (from mild to severe, based on anatomical AVA) when the transaortic flow is < 175 mL/min[21].

Thus, the major problem in assessing AS severity rests with low-flow states. The prevalence of "low-flow, low-gradient" severe AS is approximately 25% of all severe AS cases. A low flow state is defined as an indexed stroke volume < 35 mL/m^2 of the body surface area. A low-flow/low-gradient state can appear in patients with both reduced LVEF due to myocardial systolic dysfunction or preserved LVEF due to small LV cavity size[22]. These 2 conditions will be detailed below.

Low-flow, low-gradient, low-LVEF, severe AS: Low-flow, low-gradient, low-LVEF, severe AS ("classical" low-flow, low-gradient severe AS) was described for the first time by Carabello *et al*[23] in 1980. It is defined as severe AS in the presence of systolic LV dysfunction (LV ejection fraction < 40%) with a mean transaortic pressure gradient < 40 mmHg if estimated by echocardiography or < 30 mmHg if measured invasively.

When the calculated AVA is $\leq$ 1 cm^2 in low flow states, one should differentiate whether this is primarily due to the low flow (pseudo severe AS, where the anatomical AVA is > 1 cm^2) or if there is true severe AS (AVA remains fixed and $\leq$ 1 cm^2 regardless of flow). Dobutamine stress echocardiography (DSE) is typically performed to differentiate between the two conditions because it evaluates the response of AVA to increased transaortic flow. Figure 2 exemplifies the role of DSE in diagnosing low-flow, low-gradient, low-EF severe AS[24].

Thus, when the calculated AVA is $\leq$ 1 cm^2, the mean transaortic pressure gradient is < 40 mmHg and the LVEF is < 40%, the DSE will help define the following parameters: (1) the severity of AS; and (2) the presence or absence of LV flow/contractile reserve, which is defined as an increase in LV stroke volume > 20% compared with baseline at maximal dobutamine dose. Thus, the following 2 responses to dobutamine and 3 conditions associated with AS are seen when using DSE.

Low-flow, low-gradient, low-EF severe AS is diagnosed when there is increased flow/contractile reserve with a subsequent increase in transaortic pressure gradient to > 40 mmHg while AVA remains $\leq$ 1 cm^2. AVR is indicated in these patients.

Pseudo-severe AS is diagnosed when there is flow (contractile) reserve, but the AVA increases in parallel with the flow to > 1 cm^2. AVR is not indicated in these patients.

AS with undetermined severity is defined by the lack of flow/contractile reserve[25]. Even in this situation, identifying severe AS is important because the prognosis without AVR is grim, although surgical mortality is high. Identifying low-flow, low-gradient, severe AS without flow (contractile) reserve is based on the following: (1) statistical data - approximately 95% of low-flow, low-gradient, low-EF AS with undetermined severity have truly severe AS; and (2) objective data - evidence of severe aortic valve calcification (using echocardiogram, plain radiology or computed tomography) is highly specific for severe AS[26]. In this situation, a calcium score of $\geq$ 1651 Agatston units on computed tomography has an 82% sensitivity, 80% specificity, 88% negative predictive value and 70% positive predictive value for severe AS[27]. Of note, for the same hemodynamic severity of AS, women have lower aortic calcium load compared with men, so the thresholds should probably be lower in women compared with men[28].

Low-flow, low-gradient severe AS with preserved LVEF: Approximately 10% of patients with anatomically severe AS have low-flow/low-gradient characteristics despite preserved LVEF ("paradoxical" low-flow, low-gradient severe AS). This form of severe AS was first described by Hachicha *et al*[29] in 2007 and is characterized by the following features: (1) concentrically remodeled LV with preserved LVEF, severe diastolic dysfunction, impaired LV filling and low cardiac output (stroke volume < 35 mL/m^2); and (2) increased LV afterload generated by the AS and increased peripheral vascular resistance due to the rigid arterial system and frequent severe arterial hypertension in these patients.

Estimation of the global afterload faced by the LV (defined as the ventriculo-arterial impedance, Zva) is important because it is an independent negative prognostic factor and correlates with the appearance of symptoms

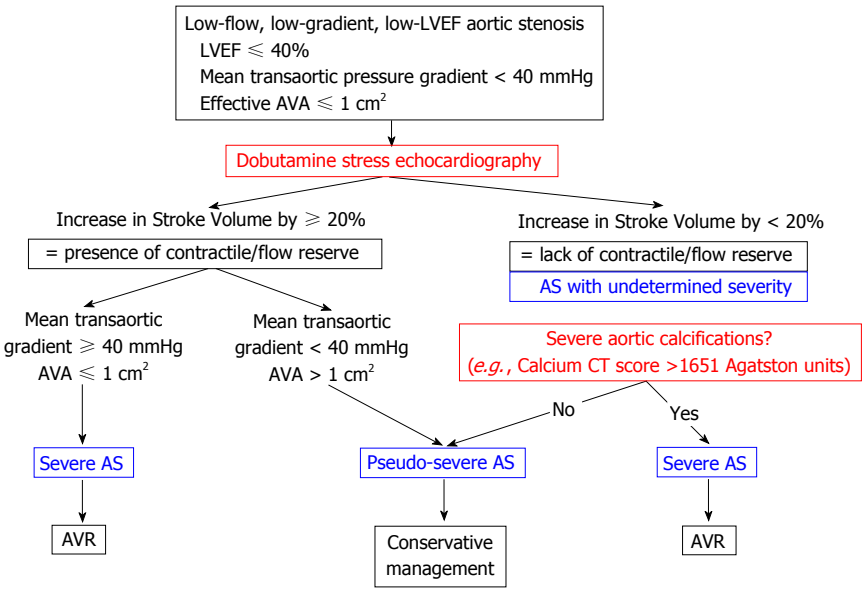


Figure 2 The role of dobutamine stress echocardiography in diagnosing low-flow, low-gradient/low-ejection fraction severe[24]. LVEF: Left ventricular ejection fraction; CT: Computed tomography; AVR: Aortic valve replacement; AVA: Aortic valve area; AS: Aortic stenosis.

in these patients[30]. Zva is calculated according to the following formula:

Zva = [Systolic blood pressure (mmHg) + mean transaortic pressure gradient (mmHg)]/[indexed stroke volume (mL/m^2)].

Taking into account the transaortic flow and pressure gradients, severe AS with preserved LVEF has been recently classified into the following 4 forms[31]: (1) normal flow, low-gradient (NFLG) - representing approximately 1/4 of patients; (2) normal flow, high-gradient: Representing approximately 2/3 of patients; (3) low-flow, low-gradient (LFLG) - also known as "paradoxical" low-flow/low-gradient - representing 10% of patients; and (4) low-flow, high-gradient - representing the remaining 10% of patients.

The principle of this classification scheme can be extended to all forms of AS, regardless of LVEF[11].

This classification has prognostic importance in patients with severe AS with preserved LVEF. The best prognosis [major adverse cardiovascular event (MACE) rate, 35% at 3 years] is carried by NFLG, and the most severe prognosis (MACE rate, 90% at 3 years) is carried by LFLG severe AS with preserved LVEF. The "high-gradient" forms have similar prognoses because they are intermediate forms between NFLG and LFLG[31]. However, this classification is limited by the fact that the existence of NFLG severe anatomical AS is counterintuitive. Indeed, the prognosis of these patients is similar to that for patients with moderate AS and is better than that for any other form of severe AS[32]. Thus, it is highly likely that what is known as NFLG severe AS with preserved LVEF is in fact moderate AS where the discrepancy between calculated AVA (which usually rests between 0.8 and 1 cm^2 in these cases) and transaortic gradients is a consequence of the inconsistency of the criteria used to define severe AS (see above) and/or measurement errors (Figure 3). Thus, when one is faced with a discrepancy between the calculated AVA and measured gradients, the following elements should be taken into account: (1) measurement errors, especially of the D_{LVOT} diameter and VTI_{LVOT} (underestimating flow); (2) extremes in body surface areas (very small or large individuals) - always use indexed measurements; and (3) inconsistency between the cut-off values used to define severe AS: An AVA of 1 cm^2 corresponds better to a transaortic pressure gradient of 30-35 mmHg and not 40 mmHg (see comments above for NFLG "severe" AS with preserved LVEF).

To establish a diagnosis of LFLG severe AS with preserved LVEF the following 3 criteria are recommended. First, confirmation of low-flow states by and indexed stroke volume < 35 mL/m^2. Second, confirmation of increased global LV afterload (ventriculo-arterial impedance) by Zva ⩾ 4.5 mmHg/mL per square meter. Third, confirmation of concentric LV remodeling by the following: (1) relative wall thickness (RWT) ⩾ 0.45. RWT is calculated using the following formula: RWT = (IVS + LVPW)/LVEDD, where IVS is the end-diastolic ventricular septal thickness; LVPW is the end-diastolic LV posterior wall thickness; and LVEDD is the end-diastolic LV diameter; (2) end-diastolic LV diameter < 47 mm; and (3) indexed end-diastolic LV volume < 55 mL/m^2.

Identification of patients with severe AS who are candidates for aortic valve replacement: After establishing the diagnosis of severe AS, the next step is to identify those patients who will benefit from AVR. The European Society of Cardiology/European Association for Cardio-Thoracic Surgery (ESC/EACTS) and the American Heart Association/American College of Cardiology (AHA/ACC) guidelines establish clear indications for AVR in patients with *symptomatic* severe AS (class I for normal flow/normal LVEF and for patients

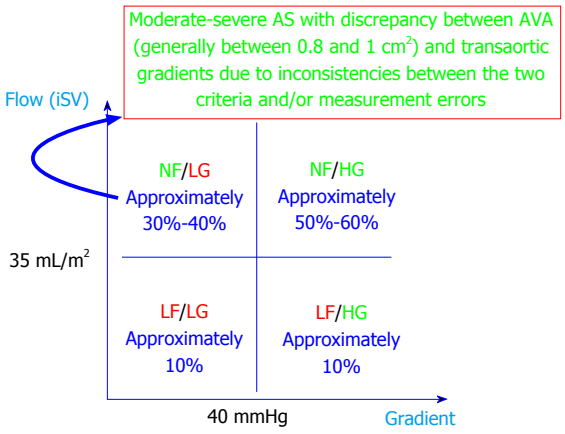


Figure 3 Classification of severe aortic stenosis with preserved left ventricular ejection fraction based on flow and transaortic pressure gradients[29]. iSV: Indexed stroke volume; NF: Normal flow; LF: Low flow; HG: High gradient; LG: Low gradient; AVA: Aortic valve area; AS: Aortic stenosis.

with normal flow/low LVEF and class Ⅱa for patients with low-flow/low-gradient/low LVEF with true severe AS) and asymptomatic severe AS with LV systolic dysfunction or symptoms unmasked at stress tests (Table 2)[33,34].

Establishing the presence or absence of symptoms can be difficult because many older patients (the majority of patients with AS) deny the presence of symptoms due to lifestyle adaptations to lower functional needs. Also, older patients refer symptoms that can be vague (*e.g.*, fatigue), related to AS or to other comorbidities related with advanced age but not caused by AS. In these patients, unmasking the presence of symptoms (by treadmill or bicycle stress test) and/or LV systolic dysfunction (by stress echocardiography) establishes the indication for AVR[35]. The prognosis of patients with asymptomatic severe AS by positive stress test is identical to that for patients with symptomatic severe AS[36,37].

The indication for AVR in patients with asymptomatic severe AS with preserved LVEF is highly controversial[38,39]. For a detailed discussion and extensive review of the literature on this highly important topic, the reader is referred to the excellent article by Généreux *et al*[10]. The 1- and 5-year mortality rates for asymptomatic severe AS with preserved LVEF are 3% and 26.4%, respectively; also, 46% of initially asymptomatic patients develop symptoms during the next 5 years, and 20% develop heart failure[40]. Among patients with asymptomatic severe AS with preserved LVEF, those with very severe AS (defined as having a maximal transaortic velocity of ⩾ 5.5 m/s) have twice the rate of MACE compared with that of patients with severe AS and a maximal transaortic velocity of 4 to 5 m/s (96% *vs* 39% at 4 years)[41]. Almost all patients (97%) with severe AS and a maximal velocity of ⩾ 5 m/s suffered a MACE within 6 years of follow-up[41]. A recent registry study on patients with asymptomatic very severe AS, which compared 102 patients who had surgical AVR with 95 patients who were treated conservatively, showed that surgical AVR was associated with an 86% reduction in mortality compared with the conservatively managed group after 6 years of follow-up (2% *vs* 32%; HR = 0.14, 95%CI: 0.03-0.6, P = 0.008)[42]. Based on these non-randomized, single-center data, current guidelines provide a class Ⅱa ("is reasonable"; "should be considered") for AVR in patients with asymptomatic very severe AS with preserved LVEF (defined as having a maximal velocity of ⩾ 5.5 m/s in the ESC/EACTS guidelines or ⩾ 5 m/s in the AHA/ACC guidelines) only if the estimated perioperative mortality in that center is low[32,34]. Current guidelines also give a class Ⅱa indication for AVR in patients with severe low-flow AS with preserved LVEF if the symptoms are judged to be secondary to AS only.

Observational and retrospective data suggest that several risk factors for MACE and poor prognosis may be useful to take into account in these cases (Table 3). However, it should be noted that the sensitivity and specificity of these parameters for the identification of patients with a good post-operative prognosis are only approximately 80%. Thus, implementation of these parameters to wide clinical practice cannot be recommended at present but can they can be useful for individual decision making in patients proposed for AVR. Among these parameters, the most widely studied are the prognostic role of aortic valvular calcifications and the hemodynamic response at stress echocardiography.

Eighty percent of patients with asymptomatic severe AS with preserved LVEF who have moderate or severe valvular calcifications develop MACE within the next 4 years, compared with only 20% of patients without moderate or severe calcifications[26,43].

The response of transaortic pressure gradient to exercise has also been suggested to have prognostic importance. Thus, MACE event rate is highest (100% at 2 years) in patients with high resting transaortic pressure gradient (> 35 mmHg) that increases by > 20 mmHg during exercise, intermediate in patients where the transaortic pressure gradient increases by < 20% during exercise (50% at 2 years for patients with high resting transaortic pressure gradient, and 20% at 2 years for patients with low transaortic pressure gradient), and lowest (10% at 2 years) in patients with low transaortic pressure gradient (⩽ 35 mmHg) that increases by < 20% during exercise[44].

Another study that evaluated 105 patients with asymptomatic severe AS with preserved LVEF showed that the inducibility of pulmonary hypertension during exercise (defined as an echocardiographically estimated systolic pulmonary arterial pressure ⩾ 60 mmHg) was associated with twice the risk of MACE within 3 years of follow-up compared with patients with asymptomatic severe AS with preserved LVEF who did not develop pulmonary hypertension during exercise (22% *vs* 55%, P = 0.014)[45]. However, the incidence of MACE in both of these groups was very high. In addition, a recent meta-analysis of 4 observational studies with a total of 2486 patients reporting on the utility of AVR (21%

Table 2 Indication for aortic valve replacement according to European Society of Cardiology/European Association for Cardio-Thoracic Surgery and American Heart Association/American College of Cardiology guidelines[33,34]

Criteria	Level of recommendation		Differences between guidelines
	ESC/EACTS	AHA/ACC	
Severe AS with any symptoms clearly due to AS, based on history or unmasked by stress test	I	I	"High-gradient" in AHA/ACC guidelines
Asymptomatic severe AS with LVEF < 50%	I	I	
Severe AS and another indication for surgery (CABG, thoracic aorta, another valve)	I	I	
Asymptomatic severe AS where the systolic blood pressure does not increase by > 20 mmHg or drops compared with baseline during the treadmill test	IIa	IIa	AHA/ACC guidelines acknowledge the presence of fatigability during stress test as an indication for AVR
Moderate AS and another indication for surgery (CABG, thoracic aorta, another valve)	IIa	IIa	
Low-flow/low-gradient/low-LVEF severe AS with proof of contractile reserve presence	IIa	IIa	
Symptomatic low-flow/low-gradient/preserved LVEF severe AS after careful confirmation of severity	IIa	IIa	
Truly asymptomatic severe AS (no symptoms during treadmill test, no risk criteria) with preserved LVEF if the surgical risk is deemed low and the following criteria are also satisfied: Very severe AS (maximal velocity ⩾ 5.5 m/s); Severe valvular calcification and increased maximal velocity by ⩾ 0.3 m/s per year	IIa	IIa for velocity ⩾ 5 m/s (see text) IIb for maximal velocity increase by ⩾ 0.3 m/s per year	AHA/ACC guideline: Velocity ⩾ 5 m/s or mean gradient ⩾ 60 mmHg AND severe calcifications; velocity 4 to 4.9 m/s or mean gradient 40 to 59 mmHg AND severe valvular calcification AND stress test demonstrating reduced tolerance or drop in blood pressure
Truly asymptomatic severe AS (no symptoms during treadmill test, no risk criteria) with preserved LVEF if the surgical risk is deemed low and 1 or more of the following criteria are also satisfied: Severely increased BNP/Nt-ProBNP levels at serial determinations and without an alternative explanation; increased transaortic pressure gradient at stress echocardiography by > 20 mmHg; excessive LV hypertrophy without an alternative explanation	IIb	-	This indication is not covered in the AHA/ACC guidelines
Low-flow/low-gradient/low-LVEF severe AS without contractile/flow reserve	IIb	-	This indication is not covered in the AHA/ACC guidelines

Class I: It is indicated, it is recommended; Class IIa: Should be considered, it is reasonable; Class IIb: May be considered; Class III: It is not indicated, it is contraindicated; ESC: European Society of Cardiology; EACTS: European Association for Cardio-Thoracic Surgery; AHA/ACC: American Heart Association/American College of Cardiology; AS: Aortic stenosis; LVEF: Left ventricular ejection fraction; CABG: Coronary artery bypass graft.

Table 3 Suggested high-risk criteria in asymptomatic severe aortic stenosis

Test	High risk criteria
Electrocardiogram	Presence of LV hypertrophy with secondary ST segment deviation ("LV strain")
Blood tests	Highly increased BNP/Nt-ProBNP levels
Stress test	Unmasked symptoms: Fatigability/dyspnea at < 75 W, syncope/near syncope; angina
	Lack of increase in systolic blood pressure by > 20 mmHg (or decrease) with exercise
	Inducible myocardial ischemia (ST segment depression ⩾ 2 mm)
	Severe ventricular arrhythmias (sustained VT, polymorphic VT, VF)
Conventional Doppler echocardiography	Very severe AS (AVA ⩽ 0.6 cm; maximal velocity ⩾ 5 m/s)
	LVEF < 50%
	Severe LV hypertrophy (⩾ 15 mm)?
	Reduced LV longitudinal strain
	Zva ⩾ 4.5 mmHg/mL per square meters
Dobutamine stress echocardiography (in low-flow, low-gradient, low LVEF)	Lack of contractile reserve
Exercise echocardiography (ergometric bicycle) - any severe AS	Increase in transvalvular pressure gradient by > 20 mmHg during exercise
	Inducible pulmonary hypertension during exercise (systolic pulmonary pressure ⩾ 60 mmHg)
Documentation of valvular calcification	Presence of severe valvular calcifications: Qualitatively (radiology, conventional echocardiography); quantitatively (computed tomography): Calcium score ⩾ 1651 Agatston units (lower in women *vs* men)

LVEF: Left ventricular ejection fraction; AS: Aortic stenosis; AVA: Aortic valve area.

of patients) *vs* watchful waiting (until development of symptoms for a class I indication of AVR) (79% of patients) found that patients who were treated medically had a 3.5-fold increase in mortality compared with those who underwent AVR, suggesting the benefit of early AVR in this population[10]. However, in these

observational studies, patients who were medically treated were older and sicker, and up to 50% of them developed a class Ⅰ indication for AVR during follow-up but were refused for various reasons - suggesting they were too sick to undergo either surgical or interventional AVR[40]. Thus, there is urgent need for a randomized trial to directly compare the two strategies[46].

Although the ESC/EACTS guidelines for valvular heart disease suggest the use of natriuretic peptide levels (Nt-ProBNP) for decisions regarding the need for AVR in patients with asymptomatic severe AS with preserved LVEF[33], a recent study found that the discriminating value of Nt-ProBNP in identifying patients who need AVR is suboptimal (area under the curve, AUC 0.73)[47]. Further research is needed to establish the use of natriuretic peptides in these patients.

Aortic valve replacement

In patients proposed for AVR, estimation of operative risk is essential. Currently, two risk scores are widely used. The EuroSCORE Ⅱ (http://www.euroscore.org/calc.html) includes 12 predictors identified from a retrospective population of 14799 patients who underwent different cardiovascular surgical interventions (mainly coronary artery bypass graft) in Europe, in 1995. The STS score (Society of Thoracic Surgeons, http://riskcalc.sts.org) includes 24 predictors identified from a population of 64292 patients who underwent surgical intervention only for AS in the United States between 2002 and 2006. The STS score is widely used in the United States for evaluating surgical risk for AS.

Both the EuroSCORE Ⅱ and the STS score are quite precise in identifying patients with low surgical risk, but they tend to overestimate the risk of patients with high surgical risk (EuroSCORE Ⅱ more than STS). For example, a patient with a logistic EuroCORE Ⅱ > 20 has an estimated surgical mortality of 39%, which much higher than the real-world mortality of 11%[43]. Importantly, both the EuroSCORE Ⅱ and the STS score can be used in practice in surgical institutions where the operative mortality lies within 1 standard deviation from the mean calculated mortality for the respective surgical procedure. None of the scores include frailty, which is a major limitation. The AHA/ACC guidelines recommend that the overall surgical risk should be divided into 4 groups (low, intermediate, high, and prohibitive) based on the overall assessment of surgical risk (STS score), patient frailty (Katz score)[48], presence of major co-morbidities (*e.g.,* severe LV systolic dysfunction, fixed pulmonary hypertension, severe chronic renal failure, respiratory failure, cerebral dysfunction, cancer, and liver cirrhosis), and anticipated difficulties for surgical intervention (*e.g.,* porcelain aorta, thoracic deformities, previous radiotherapy, internal mammary artery crossing the mid-line, and arterial bypass grafts that adhere to the posterior thoracic wall)[34]. The ESC/EACTS guidelines do not have similar recommendations[33].

Importantly, the overall decision regarding the relative risks *vs* benefits for AVR and the most appropriate type of AVR in individual patients should be made by a multidisciplinary heart team, consisting of a general cardiologist, an interventional cardiologist, a cardiac and vascular surgeon, imaging specialists (echocardiography, computed tomography), and an intensive care specialist with expertise in cardiac anesthesia.

Currently, the most effective treatment for AS is AVR. Simple valvuloplasty has no role in the treatment of severe AS except as a short-term palliation or as a bridge to more definite treatments (*e.g.,* patients with very severe AS who also have abdominal surgical emergencies). Surgical AVR remains the main treatment option, and either a mechanical valve (in younger patients or patients with other indications for long-term anticoagulant therapy) or a bioprosthesis (in older patients due to durability issues or patients with contraindications to life-long anticoagulant therapy) can be used[49]. For a detailed discussion regarding the choice of surgical prosthesis, the reader is referred to recent reviews[50,51]. The newer alternative of percutaneous transcatheter AVR (TAVR) is given a class I indication for patients who have an indication for AVR but are not candidates for surgery (*e.g.,* porcelain aorta, severe frailty) and a class Ⅱa indication for patients with high surgical risk scores[33,34,52]. The morbidity and mortality associated with TAVR have significantly decreased recently as the technique has matured and experience increased; thus, TAVR is currently being investigated for possible expansion to lower risk patients with an indication for a bioprosthesis because recent trials have suggested that TAVR compared favorably to SAVR in these groups[53]. For a detailed discussion regarding the selection of TAVR candidates, the reader is referred to excellent recent reviews[7,8].

AR

AR is defined as the presence of diastolic incompetence of the aortic valve with the subsequent regurgitation of blood back from the aorta into the LV. The generally accepted criteria for the definition of severe AR is a regurgitant volume > 60 mL/cardiac cycle or an effective regurgitant orifice area (EROA) > 0.3 cm^2. However, these parameters are very difficult to measure; therefore, numerous alternative parameters are used to define AR severity. One should be careful when using these parameters because the cut-off values are not inter-changeable, and their sensitivity and specificity are suboptimal. Similarly to any other valvular heart disease, the echocardiographic assessment has to use an integrative, complete and correct approach.

Etiology

The prevalence of AR is much lower compared with that for AS, and thus, far fewer studies are available for AR diagnosis and management. AR can be acute or chronic. Acute AR appears primarily as a result of aortic dissection or infective endocarditis. The heart cannot adapt by compensatory dilatation; as a result, the clinical picture is

dominated by signs of low cardiac output (due to reduced effective circulating volume) and pulmonary edema (due to high LV filling pressures secondary to large regurgitant volume). The classical signs of severe chronic AR (diastolic murmur, peripheral signs due to wide pulse pressure) are absent in severe acute AR because the diastolic pressure gradient between the aorta and the LV quickly equalizes. For the same reason, some echocardiographic signs of severe AR may be absent (such as the Doppler signal aliasing in the LVOT); in these situations, documenting diastolic reversal flow in the descending aorta prevents missing the diagnosis of severe AR. The presence of severe acute AR should be considered in the differential diagnosis of any patient presenting with acute severe heart failure or cardiogenic shock in the absence of obvious causes (such as myocardial infarction)[54].

Chronic AR is mostly due to BAV or aortic root dilatation. Degenerative aortic valve disease is also important, whereas other etiologies are rare. Patients remain asymptomatic for a long time, but irreversible LV dysfunction may appear before symptom onset.

Bicuspid aortic valve (BAV) is the most frequent congenital heart disease in humans (prevalence: 2% of the general population)[55]. Congenital abnormalities of the aortic valve, of which > 90% are represented by BAV, are at the base of > 50% of so-called "calcific" severe AS in adults with an indication for AVR[12]. BAV is probably a disease of the entire aortic root characterized by fragmentation of elastin fibers, alteration of the media and increased collagen deposition in the ascending aorta[56]. These alterations are frequently seen in patients with ascending aortic dilatation and increased risk for aortic dissection.

BAV is characterized by fusion of one of the aortic commissures, which results in two functional aortic cusps of different dimensions. The terminology used to classify BAV may be confusing. Depending on the commissure that is fused, the orientation of the abnormal orifice can be anterior-posterior (by fusion of the right with the left coronary cusps - encountered in 56% of cases) or right-left (by fusion of the non-coronary with the right coronary cusp - encountered in 44% of cases). Less than 2% of cases are characterized by fusion of the non-coronary with the left coronary cusp. Thus, the morphology of the BAV can be described by the orientation of the opening orifice (anterior-posterior, AP/right-left, RL)[57] or by the cusps that fuse (right - left coronary, RL/right coronary - non-coronary, RN)[58].

Recently, in a study that used 4-dimension flow magnetic resonance imaging, Mahadevia *et al*[58] suggested that the type of BAV determines the pattern of dilatation of the ascending aorta through the direction of the systolic transaortic jet and subsequent differential pressures on the various regions of the ascending aortic walls. Thus, BAV type AP/RL is associated with an excentric systolic jet and increased parietal pressures on the anterior and right ascending aortic wall and is frequently (87%) associated with dilatation of the root or the entire ascending thoracic aorta. Conversely, BAV type RL/RN determines increased parietal pressures on the right and posterior ascending aortic wall and is rarely associated with aortic dilatation. The role of hemodynamic *vs* genetic factors in stratifying the risk associated with BAV and aortic root disease is unclear[59].

Evaluation of AR

The evaluation of AR severity follows the same principles as that for the other valvular heart disease and is primarily based on echocardiography. For AR, the following goals are to be achieved by the echocardiographic evaluation: (1) identification of patients with severe AR; (2) identification of patients with an indication for AVR (surgical); and (3) identification of patients with dilated ascending aorta (with or without aortic bicuspid valves).

Identifying patients with severe AR: The most important echocardiographic criteria for identification of severe AR are listed in Table 4. For AR patients, the impact of different flow states (normal *vs* low) has not been investigated and is not applicable for routine clinical practice. Studies that validated the echocardiographic criteria for AR severity have used angiography as the comparator[60,61]. Only one study has prospectively evaluated the role of echocardiographic AR severity criteria in relation to the long-term prognosis of patients with severe, asym–ptomatic AR[62].

Identifying patients who are candidates for AVR: SAVR remains the gold-standard treatment for AR. In a few experienced centers, surgical aortic valve reconstruction may be an alternative for patients with favorable anatomy (*e.g.*, dilated aortic root, prolapsed aortic cusp)[63,64]. TAVR has a very limited role in treating AR and has only been used anecdotally in these patients[65].

Unlike AS, the current recommendations for AR evaluation and management are based on far fewer data. Additionally, most of the data on the prognosis of AR come from studies published more than 2 decades ago, which used outdated evaluation techniques.

Severe acute AR is a surgical emergency. The current indications for surgery for chronic severe AR are summarized in Table 5[33,34]. Regarding patients with dilatation of the ascending aorta, there are considerable differences between different guidelines, and a summary is provided in Table 6[33,34,66]. This summary does not cover patients with connective tissue disorders (*e.g.*, Marfan syndrome). In these patients, a recent AHA/ACC statement tried to clarify the differences between the 2 guidelines published in 2014 by the AHA/ACC (the "2014 AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease"), and in 2010 by other collaborating societies (the "2010 ACCF/AHA/AATS/ACR/ASA/SCA/SCAI/SIR/STS/SVM Guidelines for the Diagnosis and Management of Patients With Thoracic Aortic Disease")[67].

The indications for surgery in AR are based on only a few small-medium sized prospective studies all of which were observational and published before 2000. Bonow *et al*[68] evaluated the long-term prognosis (mean follow-up, 8

Table 4 Criteria for the diagnosis of severe aortic regurgitation

	Mild AR	Moderate AR	Severe AR
Ratio between the AR jet diameter and the LVOT diameter	< 25%	25%-64%	⩾ 65%
Vena contracta (mm)	< 3	3-5.9	⩾ 6
Regurgitant volume (mL/beat)	< 30	30-59	⩾ 60
Regurgitant fraction	< 30%	30%-49%	⩾ 50%
EROA (cm^2)	< 0.1	0.1-0.29	⩾ 0.3
Diastolic backflow in the descending thoracic and/or abdominal aorta	Minimal	Less than holodiastolic	Holodiastolic (especially for backflow documented in the abdominal aorta)
Angiographic	1+	2+	3-4+
LV dilatation	No	No	Yes (mandatory for chronic severe AR)

AR: Aortic regurgitation; LVOT: Left ventricular outflow tract; EROA: Effective regurgitant orifice area.

years) of 104 patients with severe AR and preserved LVEF recruited between 1973 and 1988. In these patients, the independent prognostic factors were age, the initial end-systolic LV diameter, and modification in time of the LVEF. In this study, patients with an end-systolic LV diameter > 50 mm and an end-diastolic LV diameter > 70 mm had a > 10%/year risk for death, development of symptoms or development of LV systolic dysfunction. The LV diameters were measured using simple, M-mode echocardiography, which has major limitations and is completely outdated today.

A second prospective observational study evaluated the prognosis of 104 patients with severe AR recruited beginning in 1979 and followed-up for an average of 7.3 years[69]. In this study, the most powerful prognostic factor was the rate of decline of LVEF (normalized to wall stress). Tornos *et al*[70] evaluated 101 patients with asymptomatic severe AR and normal LVEF, and followed-up these patients for up to 10 years. The rate of AVR was 12% at 5 years and 24% at 10 years. The independent prognostic factors required for AVR were an end-systolic LV diameter > 50 mm and an LVEF < 60% (determined by radionuclide cardiac scan); patients who needed AVR more frequently had progressive LV systolic dysfunction. Dujardin *et al*[71] evaluated 246 patients with severe AR included between 1985 and 1994, and followed-up these patients for an average of 10 years. The incidence of MACE during this period was very high (83%) as follows: 34% deceased; 47% developed heart failure and 62% received AVR[71]. In this study, the following were the independent predictors of survival: Age, New York Heart Association functional class, presence of co-morbidities, presence of atrial fibrillation, end-systolic LV indexed diameter > 25 mm/m^2, and the LVEF. In a retrospective cohort study of 166 patients with asymptomatic severe AR and severe systolic dysfunction (LVEF < 35%), Kamath *et al*[72] showed that those who underwent surgery had much better prognosis compared with that of patients treated medically (HR = 0.59, 95%CI: 0.42-0.98, *P* = 0.04).

Importantly, AR severity in these studies was determined by angiographic and not echocardiographic criteria. Only one study evaluated the utility of echocardiographic indices in AR severity by identifying patients who will need surgery. Detaint *et al*[62] evaluated 251 patients with asymptomatic severe AR with preserved LVEF (> 50%) recruited between 1991 and 2003 (a relatively contemporary population in comparison with previous studies). The independent prognostic factors required for AVR were severe AR as determined by quantitative echocardiographic indices and an end-systolic LV indexed volume > 45 mL/m^2 (as measured by the Simpson bi-plane method). Patients with severe AR and an end-systolic LV indexed volume > 45 mL/m^2 had an 87% risk of MACE at 10 years compared with only 40% of patients with severe AR and an end-systolic LV volume < 45 mL/m^2. This study also showed that quantitative echocardiographic indices of AR severity had superior prognostic value compared with that of qualitative echocardiographic indices[62].

These studies also suggested that patients with severe AR may have severe prognosis even before the appearance of symptoms or LV dysfunction. The mortality of patients with asymptomatic severe AR with preserved LVEF may reach 35% at 10 years[62,71]. However, there is insufficient prognostic data that can be used to identify patients at risk. The role of stress echocardiography in stratifying the risk of patients with severe AR has been much less studied compared with for patients with AS, but it may be used to evaluate the presence of contractile reserve[73].

The role of myocardial deformation imaging in the selection of patients who may need AVR is also under investigation. A study of 64 patients with moderate or severe AR (regardless of symptoms and LVEF) showed that patients for whom AVR was eventually performed (*n* = 29) had lower values of LV strain, LVEF and higher LV volumes compared with patients who did not need surgery. However, the reported cut-off values for identifying patients who will need surgery had sensitivities and specificities that make them poorly applicable in clinical practice (area under the curve < 0.77)[74].

B-type natriuretic peptide (BNP) levels may also play a role in predicting outcomes in patients with severe AR. Pizarro *et al*[75] studied 294 patients with severe asymptomatic AR and LVEF > 55%, and found that a BNP level > 130 pg/mL had 77% sensitivity and 94% specificity for predicting LV dysfunction symptoms

Table 5 Indications for aortic valve replacement in chronic aortic regurgitation[33,34]

Criteria	Class of indication		Differences between guidelines
	ESC/EACTS	AHA/ACC	
Symptomatic severe AR (any LVEF)	I	I	
Asymptomatic severe AR with depressed LV function (LVEF < 50%)	I	I	
Severe AR in patients with another indication for cardiac surgery (*e.g.*, CABG, thoracic aorta, another valve)	I	I	
Asymptomatic severe AR with normal LVEF (> 50%) but with severe LV dilatation	IIa	IIa	Definition of severe LV dilatation: ESC/EACTS guideline: End-diastolic LV diameter > 70 mm, or end-systolic LV diameter > 50 mm (or > 25 mm/m^2); AHA/ACC guidelines: End-systolic LV diameter > 50 mm
Moderate AR in patients with another indication for cardiac surgery (*e.g.*, coronary bypass, thoracic aorta, another valve)	-	IIa	This indication is not covered in the ESC/EACTS guidelines
Severe AR with normal LVEF (> 50%) but with progressive LV dilatation (end-diastolic LV diameter > 65 mm) if the surgical risk is low	-	IIb	This indication is not covered in the ESC/EACTS guidelines

Class I: It is indicated, it is recommended; Class IIa: Should be considered, it is reasonable; Class IIb: May be considered; it is contraindicated; ESC/EACTS: European Society of Cardiology/European Association for Cardio-Thoracic Surgery; AHA/ACC: American Heart Association/American College of Cardiology; AR: Aortic regurgitation; LVEF: Left ventricular ejection fraction; CABG: Coronary artery bypass graft.

Table 6 Indication for surgery in patients with bicuspid aortic valve and aortic root disease[33,34,66,67]

Class of indication	Guideline		Differences between guidelines
	ESC/ EACTS 2012	AHA/ACC 2016 Consensus on AHA/ACC 2014, and ACCF/AHA/AATS/ACR/ASA/SCA/SCAI/SIR/STS/SVM 2010 Guidelines	
I	-	Asymptomatic bicuspid aortic valve with dilatation of Valsalva sinuses or the ascending thoracic aortic diameter > 55 mm	No class I indications in the 2012 ESC/EACTS guidelines
IIa	Bicuspid aortic valve with an ascending thoracic aortic diameter > 50 mm if the patient also has at least one of the followings: Family history of aortic dissection; documented increase in the aortic diameter > 2 mm/yr (assessed using the same imaging method, at the same level, and with comparative images available); arterial hypertension; coarctation of the aorta	Bicuspid aortic valve AND dilatation of the Valsalva sinuses or of the ascending thoracic aorta (> 50 mm) AND at least one of the following Family history of aortic dissection Documented increase in aortic diameter > 5 mm/yr OR low surgical risk in an expert center	
	-	Replacement of the ascending aorta if the patient also has an indication for surgery for AS/AR, and the ascending aortic/Valsalva sinus diameter is > 45 mm	Not covered by the 2012 ESC guidelines

Class I: It is indicated, it is recommended; Class IIa: Should be considered, it is reasonable; Class IIb: May be considered; ESC: European Society of Cardiology; EACTS: European Association for Cardio-Thoracic Surgery; AHA/ACC: American Heart Association/American College of Cardiology; ACCF: American College of Cardiology Foundation; AHA: American Heart Association Task Force on Practice Guidelines; AATS: American Association for Thoracic Surgery; ACR: American College of Radiology; ASA: American Stroke Association; SCA: Society of Cardiovascular Anesthesiologists; SCAI: Society for Cardiovascular Angiography and Interventions; SIR: Society of Interventional Radiology; STS: Society of Thoracic Surgeons; SVM: Society for Vascular Medicine, North American Society for Cardiovascular Imaging; AR: Aortic regurgitation; AS: Aortic stenosis.

or death after 38 ± 9 mo of follow-up. BNP level had additive prognostic value to echocardiographic prognostic indices[75]. Further studies are needed to establish the role of BNP levels for indication of surgery in patients with AR.

A recent study of 159 patients with moderate or severe AR without a formal indication for surgery according to current guidelines (LVEF > 50%, end-diastolic LV diameter ⩽ 70 mm, end-systolic LV diameter ⩽ 70 mm or ⩽ 25 mm/m^2) showed that 31% of these patients needed AVR within 30 ± 21 mo of follow-up. The independent prognostic factors for early surgery were as follows: Global longitudinal LV strain, right ventricular longitudinal strain, and tricuspid annular peak systolic excursion (TAPSE); the combination of these 3 factors had a higher discriminating power compared with each one taken individually (χ^2 = 64.4, P < 0.001)[76]. However, the individual variability of these indices was high, and their utility for clinical practice must be validated in prospective clinical studies. This study confirmed that patients with significant AR without an initial formal indication but who eventually needed AVR, developed progressive LV dilatation and LVEF decline during follow-up, despite similar degrees of LV dilatation and LVEF at baseline, when compared to patients who did not need AVR during follow-up[76].

Cardiac magnetic resonance imaging (CMRI) is highly accurate in quantifying cardiac chamber volumes, aortic regurgitant volume and EROA. CMRI is recommended for patients with suboptimal echocardiography for whom the exact determination of AR severity is important and has therapeutic consequences (class Ⅱa indication, according to ACC/AHA guidelines)[34].

A recent study of 113 patients with moderate and severe AR (as determined by echocardiography) followed-up for up to 9 years suggested that a regurgitant fraction > 33% as determined by CMRI had a high positive predictive value (93%) in identifying patients who will need AVR. Additionally, an end-diastolic LV volume > 246 mL was also useful in identifying these patients (positive predictive value for AVR, 88%)[77]. However, contrary to previous data, in this study, the CMRI-measured LVEF was not useful in identifying patients with asymptomatic severe AR who needed AVR. More studies are needed to establish the exact role of all these parameters in selecting patients with asymptomatic severe AR who will need AVR.

CONCLUSION

AS and AR represent important health problems worldwide; when severe, they carry poor prognoses. For AS, both SAVR and TAVR may provide definite treatment in carefully selected patients. For AR, valve surgery (either SAVR or - in selected cases - aortic valve repair) remains the gold standard of care. To properly identify those patients who are candidates for surgery, the clinician has to carefully assess the severity of valve disease with an understanding of the potential pitfalls involved in these assessments. Thus, evaluation of aortic valve disease requires "a global view and a global understanding"[4].

REFERENCES

1 **Nkomo VT**, Gardin JM, Skelton TN, Gottdiener JS, Scott CG, Enriquez-Sarano M. Burden of valvular heart diseases: a population-based study. *Lancet* 2006; **368**: 1005-1011 [PMID: 16980116 DOI: 10.1016/S0140-6736(06)69208-8]

2 **Osnabrugge RL**, Mylotte D, Head SJ, Van Mieghem NM, Nkomo VT, LeReun CM, Bogers AJ, Piazza N, Kappetein AP. Aortic stenosis in the elderly: disease prevalence and number of candidates for transcatheter aortic valve replacement: a meta-analysis and modeling study. *J Am Coll Cardiol* 2013; **62**: 1002-1012 [PMID: 23727214 DOI: 10.1016/j.jacc.2013.05.015]

3 **Bonow RO**, Leon MB, Doshi D, Moat N. Management strategies and future challenges for aortic valve disease. *Lancet* 2016; **387**: 1312-1323 [PMID: 27025437 DOI: 10.1016/S0140-6736(16)00586-9]

4 **Pibarot P**, Dumesnil JG. Aortic stenosis: look globally, think globally. *JACC Cardiovasc Imaging* 2009; **2**: 400-403 [PMID: 19580720 DOI: 10.1016/j.jcmg.2009.01.004]

5 **Lindman BR**, Bonow RO, Otto CM. Current management of calcific aortic stenosis. *Circ Res* 2013; **113**: 223-237 [PMID: 23833296 DOI: 10.1161/CIRCRESAHA.111.300084]

6 **Magne J**, Lancellotti P, Piérard LA. Exercise testing in asymptomatic severe aortic stenosis. *JACC Cardiovasc Imaging* 2014; **7**: 188-199 [PMID: 24524744 DOI: 10.1016/j.jcmg.2013.08.011]

7 **Zamorano JL**, Gonçalves A, Lang R. Imaging to select and guide transcatheter aortic valve implantation. *Eur Heart J* 2014; **35**: 1578-1587 [PMID: 24459198 DOI: 10.1093/eurheartj/eht569]

8 **Bax JJ**, Delgado V, Bapat V, Baumgartner H, Collet JP, Erbel R, Hamm C, Kappetein AP, Leipsic J, Leon MB, MacCarthy P, Piazza N, Pibarot P, Roberts WC, Rodés-Cabau J, Serruys PW, Thomas M, Vahanian A, Webb J, Zamorano JL, Windecker S. Open issues in transcatheter aortic valve implantation. Part 1: patient selection and treatment strategy for transcatheter aortic valve implantation. *Eur Heart J* 2014; **35**: 2627-2638 [PMID: 25062952 DOI: 10.1093/eurheartj/ehu256]

9 **Clavel MA**, Magne J, Pibarot P. Low-gradient aortic stenosis. *Eur Heart J* 2016; **37**: 2645-2657 [PMID: 27190103 DOI: 10.1093/eurheartj/ehw096]

10 **Généreux P**, Stone GW, O'Gara PT, Marquis-Gravel G, Redfors B, Giustino G, Pibarot P, Bax JJ, Bonow RO, Leon MB. Natural History, Diagnostic Approaches, and Therapeutic Strategies for Patients With Asymptomatic Severe Aortic Stenosis. *J Am Coll Cardiol* 2016; **67**: 2263-2288 [PMID: 27049682 DOI: 10.1016/j.jacc.2016.02.057]

11 **Pierard LA**, Dulgheru R. Evaluation of aortic stenosis: an update--including low-flow States, myocardial mechanics, and stress testing. *Curr Cardiol Rep* 2015; **17**: 42 [PMID: 25902905 DOI: 10.1007/s11886-015-0601-0]

12 **Ross J**, Braunwald E. Aortic stenosis. *Circulation* 1968; **38**: 61-67 [PMID: 4894151 DOI: 10.1161/01.CIR.38.1S5.V-61]

13 **Roberts WC**, Ko JM. Frequency by decades of unicuspid, bicuspid, and tricuspid aortic valves in adults having isolated aortic valve replacement for aortic stenosis, with or without associated aortic regurgitation. *Circulation* 2005; **111**: 920-925 [PMID: 15710758 DOI: 10.1161/01.CIR.0000155623.48408.C5]

14 **Morrow AG**, Roberts WC, Ross J, Fisher RD, Behrendt DM, Mason DT, Braunwald E. Obstruction to left ventricular outflow. Current concepts of management and operative treatment. *Ann Intern Med* 1968; **69**: 1255-1286 [PMID: 5749681 DOI: 10.7326/0003-4819-69-6-1255]

15 **Coffey S**, Cox B, Williams MJ. The prevalence, incidence, progression, and risks of aortic valve sclerosis: a systematic review and meta-analysis. *J Am Coll Cardiol* 2014; **63**: 2852-2861 [PMID: 24814496 DOI: 10.1016/j.jacc.2014.04.018]

16 **Leon MB**, Smith CR, Mack M, Miller DC, Moses JW, Svensson LG, Tuzcu EM, Webb JG, Fontana GP, Makkar RR, Brown DL, Block PC, Guyton RA, Pichard AD, Bavaria JE, Herrmann HC, Douglas PS, Petersen JL, Akin JJ, Anderson WN, Wang D, Pocock S. Transcatheter aortic-valve implantation for aortic stenosis in patients who cannot undergo surgery. *N Engl J Med* 2010; **363**: 1597-1607 [PMID: 20961243 DOI: 10.1056/NEJMoa1008232]

17 **Omran H**, Schmidt H, Hackenbroch M, Illien S, Bernhardt P, von der Recke G, Fimmers R, Flacke S, Layer G, Pohl C, Lüderitz B, Schild H, Sommer T. Silent and apparent cerebral embolism after retrograde catheterisation of the aortic valve in valvular stenosis: a prospective, randomised study. *Lancet* 2003; **361**: 1241-1246 [PMID: 12699950 DOI: 10.1016/S0140-6736(03)12978-9]

18 **Baumgartner H**, Hung J, Bermejo J, Chambers JB, Evangelista A, Griffin BP, Iung B, Otto CM, Pellikka PA, Quiñones M. Echocardiographic assessment of valve stenosis: EAE/ASE recommendations for clinical practice. *Eur J Echocardiogr* 2009; **10**: 1-25 [PMID: 19065003 DOI: 10.1093/ejechocard/jen303]

19 **Leye M**, Brochet E, Lepage L, Cueff C, Boutron I, Detaint D, Hyafil F, Iung B, Vahanian A, Messika-Zeitoun D. Size-adjusted left ventricular outflow tract diameter reference values: a safeguard for the evaluation of the severity of aortic stenosis. *J Am Soc Echocardiogr* 2009; **22**: 445-451 [PMID: 19307102 DOI: 10.1016/j.echo.2009.02.007]

20 **Minners J**, Allgeier M, Gohlke-Baerwolf C, Kienzle RP, Neumann FJ, Jander N. Inconsistencies of echocardiographic criteria for the grading of aortic valve stenosis. *Eur Heart J* 2008; **29**: 1043-1048 [PMID: 18156619 DOI: 10.1093/eurheartj/ehm543]

21 **Grayburn PA**. Assessment of low-gradient aortic stenosis with dobutamine. *Circulation* 2006; **113**: 604-606 [PMID: 16461831

DOI: 10.1161/CIRCULATIONAHA.105.600684]
22 **Awtry E**, Davidoff R. Low-flow/low-gradient aortic stenosis. *Circulation* 2011; **124**: e739-e741 [PMID: 22144636 DOI: 10.1161/CIRCULATIONAHA.111.075853]
23 **Carabello BA**, Green LH, Grossman W, Cohn LH, Koster JK, Collins JJ. Hemodynamic determinants of prognosis of aortic valve replacement in critical aortic stenosis and advanced congestive heart failure. *Circulation* 1980; **62**: 42-48 [PMID: 7379284 DOI: 10.1161/01.CIR.62.1.42]
24 **Pibarot P**, Dumesnil JG. Low-flow, low-gradient aortic stenosis with normal and depressed left ventricular ejection fraction. *J Am Coll Cardiol* 2012; **60**: 1845-1853 [PMID: 23062546 DOI: 10.1016/j.jacc.2012.06.051]
25 **Tribouilloy C**, Lévy F, Rusinaru D, Guéret P, Petit-Eisenmann H, Baleynaud S, Jobic Y, Adams C, Lelong B, Pasquet A, Chauvel C, Metz D, Quéré JP, Monin JL. Outcome after aortic valve replacement for low-flow/low-gradient aortic stenosis without contractile reserve on dobutamine stress echocardiography. *J Am Coll Cardiol* 2009; **53**: 1865-1873 [PMID: 19442886 DOI: 10.1016/j.jacc.2009.02.026]
26 **Rosenhek R**, Binder T, Porenta G, Lang I, Christ G, Schemper M, Maurer G, Baumgartner H. Predictors of outcome in severe, asymptomatic aortic stenosis. *N Engl J Med* 2000; **343**: 611-617 [PMID: 10965007 DOI: 10.1056/NEJM200008313430903]
27 **Cueff C**, Serfaty JM, Cimadevilla C, Laissy JP, Himbert D, Tubach F, Duval X, Iung B, Enriquez-Sarano M, Vahanian A, Messika-Zeitoun D. Measurement of aortic valve calcification using multislice computed tomography: correlation with haemodynamic severity of aortic stenosis and clinical implication for patients with low ejection fraction. *Heart* 2011; **97**: 721-726 [PMID: 20720250 DOI: 10.1136/hrt.2010.198853]
28 **Clavel MA**, Messika-Zeitoun D, Pibarot P, Aggarwal SR, Malouf J, Araoz PA, Michelena HI, Cueff C, Larose E, Capoulade R, Vahanian A, Enriquez-Sarano M. The complex nature of discordant severe calcified aortic valve disease grading: new insights from combined Doppler echocardiographic and computed tomographic study. *J Am Coll Cardiol* 2013; **62**: 2329-2338 [PMID: 24076528 DOI: 10.1016/j.jacc.2013.08.1621]
29 **Hachicha Z**, Dumesnil JG, Bogaty P, Pibarot P. Paradoxical low-flow, low-gradient severe aortic stenosis despite preserved ejection fraction is associated with higher afterload and reduced survival. *Circulation* 2007; **115**: 2856-2864 [PMID: 17533183 DOI: 10.1161/CIRCULATIONAHA.106.668681]
30 **Dulgheru R**, Magne J, Capoulade R, Davin L, Vinereanu D, Pierard LA, Pibarot P, Lancellotti P. Impact of global hemodynamic load on exercise capacity in aortic stenosis. *Int J Cardiol* 2013; **168**: 2272-2277 [PMID: 23453444 DOI: 10.1016/j.ijcard.2013.01.205]
31 **Lancellotti P**, Magne J, Donal E, Davin L, O'Connor K, Rosca M, Szymanski C, Cosyns B, Piérard LA. Clinical outcome in asymptomatic severe aortic stenosis: insights from the new proposed aortic stenosis grading classification. *J Am Coll Cardiol* 2012; **59**: 235-243 [PMID: 22240128 DOI: 10.1016/j.jacc.2011.08.072]
32 **Jander N**, Minners J, Holme I, Gerdts E, Boman K, Brudi P, Chambers JB, Egstrup K, Kesäniemi YA, Malbecq W, Nienaber CA, Ray S, Rossebø A, Pedersen TR, Skjærpe T, Willenheimer R, Wachtell K, Neumann FJ, Gohlke-Bärwolf C. Outcome of patients with low-gradient "severe" aortic stenosis and preserved ejection fraction. *Circulation* 2011; **123**: 887-895 [PMID: 21321152 DOI: 10.1161/CIRCULATIONAHA.110.983510]
33 **Vahanian A**, Alfieri O, Andreotti F, Antunes MJ, Barón-Esquivias G, Baumgartner H, Borger MA, Carrel TP, De Bonis M, Evangelista A, Falk V, Iung B, Lancellotti P, Pierard L, Price S, Schäfers HJ, Schuler G, Stepinska J, Swedberg K, Takkenberg J, Von Oppell UO, Windecker S, Zamorano JL, Zembala M. Guidelines on the management of valvular heart disease (version 2012). *Eur Heart J* 2012; **33**: 2451-2496 [PMID: 22922415 DOI: 10.1093/eurheartj/ehs109]
34 **Nishimura RA**, Otto CM, Bonow RO, Carabello BA, Erwin JP, Guyton RA, O'Gara PT, Ruiz CE, Skubas NJ, Sorajja P, Sundt TM, Thomas JD. 2014 AHA/ACC guideline for the management of patients with valvular heart disease: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 2014; **63**: 2438-2488 [PMID: 24603192 DOI: 10.1016/j.jacc.2014.02.537]
35 **Lancellotti P**, Lebois F, Simon M, Tombeux C, Chauvel C, Pierard LA. Prognostic importance of quantitative exercise Doppler echocardiography in asymptomatic valvular aortic stenosis. *Circulation* 2005; **112**: I377-I382 [PMID: 16159850 DOI: 10.1161/CIRCULATIONAHA.104.523274]
36 **Schwarz F**, Baumann P, Manthey J, Hoffmann M, Schuler G, Mehmel HC, Schmitz W, Kübler W. The effect of aortic valve replacement on survival. *Circulation* 1982; **66**: 1105-1110 [PMID: 7127696 DOI: 10.1161/01.CIR.66.5.1105]
37 **Amato MC**, Moffa PJ, Werner KE, Ramires JA. Treatment decision in asymptomatic aortic valve stenosis: role of exercise testing. *Heart* 2001; **86**: 381-386 [PMID: 11559673 DOI: 10.1136/heart.86.4.381]
38 **Carabello BA**. Should severe aortic stenosis be operated on before symptom onset? Aortic valve replacement should be operated on before symptom onset. *Circulation* 2012; **126**: 112-117 [PMID: 22753532 DOI: 10.1161/CIRCULATIONAHA.111.079350]
39 **Shah PK**. Should severe aortic stenosis be operated on before symptom onset? Severe aortic stenosis should not be operated on before symptom onset. *Circulation* 2012; **126**: 118-125 [PMID: 22753533 DOI: 10.1161/CIRCULATIONAHA.111.079368]
40 **Taniguchi T**, Morimoto T, Shiomi H, Ando K, Kanamori N, Murata K, Kitai T, Kawase Y, Izumi C, Miyake M, Mitsuoka H, Kato M, Hirano Y, Matsuda S, Nagao K, Inada T, Murakami T, Takeuchi Y, Yamane K, Toyofuku M, Ishii M, Minamino-Muta E, Kato T, Inoko M, Ikeda T, Komasa A, Ishii K, Hotta K, Higashitani N, Kato Y, Inuzuka Y, Maeda C, Jinnai T, Morikami Y, Sakata R, Kimura T. Initial Surgical Versus Conservative Strategies in Patients With Asymptomatic Severe Aortic Stenosis. *J Am Coll Cardiol* 2015; **66**: 2827-2838 [PMID: 26477634 DOI: 10.1016/j.jacc.2015.10.001]
41 **Rosenhek R**, Zilberszac R, Schemper M, Czerny M, Mundigler G, Graf S, Bergler-Klein J, Grimm M, Gabriel H, Maurer G. Natural history of very severe aortic stenosis. *Circulation* 2010; **121**: 151-156 [PMID: 20026771 DOI: 10.1161/CIRCULATIONAHA.109.894170]
42 **Kang DH**, Park SJ, Rim JH, Yun SC, Kim DH, Song JM, Choo SJ, Park SW, Song JK, Lee JW, Park PW. Early surgery versus conventional treatment in asymptomatic very severe aortic stenosis. *Circulation* 2010; **121**: 1502-1509 [PMID: 20308614 DOI: 10.1161/CIRCULATIONAHA.109.909903]
43 **Kalavrouziotis D**, Li D, Buth KJ, Légaré JF. The European System for Cardiac Operative Risk Evaluation (EuroSCORE) is not appropriate for withholding surgery in high-risk patients with aortic stenosis: a retrospective cohort study. *J Cardiothorac Surg* 2009; **4**: 32 [PMID: 19602289 DOI: 10.1186/1749-8090-4-32]
44 **Maréchaux S**, Hachicha Z, Bellouin A, Dumesnil JG, Meimoun P, Pasquet A, Bergeron S, Arsenault M, Le Tourneau T, Ennezat PV, Pibarot P. Usefulness of exercise-stress echocardiography for risk stratification of true asymptomatic patients with aortic valve stenosis. *Eur Heart J* 2010; **31**: 1390-1397 [PMID: 20308041 DOI: 10.1093/eurheartj/ehq076]
45 **Lancellotti P**, Magne J, Donal E, O'Connor K, Dulgheru R, Rosca M, Pierard LA. Determinants and prognostic significance of exercise pulmonary hypertension in asymptomatic severe aortic stenosis. *Circulation* 2012; **126**: 851-859 [PMID: 22832784 DOI: 10.1161/CIRCULATIONAHA.111.088427]
46 **Bonow RO**. Exercise hemodynamics and risk assessment in asymptomatic aortic stenosis. *Circulation* 2012; **126**: 803-805 [PMID: 22832785 DOI: 10.1161/CIRCULATIONAHA.112.130591]
47 **Cimadevilla C**, Cueff C, Hekimian G, Dehoux M, Lepage L, Iung B, Duval X, Huart V, Tubach F, Vahanian A, Messika-Zeitoun D. Prognostic value of B-type natriuretic peptide in elderly patients with aortic valve stenosis: the COFRASA-GENERAC study. *Heart* 2013; **99**: 461-467 [PMID: 23349346 DOI: 10.1136/heartjnl-2012-303284]
48 **Katz S**, Downs TD, Cash HR, Grotz RC. Progress in development

of the index of ADL. *Gerontologist* 1970; **10**: 20-30 [PMID: 5420677]
49 **van Geldorp MW**, Eric Jamieson WR, Kappetein AP, Ye J, Fradet GJ, Eijkemans MJ, Grunkemeier GL, Bogers AJ, Takkenberg JJ. Patient outcome after aortic valve replacement with a mechanical or biological prosthesis: weighing lifetime anticoagulant-related event risk against reoperation risk. *J Thorac Cardiovasc Surg* 2009; **137**: 881-886, 886e1-5 [PMID: 19327512 DOI: 10.1016/j.jtcversus2008.09.028]
50 **Rahimtoola SH**. Choice of prosthetic heart valve in adults an update. *J Am Coll Cardiol* 2010; **55**: 2413-2426 [PMID: 20510209 DOI: 10.1016/j.jacc.2009.10.085]
51 **Pibarot P**, Dumesnil JG. Prosthetic heart valves: selection of the optimal prosthesis and long-term management. *Circulation* 2009; **119**: 1034-1048 [PMID: 19237674 DOI: 10.1161/CIRCULATIONAHA.108.778886]
52 **Holmes DR**, Mack MJ, Kaul S, Agnihotri A, Alexander KP, Bailey SR, Calhoon JH, Carabello BA, Desai MY, Edwards FH, Francis GS, Gardner TJ, Kappetein AP, Linderbaum JA, Mukherjee C, Mukherjee D, Otto CM, Ruiz CE, Sacco RL, Smith D, Thomas JD. 2012 ACCF/AATS/SCAI/STS expert consensus document on transcatheter aortic valve replacement. *J Am Coll Cardiol* 2012; **59**: 1200-1254 [PMID: 22300974 DOI: 10.1016/j.jacc.2012.01.001]
53 **Siontis GC**, Praz F, Pilgrim T, Mavridis D, Verma S, Salanti G, Søndergaard L, Jüni P, Windecker S. Transcatheter aortic valve implantation vs. surgical aortic valve replacement for treatment of severe aortic stenosis: a meta-analysis of randomized trials. *Eur Heart J* 2016; **37**: 3503-3512 [PMID: 27389906 DOI: 10.1093/eurheartj/ehw225]
54 **Hamirani YS**, Dietl CA, Voyles W, Peralta M, Begay D, Raizada V. Acute aortic regurgitation. *Circulation* 2012; **126**: 1121-1126 [PMID: 22927474 DOI: 10.1161/CIRCULATIONAHA.112. 113993]
55 **Siu SC**, Silversides CK. Bicuspid aortic valve disease. *J Am Coll Cardiol* 2010; **55**: 2789-2800 [PMID: 20579534 DOI: 10.1016/j.jacc.2009.12.068]
56 **Braverman AC**, Güven H, Beardslee MA, Makan M, Kates AM, Moon MR. The bicuspid aortic valve. *Curr Probl Cardiol* 2005; **30**: 470-522 [PMID: 16129122 DOI: 10.1016/j.cpcardiol.2005.06.002]
57 **Kang JW**, Song HG, Yang DH, Baek S, Kim DH, Song JM, Kang DH, Lim TH, Song JK. Association between bicuspid aortic valve phenotype and patterns of valvular dysfunction and bicuspid aortopathy: comprehensive evaluation using MDCT and echocardiography. *JACC Cardiovasc Imaging* 2013; **6**: 150-161 [PMID: 23489528 DOI: 10.1016/j.jcmg.2012.11.007]
58 **Mahadevia R**, Barker AJ, Schnell S, Entezari P, Kansal P, Fedak PW, Malaisrie SC, McCarthy P, Collins J, Carr J, Markl M. Bicuspid aortic cusp fusion morphology alters aortic three-dimensional outflow patterns, wall shear stress, and expression of aortopathy. *Circulation* 2014; **129**: 673-682 [PMID: 24345403 DOI: 10.1161/CIRCULATIONAHA.113.003026]
59 **Uretsky S**, Gillam LD. Nature versus nurture in bicuspid aortic valve aortopathy: more evidence that altered hemodynamics may play a role. *Circulation* 2014; **129**: 622-624 [PMID: 24345404 DOI: 10.1161/CIRCULATIONAHA.113.007282]
60 **Borrás X**, Carreras F, Augé JM, Pons-Lladó G. Prospective validation of detection and quantitative assessment of chronic aortic regurgitation by a combined echocardiographic and Doppler method. *J Am Soc Echocardiogr* 1988; **1**: 422-429 [PMID: 3078559 DOI: 10.1016/S0894-7317(88)80024-5]
61 **Chen M**, Luo H, Miyamoto T, Atar S, Kobal S, Rahban M, Brasch AV, Makkar R, Neuman Y, Naqvi TZ, Tolstrup K, Siegel RJ. Correlation of echo-Doppler aortic valve regurgitation index with angiographic aortic regurgitation severity. *Am J Cardiol* 2003; **92**: 634-635 [PMID: 12943896 DOI: 10.1016/S0002-9149(03)00743-4]
62 **Detaint D**, Messika-Zeitoun D, Maalouf J, Tribouilloy C, Mahoney DW, Tajik AJ, Enriquez-Sarano M. Quantitative echocardiographic determinants of clinical outcome in asymptomatic patients with aortic regurgitation: a prospective study. *JACC Cardiovasc Imaging* 2008; **1**: 1-11 [PMID: 19356398 DOI: 10.1016/j.jcmg.2007.10.008]
63 **David TE**, Feindel CM, David CM, Manlhiot C. A quarter of a century of experience with aortic valve-sparing operations. *J Thorac Cardiovasc Surg* 2014; **148**: 872-879; discussion 879-880 [PMID: 24930611 DOI: 10.1016/j.jtcversus2014.04.048]
64 **Bisleri G**. Aortic valve repair. *Curr Opin Cardiol* 2016; **31**: 581-584 [PMID: 27583375 DOI: 10.1097/HCO.0000000000000334]
65 **Cerillo AG**, Griese D, Berti S. Successful percutaneous implantation of symetis ACURATE neo transcatheter aortic bioprosthesis for the treatment of pure aortic regurgitation. *Catheter Cardiovasc Interv* 2016; **88**: 319-323 [PMID: 26762474 DOI: 10.1002/ccd.26402]
66 **Hiratzka LF**, Bakris GL, Beckman JA, Bersin RM, Carr VF, Casey DE, Eagle KA, Hermann LK, Isselbacher EM, Kazerooni EA, Kouchoukos NT, Lytle BW, Milewicz DM, Reich DL, Sen S, Shinn JA, Svensson LG, Williams DM. 2010 ACCF/AHA/AATS/ACR/ASA/SCA/SCAI/SIR/STS/SVM guidelines for the diagnosis and management of patients with Thoracic Aortic Disease: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, American Association for Thoracic Surgery, American College of Radiology, American Stroke Association, Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, Society of Interventional Radiology, Society of Thoracic Surgeons, and Society for Vascular Medicine. *Circulation* 2010; **121**: e266-e369 [PMID: 20233780 DOI: 10.1161/CIR. 0b013e3181d4739e]
67 **Hiratzka LF**, Creager MA, Isselbacher EM, Svensson LG, Nishimura RA, Bonow RO, Guyton RA, Sundt TM. Surgery for Aortic Dilatation in Patients With Bicuspid Aortic Valves: A Statement of Clarification From the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol* 2016; **67**: 724-731 [PMID: 26658475 DOI: 10.1016/j.jacc.2015.11.006]
68 **Bonow RO**, Lakatos E, Maron BJ, Epstein SE. Serial long-term assessment of the natural history of asymptomatic patients with chronic aortic regurgitation and normal left ventricular systolic function. *Circulation* 1991; **84**: 1625-1635 [PMID: 1914102 DOI: 10.1161/01.CIR.84.4.1625]
69 **Borer JS**, Hochreiter C, Herrold EM, Supino P, Aschermann M, Wencker D, Devereux RB, Roman MJ, Szulc M, Kligfield P, Isom OW. Prediction of indications for valve replacement among asymptomatic or minimally symptomatic patients with chronic aortic regurgitation and normal left ventricular performance. *Circulation* 1998; **97**: 525-534 [PMID: 9494022 DOI: 10.1161/01.CIR.97.6.525]
70 **Tornos MP**, Olona M, Permanyer-Miralda G, Herrejon MP, Camprecios M, Evangelista A, Garcia del Castillo H, Candell J, Soler-Soler J. Clinical outcome of severe asymptomatic chronic aortic regurgitation: a long-term prospective follow-up study. *Am Heart J* 1995; **130**: 333-339 [PMID: 7631617 DOI: 10.1016/0002-8703(95)90450-6]
71 **Dujardin KS**, Enriquez-Sarano M, Schaff HV, Bailey KR, Seward JB, Tajik AJ. Mortality and morbidity of aortic regurgitation in clinical practice. A long-term follow-up study. *Circulation* 1999; **99**: 1851-1857 [PMID: 10199882 DOI: 10.1161/01.CIR.99.14.1851]
72 **Kamath AR**, Varadarajan P, Turk R, Sampat U, Patel R, Khandhar S, Pai RG. Survival in patients with severe aortic regurgitation and severe left ventricular dysfunction is improved by aortic valve replacement: results from a cohort of 166 patients with an ejection fraction & lt; or =35%. *Circulation* 2009; **120**: S134-S138 [PMID: 19752358 DOI: 10.1161/CIRCULATIONAHA.108.839787]
73 **Lancellotti P**, Magne J. Stress echocardiography in regurgitant valve disease. *Circ Cardiovasc Imaging* 2013; **6**: 840-849 [PMID: 24046381 DOI: 10.1161/CIRCIMAGING.113.000474]
74 **Olsen NT**, Sogaard P, Larsson HB, Goetze JP, Jons C, Mogelvang R, Nielsen OW, Fritz-Hansen T. Speckle-tracking echocardiography for predicting outcome in chronic aortic regurgitation during conservative management and after surgery. *JACC Cardiovasc Imaging* 2011; **4**: 223-230 [PMID: 21414568 DOI: 10.1016/j.jcmg.2010.11.016]
75 **Pizarro R**, Bazzino OO, Oberti PF, Falconi ML, Arias AM, Krauss JG, Cagide AM. Prospective validation of the prognostic usefulness

of B-type natriuretic peptide in asymptomatic patients with chronic severe aortic regurgitation. *J Am Coll Cardiol* 2011; **58**: 1705-1714 [PMID: 21982316 DOI: 10.1016/j.jacc.2011.07.016]

76 **Kusunose K**, Agarwal S, Marwick TH, Griffin BP, Popović ZB. Decision making in asymptomatic aortic regurgitation in the era of guidelines: incremental values of resting and exercise cardiac dysfunction. *Circ Cardiovasc Imaging* 2014; **7**: 352-362 [PMID: 24503783 DOI: 10.1161/CIRCIMAGING.113.001177]

77 **Myerson SG**, d'Arcy J, Mohiaddin R, Greenwood JP, Karamitsos TD, Francis JM, Banning AP, Christiansen JP, Neubauer S. Aortic regurgitation quantification using cardiovascular magnetic resonance: association with clinical outcome. *Circulation* 2012; **126**: 1452-1460 [PMID: 22879371 DOI: 10.1161/CIRCULATIONAHA.111.083600]

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REVIEW

Atrial tachyarrhythmia in adult congenital heart disease

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Abstract

The adult congenital heart disease (ACHD) population continues to grow and most cardiologists, emergency room physicians and family doctors will intermittently come into contact with these patients. Oftentimes this may be in the setting of a presentation with atrial tachyarrhythmia; one of the commonest late complications of ACHD and problem with potentially serious implications. Providing appropriate initial care and ongoing management of atrial tachyarrhythmia in ACHD patients requires a degree of specialist knowledge and an awareness of certain key issues. In ACHD, atrial tachyarrhythmia is usually related to the abnormal anatomy of the underlying heart defect and often occurs as a result of surgical scar or a consequence of residual hemodynamic or electrical disturbances. Arrhythmias significantly increase mortality and morbidity in ACHD and are the most frequent reason for ACHD hospitalization. Intra-atrial reentrant tachycardia and atrial fibrillation are the most prevalent type of arrhythmia in this patient group. In hemodynamically unstable patients, urgent cardioversion is required. Acute management of the stable patient includes anticoagulation, rate control, and electrical or pharmacological cardioversion. In ACHD, rhythm control is the preferred management strategy and can often be achieved. However, in the long-term, medication side-effects can prove problematic. Electrophysiology studies and catheter ablation are important treatments modalities and in certain cases, surgical or percutaneous treatment of the underlying cardiac defect has a role. ACHD patients, especially those with complex CHD, are at increased risk of thromboembolic events and anticoagulation is usually required. Female ACHD patients of child bearing age may wish to pursue pregnancies. The risk of atrial arrhythmias is increased during pregnancy and management of atrial tachyarrhythmia during pregnancy needs specific consideration.

Key words: Congenital heart disease; Arrhythmia; Adult; Ablation

Core tip: This review highlights the importance of atrial tachyarrhythmia in adult congenital heart disease (ACHD) patients. It discusses causative mechanisms of arrhythmia, treatment of arrhythmia in the acute setting and on a long-term basis, including: Medications, catheter ablation, and anticoagulation. We include specific comments on the treatment of arrhythmias in ACHD patients who are pregnant.

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INTRODUCTION

With an estimated incidence of 9 per 1000 live births, congenital heart disease (CHD) is the most frequent major birth defect[1]. Improved diagnosis and management have led to recent rapid growth in numbers of adult survivors, particularly in the subset of patients with complex heart lesions[2]. Individuals with adult congenital heart disease (ACHD) often have residual cardiac lesions that promote abnormal hemodynamics and electrical disturbance. Electrical abnormalities are exacerbated by surgical scar, prosthetic patches and diffuse myocardial fibrosis and increasingly as these patients age, by the additional burden of traditional cardiovascular risk factors[3,4]. It is perhaps not surprising that arrhythmia is one of the most important problems faced by ACHD patients and has become the leading cause of ACHD hospitalization[5]. In this population, atrial arrhythmia is far more common than ventricular and is associated with substantial morbidity and mortality.

Atrial arrhythmia in ACHD occurs with a prevalence 3 times greater than that seen in the general population[6]. The risk increases with age[7] and varies according to underlying congenital cardiac anomaly (Table 1[8-16]). The prevalence is greatest in those with complex defects where it is estimated at > 50% by the age of 65 years[6]. Atrial arrhythmias in ACHD can herald adverse or declining intra-cardiac hemodynamics and their occurrence is a risk factor for other significant clinical events[6,17]. Prompt diagnosis and appropriate management may help avoid important complications, the risks of which are higher in specific ACHD subgroups. In patients with simple lesions[18], atrial arrhythmia can be managed in a similar manner to arrhythmia in patients with structurally normal hearts. However, for patients with lesions of moderate or high complexity[18], involvement of an ACHD specialist and/or electrophysiologist with subspecialty expertise is recommended[17,18]. Most ACHD patients with arrhythmia will initially present locally, to general cardiologists, family physicians and emergency doctors and given population demographics, it is increasingly likely these care providers will encounter such patients. This review is intended to raise awareness of atrial arrhythmia as a complication of ACHD and of the necessary caveats to deliver care safely. It focuses on issues seen frequently in our day-to-day clinical practice and of importance to primary care providers. For a more comprehensive analysis and further reading we suggest the 2014 PACES/HRS Expert Consensus Statement on the Recognition and Management of Arrhythmias in Adult Congenital Heart disease[17].

CLINICAL IMPLICATIONS OF ATRIAL TACHYARRHYTHMIA IN ACHD

Given the retrospective and observational nature of most studies, teasing out "cause and effect" for the clinical implications of atrial arrhythmia in ACHD is challenging. However, it is certain that ACHD patients who develop atrial arrhythmia are at increased risk of other adverse clinical events. In their large (n > 38000) analysis of Quebec's ACHD patients, Bouchardy *et al*[6] found patients with a history of atrial arrhythmia experienced a 50% increase in mortality, a 100% increase in stroke or heart failure and a 300% increase in the risk of cardiac interventions, as compared those with no history of atrial arrhythmia. These findings from a large and heterogeneous ACHD population are borne out by those from smaller studies of diagnosis-specific cohorts. Two large multi-center studies identified atrial arrhythmia as a powerful predictor of mortality and/or ventricular tachycardia in patients with tetralogy of Fallot (TOF)[19,20]. In a single-centre study of 321 Fontan patients "clinically relevant arrhythmia" was the strongest predictor of outcome, increasing the risk of death or transplant 6-fold[21]. In our own cohort of Mustard patients, patients who had experienced an atrial arrhythmia had worse subaortic right ventricular (RV) function and more tricuspid regurgitation than those who had not[22].

TYPES OF ATRIAL TACHYARRHYTHMIA IN ACHD AND THEIR MECHANISMS

Any type of atrial tachyarrhythmia can occur in ACHD patients. However, by nature of their underlying heart defects and previous surgeries, some subtypes are more frequently encountered than others. Intra-atrial reentry tachycardia (IART) is the sub-type encountered most frequently at the current time[23]. This may change as the ACHD patient population ages and increases in the incidence of atrial fibrillation have been already noted[24-26]. Atrioventricular nodal reentry, typical atrial flutter and focal atrial tachycardias[17,27] are also seen and atrial arrhythmia mediated by accessory pathway(s) is a particular idiosyncrasy of patients with Ebstein anomaly of the tricuspid valve[27].

Table 1 Summary of studies describing the prevalence of arrhythmia in adult congenital heart disease

Ref.	Diagnosis	No. of patients in study	Duration of follow-up (yr)	Prevalence of atrial arrhythmia (%)
[8]	Fontan	94	11	41
[9]	Fontan	334	9	16
[10]	TGA: Mustard or Senning	86 Mustard	8	48
[11]	TGA: Mustard or Senning	60 Mustard 62 Senning	Mustard 16 Senning 11	Mustard 28.8 Sennign 11.9
[12]	TGA: Arterial switch	374	19	2
[13]	Ebstein anomaly	285	20	36
[14]	Tetralogy of Fallot	242	16	12
[15]	Repaired AVSD	300	11	14
[16]	Repaired ASD	213	4	14

TGA: Transposition of great arteries; AVSD: Atrio-ventricular septal defect; ASD: Atrial septal defect.

Intra-atrial reentry tachycardia and atrial flutter

Macro reentry circuits within the atria of people without CHD usually produce typical isthmus-dependent atrial flutter, which can also occur in patients with ACHD. However, the scarred, dilated and thickened atria of ACHD patients produce additional barriers to conduction and promote macro reentry pathways independent of the tricuspid valve-inferior vena cava isthmus with low voltage electrocardiogram (ECG) signals and without the typical saw-toothed p-wave appearance of flutter waves. We refer to this type of arrhythmia as IART. With atrial rates ranging from 150-200 per minute, IART is usually slower than typical flutter and has a stable cycle length and p wave morphology[27]. Although both IART and atrial flutter can occur in ACHD and may coexist in individual patients[28,29] in our experience IART is the more frequently encountered and so we use this term preferentially when discussing atrial macro reentry in ACHD patients.

IART is the most common arrhythmia in adults with an atrial redirection procedure (Mustard or Senning operation) for transposition of the great arteries (TGA) and also in those with a Fontan circulation[23]. IART is also prevalent in patients with repaired TOF and reported to be an important cause of morbidity[25,30]. While the occurrence of atrial arrhythmia in ACHD increases with time[6] and subaortic ventricular dysfunction is a generalized risk factor[11], more specific risk factors for IART have been identified in some subgroups. In patients with TGA and an atrial redirection procedure identified IART risk factors include: A Mustard procedure[31], the occurrence of perioperative bradyarrhythmia, need for reoperation and loss of sinus rhythm during follow-up[26]. Older age at operation, history of an atrial septectomy, and an atriopulmonary connection have been identified as risk factors for IART in the Fontan population[10,32].

The propagation route for an IART circuit differs depending on the anatomic defect and type of surgical repair[33]. The pathway is often restricted to right atrial tissue, modified by regions of fibrosis from previous suture lines, patches, and baffles which act in combination with natural conduction barriers like crista terminalis, valve orifices, and the superior and inferior caval orifices to channel the wave front along a macroreentrant loop[34,35]. If a tricuspid valve is present, the isthmus between the valve ring and the inferior vena cava is often involved in such circuits, but in the absence of tricuspid valve or if there is a deformed valve, the circuit path is less predictable and can usually only be identified by electrophysiological mapping[36]. Multiple IART pathways can be present in the same patient[37].

In the setting of a healthy AV node A:V conduction may occur 1:1. If so, the resultant fast ventricular rhythm can produce hypotension, syncope, or possibly cardiac arrest in ACHD patients who often have abnormal baseline hemodynamics or impaired ventricular function[36]. Rapid conduction is of particular concern in patients with atrial baffles (Mustard and Senning) who are unable to augment sub-aortic RV filling rates and stroke volume during tachycardia[38,39] and also in patients with a single ventricle physiology. The clinical picture of instability combined with tachycardia sometimes give rise to erroneous interpretation of the rhythm as being of ventricular origin. We see this mistake made most frequently in patients with TOF, since they usually have a baseline broad RBBB which persists during atrial tachycardia.

Conversely, in patients who remain clinically stable, IART with 2:1 or 3:1 conduction can easily be misinterpreted as sinus rhythm on the surface ECG of a patient with ACHD. This is not infrequently encountered in patients with a Fontan circulation or atrial redirection procedure for TGA. These patients often experience IART with a ventricular rate only slightly above their baseline rate and may have fractionated, difficult to see p-waves. Reviewing previous ECGs is often key to establishing the correct diagnosis. Hidden p-waves may be uncovered by vagal maneuvers or intravenous adenosine infusion, which can be useful when used with caution if still uncertain[36]. A high degree of clinical suspicion is required when interpreting the ECG in an adult CHD patient who presents with palpitations, especially if that patient has a Fontan or Mustard/Senning circulation (Figures 1 and 2).

Atrial fibrillation

Atrial fibrillation is the result of multiple micro reentry circuits and in ACHD is less prevalent than IART. A single-

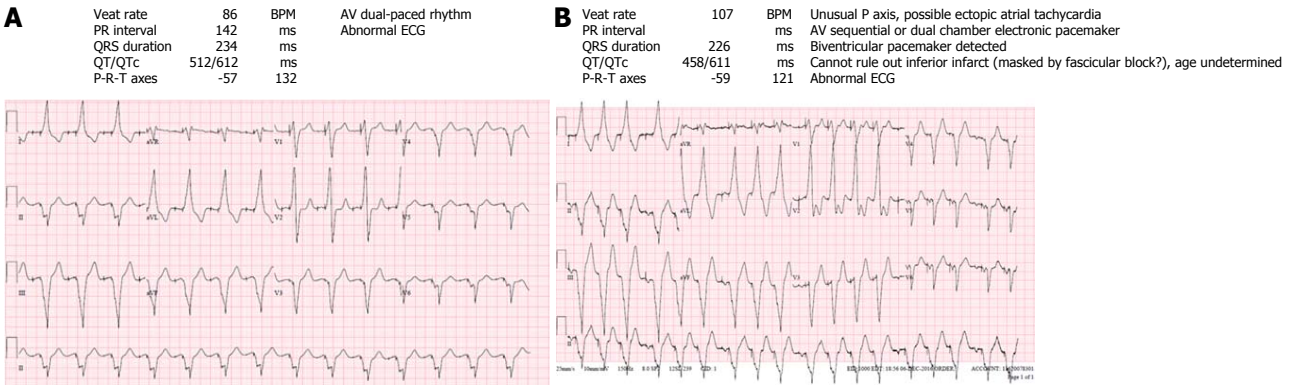

Figure 1 Electrocardiograms from a patient with an interatrial lateral tunnel Fontan for double inlet left ventricle. Patient has an epicardial DDI pacemaker for management of postoperative complete heart block. A: Atrio-ventricular sequentially paced rhythm. Patient feeling well; B: Grouped beating with V paced beats and intermittent p-waves. Underlying intra-atrial reentry tachycardia with AV Wenkebach demonstrated on device tracing (not shown). Patient complaining palpitations.

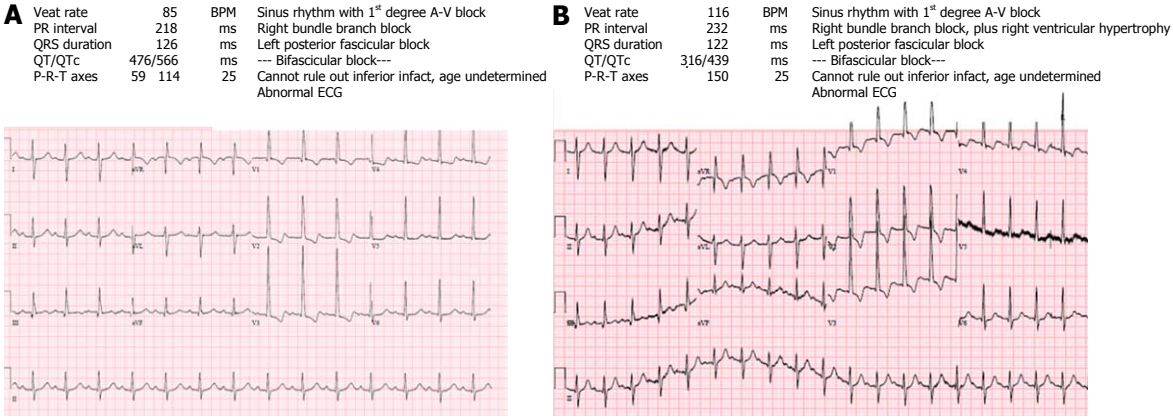

Figure 2 Electrocardiograms from a patient with a Mustard procedure. A: Sinus rhythm with 1st degree heart block. Patient feeling well; B: Intra-atrial reentry tachycardia with 2:1 ventricular conduction, alternate p-waves not seen as overlapping with QRS complexes. Patient complaining palpitations initially. Within 3 h unable to lie flat, requiring oxygen for desaturation and with pulmonary edema on chest X-ray. Note incorrect automated diagnosis of sinus tachycardia.

centre study of 471 electrical cardioversions in 149 CHD patients found that 78% were for IART and 22% for AF[23]. However, the prevalence of AF is increasing as the ACHD population ages such that this diagnosis is becoming the most common atrial arrhythmia in older cohorts. A recent study of 4781 TOF patients across the age spectrum reported the average age of onset of IART as 27 years *vs* 44 years for AF[20]. In the same study, AF was the diagnosis in 10% of arrhythmias seen in patients born prior to 1961 *vs* < 1% patients born after 1981[20]. In another cohort of TOF patients AF was the most prevalent atrial arrhythmia after 55 years of age[25]. The increasing risk of AF with age relates to the underlying mechanism, which is usually chronic hemodynamic atrial stress and remodeling as well as increase in conventional risk factors such as hypertension, diabetes mellitus, obesity, and sleep apnea. Patients with residual AV valve regurgitation or left-sided obstructive lesions as well as those with unrepaired, palliated CHD are particularly vulnerable to AF[23,24]. Patients who have undergone ablation for IART may go on to experience late atrial fibrillation in follow-up. During follow-up approximately 30% of patients with surgically closed ASD who had previously undergone successful catheter ablation for IART develop AF[40].

Atrioventricular reentrant tachycardia

Wolff-Parkinson-White syndrome (WPW) occurs in 20% of cases with Ebstein anomaly of tricuspid valve[41]. The accessory pathway in Ebstein anomaly is usually located along the posterior and septal aspect of the tricuspid ring where the valve leaflets are most abnormal, and about half of these patients have multiple accessory pathways[42,43]. Ebstein-like malformation of a left-sided tricuspid valve is common in congenitally corrected TGA and often associated with accessory pathway(s)[36]. Tachycardia events for Ebstein patients are of concern in adult years when there is increased likelihood of coexisting atrial fibrillation and 1:1 anterograde conduction over the accessory pathway[36].

MANAGEMENT OF ACUTE ATRIAL ARRHYTHMIAS IN ACHD PATIENTS

Acute management of atrial tachyarrhythmia in hemodynamically stable patients includes anticoagulation to prevent thromboembolism, rate control, and cardioversion to restore sinus rhythm. In ACHD patients with simple anatomy and an atrial arrhythmia of ⩾ 48 h or unknown duration, ⩾ 3 wk of anticoagulation or transesophageal

echocardiography (TEE) is recommended prior to cardioversion to rule out intra-cardiac thrombus[17]. In moderate and complex patients who are at higher risk of thrombosis formation, TEE or 3 wk of anticoagulation is recommended prior to cardioversion, even if the IART or atrial fibrillation is less than 48 h in duration[17,44]. In our own practice, we are reluctant to leave Fontan patients or those with a systemic right ventricle in an atrial tachyarrhythmia for a prolonged period of time, for fear of deteriorating hemodynamics and/or ventricular function. Therefore we rarely choose to anticoagulate and wait three weeks. In high-risk patients we prefer to perform TEE or low dose cardiac CT promptly followed by cardioversion within a day or two of diagnosis. Pharmacologic rate control can be useful for those who have a rapid ventricular response during their tachyarrhythmia while cardioversion is being planned. Options include use of beta-blockers, calcium channel blockers, or amiodarone[45].

Termination of atrial tachyarrhythmia can be achieved by electrical cardioversion, overdrive pacing, or drug therapy. Urgent electrical cardioversion is recommended in adults with ACHD who are hemodynamically unstable regardless of arrhythmia duration or anticoagulation status[45]. Anterior-posterior pad positioning increases cardioversion success in the face of marked atrial dilatation[17] and is important in the many ACHD patients who have a pacemaker. Patients with Fontan palliation, Mustard or Senning, and Glenn shunts, are at risk of sinus node dysfunction and may develop prolong sinus pause following rhythm conversion[17,9,46]. The team planning a cardioversion needs to be prepared for this possibility. Patients with an extra-cardiac or interatrial lateral tunnel Fontan circulation do not have ready venous access to enable ventricular pacing. The back-up plan for these patients should include percutaneous pacing and/or use of medications such as atropine or isopretrenol. Electrical cardioversion of complex CHD patients is best performed in the coronary care unit with continuous monitoring of heart rhythm post cardioversion till rhythm stability is established. Overdrive pacing of IART can be attempted in patients with either atrial or dual chamber pacemakers or defibrillators. Immediate anti-tachycardia pacing is effective in up to 50% of cases[47]. In pacemaker dependent patients, it is important to maintain back up ventricular pacing during attempted atrial overdrive pacing[17].

Pharmacologic cardioversion can be used to terminate atrial arrhythmias acutely, however, concerns include risk of torsades de pointes in Class Ⅲ and ventricular tachycardia in Class IA and IC antiarrhythmic medications[17]. Amiodarone is the medication we use most often for acute termination of atrial arrhythmias in ACHD patients. Cardioversion can sometimes be achieved by following an intravenous bolus dose with a maintenance infusion for 24-48 h. Amiodarone may restore sinus rhythm, or assist in slowing the ventricular rate if cardioversion fails. There are currently no efficacy or safety data regarding the acute use of amiodarone in treatment of atrial tachyarrhythmia in ACHD patients[17]. Ibutilide and sotalol have also been shown as effective in acute treatment of atrial tachyarrhythmia[48,49]. When compared in a randomized study in non-ACHD population, ibutilide was superior to sotalol in conversion of atrial arrhythmia[50]. If using ibutilide, one must be cautious of torsades de pointes which is reported to occur in 2%-8% of non-ACHD patients[51]. In ACHD patients presenting with IART or atrial fibrillation, 1 to 2 mg of IV ibutilide over 10 min may be given if used with continuous heart monitoring where emergency defibrillation and resuscitation is available[17].

Patients with WPW, orthodromic atrioventricular reentrant tachycardia and AVNRT, who are hemodynamically stable can be treated with intravenous adenosine, which may terminate the tachycardia and restore sinus rhythm. This is because adenosine slows AV nodal conduction and these tachycardias include the AV node as an obligatory part of their circuit. In contrast, the effects of adenosine on atrial flutter, IART and atrial ectopic tachycardia are inconsistent[52]. Adenosine will not generally terminate these arrhythmias and is more likely to produce transient or increased AV block, which can unmask atrial activity on an ECG and aid diagnosis. It is important that adenosine be given rapidly and in a sufficient dose to reach the coronary circulation. Adenosine administration is generally safe but rare proarrhythmic and potentially life-threating effects have been reported[53]. It can precipitate atrial fibrillation, which as already stated, is a risk in patients with an accessory pathway where the atrial rate may be conducted 1:1 to the ventricles. Patients with pre-excited atrial fibrillation are usually treated with urgent electrical cardioversion because of the risk of cardiovascular collapse[54].

MANAGEMENT OF CHRONIC OR RECURRENT ATRIAL ARRHYTHMIAS IN ACHD PATIENTS

Medical management

Rhythm control is generally recommended as the initial strategy for patients with moderate or complex forms of CHD[17]. This is because loss of sinus rhythm, even with a controlled heart rate can adversely and importantly impact both hemodynamics and ventricular function in ACHD patients[17,27]. However, once an ACHD patient has experienced atrial arrhythmia, recurrences are often seen. In our experience, the initiation of antiarrhythmic drugs, before further cardioversion may be beneficial to the chances of reestablishing sinus rhythm and/or reducing the frequency of recurrence.

The pro-arrhythmic risk of Class I (fast sodium channel blockers) antiarrhythmic drugs in patients with CHD includes ventricular arrhythmias[55,56]. In addition, they are not recommended for maintenance of sinus rhythm in patients with coronary artery disease or moderately to severe systolic dysfunction of either ventricle[17,45].

In general cardiology practice, sotalol is used for

maintenance of sinus rhythm in patients with AF who have normal baseline QT interval (< 460 ms) and minimal or no structural heart disease[45]. While some retrospective studies have suggested safety and efficacy of sotalol in adults with CHD[57-59], a meta-analysis of antiarrhythmic drugs for AF which included 12 clinical trials showed that sotalol doubles all-cause mortality[60]. Based on the current evidence, sotalol can be used with caution for maintenance of sinus rhythm in IART or AF in patients with ACHD[17].

In non-ACHD populations, amiodarone is the most effective antiarrhythmic medication in maintaining sinus rhythm in AF and is considered drug of choice in heart failure patients[61,62]. Expert consensus suggests amiodarone as first line for maintenance of sinus rhythm in ACHD patients with IART and those with AF in presence of ventricular hypertrophy or dysfunction, or coronary artery disease[17]. It is the drug we use most often across the spectrum in ACHD, including in patients with impaired ventricular function. Unfortunately, long-term treatment with amiodarone (which is often necessary in this population) can be complicated by pulmonary and liver toxicity, thyroid dysfunction, photosensitivity, and corneal microdeposits[63]. In our experience the most frequent problems in ACHD patients are thyroid related. Torsades de pointes is seen in fewer than 1% of non-ACHD patients[64].

Dofetilide has been shown to be safe in adult patients with recent myocardial infarction or heart failure[65]. The major concern is risk of torsade de pointes, which is seen in 0.9% to 3.3% of patients[66,67]. Dofetilide was studied in a multicenter series of 20 ACHD patients with refractory atrial arrhythmia and reasonable success was noted[68]. However, we rarely use this drug in our center and prefer the use of sotalol.

Catheter ablation

Catheter ablation is now used as an early treatment strategy for IART in many centers and is preferred over the long-term pharmacological management[17,69]. Advances in 3D mapping for improved circuit localization and irrigated-tip or large-tip ablation catheters which help with effective lesion creation has led to 81% acute success rate[69-72]. Newly developed software permits rapid automatic annotation of signals using multi-electrode catheters. This allows large chambers to be mapped rapidly and with a huge number of points reducing procedure time and potentially increasing success rates of ablation[73]. These needs to be interpreted in the context of programmed settings on the mapping system including the window of interest and electrogram annotation the discussion of which is beyond the scope of this review[74].

The acute success rate is lower in Ebstein anomaly with higher recurrence rate[75,76] due to challenges of distorted anatomic landmarks, difficulty identifying the true AV groove, extremely fractionated electrograms, and the high incidence of multiple pathways[31,75,76]. Recurrence rates following ablation are 34%-54%, mostly occurring within the first year and are higher in atriopulmonary anastomosis of Fontan palliation compared to other CHD patients[72,77,78]. Gaining access to the atrial tissue is difficult in patients with an interatrial lateral tunnel or extra-cardiac Fontan palliation and conduit puncture may be required[79]. When planning ablation, consideration should be given to the location of the AV node in the underlying CHD and the risk of AV block due to ablation. For example, the AV node is typically located anterior in the AV junction in congenitally corrected-TGA[80]. The AV node is displaced postero-inferiorly in inlet VSDs[81]. These should be kept in mind when planning ablations in that region as for typical slow fast AVNRT. The AV node does not have an intracardiac signal. The His bundle signal is used as its surrogate marker. Locating and identifying the His is often challenging in ACHD as the conduction system is often displaced in many conditions like AV canal defects and congenitally corrected transposition of great arteries. In other conditions like an extracardiac Fontan, the His bundle is not accessible unless a puncture is performed. If located, the His signal can be tagged by using 3D electroanatomic mapping systems. This is especially important in patients with single ventricle palliation where the complication of heart block would often require management with epicardial pacing[82].

Specific recommendations for AF ablation in CHD population have not yet been developed due to scarcity of published data on mechanism of arrhythmia, unclear ablation targets, and efficacy[27]. One study reported a success rate of 42% compared to 53% in controls without CHD. The value of repeat ablations and role of pulmonary vein isolation in complex CHD patients remains to be determined[40,83]. Limited experience is available on AV nodal ablation followed by permanent pacing in symptomatic patient with poor rate control[84].

Surgical treatment and percutaneous intervention

A disturbance of hemodynamics often underlies (or is a significant contributor to) atrial arrhythmia in ACHD. Sometimes the hemodynamic issues are amenable to treatment by surgery or a percutaneous intervention and if successful, such procedures may extinguish or ameliorate the patient's arrhythmia burden. Examples would be replacement of a regurgitant left atrioventricular valve in a patient with an atrioventricular septal defect, pulmonary valve replacement in a patient with repaired tetralogy of Fallot and severe pulmonary regurgitation and replacement of a stenosed conduit for pulmonary blood flow. The decision to surgically revise or upgrade a Fontan circulation as an intervention for recurrent arrhythmia can have excellent results but is a specific example with unique considerations[85-87]. When patients with ACHD experience atrial arrhythmia consideration should not only be given to correction of residual hemodynamic lesions but also to the role of specific arrhythmia surgery, which can be performed either in conjunction with

other procedures or in isolation. Mavroudis *et al*[88] have published an excellent and detailed review of arrhythmia surgery in ACHD based on their own experience in 248 patients. Most of the surgical procedures described are for the treatment of atrial arrhythmia in patients with repaired TOF or a single ventricle circulation. Operative techniques described include, methods for increasing the safety of repeat sternal reentry, direct ablation (cryoablation or radiofrequency), right atrial and biatrial Cox-maze procedures, as well as excision of automatic foci. The paper describes the differing anatomical and electrophysiological variations which need to be taken into account for each congenital cardiac diagnosis and arrhythmia[88].

Anticoagulation

Thromboembolic prevention in ACHD patients is an important aspect of pharmacological treatment of atrial arrhythmia. The prevalence of thromboembolic events in ACHD patients is estimated to be 10 to 100-fold higher than age-matched controls in the general population due to dilated chambers with sluggish flow, intracardiac prosthetic material, pacing/defibrillation leads, intracardiac shunts, and associated hypercoagulable states[89,90]. In particular, the risk of stroke is 10-fold higher in ACHD patients, with atrial arrhythmia being one of the strongest predictors[91,92]. In a small series of ACHD patients who underwent TEE prior to electrical cardioversion of an atrial arrhythmia, atrial thrombus was seen in 37%[93].

Risk scoring systems (CHA2DS2, CHA2DS2-VASc, and HAS-BLED) are widely used to guide anticoagulant prescription in non-ACHD patients, balancing the risks of thromboembolism against the risks of bleeding[94-96]. Initially, these scoring systems were not developed or tested in ACHD patients and did not include any component relating to the type or severity of congenital cardiac lesion[17]. For many years there has been controversy about whether or not they have any value in decision-making for ACHD patients. In 2015 a Dutch study of 229 ACHD patients with atrial arrhythmias attempted to address this issue[97]. The authors evaluated dichotomized CHA2-DS2-VASc and HAS-BLED scores in their ACHD cohort and reported that thrombotic and bleeding events can be predicted by using scoring systems[97]. In moderate/complex patients with IART or AF, long-term oral anticoagulation is recommended with vitamin K antagonist (VKA) however, in simple nonvalvular CHD, the decision of anticoagulation risk can be guided by CHA2DS2-VASc score[17,98]. Patients with CHA2DS2-VASc score of $\geqslant$ 2 need oral anticoagulation with VKA or novel oral anticoagulants[17].

The new oral anticoagulants (NOAC) have been introduced as an alternative to VKA in non-valvular atrial fibrillation. These drugs are either direct thrombin (Dabigatran) or factor Xa (Rivaroxaban, Apixaban) inhibitors. Limited data is available regarding the use of NOACs in ACHD population. One prospective study included data from 75 ACHD patients without prosthetic heart valves taking one of three NOACs[99]. Twenty-one percent of participants had complex CHD and the main indication was thrombosis prevention in atrial arrhythmia[99]. During a mean follow-up duration of 12 mo, there were no thrombotic or major bleeding events[99]. Results from further multi-centre studies are anticipated. However, it may be reasonable to consider NOAC in lieu of VKA in simple CHD and without prosthetic valves or hemodynamically significant valve disease[17,99].

ATRIAL ARRHYTHMIAS DURING PREGNANCY IN ACHD PATIENTS

The risk of atrial arrhythmia is known to increase during pregnancy due to anticipated adaptive hemodynamic, hormonal, and autonomic changes[100,101]. The incidence of AF/IART in patients with structural heart disease was reported at 1.3% by the Registry on Pregnancy and Cardiac Disease with the majority of arrhythmias occurring during second trimester[102]. The frequency of arrhythmia during pregnancy is higher than this in other studies and certain ACHD subgroups. In a systematic review by Drenthen *et al*[103], the highest risk of arrhythmia was reported in patients with Fontan palliation, atrial redirection for TGA (Mustard or Senning) and repaired atrio-ventricular septal defect. In a multi-centre study of 157 pregnancies in 74 women with repaired TOF the incidence of arrhythmia was 6.5% *vs* < 1% in controls[104]. In a study of women with valvular heart disease the rate of arrhythmia during pregnancy was 15% *vs* 0% in controls (P = 0.001)[105]. The following have been identified as risk factors for the occurrence of atrial arrhythmias during pregnancy: Arrhythmia before pregnancy, mitral valve disease, beta-blocker use before pregnancy, and left-sided cardiac lesions[101,102]. Atrial arrhythmias during pregnancy area associated with pregnancy-related mortality and morbidity. This may be due to severity of underlying heart disease and also to an increased risk of thromboembolic events[102].

Electrical cardioversion can be used in all trimesters of pregnancy and must not be delayed in hemodynamically unstable patients[106]. The risk of inducing fetal arrhythmias is minimal but unless cardioversion is emergent, fetal monitoring should be performed[101,106,107]. Most antiarrhythmic drugs are United States Food and Drug Administration class C medications; *i.e.*, animal studies have shown risk to the fetus, there are no controlled studies in women or studies in women and animals are not available. This is a confusing classification, meaning that there is insufficient data to make a statement regarding safety. Use of these drugs must be carefully discussed with pregnant women to allow them the ability to weigh potential pros and cons. Beta-blockers (often metoprolol) are commonly used as first line rate control therapy. Atenolol is an FDA class D medication (positive evidence of fetal risk) and should be avoided due to association with low birthweight. Oral verapamil and digoxin (FDA Class C) are used for atrial arrhythmia in pregnancy

but should not be used when an accessory pathway is suspected[106]. Sotalol (FDA class B - animal studies show no risk, no studies in humans) can be used to maintain sinus rhythm although, its side effects include fetal bradycardia and long QT in the mother and therefore, close monitoring is required. Due to its side effects on fetal thyroid function, amiodarone should not be used during pregnancy unless other antiarrhythmic agents are contraindicated or ineffective. Flecainide (FDA class C) is a drug which crosses the placenta and is often used for treatment of fetal tachycardia, however there are proarrhythmic risks in patients with structural heart disease[108,109]. Pregnancy is a prothrombotic state and sustained atrial arrhythmia will further increase risk of thromboembolic events in pregnancy, therefore anticoagulation should be considered. Specific guidelines and recommendations exist[100,110] and any decision about anticoagulation during pregnancy should be made with the input of specialist advice and in full consultation with the patient. Different regimens can be recommended depending on patient preference and the individualized balance of risks: Obstetric risks (miscarriage, retroplacental hematoma, bleeding during delivery) *vs* offspring risks (warfarin associated embryopathy, premature birth, inter-cranial bleeding) *vs* maternal risks (thrombosis and bleeding). The risk of maternal thrombosis and thromboembolism are highest in women who in addition to their atrial arrhythmia also have either mechanical valves or Fontan circulations.

CONCLUSION

The ACHD population continues to expand and is also aging. Atrial arrhythmias are common in these patients and the cause of significant morbidity. They also associated with increased risk of subsequent mortality. A comprehensive understanding of the underlying anatomy, previous surgeries and mechanism of the arrhythmia is essential to optimal management of arrhythmias in this population and clear, open communication between ACHD specialists, electrophysiologists and primary care providers necessary.

REFERENCES

1 **van der Linde D**, Konings EE, Slager MA, Witsenburg M, Helbing WA, Takkenberg JJ, Roos-Hesselink JW. Birth prevalence of congenital heart disease worldwide: a systematic review and meta-analysis. *J Am Coll Cardiol* 2011; **58**: 2241-2247 [PMID: 22078432 DOI: 10.1016/j.jacc.2011.08.025]

2 **Marelli AJ**, Mackie AS, Ionescu-Ittu R, Rahme E, Pilote L. Congenital heart disease in the general population: changing prevalence and age distribution. *Circulation* 2007; **115**: 163-172 [PMID: 17210844 DOI: 10.1161/CIRCULATIONAHA. 106.627224]

3 **Moons P**, Van Deyk K, Dedroog D, Troost E, Budts W. Prevalence of cardiovascular risk factors in adults with congenital heart disease. *Eur J Cardiovasc Prev Rehabil* 2006; **13**: 612-616 [PMID: 16874153 DOI: 10.1097/01.hjr.0000197472.81694.2b]

4 **Roche SL**, Silversides CK. Hypertension, obesity, and coronary artery disease in the survivors of congenital heart disease. *Can J Cardiol* 2013; **29**: 841-848 [PMID: 23688771 DOI: 10.1016/j.cjca.2013.03.021]

5 **Opotowsky AR**, Siddiqi OK, Webb GD. Trends in hospitalizations for adults with congenital heart disease in the U.S. *J Am Coll Cardiol* 2009; **54**: 460-467 [PMID: 19628123 DOI: 10.1016/j.jacc.2009.04.037]

6 **Bouchardy J**, Therrien J, Pilote L, Ionescu-Ittu R, Martucci G, Bottega N, Marelli AJ. Atrial arrhythmias in adults with congenital heart disease. *Circulation* 2009; **120**: 1679-1686 [PMID: 19822808 DOI: 10.1161/CIRCULATIONAHA.109.866319]

7 **Kaemmerer H**, Bauer U, Pensl U, Oechslin E, Gravenhorst V, Franke A, Hager A, Balling G, Hauser M, Eicken A, Hess J. Management of emergencies in adults with congenital cardiac disease. *Am J Cardiol* 2008; **101**: 521-525 [PMID: 18312770 DOI: 10.1016/j.amjcard.2007.09.110]

8 **Ghai A**, Harris L, Harrison DA, Webb GD, Siu SC. Outcomes of late atrial tachyarrhythmias in adults after the Fontan operation. *J Am Coll Cardiol* 2001; **37**: 585-592 [PMID: 11216983]

9 **Fishberger SB**, Wernovsky G, Gentles TL, Gauvreau K, Burnett J, Mayer JE, Walsh EP. Factors that influence the development of atrial flutter after the Fontan operation. *J Thorac Cardiovasc Surg* 1997; **113**: 80-86 [PMID: 9011705]

10 **Puley G**, Siu S, Connelly M, Harrison D, Webb G, Williams WG, Harris L. Arrhythmia and survival in patients & gt; 18 years of age after the mustard procedure for complete transposition of the great arteries. *Am J Cardiol* 1999; **83**: 1080-1084 [PMID: 10190524]

11 **Helbing WA**, Hansen B, Ottenkamp J, Rohmer J, Chin JG, Brom AG, Quaegebeur JM. Long-term results of atrial correction for transposition of the great arteries. Comparison of Mustard and Senning operations. *J Thorac Cardiovasc Surg* 1994; **108**: 363-372 [PMID: 8041184]

12 **Khairy P**, Clair M, Fernandes SM, Blume ED, Powell AJ, Newburger JW, Landzberg MJ, Mayer JE. Cardiovascular outcomes after the arterial switch operation for D-transposition of the great arteries. *Circulation* 2013; **127**: 331-339 [PMID: 23239839 DOI: 10.1161/CIRCULATIONAHA.112.135046]

13 **Brown ML**, Dearani JA, Danielson GK, Cetta F, Connolly HM, Warnes CA, Li Z, Hodge DO, Driscoll DJ. Functional status after operation for Ebstein anomaly: the Mayo Clinic experience. *J Am Coll Cardiol* 2008; **52**: 460-466 [PMID: 18672167 DOI: 10.1016/j.jacc.2008.03.064]

14 **Harrison DA**, Siu SC, Hussain F, MacLoghlin CJ, Webb GD, Harris L. Sustained atrial arrhythmias in adults late after repair of tetralogy of fallot. *Am J Cardiol* 2001; **87**: 584-588 [PMID: 11230843]

15 **El-Najdawi EK**, Driscoll DJ, Puga FJ, Dearani JA, Spotts BE, Mahoney DW, Danielson GK. Operation for partial atrioventricular septal defect: a forty-year review. *J Thorac Cardiovasc Surg* 2000; **119**: 880-889; discussion 889-890 [PMID: 10788807 DOI: 10.1016/S0022-5223(00)70082-1]

16 **Gatzoulis MA,** Freeman MA, Siu SC, Webb GD, Harris L. Atrial arrhythmia after surgical closure of atrial septal defects in adults. *New Engl J Med* 1999; **340**: 839-846 [PMID: 10080846 DOI: 10.1056/NEJM199903183401103]

17 **Khairy P**, Van Hare GF, Balaji S, Berul CI, Cecchin F, Cohen MI, Daniels CJ, Deal BJ, Dearani JA, Groot Nd, Dubin AM, Harris L, Janousek J, Kanter RJ, Karpawich PP, Perry JC, Seslar SP, Shah MJ, Silka MJ, Triedman JK, Walsh EP, Warnes CA. PACES/HRS expert consensus statement on the recognition and management of arrhythmias in adult congenital heart disease: developed in partnership between the Pediatric and Congenital Electrophysiology Society (PACES) and the Heart Rhythm Society (HRS). Endorsed by the governing bodies of PACES, HRS, the American College of Cardiology (ACC), the American Heart Association (AHA), the European Heart Rhythm Association (EHRA), the Canadian Heart Rhythm Society (CHRS), and the International Society for Adult Congenital Heart Disease (ISACHD). *Can J Cardiol* 2014; **30**: e1-e63 [PMID: 25262867 DOI: 10.1016/j.cjca.2014.09.002]

18 **Warnes CA,** Liberthson R, Danielson GK, Dore A, Harris L, Hoffman JIE, Somerville J, Williams RG, Webb GD. Task Force 1: The Changing Profile of Congenital Heart Disease in Adult Life. *J Am Coll Cardiol* 2001; **37**: 1170-1175

19 **Valente AM**, Gauvreau K, Assenza GE, Babu-Narayan SV, Schreier J, Gatzoulis MA, Groenink M, Inuzuka R, Kilner PJ, Koyak Z, Landzberg MJ, Mulder B, Powell AJ, Wald R, Geva T. Contemporary predictors of death and sustained ventricular tachycardia in patients with repaired tetralogy of Fallot enrolled in the INDICATOR cohort. *Heart* 2014; **100**: 247-253 [PMID: 24179163 DOI: 10.1136/heartjnl-2013-304958]

20 **Wu MH**, Lu CW, Chen HC, Chiu SN, Kao FY, Huang SK. Arrhythmic burdens in patients with tetralogy of Fallot: a national database study. *Heart Rhythm* 2015; **12**: 604-609 [PMID: 25461497 DOI: 10.1016/j.hrthm.2014.11.026]

21 **Diller GP**, Giardini A, Dimopoulos K, Gargiulo G, Müller J, Derrick G, Giannakoulas G, Khambadkone S, Lammers AE, Picchio FM, Gatzoulis MA, Hager A. Predictors of morbidity and mortality in contemporary Fontan patients: results from a multicenter study including cardiopulmonary exercise testing in 321 patients. *Eur Heart J* 2010; **31**: 3073-3083 [PMID: 20929979 DOI: 10.1093/eurheartj/ehq356]

22 **Gatzoulis MA**, Walters J, McLaughlin PR, Merchant N, Webb GD, Liu P. Late arrhythmia in adults with the mustard procedure for transposition of great arteries: a surrogate marker for right ventricular dysfunction? *Heart* 2000; **84**: 409-415 [PMID: 10995411]

23 **Kirsh JA**, Walsh EP, Triedman JK. Prevalence of and risk factors for atrial fibrillation and intra-atrial reentrant tachycardia among patients with congenital heart disease. *Am J Cardiol* 2002; **90**: 338-340 [PMID: 12127629]

24 **Philip F**, Muhammad KI, Agarwal S, Natale A, Krasuski RA. Pulmonary vein isolation for the treatment of drug-refractory atrial fibrillation in adults with congenital heart disease. *Congenit Heart Dis* 2012; **7**: 392-399 [PMID: 22469422 DOI: 10.1111/j.1747-0803.2012.00649.x]

25 **Khairy P**, Aboulhosn J, Gurvitz MZ, Opotowsky AR, Mongeon FP, Kay J, Valente AM, Earing MG, Lui G, Gersony DR, Cook S, Ting JG, Nickolaus MJ, Webb G, Landzberg MJ, Broberg CS. Arrhythmia burden in adults with surgically repaired tetralogy of Fallot: a multi-institutional study. *Circulation* 2010; **122**: 868-875 [PMID: 20713900 DOI: 10.1161/CIRCULATIONAHA.109.928481]

26 **Gelatt M**, Hamilton RM, McCrindle BW, Connelly M, Davis A, Harris L, Gow RM, Williams WG, Trusler GA, Freedom RM. Arrhythmia and mortality after the Mustard procedure: a 30-year single-center experience. *J Am Coll Cardiol* 1997; **29**: 194-201 [PMID: 8996314]

27 **Kumar S**, Tedrow UB, Triedman JK. Arrhythmias in Adult Congenital Heart Disease: Diagnosis and Management. *Cardiol Clin* 2015; **33**: 571-888, viii [PMID: 26471821 DOI: 10.1016/j.ccl.2015.07.007]

28 **Akar JG**, Kok LC, Haines DE, DiMarco JP, Mounsey JP. Coexistence of type I atrial flutter and intra-atrial re-entrant tachycardia in patients with surgically corrected congenital heart disease. *J Am Coll Cardiol* 2001; **38**: 377-384 [PMID: 11499727]

29 **Love BA**, Collins KK, Walsh EP, Triedman JK. Electroanatomic characterization of conduction barriers in sinus/atrially paced rhythm and association with intra-atrial reentrant tachycardia circuits following congenital heart disease surgery. *J Cardiovasc Electrophysiol* 2001; **12**: 17-25 [PMID:111204078]

30 **Roos-Hesselink J**, Perlroth MG, McGhie J, Spitaels S. Atrial arrhythmias in adults after repair of tetralogy of Fallot. Correlations with clinical, exercise, and echocardiographic findings. *Circulation* 1995; **91**: 2214-2219 [PMID: 7697851]

31 **Moons P,** Gewillig M, Sluysmans T, Verhaaren H, Viart P, Massin M, Suys B, Budts W, Pasquet A, De Wolf D, Vliers A. Long term outcome up to 30 years after the Mustard or Senning operation: a nationwide multicentre study in Belgium. *Heart* 2004; **90**: 307-313 [DOI: 10.1136/hrt.2002.007138]

32 **Stephenson EA**, Lu M, Berul CI, Etheridge SP, Idriss SF, Margossian R, Reed JH, Prakash A, Sleeper LA, Vetter VL, Blaufox AD; Pediatric Heart Network Investigators. Arrhythmias in a contemporary fontan cohort: prevalence and clinical associations in a multicenter cross-sectional study. *J Am Coll Cardiol* 2010; **56**: 890-896 [PMID: 20813285 DOI: 10.1016/j.jacc.2010.03.079]

33 **Collins KK**, Love BA, Walsh EP, Saul JP, Epstein MR, Triedman JK. Location of acutely successful radiofrequency catheter ablation of intraatrial reentrant tachycardia in patients with congenital heart disease. *Am J Cardiol* 2000; **86**: 969-974 [PMID: 11053709]

34 **Nakagawa H**, Shah N, Matsudaira K, Overholt E, Chandrasekaran K, Beckman KJ, Spector P, Calame JD, Rao A, Hasdemir C, Otomo K, Wang Z, Lazzara R, Jackman WM. Characterization of reentrant circuit in macroreentrant right atrial tachycardia after surgical repair of congenital heart disease: isolated channels between scars allow "focal" ablation. *Circulation* 2001; **103**: 699-709 [PMID: 11156882]

35 **Alexander ME**, Cecchin F, Walsh EP, Triedman JK, Bevilacqua LM, Berul CI. Implications of implantable cardioverter defibrillator therapy in congenital heart disease and pediatrics. *J Cardiovasc Electrophysiol* 2004; **15**: 72-76 [PMID: 15028076 DOI: 10.1046/j.1540-8167.2004.03388.x]

36 **Walsh EP**, Cecchin F. Arrhythmias in adult patients with congenital heart disease. *Circulation* 2007; **115**: 534-545 [PMID: 17261672 DOI: 10.1161/CIRCULATIONAHA.105.592410]

37 **Delacretaz E**, Ganz LI, Soejima K, Friedman PL, Walsh EP, Triedman JK, Sloss LJ, Landzberg MJ, Stevenson WG. Multi atrial maco-re-entry circuits in adults with repaired congenital heart disease: entrainment mapping combined with three-dimensional electroanatomic mapping. *J Am Coll Cardiol* 2001; **37**: 1665-1676 [PMID: 11345382]

38 **Derrick GP**, Narang I, White PA, Kelleher A, Bush A, Penny DJ, Redington AN. Failure of stroke volume augmentation during exercise and dobutamine stress is unrelated to load-independent indexes of right ventricular performance after the Mustard operation. *Circulation* 2000; **102**: III154-III159 [PMID: 11082379]

39 **Fratz S**, Hager A, Busch R, Kaemmerer H, Schwaiger M, Lange R, Hess J, Stern HC. Patients after atrial switch operation for transposition of the great arteries can not increase stroke volume under dobutamine stress as opposed to patients with congenitally corrected transposition. *Circ J* 2008; **72**: 1130-1135 [PMID: 18577823]

40 **Teh AW**, Medi C, Lee G, Rosso R, Sparks PB, Morton JB, Kistler PM, Halloran K, Vohra JK, Kalman JM. Long-term outcome following ablation of atrial flutter occurring late after atrial septal defect repair. *Pacing Clin Electrophysiol* 2011; **34**: 431-435 [PMID: 21208243 DOI: 10.1111/j.1540-8159.2010.03005.x]

41 **Attenhofer Jost CH**, Connolly HM, Edwards WD, Hayes D, Warnes CA, Danielson GK. Ebstein's anomaly - review of a multifaceted congenital cardiac condition. *Swiss Med Wkly* 2005; **135**: 269-281 [PMID: 15986264]

42 **Levine JC**, Walsh EP, Saul JP. Radiofrequency ablation of accessory pathways associated with congenital heart disease including heterotaxy syndrome. *Am J Cardiol* 1993; **72**: 689-693 [PMID: 8249846]

43 **Smith WM**, Gallagher JJ, Kerr CR, Sealy WC, Kasell JH, Benson DW, Reiter MJ, Sterba R, Grant AO. The electrophysiologic basis and management of symptomatic recurrent tachycardia in patients with Ebstein's anomaly of the tricuspid valve. *Am J Cardiol* 1982; **49**: 1223-1234 [PMID: 7064845]

44 **Idorn L**, Jensen AS, Juul K, Reimers JI, Johansson PI, Sørensen KE, Ostrowski SR, Søndergaard L. Thromboembolic complications in Fontan patients: population-based prevalence and exploration of the etiology. *Pediatr Cardiol* 2013; **34**: 262-272 [PMID: 22843202 DOI: 10.1007/s00246-012-0431-4]

45 **January CT**, Wann LS, Alpert JS, Calkins H, Cigarroa JE, Cleveland JC, Conti JB, Ellinor PT, Ezekowitz MD, Field ME, Murray KT, Sacco RL, Stevenson WG, Tchou PJ, Tracy CM, Yancy CW. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. *J Am Coll Cardiol* 2014; **64**: e1-76 [PMID: 24685669 DOI: 10.1016/j.jacc.2014.03.022]

46 **Flinn CJ**, Wolff GS, Dick M, Campbell RM, Borkat G, Casta A, Hordof A, Hougen TJ, Kavey RE, Kugler J. Cardiac rhythm after the Mustard operation for complete transposition of the great arteries. *N Engl J Med* 1984; **310**: 1635-1638 [PMID: 6727935

DOI: 10.1056/NEJM198406213102504]
47 **Stephenson EA**, Casavant D, Tuzi J, Alexander ME, Law I, Serwer G, Strieper M, Walsh EP, Berul CI; ATTEST Investigators. Efficacy of atrial antitachycardia pacing using the Medtronic AT500 pacemaker in patients with congenital heart disease. *Am J Cardiol* 2003; **92**: 871-876 [PMID: 14516898]
48 **Hoyer AW**, Balaji S. The safety and efficacy of ibutilide in children and in patients with congenital heart disease. *Pacing Clin Electrophysiol* 2007; **30**: 1003-1008 [PMID: 17669084 DOI: 10.1111/j.1540-8159.2007.00799.x]
49 **Rao SO**, Boramanand NK, Burton DA, Perry JC. Atrial tachycardias in young adults and adolescents with congenital heart disease: conversion using single dose oral sotalol. *Int J Cardiol* 2009; **136**: 253-257 [PMID: 18653253 DOI: 10.1016/j.ijcard.2008.04.060]
50 **Vos MA**, Golitsyn SR, Stangl K, Ruda MY, Van Wijk LV, Harry JD, Perry KT, Touboul P, Steinbeck G, Wellens HJ. Superiority of ibutilide (a new class III agent) over DL-sotalol in converting atrial flutter and atrial fibrillation. The Ibutilide/Sotalol Comparator Study Group. *Heart* 1998; **79**: 568-575 [PMID: 10078083]
51 **Kowey PR**, VanderLugt JT, Luderer JR. Safety and risk/benefit analysis of ibutilide for acute conversion of atrial fibrillation/flutter. *Am J Cardiol* 1996; **78**: 46-52 [PMID: 8903276]
52 **Trohman RG**. Adenosine for diagnosis of wide QRS tachycardia: rapid infusion for an easier conclusion. *Crit Care Med* 2009; **37**: 2651-2652 [PMID: 19687635 DOI: 10.1097/CCM.0b013e 3181abfb9f]
53 **Mallet ML**. Proarrhythmic effects of adenosine: a review of the literature. *Emerg Med J* 2004; **21**: 408-410 [PMID: 15208219 DOI: 10.1136/emj.2004.016048]
54 **Page RL**, Joglar JA, Caldwell MA, Calkins H, Conti JB, Deal BJ, Estes NA, Field ME, Goldberger ZD, Hammill SC, Indik JH, Lindsay BD, Olshansky B, Russo AM, Shen WK, Tracy CM, Al-Khatib SM. 2015 ACC/AHA/HRS Guideline for the Management of Adult Patients With Supraventricular Tachycardia: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. *J Am Coll Cardiol* 2016; **67**: e27-e115 [PMID: 26409259 DOI: 10.1016/j.jacc.2015.08.856]
55 **Khairy P**, Harris L, Landzberg MJ, Viswanathan S, Barlow A, Gatzoulis MA, Fernandes SM, Beauchesne L, Therrien J, Chetaille P, Gordon E, Vonder Muhll I, Cecchin F. Implantable cardioverter-defibrillators in tetralogy of Fallot. *Circulation* 2008; **117**: 363-370 [PMID: 18172030 DOI: 10.1161/CIRCULATIONAHA.107.726372]
56 **Fish FA**, Gillette PC, Benson DW. Proarrhythmia, cardiac arrest and death in young patients receiving encainide and flecainide. The Pediatric Electrophysiology Group. *J Am Coll Cardiol* 1991; **18**: 356-365 [PMID: 1906902]
57 **Koyak Z**, Kroon B, de Groot JR, Wagenaar LJ, van Dijk AP, Mulder BA, Van Gelder IC, Post MC, Mulder BJ, Bouma BJ. Efficacy of antiarrhythmic drugs in adults with congenital heart disease and supraventricular tachycardias. *Am J Cardiol* 2013; **112**: 1461-1467 [PMID: 23993125 DOI: 10.1016/j.amjcard.2013.07.029]
58 **Miyazaki A**, Ohuchi H, Kurosaki K, Kamakura S, Yagihara T, Yamada O. Efficacy and safety of sotalol for refractory tachyarrhythmias in congenital heart disease. *Circ J* 2008; **72**: 1998-2003 [PMID: 18931451]
59 **Beaufort-Krol GC**, Bink-Boelkens MT. Sotalol for atrial tachycardias after surgery for congenital heart disease. *Pacing Clin Electrophysiol* 1997; **20**: 2125-2129 [PMID: 9272523]
60 **Lafuente-Lafuente C**, Longas-Tejero MA, Bergmann JF, Belmin J. Antiarrhythmics for maintaining sinus rhythm after cardioversion of atrial fibrillation. *Cochrane Database Syst Rev* 2012; **5**: CD005049 [PMID: 22592700 DOI: 10.1002/14651858.CD005049.pub3]
61 **Roy D**, Talajic M, Dorian P, Connolly S, Eisenberg MJ, Green M, Kus T, Lambert J, Dubuc M, Gagné P, Nattel S, Thibault B. Amiodarone to prevent recurrence of atrial fibrillation. Canadian Trial of Atrial Fibrillation Investigators. *N Engl J Med* 2000; **342**: 913-920 [PMID: 10738049 DOI: 10.1056/NEJM200003303421302]
62 **Roy D**, Talajic M, Nattel S, Wyse DG, Dorian P, Lee KL, Bourassa MG, Arnold JM, Buxton AE, Camm AJ, Connolly SJ, Dubuc M, Ducharme A, Guerra PG, Hohnloser SH, Lambert J, Le Heuzey JY, O'Hara G, Pedersen OD, Rouleau JL, Singh BN, Stevenson LW, Stevenson WG, Thibault B, Waldo AL. Rhythm control versus rate control for atrial fibrillation and heart failure. *N Engl J Med* 2008; **358**: 2667-2677 [PMID: 18565859 DOI: 10.1056/NEJMoa0708789]
63 **Goldschlager N**, Epstein AE, Naccarelli GV, Olshansky B, Singh B, Collard HR, Murphy E. A practical guide for clinicians who treat patients with amiodarone: 2007. *Heart Rhythm* 2007; **4**: 1250-1259 [PMID: 17765636 DOI: 10.1016/j.hrthm.2007.07.020]
64 **Hohnloser SH**, Singh BN. Proarrhythmia with class III antiarrhythmic drugs: definition, electrophysiologic mechanisms, incidence, predisposing factors, and clinical implications. *J Cardiovasc Electrophysiol* 1995; **6**: 920-936 [PMID: 8548113]
65 **Køber L**, Bloch Thomsen PE, Møller M, Torp-Pedersen C, Carlsen J, Sandøe E, Egstrup K, Agner E, Videbaek J, Marchant B, Camm AJ; Danish Investigations of Arrhythmia and Mortality on Dofetilide (DIAMOND) Study Group. Effect of dofetilide in patients with recent myocardial infarction and left-ventricular dysfunction: a randomised trial. *Lancet* 2000; **356**: 2052-2058 [PMID: 11145491]
66 **Pedersen OD**, Bagger H, Keller N, Marchant B, Køber L, Torp-Pedersen C. Efficacy of dofetilide in the treatment of atrial fibrillation-flutter in patients with reduced left ventricular function: a Danish investigations of arrhythmia and mortality on dofetilide (diamond) substudy. *Circulation* 2001; **104**: 292-296 [PMID: 11457747]
67 **Singh S**, Zoble RG, Yellen L, Brodsky MA, Feld GK, Berk M, Billing CB. Efficacy and safety of oral dofetilide in converting to and maintaining sinus rhythm in patients with chronic atrial fibrillation or atrial flutter: the symptomatic atrial fibrillation investigative research on dofetilide (SAFIRE-D) study. *Circulation* 2000; **102**: 2385-2390 [PMID: 11067793]
68 **Wells R**, Khairy P, Harris L, Anderson CC, Balaji S. Dofetilide for atrial arrhythmias in congenital heart disease: a multicenter study. *Pacing Clin Electrophysiol* 2009; **32**: 1313-1318 [PMID: 19691680 DOI: 10.1111/j.1540-8159.2009.02479.x]
69 **Triedman JK**, Bergau DM, Saul JP, Epstein MR, Walsh EP. Efficacy of radiofrequency ablation for control of intraatrial reentrant tachycardia in patients with congenital heart disease. *J Am Coll Cardiol* 1997; **30**: 1032-1038 [PMID: 9316535]
70 **Triedman JK**, Alexander ME, Love BA, Collins KK, Berul CI, Bevilacqua LM, Walsh EP. Influence of patient factors and ablative technologies on outcomes of radiofrequency ablation of intra-atrial re-entrant tachycardia in patients with congenital heart disease. *J Am Coll Cardiol* 2002; **39**: 1827-1835 [PMID: 12039499]
71 **Yap SC**, Harris L, Silversides CK, Downar E, Chauhan VS. Outcome of intra-atrial re-entrant tachycardia catheter ablation in adults with congenital heart disease: negative impact of age and complex atrial surgery. *J Am Coll Cardiol* 2010; **56**: 1589-1596 [PMID: 21029876 DOI: 10.1016/j.jacc.2010.04.061]
72 **Hebe J**, Hansen P, Ouyang F, Volkmer M, Kuck KH. Radiofrequency catheter ablation of tachycardia in patients with congenital heart disease. *Pediatr Cardiol* 2000; **21**: 557-575 [PMID: 11050280 DOI: 10.1007/s002460010134]
73 **Haldar S**, Porta-Sanchez A, Oechslin E, Downar E, Benson L, Nair K. Transbaffle Multielectrode Mapping of Atrial Flutter Post-Double Switch Operation. *J Cardiovasc Electrophysiol* 2016; **27**: 1240-1241 [PMID: 27090771 DOI: 10.1111/jce.12988]
74 **Selvaraj RJ**, Shankar B, Subramanian A, Nair K. Chasing red herrings: making sense of the colors while mapping. *Circ Arrhythm Electrophysiol* 2014; **7**: 553-556 [PMID: 24951573 DOI: 10.1161/CIRCEP.113.001391]
75 **Reich JD**, Auld D, Hulse E, Sullivan K, Campbell R. The Pediatric Radiofrequency Ablation Registry's experience with Ebstein's anomaly. Pediatric Electrophysiology Society. *J Cardiovasc Electrophysiol* 1998; **9**: 1370-1377 [PMID: 9869537]

76 **Roten L**, Lukac P, DE Groot N, Nielsen JC, Szili-Torok T, Jensen HK, Zimmermann M, Delacrétaz E. Catheter ablation of arrhythmias in ebstein's anomaly: a multicenter study. *J Cardiovasc Electrophysiol* 2011; **22**: 1391-1396 [PMID: 21914017 DOI: 10.1111/j.1540-8167.2011.02161.x]

77 **Kannankeril PJ**, Anderson ME, Rottman JN, Wathen MS, Fish FA. Frequency of late recurrence of intra-atrial reentry tachycardia after radiofrequency catheter ablation in patients with congenital heart disease. *Am J Cardiol* 2003; **92**: 879-881 [PMID: 14516900]

78 **de Groot NM**, Atary JZ, Blom NA, Schalij MJ. Long-term outcome after ablative therapy of postoperative atrial tachyarrhythmia in patients with congenital heart disease and characteristics of atrial tachyarrhythmia recurrences. *Circ Arrhythm Electrophysiol* 2010; **3**: 148-154 [PMID: 20194797 DOI: 10.1161/CIRCEP.109.909838]

79 **Lobo RG**, Griffith M, De Bono J. Ablation of Arrhythmias in Patients with Adult Congenital Heart Disease. *Arrhythm Electrophysiol Rev* 2014; **3**: 36-39 [PMID: 26835063 DOI: 10.15420/aer.2011.3.1.36]

80 **Anderson RH,** Becker AE, Arnold R, Wilkinson JL. The conducting tissues in congenitally corrected transposition.*Circulation* 1974; **50**: 911-23

81 **Milo S**, Ho SY, Wilkinson JL, Anderson RH. Surgical anatomy and atrioventricular conduction tissues of hearts with isolated ventricular septal defects. *J Thorac Cardiovasc Surg* 1980; **79**: 244-255 [PMID: 7351848]

82 **A Pilcher Md T**, V Saarel Md E. Anatomic Challenges In Pediatric Catheter Ablation. *J Atr Fibrillation* 2014; **7**: 1054 [PMID: 27957095 DOI: 10.4022/jafib.1054]

83 **Mondésert B**, Abadir S, Khairy P. Arrhythmias in adult congenital heart disease: the year in review. *Curr Opin Cardiol* 2013; **28**: 354-359 [PMID: 23511123 DOI: 10.1097/HCO.0b013e32835fb7c2]

84 **Friedman RA**, Will JC, Fenrich AL, Kertesz NJ. Atrioventricular junction ablation and pacemaker therapy in patients with drug-resistant atrial tachyarrhythmias after the Fontan operation. *J Cardiovasc Electrophysiol* 2005; **16**: 24-29 [PMID: 15673382 DOI: 10.1046/j.1540-8167.2005.03272.x]

85 **Mavroudis C**, Deal BJ, Backer CL, Stewart RD, Franklin WH, Tsao S, Ward KM, DeFreitas RA. J. Maxwell Chamberlain Memorial Paper for congenital heart surgery. 111 Fontan conversions with arrhythmia surgery: surgical lessons and outcomes. *Ann Thorac Surg* 2007; **84**: 1457-1465; discussion 1465-1466 [PMID: 17954046 DOI: 10.1016/j.athoracsur.2007.06.079]

86 **Agnoletti G**, Borghi A, Vignati G, Crupi GC. Fontan conversion to total cavopulmonary connection and arrhythmia ablation: clinical and functional results. *Heart* 2003; **89**: 193-198 [PMID: 12527676]

87 **Koh M**, Yagihara T, Uemura H, Kagisaki K, Hagino I, Ishizaka T, Kitamura S. Optimal timing of the Fontan conversion: change in the P-wave characteristics precedes the onset of atrial tachyarrhythmias in patients with atriopulmonary connection. *J Thorac Cardiovasc Surg* 2007; **133**: 1295-1302 [PMID: 17467444 DOI: 10.1016/j.jtcvs.2006.12.008]

88 **Mavroudis C**, Deal B, Backer CL, Stewart RD. Operative techniques in association with arrhythmia surgery in patients with congenital heart disease. *World J Pediatr Congenit Heart Surg* 2013; **4**: 85-97 [PMID: 23799761 DOI: 10.1177/2150135112449842]

89 **Hoffmann A**, Chockalingam P, Balint OH, Dadashev A, Dimopoulos K, Engel R, Schmid M, Schwerzmann M, Gatzoulis MA, Mulder B, Oechslin E. Cerebrovascular accidents in adult patients with congenital heart disease. *Heart* 2010; **96**: 1223-1226 [PMID: 20639238 DOI: 10.1136/hrt.2010.196147]

90 **Khairy P**. Thrombosis in congenital heart disease. *Expert Rev Cardiovasc Ther* 2013; **11**: 1579-1582 [PMID: 24215186 DOI: 10.1586/14779072.2013.854703]

91 **Mandalenakis Z**, Rosengren A, Lappas G, Eriksson P, Hansson PO, Dellborg M. Ischemic Stroke in Children and Young Adults With Congenital Heart Disease. *J Am Heart Assoc* 2016; **5**: pii: e003071 [PMID: 26908411 DOI: 10.1161/JAHA.115.003071]

92 **Opotowsky AR**, Webb GD. Population-Based Data on Congenital Heart Disease and Stroke. *J Am Heart Assoc* 2016; **5**: pii: e003257 [PMID: 26908414 DOI: 10.1161/JAHA.116.003257]

93 **Feltes TF**, Friedman RA. Transesophageal echocardiographic detection of atrial thrombi in patients with nonfibrillation atrial tachyarrhythmias and congenital heart disease. *J Am Coll Cardiol* 1994; **24**: 1365-1370 [PMID: 7930262]

94 **Gage BF**, Waterman AD, Shannon W, Boechler M, Rich MW, Radford MJ. Validation of clinical classification schemes for predicting stroke: results from the National Registry of Atrial Fibrillation. *JAMA* 2001; **285**: 2864-2870 [PMID: 11401607]

95 **Olesen JB**, Torp-Pedersen C, Hansen ML, Lip GY. The value of the CHA2DS2-VASc score for refining stroke risk stratification in patients with atrial fibrillation with a CHADS2 score 0-1: a nationwide cohort study. *Thromb Haemost* 2012; **107**: 1172-1179 [PMID: 22473219 DOI: 10.1160/TH12-03-0175]

96 **Pisters R**, Lane DA, Nieuwlaat R, de Vos CB, Crijns HJ, Lip GY. A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: the Euro Heart Survey. *Chest* 2010; **138**: 1093-1100 [PMID: 20299623 DOI: 10.1378/chest.10-0134]

97 **Heidendael JF**, Bokma JP, de Groot JR, Koolbergen DR, Mulder BJ, Bouma BJ. Weighing the risks: Thrombotic and bleeding events in adults with atrial arrhythmias and congenital heart disease. *Int J Cardiol* 2015; **186**: 315-320 [PMID: 25838183 DOI: 10.1016/j.ijcard.2015.02.024]

98 **Jensen AS**, Idorn L, Nørager B, Vejlstrup N, Sondergaard L. Anticoagulation in adults with congenital heart disease: The who, the when and the how? *Heart* 2015; **101**: 424-429 [PMID: 25281599 DOI: 10.1136/heartjnl-2014-305576]

99 **Pujol C**, Niesert AC, Engelhardt A, Schoen P, Kusmenkov E, Pittrow D, Ewert P, Kaemmerer H. Usefulness of Direct Oral Anticoagulants in Adult Congenital Heart Disease. *Am J Cardiol* 2016; **117**: 450-455 [PMID: 26725103 DOI: 10.1016/j.amjcard.2015.10.062]

100 **Enriquez AD**, Economy KE, Tedrow UB. Contemporary management of arrhythmias during pregnancy. *Circ Arrhythm Electrophysiol* 2014; **7**: 961-967 [PMID: 25336366 DOI: 10.1161/CIRCEP.114.001517]

101 **Silversides CK**, Harris L, Haberer K, Sermer M, Colman JM, Siu SC. Recurrence rates of arrhythmias during pregnancy in women with previous tachyarrhythmia and impact on fetal and neonatal outcomes. *Am J Cardiol* 2006; **97**: 1206-1212 [PMID: 16616027 DOI: 10.1016/j.amjcard.2005.11.041]

102 **Salam AM**, Ertekin E, van Hagen IM, Al Suwaidi J, Ruys TP, Johnson MR, Gumbiene L, Frogoudaki AA, Sorour KA, Iserin L, Ladouceur M. Atrial fibrillation or flutter during pregnancy in patients with structural heart disease: data from the ROPAC (Registry on Pregnancy and Cardiac Disease). *JACC Clin Electrophysiol* 2015; **1**: 284-92 [DOI: 10.1016/j.jacep.2015.04.013]

103 **Drenthen W**, Pieper PG, Roos-Hesselink JW, van Lottum WA, Voors AA, Mulder BJ, van Dijk AP, Vliegen HW, Yap SC, Moons P, Ebels T, van Veldhuisen DJ; ZAHARA Investigators. Outcome of pregnancy in women with congenital heart disease: a literature review. *J Am Coll Cardiol* 2007; **49**: 2303-2311 [PMID: 17572244 DOI: 10.1016/j.jacc.2007.03.027]

104 **Balci A**, Drenthen W, Mulder BJ, Roos-Hesselink JW, Voors AA, Vliegen HW, Moons P, Sollie KM, van Dijk AP, van Veldhuisen DJ, Pieper PG. Pregnancy in women with corrected tetralogy of Fallot: occurrence and predictors of adverse events. *Am Heart J* 2011; **161**: 307-313 [PMID: 21315213 DOI: 10.1016/j.ahj.2010.10.027]

105 **Hameed A**, Karaalp IS, Tummala PP, Wani OR, Canetti M, Akhter MW, Goodwin I, Zapadinsky N, Elkayam U. The effect of valvular heart disease on maternal and fetal outcome of pregnancy. *J Am Coll Cardiol* 2001; **37**: 893-899 [PMID: 11693767]

106 **Burkart TA**, Conti JB. Cardiac arrhythmias during pregnancy. *Curr Treat Options Cardiovasc Med* 2010; **12**: 457-471 [PMID: 20842567 DOI: 10.1007/s11936-010-0084-7]

107 **Barnes EJ**, Eben F, Patterson D. Direct current cardioversion during pregnancy should be performed with facilities available for fetal monitoring and emergency caesarean section. *BJOG* 2002; **109**: 1406-1407 [PMID: 12504980]

108 **Silversides C**, Spears D. Atrial Fibrillation and atrial flutter

in pregnant women with heart disease. Contributions from the ROPAC Investigators. *JACCEP* 2015; **1**: 284-292 [DOI: 10.1016/j.jacep.2015.07.001]

109 **Knotts RJ**, Garan H. Cardiac arrhythmias in pregnancy. *Semin Perinatol* 2014; **38**: 285-288 [PMID: 25037518 DOI: 10.1053/j.semperi.2014.04.017]

110 **Regitz-Zagrosek V**, Blomstrom Lundqvist C, Borghi C, Cifkova R, Ferreira R, Foidart JM, Gibbs JS, Gohlke-Baerwolf C, Gorenek B, Iung B, Kirby M, Maas AH, Morais J, Nihoyannopoulos P, Pieper PG, Presbitero P, Roos-Hesselink JW, Schaufelberger M, Seeland U, Torracca L; ESC Committee for Practice Guidelines. ESC Guidelines on the management of cardiovascular diseases during pregnancy: the Task Force on the Management of Cardiovascular Diseases during Pregnancy of the European Society of Cardiology (ESC). *Eur Heart J* 2011; **32**: 3147-3197 [PMID: 21873418 DOI: 10.1093/eurheartj/ehr218]

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REVIEW

Influence of cardiac nerve status on cardiovascular regulation and cardioprotection

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Abstract

Neural elements of the intrinsic cardiac nervous system transduce sensory inputs from the heart, blood vessels and other organs to ensure adequate cardiac function on a beat-to-beat basis. This inter-organ crosstalk is critical for normal function of the heart and other organs; derangements within the nervous system hierarchy contribute to pathogenesis of organ dysfunction. The role of intact cardiac nerves in development of, as well as protection against, ischemic injury is of current interest since it may involve recruitment of intrinsic cardiac ganglia. For instance, ischemic conditioning, a novel protection strategy against organ injury, and in particular remote conditioning, is likely mediated by activation of neural pathways or by endogenous cytoprotective blood-borne substances that stimulate different signalling pathways. This discovery reinforces the concept that inter-organ communication, and maintenance thereof, is key. As such, greater understanding of mechanisms and elucidation of treatment strategies is imperative to improve clinical outcomes particularly in patients with comorbidities. For instance, autonomic imbalance between sympathetic and parasympathetic nervous system regulation can initiate cardiovascular autonomic neuropathy that compromises cardiac stability and function. Neuromodulation therapies that directly target the intrinsic cardiac nervous system or other elements of the nervous system hierarchy are currently being investigated for treatment of different maladies in animal and human studies.

Key words: Intrinsic cardiac nervous system; Myocardial ischemia; Ischemic conditioning; Autonomic neuropathy; Coronary blood flow regulation

Core tip: Neural elements within the intrinsic cardiac nervous system are known to transduce sensory inputs from the heart, blood vessels and surrounding organs

to ensure beat-to-beat regulation of cardiac function. Development of autonomic neurophathies in patients with comorbidities compromises clinical outcomes. Myocardial ischemia also significantly affects cardiocytes as well as cardiac neurons; post-ischemic remodelling might affect neuronal function and thereby contribute to cardiac instability. Different protection strategies including ischemic conditioning and neuromodulation interventions that limit neural injury and help maintain cardiovascular function are the subject of ongoing investigations.

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INTRODUCTION

A dense network of parasympathetic, sympathetic and sensory neurons innervates the heart and cardiac conduction system; each population of neurons is distinct with respect to functional requirements of the heart. Increased attention is being focused on the complex anatomy and function of the cardiac neuroaxis and questions abound regarding the manner in which different neuronal populations communicate with each other and between different organ systems. Ardell *et al*[1] recently made the case that the cardiac neural hierarchy functions as a distributive processor with multiple nested feedback control loops that involve peripheral and central aspects of the autonomic nervous system. Remodeling of the cardiac nervous system at morphological and phenotypic levels during disease development is also under scrutiny[2-5]; neural remodeling can cause electrical instability that increases the incidence of arrhythmogenesis. Neuromodulation-based treatments for cardiovascular disease are being investigated as evidenced by the increasing use of diverse cardiac sympathetic decentralization and bioelectric interventions[6]. Herein, we briefly discuss experimental and clinical findings that highlight a role for the intrinsic cardiac nervous system on cardiodynamics. We also discuss mechanisms relevant to diverse protection stratagems. Finally, we focus on autonomic neurophathies that accompany comorbidities (Figure 1). For this review, clinical and basic science reports were searched using MEDLINE, PubMed and Google Scholar with the keywords intrinsic cardiac nervous system, myocardial ischemia-reperfusion injury, heart and kidney disease, cardioprotection, preconditioning and combinations thereof. Findings from our own studies on this, and related subjects were also consulted.

Developmental aspects

Development of the nervous and cardiovascular systems is synchronized during embryogenesis; neural crest cells in the dorsal neural tube form the parasympathetic and sympathetic nervous systems that are important for cardiovascular function. Sympathetic interactions play a part in postnatal regulation of cardiocyte maturation; during life, cardiocytes remain quiescent and heart size increases by cellular hypertrophy[7].

Cardiac neural crest cells furnish mesenchymal cells to the heart and great arteries that are involved in vascular remodeling and development of the cardiac conduction system[8-10]. The sympathetic component of the autonomic nervous system promotes cardiac conduction while the parasympathetic selectively exerts an inhibitory influence[11,12]. The integration of information for neurocardiac regulation involves the neuraxis that comprises the cortex, amygdala and various subcortical structures with an ability to modulate lower-level neurons within the hierarchy (for a detailed explanation see ref.[12]). Principal contacts between preganglionic neurons and the heart occur *via* the vagus nerves[2,13]. Neurons of the autonomic nervous system are: (1) characterized by chemical phenotyping (cholinergic, adrenergic, *etc*.); (2) located within intrathoracic extracardiac ganglia and intrinsic cardiac ganglia[14,15]; and (3) found within atrial epicardium and ganglionated plexi along major vessels and in the ventricular wall[16,17] depending on species[18]. Sensory neurons, interneurons and sensory fibers that originate from the nucleus ambiguus are also located therein[19,20]. Sensory information from all of these peripheral structures is integrated with higher central nervous system centers to coordinate regulation of cardiovascular responses. For example, descending signals from higher brain centers as well as afferent sensory signals from systemic arteries, cardiopulmonary regions and viscera have their first synapse in the nucleus tractus solarius (NTS) found in the dorsomedial region of the medulla[21]. Transmission of afferent inputs from other sources such as skin and skeletal muscle to medullary vasomotor centers occur *via* the spinal cord. Vagal outflow to the heart is mediated by NTS neurons that synapse to preganglionic parasympathetic neurons located in the dorsal motor nucleus. All of these neural inputs to medullary vasomotor centers are involved in autonomic control of the cardiovascular system, for example, the arterial baroreceptor reflex plays a major role in blood pressure homeostasis on a beat-to-beat basis and involves stretch receptors that can be found in the carotid sinus and aortic arch. Accordingly, afferent baroreceptor discharge is relayed from the carotid sinus (*via* glossopharyngeal nerve) and aorta (*via* vagus nerve) to the NTS that stimulates afferent baroreceptor discharge and promotes efferent sympathetic and parasympathetic outflow to the heart and blood vessels, this enables adjustments of cardiac output and vessel resistance and ultimately facilitates return of blood pressure to steady state levels.

CORONARY BLOOD FLOW REGULATION AND MYOCARDIAL PERFUSION

Non-neural mechanisms (humoral, metabolic, mechanical,

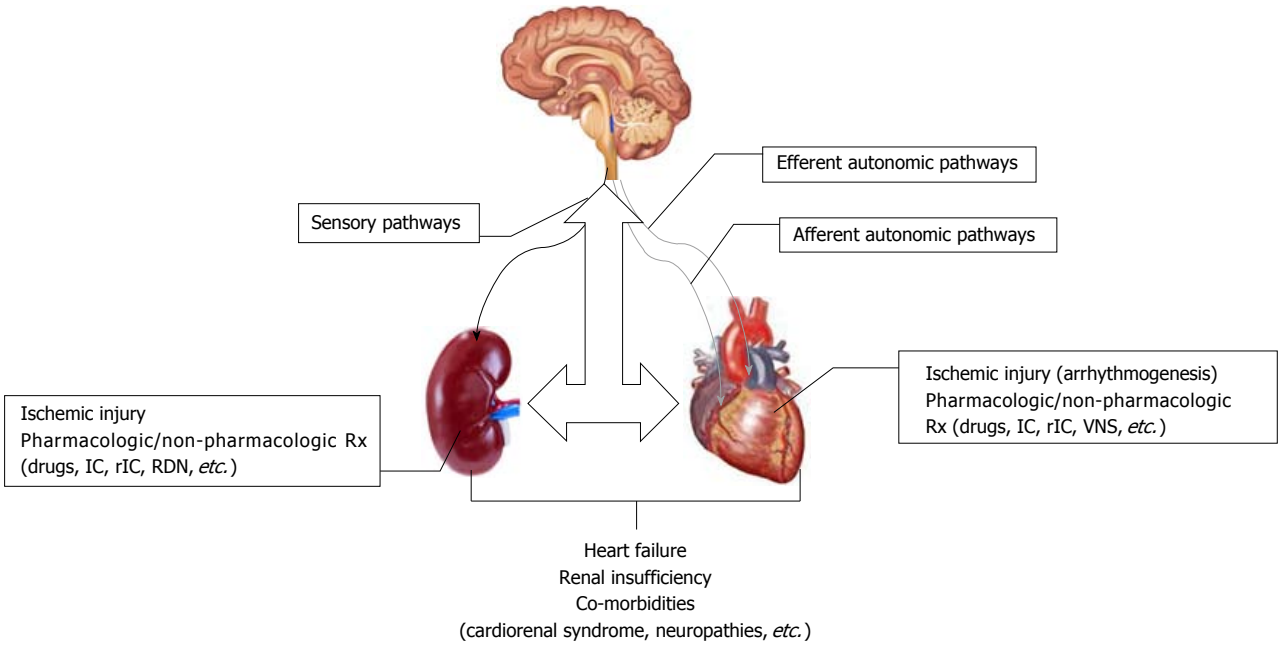

Figure 1 A schematic overview of efferent and afferent autonomic pathways on normal cardiac regulation, they also play a role in arrhythmogenesis caused by ischemic injury. Various pharmacologic/non-pharmacologic interventions that target autonomic pathways (IC: Ischemic conditioning; rIC: Remote IC; VNS: Vagus nerve stimulation) attenuate cardiac or renal symptoms. Sensory pathways are involved in renal regulation; injury (all cause) affects renal function that can be attenuated by different interventions (IC, rIC, RDN: Renal denervation). Inter-organ interactions also directly affect organ function; development of comorbidities is related to pathogenesis of disease in multiple organs (ex. heart-kidneys-brain, *etc.*). Pathology in one organ system can result in significant progression of disease in a distant organ; neuromodulation interventions may be beneficial to these patients.

etc.) that contribute to control of vascular regulation act independently from autonomic neural mechanisms. For example, under normal physiological conditions myocardial perfusion across the ventricles is uniform as long as coronary artery pressure is maintained within the range of autoregulation[22]. Shifts in the lower pressure limit are produced by changes in left ventricular pressure and volume as well as biochemical modifications by a host of endogenous compounds that exercise their effects on myocytes, conduction tissues, vascular smooth muscle, *etc*. The scientific literature that has examined coronary vasoregulation with a focus on cardiac nerve status is relatively sparse. Most studies have concentrated on control of regional cardiodynamics by the intrinsic cardiac nervous system in either normal or pathological conditions.

In healthy individuals during exercise, activation of the sympathetic nervous system stimulates metabolic vasodilatation due to increases in heart rate, cardiac contractility and ventricular work. Direct sympathetic stimulation of coronary vessels induces either vasoconstriction or vasodilatation depending on activation of either α-, or β-adrenoreceptors, or vessel size. For example, large coronary vessels (> 100 μm) constrict when exposed to norepinephrine whereas small coronary vessels relax[23]; vasodilatation in arterioles permits coordination of oxygen delivery to myocardial oxygen demand[24]. On the other hand, simultaneous vasoconstriction in medium and large coronary arteries mediated by activation of α-adrenoreceptors helps to preserve subendocardial blood flow when oxygen demand increases. In a canine study, we examined myocardial perfusion following injection of select neuropeptides into active loci of the intrinsic cardiac nervous system and documented significant coronary vasodilatation secondary to increased myocardial metabolism and oxygen demand[25]. We also examined whether intact cardiac nerves were critical for coronary blood flow autoregulation; results confirmed a role for intrinsic cardiac neurons in autoregulatory control and myocardial perfusion even after ablation of extracardiac nerves from central nervous system control[26]. Ablation of external neuronal inputs to the heart also results in reduced myocardial efficiency that is consistent with impaired glucose utilization and depletion of cardiac catecholamine levels[27,28]; the latter directly affect myocardial oxygen demand[29-31]. Other animal studies reported that heterogeneity of myocardial perfusion is similar in innervated and denervated hearts[32-34]; possible explanations include: (1) the fact that regional denervation has little effect on vascular α-adrenergic receptors (in part due to circulating catecholamines); or (2) preserved neural modulation and autoregulation at different levels of the microcirculation across the ventricular wall[35,36].

Diverse central and peripheral elements within the cardiac nervous system act in sync to regulate cardiac function[20,37]; direct stimulation of intracardiac neurons occurs through central efferent neuronal inputs from the vagi or stellate ganglia[38]. G-protein coupled receptors are known to regulate cardiac function (see recent review by Capote *et al*[39] on structure, function and signalling pathways solicited by G-protein-coupled receptors in the heart). Control of heart rate requires intricate

coordination between β-adrenergic and muscarinic cholinergic receptors found throughout the cardiac conduction system. Cardiac contraction controlled by β-adrenergic receptors are found in myocyte membranes while cardiac structure and morphology are coordinated by angiotensin Ⅱ type 1 receptors in fibroblast and both endothelial cell and myocyte membranes[40,41]. Highly distinct processing capabilities of intracardiac neurons allow this complex network to respond to multiple inputs from all cardiac regions and major vessels near the heart. Disruption of these control networks by diverse cardiac pathologies ultimately increases the potential for sudden cardiac death[42-45].

MYOCARDIAL ISCHEMIA

Myocardial ischemia significantly influences cardiocytes as well as local and remote neurons that are involved in regulation of cardiac function[1,46]; the survival threshold of intra-/extra-cardiac sympathetic/parasympathetic neurons during development of coronary artery disease is not well established. However, viable nerves that course over an infarcted region tend to remain so oxygen and energy needs are fulfilled by an independent blood supply from extracardiac sources[47]. Reorganization of cardiocytes and nerves during development of diverse cardiac pathologies could occur in response to shifts of cardiac demand and function[3,48]. Mechanisms involved in the pathogenesis of cardiac dysfunction are multifactorial; a short list of possible factors include cardiac substrates, neural/cardiocyte interface, hormonal influences, inflammation and reflex responses between intra- and extra-cardiac nervous systems and their interactions with higher center neurons. Cardiocytes and cardiac neurons conceivably share common pathways for survival but this remains to be proven.

In the setting of transient ischemia, intact cardiac nerves are believed to play a key role on post-ischemic restoration of cardiac function[49]. Direct ischemic effects include progressive neuronal dysfunction and regional nerve terminal sprouting which ultimately diminishes local sensory and motor neurite function[50,51]. Indirect effects that modulate local neurite function are caused by local release of a host of endogenous chemicals (purinergic agents, peptides, hydroxyl radicals, *etc*.) that also affect neuronal function. Post-ischemic remodeling of cardiac neural networks could promote conflicts between central and peripheral reflexes that increases the risk of autonomic imbalances, arrhythmogenesis and sudden cardiac death[3,15,37,52]. A recent position paper by Ardell *et al*[1] discussed the significance of remodeling of the cardiac neuronal hierarchy to cardiac arrhythmia induction. In addition, inotropic stimulation is deleterious to myocyte survival as it occasions an imbalance between oxygen demand and supply (*i.e*., increased oxygen demand with limited coronary vascular reserve)[49,53].

Acute occlusion of a coronary artery produces distinct alterations of myocyte pathology that lead to cell death unless blood flow is restored to the affected myocardium, a transmural gradient of cell death occurs in relation to the duration of ischemia and degree of blood perfusion *via* coronary collateral vessels to the underperfused myocardium[54]. In animal models, necrosis is generally fully developed by 6 h after which tissue salvage is not possible (this time frame may not be the same for human myocardium) with currently available interventions. In addition, early restoration of blood flow to an infarct-related coronary vessel could cause "reperfusion injury" in already damaged or otherwise affected myocytes[55]. The physiopathology of ischemic, or reperfusion injury has been reviewed and discussed over the past several decades[56-59]; however, less attention has focused on the ability of the cardiac nervous system to accommodate the stress of ischemic, or reperfusion injury. Post-ischemic changes in peptide expression due to release of inflammatory cytokines combined with nerve damage could affect neuropeptide production in sympathetic cardiac neurons. In one study, Habecker *et al*[60] documented extensive axon damage after infarction; they also reported a significant increase of galanin (promotes regeneration of sensory neurons[61]) in cardiac sympathetic neurons in the left ventricle. These findings indicate that cardiac sympathetic neurons retain a certain capability to respond to nerve growth factor which is increased during ischemia-reperfusion[62].

While sympathetic dysinnervation has been reported secondary to myocardial infarction, the injury threshold of sympathetic and parasympathetic cardiac neurons within the ischemic region has not been established[63,64]. Several studies have documented that sympathetic impairment could exceed the area of underperfusion and necrosis[65,66]. Ischemic stress stimulates release of autocoids such as adenosine and bradykinin, along with nitric oxide and reactive oxygen species that can trigger cellular signal transduction pathways. These compounds can initiate responses in somata and axons within the intrinsic cardiac nervous system[37]. Indeed, oxidative stress, changes in growth factor expression and inflammatory cytokines released within the heart and vasculature contribute to neuronal remodelling[2,3,5,67]. As mentioned earlier, the regenerative capacity of cardiocytes is limited[68]; cardiocytes withdraw from the cell cycle early after birth and subsequently remain quiescent. Transition from proliferative to hypertrophic growth corresponds to the period of sympathetic growth into the heart tissues; *in vitro* studies with neonatal cardiocytes cultivated in the presence of innervating sympathetic fibers showed significant cellular proliferation[69] thereby confirming that early sympathetic signalling plays a role. In earlier *in vitro* studies, Horackova *et al*[70] reported that adult ventricular myocytes co-cultured with intrathoracic neurons retained similar structural properties to those observed *in vivo*; cardiocytes and intrinsic cardiac neurons that were cultured alone displayed a variety of morphologies (unipolar, bipolar, multipolar).

Sympathetic regulation might also be involved in myocyte regeneration following ischemia, or reperfusion, injury; however, disruption of peripheral nerves inhibits

regeneration[71,72]. Chemical sympathectomy blocks early regeneration of damaged myocytes and increases tissue scarring[73]. Though additional studies are necessary, available data support the role of the intact cardiac nervous system on cardiocyte development and proliferation. On the other hand, post-ischemic regeneration and remodeling of the cardiac nervous system also merits further consideration and investigation. Rajendran *et al*[46] recently evaluated post-ischemic changes in neural signalling in a porcine model; they presented a "cardiac electroneurogram" between injured and adjacent non-injured myocardial tissue and reported: (1) that different intra-cardiac ganglia undergo morphological and phenotypic remodeling depending on the site of injury; (2) attenuation of afferent neural signals from the infarcted region to intra-cardiac neurons (activity in border and remote regions is apparently preserved); (3) maintenance of autonomic efferent inputs to the intrinsic cardiac nervous system; (4) augmented transduction capacity of convergent intrinsic cardiac local circuit neurons; and (5) reduced network connectivity within the intrinsic cardiac nervous system. The heterogeneity of afferent neural signals probably results from the presence of a "neural sensory border zone" (*i.e*., analogous to the so-called myocardial border zone) caused by scar formation during post-ischemic myocardial healing. This infarct-induced asymmetry of afferent inputs probably contributes to reflex activation of the autonomic nervous system; recent findings from Wang *et al*[74] using resiniferatoxin (a potent agonist of transient receptor potential vanilloid 1) showed reductions in cardiac afferent nociceptive signalling, and sympatho-excitation along with preserved cardiac function in rat hearts.

The role of intact cardiac nerves in modulating responses to ischemia and post-ischemic ventricular function has been studied in a variety of experimental models. In a cardiac decentralized porcine model subject to acute coronary artery stenosis Huang *et al*[49] reported significant ventricular dysfunction accompanied by patchy subendocardial necrosis; they proposed that the impaired recovery of left ventricular function is mediated by nitric oxide (NO) and reactive oxygen species (ROS). Cardiac nerves may help to attenuate production of ROS and/or prevent conversion of NO to peroxynitrite (*via* release of still unknown mediators/scavengers); neurotransmitters from cardiac nerves could stimulate or upregulate different isoforms of nitric oxide synthase (*i.e.*, endothelial, neural)[75]. Myocardial perfusion-function relations are not altered by cardiac denervation[49]; this can be partly explained by the similarity between intact innervated and denervated hearts with regard to determinants of myocardial oxygen demand. In a recent study, we reported no significant change in coronary vascular reserve (intact cardiac nerves *vs* acute decentralized) in a canine model of ischemia-reperfusion injury[76]; these findings concur with most[77,78], but not all, earlier studies[79]. Of particular note is that protection against ischemic injury occurred even when affected myocardium was disconnected from central command; this suggests that local intrinsic cardiac neurons share common protection pathways to delay progression of cellular necrosis. Neurotransmitters that originate from cardiac nerves or intrinsic cardiac neurons might stimulate release of endogenous compounds that activate intracellular signalling pathways involved in cytoprotection; they could also inhibit peroxynitrite formation by modulating activation of various nitric oxide synthase isoforms. Indeed, many questions remain regarding the role of intact cardiac nerves within the context of cardioprotection against ischemia-reperfusion injury.

Myocardial ischemia also results in excessive activation of extracardiac cholinergic and adrenergic inputs of local circuit neurons within the intrinsic cardiac nervous system[38,80] that initiate cardiac arrhythmias[81]. A novel treatment for suppression of ventricular arrhythmias and treatment of refractory angina pectoris in current use in preclinical and clinical studies is spinal cord stimulation[80,82-84]; this intervention alters peripheral ganglia neural processing along the neural end-organ interface[85,86] and transduces neural signals to higher centers *via* the spinal cord[1,87,88]. Spinal cord stimulation influences autonomic reflexes within the neuroaxis and stimulates discharge of neuromodulators that limit release of select neurotransmitters and alter basal activity of sympathetic preganglionic neurons[89,90]. Intermittent spinal cord stimulation is suggested to stimulate neural memory and may be used for management of cardiac control and angina[91]; this could be akin to "electrical conditioning" and may be useful to limit cellular injury caused by ischemia. Vagus nerve stimulation is also being used to protect against ischemic injury and its consequences[92]; vagus nerve stimulation activates a host of signalling pathways and inhibits release of pro-inflammatory cytokines (see Ardell *et al*[1] for an up-to-date review). Vagus nerve stimulation might also affect myocardial energetics and maintain the equilibrium between energy supply and demand in the failing heart[93,94]. Interventions using vagus nerve stimulation favourably modulate cardiac disease as well as arrhythmogenesis; in several clinical studies this non-pharmacologic treatment is safe and well tolerated and is documented to improve cardiodynamics in patients with compromised ventricular function[95,96].

MYOCARDIAL PROTECTION

Sympathetic and parasympathetic nerves located near cardiocytes permit rapid crosstalk between cell types that may, or may not, activate cytoprotective pathways. Ischemic conditioning was first described by Murry *et al*[97] in 1986 in barbiturate-anesthetized dogs subjected to repeated episodes of sublethal coronary occlusion/reperfusion in advance of a prolonged period of acute ischemia. To date, ischemic conditioning has been reported to delay development of cellular necrosis in all organs examined in animals and in humans[98]; two distinct windows of cellular protection have been described but the causative mechanism(s) remain unanswered. The reader is referred to a recent review that summarizes

research into this cytoprotective intervention over the past 30 years[99]. Interestingly, Kudej *et al*[100] showed that intact cardiac nerves were not required for first window protection in a porcine ischemia-reperfusion injury model; however, the presence of functional cardiac nerves was considered essential for development of second window protection. This delayed protection could occur through α_1-adrenergic receptor pathways mediated by iNOS and COX-2[101].

A host of conditioning strategies have been described in animal and clinical studies; however, the potential to translate conditioning-mediated protection in patients remains controversial[102,103]. Remote conditioning was first described in dogs subject to acute coronary occlusion and was referred to as "preconditioning at a distance"[104]. In that study, animals were subject to repetitive periods of non-lethal ischemia of the left circumflex artery vascular bed before exposure to a prolonged occlusion of the left anterior descending coronary artery; results demonstrated that a cytoprotective factor could be activated, produced, or transported from the heart or elsewhere to affected tissues to afford protection. Since the publication of these key findings numerous studies using remote conditioning either before, during or after coronary occlusion have been reported[105-109] but the mechanisms involved have not been established. An important but unanswered question that persists is how the protective signals are transferred from distant tissues to the target organ. Various hypotheses (not mutually exclusive) including: (1) communication *via* blood or perfusate borne humoral factors; (2) communication by neuronal stimulation and transmission; and (3) communication by systemic alteration of circulating immune cells have been proposed[106,110,111]. Intrinsic neural loops in the heart process sensory information from the myocardium that modulate efferent autonomic output from the intrinsic cardiac ganglia even in the absence of input from the central nervous system[37,38,93,112]. Transmission of sensory messages within intrinsic cardiac ganglia is regulated by release of acetylcholine into the synaptic cleft; nerve impulses are initiated by acetylcholine that activates specific receptors in post-ganglionic nerves[112-114]. The risk of injury or remodeling of these neural loops escalates during myocardial ischemia; studies with pharmacologic ganglionic blockade document abolition of remote conditioning-mediated cytoprotection and suggest that protective signals could transfer between organs *via* neural pathways[112,115-117]. Early preclinical studies in different experimental models (including heart failure) reported positive results with vagal nerve stimulation (VNS) with respect to ventricular remodeling, ejection fraction and biomarker levels[118-120]. In patients with advanced heart failure, VNS reportedly attenuates left ventricular contractile dysfunction[121] and may reduce ischemic injury[122-124]. Clinical studies show that diminished heart-rate responses and depressed sensitivity of vagal reflexes are associated with poor cardiovascular outcomes and cardiac-related mortality[125-127]. Smith *et al*[127] recently reviewed efficacy of VNS for hypertension and heart failure in several small, randomized clinical trials (ANTHEM-HF, NECTAR-HF, INOVATE-HF, *etc*.) and concluded that further studies are required; VNS titration studies are also needed to validate potential clinical benefits of these interventions[128]. Stimulation of vagal nerves activate a host of signalling pathways *via* increased release of acetylcholine that activates downstream receptors (cholinergic, muscarinic, *etc*.) to impact cardiodynamics and could also promote myocyte resistance to stress by improving myocyte energetics[93]. Cross-talk between humoral mediators and neural pathways could also produce cytoprotection by stimulation of local afferent nerves[129,130]; but it remains unclear whether intact, functional nerves are required to assure conditioning-mediated cytoprotection[131,132]. On the basis of data showing that intact sensory innervation of peripheral ischemic tissue is essential to remote conditioning protection, Mastitskaya *et al*[133] proposed a "remote preconditioning reflex" that requires sensory input from remote ischemic tissue; recruitment of vagal pre-ganglionic neurons within the dorsal motor nucleus of the vagus nerve was considered to be critical for cytoprotection. While this data does not negate the concept that humoral factors are required for protection by remote conditioning, they strongly suggest that functional neurons within the parasympathetic nervous system are critical[134,135]. Bilateral vagotomy reportedly abolished protection afforded by remote conditioning[136]. On the other hand, findings from our laboratory (summarized in Figure 2) documented significant protection against ischemic injury independent of intact extrinsic cardiac nerves (note the similarity between groups with respect to reduction in infarct size) regardless of the conditioning protocol[76,137]. Briefly, in those studies isoflurane anesthetized dogs underwent remote conditioning (4 × 5-min renal artery occlusion/reperfusion) combined with/without treatment with the autonomic ganglionic blocker, hexamethonium (HEXA; 20 mg/kg, *IV*) or acute cardiac decentralization (DCN). Additional experiments were performed in dogs subject to classical preconditioning either before or after DCN. Based on these findings we suggested that neural pathways might not directly influence ischemic conditioning (either classical or remote) mediated cardioprotection. Moreover, others have brought forward the view that intact connections between the heart and central nervous system are not necessary for remote conditioning-mediated cardioprotection as long as recruitable parasympathetic neurons within a target organ can be activated. Use of remote conditioning as a potential therapeutic intervention for organ protection in man continues to merit investigation because it is non-invasive, cost-effective and easily applicable; however, the period for successful application of this intervention has yet to be determined and clinical strategies aimed at reducing myocardial damage by ischemic conditioning have been unsuccessful. While cellular protection by ischemic conditioning is possible in the presence of comorbidities, a stronger triggering stimulus appears necessary to assure cytoprotection[138].

Understanding bidirectional interactions between

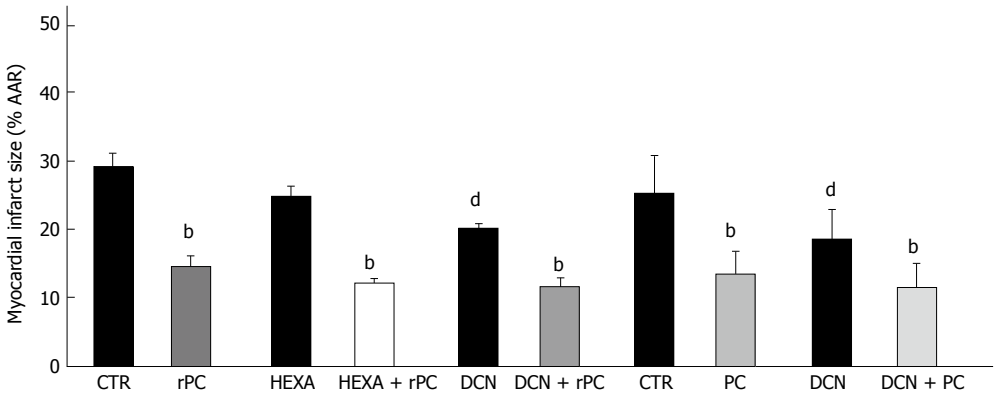

Figure 2 Myocardial infarct size (% anatomic area at risk: AAR) is shown for different study groups subject to ischemia-reperfusion injury. Data are means ± 1SD; $^{b}P \leqslant 0.01$ *vs* respective control (CTR), HEXA (hexmethonium; 20 mg/kg, *IV*), or DCN (acute cardiac decentralized) group; $^{d}P \leqslant 0.01$ *vs* CTR groups. Group differences determined by ANOVA. PC: Ischemic preconditioning; rPC: Remote preconditioning. Data reported in earlier studies from our laboratory[76,137].

elements of the nervous system and its remodeling during evolution of different comorbidities (senescence, kidney dysfunction, diabetes, *etc*.) is essential to help in the development of strategies to delay progression of disease not only in the heart but also in other organs. For instance, autonomic neuropathies defined by abnormalities of the sympathetic and parasympathetic nervous systems could be responsible for significant morbidity and mortality in patients; cardiovascular events are considered a primary risk factor for mortality. Cardiovascular autonomic dysfunction is the result of complex interplay between vascular, neural, cardiac, paracrine and endocrine entities; the outcome is tissue injury that compromises integrity of cardiac reflexes.

HEART FAILURE

Heart failure subsequent to cardiac injury or chronic stress causes significant loss of contractile efficacy. Investigations into the role of autonomic imbalance between sympathetic and parasympathetic nervous systems and its contribution to pathogenesis of heart failure is ongoing for more than 25 years. Altered autonomic function also plays a role in other cardiac interrelated conditions such as hypertension, myocardial ischemia, cardiac arrhythmogenesis and sudden cardiac death[48], see recent review by Florea and Cohn[139]. Dynamic interactions between cardiocytes and compensatory neurohumoral mechanisms allow the heart to maintain cardiac output; stimulation of the adrenergic nervous and renin-angiotensin-aldosterone systems along with activation of cytokines play a critical role to prevent progressive worsening of cardiac function associated with heart failure[140,141]. Lymperopoulos *et al*[141] recently reviewed: (1) the actions of neurotransmitters on cell surface adrenergic and G-protein-coupled receptors; and (2) adrenergic receptor polymorphisms in the physiopathology of heart failure. They concluded that activation of the autonomic nervous system plays a critical role in compensatory responses to progressive cardiac dysfunction; however, excessive activation of these compensatory pathways could accelerate development of heart failure. In addition, they examined various therapeutic approaches (*i.e.*, sympathomimetic drugs, activation of cardiac parasympathetic nervous system, increasing β-adrenergic receptor function using novel G-protein-coupled receptor blockade, *etc*.).

CHRONIC KIDNEY DISEASE AND NEUROPATHY

Physiopathology of chronic kidney disease (CKD) is complex and results either from a primary renal disorder or from multisystem disorders related to various comorbidities such as diabetes. Indeed, diabetes is considered to be the most common cause of CKD in patients. Neurological derangements are a common occurrence in CKD[142]. The spectrum of CKD ranges from mild kidney damage (largely asymptomatic) to end-stage renal disease (potentially fatal); neurological complications that include cognitive dysfunction, stroke, as well as peripheral and autonomic neuropathy can markedly affect clinical outcomes[143]. Accumulation of urea, creatinine, parathyroid hormone in high concentrations provide a biochemical milieu that rapidly produces neurological dysfunction; however, most symptoms can be reversed with treatments such as hemodialysis[144]. Mechanisms responsible for increased cardiovascular risk in patients with CKD are multifactorial and include hypertension and diabetes[145], along with increased oxidative stress, decreased bioavailability of nitric oxide, inflammation, abnormal calcium and phosphorous metabolism, overstimulation of the sympathetic nervous system, *etc*.[146-148]. Anemia is another major complication associated with both CKD and diabetes[149]; the latter may be present before overt evidence of symptoms of renal impairment[150].

Essential structures of the kidneys (renal vessels, tubules, juxtaglomerular apparatus, *etc*.) are richly innervated. Renal afferent nerves transmit sensory information *via* chemo- and mechano-receptors to higher centers within the brain[151,152], to maintain water retention, sodium reabsorption and blood flow. These

nerves might also play a role in renal inflammation and injury; suggested mechanisms include β-adrenergic receptor activation, release of neuropeptides (neuropeptide Y, vasoactive intestinal polypeptide, substance P, *etc*.), renin release from juxtaglomerular cells (increases plasma angiotensin Ⅱ levels) and other pro-inflammatory cytokines (tumor necrosis factor, IL-1β, *etc*.).

Autonomic dysfunction is prevalent (> 60%) in CKD patients and is associated with vascular calcification, cardiac arrhythmias and sudden cardiac death[153]. Reduced sensitivity to baroreceptors in the vessel wall caused by autonomic dysfunction can modulate cardiac regulation and contribute to intradialytic hypotension (*i.e.*, no increase in heart rate to compensate the decrease in arterial pressure)[154]; these symptoms can be corrected with pharmaceuticals or, if necessary, renal transplantation.

DIABETIC AUTONOMIC NEUROPATHY

Autonomic dysfunction is a recognized complication of diabetes mellitus; diverse contributory mechanisms to increased mortality includes medial hyperplasia at baroreceptor sites, impaired cardiac vagal function, left ventricular hypertrophy and endothelial dysfunction[155] due in part to oxidative stress and reduced availability of nitric oxide which can affect sympathetic nerve activity[156]. Endothelial nitric oxide synthesis is known to be defective in insulin resistant states and is a central factor to neuronal abnormalities during metabolic syndrome (increases cardiovascular risk to some extent due to sympathetic activation)[155]. Insulin also plays a key role in nitric oxide and autonomic nervous system interactions and is involved in regulation of peripheral vascular tone and arterial blood pressure. Significant evidence shows that nitric oxide is critical to the vasodilator actions of insulin[157]; sympathectomy and autonomic failure can severely limit insulin-induced vasodilatation in patients[158]. Vulnerability to lethal arrhythmias in diabetic patients with autonomic dysfunction is also elevated[159]. Cardiac autonomic dysfunction may occur more frequently when diabetes is coupled with micro albuminuria caused by microvascular damage and endothelial dysfunction[160-162]; however, it was reported in the Hoorn Study that cardiovascular autonomic dysfunction and microalbuminuria were independently associated with mortality[163]. Additionally, in that study the presence of cardiovascular autonomic dysfunction doubled the 9-year mortality risk[155,164]; the ACCORD study also confirmed a significantly higher rate of mortality in patients with autonomic dysfunction[165].

CONCLUSION

Impaired sympathetic and parasympathetic nervous system regulation contributes to organ dysfunction and leads to significant morbidity and mortality particularly in patients with comorbidities. Early detection and management of these patients could markedly reduce adverse effects and thereby affect clinical outcomes. Prospectively, autonomic dysfunction develops because of damage at multiple sites within organs but pathogenesis remains to be clarified. Cardiovascular autonomic dysfunction, for instance, reflects compromised interactions between vascular, neural, cardiac, inflammatory, paracrine and endocrine mechanisms. Restoration of autonomic equilibrium in animal and clinical studies using either pharmacologic or non-pharmacologic interventions is currently possible. Further investigations in neurocardiology should continue to provide important findings apropos connections between cardiac and neurohumoral control systems and thereby allow continued development of clinically relevant opportunities for neuroscience-based treatments.

REFERENCES

1 **Ardell JL**, Andresen MC, Armour JA, Billman GE, Chen PS, Foreman RD, Herring N, O'Leary DS, Sabbah HN, Schultz HD, Sunagawa K, Zucker IH. Translational neurocardiology: preclinical models and cardioneural integrative aspects. *J Physiol* 2016; **594**: 3877-3909 [PMID: 27098459 DOI: 10.1113/JP271869]

2 **Kimura K**, Ieda M, Fukuda K. Development, maturation, and transdifferentiation of cardiac sympathetic nerves. *Circ Res* 2012; **110**: 325-336 [PMID: 22267838 DOI: 10.1161/CIRCRESAHA.111.257253]

3 **Fukuda K**, Kanazawa H, Aizawa Y, Ardell JL, Shivkumar K. Cardiac innervation and sudden cardiac death. *Circ Res* 2015; **116**: 2005-2019 [PMID: 26044253 DOI: 10.1161/CIRCRESAHA.116.304679]

4 **Habecker BA**, Anderson ME, Birren SJ, Fukuda K, Herring N, Hoover DB, Kanazawa H, Paterson DJ, Ripplinger CM. Molecular and cellular neurocardiology: development, and cellular and molecular adaptations to heart disease. *J Physiol* 2016; **594**: 3853-3875 [PMID: 27060296 DOI: 10.1113/JP271840]

5 **Gardner RT**, Ripplinger CM, Myles RC, Habecker BA. Molecular Mechanisms of Sympathetic Remodeling and Arrhythmias. *Circ Arrhythm Electrophysiol* 2016; **9**: e001359 [PMID: 26810594 DOI: 10.1161/CIRCEP.115.001359]

6 **Shivkumar K**, Ardell JL. Cardiac autonomic control in health and disease. *J Physiol* 2016; **594**: 3851-3852 [PMID: 27417670 DOI: 10.1113/JP272580]

7 **Ahuja P**, Perriard E, Pedrazzini T, Satoh S, Perriard JC, Ehler E. Re-expression of proteins involved in cytokinesis during cardiac hypertrophy. *Exp Cell Res* 2007; **313**: 1270-1283 [PMID: 17316608 DOI: 10.1016/j.yexcr.2007.01.009]

8 **Stoller JZ**, Epstein JA. Cardiac neural crest. *Semin Cell Dev Biol* 2005; **16**: 704-715 [PMID: 16054405 DOI: 10.1016/j.semcdb.2005.06.004]

9 **Creazzo TL**, Godt RE, Leatherbury L, Conway SJ, Kirby ML. Role of cardiac neural crest cells in cardiovascular development. *Annu Rev Physiol* 1998; **60**: 267-286 [PMID: 9558464 DOI: 10.1146/annurev.physiol.60.1.267]

10 **Coskun V**, Lombardo DM. Studying the pathophysiologic connection between cardiovascular and nervous systems using stem cells. *J Neurosci Res* 2016; **94**: 1499-1510 [PMID: 27629698 DOI: 10.1002/jnr.23924]

11 **Pardini BJ**, Lund DD, Schmid PG. Organization of the sympathetic postganglionic innervation of the rat heart. *J Auton Nerv Syst* 1989; **28**: 193-201 [PMID: 2628461]

12 **Wallis D**, Watson AH, Mo N. Cardiac neurones of autonomic ganglia. *Microsc Res Tech* 1996; **35**: 69-79 [PMID: 8873060 DOI: 10.1002/(SICI)1097-0029(19960901)35:1<69::AID-JEMT6>3.0.CO;2-N]

13 **Hasan W**. Autonomic cardiac innervation: development and adult plasticity. *Organogenesis* 2013; **9**: 176-193 [PMID: 23872607 DOI: 10.4161/org.24892]

14 **Cardinal R**, Pagé P, Vermeulen M, Ardell JL, Armour JA. Spatially divergent cardiac responses to nicotinic stimulation of ganglionated plexus neurons in the canine heart. *Auton Neurosci* 2009; **145**: 55-62 [PMID: 19071069 DOI: 10.1016/j.autneu.2008.11.007]

15 **Kember G**, Armour JA, Zamir M. Neural control hierarchy of the heart has not evolved to deal with myocardial ischemia. *Physiol Genomics* 2013; **45**: 638-644 [PMID: 23695889 DOI: 10.1152/physiolgenomics.00027.2013]

16 **Randall WC**, Milosavljevic M, Wurster RD, Geis GS, Ardell JL. Selective vagal innervation of the heart. *Ann Clin Lab Sci* 1986; **16**: 198-208 [PMID: 2872849]

17 **Singh S**, Johnson PI, Lee RE, Orfei E, Lonchyna VA, Sullivan HJ, Montoya A, Tran H, Wehrmacher WH, Wurster RD. Topography of cardiac ganglia in the adult human heart. *J Thorac Cardiovasc Surg* 1996; **112**: 943-953 [PMID: 8873720 DOI: 10.1016/S0022-5223(96)70094-6]

18 **Kuder T**, Nowak E, Szczurkowski A, Kuchinka J. A comparative study on cardiac ganglia in midday gerbil, Egyptian spiny mouse, chinchilla laniger and pigeon. *Anat Histol Embryol* 2003; **32**: 134-140 [PMID: 12823098]

19 **Ai J**, Epstein PN, Gozal D, Yang B, Wurster R, Cheng ZJ. Morphology and topography of nucleus ambiguus projections to cardiac ganglia in rats and mice. *Neuroscience* 2007; **149**: 845-860 [PMID: 17942236 DOI: 10.1016/j.neuroscience.2007.07.062]

20 **McAllen RM**, Salo LM, Paton JF, Pickering AE. Processing of central and reflex vagal drives by rat cardiac ganglion neurones: an intracellular analysis. *J Physiol* 2011; **589**: 5801-5818 [PMID: 22005679 DOI: 10.1113/jphysiol.2011.214320]

21 **Thomas GD**. Neural control of the circulation. *Adv Physiol Educ* 2011; **35**: 28-32 [PMID: 21385998 DOI: 10.1152/advan. 00114.2010]

22 **Rouleau J**, Boerboom LE, Surjadhana A, Hoffman JI. The role of autoregulation and tissue diastolic pressures in the transmural distribution of left ventricular blood flow in anesthetized dogs. *Circ Res* 1979; **45**: 804-815 [PMID: 498444]

23 **Chilian WM**, Layne SM, Eastham CL, Marcus ML. Heterogeneous microvascular coronary alpha-adrenergic vasoconstriction. *Circ Res* 1989; **64**: 376-388 [PMID: 2563238]

24 **Tune JD**, Gorman MW, Feigl EO. Matching coronary blood flow to myocardial oxygen consumption. *J Appl Physiol* (1985) 2004; **97**: 404-415 [PMID: 15220323]

25 **Kingma JG**, Armour JA, Rouleau JR. Chemical modulation of in situ intrinsic cardiac neurones influences myocardial blood flow in the anaesthetised dog. *Cardiovasc Res* 1994; **28**: 1403-1406 [PMID: 7954653]

26 **Rouleau JR**, Simard D, Rodrigue N, Blouin A, Kingma JG. Myocardial blood flow after chronic cardiac decentralization in anesthetized dogs: effects of ACE-inhibition. *Auton Neurosci* 2002; **97**: 12-18 [PMID: 12036181]

27 **Drake AJ**, Papadoyannis DE, Butcher RG, Stubbs J, Noble MI. Inhibition of glycolysis in the denervated dog heart. *Circ Res* 1980; **47**: 338-345 [PMID: 6773695]

28 **van der Vusse GJ**, Dubelaar ML, Coumans WA, Seymour AM, Clarke SB, Bonen A, Drake-Holland AJ, Noble MI. Metabolic alterations in the chronically denervated dog heart. *Cardiovasc Res* 1998; **37**: 160-170 [PMID: 9539870]

29 **Butcher RG**, Drake-Holland AJ, Wanless RB, Papadoyannis DE, Noble MI. Effect of lack of noradrenaline on myocardial oxygen consumption in denervated dog hearts. *Cardiovasc Res* 1987; **21**: 515-520 [PMID: 2824057]

30 **Vatner DE**, Lavallee M, Amano J, Finizola A, Homcy CJ, Vatner SF. Mechanisms of supersensitivity to sympathomimetic amines in the chronically denervated heart of the conscious dog. *Circ Res* 1985; **57**: 55-64 [PMID: 2988820]

31 **Vergroesen I**, Merkus D, van Teeffelen JW, Dankelman J, Spaan JA, van Wezel HB, Noble MI, Drake-Holland AJ. Chronic cardiac denervation affects the speed of coronary vascular regulation. *Cardiovasc Res* 1999; **44**: 615-622 [PMID: 10690295]

32 **Rimoldi OE**, Drake-Holland AJ, Noble MI, Camici PG. Basal and hyperaemic myocardial blood flow in regionally denervated canine hearts: an in vivo study with positron emission tomography. *Eur J Nucl Med Mol Imaging* 2007; **34**: 197-205 [PMID: 16951953 DOI: 10.1007/s00259-006-0233-0]

33 **Alders DJ**, Cornelussen RN, Prinzen FW, Specht PA, Noble MI, Drake-Holland AJ, de Kanter FJ, van Beek JH. Regional sympathetic denervation affects the relation between canine local myocardial blood flow and oxygen consumption. *Exp Physiol* 2007; **92**: 541-548 [PMID: 17303649 DOI: 10.1113/expphysiol.2006.036228]

34 **Chilian WM**, Ackell PH. Transmural differences in sympathetic coronary constriction during exercise in the presence of coronary stenosis. *Circ Res* 1988; **62**: 216-225 [PMID: 2827908]

35 **Marcus ML**, Chilian WM, Kanatsuka H, Dellsperger KC, Eastham CL, Lamping KG. Understanding the coronary circulation through studies at the microvascular level. *Circulation* 1990; **82**: 1-7 [PMID: 2114232]

36 **Chilian WM**, Harrison DG, Haws CW, Snyder WD, Marcus ML. Adrenergic coronary tone during submaximal exercise in the dog is produced by circulating catecholamines. Evidence for adrenergic denervation supersensitivity in the myocardium but not in coronary vessels. *Circ Res* 1986; **58**: 68-82 [PMID: 3002658]

37 **Armour JA**. Potential clinical relevance of the 'little brain' on the mammalian heart. *Exp Physiol* 2008; **93**: 165-176 [PMID: 17981929 DOI: 10.1113/expphysiol.2007.041178]

38 **Beaumont E**, Salavatian S, Southerland EM, Vinet A, Jacquemet V, Armour JA, Ardell JL. Network interactions within the canine intrinsic cardiac nervous system: implications for reflex control of regional cardiac function. *J Physiol* 2013; **591**: 4515-4533 [PMID: 23818689 DOI: 10.1113/jphysiol.2013.259382]

39 **Capote LA**, Mendez Perez R, Lymperopoulos A. GPCR signaling and cardiac function. *Eur J Pharmacol* 2015; **763**: 143-148 [PMID: 25981298 DOI: 10.1016/j.ejphar.2015.05.019]

40 **Lymperopoulos A**, Bathgate A. Arrestins in the cardiovascular system. *Prog Mol Biol Transl Sci* 2013; **118**: 297-334 [PMID: 23764059 DOI: 10.1016/B978-0-12-394440-5.00012-7]

41 **Siryk-Bathgate A**, Dabul S, Lymperopoulos A. Current and future G protein-coupled receptor signaling targets for heart failure therapy. *Drug Des Devel Ther* 2013; **7**: 1209-1222 [PMID: 24143078 DOI: 10.2147/DDDT.S35905]

42 **Arora RC**, Cardinal R, Smith FM, Ardell JL, Dell'Italia LJ, Armour JA. Intrinsic cardiac nervous system in tachycardia induced heart failure. *Am J Physiol Regul Integr Comp Physiol* 2003; **285**: R1212-R1223 [PMID: 12893651 DOI: 10.1152/ajpregu.00131.2003]

43 **Hardwick JC**, Southerland EM, Girasole AE, Ryan SE, Negrotto S, Ardell JL. Remodeling of intrinsic cardiac neurons: effects of β-adrenergic receptor blockade in guinea pig models of chronic heart disease. *Am J Physiol Regul Integr Comp Physiol* 2012; **303**: R950-R958 [PMID: 22933026 DOI: 10.1152/ajpregu.00223.2012]

44 **Nguyen BL**, Li H, Fishbein MC, Lin SF, Gaudio C, Chen PS, Chen LS. Acute myocardial infarction induces bilateral stellate ganglia neural remodeling in rabbits. *Cardiovasc Pathol* 2012; **21**: 143-148 [PMID: 22001051 DOI: 10.1016/j.carpath.2011.08.001]

45 **Zucker IH**, Patel KP, Schultz HD. Neurohumoral stimulation. *Heart Fail Clin* 2012; **8**: 87-99 [PMID: 22108729 DOI: 10.1016/j.hfc.2011.08.007]

46 **Rajendran PS**, Nakamura K, Ajijola OA, Vaseghi M, Armour JA, Ardell JL, Shivkumar K. Myocardial infarction induces structural and functional remodelling of the intrinsic cardiac nervous system. *J Physiol* 2016; **594**: 321-341 [PMID: 26572244 DOI: 10.1113/JP271165]

47 **Janes RD**, Johnstone DE, Armour JA. Functional integrity of intrinsic cardiac nerves located over an acute transmural myocardial infarction. *Can J Physiol Pharmacol* 1987; **65**: 64-69 [PMID: 3567722]

48 **Vaseghi M**, Shivkumar K. The role of the autonomic nervous system in sudden cardiac death. *Prog Cardiovasc Dis* 2008; **50**: 404-419 [PMID: 18474284 DOI: 10.1016/j.pcad.2008.01.003]

49 **Huang CH**, Vatner SF, Peppas AP, Yang G, Kudej RK. Cardiac nerves affect myocardial stunning through reactive oxygen and nitric oxide mechanisms. *Circ Res* 2003; **93**: 866-873 [PMID:

14512445 DOI: 10.1161/01.RES.0000097762.64561.D2]
50 **Armour JA**. Cardiac neuronal hierarchy in health and disease. *Am J Physiol Regul Integr Comp Physiol* 2004; **287**: R262-R271 [PMID: 15271675 DOI: 10.1152/ajpregu.00183.2004]
51 **Chen PS**, Chen LS, Cao JM, Sharifi B, Karagueuzian HS, Fishbein MC. Sympathetic nerve sprouting, electrical remodeling and the mechanisms of sudden cardiac death. *Cardiovasc Res* 2001; **50**: 409-416 [PMID: 11334845]
52 **Nakamura K**, Ajijola OA, Aliotta E, Armour JA, Ardell JL, Shivkumar K. Pathological effects of chronic myocardial infarction on peripheral neurons mediating cardiac neurotransmission. *Auton Neurosci* 2016; **197**: 34-40 [PMID: 27209472 DOI: 10.1016/j.autneu.2016.05.001]
53 **Schulz R**, Rose J, Martin C, Brodde OE, Heusch G. Development of short-term myocardial hibernation. Its limitation by the severity of ischemia and inotropic stimulation. *Circulation* 1993; **88**: 684-695 [PMID: 8393390]
54 **Reimer KA**, Lowe JE, Rasmussen MM, Jennings RB. The wavefront phenomenon of ischemic cell death. 1. Myocardial infarct size vs duration of coronary occlusion in dogs. *Circulation* 1977; **56**: 786-794 [PMID: 912839]
55 **Braunwald E**, Kloner RA. Myocardial reperfusion: a double-edged sword? *J Clin Invest* 1985; **76**: 1713-1719 [PMID: 4056048 DOI: 10.1172/JCI112160]
56 **Jennings RB**. Historical perspective on the pathology of myocardial ischemia/reperfusion injury. *Circ Res* 2013; **113**: 428-438 [PMID: 23908330 DOI: 10.1161/CIRCRESAHA.113.300987]
57 **Kloner RA**, Jennings RB. Consequences of brief ischemia: stunning, preconditioning, and their clinical implications: part 1. *Circulation* 2001; **104**: 2981-2989 [PMID: 11739316]
58 **Kloner RA**, Jennings RB. Consequences of brief ischemia: stunning, preconditioning, and their clinical implications: part 2. *Circulation* 2001; **104**: 3158-3167 [PMID: 11748117]
59 **Yellon DM**, Hausenloy DJ. Myocardial reperfusion injury. *N Engl J Med* 2007; **357**: 1121-1135 [PMID: 17855673 DOI: 10.1056/NEJMra071667]
60 **Habecker BA**, Gritman KR, Willison BD, Van Winkle DM. Myocardial infarction stimulates galanin expression in cardiac sympathetic neurons. *Neuropeptides* 2005; **39**: 89-95 [PMID: 15752542 DOI: 10.1016/j.npep.2004.11.003]
61 **Mahoney SA**, Hosking R, Farrant S, Holmes FE, Jacoby AS, Shine J, Iismaa TP, Scott MK, Schmidt R, Wynick D. The second galanin receptor GalR2 plays a key role in neurite outgrowth from adult sensory neurons. *J Neurosci* 2003; **23**: 416-421 [PMID: 12533601]
62 **Abe T**, Morgan DA, Gutterman DD. Protective role of nerve growth factor against postischemic dysfunction of sympathetic coronary innervation. *Circulation* 1997; **95**: 213-220 [PMID: 8994439]
63 **Fallavollita JA**, Canty JM. Dysinnervated but viable myocardium in ischemic heart disease. *J Nucl Cardiol* 2010; **17**: 1107-1115 [PMID: 20857351 DOI: 10.1007/s12350-010-9292-5]
64 **Bulow HP**, Stahl F, Lauer B, Nekolla SG, Schuler G, Schwaiger M, Bengel FM. Alterations of myocardial presynaptic sympathetic innervation in patients with multi-vessel coronary artery disease but without history of myocardial infarction. *Nucl Med Commun* 2003; **24**: 233-239 [PMID: 12612463 DOI: 10.1097/01.mnm.0000061044.24401.6d]
65 **Barber MJ**, Mueller TM, Henry DP, Felten SY, Zipes DP. Transmural myocardial infarction in the dog produces sympathectomy in noninfarcted myocardium. *Circulation* 1983; **67**: 787-796 [PMID: 6825234]
66 **Dae MW**, Herre JM, O'Connell JW, Botvinick EH, Newman D, Munoz L. Scintigraphic assessment of sympathetic innervation after transmural versus nontransmural myocardial infarction. *J Am Coll Cardiol* 1991; **17**: 1416-1423 [PMID: 2016460]
67 **Olivas A**, Gardner RT, Wang L, Ripplinger CM, Woodward WR, Habecker BA. Myocardial Infarction Causes Transient Cholinergic Transdifferentiation of Cardiac Sympathetic Nerves via gp130. *J Neurosci* 2016; **36**: 479-488 [PMID: 26758839 DOI: 10.1523/JNEUROSCI.3556-15.2016]
68 **Zak R**. Cell proliferation during cardiac growth. *Am J Cardiol* 1973; **31**: 211-219 [PMID: 4265520]
69 **Kreipke RE**, Birren SJ. Innervating sympathetic neurons regulate heart size and the timing of cardiomyocyte cell cycle withdrawal. *J Physiol* 2015; **593**: 5057-5073 [PMID: 26420487 DOI: 10.1113/JP270917]
70 **Horackova M**, Croll RP, Hopkins DA, Losier AM, Armour JA. Morphological and immunohistochemical properties of primary long-term cultures of adult guinea-pig ventricular cardiomyocytes with peripheral cardiac neurons. *Tissue Cell* 1996; **28**: 411-425 [PMID: 8760856]
71 **Mahmoud AI**, O'Meara CC, Gemberling M, Zhao L, Bryant DM, Zheng R, Gannon JB, Cai L, Choi WY, Egnaczyk GF, Burns CE, Burns CG, MacRae CA, Poss KD, Lee RT. Nerves Regulate Cardiomyocyte Proliferation and Heart Regeneration. *Dev Cell* 2015; **34**: 387-399 [PMID: 26256209 DOI: 10.1016/j.devcel.2015.06.017]
72 **Bryant DM**, O'Meara CC, Ho NN, Gannon J, Cai L, Lee RT. A systematic analysis of neonatal mouse heart regeneration after apical resection. *J Mol Cell Cardiol* 2015; **79**: 315-318 [PMID: 25533939 DOI: 10.1016/j.yjmcc.2014.12.011]
73 **White IA**, Gordon J, Balkan W, Hare JM. Sympathetic Reinnervation Is Required for Mammalian Cardiac Regeneration. *Circ Res* 2015; **117**: 990-994 [PMID: 26371181 DOI: 10.1161/CIRCRESAHA.115.307465]
74 **Wang HJ**, Wang W, Cornish KG, Rozanski GJ, Zucker IH. Cardiac sympathetic afferent denervation attenuates cardiac remodeling and improves cardiovascular dysfunction in rats with heart failure. *Hypertension* 2014; **64**: 745-755 [PMID: 24980663 DOI: 10.1161/HYPERTENSIONAHA.114.03699]
75 **Sears CE**, Bryant SM, Ashley EA, Lygate CA, Rakovic S, Wallis HL, Neubauer S, Terrar DA, Casadei B. Cardiac neuronal nitric oxide synthase isoform regulates myocardial contraction and calcium handling. *Circ Res* 2003; **92**: e52-e59 [PMID: 12623875 DOI: 10.1161/01.RES.0000064585.95749.6D]
76 **Kingma JG**, Simard D, Voisine P, Rouleau JR. Influence of cardiac decentralization on cardioprotection. *PLoS One* 2013; **8**: e79190 [PMID: 24236106 DOI: 10.1371/journal.pone.0079190]
77 **Jones CE**, Devous MD, Thomas JX, DuPont E. The effect of chronic cardiac denervation on infarct size following acute coronary occlusion. *Am Heart J* 1978; **95**: 738-746 [PMID: 655087]
78 **Jones CE**, Beck LY, DuPont E, Barnes GE. Effects of coronary ligation of the chromically sympathectomized dog ventricle. *Am J Physiol* 1978; **235**: H429-H434 [PMID: 696884]
79 **Lavallee M**, Amano J, Vatner SF, Manders WT, Randall WC, Thomas JX. Adverse effects of chronic cardiac denervation in conscious dogs with myocardial ischemia. *Circ Res* 1985; **57**: 383-392 [PMID: 4028344]
80 **Gibbons DD**, Southerland EM, Hoover DB, Beaumont E, Armour JA, Ardell JL. Neuromodulation targets intrinsic cardiac neurons to attenuate neuronally mediated atrial arrhythmias. *Am J Physiol Regul Integr Comp Physiol* 2012; **302**: R357-R364 [PMID: 22088304 DOI: 10.1152/ajpregu.00535.2011]
81 **Armour JA**, Richer LP, Pagé P, Vinet A, Kus T, Vermeulen M, Nadeau R, Cardinal R. Origin and pharmacological response of atrial tachyarrhythmias induced by activation of mediastinal nerves in canines. *Auton Neurosci* 2005; **118**: 68-78 [PMID: 15795179 DOI: 10.1016/j.autneu.2005.01.006]
82 **Cardinal R**, Pagé P, Vermeulen M, Bouchard C, Ardell JL, Foreman RD, Armour JA. Spinal cord stimulation suppresses bradycardias and atrial tachyarrhythmias induced by mediastinal nerve stimulation in dogs. *Am J Physiol Regul Integr Comp Physiol* 2006; **291**: R1369-R1375 [PMID: 16778070 DOI: 10.1152/ajpregu.00056.2006]
83 **Armour JA**, Linderoth B, Arora RC, DeJongste MJ, Ardell JL, Kingma JG, Hill M, Foreman RD. Long-term modulation of the intrinsic cardiac nervous system by spinal cord neurons in normal and ischaemic hearts. *Auton Neurosci* 2002; **95**: 71-79 [PMID: 11873770]
84 **Kingma JG**, Linderoth B, Ardell JL, Armour JA, DeJongste

MJ, Foreman RD. Neuromodulation therapy does not influence blood flow distribution or left-ventricular dynamics during acute myocardial ischemia. *Auton Neurosci* 2001; **91**: 47-54 [PMID: 11515801 DOI: 10.1016/S1566-0702(01)00285-5]

85 **Ardell JL**, Cardinal R, Vermeulen M, Armour JA. Dorsal spinal cord stimulation obtunds the capacity of intrathoracic extracardiac neurons to transduce myocardial ischemia. *Am J Physiol Regul Integr Comp Physiol* 2009; **297**: R470-R477 [PMID: 19515981 DOI: 10.1152/ajpregu.90821.2008]

86 **Southerland EM**, Milhorn DM, Foreman RD, Linderoth B, DeJongste MJ, Armour JA, Subramanian V, Singh M, Singh K, Ardell JL. Preemptive, but not reactive, spinal cord stimulation mitigates transient ischemia-induced myocardial infarction via cardiac adrenergic neurons. *Am J Physiol Heart Circ Physiol* 2007; **292**: H311-H317 [PMID: 16920800 DOI: 10.1152/ajpheart.00087.2006]

87 **Linderoth B**, Foreman RD. Physiology of spinal cord stimulation: review and update. *Neuromodulation* 1999; **2**: 150-164 [PMID: 22151202 DOI: 10.1046/j.1525-1403.1999.00150.x]

88 **Yamakawa K**, Howard-Quijano K, Zhou W, Rajendran P, Yagishita D, Vaseghi M, Ajijola OA, Armour JA, Shivkumar K, Ardell JL, Mahajan A. Central vs. peripheral neuraxial sympathetic control of porcine ventricular electrophysiology. *Am J Physiol Regul Integr Comp Physiol* 2016; **310**: R414-R421 [PMID: 26661096 DOI: 10.1152/ajpregu.00252.2015]

89 **Ding X**, Ardell JL, Hua F, McAuley RJ, Sutherly K, Daniel JJ, Williams CA. Modulation of cardiac ischemia-sensitive afferent neuron signaling by preemptive C2 spinal cord stimulation: effect on substance P release from rat spinal cord. *Am J Physiol Regul Integr Comp Physiol* 2008; **294**: R93-101 [PMID: 17989135 DOI: 10.1152/ajpregu.00544.2007]

90 **Ding X**, Hua F, Sutherly K, Ardell JL, Williams CA. C2 spinal cord stimulation induces dynorphin release from rat T4 spinal cord: potential modulation of myocardial ischemia-sensitive neurons. *Am J Physiol Regul Integr Comp Physiol* 2008; **295**: R1519-R1528 [PMID: 18753268 DOI: 10.1152/ajpregu.00899.2007]

91 **Foreman RD**, Linderoth B. Neural mechanisms of spinal cord stimulation. *Int Rev Neurobiol* 2012; **107**: 87-119 [PMID: 23206679 DOI: 10.1016/B978-0-12-404706-8.00006-1]

92 **Jänig W**. Autonomic nervous system and inflammation. *Auton Neurosci* 2014; **182**: 1-3 [PMID: 24581951 DOI: 10.1016/j.autneu.2014.02.002]

93 **Beaumont E**, Southerland EM, Hardwick JC, Wright GL, Ryan S, Li Y, KenKnight BH, Armour JA, Ardell JL. Vagus nerve stimulation mitigates intrinsic cardiac neuronal and adverse myocyte remodeling postmyocardial infarction. *Am J Physiol Heart Circ Physiol* 2015; **309**: H1198-H1206 [PMID: 26276818 DOI: 10.1152/ajpheart.00393.2015]

94 **De Ferrari GM**, Vanoli E, Stramba-Badiale M, Hull SS, Foreman RD, Schwartz PJ. Vagal reflexes and survival during acute myocardial ischemia in conscious dogs with healed myocardial infarction. *Am J Physiol* 1991; **261**: H63-H69 [PMID: 1858931]

95 **Premchand RK**, Sharma K, Mittal S, Monteiro R, Dixit S, Libbus I, DiCarlo LA, Ardell JL, Rector TS, Amurthur B, KenKnight BH, Anand IS. Autonomic regulation therapy via left or right cervical vagus nerve stimulation in patients with chronic heart failure: results of the ANTHEM-HF trial. *J Card Fail* 2014; **20**: 808-816 [PMID: 25187002 DOI: 10.1016/j.cardfail.2014.08.009]

96 **De Ferrari GM**, Tuinenburg AE, Ruble S, Brugada J, Klein H, Butter C, Wright DJ, Schubert B, Solomon S, Meyer S, Stein K, Ramuzat A, Zannad F. Rationale and study design of the NEuroCardiac TherApy foR Heart Failure Study: NECTAR-HF. *Eur J Heart Fail* 2014; **16**: 692-699 [PMID: 24846173 DOI: 10.1002/ejhf.80]

97 **Murry CE**, Jennings RB, Reimer KA. Preconditioning with ischemia: a delay of lethal cell injury in ischemic myocardium. *Circulation* 1986; **74**: 1124-1136 [PMID: 3769170]

98 **Yellon DM**, Downey JM. Preconditioning the myocardium: from cellular physiology to clinical cardiology. *Physiol Rev* 2003; **83**: 1113-1151 [PMID: 14506302 DOI: 10.1152/physrev.00009.2003]

99 **Hausenloy DJ**, Barrabes JA, Bøtker HE, Davidson SM, Di Lisa F, Downey J, Engstrom T, Ferdinandy P, Carbrera-Fuentes HA, Heusch G, Ibanez B, Iliodromitis EK, Inserte J, Jennings R, Kalia N, Kharbanda R, Lecour S, Marber M, Miura T, Ovize M, Perez-Pinzon MA, Piper HM, Przyklenk K, Schmidt MR, Redington A, Ruiz-Meana M, Vilahur G, Vinten-Johansen J, Yellon DM, Garcia-Dorado D. Ischaemic conditioning and targeting reperfusion injury: a 30 year voyage of discovery. *Basic Res Cardiol* 2016; **111**: 70 [PMID: 27766474 DOI: 10.1007/s00395-016-0588-8]

100 **Kudej RK**, Shen YT, Peppas AP, Huang CH, Chen W, Yan L, Vatner DE, Vatner SF. Obligatory role of cardiac nerves and alpha1-adrenergic receptors for the second window of ischemic preconditioning in conscious pigs. *Circ Res* 2006; **99**: 1270-1276 [PMID: 17068289 DOI: 10.1161/01.RES.0000251282.79411.44]

101 **Shinmura K**, Tang XL, Wang Y, Xuan YT, Liu SQ, Takano H, Bhatnagar A, Bolli R. Cyclooxygenase-2 mediates the cardioprotective effects of the late phase of ischemic preconditioning in conscious rabbits. *Proc Natl Acad Sci USA* 2000; **97**: 10197-10202 [PMID: 10963682]

102 **Ovize M**, Thibault H, Przyklenk K. Myocardial conditioning: opportunities for clinical translation. *Circ Res* 2013; **113**: 439-450 [PMID: 23908331 DOI: 10.1161/CIRCRESAHA.113.300764]

103 **Vander Heide RS**, Steenbergen C. Cardioprotection and myocardial reperfusion: pitfalls to clinical application. *Circ Res* 2013; **113**: 464-477 [PMID: 23908333 DOI: 10.1161/CIRCRESAHA. 113.300765]

104 **Przyklenk K**, Bauer B, Ovize M, Kloner RA, Whittaker P. Regional ischemic 'preconditioning' protects remote virgin myocardium from subsequent sustained coronary occlusion. *Circulation* 1993; **87**: 893-899 [PMID: 7680290]

105 **Konstantinov IE**, Arab S, Kharbanda RK, Li J, Cheung MM, Cherepanov V, Downey GP, Liu PP, Cukerman E, Coles JG, Redington AN. The remote ischemic preconditioning stimulus modifies inflammatory gene expression in humans. *Physiol Genomics* 2004; **19**: 143-150 [PMID: 15304621 DOI: 10.1152/physiolgenomics.00046.2004]

106 **Saxena P**, Newman MA, Shehatha JS, Redington AN, Konstantinov IE. Remote ischemic conditioning: evolution of the concept, mechanisms, and clinical application. *J Card Surg* 2010; **25**: 127-134 [PMID: 19549044 DOI: 10.1111/j.1540-8191.2009.00820.x]

107 **Kharbanda RK**, Mortensen UM, White PA, Kristiansen SB, Schmidt MR, Hoschtitzky JA, Vogel M, Sorensen K, Redington AN, MacAllister R. Transient limb ischemia induces remote ischemic preconditioning in vivo. *Circulation* 2002; **106**: 2881-2883 [PMID: 12460865]

108 **Vinten-Johansen J**, Shi W. Perconditioning and postconditioning: current knowledge, knowledge gaps, barriers to adoption, and future directions. *J Cardiovasc Pharmacol Ther* 2011; **16**: 260-266 [PMID: 21821526 DOI: 10.1177/1074248411415270]

109 **Lim SY**, Hausenloy DJ. Remote ischemic conditioning: from bench to bedside. *Front Physiol* 2012; **3**: 27 [PMID: 22363297 DOI: 10.3389/fphys.2012.00027]

110 **Przyklenk K**. Reduction of myocardial infarct size with ischemic "conditioning": physiologic and technical considerations. *Anesth Analg* 2013; **117**: 891-901 [PMID: 23960036 DOI: 10.1213/ANE.0b013e318294fc63]

111 **Weber C**. Far from the heart: Receptor cross-talk in remote conditioning. *Nat Med* 2010; **16**: 760-762 [PMID: 20613755 DOI: 10.1038/nm0710-760]

112 **Pickard JM**, Davidson SM, Hausenloy DJ, Yellon DM. Co-dependence of the neural and humoral pathways in the mechanism of remote ischemic conditioning. *Basic Res Cardiol* 2016; **111**: 50 [PMID: 27338249 DOI: 10.1007/s00395-016-0568-z]

113 **Gotti C**, Clementi F. Neuronal nicotinic receptors: from structure to pathology. *Prog Neurobiol* 2004; **74**: 363-396 [PMID: 15649582 DOI: 10.1016/j.pneurobio.2004.09.006]

114 **Bibevski S**, Zhou Y, McIntosh JM, Zigmond RE, Dunlap ME. Functional nicotinic acetylcholine receptors that mediate ganglionic transmission in cardiac parasympathetic neurons. *J Neurosci* 2000; **20**: 5076-5082 [PMID: 10864965]

115 **Gho BC**, Schoemaker RG, van den Doel MA, Duncker DJ, Verdouw PD. Myocardial protection by brief ischemia in noncardiac tissue. *Circulation* 1996; **94**: 2193-2200 [PMID: 8901671]

116 **Weinbrenner C**, Nelles M, Herzog N, Sárváry L, Strasser RH. Remote preconditioning by infrarenal occlusion of the aorta protects the heart from infarction: a newly identified non-neuronal but PKC-dependent pathway. *Cardiovasc Res* 2002; **55**: 590-601 [PMID: 12160957]

117 **Loukogeorgakis SP**, Panagiotidou AT, Broadhead MW, Donald A, Deanfield JE, MacAllister RJ. Remote ischemic preconditioning provides early and late protection against endothelial ischemia-reperfusion injury in humans: role of the autonomic nervous system. *J Am Coll Cardiol* 2005; **46**: 450-456 [PMID: 16053957 DOI: 10.1016/j.jacc.2005.04.044]

118 **Sabbah HN**, Ilsar I, Zaretsky A, Rastogi S, Wang M, Gupta RC. Vagus nerve stimulation in experimental heart failure. *Heart Fail Rev* 2011; **16**: 171-178 [PMID: 21128115 DOI: 10.1007/s10741-010-9209-z]

119 **Zhang Y**, Popovic ZB, Bibevski S, Fakhry I, Sica DA, Van Wagoner DR, Mazgalev TN. Chronic vagus nerve stimulation improves autonomic control and attenuates systemic inflammation and heart failure progression in a canine high-rate pacing model. *Circ Heart Fail* 2009; **2**: 692-699 [PMID: 19919995 DOI: 10.1161/CIRCHEARTFAILURE.109.873968]

120 **Hamann JJ**, Ruble SB, Stolen C, Wang M, Gupta RC, Rastogi S, Sabbah HN. Vagus nerve stimulation improves left ventricular function in a canine model of chronic heart failure. *Eur J Heart Fail* 2013; **15**: 1319-1326 [PMID: 23883651 DOI: 10.1093/eurjhf/hft118]

121 **De Ferrari GM**, Crijns HJ, Borggrefe M, Milasinovic G, Smid J, Zabel M, Gavazzi A, Sanzo A, Dennert R, Kuschyk J, Raspopovic S, Klein H, Swedberg K, Schwartz PJ. Chronic vagus nerve stimulation: a new and promising therapeutic approach for chronic heart failure. *Eur Heart J* 2011; **32**: 847-855 [PMID: 21030409 DOI: 10.1093/eurheartj/ehq391]

122 **Katare RG**, Ando M, Kakinuma Y, Arikawa M, Handa T, Yamasaki F, Sato T. Vagal nerve stimulation prevents reperfusion injury through inhibition of opening of mitochondrial permeability transition pore independent of the bradycardiac effect. *J Thorac Cardiovasc Surg* 2009; **137**: 223-231 [PMID: 19154929 DOI: 10.1016/j.jtcvs.2008.08.020]

123 **Calvillo L**, Vanoli E, Andreoli E, Besana A, Omodeo E, Gnecchi M, Zerbi P, Vago G, Busca G, Schwartz PJ. Vagal stimulation, through its nicotinic action, limits infarct size and the inflammatory response to myocardial ischemia and reperfusion. *J Cardiovasc Pharmacol* 2011; **58**: 500-507 [PMID: 21765369 DOI: 10.1097/FJC.0b013e31822b7204]

124 **Mioni C**, Bazzani C, Giuliani D, Altavilla D, Leone S, Ferrari A, Minutoli L, Bitto A, Marini H, Zaffe D, Botticelli AR, Iannone A, Tomasi A, Bigiani A, Bertolini A, Squadrito F, Guarini S. Activation of an efferent cholinergic pathway produces strong protection against myocardial ischemia/reperfusion injury in rats. *Crit Care Med* 2005; **33**: 2621-2628 [PMID: 16276189]

125 **Mortara A**, La Rovere MT, Pinna GD, Prpa A, Maestri R, Febo O, Pozzoli M, Opasich C, Tavazzi L. Arterial baroreflex modulation of heart rate in chronic heart failure: clinical and hemodynamic correlates and prognostic implications. *Circulation* 1997; **96**: 3450-3458 [PMID: 9396441]

126 **Zoccali C**, Mallamaci F, Parlongo S, Cutrupi S, Benedetto FA, Tripepi G, Bonanno G, Rapisarda F, Fatuzzo P, Seminara G, Cataliotti A, Stancanelli B, Malatino LS. Plasma norepinephrine predicts survival and incident cardiovascular events in patients with end-stage renal disease. *Circulation* 2002; **105**: 1354-1359 [PMID: 11901048]

127 **Smith S**, Rossignol P, Willis S, Zannad F, Mentz R, Pocock S, Bisognano J, Nadim Y, Geller N, Ruble S, Linde C. Neural modulation for hypertension and heart failure. *Int J Cardiol* 2016; **214**: 320-330 [PMID: 27085120 DOI: 10.1016/j.ijcard. 2016.03.078]

128 **Kishi T**. Deep and future insights into neuromodulation therapies for heart failure. *J Cardiol* 2016; **68**: 368-372 [PMID: 27293020 DOI: 10.1016/j.jjcc.2016.05.010]

129 **Manintveld OC**, te Lintel Hekkert M, Keijzer E, Verdouw PD, Duncker DJ. Intravenous adenosine protects the myocardium primarily by activation of a neurogenic pathway. *Br J Pharmacol* 2005; **145**: 703-711 [PMID: 15895104 DOI: 10.1038/sj.bjp.0706258]

130 **Ding YF**, Zhang MM, He RR. Role of renal nerve in cardioprotection provided by renal ischemic preconditioning in anesthetized rabbits. *Sheng Li Xue Bao* 2001; **53**: 7-12 [PMID: 11354802]

131 **Ardell JL**, Butler CK, Smith FM, Hopkins DA, Armour JA. Activity of in vivo atrial and ventricular neurons in chronically decentralized canine hearts. *Am J Physiol* 1991; **260**: H713-H721 [PMID: 2000967]

132 **Vander Heide RS**, Schwartz LM, Jennings RB, Reimer KA. Effect of catecholamine depletion on myocardial infarct size in dogs: role of catecholamines in ischemic preconditioning. *Cardiovasc Res* 1995; **30**: 656-662 [PMID: 8595609]

133 **Mastitskaya S**, Marina N, Gourine A, Gilbey MP, Spyer KM, Teschemacher AG, Kasparov S, Trapp S, Ackland GL, Gourine AV. Cardioprotection evoked by remote ischaemic preconditioning is critically dependent on the activity of vagal pre-ganglionic neurones. *Cardiovasc Res* 2012; **95**: 487-494 [PMID: 22739118 DOI: 10.1093/cvr/cvs212]

134 **Lim SY**, Yellon DM, Hausenloy DJ. The neural and humoral pathways in remote limb ischemic preconditioning. *Basic Res Cardiol* 2010; **105**: 651-655 [PMID: 20449597 DOI: 10.1007/s00395-010-0099-y]

135 **Redington KL**, Disenhouse T, Strantzas SC, Gladstone R, Wei C, Tropak MB, Dai X, Manlhiot C, Li J, Redington AN. Remote cardioprotection by direct peripheral nerve stimulation and topical capsaicin is mediated by circulating humoral factors. *Basic Res Cardiol* 2012; **107**: 241 [PMID: 22231674 DOI: 10.1007/s00395-011-0241-5]

136 **Basalay M**, Barsukevich V, Mastitskaya S, Mrochek A, Pernow J, Sjöquist PO, Ackland GL, Gourine AV, Gourine A. Remote ischaemic pre- and delayed postconditioning - similar degree of cardioprotection but distinct mechanisms. *Exp Physiol* 2012; **97**: 908-917 [PMID: 22427438 DOI: 10.1113/expphysiol.2012.064923]

137 **Kingma JG**, Simard D, Voisine P, Rouleau JR. Role of the autonomic nervous system in cardioprotection by remote preconditioning in isoflurane-anaesthetized dogs. *Cardiovasc Res* 2011; **89**: 384-391 [PMID: 20876586 DOI: 10.1093/cvr/cvq306]

138 **Tsang A**, Hausenloy DJ, Mocanu MM, Carr RD, Yellon DM. Preconditioning the diabetic heart: the importance of Akt phosphorylation. *Diabetes* 2005; **54**: 2360-2364 [PMID: 16046302]

139 **Florea VG**, Cohn JN. The autonomic nervous system and heart failure. *Circ Res* 2014; **114**: 1815-1826 [PMID: 24855204 DOI: 10.1161/CIRCRESAHA.114.302589]

140 **Mudd JO**, Kass DA. Tackling heart failure in the twenty-first century. *Nature* 2008; **451**: 919-928 [PMID: 18288181 DOI: 10.1038/nature06798]

141 **Lymperopoulos A**, Rengo G, Koch WJ. Adrenergic nervous system in heart failure: pathophysiology and therapy. *Circ Res* 2013; **113**: 739-753 [PMID: 23989716 DOI: 10.1161/CIRCRESAHA.113.300308]

142 **Arnold R**, Issar T, Krishnan AV, Pussell BA. Neurological complications in chronic kidney disease. *JRSM Cardiovasc Dis* 2016; **5**: 2048004016677687 [PMID: 27867500 DOI: 10.1177/2048004016677687]

143 **Krishnan AV**, Kiernan MC. Neurological complications of chronic kidney disease. *Nat Rev Neurol* 2009; **5**: 542-551 [PMID: 19724248 DOI: 10.1038/nrneurol.2009.138]

144 **Kiernan MC**, Walters RJ, Andersen KV, Taube D, Murray NM, Bostock H. Nerve excitability changes in chronic renal failure indicate membrane depolarization due to hyperkalaemia. *Brain* 2002; **125**: 1366-1378 [PMID: 12023325]

145 **Park J**. Cardiovascular risk in chronic kidney disease: role of the sympathetic nervous system. *Cardiol Res Pract* 2012; **2012**: 319432 [PMID: 22919537 DOI: 10.1155/2012/319432]

146 **Grassi G**. Sympathetic neural activity in hypertension and related

diseases. *Am J Hypertens* 2010; **23**: 1052-1060 [PMID: 20651696 DOI: 10.1038/ajh.2010.154]
147 **Grassi G**, Quarti-Trevano F, Seravalle G, Arenare F, Volpe M, Furiani S, Dell'Oro R, Mancia G. Early sympathetic activation in the initial clinical stages of chronic renal failure. *Hypertension* 2011; **57**: 846-851 [PMID: 21300663 DOI: 10.1161/HYPERTENSIONAHA.110.164780]
148 **Converse RL**, Jacobsen TN, Toto RD, Jost CM, Cosentino F, Fouad-Tarazi F, Victor RG. Sympathetic overactivity in patients with chronic renal failure. *N Engl J Med* 1992; **327**: 1912-1918 [PMID: 1454086 DOI: 10.1056/NEJM199212313272704]
149 **McClellan W**, Aronoff SL, Bolton WK, Hood S, Lorber DL, Tang KL, Tse TF, Wasserman B, Leiserowitz M. The prevalence of anemia in patients with chronic kidney disease. *Curr Med Res Opin* 2004; **20**: 1501-1510 [PMID: 15383200 DOI: 10.1185/030079904X2763]
150 **Bosman DR**, Winkler AS, Marsden JT, Macdougall IC, Watkins PJ. Anemia with erythropoietin deficiency occurs early in diabetic nephropathy. *Diabetes Care* 2001; **24**: 495-499 [PMID: 11289474]
151 **DiBona GF**, Kopp UC. Neural control of renal function. *Physiol Rev* 1997; **77**: 75-197 [PMID: 9016301]
152 **DiBona GF**. Nervous kidney. Interaction between renal sympathetic nerves and the renin-angiotensin system in the control of renal function. *Hypertension* 2000; **36**: 1083-1088 [PMID: 11116129]
153 **Jassal SV**, Coulshed SJ, Douglas JF, Stout RW. Autonomic neuropathy predisposing to arrhythmias in hemodialysis patients. *Am J Kidney Dis* 1997; **30**: 219-223 [PMID: 9261032]
154 **Henderson LW**. Symptomatic hypotension during hemodialysis. *Kidney Int* 1980; **17**: 571-576 [PMID: 6995689]
155 **Lefrandt JD**, Smit AJ, Zeebregts CJ, Gans RO, Hoogenberg KH. Autonomic dysfunction in diabetes: a consequence of cardiovascular damage. *Curr Diabetes Rev* 2010; **6**: 348-358 [PMID: 20879972]
156 **Sartori C**, Scherrer U. Insulin, nitric oxide and the sympathetic nervous system: at the crossroads of metabolic and cardiovascular regulation. *J Hypertens* 1999; **17**: 1517-1525 [PMID: 10608463]
157 **Steinberg HO**, Brechtel G, Johnson A, Fineberg N, Baron AD. Insulin-mediated skeletal muscle vasodilation is nitric oxide dependent. A novel action of insulin to increase nitric oxide release. *J Clin Invest* 1994; **94**: 1172-1179 [PMID: 8083357 DOI: 10.1172/JCI117433]
158 **Sartori C**, Trueb L, Nicod P, Scherrer U. Effects of sympathectomy and nitric oxide synthase inhibition on vascular actions of insulin in humans. *Hypertension* 1999; **34**: 586-589 [PMID: 10523331]
159 **Gill GV**, Woodward A, Casson IF, Weston PJ. Cardiac arrhythmia and nocturnal hypoglycaemia in type 1 diabetes--the 'dead in bed' syndrome revisited. *Diabetologia* 2009; **52**: 42-45 [PMID: 18972096 DOI: 10.1007/s00125-008-1177-7]
160 **Deckert T**, Feldt-Rasmussen B, Borch-Johnsen K, Jensen T, Kofoed-Enevoldsen A. Albuminuria reflects widespread vascular damage. The Steno hypothesis. *Diabetologia* 1989; **32**: 219-226 [PMID: 2668076]
161 **Jensen T**, Bjerre-Knudsen J, Feldt-Rasmussen B, Deckert T. Features of endothelial dysfunction in early diabetic nephropathy. *Lancet* 1989; **1**: 461-463 [PMID: 2563840]
162 **Pavy-Le Traon A**, Fontaine S, Tap G, Guidolin B, Senard JM, Hanaire H. Cardiovascular autonomic neuropathy and other complications in type 1 diabetes. *Clin Auton Res* 2010; **20**: 153-160 [PMID: 20354891 DOI: 10.1007/s10286-010-0062-x]
163 **Beijers HJ**, Ferreira I, Bravenboer B, Dekker JM, Nijpels G, Heine RJ, Stehouwer CD. Microalbuminuria and cardiovascular autonomic dysfunction are independently associated with cardiovascular mortality: evidence for distinct pathways: the Hoorn Study. *Diabetes Care* 2009; **32**: 1698-1703 [PMID: 19564456 DOI: 10.2337/dc08-1544]
164 **Gerritsen J**, Dekker JM, TenVoorde BJ, Kostense PJ, Heine RJ, Bouter LM, Heethaar RM, Stehouwer CD. Impaired autonomic function is associated with increased mortality, especially in subjects with diabetes, hypertension, or a history of cardiovascular disease: the Hoorn Study. *Diabetes Care* 2001; **24**: 1793-1798 [PMID: 11574444]
165 **Pop-Busui R**, Evans GW, Gerstein HC, Fonseca V, Fleg JL, Hoogwerf BJ, Genuth S, Grimm RH, Corson MA, Prineas R. Effects of cardiac autonomic dysfunction on mortality risk in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial. *Diabetes Care* 2010; **33**: 1578-1584 [PMID: 20215456 DOI: 10.2337/dc10-0125]

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MINIREVIEWS

Management of ventricular tachycardia storm in patients with structural heart disease

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Abstract

Electrical storm (ES) is a medical emergency characterized by repetitive episodes of sustained ventricular arrhythmias (VAs) in a limited amount of time (at least 3 within a 24-h period) leading to repeated appropriate implantable cardioverter defibrillator therapies. The occurrence of ES represents a major turning point in the natural history of patients with structural heart disease being associated with poor short- and long-term survival particularly in those with compromised left ventricular ejection fraction (LVEF) that can develop hemodynamic decompensation and multi-organ failure. Management of ES is challenging with limited available evidence coming from small retrospective series and a substantial lack of randomized-controlled trials. In general, a multidisciplinary approach including medical therapies such as anti-arrhythmic drugs, sedation, as well as interventional approaches like catheter ablation, may be required. Accurate patient risk stratification at admission for ES is pivotal and should take into account hemodynamic tolerability of VAs as well as comorbidities like low LVEF, advanced NYHA class and chronic pulmonary disease. In high risk patients, prophylactic mechanical circulatory support with left ventricular assistance devices or extracorporeal membrane oxygenation should be considered as bridge to ablation and recovery. In the present manuscript we review the available strategies for management of ES and the evidence supporting them.

Key words: Electrical storm; Ventricular tachycardia; Catheter ablation; Mechanical hemodynamic support; Anti-arrhythmic drugs

Core tip: Electrical storm (ES) is a life-threatening condition characterized by ongoing ventricular arrhythmias leading to appropriate implantable cardioverter defibrillator therapies. It is associated with increased mortality and requires urgent medical care. In this review, we summarize the prognostic implications for ES as well as available treatment strategies to manage ES.

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INTRODUCTION

Ventricular tachycardia (VT) electrical storm (ES) is a severe clinical condition characterized by clustering episodes of ventricular arrhythmia in a short amount of time. The current definition of ES implies at least 3 distinct episodes of sustained VT or ventricular fibrillation (VF) within the last 24-h or the occurrence of incessant VT for at least 12-h. In patients with ICD, ES is defined by $\geqslant$ 3 appropriate device interventions in the last 24-h (separated by at least 5-min one from the other) either with antitachycardia pacing (ATP) or direct-current shock[1]. Although ES mainly occurs in patients with structural heart disease and low left ventricular ejection fraction (LVEF), it may affect also patients with inherited arrhythmic syndromes and structurally normal heart (*i.e.*, Brugada syndrome and catecholaminergic polymorphic VT) representing a life-threatening condition requiring urgent medical care[2]. Several strategies have been proposed to manage ES with most of the data coming from small retrospective series, lacking large randomized-controlled trials. There are several substantial differences in the approach and treatment of ES in the setting of structural heart disease compared to primitive arrhythmic syndromes. In this review, we will focus on the management of ES in the setting of structural heart disease by summarizing the current therapeutic strategies in a stepwise approach based on available evidence (Figure 1).

INITIAL CARE

Prolonged sustained VAs as well as multiple ICD shocks in the setting of ES, may contribute to worsening of systolic function and development of a low-output state leading to cardiogenic shock and multiple organ failure. In this setting, urgent ICD interrogation and reprogramming is mandatory. Documentation of appropriate ICD interventions triggered by VT/VF episodes is necessary to rule out all potentially reversible causes like electrolyte imbalances, acute ischemia, pro-arrhythmic drug effects, hyperthyroidism, infections and decompensated HF. However, reversible causes of ES account for less than 10%, and in the majority of cases no precipitating cause is identified (Table 1)[3]. Initial evaluation should include accurate patient risk stratification according to hemodynamic tolerability of the arrhythmia and presence of comorbidities (Figure 1)[4]. All patients with hemodynamic decompensation (persistent systolic blood pressure < 80-90 mmHg despite temporary resumption of sinus/paced rhythm and despite increasing doses of vasopressors) as well as patients with hemodynamically tolerated VT but with major comorbidities (*i.e.*, LVEF $\leqslant$ 30%, moderate to severe chronic kidney disease and severe pulmonary obstructive disease) are considered at high risk and should be admitted to the intensive care unit in order to correct metabolic, respiratory and circulatory imbalances [mechanical ventilation and circulatory support with intra-aortic balloon pump (IABP), left ventricular assist device (LVAD), or extracorporeal membrane oxygenation (ECMO) may be required] and eventually undergo emergent CA. In both high and low-risk patients, every effort should be made to suppress VAs and avoid further ICD-shocks.

ICD PROGRAMMING

Reprogramming of ICD settings is of great importance in the initial workup of patients presenting with ES. Repeated ICD-shocks are associated with increased mortality and low quality of life[5,6]. The end-point of ICD reprogramming should be the reduction of ICD-shocks favoring interruption of VAs with ATP. In large trials, increases in both detection duration and heart rate detection threshold have been shown to reduce ICD-shocks without increasing mortality or the incidence of syncope[5,7,8]. Moreover, ATP can effectively terminate most slow VTs with a low risk of acceleration[9,10].

ANTIARRHYTHMIC DRUG THERAPY

Antiarrhythmic drugs (AADs) are usually required for the acute management of ES and are often used as an adjunctive therapy to prevent long-term recurrences. In a recent meta-analysis of randomized-controlled trials, we found a 1.5-fold reduction of appropriate ICD interventions with AADs compared to standard medical therapy with also a significant reduction of inappropriate ICD interventions. However, pooled analysis did not show a significant impact of AADs on all-cause mortality compared to standard medical therapy[11]. The choice of a particular drug and its dose should take into account its efficacy in controlling VA but also potential pro-arrhythmic effects as well as other side effects. Pro-arrhythmic effects have been reported in up to 7% of the patients treated with AADs for VT/VF with the higher incidence in patients with severely reduced LVEF[12]. A list of the most common AADs used in the acute and long-term management of ES as well as indications on the proper use of them and their therapeutic drug monitoring is presented in Table 2.

Beta-blockers

A significant increase in the sympathetic tone is inevitably observed in patients experiencing ES, being responsible for the occurrence and maintenance of VAs. In these patients a spiral of events may occur: ICD shocks may precipitate increased sympathetic tone, resulting in further VAs and shocks, and so forth. Therefore, suppression of adrenergic tone with β-blockers represents

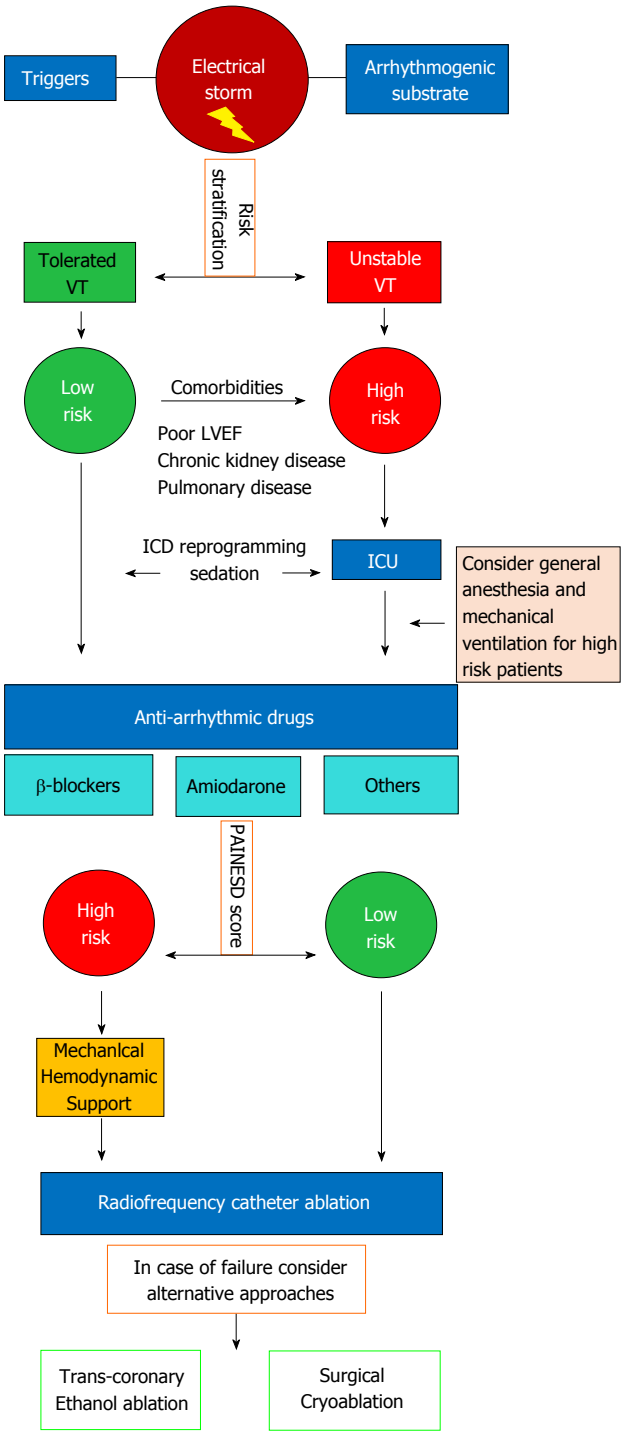

Figure 1 Proposed algorithm for acute management of patients presenting with electrical storm. VT: Ventricular tachycardia; LVEF: Left ventricular ejection fraction; ICU: Intensive care unit.

the cornerstone of AAD therapy of ES[13]. Although most of the benefits of β-blockers are related to a class effect, in this setting there are some important advantages of nonselective β_1 and β_2 blockade. Ventricular remodeling in patients with chronic HF leads to a downregulation of β-receptors mostly involving β_1-receptors with relative spearing of β_2-receptors. Moreover, the lipophilic nature of some unselective β-blockers like propranolol, enables their penetration into the central nervous system where

Table 1 Reversible causes of electrical storm

Acute myocardial ischemia
Electrolyte imbalances
Decompensated heart failure
Hyperthyroidism
Infections, fever
Pro-arrhythmic drug Effects
Early postoperative period

they act by blocking presynaptic adrenergic receptors[14,15]. Propranolol has been demonstrated to be effective in suppressing VAs refractory to both metoprolol and amiodarone[16]. Short-acting intravenous drugs like esmolol can also be used, especially in patients at highest risk for hemodynamic compromise such as those with severely reduced LVEF[17].

Amiodarone

Amiodarone is widely used in the acute management of ES and can generally be safely administered unless hyperthyroidism or QT prolongation are present. Amiodarone has a mixed antiarrhythmic class action with a prevalent class Ⅲ action (potassium channel blocker) prolonging the ventricular refractory period when administered orally and a prevalent class Ⅰ (sodium channel), class Ⅳ (L-calcium channels) and class Ⅱ (sympathetic blocker) action, not prolonging ventricular refractoriness, when is administered intravenously[18]. Amiodarone has demonstrated its efficacy in several trials being able to control VAs in up to 40% of patients within 24-h from intravenous administration as well as to reduce recurrent VT over follow-up[19-22]. The combined use of both amiodarone plus β-blockers significantly reduces the risk of recurrent ICD-shocks compared *vs* β-blockers alone[22]. In the specific setting of ES, amiodarone has been shown to reduce the risk of ES recurrence by 50% over 5-years follow-up[23]. Patients already under amiodarone treatment may benefit from a reloading dose or a dose adjustment based upon serum levels of amiodarone even if plasma concentration monitoring has been reported of very limited benefit because the drug and its active metabolite (desethylamiodarone) accumulates in tissues at higher concentrations that in plasma[24]. Importantly, amiodarone may increase defibrillation thresholds in patients with ICDs[25] and the risks and benefits of long-term administration of amiodarone should be carefully weighed because of its several side effects including liver dysfunction (elevated AST/ALT levels in up to 30% of patients but hepatitis requiring drug discontinuation in < 3% of the cases), thyroid disorders (hypothyroidism in up to 22%, hyperthyroidism in up to 12%), pulmonary fibrosis (2%), corneal deposits (> 90%, usually of no clinical importance), optic neuropathy (< 1%) and pro-arrhythmic effect (< 1%)[26]. A recent pooled analysis of randomized controlled trials comparing CA *vs* AADs demonstrated an association between amiodarone and increased mortality[11]. Furthermore, among patients

Table 2 Anti-arrhythmic medications for acute and long-term treatment of electrical storm

		Acute management	Long-term treatment	Desired plasma concentration
β-blockers	Propranolol	Bolus: 0.15 mg/kg IV over 10 min	10-40 mg by mouth three-four times a day	NA
	Metoprolol	Bolus: 2-5 mg IV every 5 min up to 3 doses in 15 min	25 mg by mouth twice a day up to 200 mg a day	NA
	Esmolol	Bolus: 300 to 500 mg/kg *IV* for 1 min Infusion: 25-50 mg/kg per minute up to a maximum dose of 250 mg/kg per minute (titration every 5-10 min)	Not recommended	NA
Class Ⅲ agents	Amiodarone	Bolus: 150 mg *IV* over 10 min, up to total 2.2 g in 24 h	Oral load: 800 mg by mouth twice a day until 10 g total	1.0-2.5 μg/mL No efficacy proven for plasma concentrations < 0.5 μg/mL
		Infusion: 1 mg/min for 6 h, then 0.5 mg/min for 18 h	Maintenance dose: 200-400 mg by mouth daily	Serious toxicity risk for plasma concentrations > 2.5 μg/mL
	Sotalol	Not recommended	80 mg by mouth twice a day, up to 160 mg twice a day (serious side effects > 320 mg/d)	1-3 μg/mL (not of great value, usually monitored by QT prolongation with indication to reduction/discontinuation if prolongation > 15%-20%)
Class Ⅰ agents	Procainamide	Bolus: 10 mg/kg *IV* over 20 min Infusion: up to 2-3 g/24 h	3-6 g by mouth daily fractionated in ⩾ 3 administrations	4-12 μg/mL
	Lidocaine	Bolus: 1.0 to 1.5 mg/kg *IV*, repeat dose of 0.5-0.75 mg/kg *IV* up to a total dose of 3 mg/kg Infusion: 20 μcg/kg per minute *IV*	Not recommended	2-6 μg/mL
	Mexiletine	Not recommended	200 mg by mouth three times a day, up to 400 mg by mouth three times a day	0.6-1.7 μg/mL

undergoing CA for VT in the setting of structural heart disease, we have recently shown that higher amiodarone dose at discharge after CA was associated with increased mortality, suggesting that discontinuation or dose reduction of amiodarone should be considered in certain patients after successful CA[27].

Procainamide

Procainamide is a class IC agent no longer widely used (unavailable in most countries) that may be helpful to acutely terminate VAs and prevent recurrences. It acts as fast sodium channel blocker, while its active metabolite N-acetylprocainamide blocks potassium channels and accounts for much of the antiarrhythmic effect *in vivo* as well as side effects like QT interval prolongation. Up to date there are only two small randomized controlled trials analyzing its role in the acute treatment of tolerated VT. In the study by Gorgels *et al*[28], procainamide demonstrated its superiority to lidocaine in acute VT termination in 29 patients while in the more recent PROCAMIO trial, intravenous administration of procainamide was shown to be safe and more effective compared to amiodarone in the treatment of tolerated monomorphic VT[29,30]. The most important acute adverse reaction is hypotension (up to 30% patients) which requires drug discontinuation in 11% of cases[28-30]. Data regarding the long-term efficacy of procainamide in preventing VT are lacking, moreover chronic therapy is limited by a number of systemic side effects including lupus-like syndrome, gastrointestinal disturbances, and autoimmune blood impairments. Plasma procainamide concentrations can be useful in initial dose titration; however, monitoring of QRS and QT interval is a valid alternative to prevent drug toxicity.

Lidocaine and mexiletine

Lidocaine and mexiletine are both class IB AADs, acting as rapid sodium channel blockers binding to the receptor in a use-dependent fashion. The main difference between them is the bioavailability of mexiletine (80%) that allows its oral administration. The use of lidocaine in ES is more limited due to its lower efficacy in terminating scar-related VTs. During ischemic VT, the altered membrane potential as well as pH reduction increase the rate of drug binding, making lidocaine more effective in terminating VAs[31]. For this reason lidocaine is currently recommended mostly for the suppression of VAs in the setting of acute ischemia[32]. Mexiletine has shown to reduce the burden of VAs but with a trend toward increased mortality and is mostly used as a an adjunctive therapy to amiodarone being able to reduce appropriate therapies in patients with ICD in case of amiodarone inefficacy[33,34]. Side effects of lidocaine and mexiletine are dose dependent and predominantly related to central nervous system accumulation (particularly in patients with HF) including tremors, seizures and hallucinations. They are generally rapidly reversible with drug reduction or discontinuation.

Sotalol

The commercially available form of Sotalol is a racemic mix of d-isomer (acting as a class Ⅲ potassium channel blocker) and l-isomer (acting as a non-selective β-blocker). Most of its antiarrhythmic (as well as pro-arrhythmic) effects result from its action on potassium channels

resulting in prolongation of repolarization and the QT interval. While sotalol has shown to reduce the frequency of ICD-shocks among patients implanted for secondary prevention, it has failed to demonstrate his superiority to β-blocker therapy in preventing recurrent ICD-shocks in several randomized-controlled trials[22,35,36]. Moreover, an increased rate of arrhythmic deaths has been observed among patients with LV dysfunction and previous myocardial infarction treated with sotalol d-isomer alone for primary prevention of sudden death[37]. Basing upon this data it seems appropriate to consider sotalol only for VAs irresponsive to β-blockers. However, in patients with chronic kidney disease and severely depressed LVEF, it still should be avoided in favor of other medications like amiodarone[22].

GENERAL ANESTHESIA AND MECHANICAL HEMODYNAMIC SUPPORT

Sedation should be considered in all patients presenting with ES in order to minimize pain related to ICD-shocks and reduce the sympathetic surge triggered by repeated ICD therapies. Benzodiazepines such as midazolam in addition to short-acting analgesics such as remifentanil should be the first choice being able to suppress the sympathetic hyperactivity and provide analgesia without negative inotropic effects[38,39]. Propofol has been reported to suppress ES but must be used carefully since its negative inotropic effects can lead to cardiogenic shock[40]. Dexmedetomidine is an α_2-presynaptic receptor agonist that reduces sympathetic activity by enhancing central vagal tone and inhibiting presynaptic catecholamine release. It should be used cautiously, however, since it may result in severe hypotension and bradycardia[41,42]. General anesthesia and mechanical ventilation should be preferred for patients with hemodynamic unstable VTs, because drugs used for anesthesia induction and maintenance can further depress cardiac function[43]. Patients with unstable VTs may also benefit from mechanical hemodynamic support like IABP, LVAD and ECMO. Hemodynamic support can reduce the arrhythmic burden by increasing coronary perfusion, reducing afterload and therefore myocardial wall stress and prevent multiple organ failure guarantying and adequate cardiac output[44-46].

NEURAXIAL MODULATION

Sympathetic hyperactivity plays a critical role in the onset and maintenance of VAs. Therefore, modulation of neuraxial efferents to the heart with epidural anesthesia or cardiac sympathetic denervation (CSD) may be a valuable option in selected patients refractory to standard medical treatment and CA[47,48]. Sympathetic denervation has been effectively used in the setting of inherited arrhythmic syndromes like long QT syndrome and catecholaminergic polymorphic VT[49,50]. However, it has been recently applied even to ES in patients with structural heart disease[47,48]. Surgical CSD is usually performed on the left side through a video-assisted thoracoscopic approach and entails removal of the lower third of the stellate ganglion (to avoid Horner syndrome) and T2-T4 thoracic ganglia. It has shown to suppress/significantly decrease the arrhythmic burden in 56% of patients refractory to AADs and CA[47]. Bilateral CSD may be considered in cases of failure of left CSD. In a small study involving 6 patients undergoing bilateral CSD after failed medical therapy, CA and epidural anesthesia, a complete response was observed in 4 (67%) of them and a partial response in another one (17%)[48]. In a recent series of 41 patients with refractory VT undergoing either left (14) or bilateral (27) CSD, a significant reduction of ICD-shocks during a mean follow-up of 367 ± 251 d was observed in 90% of the patients with a significantly higher ICD-shock free survival of 48% in the bilateral CSD group compared to 30% in the left CSD group[51].

CATHETER ABLATION

The last decade has seen a growing role for catheter ablation (CA) in the management of VT. Even if a mortality benefit has never been demonstrated in randomized-controlled trials, CA has repeatedly shown its superiority to medical therapy in reducing the arrhythmic burden[11,52,53]. Moreover, freedom from recurrent VT after CA ablation has been associated with improved survival[54,55]. For these reasons, CA should not be considered a bailout therapy but a valuable option in all patients presenting with ES related to structural heart disease. Radiofrequency CA is effective not only in the acute management of ES, leading to a control of VAs in up to 80%-90% of the patients but also over the long-term follow-up improving either VT- and ES-free survival (Table 3)[56,57]. In the recently published VANISH trial, a trend towards a 34% relative risk reduction of ES recurrences was observed in patients treated by CA compared to escalation of AADs[52]. In a pooled meta-analysis including 471 patients with ES treated invasively by different ablation strategies (*i.e.*, CA, ethanol ablation and surgical ablation), acute elimination of all inducible VAs was reached in 72% of the cases with the clinical arrhythmia effectively suppressed in 91% of the patients and a complication rate of 2% with a procedure-related death < 1%. In terms of long-term outcomes, after a median follow-up of 1.2 years, 94% of the patients were free from ES and 72% were free from any VT. Overall mortality was 17% at 1.2-years follow-up with most of the deaths related to progressive HF (62%)[58]. Similar positive results have recently been found by our group in a large series of 267 patients undergoing CA for drug-refractory ES with an acute procedural success (non inducibility of any VT with cycle length < 250 ms at the end of the procedure) of 73%, a 54% VT-free survival and a 93% ES-free survival at 60-mo follow-up. We also observed a significant reduction of VT burden in patients experiencing VT recurrence after CA[59]. Regardless, patients with ES tend to have worse prognosis after CA compared *vs* patients without ES, as evidenced by the fact that those with ES have higher VT recurrence rates

Table 3 Principal studies analyzing the role of catheter ablation in controlling electrical storm

Ref.	No. of patients	Left ventricular ejection fraction	Epicardial procedures	Acute success	VT recurrence	ES recurrence	Death	Follow-up duration, mo
Sra *et al*[64]	19	27 ± 8	0%	87%	37%	-	0%	7 ± 2
Silva *et al*[65]	14	31 ± 13	20%	80%	13%	-	27%	12 ± 17
Carbucicchio *et al*[56]	95	36 ± 11	11%	89%	34%	8%	16%	Median 22
Arya *et al*[66]	13	33 ± 9	31%	100%	38%	-	31%	Median 23
Pluta *et al*[67]	21	-	0%	81%	19%	0%	0%	3
Deneke *et al*[68]	31	28 ± 15	9%	94%	25%	12%	9%	Median 15
Kozeluhova *et al*[69]	50	29 ± 11	0%	85%	52%	26%	29%	18 ± 16
Koźluk *et al*[70]	24	27 ± 7	7%	-	34%	12%	13%	28 ± 16
Di Biase *et al*[57]	92	27 ± 5	47%	100%	34%	0%	2%	25 ± 10
Izquierdo *et al*[71]	23	34 ± 10	0%	56%	-	35%	30%	Median 18
Jin *et al*[72]	40	21 ± 7	0%	80%	53%	-	25%	17 ± 17
Kumar *et al*[73]	287	27 ± 10 in ICM and 33 ± 16 in NICM	3.8% in ICM and 24% in NICM	60% in ICM and 50% in NICM	49% in ICM and 64% in NICM	17% in ICM and 27% in NICM	25% in ICM and 28% in NICM	Median 42
Muser *et al*[59]	267	29 ± 13	22%	73%	33%	5%	29%	Median 45

VT: Ventricular tachycardia; ES: Electrical storm.

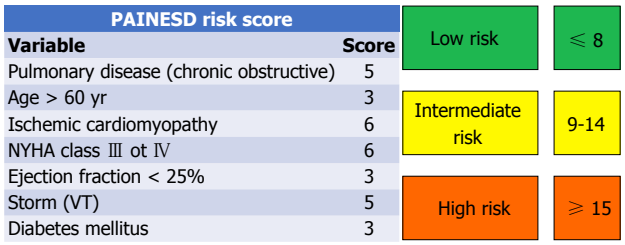

Figure 2 Proposed scoring system to identify patients at high risk of hemodynamic decompensation undergoing catheter ablation that may benefit from prophylactic mechanical circulatory support. Modified from Santangeli *et al*[43]. VT: Ventricular tachycardia.

and are more likely to die or require heart transplantation or surgical LVAD over long-term follow-up after CA[60].

As patients with chronic HF are living longer with their condition, technological advances to CA and better understanding of VT substrate has led to an increased number of procedures performed in high risk patients. Patients with advanced HF, several comorbidities as well as patients with unstable VTs are at highest risk of hemodynamic collapse during the ablation procedure and subsequent post-procedural mortality[43,61]. In a preliminary study of our group, a simple score (PAINESD score) accounting for baseline patient characteristics such as pulmonary chronic obstructive disease, age, Ischemic cardiomyopathy, NYHA class, LVEF, ES at presentation and diabetes has been demonstrated able to predict acute decompensation during VT ablation procedures and therefore has been proposed to select patients who may benefit from prophylactic mechanical support (Figure 2)[43]. Recently, the PAINESD score has been validated in a study assessing the outcomes of prophylactic *vs* rescue percutaneous LVAD in a cohort of 93 patients undergoing CA for VT related to structural heart disease[61]. The authors reported a higher 30-d mortality in patients who underwent rescue LVAD (58%) compared to patients who underwent prophylactic LVAD (4%) placement and patients who were ablated without LVAD (3%). Interestingly, patients who underwent rescue LVAD had similar PAINESD scores compared to those who underwent prophylactic LVAD insertion (mean 17.8 *vs* 16.5) while had a significantly higher score compared to the control group (mean 13.4), highlighting the importance of prophylactic mechanical support in high risk patients in order to improve post-procedural mortality[61]. Mechanical support is helpful in that it allows for prolonged mapping and ablation of inducible unstable arrhythmias. However, we have also found it to be useful when used prophylactically in high-risk patients with large areas of VT substrate undergoing a purely substrate-based ablation approach in which the long procedural times necessarily for complete substrate ablation and the consequent fluid overload related to irrigated CA may precipitate acute decompensation[43]. Importantly, some patients with advanced HF have significant biventricular dysfunction and LVAD support may be inadequate. In these cases, devices providing biventricular support like ECMO should be considered. In a recent study involving 64 patients undergoing CA of unstable VTs, the prophylactic use of ECMO has shown to allow to safely complete the procedure in 92% of the patients reaching the endpoint of VT non inducibility in 69% of them with a 88% overall survival after a median follow-up of 21 mo[46].

ALTERNATIVE APPROACHES

In cases in whom radiofrequency CA has failed or is challenging (*i.e.*, presence of mitral and aortic mechanical valves), alternative approaches like trans-coronary ethanol ablation and surgical cryoablation has been described[62]. Our group has recently reported a 73% VT-free survival at 1-year follow-up in a series of 20 consecutive patients with non-ischemic cardiomyopathy and VT refractory to conventional therapy who underwent surgical cryoablation[63]. Trans-coronary ethanol ablation performed through selective coronary angiography to identify the branches

supplying the putative VT site of origin has been recently reported in a series of 46 patients with VT related to structural heart disease and refractory to CA[62]. At least partial procedural success was reached in 66% of the patients with a 74% and 82% VT recurrence rate at 6- and 12-mo follow-up, respectively and a complication rate of 32% (1 procedure related death).

CONCLUSION

Electrical storm is a life-threatening condition with an increasing incidence related to the wider use of ICD and the improved survival of patients with advanced HF. Management of ES requires a multimodality approach including optimal ICD-reprogramming, treatment of underlying conditions, anti-arrhythmic drug therapy, sedation and CA. Radiofrequency CA appears to be the most effective treatment option, being able to control arrhythmia burden in the acute phase and improve long-term arrhythmia free survival and therefore should be considered in all patients presenting with ES. A growing evidence supports the use of prophylactic mechanical hemodynamic support as a bridge to ablation and/or recovery in high risk patients.

REFERENCES

1 **Pedersen CT**, Kay GN, Kalman J, Borggrefe M, Della-Bella P, Dickfeld T, Dorian P, Huikuri H, Kim YH, Knight B, Marchlinski F, Ross D, Sacher F, Sapp J, Shivkumar K, Soejima K, Tada H, Alexander ME, Triedman JK, Yamada T, Kirchhof P, Lip GY, Kuck KH, Mont L, Haines D, Indik J, Dimarco J, Exner D, Iesaka Y, Savelieva I; EP-Europace,UK. EHRA/HRS/APHRS expert consensus on ventricular arrhythmias. *Heart Rhythm* 2014; **11**: e166-e196 [PMID: 25179489 DOI: 10.1016/j.hrthm.2014.07.024]

2 **Conte G**, Sieira J, Ciconte G, de Asmundis C, Chierchia GB, Baltogiannis G, Di Giovanni G, La Meir M, Wellens F, Czapla J, Wauters K, Levinstein M, Saitoh Y, Irfan G, Julià J, Pappaert G, Brugada P. Implantable cardioverter-defibrillator therapy in Brugada syndrome: a 20-year single-center experience. *J Am Coll Cardiol* 2015; **65**: 879-888 [PMID: 25744005 DOI: 10.1016/j.jacc.2014.12.031]

3 **Hohnloser SH**, Al-Khalidi HR, Pratt CM, Brum JM, Tatla DS, Tchou P, Dorian P; SHock Inhibition Evaluation with AzimiLiDe (SHIELD) Investigators. Electrical storm in patients with an implantable defibrillator: incidence, features, and preventive therapy: insights from a randomized trial. *Eur Heart J* 2006; **27**: 3027-3032 [PMID: 17050586 DOI: 10.1093/eurheartj/ehl276]

4 **Della Bella P**, Baratto F, Tsiachris D, Trevisi N, Vergara P, Bisceglia C, Petracca F, Carbucicchio C, Benussi S, Maisano F, Alfieri O, Pappalardo F, Zangrillo A, Maccabelli G. Management of ventricular tachycardia in the setting of a dedicated unit for the treatment of complex ventricular arrhythmias: long-term outcome after ablation. *Circulation* 2013; **127**: 1359-1368 [PMID: 23439513 DOI: 10.1161/CIRCULATIONAHA.112.000872]

5 **Moss AJ**, Schuger C, Beck CA, Brown MW, Cannom DS, Daubert JP, Estes NA, Greenberg H, Hall WJ, Huang DT, Kautzner J, Klein H, McNitt S, Olshansky B, Shoda M, Wilber D, Zareba W. Reduction in inappropriate therapy and mortality through ICD programming. *N Engl J Med* 2012; **367**: 2275-2283 [PMID: 23131066 DOI: 10.1056/NEJMoa1211107]

6 **Poole JE**, Johnson GW, Hellkamp AS, Anderson J, Callans DJ, Raitt MH, Reddy RK, Marchlinski FE, Yee R, Guarnieri T, Talajic M, Wilber DJ, Fishbein DP, Packer DL, Mark DB, Lee KL, Bardy GH. Prognostic importance of defibrillator shocks in patients with heart failure. *N Engl J Med* 2008; **359**: 1009-1017 [PMID: 18768944 DOI: 10.1056/NEJMoa071098]

7 **Wilkoff BL**, Williamson BD, Stern RS, Moore SL, Lu F, Lee SW, Birgersdotter-Green UM, Wathen MS, Van Gelder IC, Heubner BM, Brown ML, Holloman KK;PREPARE Study Investigators. Strategic programming of detection and therapy parameters in implantable cardioverter-defibrillators reduces shocks in primary prevention patients: results from the PREPARE (Primary Prevention Parameters Evaluation) study. *J Am Coll Cardiol* 2008; **52**: 541-550 [PMID: 18687248 DOI: 10.1016/j.jacc.2008.05.011]

8 **Auricchio A**, Schloss EJ, Kurita T, Meijer A, Gerritse B, Zweibel S, AlSmadi FM, Leng CT, Sterns LD; PainFree SST Investigators. Low inappropriate shock rates in patients with single- and dual/triple-chamber implantable cardioverter-defibrillators using a novel suite of detection algorithms: PainFree SST trial primary results. *Heart Rhythm* 2015; **12**: 926-936 [PMID: 25637563 DOI: 10.1016/j.hrthm.2015.01.017]

9 **Sweeney MO**. Antitachycardia pacing for ventricular tachycardia using implantable cardioverter defibrillators. *Pacing Clin Electrophysiol* 2004; **27**: 1292-1305 [PMID: 15461721 DOI: 10.1111/j.1540-8159.2004.00622.x]

10 **Wathen MS**, DeGroot PJ, Sweeney MO, Stark AJ, Otterness MF, Adkisson WO, Canby RC, Khalighi K, Machado C, Rubenstein DS, Volosin KJ; PainFREE Rx II Investigators. Prospective randomized multicenter trial of empirical antitachycardia pacing versus shocks for spontaneous rapid ventricular tachycardia in patients with implantable cardioverter-defibrillators: Pacing Fast Ventricular Tachycardia Reduces Shock Therapies (PainFREE Rx II) trial results. *Circulation* 2004; **110**: 2591-2596 [PMID: 15492306 DOI: 10.1161/01.CIR.0000145610.64014.E4]

11 **Santangeli P**, Muser D, Maeda S, Filtz A, Zado ES, Frankel DS, Dixit S, Epstein AE, Callans DJ, Marchlinski FE. Comparative effectiveness of antiarrhythmic drugs and catheter ablation for the prevention of recurrent ventricular tachycardia in patients with implantable cardioverter-defibrillators: A systematic review and meta-analysis of randomized controlled trials. *Heart Rhythm* 2016; **13**: 1552-1559 [PMID: 26961297 DOI: 10.1016/j.hrthm.2016.03.004]

12 **Stanton MS**, Prystowsky EN, Fineberg NS, Miles WM, Zipes DP, Heger JJ. Arrhythmogenic effects of antiarrhythmic drugs: a study of 506 patients treated for ventricular tachycardia or fibrillation. *J Am Coll Cardiol* 1989; **14**: 209-215; discussion 216-217 [PMID: 2738263]

13 **Nademanee K**, Taylor R, Bailey WE, Rieders DE, Kosar EM. Treating electrical storm: sympathetic blockade versus advanced cardiac life support-guided therapy. *Circulation* 2000; **102**: 742-747 [PMID: 10942741]

14 **Bristow MR**, Ginsburg R, Umans V, Fowler M, Minobe W, Rasmussen R, Zera P, Menlove R, Shah P, Jamieson S. Beta 1- and beta 2-adrenergic-receptor subpopulations in nonfailing and failing human ventricular myocardium: coupling of both receptor subtypes to muscle contraction and selective beta 1-receptor down-regulation in heart failure. *Circ Res* 1986; **59**: 297-309 [PMID: 2876788]

15 **Billman GE**, Castillo LC, Hensley J, Hohl CM, Altschuld RA. Beta2-adrenergic receptor antagonists protect against ventricular fibrillation: in vivo and in vitro evidence for enhanced sensitivity to beta2-adrenergic stimulation in animals susceptible to sudden death. *Circulation* 1997; **96**: 1914-1922 [PMID: 9323081]

16 **Tsagalou EP**, Kanakakis J, Rokas S, Anastasiou-Nana MI. Suppression by propranolol and amiodarone of an electrical storm refractory to metoprolol and amiodarone. *Int J Cardiol* 2005; **99**: 341-342 [PMID: 15749200 DOI: 10.1016/j.ijcard.2003.11.033]

17 **Brodine WN**, Tung RT, Lee JK, Hockstad ES, Moss AJ, Zareba W, Hall WJ, Andrews M, McNitt S, Daubert JP; MADIT-II Research Group. Effects of beta-blockers on implantable cardioverter defibrillator therapy and survival in the patients with ischemic cardiomyopathy (from the Multicenter Automatic Defibrillator Implantation Trial-II). *Am J Cardiol* 2005; **96**: 691-695 [PMID: 16125497 DOI: 10.1016/j.amjcard.2005.04.046]

18 **Connolly SJ**. Evidence-based analysis of amiodarone efficacy and

safety. *Circulation* 1999; **100**: 2025-2034 [PMID: 10556230]
19 **Antiarrhythmics versus Implantable Defibrillators (AVID) Investigators.** A comparison of antiarrhythmic-drug therapy with implantable defibrillators in patients resuscitated from near-fatal ventricular arrhythmias. *N Engl J Med* 1997; **337**: 1576-1583 [PMID: 9411221 DOI: 10.1056/NEJM199711273372202]
20 **Kuck KH**, Cappato R, Siebels J, Rüppel R. Randomized comparison of antiarrhythmic drug therapy with implantable defibrillators in patients resuscitated from cardiac arrest: the Cardiac Arrest Study Hamburg (CASH). *Circulation* 2000; **102**: 748-754 [PMID: 10942742]
21 **Kowey PR**, Crijns HJ, Aliot EM, Capucci A, Kulakowski P, Radzik D, Roy D, Connolly SJ, Hohnloser SH; ALPHEE Study Investigators. Efficacy and safety of celivarone, with amiodarone as calibrator, in patients with an implantable cardioverter-defibrillator for prevention of implantable cardioverter-defibrillator interventions or death: the ALPHEE study. *Circulation* 2011; **124**: 2649-2660 [PMID: 22082672 DOI: 10.1161/CIRCULATIONAHA.111.072561]
22 **Connolly SJ**, Dorian P, Roberts RS, Gent M, Bailin S, Fain ES, Thorpe K, Champagne J, Talajic M, Coutu B, Gronefeld GC, Hohnloser SH; Optimal Pharmacological Therapy in Cardioverter Defibrillator Patients (OPTIC) Investigators. Comparison of beta-blockers, amiodarone plus beta-blockers, or sotalol for prevention of shocks from implantable cardioverter defibrillators: the OPTIC Study: a randomized trial. *JAMA* 2006; **295**: 165-171 [PMID: 16403928 DOI: 10.1001/jama.295.2.165]
23 **Greene M**, Newman D, Geist M, Paquette M, Heng D, Dorian P. Is electrical storm in ICD patients the sign of a dying heart? Outcome of patients with clusters of ventricular tachyarrhythmias. *Europace* 2000; **2**: 263-269 [PMID: 11227599 DOI: 10.1053/eupc.2000.0104]
24 **Holt DW**, Tucker GT, Jackson PR, Storey GC. Amiodarone pharmacokinetics. *Am Heart J* 1983; **106**: 840-847 [PMID: 6613830]
25 **Jung W**, Manz M, Pizzulli L, Pfeiffer D, Lüderitz B. Effects of chronic amiodarone therapy on defibrillation threshold. *Am J Cardiol* 1992; **70**: 1023-1027 [PMID: 1414899]
26 **Dixon DL**, Dunn SP, Kelly MS, McLlarky TR, Brown RE. Effectiveness of Pharmacist-Led Amiodarone Monitoring Services on Improving Adherence to Amiodarone Monitoring Recommendations: A Systematic Review. *Pharmacotherapy* 2016; **36**: 230-236 [PMID: 26846446 DOI: 10.1002/phar.1697]
27 **Liang JJ,** Yang W, Santangeli P, Schaller RD, Supple GE, Hutchinson MD, Garcia F, Lin D, Dixit S, Epstein AE, Callans DJ, Marchlinski FE, Frankel DS. Amiodarone Discontinuation or Dose Reduction Following Catheter Ablation for Ventricular Tachycardia in Structural Heart Disease. *JACC Clin Electrophysiol* 2017: **309** [DOI: 10.1016/j.jacep.2016.11.005]
28 **Gorgels AP**, van den Dool A, Hofs A, Mulleneers R, Smeets JL, Vos MA, Wellens HJ. Comparison of procainamide and lidocaine in terminating sustained monomorphic ventricular tachycardia. *Am J Cardiol* 1996; **78**: 43-46 [PMID: 8712116]
29 **Ortiz M**, Martín A, Arribas F, Coll-Vinent B, Del Arco C, Peinado R, Almendral J; PROCAMIO Study Investigators. Randomized comparison of intravenous procainamide vs. intravenous amiodarone for the acute treatment of tolerated wide QRS tachycardia: the PROCAMIO study. *Eur Heart J* 2016 [PMID: 27354046 DOI: 10.1093/eurheartj/ehw230]
30 **Marill KA**, deSouza IS, Nishijima DK, Senecal EL, Setnik GS, Stair TO, Ruskin JN, Ellinor PT. Amiodarone or procainamide for the termination of sustained stable ventricular tachycardia: an historical multicenter comparison. *Acad Emerg Med* 2010; **17**: 297-306 [PMID: 20370763 DOI: 10.1111/j.1553-2712.2010.00680.x]
31 **MacMahon S**, Collins R, Peto R, Koster RW, Yusuf S. Effects of prophylactic lidocaine in suspected acute myocardial infarction. An overview of results from the randomized, controlled trials. *JAMA* 1988; **260**: 1910-1916 [PMID: 3047448]
32 **European Heart Rhythm Association;** Heart Rhythm Society, Zipes DP, Camm AJ, Borggrefe M, Buxton AE, Chaitman B, Fromer M, Gregoratos G, Klein G, Moss AJ, Myerburg RJ, Priori SG, Quinones MA, Roden DM, Silka MJ, Tracy C, Smith SC, Jacobs AK, Adams CD, Antman EM, Anderson JL, Hunt SA, Halperin JL, Nishimura R, Ornato JP, Page RL, Riegel B, Priori SG, Blanc JJ, Budaj A, Camm AJ, Dean V, Deckers JW, Despres C, Dickstein K, Lekakis J, McGregor K, Metra M, Morais J, Osterspey A, Tamargo JL, Zamorano JL; American College of Cardiology; American Heart Association Task Force; European Society of Cardiology Committee for Practice Guidelines. ACC/AHA/ESC 2006 guidelines for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: a report of the American College of Cardiology/American Heart Association Task Force and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Develop Guidelines for Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death). *J Am Coll Cardiol* 2006; **48**: e247-e346 [PMID: 16949478 DOI: 10.1016/j.jacc.2006.07.010]
33 **Chamberlain DA**, Jewitt DE, Julian DG, Campbell RW, Boyle DM, Shanks RG. Oral mexiletine in high-risk patients after myocardial infarction. *Lancet* 1980; **2**: 1324-1327 [PMID: 6109149]
34 **Gao D**, Van Herendael H, Alshengeiti L, Dorian P, Mangat I, Korley V, Ahmad K, Golovchiner G, Aves T, Pinter A. Mexiletine as an adjunctive therapy to amiodarone reduces the frequency of ventricular tachyarrhythmia events in patients with an implantable defibrillator. *J Cardiovasc Pharmacol* 2013; **62**: 199-204 [PMID: 23609328 DOI: 10.1097/FJC.0b013e31829651fe]
35 **Pacifico A**, Hohnloser SH, Williams JH, Tao B, Saksena S, Henry PD, Prystowsky EN. Prevention of implantable-defibrillator shocks by treatment with sotalol. d,l-Sotalol Implantable Cardioverter-Defibrillator Study Group. *N Engl J Med* 1999; **340**: 1855-1862 [PMID: 10369848 DOI: 10.1056/NEJM199906173402402]
36 **Kettering K**, Mewis C, Dörnberger V, Vonthein R, Bosch RF, Kühlkamp V. Efficacy of metoprolol and sotalol in the prevention of recurrences of sustained ventricular tachyarrhythmias in patients with an implantable cardioverter defibrillator. *Pacing Clin Electrophysiol* 2002; **25**: 1571-1576 [PMID: 12494613]
37 **Waldo AL**, Camm AJ, deRuyter H, Friedman PL, MacNeil DJ, Pauls JF, Pitt B, Pratt CM, Schwartz PJ, Veltri EP. Effect of d-sotalol on mortality in patients with left ventricular dysfunction after recent and remote myocardial infarction. The SWORD Investigators. Survival With Oral d-Sotalol. *Lancet* 1996; **348**: 7-12 [PMID: 8691967]
38 **Mandel JE**, Hutchinson MD, Marchlinski FE. Remifentanil-midazolam sedation provides hemodynamic stability and comfort during epicardial ablation of ventricular tachycardia. *J Cardiovasc Electrophysiol* 2011; **22**: 464-466 [PMID: 20812933 DOI: 10.1111/j.1540-8167.2010.01889.x]
39 **Ogletree ML**, Sprung J, Moravec CS. Effects of remifentanil on the contractility of failing human heart muscle. *J Cardiothorac Vasc Anesth* 2005; **19**: 763-767 [PMID: 16326302 DOI: 10.1053/j.jvca.2004.11.034]
40 **Mulpuru SK**, Patel DV, Wilbur SL, Vasavada BC, Furqan T. Electrical storm and termination with propofol therapy: a case report. *Int J Cardiol* 2008; **128**: e6-e8 [PMID: 17692956 DOI: 10.1016/j.ijcard.2007.05.052]
41 **Tarvainen MP**, Georgiadis S, Laitio T, Lipponen JA, Karjalainen PA, Kaskinoro K, Scheinin H. Heart rate variability dynamics during low-dose propofol and dexmedetomidine anesthesia. *Ann Biomed Eng* 2012; **40**: 1802-1813 [PMID: 22419196 DOI: 10.1007/s10439-012-0544-1]
42 **Gerlach AT**, Murphy CV. Dexmedetomidine-associated bradycardia progressing to pulseless electrical activity: case report and review of the literature. *Pharmacotherapy* 2009; **29**: 1492 [PMID: 19947809 DOI: 10.1592/phco.29.12.1492]
43 **Santangeli P**, Muser D, Zado ES, Magnani S, Khetpal S, Hutchinson MD, Supple G, Frankel DS, Garcia FC, Bala R, Riley MP, Lin D, Rame JE, Schaller R, Dixit S, Marchlinski FE, Callans DJ. Acute hemodynamic decompensation during catheter ablation of scar-related ventricular tachycardia: incidence, predictors, and impact on mortality. *Circ Arrhythm Electrophysiol* 2015; **8**: 68-75 [PMID: 25491601 DOI: 10.1161/CIRCEP.114.002155]
44 **Miller MA**, Dukkipati SR, Mittnacht AJ, Chinitz JS, Belliveau

L, Koruth JS, Gomes JA, d'Avila A, Reddy VY. Activation and entrainment mapping of hemodynamically unstable ventricular tachycardia using a percutaneous left ventricular assist device. *J Am Coll Cardiol* 2011; **58**: 1363-1371 [PMID: 21920266 DOI: 10.1016/j.jacc.2011.06.022]

45 **Miller MA**, Dukkipati SR, Chinitz JS, Koruth JS, Mittnacht AJ, Napolitano C, d'Avila A, Reddy VY. Percutaneous hemodynamic support with Impella 2.5 during scar-related ventricular tachycardia ablation (PERMIT 1). *Circ Arrhythm Electrophysiol* 2013; **6**: 151-159 [PMID: 23255277 DOI: 10.1161/CIRCEP.112.975888]

46 **Baratto F**, Pappalardo F, Oloriz T, Bisceglia C, Vergara P, Silberbauer J, Albanese N, Cireddu M, D'Angelo G, Di Prima AL, Monaco F, Paglino G, Radinovic A, Regazzoli D, Silvetti S, Trevisi N, Zangrillo A, Della Bella P. Extracorporeal Membrane Oxygenation for Hemodynamic Support of Ventricular Tachycardia Ablation. *Circ Arrhythm Electrophysiol* 2016; **9** [PMID: 27932426 DOI: 10.1161/CIRCEP.116.004492]

47 **Bourke T**, Vaseghi M, Michowitz Y, Sankhla V, Shah M, Swapna N, Boyle NG, Mahajan A, Narasimhan C, Lokhandwala Y, Shivkumar K. Neuraxial modulation for refractory ventricular arrhythmias: value of thoracic epidural anesthesia and surgical left cardiac sympathetic denervation. *Circulation* 2010; **121**: 2255-2262 [PMID: 20479150 DOI: 10.1161/CIRCULATIONAHA.109.929703]

48 **Ajijola OA**, Lellouche N, Bourke T, Tung R, Ahn S, Mahajan A, Shivkumar K. Bilateral cardiac sympathetic denervation for the management of electrical storm. *J Am Coll Cardiol* 2012; **59**: 91-92 [PMID: 22192676 DOI: 10.1016/j.jacc.2011.09.043]

49 **Schwartz PJ**, Priori SG, Cerrone M, Spazzolini C, Odero A, Napolitano C, Bloise R, De Ferrari GM, Klersy C, Moss AJ, Zareba W, Robinson JL, Hall WJ, Brink PA, Toivonen L, Epstein AE, Li C, Hu D. Left cardiac sympathetic denervation in the management of high-risk patients affected by the long-QT syndrome. *Circulation* 2004; **109**: 1826-1833 [PMID: 15051644 DOI: 10.1161/01.CIR.0000125523.14403.1E]

50 **Wilde AA**, Bhuiyan ZA, Crotti L, Facchini M, De Ferrari GM, Paul T, Ferrandi C, Koolbergen DR, Odero A, Schwartz PJ. Left cardiac sympathetic denervation for catecholaminergic polymorphic ventricular tachycardia. *N Engl J Med* 2008; **358**: 2024-2029 [PMID: 18463378 DOI: 10.1056/NEJMoa0708006]

51 **Vaseghi M**, Gima J, Kanaan C, Ajijola OA, Marmureanu A, Mahajan A, Shivkumar K. Cardiac sympathetic denervation in patients with refractory ventricular arrhythmias or electrical storm: intermediate and long-term follow-up. *Heart Rhythm* 2014; **11**: 360-366 [PMID: 24291775 DOI: 10.1016/j.hrthm.2013.11.028]

52 **Sapp JL**, Wells GA, Parkash R, Stevenson WG, Blier L, Sarrazin JF, Thibault B, Rivard L, Gula L, Leong-Sit P, Essebag V, Nery PB, Tung SK, Raymond JM, Sterns LD, Veenhuyzen GD, Healey JS, Redfearn D, Roux JF, Tang AS. Ventricular Tachycardia Ablation versus Escalation of Antiarrhythmic Drugs. *N Engl J Med* 2016; **375**: 111-121 [PMID: 27149033 DOI: 10.1056/NEJMoa1513614]

53 **Liang JJ**, Muser D, Santangeli P. Ventricular Tachycardia Ablation Clinical Trials. *Card Electrophysiol Clin* 2017; **9**: 153-165 [PMID: 28167083 DOI: 10.1016/j.ccep.2016.10.012]

54 **Tung R**, Vaseghi M, Frankel DS, Vergara P, Di Biase L, Nagashima K, Yu R, Vangala S, Tseng CH, Choi EK, Khurshid S, Patel M, Mathuria N, Nakahara S, Tzou WS, Sauer WH, Vakil K, Tedrow U, Burkhardt JD, Tholakanahalli VN, Saliaris A, Dickfeld T, Weiss JP, Bunch TJ, Reddy M, Kanmantharedy A, Callans DJ, Lakkireddy D, Natale A, Marchlinski F, Stevenson WG, Della Bella P, Shivkumar K. Freedom from recurrent ventricular tachycardia after catheter ablation is associated with improved survival in patients with structural heart disease: An International VT Ablation Center Collaborative Group study. *Heart Rhythm* 2015; **12**: 1997-2007 [PMID: 26031376 DOI: 10.1016/j.hrthm.2015.05.036]

55 **Muser D**, Santangeli P, Castro SA, Pathak RK, Liang JJ, Hayashi T, Magnani S, Garcia FC, Hutchinson MD, Supple GG, Frankel DS, Riley MP, Lin D, Schaller RD, Dixit S, Zado ES, Callans DJ, Marchlinski FE. Long-Term Outcome After Catheter Ablation of Ventricular Tachycardia in Patients With Nonischemic Dilated Cardiomyopathy. *Circ Arrhythm Electrophysiol* 2016; **9**: pii: e004328 [PMID: 27733494 DOI: 10.1161/CIRCEP.116.004328]

56 **Carbucicchio C**, Santamaria M, Trevisi N, Maccabelli G, Giraldi F, Fassini G, Riva S, Moltrasio M, Cireddu M, Veglia F, Della Bella P. Catheter ablation for the treatment of electrical storm in patients with implantable cardioverter-defibrillators: short- and long-term outcomes in a prospective single-center study. *Circulation* 2008; **117**: 462-469 [PMID: 18172038 DOI: 10.1161/CIRCULATIONAHA.106.686534]

57 **Di Biase L**, Santangeli P, Burkhardt DJ, Bai R, Mohanty P, Carbucicchio C, Dello Russo A, Casella M, Mohanty S, Pump A, Hongo R, Beheiry S, Pelargonio G, Santarelli P, Zucchetti M, Horton R, Sanchez JE, Elayi CS, Lakkireddy D, Tondo C, Natale A. Endo-epicardial homogenization of the scar versus limited substrate ablation for the treatment of electrical storms in patients with ischemic cardiomyopathy. *J Am Coll Cardiol* 2012; **60**: 132-141 [PMID: 22766340 DOI: 10.1016/j.jacc.2012.03.044]

58 **Nayyar S**, Ganesan AN, Brooks AG, Sullivan T, Roberts-Thomson KC, Sanders P. Venturing into ventricular arrhythmia storm: a systematic review and meta-analysis. *Eur Heart J* 2013; **34**: 560-571 [PMID: 23264584 DOI: 10.1093/eurheartj/ehs453]

59 **Muser D,** Liang JJ, Pathak RK, Magnani S, Castro SA, Hayashi T, Garcia FC, Supple GE, Riley MP, Lin D, Dixit S, Zado ES, Frankel DS, Callans DJ, Marchlinski FE, Santangeli P. Long-Term Outcomes of Catheter Ablation of Electrical Storm in Nonischemic Dilated Cardiomyopathy Compared With Ischemic Cardiomyopathy. *JACC Clin Electrophysiol* 2017: 371 [DOI: 10.1016/j.jacep.2017.01.020]

60 **Frankel DS,** Liang JJ, Supple G, Dixit S, Hutchinson MD, Elafros MA, Callans DJ, Marchlinski FE. Electrophysiological Predictors of Transplantation and Left Ventricular Assist Device-Free Survival in Patients With Nonischemic Cardiomyopathy Undergoing Ventricular Tachycardia Ablation. *JACC Clin Electrophysiol* 2015; **1:** 398-407 [DOI: 10.1016/j.jacep.2015.07.005]

61 **Mathuria N**, Wu G, Rojas-Delgado F, Shuraih M, Razavi M, Civitello A, Simpson L, Silva G, Wang S, Elayda M, Kantharia B, Singh S, Frazier OH, Cheng J. Outcomes of pre-emptive and rescue use of percutaneous left ventricular assist device in patients with structural heart disease undergoing catheter ablation of ventricular tachycardia. *J Interv Card Electrophysiol* 2017; **48**: 27-34 [PMID: 27497847 DOI: 10.1007/s10840-016-0168-8]

62 **Kumar S**, Barbhaiya CR, Sobieszczyk P, Eisenhauer AC, Couper GS, Nagashima K, Mahida S, Baldinger SH, Choi EK, Epstein LM, Koplan BA, John RM, Michaud GF, Stevenson WG, Tedrow UB. Role of alternative interventional procedures when endo- and epicardial catheter ablation attempts for ventricular arrhythmias fail. *Circ Arrhythm Electrophysiol* 2015; **8**: 606-615 [PMID: 25925229 DOI: 10.1161/CIRCEP.114.002522]

63 **Liang JJ**, Betensky BP, Muser D, Zado ES, Anter E, Desai ND, Callans DJ, Deo R, Frankel DS, Hutchinson MD, Lin D, Riley MP, Schaller RD, Supple GE, Santangeli P, Acker MA, Bavaria JE, Szeto WY, Vallabhajosyula P, Marchlinski FE, Dixit S. Long-term outcome of surgical cryoablation for refractory ventricular tachycardia in patients with non-ischemic cardiomyopathy. *Europace* 2017 [PMID: 28402404 DOI: 10.1093/europace/eux029]

64 **Sra J**, Bhatia A, Dhala A, Blanck Z, Deshpande S, Cooley R, Akhtar M. Electroanatomically guided catheter ablation of ventricular tachycardias causing multiple defibrillator shocks. *Pacing Clin Electrophysiol* 2001; **24**: 1645-1652 [PMID: 11816634]

65 **Silva RM**, Mont L, Nava S, Rojel U, Matas M, Brugada J. Radiofrequency catheter ablation for arrhythmic storm in patients with an implantable cardioverter defibrillator. *Pacing Clin Electrophysiol* 2004; **27**: 971-975 [PMID: 15271018 DOI: 10.1111/j.1540-8159.2004.00567.x]

66 **Arya A**, Bode K, Piorkowski C, Bollmann A, Sommer P, Gaspar T, Wetzel U, Husser D, Kottkamp H, Hindricks G. Catheter ablation of electrical storm due to monomorphic ventricular tachycardia in patients with nonischemic cardiomyopathy: acute results and its effect on long-term survival. *Pacing Clin Electrophysiol* 2010; **33**: 1504-1509 [PMID: 20636312 DOI: 10.1111/j.1540-8159.2010.02835.x]

67 **Pluta S**, Lenarczyk R, Pruszkowska-Skrzep P, Kowalski O, Sokal

A, Sredniawa B, Mazurek M, Kalarus Z. Transseptal versus transaortic approach for radiofrequency ablation in patients with cardioverter-defibrillator and electrical storm. *J Interv Card Electrophysiol* 2010; **28**: 45-50 [PMID: 20180007 DOI: 10.1007/s10840-009-9464-x]

68 **Deneke T**, Shin DI, Lawo T, Bösche L, Balta O, Anders H, Bünz K, Horlitz M, Grewe PH, Lemke B, Mügge A. Catheter ablation of electrical storm in a collaborative hospital network. *Am J Cardiol* 2011; **108**: 233-239 [PMID: 21529742 DOI: 10.1016/j.amjcard.2011.03.030]

69 **Kozeluhova M**, Peichl P, Cihak R, Wichterle D, Vancura V, Bytesnik J, Kautzner J. Catheter ablation of electrical storm in patients with structural heart disease. *Europace* 2011; **13**: 109-113 [PMID: 20947570 DOI: 10.1093/europace/euq364]

70 **Koźluk E**, Gaj S, Kiliszek M, Lodziński P, Piątkowska A, Opolski G. Efficacy of catheter ablation in patients with an electrical storm. *Kardiol Pol* 2011; **69**: 665-670 [PMID: 21769783]

71 **Izquierdo M**, Ruiz-Granell R, Ferrero A, Martínez A, Sánchez-Gomez J, Bonanad C, Mascarell B, Morell S, García-Civera R. Ablation or conservative management of electrical storm due to monomorphic ventricular tachycardia: differences in outcome. *Europace* 2012; **14**: 1734-1739 [PMID: 22696517 DOI: 10.1093/europace/eus186]

72 **Jin Q**, Jacobsen PK, Pehrson S, Chen X. Acute and long term outcomes of catheter ablation using remote magnetic navigation for the treatment of electrical storm in patients with severe ischemic heart failure. *Int J Cardiol* 2015; **183**: 11-16 [PMID: 25662047 DOI: 10.1016/j.ijcard.2015.01.066]

73 **Kumar S**, Fujii A, Kapur S, Romero J, Mehta NK, Tanigawa S, Epstein LM, Koplan BA, Michaud GF, John RM, Stevenson WG, Tedrow UB. Beyond the Storm: Comparison of Clinical Factors, Arrhythmogenic Substrate, and Catheter Ablation Outcomes in Structural Heart Disease Patients With versus Those Without a History of Ventricular Tachycardia Storm. *J Cardiovasc Electrophysiol* 2017; **28**: 56-67 [PMID: 27781325 DOI: 10.1111/jce.13117]

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MINIREVIEWS

Wearable cardioverter defibrillator: Bridge or alternative to implantation?

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Abstract

The implantable cardioverter-defibrillator (ICD) is effective to prevent sudden cardiac death (SCD) in selected patients with heart disease known to be at high risk for ventricular arrhythmia. Nevertheless, this invasive and definitive therapy is not indicated in patients with potentially transient or reversible causes of sudden death, or in patients with temporary contra-indication for ICD placement. The wearable cardioverter defibrillator (WCD) is increasingly used for SCD prevention both in patients awaiting ICD implantation or with an estimated high risk of ventricular arrhythmia though to be transient. We conducted a review of current clinical uses and benefits of the WCD, and described its technical aspects, limitations and perspectives.

Key words: Wearable cardioverter/defibrillator; Sudden cardiac death; Secondary prevention; Primary prevention; Ventricular arrhythmias

Core tip: The wearable cardioverter defibrillator is increasingly used for sudden cardiac death prevention in patients thought to have a transient and/or reversible high risk for life-threatening ventricular arrhythmia. Evidences sustaining the use of this external device are growing. We provided an evidence base review in the light of new data.

Barraud J, Cautela J, Orabona M, Pinto J, Missenard O, Laine M, Thuny F, Paganelli F, Bonello L, Peyrol M. Wearable cardioverter defibrillator: Bridge or alternative to implantation? *World J Cardiol* 2017; 9(6): 531-538 Available from: URL: http://www.wjgnet.com/1949-8462/full/v9/i6/531.htm DOI: http://dx.doi.org/10.4330/wjc.v9.i6.531

INTRODUCTION

Sudden cardiac death (SCD) is an unpredictable event which leads to death in the absence of immediate resuscitation maneuvers and adequate therapies. Up to 23% of SCD are attributable to ventricular arrhythmias (VA)[1]. The implantable cardioverter-defibrillator (ICD) has proved to be highly effective for SCD secondary prevention. Otherwise, it has also been demonstrated to prevent SCD in selected patients with heart disease known to be at high risk for life-threatening VA[2-4]. However, long-term ICD-related complications, cost issues, social impact and quality of life force a rigorous evaluation of patients before ICD placement. Furthermore, some situations at high risk of VA-related SCD are known to be limited in time. For example, although SCD rate was 2.3% in patients with low left ventricular ejection fraction (LVEF) during the first month following myocardial infarction (MI), ICD implantation during the first 40 d post-MI failed to reduce total mortality. This result was essentially due to a large amount of non-arrhythmic death during this period[5]. In addition, up to 40% of patients with coronary artery disease and low LVEF do not meet the current criteria for ICD implantation after complete myocardial revascularization and/or optimization of medical therapy[6].

The wearable cardioverter defibrillator (WCD) is increasingly used for SCD prevention both in patients awaiting ICD implantation or with an estimated high risk of VA though to be transient. This external device, which has been demonstrated to effectively terminate spontaneous and induced VA by automatic defibrillation shock delivery, requires no surgical intervention and is entirely removable. We conducted a review of current clinical uses and benefits of WCD, and described its technical aspects, limitations and perspectives.

TECHNICAL ASPECT

Currently available WCD is the Lifevest 4000® [ZOLL Lifecor Corporation (ZOLL), Pittsburgh, PA, United States]. With the LifeVest 4000®, the chest is surrounded by an elastic belt including an electrocardiographic (ECG) monitoring system with four dry, non-adhesive electrodes and the defibrillation system consisting in two posterior and one apical electrodes (Figure 1). The whole is maintained by shoulder straps forming a light washable vest and connected to a monitor unit including the battery, an LCD screen for message display and two "response buttons" for patient defibrillation shock withholding. The monitor unit is held in a holster or around the waist (Figure 2). Two batteries are delivered with the WCD; each one lasts for 24 h so that one is always in charge during the use of the other Total device weight is about 600 g. ECG electrodes provide two left-right and front-back bipolar ECG signals (Figure 3). The ECG is continuously recorded and analyzed. Following parameters can be programmed: (1) rate intervals for ventricular fibrillation (VF) zone: 120 to 250 bpm, default 200 bpm and ventricular tachycardia (VT) zone: 120 bpm to VF zone; (2) shock delay, *i.e.,* time from arrhythmia detection to shock delivery: 60 to 180 s in VT zone and 25 to 55 s for VF zone. Further delay up to 30 s may be added at night; and (3) shock energy: 75 to 150 J.

The WCD automatically delivers, *i.e.,* without neither patient nor witness intervention, defibrillation shocks for termination of life-threatening VA. Arrhythmia detection and discrimination (for arrhythmia detected in the VT zone) occur within few seconds after the rhythm disorder onset. In case of VA detection within the programmed VT or VF zone, the device alerts the patient of the imminence of a shock starting by vibrations of the defibrillation electrodes during 5 s, followed by a low monotonal sound signal then high bitonal sound signal. Finally, a voice warning during the few lasts s precedes the shock delivery. During this period, the patient, if still conscious, can withhold shock delivery by pressing the two response buttons on the monitor unit. Without this well-done intervention, defibrillation shock is delivered, synchronized to the R-wave signal in case of monomorphic VT. In order to improve shock impedance, and to prevent skin burns, the defibrillation electrodes release a conductive gel contained in small capsules before shock delivery (Figure 4). Up to five shocks can be delivered for the same episode. ECG signal is continuously recorded and reviewable 30 s prior to the detection of arrhythmia to 15 s after the alarms stop (Figure 5). Total duration from the onset of the arrhythmia to shock delivery, (including time of fulfilling detection criteria, confirmation, alarms and capacitor charging) is about 50 s. Daily remote monitoring advices medical staff about VA occurrence and therapies, daily ECGs, as well as patient compliance (assessed by the daily wear time).

PATIENT EDUCATION AND COMPLIANCE

Patient education by specialized healthcare givers on how to properly wear the device, change the battery and disable shock delivery is a crucial step. In our experience, 10% to 15% patients eligible for this therapy are not able to understand instructions to withhold therapies or change battery and therefore are not treated with the WCD. In order to improve patient knowledge and handle of the WCD, we systematically schedule an additional patient education session 10 to 15 d after hospital discharge.

Similarly, understanding and knowledge of his cardiac disease and potentials benefits associated with the use of the WCD is a critical part of patient care, aiming high device compliance which is the prerequisite of effective SCD protection. Lack of compliance might have dramatics consequences. Indeed, in various studies, the majority of SCD observed during follow-up were observed in patients not or not-correctly wearing the WCD[7,8]. Weight and footprint of the device were the main reasons for low compliance. On the other hand, as high as 22.5% of patients discontinued the use of WCD due to comfort or lifestyle issues in study from Feldman *et al*[8]. A 40% reduction of size and weight of the device was associated with a significant decrease in the rate of WCD therapy

Figure 1 Wearable cardioverter defibrillator. The two defibrillator electrodes are worn on the back of the garment, when the four monitoring electrodes are placed on the elastic belt around the chest. Both systems are connected to the monitor unit.

Figure 2 Wearable cardioverter defibrillator worn by a patient under clothes; monitor unit is worn on waist belt or in a holster.

interruption (14.2%) in a more recent report[9].

Overall, national registries showed good compliance with the actual WCD[6,10]. In United States' experience, of 3569 patients wearing WCD, > 50% of patients achieved a 90% wear time compliance[9]. In the German registry, this number grows to 72%[11]. In both studies, long period of therapy was associated with higher time of wearing. Otherwise, remote monitoring allows measurement of daily WCD wear time and medical staff is alerted in case of low patient compliance so that prompt corrective measures can be taken.

CLINICAL STUDIES

Efficacy

Auricchio *et al*[12] were the firsts to report the efficacy of the first generation WCD (WCD™ device, LIFECOR, Pittsburgh, Pennsylvania) for termination of life-threatening VA. This device reliably stopped induced VT or VF by automatically delivering a 230 J defibrillation shock in 15 SCD survivors. The firsts prospective multicenter studies demonstrating clinical benefit of the WCD were the Wearable Defibrillator Investigate Trial (WEARIT) and Bridge to ICD in Patients at Risk Of Arrhythmic Death (BIROAT) studies[8]. Inclusion criteria for the WEARIT study was

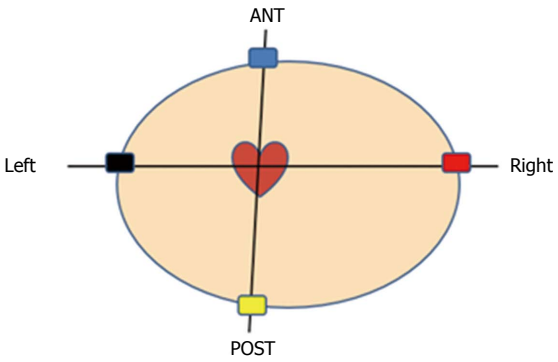

Figure 3 Four electrocardiographic electrodes position, and two left-right and front-back bipolar electrocardiographic vectors.

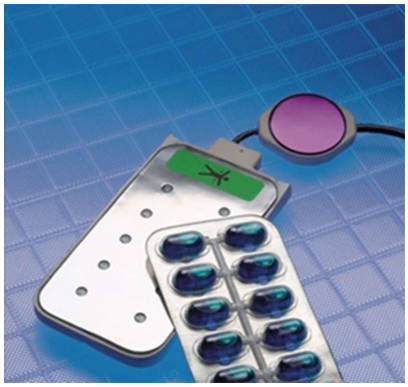

Figure 4 One defibrillator electrode with ten gel capsules inserted in, and one non-adhesive electrocardiogram electrode.

symptomatic NYHA Ⅲ or Ⅳ ambulatory heart failure and LVEF < 0.30. Differently, the BIROAD study enrolled: (1) patients after a recent MI or coronary artery bypass grafting (CABG) and having complications such as VA, syncope or low LVEF < 0.30, but not receiving an ICD for up to 4 mo; and (2) patients who met criteria for an ICD but refused therapy or had to wait for at least 4 mo before implantation. A total of 289 patients were enrolled in both studies, united into one at the request of the Federal Drug Administration, and followed during a total of 901 mo of patient use. During the follow-up, 6 of 8 defibrillation attempts were successful. No patient died while correctly wearing the WCD.

Thereafter, some large studies validated the clinical benefit of this therapy and evaluated the occurrence of VA during the period of the WCD use in patients with low LVEF in the setting of ischemic heart disease. Rate of patients receiving appropriate shock within the 3 mo following percutaneous coronary intervention (PCI) or CABG varied from 1.3% to 1.7%[9,10]. Prolonging WCD wearing period to 15 mo resulted in increasing rate of appropriate WCD shock to 4.1%[13]. In the United States' experience, first shock success was of 99% for all VT/VF events, and survival after VT/VF events was 89.5%[9]. Importantly, no death could be attributed to WCD technical failure since its introduction. For note, at the end of the WCD period use, about 60% of patients were not

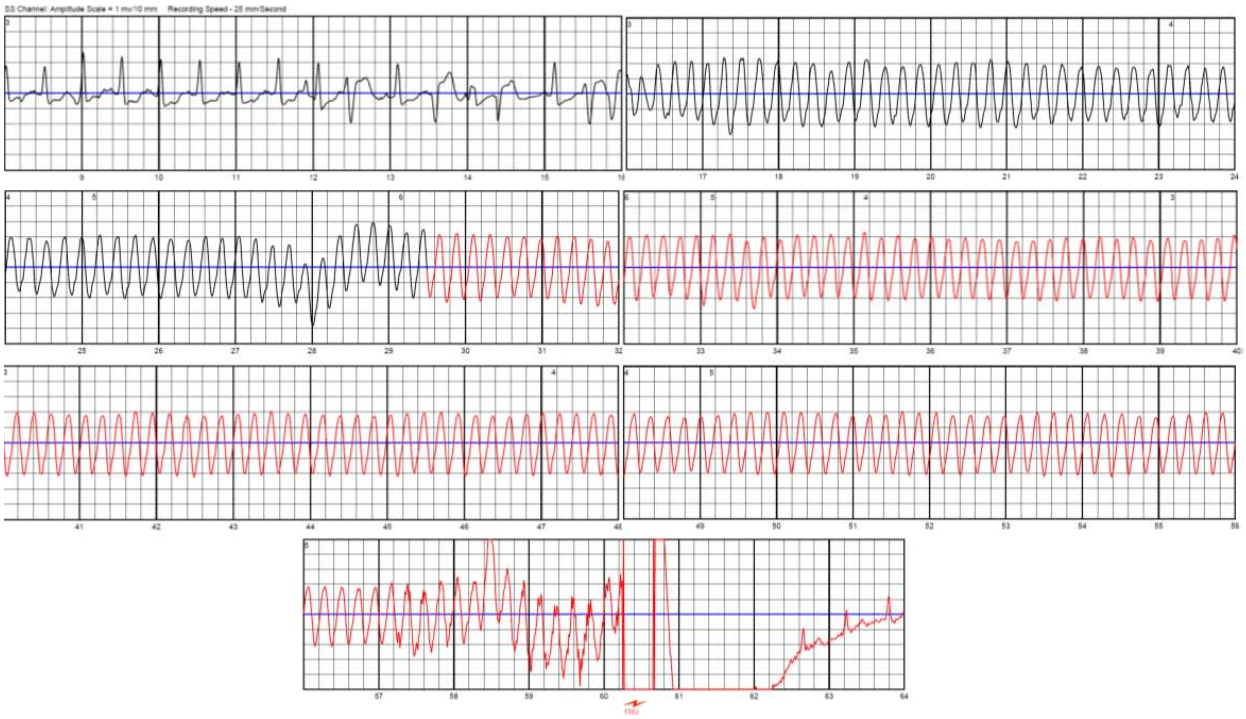

Figure 5 Ventricular tachycardia correctly diagnosed and treated by wearable cardioverter defibrillator. Red line corresponds to sound signal. A 150-J defibrillation shock, automatically delivered by the device, terminated the arrhythmia.

eligible anymore for ICD implantation, mainly because of left ventricular ejection fraction improvement[6].

Inappropriate shock

From 0.4% to 3% of patients experienced inappropriate WCD shock[6,9,10,14]. The WCD is an external device, which is dramatically exposed to noise detection. Inappropriate shocks are mainly related to noise artifacts or T wave oversensing[15]. Compared to conventional transvenous ICD, the rate of inappropriate shock with the WCD is low. This fact is explained by the possibility for the patient to withhold shock delivery while pressing the response buttons. Incidence of false alarms attributable to artifacts is unknown.

Current indications

According to current guidelines for management of patients presenting with VA and the prevention of SCD, "the WCD may be considered for adult patients with poor LV systolic function who are at risk of sudden arrhythmic death for a limited period, but are not candidates for an implantable defibrillator *(e.g.,* bridge to transplant, bridge to transvenous implant, peripartum cardiomyopathy, active myocarditis and arrhythmias in the early post-myocardial infarction phase). In patients presenting with high risk of SCD, but non-indicated for an ICD implantation because of temporary contra-indication, in expectation of a diagnosis, or if the arrhythmic risk may evolve"[16]. For the Heart Rhythm Society, the use of WCD is reasonable in patients with a clear indication of ICD placement but with temporary contra indication to the procedure (infection for example) or as a bridge therapy to heart transplantation. Otherwise, the use of the WCD should be considered in additional clinical situations: In patients with high risk for SCD due to LV dysfunction that may resolve over time (following myocardial revascularization, myocarditis…) or with a potentially treatable cause (arrhythmia-induced or chemotherapy-induced LV dysfunction)[17].

Well-validated clinical situation to consider the WCD

After acute myocardial infarction: Sudden cardiac death occurred in 2.3% of patients with severely depressed LVEF during the first month post-MI[18]. However, the risk of life-threatening VA significantly decreases with LVEF recovery after acute event[19]. Furthermore, in primary prevention studies, ICD benefit occurred years after implantation[3,20]. Former studies showed no impact of early implantation of ICD after AMI on overall mortality[5,21]. The DINAMIT was an open-label trial including 674 patients 6 to 40 d after an AMI, with LVEF > 0.35 and impaired cardiac autonomic function. Patients were randomized in a 1/1 fashion for medical treatment or medical treatment and ICD placement. This study did not found statistical difference in overall mortality between the 2 groups. Indeed, a smaller proportion of SCD observed in the ICD group was offset by an increase in the rate of non-arrhythmic deaths among these patients. These results are consistent with findings from the IRIS study[21]. The United States' experience with the WCD was derived from a national database and included 8453 patients with ejection fraction < 0.35 early after acute MI[10]. One point four percent of patients were correctly treated by WCD, whose 75% in the first month of use. The median time to first WCD therapy was 9 d. The resuscitation

survival rate was of 91%. The VEST Prevention of Early Sudden Death Trial and VEST Registry (VEST) is a randomized simple blind trial currently enrolling patients with LVEF < 0.35 following AMI. This study aims to demonstrate a reduction of SCD within the first three mo following AMI. Enrollment exceeded 1700 patients in 2015, results are awaited[22].

After revascularization procedures: Life-threatening VA are a frequent cause of SCD after elective revascularization CABG or PCI[23]. ICD implantation is mandated in patients with reduced LVEF < 0.35 evaluated at least 3 mo after revascularization because of possible LV systolic function recovery. In the setting of LV dysfunction <0.35 after CABG or PCI, Zishiri *et al*[24] found a significant reduction in early mortality hazard in patients treated with the WCD (3% *vs* 7%, $P < 0.05$). In this subset of patients, appropriate therapy rate was 1.3%.

Terminal cardiomyopathy listed for heart transplantation: The risk of SCD in patients awaiting heart transplantation is about 10% at one year[25]. Although ICD is largely used in this population of patients, complications, such as infection, are frequent, particularly in LV assist devices receivers[26]. The WCD was found to be a safe and efficient transitory solution to protect this population as a bridge to transplantation[27].

ICD infections, before re-implantation: Cardiac implanted electronic devices infections require complete system removal, associated with antibiotic therapy for 2 to 6 wk. Period before re-implantation is long, so that patients could beneficiate from WCD protection without deleting hospital discharge, as the risk of SCD remains unchanged[7] during this period. Highest incidence rate of appropriate therapies remains to patients after ICD explantation for infection in expectation of reimplantation compared with other indications[14]. Therefore, the AHA guidelines sustain its use in this clinical setting with a Class ⅡA recommendation (level of evidence C)[17].

Nonischemic cardiomyopathy: Benefice of ICD in prevention of SCA in non-ischemic cardiomyopathy (NICM) patients is still a matter of debate. Low LVEF < 0.35 remains the only criterion validated to stratify the risk of SCD among these patients[4,28,29]. Plurality of etiologies, absence of criteria that define the likelihood of reversibility and potential for recovery after optimal medical therapy[30] make difficult the assessment of the long term risk of VA in this population of patients. Early ICD implantation, within the firsts mo after diagnosis failed to improve long term survival[28,31]. Therefore, LVEF assessment for SCD risk stratification is recommended at least 3 mo after optimal medical treatment[16], and some studies tend to delay ICD placement to 9 mo[32-34]. Furthermore, in a recent large randomized study, prophylactic ICD implantation in patients with symptomatic NICM showed no impact on mortality[35]. Indeed, the DANISH study included 556 patients with symptomatic systolic NICM and LVEF ⩽ 0.35 who were assigned to receive an ICD, and 560 patients assigned to receive medical care, both group receiving CRT if indicated. Primary evaluation criteria was death from any cause. No difference was observed between the two groups after a median follow-up period of 67 mo. Only patients younger than 68 years of age showed a lower rate of death after ICD implantation, independent of CRT status.

Small cohorts aimed to evaluate the benefit of WCD in patients with NICM. Incidence of appropriate therapies varied from 0% to 5.5%[6,8,9,15,36]. Prospective studies are lacking in this heterogeneous population to specify real benefit.

Unfrequent clinical presentation

Tako-tsubo cardiomyopathy: Tako-tsubo cardiomyopathy is a heterogeneous provider of SCD, and life-threatening VA occur during the first wk after disease onset. Prevalence of VA varies between 8% and 13.5%[37,38]. Patients with QT prolongation after stress cardiomyopathy demonstrated a higher risk of VA. This subset of patients might have substantial benefit of the WCD use[39,40].

Peripartum cardiomyopathy: Peripartum cardiomyopathy patients with severely reduced LVEF have an elevated risk of VA[41,42]. Up to 38% of deaths in this population are sudden and most of them (87%) occur within the 6 mo following the diagnosis[43]. The WCD was found to correctly treat these VA during the first mo after diagnosis, until ICD implantation or systolic function recovery[44].

Prediction of cardiomyopathy and evaluation of SCD risk after acute myocarditis is difficult. Assessment of the LVEF appears to be an insufficient criterion[45,46]. Similarly to Tako-tsubo cardiomyopathy or peripartum cardiomyopathy, myocarditis has a potentially high likelihood of cardiac recovery so that the WCD may be limited to patients in secondary prevention or with particularly high-risk features[17].

Pharmacology-induced cardiomyopathies (alcohol, methamphetamine, trastuzumab) are associated with a great potential of recovery of LV systolic function after withdrawal of the putative agent and optimal medical therapy.

In all these various clinical settings known to result in both potentially transient LV dysfunction and high SCD risk, the WCD might be a valuable tool in both for SCD prevention and to provide additional information for subsequent SCD risk stratification.

Clinical perspectives

Unexplained syncope: The diagnostic of syncope encompass various causes. First, it can be the precursor event of SCD. Then it is a major step in the rhythmic risk in patients presenting with inherited arrhythmia syndromes or structural heart diseases such as hypertrophic cardiomyopathy. During this time of evaluation, no rhythmic

protection can be offered by classical monitoring approaches, such as implantable cardiac monitors. The WCD may bridge this vulnerable period until diagnostic has been established. The Ambulatory Post-Syncope Arrhythmia Protection Feasibility Study currently enrolling patients, aims to assess utility of WCD in patients with high rhythmic risk after unexplained syncope[47].

End-stage renal disease: Hemodialysed (HD) patients are known to be at high risk of SCD[48]. In a retrospective study, 75 hemodialysed patients presenting with SCD while wearing a WCD were included[49]. Seventy-eight point six percent of SCD were linked to VT/VF episodes. One-year survival after SCA was 31.4%. In comparison with historical data, the WCD therapy was associated with an improved survival ref. The ICD was associated with better survival in HD patients yet[50], but is more exposed to complications such as device infections[51].

Limitations of the WCD

Although the WCD is able to automatically terminate VA, daily maintenance is necessary. A non-negligible proportion of patients are unable to correctly use and handle the device, change battery or respond to device alarms. This issue might be kept in mind before patient selection. The WCD cannot deliver antitachycardia and/or anti-bradycardia pacing. In patients with cardiac pacemakers, bipolar pacing mode should be programmed in order to avoid oversensing of pacing artifacts during VF leading to termination of the treatment algorithm[52]. In contrast, time to shock delivery, which is substantially longer compared to ICD, doesn't seem to be a limitation. As shown in the MADIT-RIT trial[53], prolonged delays in therapy delivery were associated with reductions in inappropriate therapies and overall mortality. Finally, cost impact of this device has to be underlined. Few studies evaluated the cost-effectiveness of the WCD. After ICD removal for infection, WCD seemed to be cost-effective for SCD prevention compared to in-hospital monitoring or discharge to a skilled nursing facility before reimplantation[54].

CONCLUSION

The WCD is a life-saving therapy as it has been demonstrated to promptly detect and terminate VT/VF by automatically delivering defibrillation shock. This device represents a safe, easy to handle, non-invasive and reversible way to prevent SCD in patients with SCD risk though to be high for a limited period or having a transient contraindication to permanent ICD implantation. Data sustaining the use of the WCD therapy in patients with low LVEF following myocardial revascularization are strong. Similarly, current guidelines sustain the use of the WCD in patients with ICD infection requiring device removal. Further prospective and randomized studies are awaited to better guide its indications and its benefit in other clinical settings.

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REFERENCES

1 **Mozaffarian D**, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, Cushman M, Das SR, de Ferranti S, Després JP, Fullerton HJ, Howard VJ, Huffman MD, Isasi CR, Jiménez MC, Judd SE, Kissela BM, Lichtman JH, Lisabeth LD, Liu S, Mackey RH, Magid DJ, McGuire DK, Mohler ER, Moy CS, Muntner P, Mussolino ME, Nasir K, Neumar RW, Nichol G, Palaniappan L, Pandey DK, Reeves MJ, Rodriguez CJ, Rosamond W, Sorlie PD, Stein J, Towfighi A, Turan TN, Virani SS, Woo D, Yeh RW, Turner MB. Heart Disease and Stroke Statistics-2016 Update: A Report From the American Heart Association. *Circulation* 2016; **133**: e38-360 [PMID: 26673558 DOI: 10.1161/CIR.0000000000000350]

2 **Moss AJ**, Hall WJ, Cannom DS, Daubert JP, Higgins SL, Klein H, Levine JH, Saksena S, Waldo AL, Wilber D, Brown MW, Heo M. Improved survival with an implanted defibrillator in patients with coronary disease at high risk for ventricular arrhythmia. Multicenter Automatic Defibrillator Implantation Trial Investigators. *N Engl J Med* 1996; **335**: 1933-1940 [PMID: 8960472 DOI: 10.1056/NEJM199612263352601]

3 **Moss AJ**, Zareba W, Hall WJ, Klein H, Wilber DJ, Cannom DS, Daubert JP, Higgins SL, Brown MW, Andrews ML. Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. *N Engl J Med* 2002; **346**: 877-883 [PMID: 11907286 DOI: 10.1056/NEJMoa013474]

4 **Bardy GH**, Lee KL, Mark DB, Poole JE, Packer DL, Boineau R, Domanski M, Troutman C, Anderson J, Johnson G, McNulty SE, Clapp-Channing N, Davidson-Ray LD, Fraulo ES, Fishbein DP, Luceri RM, Ip JH. Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. *N Engl J Med* 2005; **352**: 225-237 [PMID: 15659722 DOI: 10.1056/NEJMoa043399]

5 **Hohnloser SH**, Kuck KH, Dorian P, Roberts RS, Hampton JR, Hatala R, Fain E, Gent M, Connolly SJ. Prophylactic use of an implantable cardioverter-defibrillator after acute myocardial infarction. *N Engl J Med* 2004; **351**: 2481-2488 [PMID: 15590950 DOI: 10.1056/NEJMoa041489]

6 **Kutyifa V**, Moss AJ, Klein H, Biton Y, McNitt S, MacKecknie B, Zareba W, Goldenberg I. Use of the wearable cardioverter defibrillator in high-risk cardiac patients: data from the Prospective Registry of Patients Using the Wearable Cardioverter Defibrillator (WEARIT-II Registry). *Circulation* 2015; **132**: 1613-1619 [PMID: 26316618 DOI: 10.1161/CIRCULATIONAHA.115.015677]

7 **Tanawuttiwat T**, Garisto JD, Salow A, Glad JM, Szymkiewicz S, Saltzman HE, Kutalek SP, Carrillo RG. Protection from outpatient sudden cardiac death following ICD removal using a wearable cardioverter defibrillator. *Pacing Clin Electrophysiol* 2014; **37**: 562-568 [PMID: 24762055 DOI: 10.1111/pace.12319]

8 **Feldman AM**, Klein H, Tchou P, Murali S, Hall WJ, Mancini D, Boehmer J, Harvey M, Heilman MS, Szymkiewicz SJ, Moss AJ. Use of a wearable defibrillator in terminating tachyarrhythmias in patients at high risk for sudden death: results of the WEARIT/BIROAD. *Pacing Clin Electrophysiol* 2004; **27**: 4-9 [PMID: 14720148 DOI: 10.1111/j.1540-8159.2004.00378.x]

9 **Chung MK**, Szymkiewicz SJ, Shao M, Zishiri E, Niebauer MJ, Lindsay BD, Tchou PJ. Aggregate national experience with the wearable cardioverter-defibrillator: event rates, compliance, and survival. *J Am Coll Cardiol* 2010; **56**: 194-203 [PMID: 20620738 DOI: 10.1016/j.jacc.2010.04.016]

10 **Epstein AE**, Abraham WT, Bianco NR, Kern KB, Mirro M, Rao SV, Rhee EK, Solomon SD, Szymkiewicz SJ. Wearable cardioverter-defibrillator use in patients perceived to be at high risk early post-myocardial infarction. *J Am Coll Cardiol* 2013; **62**: 2000-2007 [PMID: 23916930 DOI: 10.1016/j.jacc.2013.05.086]

11 **Klein HU**, Meltendorf U, Reek S, Smid J, Kuss S, Cygankiewicz

I, Jons C, Szymkiewicz S, Buhtz F, Wollbrueck A, Zareba W, Moss AJ. Bridging a temporary high risk of sudden arrhythmic death. Experience with the wearable cardioverter defibrillator (WCD). *Pacing Clin Electrophysiol* 2010; **33**: 353-367 [PMID: 19889186 DOI: 10.1111/j.1540-8159.2009.02590.x]

12 **Auricchio A**, Klein H, Geller CJ, Reek S, Heilman MS, Szymkiewicz SJ. Clinical efficacy of the wearable cardioverter-defibrillator in acutely terminating episodes of ventricular fibrillation. *Am J Cardiol* 1998; **81**: 1253-1256 [PMID: 9604964 DOI: 10.1016/S0002- 9149 (98)00120-9]

13 **Lamichhane M**, Gardiner JC, Bianco NR, Szymkiewicz SJ, Thakur RK. National experience with long-term use of the wearable cardioverter defibrillator in patients with cardiomyopathy. *J Interv Card Electrophysiol* 2017; **48**: 11-19 [PMID: 27752809 DOI: 10.1007/s10840-016-0194-6]

14 **Wäßnig NK**, Günther M, Quick S, Pfluecke C, Rottstädt F, Szymkiewicz SJ, Ringquist S, Strasser RH, Speiser U. Experience With the Wearable Cardioverter-Defibrillator in Patients at High Risk for Sudden Cardiac Death. *Circulation* 2016; **134**: 635-643 [PMID: 27458236 DOI: 10.1161/CIRCULATIONAHA.115.019124]

15 **Salehi N**, Nasiri M, Bianco NR, Opreanu M, Singh V, Satija V, Jhand AS, Karapetyan L, Safadi AR, Surapaneni P, Thakur RK. The Wearable Cardioverter Defibrillator in Nonischemic Cardiomyopathy: A US National Database Analysis. *Can J Cardiol* 2016; **32**: 1247.e1-1247.e6 [PMID: 26975224 DOI: 10.1016/j.cjca.2015.12.035]

16 **Priori SG**, Blomström-Lundqvist C, Mazzanti A, Blom N, Borggrefe M, Camm J, Elliott PM, Fitzsimons D, Hatala R, Hindricks G, Kirchhof P, Kjeldsen K, Kuck KH, Hernandez-Madrid A, Nikolaou N, Norekvål TM, Spaulding C, Van Veldhuisen DJ. 2015 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: The Task Force for the Management of Patients with Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death of the European Society of Cardiology (ESC)Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC). *Europace* 2015; **17**: 1601-1687 [PMID: 26318695 DOI: 10.1093/europace/euv319]

17 **Piccini JP**, Allen LA, Kudenchuk PJ, Page RL, Patel MR, Turakhia MP. Wearable Cardioverter-Defibrillator Therapy for the Prevention of Sudden Cardiac Death: A Science Advisory From the American Heart Association. *Circulation* 2016; **133**: 1715-1727 [PMID: 27022063 DOI: 10.1161/CIR.0000000000000394]

18 **Solomon SD**, Zelenkofske S, McMurray JJ, Finn PV, Velazquez E, Ertl G, Harsanyi A, Rouleau JL, Maggioni A, Kober L, White H, Van de Werf F, Pieper K, Califf RM, Pfeffer MA. Sudden death in patients with myocardial infarction and left ventricular dysfunction, heart failure, or both. *N Engl J Med* 2005; **352**: 2581-2588 [PMID: 15972864 DOI: 10.1056/NEJMoa043938]

19 **Exner DV**, Kavanagh KM, Slawnych MP, Mitchell LB, Ramadan D, Aggarwal SG, Noullett C, Van Schaik A, Mitchell RT, Shibata MA, Gulamhussein S, McMeekin J, Tymchak W, Schnell G, Gillis AM, Sheldon RS, Fick GH, Duff HJ. Noninvasive risk assessment early after a myocardial infarction the REFINE study. *J Am Coll Cardiol* 2007; **50**: 2275-2284 [PMID: 18068035 DOI: 10.1016/j.jacc.2007.08.042]

20 **Wilber DJ**, Zareba W, Hall WJ, Brown MW, Lin AC, Andrews ML, Burke M, Moss AJ. Time dependence of mortality risk and defibrillator benefit after myocardial infarction. *Circulation* 2004; **109**: 1082-1084 [PMID: 14993128 DOI: 10.1161/01.CIR.0000121328.12536.07]

21 **Steinbeck G**, Andresen D, Seidl K, Brachmann J, Hoffmann E, Wojciechowski D, Kornacewicz-Jach Z, Sredniawa B, Lupkovics G, Hofgärtner F, Lubinski A, Rosenqvist M, Habets A, Wegscheider K, Senges J. Defibrillator implantation early after myocardial infarction. *N Engl J Med* 2009; **361**: 1427-1436 [PMID: 19812399 DOI: 10.1056/NEJMoa0901889]

22 **Olgin JE**. Vest Prevention of Early Sudden Death Trial and VEST Registry. [accessed 2015 Feb 18]. Available from: URL: https://clinicaltrials.gov/ct2/show/NCT01446965

23 **Vaughan-Sarrazin MS**, Hannan EL, Gormley CJ, Rosenthal GE. Mortality in Medicare beneficiaries following coronary artery bypass graft surgery in states with and without certificate of need regulation. *JAMA* 2002; **288**: 1859-1866 [PMID: 12377084 DOI: 10.1001/jama.288.15.1859]

24 **Zishiri ET**, Williams S, Cronin EM, Blackstone EH, Ellis SG, Roselli EE, Smedira NG, Gillinov AM, Glad JA, Tchou PJ, Szymkiewicz SJ, Chung MK. Early risk of mortality after coronary artery revascularization in patients with left ventricular dysfunction and potential role of the wearable cardioverter defibrillator. *Circ Arrhythm Electrophysiol* 2013; **6**: 117-128 [PMID: 23275233 DOI: 10.1161/CIRCEP.112.973552]

25 **Fieguth HG**, Wahlers T, Trappe HJ, Borst HG. Arrhythmogenic mortality in heart-transplant candidates. *Transpl Int* 1996; **9** Suppl 1: S219-S220 [PMID: 8959831 DOI: 10.1111/j.1432-2277.1996.tb01613.x]

26 **Pettit SJ**, Petrie MC, Connelly DT, Japp AG, Payne JR, Haj-Yahia S, Gardner RS. Use of implantable cardioverter defibrillators in patients with left ventricular assist devices. *Eur J Heart Fail* 2012; **14**: 696-702 [PMID: 22547745 DOI: 10.1093/eurjhf/hfs062]

27 **Opreanu M**, Wan C, Singh V, Salehi N, Ahmad J, Szymkiewicz SJ, Thakur RK. Wearable cardioverter-defibrillator as a bridge to cardiac transplantation: A national database analysis. *J Heart Lung Transplant* 2015; **34**: 1305-1309 [PMID: 26094085 DOI: 10.1016/j.healun.2015.04.004]

28 **Kadish A**, Dyer A, Daubert JP, Quigg R, Estes NA, Anderson KP, Calkins H, Hoch D, Goldberger J, Shalaby A, Sanders WE, Schaechter A, Levine JH. Prophylactic defibrillator implantation in patients with nonischemic dilated cardiomyopathy. *N Engl J Med* 2004; **350**: 2151-2158 [PMID: 15152060 DOI: 10.1056/NEJMoa033088]

29 **Iacoviello M**, Monitillo F. Non-invasive evaluation of arrhythmic risk in dilated cardiomyopathy: From imaging to electrocardiographic measures. *World J Cardiol* 2014; **6**: 562-576 [PMID: 25068017 DOI: 10.4330/wjc.v6.i7.562]

30 **Cohn JN**, Tognoni G. A randomized trial of the angiotensin-receptor blocker valsartan in chronic heart failure. *N Engl J Med* 2001; **345**: 1667-1675 [PMID: 11759645 DOI: 10.1056/NEJMoa010713]

31 **Bänsch D**, Antz M, Boczor S, Volkmer M, Tebbenjohanns J, Seidl K, Block M, Gietzen F, Berger J, Kuck KH. Primary prevention of sudden cardiac death in idiopathic dilated cardiomyopathy: the Cardiomyopathy Trial (CAT). *Circulation* 2002; **105**: 1453-1458 [PMID: 11914254 DOI: 10.1161/01.CIR.0000012350.99718.AD]

32 **Marchlinski FE**, Jessup M. Timing the implantation of implantable cardioverter-defibrillators in patients with nonischemic cardiomyopathy. *J Am Coll Cardiol* 2006; **47**: 2483-2485 [PMID: 16781377 DOI: 10.1016/j.jacc.2006.01.075]

33 **Kadish A**, Schaechter A, Subacius H, Thattassery E, Sanders W, Anderson KP, Dyer A, Goldberger J, Levine J. Patients with recently diagnosed nonischemic cardiomyopathy benefit from implantable cardioverter-defibrillators. *J Am Coll Cardiol* 2006; **47**: 2477-2482 [PMID: 16781376 DOI: 10.1016/j.jacc.2005.11.090]

34 **McClellan MB**, Tunis SR. Medicare coverage of ICDs. *N Engl J Med* 2005; **352**: 222-224 [PMID: 15659721 DOI: 10.1056/NEJMp048354]

35 **Køber L**, Thune JJ, Nielsen JC, Haarbo J, Videbæk L, Korup E, Jensen G, Hildebrandt P, Steffensen FH, Bruun NE, Eiskjær H, Brandes A, Thøgersen AM, Gustafsson F, Egstrup K, Videbæk R, Hassager C, Svendsen JH, Høfsten DE, Torp-Pedersen C, Pehrson S. Defibrillator Implantation in Patients with Nonischemic Systolic Heart Failure. *N Engl J Med* 2016; **375**: 1221-1230 [PMID: 27571011 DOI: 10.1056/NEJMoa1608029]

36 **Singh M**, Wang NC, Jain S, Voigt AH, Saba S, Adelstein EC. Utility of the Wearable Cardioverter-Defibrillator in Patients With Newly Diagnosed Cardiomyopathy: A Decade-Long Single-Center Experience. *J Am Coll Cardiol* 2015; **66**: 2607-2613 [PMID: 26670060 DOI: 10.1016/j.jacc.2015.09.079]

37 **Stiermaier T**, Rommel KP, Eitel C, Möller C, Graf T, Desch S, Thiele H, Eitel I. Management of arrhythmias in patients with Takotsubo cardiomyopathy: Is the implantation of permanent

devices necessary? *Heart Rhythm* 2016; **13**: 1979-1986 [PMID: 27298201 DOI: 10.1016/j.hrthm.2016.06.013]
38 **Stiermaier T**, Eitel C, Denef S, Desch S, Schuler G, Thiele H, Eitel I. Prevalence and Clinical Significance of Life-Threatening Arrhythmias in Takotsubo Cardiomyopathy. *J Am Coll Cardiol* 2015; **65**: 2148-2150 [PMID: 25975480 DOI: 10.1016/j.jacc.2015.02.062]
39 **Nascimento FO**, Krishna RK, Hrachian H, Santana O. Wearable cardioverter defibrillator in stress cardiomyopathy and cardiac arrest. *BMJ Case Rep* 2013; **2013**: pii: bcr2013009789 [PMID: 24038288 DOI: 10.1136/bcr-2013-009789]
40 **Peters S**, Klein HU. WCD LifeVest: risk stratification in a case of Tako-Tsubo cardiomyopathy with QT interval prolongation. *Herz* 2012; **37**: 219-221 [PMID: 21437701 DOI: 10.1007/s00059-011-3440-9]
41 **Elkayam U**. Clinical characteristics of peripartum cardiomyopathy in the United States: diagnosis, prognosis, and management. *J Am Coll Cardiol* 2011; **58**: 659-670 [PMID: 21816300 DOI: 10.1016/j.jacc.2011.03.047]
42 **Honigberg MC**, Givertz MM. Arrhythmias in peripartum cardiomyopathy. *Card Electrophysiol Clin* 2015; **7**: 309-317 [PMID: 26002395 DOI: 10.1016/j.ccep.2015.03.010]
43 **Whitehead SJ**, Berg CJ, Chang J. Pregnancy-related mortality due to cardiomyopathy: United States, 1991-1997. *Obstet Gynecol* 2003; **102**: 1326-1331 [PMID: 14662222 DOI: 10.1097/00006250-200312000-00019]
44 **Duncker D**, Haghikia A, König T, Hohmann S, Gutleben KJ, Westenfeld R, Oswald H, Klein H, Bauersachs J, Hilfiker-Kleiner D, Veltmann C. Risk for ventricular fibrillation in peripartum cardiomyopathy with severely reduced left ventricular function-value of the wearable cardioverter/defibrillator. *Eur J Heart Fail* 2014; **16**: 1331-1336 [PMID: 25371320 DOI: 10.1002/ejhf.188]
45 **Kawai C**. From myocarditis to cardiomyopathy: mechanisms of inflammation and cell death: learning from the past for the future. *Circulation* 1999; **99**: 1091-1100 [PMID: 10051305 DOI: 10.1161/01.CIR.99.8.1091]
46 **Kindermann I**, Kindermann M, Kandolf R, Klingel K, Bültmann B, Müller T, Lindinger A, Böhm M. Predictors of outcome in patients with suspected myocarditis. *Circulation* 2008; **118**: 639-648 [PMID: 18645053 DOI: 10.1161/CIRCULATIONAHA.108.769489]
47 **Szymkiewicz S**. Ambulatory Post-Syncope Arrhythmia Protection Feasibility Study (ASAP). [accessed 2015 Feb 18]. Available from: URL: https://clinicaltrials.gov/ct2/show/NCT02188147
48 **Collins AJ**, Foley RN, Chavers B, Gilbertson D, Herzog C, Johansen K, Kasiske B, Kutner N, Liu J, St Peter W, Guo H, Gustafson S, Heubner B, Lamb K, Li S, Li S, Peng Y, Qiu Y, Roberts T, Skeans M, Snyder J, Solid C, Thompson B, Wang C, Weinhandl E, Zaun D, Arko C, Chen SC, Daniels F, Ebben J, Frazier E, Hanzlik C, Johnson R, Sheets D, Wang X, Forrest B, Constantini E, Everson S, Eggers P, Agodoa L. 'United States Renal Data System 2011 Annual Data Report: Atlas of chronic kidney disease & amp; end-stage renal disease in the United States. *Am J Kidney Dis* 2012; **59**: A7, e1-420 [PMID: 22177944 DOI: 10.1053/j.ajkd.2011.11.015]
49 **Wan C**, Herzog CA, Zareba W, Szymkiewicz SJ. Sudden cardiac arrest in hemodialysis patients with wearable cardioverter defibrillator. *Ann Noninvasive Electrocardiol* 2014; **19**: 247-257 [PMID: 24252154 DOI: 10.1111/anec.12119]
50 **Herzog CA**, Li S, Weinhandl ED, Strief JW, Collins AJ, Gilbertson DT. Survival of dialysis patients after cardiac arrest and the impact of implantable cardioverter defibrillators. *Kidney Int* 2005; **68**: 818-825 [PMID: 16014061 DOI: 10.1111/j.1523-1755.2005.00462.x]
51 **Guha A**, Maddox WR, Colombo R, Nahman NS, Kintziger KW, Waller JL, Diamond M, Murphy M, Kheda M, Litwin SE, Sorrentino RA. Cardiac implantable electronic device infection in patients with end-stage renal disease. *Heart Rhythm* 2015; **12**: 2395-2401 [PMID: 26253036 DOI: 10.1016/j.hrthm.2015.08.003]
52 **LaPage MJ**, Canter CE, Rhee EK. A fatal device-device interaction between a wearable automated defibrillator and a unipolar ventricular pacemaker. *Pacing Clin Electrophysiol* 2008; **31**: 912-915 [PMID: 18684292 DOI: 10.1111/j.1540-8159.2008.01110.x]
53 **Moss AJ**, Schuger C, Beck CA, Brown MW, Cannom DS, Daubert JP, Estes NA, Greenberg H, Hall WJ, Huang DT, Kautzner J, Klein H, McNitt S, Olshansky B, Shoda M, Wilber D, Zareba W. Reduction in inappropriate therapy and mortality through ICD programming. *N Engl J Med* 2012; **367**: 2275-2283 [PMID: 23131066 DOI: 10.1056/NEJMoa1211107]
54 **Healy CA**, Carrillo RG. Wearable cardioverter-defibrillator for prevention of sudden cardiac death after infected implantable cardioverter-defibrillator removal: A cost-effectiveness evaluation. *Heart Rhythm* 2015; **12**: 1565-1573 [PMID: 25839113 DOI: 10.1016/j.hrthm.2015.03.061]

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ORIGINAL ARTICLE

Clinical Trials Study

Catheter ablation of atrial fibrillation facilitated by preprocedural three-dimensional transesophageal echocardiography: Long-term outcome

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Abstract

AIM

To evaluate the long-term outcome of catheter ablation of atrial fibrillation (AF) facilitated by preprocedural three-dimensional (3-D) transesophageal echocardiography.

METHODS

In 50 patients, 3D transesophageal echocardiography (3D TEE) was performed immediately prior to an ablation procedure (paroxysmal AF: 30 patients, persistent AF: 20 patients). The images were available throughout the ablation procedure. Two different ablation strategies were used. In most of the patients with paroxysmal AF, the cryoablation technique was used (Arctic Front Balloon, CryoCath Technologies/Medtronic; group A2). In the other patients, a circumferential pulmonary vein ablation was performed using the CARTO system [Biosense Webster; group A1 (paroxysmal AF), group B (persistent AF)]. Success rates and complication rates were analysed at 4-year follow-up.

RESULTS

A 3D TEE could be performed successfully in all patients prior to the ablation procedure and all four pulmonary

vein ostia could be evaluated in 84% of patients. The image quality was excellent in the majority of patients and several variations of the pulmonary vein anatomy could be visualized precisely (*e.g.*, common pulmonary vein ostia, accessory pulmonary veins, varying diameter of the left atrial appendage and its distance to the left superior pulmonary vein). All ablation procedures could be performed as planned and almost all pulmonary veins could be isolated successfully. At 48-mo follow-up, 68.0% of all patients were free from an arrhythmia recurrence (group A1: 72.7%, group A2: 73.7%, group B: 60.0%). There were no major complications.

CONCLUSION

3D TEE provides an excellent overview over the left atrial anatomy prior to AF ablation procedures and these procedures are associated with a favourable long-term outcome.

Key words: Pulmonary veins; Catheter ablation; Atrial fibrillation; Transesophageal echocardiography; Three-dimensional echocardiography

Core tip: Three-dimensional (3-D) transesophageal echocardiography has been shown to be a useful tool for analysing the individual left atrial morphology prior to an ablation procedure. The aim of this study was to evaluate whether favourable long-term results can be obtained by catheter ablation of atrial fibrillation after prior pulmonary vein imaging using 3-D transesophageal echocardiography. In 50 patients, 3-D transesophageal echocardiography was performed immediately prior to an ablation procedure. The image quality was excellent in the majority of patients and several variations of the pulmonary vein anatomy could be visualized precisely. At 48-mo follow-up, 68.0% of all patients were free from an arrhythmia recurrence.

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INTRODUCTION

Catheter ablation is an important therapeutic option in patients with symptomatic atrial fibrillation (AF)[1-21]. However, these procedures can be quite challenging because of the variability of the individual left atrial anatomy.

Magnetic resonance imaging (MRI) or multi-detector spiral computed tomography (MDCT) are frequently used prior to an ablation procedure. These three-dimensional (3D) imaging systems provide insights into the morphology of the left atrium (LA). Obviously, the precise knowledge of the left atrial anatomy facilitates the ablation procedures and enhances the saftey of these interventions. However, these imaging techniques are associated with significant limitations [*e.g.*, radiation exposure (MDCT), impaired image quality in patients suffering from AF with fast AV-nodal conduction (especially MRI) and addtitional costs]. Three-dimensional transesophageal echocardiography (3D TEE) provides excellent insights into the left atrial anatomy of individual patients and is free from most of the difficulties associated with MRI or MDCT[22-26]. It has been shown to be associated with a favourable short-term outcome after catheter ablation of AF[27].

The target of this study was to analyse the long-term outcome of AF ablation procedures facilitated by preprocedural 3D TEE with regard to success rates and complication rates.

MATERIALS AND METHODS

Patient population

A total of 50 patients [35 men, 15 women; mean age 60.8 years (SD ± 9.2 years)] were enrolled in this study. All of them underwent 3D transesophageal echocardiography immediately before the ablation procedure, so that a 3D TEE reconstruction of the left atrium and the pulmonary veins (PVs) could be generated.

Catheter ablation was performed for paroxysmal AF in 30 patients and for persistent AF in 20 patients. All patients were highly symptomatic and at least one failed attempt of an antiarrhythmic drug therapy was a prerequisite for being accepted for catheter ablation. Table 1 summarizes clinical characteristics of the patients enrolled in our study. For all patients, this was the first AF ablation procedure.

The ablation procedures were performed at our University Hospital Center between October 2007 and May 2011.

Inclusion criteria were: (1) documented episodes of recurrent AF (≥ 30 s); (2) severe symptoms despite antiarrhythmic drug therapy (including beta-blockers) or prior attemps of electrical cardioversion; (3) ability and willingness to give informed consent; and (4) age between 18 and 85 years. Patients were not accepted for catheter ablation if one of the following conditions was present: Severe valvular heart disease or any other concomitant cardiac disease requiring surgery, severely impaired left ventricular function (left ventricular ejection fraction < 20%), left atrial diameter > 65 mm (parasternal long-axis view), left atrial thrombus, hyperthyroidism, severe renal insufficiency (creatinine ≥ 3 mg/dL) or another severe concomitant illness.

Cardiac imaging

In all patients, a 3D TEE was performed immediately before the ablation procedure (X7-2t, 7 MHz/IE 33;

Table 1 Clinical data

	Group A	Group A1	Group A2	Group B	*P*
Patients	30	11	19	20	0.07
Men:Women	18:12	5:6	13:6	17:3	
Age (yr), mean (SD)	60.0 (9.7)	61.6 (8.0)	59.1 (10.7)	62.1 (8.4)	0.57
Cardiac disease					0.05
None	13	8	5	2	
CAD	3	1	2	9	
DCM	0	0	0	1	
Valvular heart disease[1]	5	1	4	5	
Arterial hypertension	9	1	8	2	
Other	0	0	0	1	
Previous cardiac surgery	1	0	1	0	0.43
Left ventricular ejection fraction, mean (SD)	58.0% (5.8%)	59.1% (7.4%)	57.4% (4.8%)	52.6% (9.9%)	0.06
Antiarrhythmic drug therapy prior to the ablation procedure					0.68
Class Ⅰc (*e.g.*, flecainide, propafenone)	1	0	1	2	
Class Ⅲ (*e.g.*, amiodarone, sotalol)	5	0	5	2	
Beta-blocker in combination with a class Ⅰc or class Ⅲ antiarrhythmic drug	16/7	7/3	9/4	3/7	
Beta-blocker	1	1	0	6	
Digitalis	0	0	0	0	
Other	0	0	0	0	

[1]Not requiring surgery. CAD: Coronary artery disease; DCM: Dilated cardiomyopathy (left ventricular ejection fraction < 40%).

Philips Healthcare, Best, the Netherlands). The images were available throughout the ablation procedures. They were displayed in a synchronised way with the geometry created with the 3D mappig system (if available).

The echocardiographic examination was performed extensively to acquire all relevant information about the left/right atrium, all cardiac valves, the left/right ventricular function and the aorta. In addition, 3D reconstructions of the left atrium and the pulmonary vein ostia were generated. The image quality was classified as: (1) good; (2) acceptable; or (3) not appropriate (for each pulmonay vein ostium). If it was not possible to visualize the right-sided or left-sided PVs at all this was noted as well. The variations of the PV anatomy are summarized in Table 2. A detailed analysis of the 3D TEE findings concerning the left atrial anatomy has been published elsewhere[27].

No other imaging techniques (MDCT or MRI) were used before or after the ablation procedures routinely.

Ablation procedure

The ablation strategy was depending on the type of AF.

In patients with paroxysmal AF, two strategies were used. In some patients with paroxysmal AF, a cicumferential pulmonary vein ablation was performed in combination with a potential-guided segmental approach in order to achieve complete pulmonary vein isolation [group A1; CARTO system (Biosense Webster, Diamond Bar, CA, United States)]. In most of the patients with paroxysmal AF, the cryoballoon technique (Medtronic, Minneapolis, MN, United States) was used (group A2). We refrained from using the cryoballoon technique if any variations of the pulmonary veins were detected by 3D TEE (*e.g.*, common ostium, accessory pulmonary vein). In patients with persistent AF, a circumferential pulmonary vein ablation was performed in combination with a potential-guided segmental approach to achieve complete pulmonary vein isolation (group B). Furthermore, a linear lesion was created at the roof of the left atrium in some patients. In addition, catheter ablation of the mitral isthmus was performed in selected cases [CARTO system (Biosense Webster)]. The ablation strategies have been described in detail in previous publications[20,27].

In addition, catheter ablation of the right atrial isthmus was performed in patients with inducible or clinically documented episodes of typical atrial flutter. The completeness of the right atrial isthmus lines was confirmed by differential pacing maneuvers in all cases.

Follow-up

After hospital discharge, patients were seen regularly on an outpatient basis. One month after the procedure, a physical examination, a resting electrocardiogram (ECG) and a transthoracic echocardiogram were performed. The patients were questioned whether there was any evidence for an arrhythmia recurrence. In addition, a long-term ECG recording (24-h) was performed.

Three months after the ablation procedure, the patients were re-examined in the same way except for the fact that a 7-d Holter monitoring was performed and that each patient underwent a repeat 3D TEE to rule out a pulmonary vein stenosis. Then, the patients were seen at 3-mo intervals if asymptomatic. If there was an arrhythmia recurrence or other problems occurred, the further follow-up and future strategy (*e.g.*, medical therapy, electrical cardioversion, repeat ablation procedure) were planned on an individual basis.

Twelve months, twenty-four and fourty-eight months after the ablation procedure another 7-d Holter monitoring was performed (or the results of repeated 24-h recordings obtained by the referring physicians were reviewed). A blanking period of 3 mo was employed after

Table 2 Left atrial anatomy

	Total
Common PV ostium[1,2] (left PVs/right PVs)	2 (1/1)
Accessory PVs[1,2] (left PVs/right PVs)	1 (0/1)
Early PV branching[2]	3
LSPV	0
LIPV	0
RSPV	2
RIPV	1
Extremely short distance between the LAA and the LSPV[1]	3
Very prominent left atrial appendage[1]	2

[1]3D TEE; [2]Invasive PV angiography. LAA: Left atrial appendage; LIPV: Left inferior pulmonary vein; LSPV: Left superior pulmonary vein; PV(s): Pulmonary vein(s); RIPV: Right inferior pulmonary vein; RSPV: Right superior pulmonary vein.

ablation when evaluating the follow-up results.

Oral anticoagulation was continued for at least 3 mo after the procedure in all patients and was discontinued only in patients with a CHADS2 score $\leqslant$ 1 thereafter. Since October 2010 the CHADS2-VASc score was used for risk assessment and oral anticoagulation was only discontinued in patients with a CHADS2-VASc score $\leqslant$ 1 three months after the ablation procedure (vitamin K antagonist/novel oral anticoagulants). During the first three months after catheter ablation the patients received the same antiarrhythmic medication as prior to the ablation procedure. If there was no evidence for an arrhythmia recurrence all antiarrhythmic drugs were discontinued thereafter except for beta-blockers.

Statistical analysis

Clinical characteristics of the three study groups were compared at baseline to discover potential sources of bias. All parameters with a normal distribution are given as mean (± 1 SD). Age, left ventricular ejection fraction, total procedure time, fluoroscopy dosage and follow-up duration were compared using an one-way ANOVA. All other parameters (underlying cardiac disease, gender) were analysed using the χ^2 test. The χ^2 test was also used for analysing the clinical endpoints (arrhythmia recurrence rate at 48-mo follow-up). Significance was accepted if the *P* value was $\leqslant$ 0.05. The statistical package of JMP (Version 3.2.6, SAS Institute, Cary, NC, United States) was used for data analysis. The data evaluation was reviewed by an expert in biostatistics of our institution.

RESULTS

The study cohort consistent of fifty patients who were enrolled between October 2007 and May 2011. They had recurrent episodes of persistent or paroxysmal AF. Catheter ablation was performed in these patients after prior 3D TEE data acquisition. In all patients, this was the first AF ablation procedure. Catheter ablation of AF could be carried out as intended in all of them.

Ablation strategy

In some patients with paroxysmal AF a circumferential pulmonary vein ablation in combination with a potential-guided segmental approach was carried out [group A1: 11 patients; Carto system (Biosense Webster)].

In the remaining 19 patients with paroxysmal AF, the cryoballoon technique was used (group A2; Medtronic). In all of them, a 28-mm cryoballoon was chosen at the beginning of the procedure. In 4 patients, a second cryoballoon (23 mm; *n* = 1; poorly accessible right inferior pulmonary vein) or a standard cryoablation catheter (Freezor Max, Medtronic; *n* = 3; rather large left-sided PVs as identified by 3D TEE) had to be used to achieve complete isolation of the PVs.

In all twenty patients with persistent AF, a circumferential pulmonary vein ablation in combination with a potential-guided segmental approach was the standard strategy (group B). Moreover, linear ablation across the left atrial roof was carried out in 7 patients with persistent AF. A mitral isthmus line was created in two patients in group B.

Additionally, catheter ablation of the cavotricuspid isthmus was carried out in 5 patients in group A (A1: 4 patients, A2: 1 patient) and in 2 patients in group B.

Procedural results

The procedural results were published elsewhere[27]. In brief, a circumferential pulmonary vein ablation was carried out in all patients in group A1. This was combined with a potential-guided segmental approach if necessary. This resulted in the complete isolation of all 4 PVs in all patients in group A1.

In group A2, all cryoablation procedures could be completed successfully using this technique (mean number of successfully isolated PVs per patient: 3.9 (SD ± 0.7 PVs).

The circumferential ablation strategy encircling the lateral and the septal PVs could be carried out successfully in all patients in group B [sometimes in combination with with a potential-guided segmental approach (12 out of 20 patients)]. This resulted in complete isolation of a mean number of 3.8 PVs/patient [(SD ± 0.9 PVs); group B]. A complete linear lesion across the left atrial roof could be created in 7 patients in group B (7/7 patients). In addition, a continuous mitral isthmus line was achieved in two patients (10%) in this group B.

Successful ablation of the cavotricuspid isthmus was carried out in a total of 7 patients (group A1: 4 patients, group A2: 1 patient, group B: 2 patients).

In both groups, no major complications (*e.g.,* neurologic disorders, significant pericardial effusion, PV stenosis $\geqslant$ 70%, periprocedural death) were observed during the procedure.

Clinical outcomes

In group A, the mean follow-up duration was 1526 d (SD ± 423 d). In group B, the mean follow-up duration was 1697 d (SD ± 208 d; *P* = 0.1). Thus, the mean overall

Table 3 Long-term follow-up data

	Group A	Group A1	Group A2	Group B	Total	*P*
Midterm follow-up (12 mo)	26/30	10/11	16/19	15/20	41/50	0.82
No. of patients without any arrhythmia recurrence	(86.7%)	(90.6%)	(84.2%)	(75.0%)	(82.0%)	
Long-term follow-up (4 yr)	22/30	8/11	14/19	12/20	34/50	0.62
No. of patients without any arrhythmia recurrence	(73.3%)	(72.7%)	(73.7%)	(60.0%)	(68.0%)	

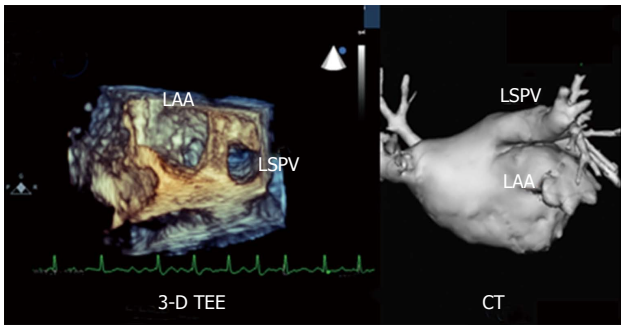

Figure 1 Three-dimensional transesophageal echocardiography-reconstruction providing an overview over the left atrial anatomy. LSPV: Left superior pulmonary vein; LAA: Left atrial appendage; CT: Computed tomography; 3-D TEE: Three-dimensional transesophageal echocardiography.

follow-up duration was 1595 d (SD ± 360 d) (Table 3).

At 4-year follow-up, 73.3% of the study population in group A [22/30; A1: 72.7% (8/11)/A2: 73.7% (14/19)] and 60.0% of the study population in group B (12/20) were free from atrial tachyarrhythmias (P = 0.62). Thus, the overall rate of freedom from arrhythmia recurrences was 68.0% (no more atrial tachyarrhythmias in 34 out of 50 patients).

Four years after the procedure, 39/50 patients (78%) were clinically asymptomatic.

No major complications were observed within a follow-up period of 48 mo. Minor complications were observed in 10 patients (group: A1/A2/B: 3/2/5 patients; groin hematoma: 3 patients, pulmonary vein stenosis 30%: 1 patient, noninfectious pericarditis: 3 patients, minor pericardial effusion: 1 patient, hyperthyroidism; 1 patient, residual defect of the atrial septum; 1 patient).

In patients with recurrent atrial tachyarrhythmias, 7-d Holter monitoring demonstrated recurrent episodes of paroxysmal AF in 12 patients [group A: 9 patients (A1: 7/A2: 2); group B: 3 patients] and persistent AF in 4 patients [group A: 2 patients (A1: 1/A2: 1); group B: 2 patients]. No modification of the antiarrhythmic drug regimen and no redo procedure was necessary in 5 patients (group A1/A2/B: 1/1/3 patients) with recurrent atrial arrhythmias because they were almost free of symptoms. In 4 patients (group A1/A2/B: 1/0/3) relief of symptoms could be achieved by changing the antiarrhythmic drug regimen or an electrical cardioversion. In seven symptomatic patients a repeat ablation was necessary (group A1/A2/B: 1/4/2 patients).

Cardiac imaging

A 3D transesophageal echocardiography was carried out in all 50 patients. All pulmonary veins could be visualized in 42/50 patients (84%; group A1/A2/B: 8/16/18 patients). In 8 patients (group A1/A2/B: 3/3/2), the right PVs could not be evaluated (RSPV: 0 patients; RIPV: 2 patients; RSPV+RIPV: 6 patients). The left-sided PVs could not be evaluated in 5/50 patients (group A1/A2/B: 3/0/2 patients). In all of these patients, both left-sided PVs could not be evaluated (Figures 1 and 2).

Some variations of the left atrial morphology were revealed (such as a right-sided accessory pulmonary vein or a common ostium of the left-sided or the right-sided PVs) (Table 2).

Based on the detailed knowledge of the individual left atrial anatomy the ablation strategy could be modified appropriately if necessary[27]. Threreby, major complications were avoided.

DISCUSSION

Catheter ablation is an important therapeutic tool in patients with recurrent symptomatic episodes of paroxysmal or persistent AF. This technique is effective in restoring and maintaining sinus rhythm even if antiarrhythmic drugs have failed or should be avoided. However, these ablation procedures are quite challenging. This is due to the fact that there are a lot of variations concerning the pulmonary vein and left atrial anatomy. 3D TEE provides detailed insights into the pulmonary vein anatomy of individual patients. In contrast to MDCT or MRI it is not associated with problems such as radiation exposure or impaired image quality if AF with rapid atrioventricular nodal conduction is present[27].

The study was performed to evaluate whether catheter ablation of atrial fibrilllation facilitated by preprocedural 3D TEE is associated with a favourable long-term outcome.

Main results

The ablation procedures could be performed sucessfully in all patients in both groups after prior pulmonary vein imaging using 3D transesophageal echocardiography.

During a follow-up duration fo 4 years, 73.3% of patients in group A (22/30) remained free from recurrent atrial tachyarrhythmias. In group B, 60.0% of patients (12/20, P = 0.62) remained free from an arrhythmia recurrence during a follow-up duration of 4 years. Thus, the overall rate of patients free from an arrhythmia recurrence was 68% at 4-year follow-up. No major complications were observed in both groups during long-term follow-up.

The data provided by our study shows that radio-

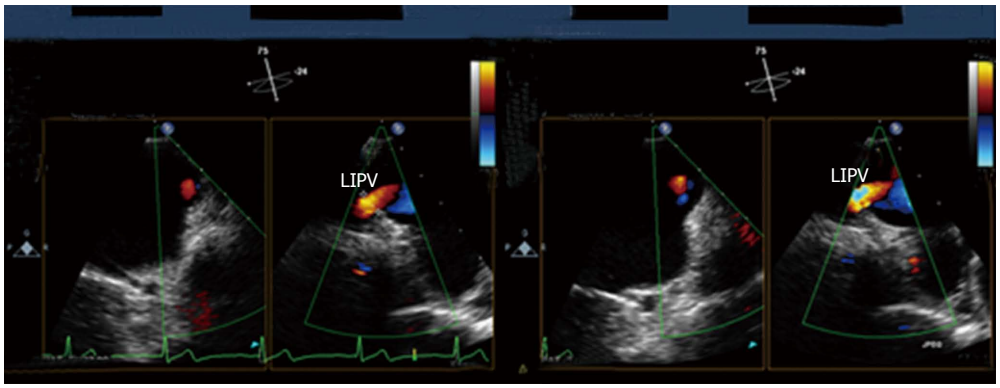

Figure 2 Three-dimensional transesophageal echocardiography performed 3 years after catheter ablation of atrial fibrillation. Slightly increased flow velocity in the left inferior pulmonary vein (LIPV) ostium indicating a minor pulmonary vein stenosis [pulmonary vein diameter at 3-year follow-up: 2.1 mm (compared to 2.6 mm at baseline)].

frequency catheter ablation as well as cryoablation of AF can be performed effectively and safely after pre-procedural 3D TEE imaging. Pulmonary vein imaging prior to an ablation procedure using 3D TEE is associated with favourable long-term follow-up results concerning safety as well as efficacy of the procedures. Transesophageal echocardiography is recommended prior to catheter ablation of AF anyway (to rule out left atrial thrombus formation). Therefore, a 3D transesophageal echocardiography does not result in additional discomfort for the patient or additional cost. Furthermore, it is less time-consuming than performing an additional MDCT or MRI.

Limitations

This is the long-term follow-up data of a feasibility study analysing our initial experience with AF ablation procedures facilitated by pre-procedural 3D TEE imaging. The target of our present study was to evaluate the usefulness of 3D TEE for LA visualization prior to an ablation procedure and to show that it is associated with a favourable outcome after catheter ablation of AF. The study was not designed to prove that this technique is equivalent to or superior to other imaging techniques (MDCT/MRI). Therefore, no comparison to MDCT or MRI data is provided.

Furthermore, this study was not designed to prove that pulmonary vein imaging (3D TEE, MDCT or MRI) does significantly improve the long-term outcome in comparison to patients not undergoing preprocedural PV imaging in a propective randomized way.

Moreover, there are some technical limitations of 3D transesophageal echocardiography: First, the right pulmonary veins are sometimes difficult to visualize. Second, the 3D TEE images can only be displayed in a synchronized way during the ablation procedure and no direct image fusion with the geometry created with a 3D mapping system [Navx/Ensite (St. Jude Medical, Saint Paul, MN, United States) or CARTO (Biosense Webster)] is available so far.

In conclusion, Catheter ablation of AF can be performed with favourable results with regard to the success rate as well as to the complication rate based on prior 3D TEE imaging. Three-dimensional TEE-models provide a good overview over the left atrial anatomy, thereby facilitating the procedure. Typical problems (such as atypical PV anatomy, variable relationship between the left atrial appendage and the left superior pulmonary vein) can be revealed. Then, the ablation strategy can be modified and complications can be avoided.

The results of our study demonstrate that pulmonary vein imaging prior to catheter ablation of AF is associated with a favourable long-term outcome with regard to a relatively high success rate and a very low complication rate. However, large randomized studies are needed to prove that this approch is superior to standard ablation procedures (either using 3D MRI-/MDCT reconstructions or no preprocedural imaging) with regard to various outcome parameters (*e.g.,* success and complication rates, procedure duration, radiation exposure).

COMMENTS

Background

Catheter ablation is an important therapeutic tool in patients with symptomatic atrial fibrillation (AF). However, these ablation procedures are quite challenging. This is due to the fact that there are a lot of variations concerning the pulmonary vein and left atrial anatomy. Three-dimensional transesophageal echocardiography (3D TEE) might be useful for analysing the individual left atrial morphology prior to an ablation procedure.

Research frontiers

However, it is a matter of discussion whether the use of this technique is associated with a favourable long-term outcome with regard to the safety and efficacy of the procedures.

Innovations and breakthroughs

A 3D TEE was performed successfully before the ablation procedure in all patients. All four pulmonary veins could be visualized in 84% of patients. The image quality was excellent in the majority of patients. Several pitfalls of the pulmonary vein morphology could be revealed (*e.g.,* accessory pulmonary veins, common pulmonary vein ostia, variable relationship between the left atrial appendage and the left superior pulmonary vein). All ablation procedures could be performed as planned. At 48-mo follow-up, 68.0% of all patients remained free from atrial tachyarrhythmias (group A1: 72.7%, group A2: 73.7%, group B: 60.0%). There was no major complications.

Applications

The results of the study demonstrate that 3D TEE allows detailed insights into the left atrial anatomy. Catheter ablation of AF can be performed safely based on prior 3D TEE imaging.

Terminology

Catheter ablation: Therapeutic option for the treatment of cardiac arrhythmias (catheter-based); atrial fibrillation: Atrial arrhythmia with a disorganized activation sequence.

Peer-review

This is an interesting article. The authors have provided us with a semi-invasive method (first line or complementary) for monitoring the procedure during catheter ablation of paroxysmal and persistent AF.

REFERENCES

1 **Kettering K**, Al-Ghobainy R, Wehrmann M, Vonthein R, Mewis C. Atrial linear lesions: feasibility using cryoablation. *Pacing Clin Electrophysiol* 2006; **29**: 283-289 [PMID: 16606396 DOI: 10.1111/j.1540-8159.2006.00335.x]

2 **Oral H**, Knight BP, Ozaydin M, Chugh A, Lai SW, Scharf C, Hassan S, Greenstein R, Han JD, Pelosi F, Strickberger SA, Morady F. Segmental ostial ablation to isolate the pulmonary veins during atrial fibrillation: feasibility and mechanistic insights. *Circulation* 2002; **106**: 1256-1262 [PMID: 12208802 DOI: 10.1161/01.CIR.0000027821.55835.00]

3 **Haïssaguerre M**, Shah DC, Jaïs P, Hocini M, Yamane T, Deisenhofer I, Garrigue S, Clémenty J. Mapping-guided ablation of pulmonary veins to cure atrial fibrillation. *Am J Cardiol* 2000; **86**: 9K-19K [PMID: 11084094 DOI: 10.1016/S0002-9149(00)01186-3]

4 **Gerstenfeld EP**, Guerra P, Sparks PB, Hattori K, Lesh MD. Clinical outcome after radiofrequency catheter ablation of focal atrial fibrillation triggers. *J Cardiovasc Electrophysiol* 2001; **12**: 900-908 [PMID: 11513440 DOI: 10.1046/j.1540-8167.2001.00900.x]

5 **Marrouche NF**, Dresing T, Cole C, Bash D, Saad E, Balaban K, Pavia SV, Schweikert R, Saliba W, Abdul-Karim A, Pisano E, Fanelli R, Tchou P, Natale A. Circular mapping and ablation of the pulmonary vein for treatment of atrial fibrillation: impact of different catheter technologies. *J Am Coll Cardiol* 2002; **40**: 464-474 [PMID: 12142112 DOI: 10.1016/S0735-1097(02)01972-1]

6 **Swartz J**, Pellersels G, Silvers J, Patten L, Cervantez D: A catheter-based curative approach to atrial fibrillation in humans. *Circulation* 1994; **90**: I-335 (abstract)

7 **Haïssaguerre M**, Jaïs P, Shah DC, Gencel L, Pradeau V, Garrigues S, Chouairi S, Hocini M, Le Métayer P, Roudaut R, Clémenty J. Right and left atrial radiofrequency catheter therapy of paroxysmal atrial fibrillation. *J Cardiovasc Electrophysiol* 1996; **7**: 1132-1144 [PMID: 8985802 DOI: 10.1111/j.1540-8167.1996.tb00492.x]

8 **Ernst S**, Schlüter M, Ouyang F, Khanedani A, Cappato R, Hebe J, Volkmer M, Antz M, Kuck KH. Modification of the substrate for maintenance of idiopathic human atrial fibrillation: efficacy of radiofrequency ablation using nonfluoroscopic catheter guidance. *Circulation* 1999; **100**: 2085-2092 [PMID: 10562265 DOI: 10.1161/01.CIR.100.20.2085]

9 **Jaïs P**, Hocini M, Hsu LF, Sanders P, Scavee C, Weerasooriya R, Macle L, Raybaud F, Garrigue S, Shah DC, Le Metayer P, Clémenty J, Haïssaguerre M. Technique and results of linear ablation at the mitral isthmus. *Circulation* 2004; **110**: 2996-3002 [PMID: 15520313 DOI: 10.1161/01.CIR.0000146917.75041.58]

10 **Oral H**, Chugh A, Lemola K, Cheung P, Hall B, Good E, Han J, Tamirisa K, Bogun F, Pelosi F, Morady F. Noninducibility of atrial fibrillation as an end point of left atrial circumferential ablation for paroxysmal atrial fibrillation: a randomized study. *Circulation* 2004; **110**: 2797-2801 [PMID: 15505091 DOI: 10.1161/01.CIR.0000146786.87037.26]

11 **Avitall B**, Helms RW, Koblish JB, Sieben W, Kotov AV, Gupta GN. The creation of linear contiguous lesions in the atria with an expandable loop catheter. *J Am Coll Cardiol* 1999; **33**: 972-984 [PMID: 10091824 DOI: 10.1016/S0735-1097(98)00686-X]

12 **Mitchell MA**, McRury ID, Haines DE. Linear atrial ablations in a canine model of chronic atrial fibrillation: morphological and electrophysiological observations. *Circulation* 1998; **97**: 1176-1185 [PMID: 9537344 DOI: 10.1161/01.CIR.97.12.1176]

13 **Schwartzman D**, Kuck KH. Anatomy-guided linear atrial lesions for radiofrequency catheter ablation of atrial fibrillation. *Pacing Clin Electrophysiol* 1998; **21**: 1959-1978 [PMID: 9793093 DOI: 10.1111/j.1540-8159.1998.tb00016.x]

14 **Ouyang F**, Bänsch D, Ernst S, Schaumann A, Hachiya H, Chen M, Chun J, Falk P, Khanedani A, Antz M, Kuck KH. Complete isolation of left atrium surrounding the pulmonary veins: new insights from the double-Lasso technique in paroxysmal atrial fibrillation. *Circulation* 2004; **110**: 2090-2096 [PMID: 15466640 DOI: 10.1161/01.CIR.0000144459.37455.EE]

15 **Ouyang F**, Antz M, Ernst S, Hachiya H, Mavrakis H, Deger FT, Schaumann A, Chun J, Falk P, Hennig D, Liu X, Bänsch D, Kuck KH. Recovered pulmonary vein conduction as a dominant factor for recurrent atrial tachyarrhythmias after complete circular isolation of the pulmonary veins: lessons from double Lasso technique. *Circulation* 2005; **111**: 127-135 [PMID: 15623542 DOI: 10.1161/01.CIR.0000151289.73085.36]

16 **Ouyang F**, Ernst S, Chun J, Bänsch D, Li Y, Schaumann A, Mavrakis H, Liu X, Deger FT, Schmidt B, Xue Y, Cao J, Hennig D, Huang H, Kuck KH, Antz M. Electrophysiological findings during ablation of persistent atrial fibrillation with electroanatomic mapping and double Lasso catheter technique. *Circulation* 2005; **112**: 3038-3048 [PMID: 16275866 DOI: 10.1161/CIRCULATIONAHA.105.561183]

17 **Kettering K**, Greil GF, Fenchel M, Kramer U, Weig HJ, Busch M, Miller S, Sieverding L, Laszlo R, Schreieck J. Catheter ablation of atrial fibrillation using the Navx-/Ensite-system and a CT-/MRI-guided approach. *Clin Res Cardiol* 2009; **98**: 285-296 [PMID: 19283334 DOI: 10.1007/s00392-009-0001-9]

18 **Kettering K**, Greil GF, Busch M, Miller S, Sieverding L, Schreieck J. Catheter ablation of atrial fibrillation: ongoing atrial fibrillation inside a single pulmonary vein after successful electrical disconnection and restoration of sinus rhythm in both atria. *Clin Res Cardiol* 2006; **95**: 663-667 [PMID: 16998744 DOI: 10.1007/s00392-006-0437-0]

19 **Kettering K**, Weig HJ, Busch M, Laszlo R, Schreieck J. Segmental pulmonary vein ablation: success rates with and without exclusion of areas adjacent to the esophagus. *Pacing Clin Electrophysiol* 2008; **31**: 652-659 [PMID: 18507536 DOI: 10.1111/j.1540-8159.2008.01067.x]

20 **Kettering K**, Weig HJ, Busch M, Schneider KM, Eick C, Weretka S, Laszlo R, Gawaz M, Schreieck J. Catheter ablation of persistent atrial fibrillation: anatomically based circumferential pulmonary vein ablation in combination with a potential-guided segmental approach to achieve complete pulmonary vein isolation. *J Interv Card Electrophysiol* 2011; **30**: 63-72 [PMID: 21253841 DOI: 10.1007/s10840-010-9533-1]

21 **Neumann T**, Vogt J, Schumacher B, Dorszewski A, Kuniss M, Neuser H, Kurzidim K, Berkowitsch A, Koller M, Heintze J, Scholz U, Wetzel U, Schneider MA, Horstkotte D, Hamm CW, Pitschner HF. Circumferential pulmonary vein isolation with the cryoballoon technique results from a prospective 3-center study. *J Am Coll Cardiol* 2008; **52**: 273-278 [PMID: 18634982 DOI: 10.1016/j.jacc.2008.04.021]

22 **Kettering K**, Gramley F, von Bardeleben S: Catheter ablation of AF: three-dimensional TEE replaces other imaging techniques for pulmonary vein visualization prior to an ablation procedure - long-term follow-up results. *Eur Heart Journal* 2012; **32** (abstract supplement): 229

23 **Kettering K**, Gramley F: Catheter ablation of atrial fibrillation: three-dimensional transesophageal echocardiography provides an excellent overview over the pulmonary vein anatomy prior to an ablation procedure - long-term follow-up results. *Circulation*

(abstract supplement) 2012: 13347
24 **Kühl H**. Left ventricular function. In: Buck T, Franke A, Monaghan M, editors: Three-dimensional echocardiography, 1st ed. Berlin: Springer, 2011: 68-69 [DOI: 10.1007/978-3-642-11179-2_4]
25 **Kühl H**, Franke A, Buck T. Monitoring and guiding cardiac interventions and surgery. In: Buck T, Franke A, Monaghan M, editors: Three-dimensional echocardiography, 1st ed. Berlin: Springer, 2011: 262-263 [DOI: 10.1007/978-3-642-11179-2_13]
26 **Neumann T**, Kuniss M. Balloon-based cryoablation of atrial fibrillation. In: Bredikis A, Wilber D, editors: Cryoablation of cardiac arrhythmias, 1st ed. Philadelphia: Elsevier Saunders, 2011: 176-177 [DOI: 10.1016/B978-1-4377-1615-3.00015-0]
27 **Kettering K**, Gramley F, Bardeleben S. Catheter ablation of atrial fibrillation: three-dimensional transesophageal echocardiography provides an excellent overview over the pulmonary vein anatomy. *Cardiology and Angiology* 2017; In press

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ORIGINAL ARTICLE

Observational Study

Entirely subcutaneous defibrillator and complex congenital heart disease: Data on long-term clinical follow-up

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Author contributions: Ferrero P and Stuart AG developed the idea of the study; Ferrerp P and Ali H equally contributed to collection of data; Ferrero P and Barman P wrote the paper; Foresti S and Lupo P contributed to interpret the data; D'Elia E and Cappato R reviewed and edited the manuscript.

Institutional review board statement: The study was reviewed and approved by the Adult Congenital Heart disease unit, Bristol Heart Institute Bristol United Kingdom.

Informed consent statement: All study participants, provided informed written consent prior to device implantation and verbally consented to collect follow-up data.

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Abstract

AIM

To describe the long-term follow-up of patients with complex congenital heart disease who underwent subcutaneous implantable cardiac defibrillator (S-ICD), focusing on local complications, appropriate and inappropriate shocks.

METHODS

Patients with complex congenital heart disease underwent S-ICD implant in two centers with the conventional technique. Data at follow-up were retrieved from clinical notes and institutional database.

RESULTS

Eight patients were implanted in two centres between 2010 and 2016. Median age at implant was 37.5 years (range 13-57). All patients who were deemed suitable for S-ICD implant passed the pre-procedural screening. Three patients were previously implanted with a anti-bradycardia device, one of whom with CRT. In one patient the device was explanted due to local infection. During

the total median follow-up of 874 d, one patient had an appropriate and one inappropriate shock triggered by fast atrial tachycardia. None of the patients had inappropriate shocks secondary to T wave oversensing or electrical interference with anti- bradycardia devices.

CONCLUSION
S-ICD appears to be effective and safe in patients with complex congenital heart disease.

Key words: Subcutaneous defibrillator; Congenital heart disease; Outcomes

Core tip: Implantation of subcutaneous implantable cardiac defibrillator in patients with complex congenital heart disease appears to be effective and reliable at long term follow-up. The high proportion of grossly abnormal baseline electrocardiogram and the significant incidence of atrial arrhythmias does not seem to affect the rate of inappropriate shocks.

Ferrero P, Ali H, Barman P, Foresti S, Lupo P, D'Elia E, Cappato R, Stuart AG. Entirely subcutaneous defibrillator and complex congenital heart disease: Data on long-term clinical follow-up. *World J Cardiol* 2017; 9(6): 547-552 Available from: URL: http://www.wjgnet.com/1949-8462/full/v9/i6/547.htm DOI: http://dx.doi.org/10.4330/wjc.v9.i6.547

INTRODUCTION

Arrhythmic complications are common in patients with congenital heart disease (CHD) requiring implantation of an anti-tachycardic device[1]. Traditional endocardial approach can be particularly challenging in these patients due to limited vascular access, intracardiac shunts or abnormal cardiac chambers[2]. Furthermore the trans venous implantable cardiac defibrillator (ICD) implant carries a risk of long term lead related complication, which have been reported in up to 20% of cases at 10 years[3]. This figure is thought to be even higher in the pediatric and CHD population. Most of the long-term event in this clinical setting are lead related[4]. Alternative implant techniques have been devised in this population, including surgical epicardial or subcutaneous coils implant. Unfortunately, these non trans-venous approaches are associated with a higher procedural risk and have a significant failure rate during follow-up[5]. The entirely subcutaneous ICD (S-ICD) proved to be effective and safe in patients fulfilling both primary and secondary prevention indication[6]. This technology is particular appealing for CHD subjects, as it does not involve the implantation of lead within the cardiac chambers. Data about the performance of S-ICD in this subset of patients are still scant, particularly as far as the long-term outcomes are concerned. A major theoretical concern of the S-ICD in this population is related to the presence of significant ventricular hypertrophy causing profound anomalies of both depolarization and repolarization phase on the surface electrocardiogram (ECG) and the high incidence of atrial tachycardia[7]. In theory, both these issues could lead to an inappropriate shock in the long-term follow-up. Furthermore, a significant proportion of patient with CHD develop atrial-ventricular conduction impairment either as the result of their specific congenital lesion or after cardiac surgery requiring long term pacing. A recent sub analysis from a pooled analysis of the IDE and EFFORTLESS registry showed the safety of S-ICD in patients with CHD[8]. However, during the median follow-up of 567 d none of the patients had any appropriate shocks, consequently no observations about the efficacy of this technology could be performed[9].

In this article, we report medium and long term follow-up in eight patients with complex CHD implanted with a S-ICD, reflecting the experience of two adult CHD referral centres. The details of previous surgical history, the occurrence of either appropriate or inappropriate shocks, local complications, and interference with previously implanted anti-bradycardia and CRT devices are described.

MATERIALS AND METHODS

Patients with CHD were implanted with a S-ICD in two centres between 2010 and 2016. All patients underwent pre-implant eligibility screening. Suitability for S-ICD implantation was pre-assessed by a standardized protocol recommended by the manufacture, as previously published. This included assessment of the QRS and T wave amplitude ratio in at least two different postures (supine and standing), and during exercise on a treadmill[10]. Implant was performed under general anaesthesia with the conventional technique. Briefly, the device and lead positioning was guided by standard chest anatomical landmarks and fluoroscopy to ensure proper vector configuration across the cardiac silhouette. All devices but one were programmed from the beginning with a shock conditional zone (180-240 beats per minute, bpm) and a shock only zone above 240 bpm. All patients underwent defibrillation testing by induction of ventricular fibrillation using 50 Hz current to assess accurate detection and effective termination of the arrhythmia. Clinical and surgical details were retrieved from institutional databases. All patients implanted underwent regular follow-up at 1 and 6 mo thereafter. Data about patient clinical status, occurrence of local complication, arrhythmic burden, inappropriate and appropriate shocks were recorded.

RESULTS

Pre implant clinical details

Eight patients were implanted with a S-ICD device between 2010 and 2016 in two centres. Median age at implant was 37.5 years (range 13-57). Seven patients had a secondary prevention indication while one patient was implanted after one episode of syncope and documented

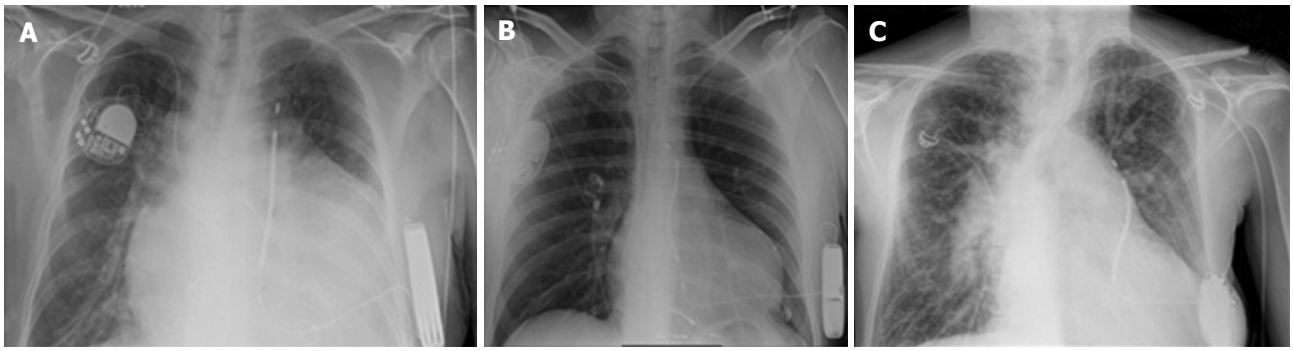

Figure 1 A new transeptal endocardial lead was implanted in the left ventricle and the atrial septal defect was thereafter successfully closed with an occlude device. A: Subcutaneous implantable cardiac defibrillator and endocardial pacing system in a patient post Mustard operation; B: Patient with ASD and dilatative DCM who previously underwent left ventricle lead implant; C: Patient with Eisenmenger syndrome. ASD: Atrial septal defect; DCM: Dilatative cardiomyopathy.

Table 1 Pre implant clinical and anatomical characteristics

Anatomical diagnosis	Sex	Age at implant (yr)	Pre implant ECG	Indication	Reason for SICD	Prev implant	F.U (d)
TOF	F	47	RBBB + RVH	VT	Tricuspid mech valve	No	360
VSD subaortic obstr.	M	52	LVH	Out hospital card arrest	Previous endocarditis	No	334
TGA, Mustard	M	36	RBBB + RVH	VF	SVC baffle stenosis	Yes	486
DILV TGA Eisemenger	M	57	IVCD (aspecific)	Sustained VT	Right to left shunt	No	1139
ASD DCM	M	39	Paced LV endo	Syncope sustained VT	Previous leads implanted	Yes	1827
TGA, Mustard	M	24	Paced sub pulm vent.	Syncope NOT Sustained VT	SVC baffle occlusion	No	1890
HLVS Fontan	M	13	IVCD + RVH	Sustained VT	Extracardiac Fontan	No	1499
TGA VSD	M	23	RBBB + RVH	Sustained VT	TV repair	Yes	90

TOF: Tetralogy of Fallot; VSD: Ventricular septal defect; TGA: Transposition of great arteries; DILV: Double inlet left ventricle; ASD: Atrial septal defect; HLVS: Hypoplastic left ventricle syndrome; ECG: Electrocardiogram; RBBB: Right bundle branch block; RVH: Right ventricular hypertrophy; LVH: Left ventricular hypertrophy; IVCD: Inferior vena cava diameter; VF: Ventricular fibrillatio; LV: Left ventricular; DCM: Dilatative cardiomyopathy; VT: Ventricular tachycardia; SICD: Subcutaneous implantable cardiac defibrillator; SVC: Superior vena cava; TV: Tricuspid Valve.

not-sustained ventricular tachycardia. The anatomical diagnoses were: Tetralogy of Fallot, repaired ventricular septal defect with subaortic obstruction, transposition of the great arteries that underwent Mustard repair, double inlet left ventricle with Eisenmenger physiology, atrial septal defect associated with cardiomyopathy. Three patients (37.5%) had previously undergone endocardial pacemaker implantation due to brady-tachyarrhythmic syndrome in two cases, and a CRT device in the other one (Figures 1A, B and 2). Four patients (50%) had a previous history of documented paroxysmal atrial tachyarrhythmia. The reasons for S-ICD *vs* conventional endocardial approach were limited or difficult access to the cardiac chambers in five patient, high infective risk in two patients and presence of right to left shunt in one patient (Table 1). In all patients, the option of conventional ICD was offered and discussed as part of the preoperative consent process.

Pre implant ECG and screening details

Pre implant ECG showed right bundle branch block in 3 patients (37.5 %), non specific interventricular conduction delay in two patients (28%), narrow QRS with left ventricular (LV) hypertrophy in one patient (12.5%), and paced QRS in two patients. Overall the QRS duration ranged from 110 ms to 180 ms (Table 1). All patients clinically deemed as good candidate for S-ICD passed the pre-implant screening (100% success rate). We did not observe any difference in the QRS/T ratio between the left and right position of the electrodes.

Operative issues

Median procedural time was 65 min (range 58-90 min). The use of fluoroscopy was limited to check the proper position of the device and coil relative to the cardiac silhouette. In the patient with an epicardial pacing system, the coil was tunnelled in the usual way without creating any mechanical interference with the previously implanted pacing lead (Figure 2). In one patient with a systemic right ventricle following Mustard operation the defibrillation test was effective only at 80 J despite repositioning of the pulse generator. None of the patients had significant bleeding during the procedure.

Follow-up and outcomes

Median follow-up was 812 d (range 90-1890). In four patients (50%) a follow-up longer than three years was available. Figure 3 depicts a summary of the events occurred in each individual patient according to the background anatomy. During follow-up, one patient underwent device extraction due to local infection secondary to hematoma eight months after the implant. This patient did not develop any signs of systemic infection and underwent subsequent surgical epicardial implantation. Three patients had multiple episodes of

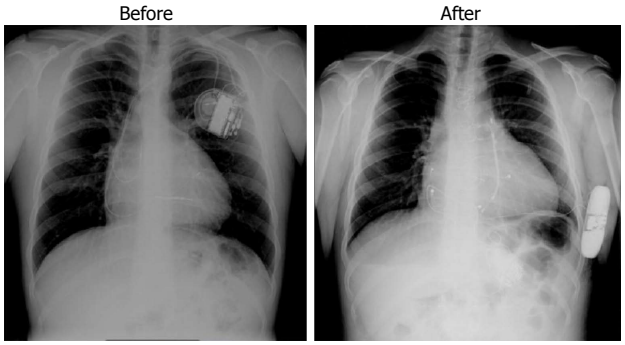

Figure 2 Hybrid implant (subcutaneous implantable cardiac defibrillator and epicardial pacing). The patient developed severe tricuspid regurgitation related to the endocardial lead previously implanted.

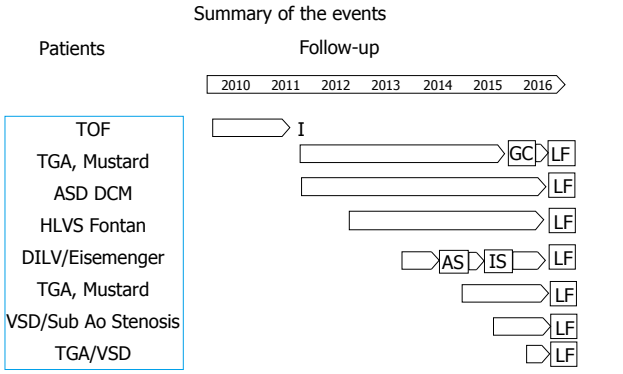

Figure 3 Summary of the events during follow-up according to different anatomic background. TOF: Tetralogy of Fallot; VSD: Ventricular septal defect; TGA: Transposition of great arteries; DILV: Double inlet left ventricle; ASD: Atrial septal defect; HLVS: Hypoplastic left ventricle syndrome; I: Infection; IS: Inappropriate shock; AS: Appropriate shock; GC: Generator change; LF: Last follow-up; DCM: Dilatative cardiomyopathy.

documented sustained atrial tachycardia (four clinically relevant episodes requiring admission and arrhythmia termination), triggering an inappropriate shock in one patient 18 mo after the implant (inappropriate discharge overall rate 12.5%). These patients had a history of atrial tachycardia before the implant. The same patient had an effective, appropriate shock due to fast ventricular tachycardia that occurred after eight months (appropriate discharge overall rate 12.5%). None of the patients had inappropriate shocks related to over-sensing. One patient underwent uncomplicated pulse generator replacement owing to battery depletion. One patient with large atrial septal defect associated with cardiomyopathy developed progressive LV dysfunction and underwent upgrading to biventricular stimulation. The trans-coronary sinus left LV lead was then switched off as it was causing diaphragmatic capture in the bipolar configuration and interference with the S-ICD in the unipolar one. A new transeptal endocardial lead was implanted in the left ventricle and the atrial septal defect was thereafter successfully closed with an occlude device (Figure 1). In the remaining two patients with conventional endocardial pacing system we did not observe any electrical interference during follow-up.

DISCUSSION

Abnormal cardiac rhythm is the most common cause of hospital admission in adults with CHD. The absolute risk of sudden death and/or ventricular arrhythmias increases with prolonged follow-up, particularly in the subset of patients with reduced systemic ventricular function and evidence of extensive scar within the ventricular mass[11]. The risk of sudden death in the adult CHD population ranges from 0.1% and 0.5% per year[12,13]. However, there is no established guidance for ICD implantation in this group of patients apart from those fulfilling a secondary prevention indication. It is well recognized that ICD implantation in adult CHD might be particularly technically challenging due to vascular access issues or to the complex anatomy. Furthermore, complications at follow-up are significantly higher when compared to the general population of ICD recipients. These include endocarditis in patient with prosthetic valve or residual native valve disease, baffle obstruction in patients who underwent atrial switch, and thromboembolism in patient with intracardiac shunts. S-ICD represents an attractive alternative for this population and may offer an effective protection against sudden death in a higher proportion of patients with reduced morbidity.

Screening issues

Effective screening plays a pivotal role in selecting CHD subjects for the S-ICD. In congenital heart patients, a particular concern is the presence of a large percentage of T wave inversion or enlargement throughout the precordial leads, secondary to ventricular hypertrophy, right bundle branch block, or a paced QRS complex. These features, have been reported as a risk factor for ECG screening failure in the S-ICD[14,15]. Despite the fact that most of our patient had right bundle branch block and two had a paced ventricular complex, all passed the preimplant screening. Contrary to experience reported previously, all patients passed the screening with electrodes positioned on the left parasternal edge[16]. This finding should be interpreted cautiously owing to the small sample size, and might simply reflect the variability in ECG presentation in this population or the highly unpredictable vector configuration.

Long-term outcomes

As expected, a significant proportion of patient (37%) had multiple episodes of sustained atrial tachycardia that were correctly discriminated by the device. Overall two patients had device related complications (an early local hematoma and an inappropriate shock). Only one patient had one appropriate and one inappropriate shock, accounting for a cumulative incidence of inappropriate shock over the follow-up of 1.5%. The device settings were optimized by activating the conditional shock zone. However, this percentage is consistent with the one reported in the IDE and EFFORTLESS, confirming

the reliability of the S-ICD algorhythm in discriminating supraventricular from ventricular tachycardias, even in this clinical setting charachterized by a high incidence of atrial arrhythmias[17]. One patient had an appropriate shock during the entire follow-up (cumulative prevalence 12.5%). Although consistent with the EFFORTLESS registry data, this percentage was lower compared with the population of patients with endocardial ICD[18]. Interestingly, a significant number of self-terminating ventricular tachycardia episodes were detected at follow-up, underscoring the appropriateness of a deliberate high cut-off rate and long time to therapy setting in this subset of patient. Furthermore, the low percentage of shocks also reflects the overall lower arrhythmic risk in patients with CHD as compared with patients with cardiomyopathies or ischaemic substrates, as already observed[12].

S-ICD in patients requiring anti- bradycardic pacing

A theoretical major limitation in the eligibility of CHD patient for S-ICD is the high likelihood of developing pacing dependency during follow-up. Data about the effect of a previously implanted endocardial pulse generator on the long term performance of the S-ICD are limited. In the EFFORTLESS registry, 2.8% of patients had a anti-bradycardic pacemaker implanted. In the CHD population, the experience of combined implantation of S-ICD and pacemaker did not raise concern regarding electrical interferences[19]. Although a significant proportion of patients had a pacemaker previously implanted, we did not reported clinical relevant electrical interferences in any patient but one in which the LV lead was temporarily programmed in the unipolar configuration. This finding suggest the long-term compatibility of the S-ICD with an endocardial anti-bradycardic device, provided that pacing configuration is bipolar. This safety issue, if consistently confirmed, may theoretically extend the indication to S-ICD in this particular subset of patients.

Our data suggest that S-ICD might represent a valid option for patient with complex CHD at high risk of sudden death. This technology may overcome some of the technical constrain and long-term risk related to the conventional transvenous ICD, eventually expanding the eligibility of this subset of patient for anti-tachycardic therapy.

Limitations

A major limitation of this paper is the low number of patients, which reflect the experience of only two centres. Furthermore, we do not have a matched group of CHD patients who underwent transvenous ICD implant as control group. Systematic collection of prospective data is needed to support S-ICD as a routine alternative in this population.

COMMENTS

Background

Endocardial implant of devices in patients with congenital heart disease may pose a particular challenge owing to limited vascular access and complex anatomy. Furthermore conventional endocardial pacing in this population is associated with a higher risk of lead related complications.

Research frontiers

Subcutaneous implantable cardiac defibrillator (S-ICD) has been proved to be effective and safe in patients with a wide range of cardiomyopathies and arrhythmogenic syndromes. Limited evidences from subgroup of patients enrolled in clinical trials support the extension of the use of this technology in patients with structural heart disease.

Innovations and breakthroughs

This paper report data relative to a uniquely long follow-up patients with congenital heart disease that underwent S-ICD implantation. Although the number of patients is low they represent a wide range of clinical settings, including single ventricle physiology.

Applications

ICD implantation in patients with congenital heart disease is still a matter of debate, particularly concerning primary prevention indication. The development and optimization of subcutaneous technology might be a suitable tool to provide and extend the protection against sudden death in this group of patients.

Terminology

S-ICD is a relative new technology made of a pulse generator connected with a coil. The whole system is implanted subcutaneously and is able to provide effective termination of fast rhythm by DC shock and only limited back up pacing.

Peer-review

Very interesting and well written article. It gives an important overview of the topic in a subgroup of very complex patients.

REFERENCES

1 **Oechslin EN**, Harrison DA, Connelly MS, Webb GD, Siu SC. Mode of death in adults with congenital heart disease. *Am J Cardiol* 2000; **86**: 1111-1116 [PMID: 11074209 DOI: 10.1016/S0002-9149(00)01169-3]

2 **Walsh EP**. Practical aspects of implantable defibrillator therapy in patients with congenital heart disease. *Pacing Clin Electrophysiol* 2008; **31** Suppl 1: S38-S40 [PMID: 18226034 DOI: 10.1111/j.1540-8159.2008.00954.x]

3 **Borleffs CJ**, van Erven L, van Bommel RJ, van der Velde ET, van der Wall EE, Bax JJ, Rosendaal FR, Schalij MJ. Risk of failure of transvenous implantable cardioverter-defibrillator leads. *Circ Arrhythm Electrophysiol* 2009; **2**: 411-416 [PMID: 19808497 DOI: 10.1161/CIRCEP.108.834093]

4 **Fortescue EB**, Berul CI, Cecchin F, Walsh EP, Triedman JK, Alexander ME. Patient, procedural, and hardware factors associated with pacemaker lead failures in pediatrics and congenital heart disease. *Heart Rhythm* 2004; **1**: 150-159 [PMID: 15851146 DOI: 10.1016/j.hrthm.2004.02.020]

5 **Griksaitis MJ**, Rosengarten JA, Gnanapragasam JP, Haw MP, Morgan JM. Implantable cardioverter defibrillator therapy in paediatric practice: a single-centre UK experience with focus on subcutaneous defibrillation. *Europace* 2013; **15**: 523-530 [PMID: 23333943 DOI: 10.1093/europace/eus388]

6 **Bardy GH**, Smith WM, Hood MA, Crozier IG, Melton IC, Jordaens L, Theuns D, Park RE, Wright DJ, Connelly DT, Fynn SP, Murgatroyd FD, Sperzel J, Neuzner J, Spitzer SG, Ardashev AV, Oduro A, Boersma L, Maass AH, Van Gelder IC, Wilde AA, van Dessel PF, Knops RE, Barr CS, Lupo P, Cappato R, Grace AA. An entirely subcutaneous implantable cardioverter-defibrillator. *N Engl J Med* 2010; **363**: 36-44 [PMID: 20463331 DOI: 10.1056/NEJMoa0909545]

7 **Bouchardy J**, Therrien J, Pilote L, Ionescu-Ittu R, Martucci G, Bottega N, Marelli AJ. Atrial arrhythmias in adults with congenital heart disease. *Circulation* 2009; **120**: 1679-1686 [PMID: 19822808

DOI: 10.1161/CIRCULATIONAHA.109.866319]

8 **Knops RE**, Brouwer TF, Barr CS, Theuns DA, Boersma L, Weiss R, Neuzil P, Scholten M, Lambiase PD, Leon AR, Hood M, Jones PW, Wold N, Grace AA, Olde Nordkamp LR, Burke MC; IDE and EFFORTLESS investigators. The learning curve associated with the introduction of the subcutaneous implantable defibrillator. *Europace* 2016; **18**: 1010-1015 [PMID: 26324840 DOI: 10.1093/europace/euv299]

9 **Bordachar P**, Marquié C, Pospiech T, Pasquié JL, Jalal Z, Haissaguerre M, Thambo JB. Subcutaneous implantable cardioverter defibrillators in children, young adults and patients with congenital heart disease. *Int J Cardiol* 2016; **203**: 251-258 [PMID: 26519678 DOI: 10.1016/j.ijcard.2015.09.083]

10 **Ali H**, Lupo P, Cappato R. The Entirely Subcutaneous Defibrillator - A New Generation and Future Expectations. *Arrhythm Electrophysiol Rev* 2015; **4**: 116-121 [PMID: 26835112 DOI: 10.15420/aer.2015.04.02.116]

11 **Khairy P**, Van Hare GF, Balaji S, Berul CI, Cecchin F, Cohen MI, Daniels CJ, Deal BJ, Dearani JA, Groot Nd, Dubin AM, Harris L, Janousek J, Kanter RJ, Karpawich PP, Perry JC, Seslar SP, Shah MJ, Silka MJ, Triedman JK, Walsh EP, Warnes CA. PACES/HRS Expert Consensus Statement on the Recognition and Management of Arrhythmias in Adult Congenital Heart Disease: developed in partnership between the Pediatric and Congenital Electrophysiology Society (PACES) and the Heart Rhythm Society (HRS). Endorsed by the governing bodies of PACES, HRS, the American College of Cardiology (ACC), the American Heart Association (AHA), the European Heart Rhythm Association (EHRA), the Canadian Heart Rhythm Society (CHRS), and the International Society for Adult Congenital Heart Disease (ISACHD). *Heart Rhythm* 2014; **11**: e102-e165 [PMID: 24814377 DOI: 10.1016/j.hrthm.2014.05.009]

12 **Gatzoulis MA**, Balaji S, Webber SA, Siu SC, Hokanson JS, Poile C, Rosenthal M, Nakazawa M, Moller JH, Gillette PC, Webb GD, Redington AN. Risk factors for arrhythmia and sudden cardiac death late after repair of tetralogy of Fallot: a multicentre study. *Lancet* 2000; **356**: 975-981 [PMID: 11041398 DOI: 10.1016/S0140-6736(00)02714-8]

13 **Silka MJ**, Hardy BG, Menashe VD, Morris CD. A population-based prospective evaluation of risk of sudden cardiac death after operation for common congenital heart defects. *J Am Coll Cardiol* 1998; **32**: 245-251 [PMID: 9669277 DOI: 10.1016/S0735-1097(98)00187-9]

14 **Okamura H**, McLeod CJ, DeSimone CV, Webster TL, Bonnichsen CR, Grogan M, Phillips SD, Connolly HM, Ammash NM, Warnes CA, Friedman PA. Right Parasternal Lead Placement Increases Eligibility for Subcutaneous Implantable Cardioverter Defibrillator Therapy in Adults With Congenital Heart Disease. *Circ J* 2016; **80**: 1328-1335 [PMID: 27109124 DOI: 10.1253/circj.CJ-16-0153]

15 **Groh CA**, Sharma S, Pelchovitz DJ, Bhave PD, Rhyner J, Verma N, Arora R, Chicos AB, Kim SS, Lin AC, Passman RS, Knight BP. Use of an electrocardiographic screening tool to determine candidacy for a subcutaneous implantable cardioverter-defibrillator. *Heart Rhythm* 2014; **11**: 1361-1366 [PMID: 24755323 DOI: 10.1016/j.hrthm.2014.04.025]

16 **Wilson DG**, Zeb M, Veldtman G, Dimitrov BD, Morgan JM. Left and Right Parasternal Sensing for the S-ICD in Adult Congenital Heart Disease Patients and Normal Controls. *Pacing Clin Electrophysiol* 2016; **39**: 282-290 [PMID: 26694691 DOI: 10.1111/pace.12802]

17 **Gold MR**, Theuns DA, Knight BP, Sturdivant JL, Sanghera R, Ellenbogen KA, Wood MA, Burke MC. Head-to-head comparison of arrhythmia discrimination performance of subcutaneous and transvenous ICD arrhythmia detection algorithms: the START study. *J Cardiovasc Electrophysiol* 2012; **23**: 359-366 [PMID: 22035049 DOI: 10.1111/j.1540-8167.2011.02199]

18 **Germano JJ**, Reynolds M, Essebag V, Josephson ME. Frequency and causes of implantable cardioverter-defibrillator therapies: is device therapy proarrhythmic? *Am J Cardiol* 2006; **97**: 1255-1261 [PMID: 16616037 DOI: 10.1016/j.amjcard.2005.11.048]

19 **Hong PS**, Callinan P, Amit G, Healey JS. Successful Implant of a Subcutaneous ICD System in a Patient with an Ipsilateral Epicardial Pacemaker. *Indian Pacing Electrophysiol J* 2015; **15**: 62-64 [PMID: 25852244 DOI: 10.1016/S0972-6292(16)30843-9]

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SYSTEMATIC REVIEWS

Interferon related pericarditis: Review

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Abstract

AIM

To conduct a review of "interferon related pericarditis".

METHODS

We searched MEDLINE, EMBASE, Cinahl, and the Cochrane Database from the earliest available date through September 2016. A search strategy using the Medical Subject Headings and text keywords "interferon" and " pericarditis" were used.

RESULTS

Nine case reports were eligible for the present study. Six of 8 cases were women and the mean age was 43.8 ± 13.8 years with chronic hepatitis C in 6 cases, malignant melanoma in 2 cases and chronic myelogenous leukemia in 1 case. The patients complained of chest pain in 6 cases, dyspnea in 5 cases and edema in 2 cases. Pericardial friction rub was heard in 3 of 9 cases. Congestive heart failure occurred in 3 of 9 cases. Two mechanisms for pericarditis were demonstrated, one is autoimmune included lupus like syndrome in 2 cases and the other is cardio toxicity in 4 cases. Treatment of interferon related pericarditis is discontinuation of Interferon treatment. Four of 9 cases were treated with prednisone and 4 with nonsteroidal anti-inflammatory drugs.

CONCLUSION

Interferon related pericarditis still remains uncertain. Treatment of interferon related pericarditis rests mainly on early recognition and drug discontinuation. Interferon related pericarditis was treated with steroid and/or non-steroidal anti-inflammatory drugs.

Key words: Chronic hepatitis C; Chronic myelogeneous leukemia; Interferon; Malignant lymphoma; Pericarditis

Core tip: Interferon is considered to be one of the treatments for many diseases. However, interferon therapy is associated with side effects. Recently some reports demonstrated acute pericarditis complicating interferon therapy. Two mechanisms for pericarditis were demonstrated, one is autoimmune included lupus like syndrome and the other is cardio toxicity. However, these two mechanisms are controversial. The aim of this study is to review of "interferon related pericarditis".

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INTRODUCTION

Interferon is considered to be one of the treatments for many diseases. However, interferon therapy is associated with side effects, the most common being general symptoms such as fever, weight loss and headache. Some studies have demonstrated cardiac adverse effects of interferon for chronic hepatitis C (CHC)[1,2]. Most frequently reported are arrhythmia, congestive heart failure and sudden death. Reported with rarer frequency are polyneuropathy, paranoia and suicidal thoughts, diabetes mellitus, retinopathy, optical neuritis, diminution of hearing, seizures, loss of libido and cardio toxicity[3]. Recently some reports demonstrated acute pericarditis complicating interferon therapy[4-12]. We conducted a review of "interferon related pericarditis".

MATERIALS AND METHODS

Selection of case reports

We searched MEDLINE, EMBASE, Cinahl, and the Cochrane Database from the earliest available date through September 2016. A search strategy using the Medical Subject Headings and text keywords "interferon" and "pericarditis" were used. The retrieved studies were manually screened to assess their appropriateness for this study. All references cited in the studies were also reviewed to identify additional published articles not indexed in the database. The search was not restricted by language.

RESULTS

Patients

Nine case reports were eligible for the present study; seven were in English[4,5,7,8,10-12] and two in French[6,9]. Clinical characteristics of patients are shown in Table 1. Six of 8 cases were women and the mean age was 43.8 ± 13.8 years with CHC in 6 cases, malignant melanoma in 2 cases and chronic myelogenous leukemia in 1 case. The patients complained of chest pain in 6 cases, dyspnea in 5 cases and edema in 2 cases. Pericardial friction rub was heard in 3 of 9 cases[5,8,9]. Congestive heart failure occurred in 3 of 9 cases[8-10]. Two mechanisms for pericarditis were demonstrated, one is autoimmune included lupus like syndrome (AI group) in 2 cases and the other is cardio toxicity (CT group) in 4 cases. Three of 9 articles didn't mention the mechanisms for pericarditis.

Clinical history

Three cases had clinical history. The 28-year-old patient had allergic asthma since infancy[4]. The 24-year-old woman following therapy with interferon α was diagnosed with systemic lupus erythematosus (SLE), and she was treated with prednisone (40 mg/d)[5]. When prednisone had been stopped completely for 3 mo, a pericarditis occurred. The patient had a recurrence of SLE. The 63-year-old man was diagnosed as diffuse large B cell non-Hodgkin's lymphoma and was treated with a full course of chemotherapy consisting of cyclophosphamide, adriamycin, vincristine and dexamethasone[8].

Laboratory findings

The woman with SLE[5] experienced four episodes of fever and pain in the left shoulder while breathing. Antinuclear antibody and anti-ds DNA antibody tests were negative, whereas circulating immune complexes were positive at the second and the third episode. CH50 and C4 levels were decreased with slightly elevated C3d level. Laboratory results of the 63-year-old man with non-Hodgkin's lymphoma presented antinuclear antibodies (titer 1/40)[8]. The blood sample examination of the 67-year-old man with CHC showed anti-DNA antibody and anti-ds DNA IgM were positive[10].

Interferon daily dose and duration of treatment with interferon

Figure 1 showed a relationship between the daily dose of interferon and the duration of treatment with interferon. Autoimmune due to interferon does not dependent on the daily dose but developed within one month with interferon treatment. Cardio toxicity due to interferon does not dependent on the daily dose or the duration of treatment with interferon.

Chest radiography

Chest radiography demonstrated abnormalities in three cases. Chest X-ray of the 63-year-old man showed an enlarged heart silhouette and bilateral pleural effusion[8]. Chest radiograph of the 53-year-old woman showed cardiomegaly[9]. Portable chest radiograph of the 67-year-old man revealed pulmonary vascular congestion without pleural effusion[10].

Electrocardiogram

Electrocardiogram (ECG) demonstrated abnormality in one case. ECG showed gradual ST-segment elevation in leads V1 through V6 without elevated myocardial enzyme in the 67-year-old man[10]. Coronary angiography showed that there was no significant coronary arterial stenosis in this case.

Ultrasound cardiology

Ultrasound cardiology (UCG) demonstrated pericardial effusion in 7 of 9 cases; mild in 2 cases[6,12], moderate in 2 cases[4,10], severe in 1 case[9], and no presentation in 2 cases[7,11]. The 53-year-old female was diagnosed with constructive pericarditis with pre-tamponade[9].

Re-start and re-challenge test

The interferon treatment was restarted in three cases[4,6,11]. The 28-year-old patient suffered a pericarditis relapse at

Table 1 Case reports of pericarditis associated with interferon

Ref.	Age/gender	Disease	Administered	Duration of IFN therapy	Mechanism
Fava *et al*[4]	28/NA	CML	IFNα	13 mo	NA
Boonen *et al*[5]	24/F	CHC	IFNα	1 mo	Autoimmune
Wisniewski *et al*[6]	42/F	CHC	IFNα	6 h	Cardio toxicity
Gressens *et al*[7]	40/F	CHC	IFNα2b	3 mo	Cardio toxicity
Benjamini *et al*[8]	63/M	MM	IFNα2b	1 mo	Cardio toxicity
Hamdani *et al*[9]	53/F	CHC	PEG IFN α2a	6 mo	NA
Nishio *et al*[10]	67/M	CHC	PEG IFN 2a	15 d	Lupus like syndrome
Popescu *et al*[11]	38/F	CHC	PEG IFN 2a	7 mo	Cardio toxicity
Ashraf *et al*[12]	39/F	MM	IFNα	1 d	NA

CHC: Chronic hepatitis C; CML: Chronic myelogenous leukemia; F: Female; IFN: Interferon; M: Male; MM: Malignant melanoma; NA: Data not available; PEG IFN: Pegylated interferon.

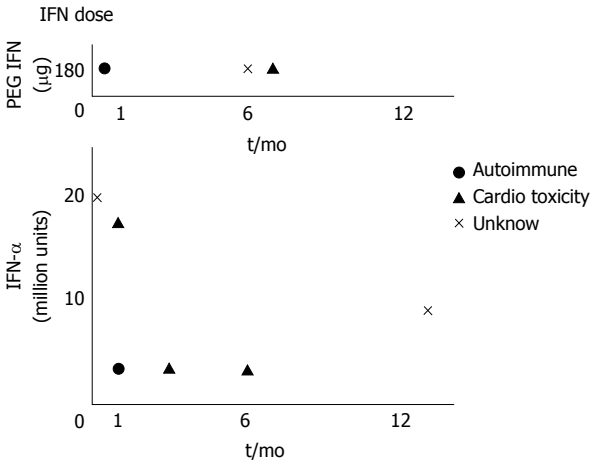

Figure 1 The relationship between interferon dose and duration of interferon therapy. PEG IFN: Pegylated interferon.

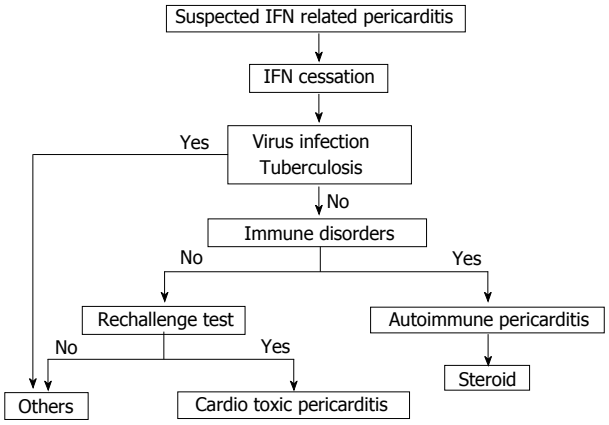

Figure 2 Algorithm of diagnoses and treatments for interferon related pericarditis. IFN: Interferon.

seven months after resumption of interferon α therapy[4]. The 42-year-old female felt chest pain, after 7 h from administration of 1 million interferon α[6]. After the first dose of interferon administration symptoms reappeared and UCG showed an increase of pericardial fluid in the 38-year-old female[11]. Re-challenge test was performed in one case[12]. Within ten hours of the re-initiation of interferon therapy, the 39-year-old woman developed chest pain identical to her previous pain.

Complications

Two cases developed other complications. An electromyography showed signs of polyneuropathy in the 40-year-old female[7]. The 67-year-old man developed chronic inflammatory demyelinating polyneuropathy during treatment with pegylated interferon-2a for chronic active hepatitis C viral infection[10].

Treatment

Treatment of drug-induced cardio toxicity rests mainly on early recognition and drug discontinuation. Interferon treatment was stopped in 7 of 9 cases. Four of 9 cases were treated with prednisone from 10 mg per day to 50 mg/d[4,5,8,10] and 4 with nonsteroidal anti-inflammatory drugs (NSAIDs)[5,7,11,12]. All of the AI group was treated with prednisone[5,10] and two of the CT group were treated with NSAIDs[7,11] and one of the CT group dexamethasone[8]. The 53-year-old female was treated with medications of anti-tuberculosis, but died because multiple organ failure[9]. Figure 2 showed an algorithm of the suspected interferon related pericarditis management.

DISCUSSION

Cardiac adverse effects of interferon α for CHC have been demonstrated[1,2]. Most frequently reported are arrhythmias, congestive heart failure and sudden death. These side effects occurred during treatment with interferon α. However, pericarditis as a side effect of treatment with interferon is rare.

In 1988, the first report concerning interferon related pericarditis was presented by anonymity[13]. This report demonstrated two patients with continuous interferon therapy for chronic myelogenous leukemia had severe side effects consisting of pleural effusions and pericarditis. Montastruc *et al*[14] presented that there was an isolated pericarditis for which it was necessary to interrupt the interferon α treatment. However, these two articles didn't describe in detail. Consequently, 9 articles were enrolled in the present study. Two mechanisms for pericarditis were demonstrated, one is autoimmune in 2 articles and

the other is cardio toxicity in 4 articles. Three of 9 articles didn't mention the mechanisms for pericarditis.

Prospective study reported on autoimmune phenomena in 987 patients treated with interferonα for CHC. Twelve patients developed hyperthyroidism, 6 hypothyroidism, 3 interstitial pneumonia, 1 SLE, 2 rheumatoid arthritis, 2 autoimmune hepatitis and 1 autoimmune thrombocytopenic purpura[15]. In the present study, the appearance of lupus-like syndrome by the interferon treatment has been reported in 1 article and autoimmune in 1 article. The mechanism by which interferon α induces autoimmune mediated complications is largely unknown. However, interferon alpha induses numerous target genes in antigen-presenting cells (APCs), such that APCs are stimulated and enhance humoral autoimmunity, promote isotype switching, and potently activate autoreactive T cells. Moreover, interferon alpha can synergistically amplify T cell autoreactivity by directly promoting T-cell activation and keeping activated T cells alive. *Via* the latter mechanisms, interferon can trigger autoimmune diseases[16]. There is a possibility that interferon may damage endothelial cells, cause the thickening of capillary walls, and induce deposition of immune complexes. Interferon evokes the release of several cytokines, including tumor necrosis factor alpha, and interleukins 2, 6 and 1, affecting autonomic sympathetic nerve activity and vasopressor responses[17]. Interferon induces an autoimmune reaction through various mechanisms including production of gamma globulins and interleukin-6 (IL-6)[18] and inhibition of Allo-specific suppressor T lymphocytes, as well as activation of natural killer cells[19]. IL-6 was significantly increased in pericardial effusion[20]. Interferon has been associated with exacerbation or induction of a wide variety of clinical and serological immune disorders, including systemic lupus erythematosus, rheumatoid arthritis, autoimmune hepatitis, thyroid disease and diabetes mellitus. On the other hand, Orságová *et al*[21] demonstrated that positivity of antinuclear antibodies and smooth muscle antibodies or increased rheumatoid factor and circulating immune complexes are often found in patients with chronic hepatitis B and CHC treated with interferon, but their presence does not correlate with the development of autoimmune diseases.

The cardiac toxicity of interferon alpha is also well known and uncommon. The mechanism of interferon cardio toxicity is unclear and probably multifactorial. There are no established predisposing factors for interferon cardio toxicity. The secondary effects of interferon described include arrhythmia (atrial fibrillation, sinus bradycardia, atrioventricular block), ischemic cardiomyopathy and cardiomyopathy with the dosage levels used in the treatment of hepatitis C[2]. Myocardial ischemia is mainly caused by cardio toxicity of interferon and antimetabolites[22]. Patients with previous heart disease are probably at higher risk for arrhythmia and ischemic manifestations[1]. Concerning drug toxicity, there have been reported cases of acute pericarditis after the administration of: Hydralazine, procainamide, izoniazid, phenylbutazone, dantrolene, doxorubicin, and penicillin. These situations are extremely rare. Sonnenblick *et al*[23] demonstrated that the cardiac effects of interferon were not related to the daily dose, cumulative total dose, or period of therapy and cardiac toxicity was reversible following the cessation of the drug therapy. Interferon inhibits cardiac cell function *in vitro*[24].

The Naranjo adverse drug reactions (ADR) Probability Scale[25] is a validated tool used to determine the likelihood that the adverse drug reaction is caused by the implicated medication. The Naranjo algorithm requires a series of questions to be answered and scored. The total calculated score indicates the likelihood of causing an adverse drug reaction. Popescu *et al*[11] used the Naranjo ADR Probability Scale to evaluate the correlation of pericarditis with interferon administration. This scale indicated a very probable association.

Treatment of interferon-induced cardio toxicity rests mainly on early recognition and drug discontinuation. There is a high degree of individual variation in toxicity, but most adverse events are reversible upon cessation of the drug[8]. In the present study, 4 of 9 patients were treated with prednisone and 4 with NSAIDs.

Chronic hepatitis C viral (HCV) infection and treatment with interferon are both associated with serological and clinical autoimmune manifestations[26,27]. The serological immune response to HCV infection may include the development of cryoglobulinemia, rheumatoid factor, anti-cardiolipin, antinuclear, anti-liver-kidney-microsome 1 and anti-smooth muscle antibodies. Serological autoimmune manifestations were explained by the lymphotropism of HCV and the polyclonal activation of B cells. Interferon-based treatment of HCV infection may precipitate or exacerbate the associated autoimmune disease. Classically, type Ⅱ Cryoglobulinaemia, glomerulonephritis and thyroiditis are described.

Interferon related pericarditis still remains uncertain. There may be two mechanisms for pericarditis, one is autoimmune and the other is cardio toxicity. Treatment of interferon related pericarditis rests mainly on early recognition and drug discontinuation. Interferon related pericarditis was treated with steroid and/or NSAIDs.

COMMENTS

Background

When the authors examine a new unusual patient that the authors have never treated before, the authors need to research previous case reports. However, the case report is individual. The authors need to know what kind of examinations they need and what kind of treatments they need as soon as possible. This manuscript aimed to summarize those previous case reports concerning interferon related pericarditis.

Research frontiers

There may be two mechanisms for interferon related pericarditis, one is autoimmune and the other is cardio toxicity. Treatment of interferon related pericarditis rests mainly on early recognition and drug discontinuation. Interferon related pericarditis was treated with steroid and/or nonsteroidal anti-inflammatory drugs.

Innovations and breakthroughs

This is the first article that was summarized interferon related pericarditis.

Applications
Readers will understand the previous case reports concerning interferon related pericarditis in a short time.

Terminology
Interferon related pericarditis is one of the side effects of interferon treatment.

Peer-review
In the current manuscript, the authors reviewed the 9 published interferon-related pericarditis cases. This interferon regimen complication is rare and this review is helpful to understand this rare complication.

REFERENCES

1 **Mansat-Krzyzanowska E**, Dréno B, Chiffoleau A, Litoux P. [Cardiovascular manifestations associated with interferon alfa-2A]. *Ann Med Interne* (Paris) 1991; **142**: 576-581 [PMID: 1807177]
2 **Teragawa H**, Hondo T, Amano H, Hino F, Ohbayashi M. Adverse effects of interferon on the cardiovascular system in patients with chronic hepatitis C. *Jpn Heart J* 1996; **37**: 905-915 [PMID: 9057685 DOI: 10.1536/ihj.37.905]
3 **Georg M,** Walker B. Hepatitis C virus infection. *N Engl J Med* 2001; **345**: 41-52 [DOI 10.1056/NEJM200107053450107]
4 **Fava S**, Luoni M, Stioui S. Pericarditis during interferon-alpha therapy in chronic myelogenous leukemia. *Haematologica* 1996; **81**: 484 [PMID: 8952166]
5 **Boonen A**, Stockbrügger RW, van der Linden S. Pericarditis after therapy with interferon-alpha for chronic hepatitis C. *Clin Rheumatol* 1999; **18**: 177-179 [PMID: 10357129 DOI: 10.1007/s100670050081]
6 **Wisniewski B**, Denis J, Fischer D, Labayle D. [Pericarditis secondary to interferon alpha in chronic hepatitis C]. *Gastroenterol Clin Biol* 2004; **28**: 315-316 [PMID: 15094688 DOI: 10.1016/S0399-8320(04)94929-9]
7 **Gressens B**, Gohy P. Pericarditis due to interferon-alpha therapy during treatment for chronic hepatitis C. *Acta Gastroenterol Belg* 2004; **67**: 301-302 [PMID: 15587340]
8 **Benjamini O,** Kimhi O, Lishner M. Severe pleuropericarditis and cardiomyopathy induced by high dose interferon alpha-2b. *Isr Med Assoc J* 2007; **9**: 486-7 [PMID: 17642403]
9 **Hamdani I**, Kochlef A, Belhadj N, Kharrat J, Ghorbel A. [Acute pericardite which has occurred during the treatment of chronic hepatitis C by the interferon alpha2A]. *Tunis Med* 2008; **86**: 404-405 [PMID: 19476158]
10 **Nishio K**, Konndo T, Okada S, Enchi M. Pericarditis and chronic inflammatory demyelinating polyneuropathy during therapy with pegylated interferon alfa-2a for chronic hepatitis C. *World J Hepatol* 2010; **2**: 358-361 [PMID: 21161021 DOI: 10.4254/wjh.v2.i9.358]
11 **Popescu C**, Arama V, Gliga S. Acute pericarditis due to pegylated interferon alpha therapy for chronic HCV hepatitis - case report. *BMC Gastroenterol* 2011; **11**: 30 [PMID: 21453456 DOI: 10.1186/1471-230X-11-30]
12 **Ashraf F**, Marmoush F, Shafi MI, Shah A. Recurrent Pericarditis, an Unexpected Effect of Adjuvant Interferon Chemotherapy for Malignant Melanoma. *Case Rep Cardiol* 2016; **2016**: 1342028 [PMID: 27418981 DOI: 10.1155/2016/1342028]
13 Interferon in CML. *Br J Hospital Med* 1988; **1**: 77
14 **Montastruc M,** Reiffers J, Bilhou-Nabera C. Recombinant interferon alpha (IFN) as initial treatment for chronic myelogenous leukemia (CML). Journal Chronic Myeloid Leukemia, 2nd International Conference, Bologna 1992: 103
15 **Okanoue T**, Sakamoto S, Itoh Y, Minami M, Yasui K, Sakamoto M, Nishioji K, Katagishi T, Nakagawa Y, Tada H, Sawa Y, Mizuno M, Kagawa K, Kashima K. Side effects of high-dose interferon therapy for chronic hepatitis C. *J Hepatol* 1996; **25**: 283-291 [PMID: 8895006 DOI: 10.1016/S0168-8278(96)80113-9]
16 **Silva MO**. Risk of autoimmune complications associated with interferon therapy. *Gastroenterol Hepatol* (N Y) 2012; **8**: 540-542 [PMID: 23293568]
17 **Takahashi H**, Nishimura M, Sakamoto M, Ikegaki I, Nakanishi T, Yoshimura M. Effects of interleukin-1 beta on blood pressure, sympathetic nerve activity, and pituitary endocrine functions in anesthetized rats. *Am J Hypertens* 1992; **5**: 224-229 [PMID: 1318054 DOI: 10.1093/ajh/5.4.224]
18 **Itoh Y**, Okanoue T, Enjyo F, Morimoto M, Takeuchi T, Kagawa K, Kashima K. Elevated interleukin-6 and gamma-globulin during interferon therapy of hepatitis B. *Am J Gastroenterol* 1992; **87**: 1485-1487 [PMID: 1384310]
19 **Edwards BS**, Merritt JA, Fuhlbrigge RC, Borden EC. Low doses of interferon alpha result in more effective clinical natural killer cell activation. *J Clin Invest* 1985; **75**: 1908-1913 [PMID: 4008643 DOI: 10.1172/JCI111905]
20 **Ristić AD**, Pankuweit S, Maksimović R, Moosdorf R, Maisch B. Pericardial cytokines in neoplastic, autoreactive, and viral pericarditis. *Heart Fail Rev* 2013; **18**: 345-353 [PMID: 22850905 DOI: 10.1007/s10741-012-9334-y]
21 **Orságová I**, RoŽnovský L, Petroušová L, Konečná M, Kabieszová L, Martinek J, Kloudová A, Pavliska L. [Investigation of autoimmunity markers during interferon alpha therapy of chronic hepatitis B and C - twenty years of experience]. *Klin Mikrobiol Infekc Lek* 2016; **22**: 61-67 [PMID: 27450524]
22 **Castel M**, Despas F, Modesto A, Gales C, Honton B, Galinier M, Senard JM, Pathak A. [Cardiotoxicity of chemotherapies]. *Presse Med* 2013; **42**: 26-39 [PMID: 22727981 DOI: 10.1016/j.lpm.2012.04.014]
23 **Sonnenblick M**, Rosin A. Cardiotoxicity of interferon. A review of 44 cases. *Chest* 1991; **99**: 557-561 [PMID: 1704826 DOI: 10.1378/chest.99.3.557]
24 **Lampidis TJ**, Brouty-Boyé D. Interferon inhibits cardiac cell function in vitro. *Proc Soc Exp Biol Med* 1981; **166**: 181-185 [PMID: 6163151 DOI: 10.3181/00379727-166-41043]
25 **Naranjo CA**, Busto U, Sellers EM, Sandor P, Ruiz I, Roberts EA, Janecek E, Domecq C, Greenblatt DJ. A method for estimating the probability of adverse drug reactions. *Clin Pharmacol Ther* 1981; **30**: 239-245 [PMID: 7249508 DOI: 10.1038/clpt.1981.154]
26 **Pawlotsky JM**, Ben Yahia M, Andre C, Voisin MC, Intrator L, Roudot-Thoraval F, Deforges L, Duvoux C, Zafrani ES, Duval J. Immunological disorders in C virus chronic active hepatitis: a prospective case-control study. *Hepatology* 1994; **19**: 841-848 [PMID: 8138255 DOI: 10.1002/hep.1840190407]
27 **Pawlotsky JM**, Roudot-Thoraval F, Simmonds P, Mellor J, Ben Yahia MB, André C, Voisin MC, Intrator L, Zafrani ES, Duval J, Dhumeaux D. Extrahepatic immunologic manifestations in chronic hepatitis C and hepatitis C virus serotypes. *Ann Intern Med* 1995; **122**: 169-173 [PMID: 7810933 DOI: 10.7326/0003-4819-122-3-199502010-00002]

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CASE REPORT

Inadvertent cardiac phlebography

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Author contributions: Aznaouridis K and Alahmar A designed the report and revised the drafted manuscript; Masoura C collected the clinical data and drafted the manuscript; Kastellanos S collected the clinical data and drafted the manuscript.

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Abstract

We are reporting a case of a 80-year-old lady with effort angina who underwent coronary angiography through the right radial artery, using a dedicated radial multipurpose 5 French Optitorque Tiger catheter. The catheter was advanced into the left ventricle and a left ventriculogram was obtained, while the catheter appeared optimally placed at the centre of the ventricle and the pressure waveform was normal. A large posterior interventricular vein draining into the right atrium was opacified, presumably because the catheter's end hole inadvertently cannulated an endocardial opening of a small thebesian vein, with subsequent retrograde filling of the epicardial vein. Our case suggests that caution is needed when a dedicated radial catheter with both an end-hole and a side hole is used for a ventriculogram, as a normal left ventricular pressure waveform does not exclude malposition of the end-hole against the ventricular wall.

Key words: Thebesian vein; Radial access; Transradial; Cardiac phlebography

Core tip: Use of a dedicated radial catheter with both an end-hole and a side hole to perform a left ventriculogram, can result in inadvertent cannulation of a small Thebesian vein and subsequent opacification of a large epicardial vein. When such catheters are used for ventriculogram, a normal ventricular pressure waveform does not exclude malposition of the end-hole against the ventricular wall and extra caution is needed in order to prevent iatrogenic myocardial injury. We review current literature on myocardial injury induced by end-hole catheters used for left ventriculograms.

Aznaouridis K, Masoura C, Kastellanos S, Alahmar A. Inadvertent cardiac phlebography. *World J Cardiol* 2017; 9(6): 558-561

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INTRODUCTION

In the last years, the use of radial artery as an arterial access site for coronary procedures has gained increasing popularity, as it is considered safer compared to transfemoral procedures. Recent data from large randomized trials suggest that the radial access is associated with a reduction of major adverse events in patients with acute coronary syndrome undergoing invasive management[1]. Furthermore, there is expanding use of dedicated "multipurpose" radial catheters, which enable the operator to cannulate both coronary arteries, and also to perform chamber injection and left ventriculogram. For transradial procedures, this single-catheter approach has been shown to decrease radiation exposure, fluoroscopy time, contrast volume and total procedure time compared with standard Judkins catheters[2]. Using a single catheter also reduces the risk of spasm of the radial artery. On the other hand, those dedicated radial catheters may rarely cause myocardial injury when used for a left ventriculogram. We present a rare angiographic finding in a patient who underwent cardiac catheterization through the radial artery using a dedicated radial catheter.

CASE REPORT

A 80-year-old lady with effort angina underwent coronary angiography through the right radial artery, using a dedicated radial "multipurpose" 5 French Optitorque Tiger catheter (Terumo, Somerset, New Jersey). Coronary angiogram of the left and right coronary arteries demonstrated a significant stenosis in the ostium of a modest sized intermediate artery. The catheter was then advanced into the left ventricle (LV) and appeared optimally placed at the centre of the LV, while the LV pressure waveform was normal. A left ventriculogram was obtained after delivering 10 mL of contrast with a vigorous hand injection. Few ectopics were noticed at the beginning of the injection, followed by a small deflection of the catheter's tip, a minor subendocardial staining (arrowhead in panel A) and visualization of a large posterior interventricular vein, which seemed to drain directly into the right atrium (arrows in Figure 1 and supplementary Video 1).

We observed no persistent staining of the myocardium and the patient did not experience any discomfort, arrhythmia or electrocardiographic changes. The patient was monitored and was discharged few hours later.

DISCUSSION

Dedicated radial "multipurpose" catheters such as the Tiger catheter have been specifically designed to minimise catheter exchange with ability to access both coronary ostia from the radial approach, and also provide ability to perform chamber injection with the presence of both an end hole and a single side hole. In our case, we assume that the catheter's end hole cannulated an endocardial opening of a small Thebesian vein, with subsequent retrograde filling of the epicardial vein. Venae cordis minimae (Thebesian veins) are small valveless venous conduits that connect the coronary arteries, veins or capillaries with the cardiac chambers. Most Thebesian veins of the ventricles are connected to the cardiac venous system[3], as was the case in our patient.

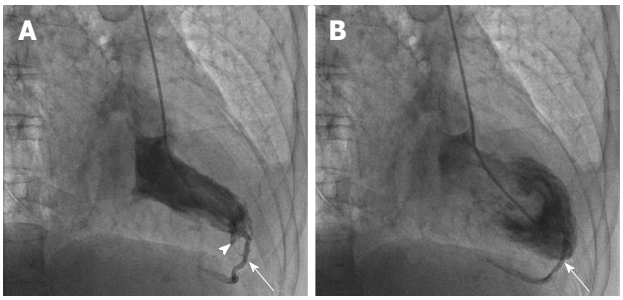

Figure 1 Inadvertent phlebography of the posterior interventricular vein. Right anterior oblique image taken at time of left ventriculography. Arrows show the posterior interventricular vein in systole (A) and diastole (B). Arrowhead shows a minor subendocardial staining (A).

We screened the available literature and we identified a total of 7 reports with 8 cases of myocardial injury following contrast injection with end-hole catheters for left ventriculogram[4-10]. The characteristics of the patients and procedures and the type of myocardial injury and outcome are shown in Table 1. In 5 of those cases, a dedicated transradial end-hole catheter with one side hole near the tip (radial Tiger catheter) or two side holes (radial Jacky catheter) was used[4,6,7,9,10]. Traditional multipurpose (MPA) catheters with an end-hole and 2 side holes near the tip were used in 2 cases[4,5], whereas a catheter with a single end-hole (Judkins right 4) was used from femoral access in 1 case[8]. The Thebesian venous network and/or cardiac veins were visualized in 4 cases[4,5,8,9]. A high-pressure power injection had been performed in most cases describing myocardial laceration/dissection and persistent myocardial staining[6,7,9,10]. Complete myocardial "perforation" with presence of contrast in the pericardial space was confirmed in 2 of those cases[6,10], and emergency pericardiocentesis due to tamponade was performed in one patient[6]. No fatalities were reported (Table 1).

Even a pigtail catheter can rarely cause severe myocardial injury during ventriculography when its tip is inappropriately positioned[11]. However, apposition of the pigtail catheter's end-hole against the endocardium or cannulation of Thebesian veins is extremely unlikely, and therefore this catheter should be the preferred option for ventriculograms.

Caution is needed when a dedicated radial catheter with both an end-hole and side holes is used for a ventriculogram, as a normal left ventricular pressure waveform (likely from the side hole) does not exclude unsafe posi-

Table 1 Patient and procedure-related characteristics and outcomes of published cases describing myocardial laceration or cannulation of Thebesian veins following left ventriculogram with end-hole catheters

Case	Ref.	Demographics	Catheter, access	Injection characteristics	Complication	Clinical findings/outcome
1	Judkins *et al*[4]	72 yr, woman, aortic stenosis	Multipurpose-1 (right radial access)	Not provided	Opacification of Thebesian veins, coronary veins and coronary sinus	Not provided
2	Judkins *et al*[4]	77 yr, woman, chest pain	Optitorque Tiger (right radial access)	Not provided	Opacification of Thebesian veins and coronary veins	Not provided
3	Singhal *et al*[5]	46 yr, man, hypertrophic cardiomyopathy	Multipurpose-2 (femoral access)	Power injection, 25 mL of contrast, 10 mL/s	Opacification of Thebesian veins, coronary veins and coronary sinus	Ventricular tachycardia requiring cardioversion/ uneventful recovery and next day discharge
4	Frizzell *et al*[6]	76 yr, woman, myocardial infarction	Optitorque Tiger (radial access)	Power injection, 30 mL of contrast over 10 s	Laceration/dissection of anterolateral myocardium and pericardial staining	Chest discomfort, pericardial effusion and cardiac tamponade/ pericardiocentesis, uneventful recovery
5	Rossington *et al*[7]	71 yr, woman, angina	Optitorque Tiger (right radial access)	Power injection, 25 mL of contrast, 8 mL/s, 600 psi	Laceration/dissection of anterolateral myocardium	Chest discomfort, transient bundle branch block/ uneventful course and next day discharge
6	Aqel *et al*[8]	50 yr, woman, chest pain	Judkins right 4 (femoral access)	Hand injection	Opacification of Thebesian veins, coronary veins and coronary sinus	Not provided
7	Kang *et al*[9]	66 yr, woman, angina	Optitorque Jacky radial (radial access)	Power injection, 30 mL of contrast over 2 s, 600 psi	Laceration/dissection of anterior myocardium and opacification of anterior interventricular vein and coronary sinus	Not provided
8	Basit *et al*[10]	69 yr, man, inferior wall ischemia	Optitorque Jacky radial (radial access)	Not provided	Laceration/dissection of myocardium with pericardial opacification	Chest pain, trivial pericardial effusion/ uneventful recovery

tioning of the end-hole against the ventricular wall[6,7]. This malposition of the catheter may result in cannulation and injection in a Thebesian vein[4,5,8], or injection against the endocardial layer. In our case, only a small volume of contrast was delivered in an endocardial opening of the Thebesian network with a hand injection, and this may partly explain the relatively "benign" outcome of opacifying an epicardial vein without causing any major myocardial injury. In this scenario, it seems that the injected contrast drains through the Thebesian network into the cardiac veins and therefore no significant intramyocardial shearing forces are generated. However, serious complications such as laceration/dissection of the myocardium or even catastrophic "perforation" of the ventricular wall[6,7,9,10] may occur when the contrast is injected against the endocardium, or when of a large contrast volume is injected in a Thebesian vein with high-pressure (with an automated power injector), as in this case the small Thebesian network would likely be unable to accommodate the forcefully injected large volume of contrast. Hence, we believe that our case indirectly supports the common practice of avoiding the use of radial multipurpose catheters with automated high-pressure power injectors and large volume of contrast for ventriculograms. Therefore, additional care should be taken to confirm that the catheter is optimally positioned at the centre of the left ventricular cavity and that the catheter's tip is free before contrast injection, and the operator should not rely only on a normal waveform of ventricular pressure. Finally, the injection of contrast must stop immediately when subendocardial or myocardial staining or opacification of an epicardial vein occurs during a ventriculogram with a dedicated radial multipurpose catheter, as this invariably indicates myocardial injury due to malposition of the catheter's end hole against the endocardium.

COMMENTS

Case characteristics

This case shows that using a dedicated radial catheter with both an end-hole and a side hole for a left ventriculogram can result in inadvertent cannulation of a small Thebesian vein and subsequent opacification of an epicardial cardiac vein. This was not related to any symptoms or adverse outcomes.

Clinical diagnosis

Minor catheter-induced endocardial staining and visualization of posterior interventricular vein.

Differential diagnosis

Catheter-induced laceration/dissection of myocardial wall.

Imaging diagnosis

Left ventriculogram with a dedicated radial Tiger catheter.

Related reports

Current literature on myocardial injury induced by end-hole catheters used for

left ventriculogram is reviewed.

Experiences and lessons

When dedicated radial end-hole catheters are used for ventriculogram, a normal ventricular pressure waveform does not exclude malposition of the end-hole against the ventricular wall and extra caution is needed in order to prevent iatrogenic myocardial injury.

Peer-review

This is a case report about an unexpected cardiac phlebography. The manuscript is well written and describes an important aspect related to the use of multipurpose radial catheters.

REFERENCES

1 **Valgimigli M**, Gagnor A, Calabró P, Frigoli E, Leonardi S, Zaro T, Rubartelli P, Briguori C, Andò G, Repetto A, Limbruno U, Cortese B, Sganzerla P, Lupi A, Galli M, Colangelo S, Ierna S, Ausiello A, Presbitero P, Sardella G, Varbella F, Esposito G, Santarelli A, Tresoldi S, Nazzaro M, Zingarelli A, de Cesare N, Rigattieri S, Tosi P, Palmieri C, Brugaletta S, Rao SV, Heg D, Rothenbühler M, Vranckx P, Jüni P. Radial versus femoral access in patients with acute coronary syndromes undergoing invasive management: a randomised multicentre trial. *Lancet* 2015; **385**: 2465-2476 [PMID: 25791214 DOI: 10.1016/S0140-6736(15)60292-6]

2 **Chen O**, Goel S, Acholonu M, Kulbak G, Verma S, Travlos E, Casazza R, Borgen E, Malik B, Friedman M, Moskovits N, Frankel R, Shani J, Ayzenberg S. Comparison of Standard Catheters Versus Radial Artery-Specific Catheter in Patients Who Underwent Coronary Angiography Through Transradial Access. *Am J Cardiol* 2016; **118**: 357-361 [PMID: 27269989 DOI: 10.1016/j.amjcard.2016.05.010]

3 **Jain AK**, Smith EJ, Rothman MT. The coronary venous system: an alternative route of access to the myocardium. *J Invasive Cardiol* 2006; **18**: 563-568 [PMID: 17090824]

4 **Judkins C**, Yamen E. Inadvertent thebesian vein cannulation during radial access ventriculography. *JACC Cardiovasc Interv* 2013; **6**: e9-e10 [PMID: 23428022 DOI: 10.1016/j.jcin.2012.09.014]

5 **Singhal S**, Khoury S. Images in clinical medicine. Imaging of thebesian venous system. *N Engl J Med* 2008; **359**: e8 [PMID: 18703466 DOI: 10.1056/NEJMicm072885]

6 **Frizzell JD**, Alkouz M, Sheldon MW. Left ventricular perforation during ventriculogram using an optitorque tiger catheter. *JACC Cardiovasc Interv* 2014; **7**: 1456-1457 [PMID: 25457057 DOI: 10.1016/j.jcin.2014.07.014]

7 **Rossington JA**, Aznaouridis K, Davison B, Oliver RM. A Tear in the Heart: Myocardial Laceration Following Left Ventriculogram With a Dedicated Radial Catheter. *Am J Med Sci* 2016; **352**: 533 [PMID: 27865303 DOI: 10.1016/j.amjms.2016.01.009]

8 **Aqel R**, Gupta R, Zoghbi GJ. Images in cardiology: Thebesian venous lake. *Heart* 2005; **91**: 1318 [PMID: 16162625]

9 **Kang G**, Kang K, Jurado J, Byrnes L. Left ventricular angiography with a Jacky radial catheter at high pressure leading to myocardial staining and opacification of the great cardiac vein and coronary sinus. *EuroIntervention* 2012; **8**: 410 [PMID: 22829515 DOI: 10.4244/EIJV8I3A62]

10 **Basit A**, Nazir R, Hahn H. Myocardial and pericardial staining by transradial Optitorque Jacky shape catheter during left ventriculogram. *J Invasive Cardiol* 2012; **24**: 128 [PMID: 22388306]

11 **Gach O**, Lempereur M, Eeckhout E, Legrand V. Unintentional "ventriculo-phlebo-myo-pericardiography". *JACC Cardiovasc Interv* 2014; **7**: 577-578 [PMID: 24746658 DOI: 10.1016/j.jcin.2013.07.024]

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