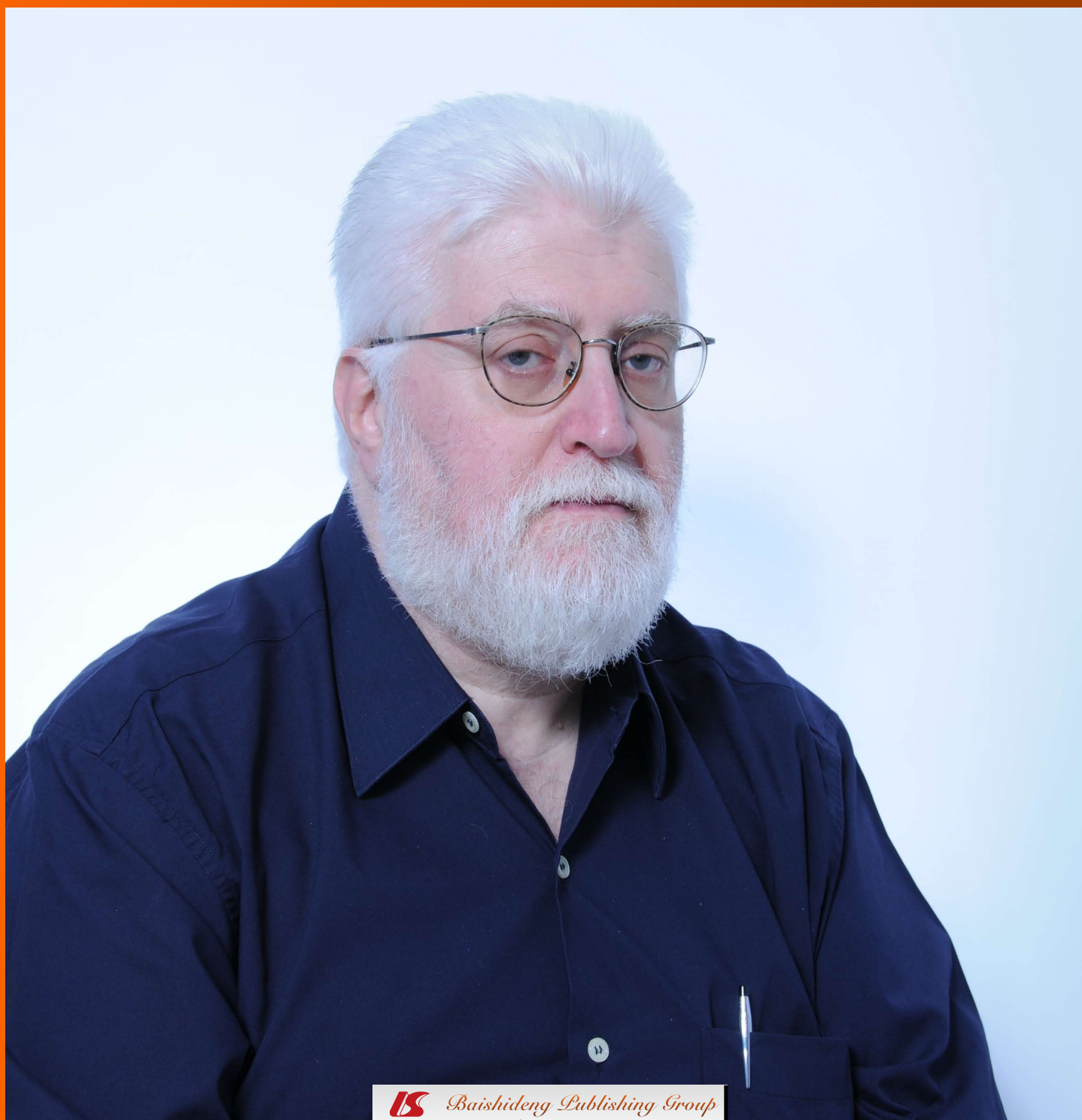


World Journal of *Cardiology*

World J Cardiol 2013 July 26; 5(7): 210-269





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NAME OF JOURNAL
World Journal of Cardiology

ISSN
ISSN 1949-8462 (online)

LAUNCH DATE
December 31, 2009

FREQUENCY
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Telephone: +852-31779906
E-mail: bpgoffice@wjgnet.com
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PUBLICATION DATE
July 26, 2013

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High density lipoprotein and cardiovascular diseases

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Received: April 24, 2013 Revised: May 19, 2013

Accepted: June 18, 2013

Published online: July 26, 2013

Abstract

Several epidemiological studies have clearly shown that low plasma levels of high density lipoprotein cholesterol (HDL-C) represent a cardiovascular disease (CVD) risk factor. However, it is unclear if there is a causal association between HDL-C concentration and CVD. A recent study published in the *Lancet*, which performed two Mendelian randomization analyses, showed that increased HDL-C levels were not associated with a decreased risk of myocardial infarction. These findings, together with the termination of the niacin-based AIM-HIGH trial and the discontinuation of cholesteryl ester transfer protein inhibitor dalcetrapib, challenge the concept that raising of plasma HDL-C will uniformly translate into reductions in CVD risk. HDL particles exhibit several anti-atherosclerotic properties, such as anti-inflammatory and anti-oxidative activities and cellular cholesterol efflux activity. Furthermore, HDL particles are very heterogeneous in terms of size, structure, composition and metabolism. HDL functionality may be associated more strongly with CVD risk than the traditional HDL-C levels. More research is needed to assess the association of the structure of HDL particle with its functionality and metabolism.

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Key words: High density lipoprotein; Functionality; Structure; Cardiovascular risk; Niacin; Cholesteryl ester transfer protein inhibitors

Core tip: Epidemiological studies have shown that low plasma levels of high density lipoprotein cholesterol (HDL-C) represent a cardiovascular disease (CVD) risk factor. However, recent studies challenge the concept that an increase of plasma HDL-C will uniformly translate into a reduction in CVD risk. Certain patients with atherosclerosis may have "dysfunctional" HDL despite normal HDL-C levels. Furthermore, HDL-C levels are influenced by dietary patterns, drugs or concomitant diseases. The association of the structure of HDL particle with its functionality and metabolism has not been fully clarified. More research is needed to assess the association of HDL functionality with CVD risk.

Filippatos TD, Elisaf MS. High density lipoprotein and cardiovascular diseases. *World J Cardiol* 2013; 5(7): 210-214 Available from: URL: <http://www.wjgnet.com/1949-8462/full/v5/i7/210.htm> DOI: <http://dx.doi.org/10.4330/wjc.v5.i7.210>

COMMENTARY ARTICLE

Several epidemiological studies have clearly shown that low plasma levels of high density lipoprotein cholesterol (HDL-C) represent a cardiovascular disease (CVD) risk factor^[1-5]. Furthermore, some large randomized clinical trials have provided evidence of a clinical benefit of drugs increasing HDL-C, such as fibrates, in patients with combined low HDL-C and high triglyceride levels^[6-12]. However, whether there is a causal association between HDL-C concentration and CVD is unclear.

A recent study published in the *Lancet* performed two mendelian randomisation analyses, testing a single nucleotide polymorphism (SNP) in the endothelial lipase gene (LIPG Asn396Ser) in 20 studies (20913 myocardial infarction cases, 95407 controls) and a genetic score con-

sisting of 14 common SNPs that exclusively associate with HDL-C (12482 cases of myocardial infarction and 41331 controls)^[13]. Carriers of the LIPG 396Ser allele (2.6% frequency) had significantly higher HDL-C levels (0.14 mmol/L higher, $P < 0.001$) but similar levels of other lipid and non-lipid CVD risk factors compared with non-carriers. This difference in HDL-C is expected to decrease the risk of myocardial infarction by 13% (OR = 0.87, 95%CI: 0.84-0.91). However, the LIPG 396Ser allele was not associated with a reduced risk of myocardial infarction (OR = 0.99, 95%CI: 0.88-1.11, $P = 0.85$). Furthermore, whereas it is expected from observational epidemiology that an increase of 1 SD in HDL-C will be associated with a 38% reduced risk of myocardial infarction (OR = 0.62, 95%CI: 0.58-0.66), an 1 SD increase in HDL-C due to genetic score was not associated with a reduced risk of myocardial infarction (OR = 0.93, 95%CI: 0.68-1.26, $P = 0.63$)^[13]. These results became more intriguing when a genetic score of 13 common SNPs exclusively associated with low density lipoprotein cholesterol (LDL-C), used as a positive control, was associated with myocardial infarction risk in concordance with observational epidemiology^[13].

Additionally, the termination of the cholesteryl ester transfer protein (CETP) inhibitor dalcetrapib was recently announced. Dalcetrapib, in contrast with torcetrapib, was not associated with non-lipid adverse effects^[14]. In the dal-VESSEL trial, dalcetrapib reduced CETP activity and increased HDL-C levels without affecting nitric oxide-dependent endothelial function, blood pressure, or markers of inflammation and oxidative stress^[15]. Furthermore, co-administration of dalcetrapib with pravastatin resulted in decreased CETP activity, increased HDL-C, apolipoprotein (apo) A-I and A-II levels and increased CETP mass. A relative increase in large HDL and LDL subfractions, combined with adenosine triphosphate (ATP)-binding cassette A1- and scavenger receptor type BI-mediated cholesterol efflux increase were also observed^[16]. These effects seemed promising, but recently Roche announced that, following the results of the second interim analysis of the dalcetrapib dal-OUTCOMES Phase III trial (aimed to evaluate the efficacy and safety profile of dalcetrapib when added to existing standard of care in patients with stable coronary heart disease following an acute coronary syndrome), the independent Data and Safety Monitoring Board recommended stopping the trial due to a lack of clinically meaningful efficacy^[17].

Furthermore, the results of two large studies of niacin were recently added to these disappointing results. In AIM-HIGH (Atherothrombosis Intervention in Metabolic Syndrome With Low HDL/High Triglycerides: Impact on Global Health Outcomes) trial there was no incremental clinical benefit from the addition of niacin to statin therapy during a 36 mo follow-up period, despite significant improvements in HDL-C and triglyceride levels^[18]. More specifically, 3314 patients with atherosclerotic CVD and LDL-C levels < 70 mg/dL (1.81 mmol/L), were randomly assigned to extended-release

niacin (1500-2000 mg/d) or placebo. All patients received simvastatin (40-80 mg/d) plus ezetimibe (10 mg/d), if needed, to maintain an LDL-C level of 40-80 mg/dL (1.03-2.07 mmol/L). The trial was stopped after a mean follow-up period of 3 years owing to a lack of efficacy. At 2 years, niacin therapy had significantly increased the median HDL-C level from 35 mg/dL (0.91 mmol/L) to 42 mg/dL (1.08 mmol/L) and decreased triglyceride level from 164 mg/dL (1.85 mmol/L) to 122 mg/dL (1.38 mmol/L) and LDL-C concentration from 74 mg/dL (1.91 mmol/L) to 62 mg/dL (1.60 mmol/L). However, the primary end point did not differ significantly between niacin (282 patients, 16.4%) and placebo (274 patients, 16.2%) groups (HR = 1.02; 95%CI: 0.87-1.21; $P = 0.79$)^[18]. In the HPS2-THRIVE (Heart Protection Study 2-Treatment of HDL to Reduce the Incidence of Vascular Events) study, the combination of niacin and laropiprant in addition to statin therapy did not significantly reduce the risk of major vascular events in patients with well-controlled LDL-C levels^[19,20]. More specifically, the primary end point (the combination of coronary death, nonfatal myocardial infarction, stroke, or coronary revascularization) occurred in 13.7% of patients in the control arm and 13.2% of patients in the niacin/laropiprant arm (RR = 0.96, 95%CI: 0.90-1.03, $P = 0.29$)^[20].

These data challenge the concept that an increase of plasma HDL-C will uniformly translate into a reduction in CVD risk. HDL-C may simply be a marker of CVD risk, or, alternatively, may represent a biomarker of adverse metabolic processes, as for example of insulin resistance and inflammation.

Some investigators proposed that the failure of dalcetrapib and niacin is related to the only moderate elevation of HDL-C and we have to wait until more potent HDL-increasing drugs to be tested. This thought is based on findings from previous trials. A meta-analysis of 23 trials showed that the sum of percent reduction in LDL-C plus the percent increase in HDL-C predicts CVD benefits much more effectively than either lipoprotein component^[21]. Hence, in populations that have already low LDL-C we need potent HDL-elevating drugs to produce significant increases in HDL-C in order to show clinical benefit.

Moreover, differences between levels of LDL-C and HDL-C and their corresponding particle number measures were observed in many trials. This may be of clinical importance since recent studies have shown that CVD risk in patients with discordance between cholesterol and particle measures of LDL and HDL may be associated more with particle measures^[22,23]. For example, the significant CVD event reduction in the Veterans Affairs High-Density Lipoprotein Intervention Trial (VA-HIT) could not be fully explained by the 6% increase in HDL-C with gemfibrozil^[6,8]. When HDL subpopulations (characterized by 2-dimensional gel electrophoresis) were determined in subjects who were treated with gemfibrozil ($n = 754$) or placebo ($n = 741$), it was shown that gemfibrozil-mediated improvement in CVD risk might not be reflected

by changes in blood lipids and HDL subpopulations^[24]. In contrast, when nuclear magnetic resonance (NMR) spectroscopy was used to quantify levels of LDL and HDL particle subclasses and mean particle sizes during treatment with gemfibrozil (364 men) or placebo (697 age-matched controls), it was shown that gemfibrozil increased LDL size and lowered numbers of LDL particles (-5%), whereas it increased the numbers of HDL particles (+10%) and small HDL subclass particles (+21%). In fact, the concentrations of these LDL and HDL particles achieved with gemfibrozil were independent predictors of new CHD events [total LDL particles: OR = 1.28 (95%CI: 1.12-1.47), total HDL particles: OR 0.71 (95%CI: 0.61-0.81)], whereas mean LDL and HDL particle sizes were not associated with CHD events^[25]. Additionally, a nested case-control study within the EPIC (European Prospective Investigation into Cancer and Nutrition)-Norfolk cohort showed that both HDL size and HDL particle concentration were independently associated with coronary artery disease (CAD), but only HDL particle concentration was independently associated with CAD risk after adjustment for apoB and triglyceride levels [adjusted OR = 0.50 (95%CI: 0.37-0.66)]^[26]. These findings suggest that increasing HDL-C without increasing HDL particle number may influence the clinical outcome. The results of AIM-HIGH could be partly explained by these observations^[27]. Niacin, similarly to CETP inhibitors, alters the composition of HDL, making the particle larger. However, whereas it significantly decreases the mean number of small HDL particles and increases the mean number of large HDL particles, niacin does not significantly alter the total number of NMR-determined HDL particles^[28]. If these effects played significant role in the negative clinical outcomes of AIM-HIGH remains to be established.

HDL particles exhibit several anti-atherosclerotic properties, such as anti-inflammatory and anti-oxidative activities and cellular cholesterol efflux activity^[29-32]. In this setting it is important that certain patients with atherosclerosis may have “dysfunctional” HDL despite normal HDL-C levels^[33-35]. Furthermore, HDL-C levels are influenced by many factors, such as dietary patterns, drugs or concomitant diseases^[36-42]. The heterogeneity in functionality should be taken into account when assessing the association of HDL with CVD risk^[43]. HDL functionality may be associated more strongly with CVD risk than the traditional HDL-C levels. However, we do not know which of the HDL functions is more strongly associated with CVD in order to use it in clinical trials. Furthermore, there are several methods assessing different aspects of HDL functionality and many of them are complex and not part of routine bioassays^[44]. More research is needed to assess the association of HDL functionality with CVD risk and to simplify its determination.

Additionally, HDL particles are very heterogeneous in terms of size, structure, composition and metabolism^[45]. These characteristics may play divergent roles and result in different clinical outcomes^[46-48]. Hence, the association of the structure of HDL particle with its functionality

and metabolism should be clarified and accordingly used in the clinical setting.

The role of HDL in CVD may be clarified by the Randomized Evaluation of the Effects of Anacetrapib Through Lipid-modification (REVEAL) trial which includes 30000 patients and is currently testing whether the CETP inhibitor anacetrapib (which markedly increases HDL-C along with a lowering of LDL-C) on top of statin therapy will reduce the incidence of major coronary events (coronary mortality, myocardial infarction, and coronary revascularization) in patients with a history of CVD^[49]. This phase III study is expected to be completed by 2017. It should be mentioned that niacin and other HDL-increasing drugs, such as anacetrapib, also exhibit beneficial effects on atherogenic lipoproteins, such as LDL or lipoprotein a, so the results of on-going trials will not definitely answer the HDL hypothesis. In this setting, the results of on-going trials with drugs increasing apolipoprotein A- I^[50,51] may help to clarify the role of HDL in CVD.

Overall, based on the current evidence, it is unclear if there is a causal association between HDL-C concentration and CVD. HDL particles are very heterogeneous in terms of size, structure, composition and metabolism and exhibit several anti-atherosclerotic properties. The conflicting results of epidemiological and interventional studies may be attributed to the fact that HDL functionality may be associated more strongly with CVD risk than the traditional HDL-C levels. More research is needed to assess the association of CVD risk with HDL functionality and metabolism.

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P-Reviewers Norozi K, Simkhovich B, Vassalle C
S-Editor Wen LL **L-Editor** A **E-Editor** Lu YJ



Atrial fibrillation in heart failure: The sword of Damocles revisited

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Received: May 11, 2013 Revised: June 6, 2013

Accepted: June 19, 2013

Published online: July 26, 2013

variety of new pathways including selective atrial antiarrhythmic agents and genomic polymorphisms in AF with HF.

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Key words: Heart failure; Atrial fibrillation; Epidemiology; Prognosis; Thromboprophylaxis

Core tip: Atrial fibrillation commonly coexists with heart failure and there is growing evidence that it confers an adverse prognostic impact on the natural course of the disease. This review analyses the demographics and relevant literature highlighting this impact as well as the effect of various therapeutic modalities in improving outcomes. Finally some of the future trends in this exciting cardiovascular discipline are discussed.

Abstract

Heart failure (HF) and atrial fibrillation (AF) frequently coexist and have emerged as major cardiovascular epidemics. There is growing evidence that AF is an independent prognostic marker in HF and affects patients with both reduced as well as preserved LV systolic function. There has been a general move in clinical practice from a rhythm control to a rate control strategy in HF patients with AF, although recent data suggests that rhythm control strategies may provide better outcomes in selected subgroups of HF patients. Furthermore, various therapeutic modalities including pace and ablate strategies with cardiac resynchronisation or radio-frequency ablation have become increasingly adopted, although their role in the management of AF in patients with HF remains uncertain. This article presents an overview of the multidimensional impact of AF in patients with HF. Relevant literature is highlighted and the effect of various therapeutic modalities on prognosis is discussed. Finally, while novel anticoagulants usher in a new era in thromboprophylaxis, research continues in a

Khan MA, Ahmed F, Neyses L, Mamas MA. Atrial fibrillation in heart failure: The sword of Damocles revisited. *World J Cardiol* 2013; 5(7): 215-227 Available from: URL: <http://www.wjgnet.com/1949-8462/full/v5/i7/215.htm> DOI: <http://dx.doi.org/10.4330/wjc.v5.i7.215>

INTRODUCTION

Heart failure (HF) and atrial fibrillation (AF) have emerged as major global epidemics^[1]. Both frequently coexist and are associated with several common predisposing risk factors such as hypertension, coronary artery disease, structural heart disease (non-ischaemic, valvular), diabetes mellitus, obesity and obstructive sleep apnoea. This co-prevalence increases with advancing age and each predicts/compounds the course of the other^[2,3].

Data from Acute Decompensated Heart Failure National Registry demonstrated a 30% prevalence of AF among patients admitted with acute decompensated HF^[4].

The EuroHeart survey looked at HF hospitalisation data from 24 countries over a 6-wk duration. It revealed that out of a total of 10701 patients, 34% were known to have AF previously while 9% developed new onset AF^[5]. There is good data suggesting that AF is more prevalent in HF with preserved ejection fraction as compared to HF with reduced ejection fraction^[6-8]. The prevalence of AF also correlates directly with the severity of HF symptoms. It can vary from under 10% in those with functional New York Heart Association (NYHA) class 1 to as high as 50% in those in NYHA class 4^[9]. Similar prevalence figures have been reported from the T-wave Alternans in Patients with Heart Failure^[10] as well.

PATHOPHYSIOLOGICAL INTER-RELATIONSHIP

The interplay between HF and AF is complex. HF predicts the development of AF and conversely AF predisposes to HF^[2]. There are a number of mechanisms through which HF predisposes to an arrhythmogenic atrial substrate. These include elevated left sided-filling pressures, mitral regurgitation, atrial enlargement, interstitial fibrosis and electromechanical remodelling^[3]. Activation of autonomic and renin-angiotensin axis contributes while changes in the intracellular calcium are thought to play a role as well^[11].

Conversely, AF can lead to HF through multiple adverse effects including loss of atrial systole, functional mitral/tricuspid regurgitation, tachycardiomyopathy and reduced ventricular diastolic filling time^[2]. Irregularity in the RR interval can also have a potentially deteriorating influence on cardiac output irrespective of the heart rate^[12]. Moreover, deterioration of sinus rhythm into AF in patients with HF can lead to acute decompensation. A prospective study of 344 HF patients (who were in sinus rhythm at baseline) revealed significant haemodynamic deterioration with the onset of AF. Development of AF in this cohort led to reduced cardiac output, bi-atrial dilatation and functional atrioventricular valve regurgitation. This was reflected as a decline in the functional NYHA symptom class as well as peak exercise oxygen consumption^[13]. Details of the pathophysiological pathways involved are beyond the remit of this review and have been reviewed well previously^[14].

EPIDEMIOLOGY

According to the National Health And Nutrition Examination Survey, the prevalence of HF in Americans older than 20 years of age, is around 5.7 million (2.4%). It ranges from around 1.5% in those over 40 years to as high as 11% in the above 80 years age group. The lifetime likelihood of developing HF at the age of forty years has been estimated as 1 in 5^[15]. Similarly, estimate from existing data suggests that as many as 30 million people in Europe are living with HF^[16]. HF incidence also increases progressively with age ranging from a rate of 1.4 per 1000 person-years in 55-59 year-old

group to 47.4 per 1000 person-years in above 90-year-old bracket^[17].

AF is the commonest arrhythmia encountered in medical practice^[18]. The prevalence of AF in the United States is estimated between 2.7 and 6.1 million. This is projected to increase to between 5.6 and 12.0 million^[15] rising progressively to two and a half-fold by 2050^[19]. According to the Rotterdam as well as the Framingham studies, the lifetime risk of developing AF has been estimated to be around 1 in 4^[20,21]. Incidence of AF also increases progressively with age approaching a risk of 11%-18% by 90 years^[22].

IMPACT OF AF ON HF PROGNOSIS

There has been increasing evidence regarding the adverse role of AF in patients with HF, both in terms of morbidity as well as prognosis (Table 1).

Mountantonakis *et al*^[23] analysed the data from patients enrolled in the Get With The Guidelines-Heart Failure Registry between 2005 and 2010. They looked at 99810 patients hospitalised with HF across 255 United States sites. One-third of the cohort had AF and when compared to those in sinus rhythm, it was independently associated with a longer length of hospital stay (mean 5 *vs* 4 d; $P < 0.001$) as well as higher in-hospital mortality (4.0% *vs* 2.6%, $P < 0.001$). A post hoc analysis of the data from the Efficacy of Vasopressin antagonism in hEart failuRE: outcome Study with Tolvaptan looked at the clinical characteristics of 4133 patients out of which 29% had atrial fibrillation/atrial flutter at baseline. In contrast to patients in sinus rhythm, AF was found to confer an increased risk of death (HR = 1.23, 95%CI: 1.04-1.46) and cardiovascular mortality/HF admission (HR = 1.26, 95%CI: 1.07-1.47)^[24]. Retrospective subset analysis of studies of left ventricular dysfunction (SOLVD) looked at 6517 patients with LVEF less than 35%^[25]. It showed that patients in AF had an increased risk of all-cause mortality of 34% as compared to 23% for those in sinus rhythm. The higher mortality was largely attributable to increased risk of pump failure deaths. These findings were applicable to symptomatic as well as asymptomatic patients. Data from the Candesartan in Heart failure Assessment of Reduction in Mortality and morbidity trials demonstrated an independent detrimental effect of AF on long term cardiovascular outcomes in HF patients (either reduced or preserved LV systolic function)^[26]. Similarly, an adjusted meta-analysis by Mamas *et al*^[27] has demonstrated a worse prognostic impact of AF in HF. This was based on 16 studies including 7 randomised trials and 9 observational studies and included data from 53969 patients. The impact of AF on mortality was reflected by an OR of 1.40 (95%CI: 1.32-1.48, $P < 0.0001$) in randomised trials and an OR of 1.14 (95%CI: 1.03-1.26, $P < 0.05$) in observational trials. This was irrespective of the LV systolic function. Middlekauff *et al* conducted a prospective study of 390 patients with NYHA class 3-4 symptoms and a mean LV Ejection Fraction (LVEF) of

Table 1 Prognostic impact of atrial fibrillation in heart failure

Ref.	Setting	n	LVEF	Mean follow up (yr)	AF	Deaths n (%)		P-value
						SR	AF	
Randomised trials								
Dries <i>et al</i> ^[25]	SOLVD	6517	< 35%	2.8	6%	1395 (23)	149 (34)	< 0.0001
Olsson <i>et al</i> ^[26]	CHARM	7601	All LVEF included	3.1	15%	1466 (23)	365 (32)	< 0.001
Swedberg <i>et al</i> ^[38]	COMET	3029	< 35%	4.8	20%	874 (36)	258 (43)	< 0.0005
Carson <i>et al</i> ^[109]	V-HEFT I&II	1427	< 45%	2.5	19%	480 (39)	75 (36)	NS
Mathew <i>et al</i> ^[110]	DIG	7788	All LVEF included	3.1	11%	2231 (32)	375 (43)	< 0.0001
Crijns <i>et al</i> ^[111]	PRIME II	409	< 35%	3.4	21%	153 (47)	50 (60)	< 0.05
Pederson <i>et al</i> ^[112]	DIAMOND	3587	< 35%	N/A	24%	1951 (73)	634 (77)	< 0.001
Observational studies								
Rivero-Ayerza <i>et al</i> ^[5]	EuroHeart Failure Survey	10701	All LVEF included	N/A	43%	419 (7)	372 (8)	< 0.05
Ahmed <i>et al</i> ^[28]	Medicare AL	944	All LVEF included	4.0 yr	27%	439 (62)	166 (71)	< 0.01
Mahoney <i>et al</i> ^[37]	Heart Transplantation	234	< 45%	1.1 yr	27%	26 (15)	14 (22)	NS
Middlekauff <i>et al</i> ^[113]	Heart Transplantation	390	< 35%	265 d	19%	123 (29)	36 (48)	< 0.005
Stevenson <i>et al</i> ^[114]	Heart Transplantation	750	< 40%	2.0 yr	22%	336 (45)	104 (61)	< 0.01
Wojtkowska <i>et al</i> ^[115]	Bilastok, Poland	120	< 30%	3.0 yr	50%	26 (43)	33 (55)	NS
Corell <i>et al</i> ^[116]	Danish HF clinic Network	1019	< 45%	1.9 yr	26%	180 (24)	89 (33)	< 0.05
Pai <i>et al</i> ^[117]	Loma Linda VA	8931	All LVEF included	2.5 yr	18%	2164 (28)	529 (44)	< 0.0001
Rusinaru <i>et al</i> ^[118]	Somme, France	368	> 50%	N/A	36%	125 (53)	84 (64)	< 0.05
Hamaguchi <i>et al</i> ^[119]	Japanese Registry data	2659	All LVEF included	2.4 yr	35%	N/A	N/A	NS
Shotan <i>et al</i> ^[120]	National HF Survey, Israel	4102	All LVEF included	4	33%	1480 (54.3)	882 (64.9)	0.000

SR: Sinus rhythm; AF: Atrial fibrillation; LVEF: Left ventricular ejection fraction; NS: Not significant; N/A: Not applicable; SOLVD: Studies of left ventricular dysfunction; CHARM: Candesartan in heart failure assessment of reduction in mortality and morbidity; COMET: Carvedilol or metoprolol European trial; DIG: Digitalis investigation group; DIAMOND: Danish investigations of arrhythmia and mortality on dofetilide.

around 20%. Nineteen percent of this cohort had AF and this was shown to be an independent predictor of all-cause mortality (actuarial survival at 1 year with AF 52% *vs* 71% with sinus rhythm). A retrospective study of 944 Medicare beneficiaries looked at 30-d re-hospitalisation and 4-year mortality figures in HF patients older than 65 years (mean age of 79 years). No distinction was made between reduced and preserved LV systolic function. Risk of readmission was not significantly higher^[28] but patients in AF had a 52% increased likelihood of mortality over 4 years as compared to the ones in sinus rhythm. Finally, Caldwell *et al*^[29] studied a cohort of 162 patients who had received biventricular device implants for advanced HF (NYHA 3 and 4). Almost a third of the patients (who were thought to be in sinus rhythm) were found to have silent episodes of paroxysmal AF. There was a trend of increased mortality but not towards thromboembolic episodes or hospitalisation.

Studies have also focused specifically on the prognostic effect of AF in ischaemic cardiomyopathy. The VALsartan In Acute myocardial iNfarction Trial involved over 14000 patients who had suffered from acute myocardial infarction complicated with LV systolic dysfunction. Patients in AF (both chronic AF at baseline as well as new-onset) had higher mortality at 3 years follow up as compared to those in sinus rhythm (37% *vs* 20%)^[30]. Analysis of the danish investigations of arrhythmia and mortality on dofetilide in congestive heart failure (DIAMOND-CHF) data compared ischaemic *vs* non ischaemic subsets^[31]. Three thousand five hundred and eighty-seven HF patients were followed for up to 8 years. AF had a

significant prognostic effect in those with ischaemic heart disease (HR = 1.25, 95%CI: 1.09-1.42, *P* < 0.001] as compared to those without ischaemic heart disease (HR = 1.01, 95%CI: 0.88-1.16, *P* = 0.88]. A likely explanation may be that AF aggravates ischaemia in such cases (due to its association with increased coronary vascular resistance and reduced myocardial perfusion) thus affecting prognosis adversely^[32]. Four-year follow up of 2881 participants of the Echocardiographic Heart Of England Screening study showed similar results^[33].

A limited number of small studies have been conducted to evaluate the temporal significance of AF and it is not entirely clear whether AF prior to HF portends a worse prognostic influence or vice versa. The EuroHeart Failure survey indicated that new onset acute AF is associated with increased mortality as compared to chronic AF (12% *vs* 7%). The likely explanation may be related to tachycardia-related adverse haemodynamics as well as higher utilization of anti-arrhythmic agents in the acute setting^[5]. Data from the community-based study by Chamberlain *et al*^[34] divided 1664 HF patients into 3 groups namely HF without AF (*n* = 727), HF with AF preceding HF (*n* = 553) and HF with onset of AF after developing HF (*n* = 384). In comparison to the group in sinus rhythm, the prior-AF group had 29% higher all-cause mortality. This contrasted to the AF-after-HF group who had more than twice the mortality. Similarly, in the cohort assessed by Smit *et al*^[35], prognosis of patients who developed AF first was comparatively better as compared to those who developed AF after HF. A hundred and eighty two consecutive AF patients admitted for HF were

followed up for 16 ± 11 mo looking at the primary composite end point of cardiovascular hospitalisation and all-cause mortality. Seventy five percent of the cohort were known to have AF prior to onset of HF while 25% developed AF preceding HF. When compared to the HF-first group, AF-first cohort was less likely to reach the primary end-point (49.6% *vs* 77.7% , $P = 0.001$). The recently published Worcester HF Study has also demonstrated higher inpatient death rates as well as post-discharge mortality in HF patients with concurrent AF^[36].

Other studies, however, have not corroborated this independent impact of AF in HF. For instance, Mahoney *et al*^[37] showed that in patients referred for cardiac transplantation, AF was not associated with an increased mortality. However, given the end-stage disease (where prognosis is poor irrespective of AF) and small numbers involved (as well as the cross-sectional design of the study), it is difficult to generalize these results to a wider non-selected HF population. Similarly, an analysis of the Carvedilol Or Metoprolol European Trial data looked at the potential prognostic effect of AF in HF. When corrected for other prognostic markers, AF lost its independent effect on mortality^[38]. However, the criterion for diagnosing AF was limited to a single baseline ECG. This may have failed to pick up paroxysmal AF or future AF events. Thus, the reported prevalence of 19.8% of the study cohort who had AF may represent an underestimate.

Conversely, HF also impacts prognosis in AF. This is in keeping with the bidirectional interaction between the two disorders. For instance, the Framingham studies as well as EuroHeart Survey have demonstrated the vicious effect one condition has on the prognosis of the other^[39,40].

EFFECT OF AF THERAPY ON PROGNOSIS

Although several of the studies outlined above demonstrate an adverse prognostic influence of AF in HF, yet the optimal approach of managing such patients still remains unclear.

Pharmacological therapy

Rate control: Ventricular rate control remains a major therapeutic target for AF in HF patients. Beta-blockers and digoxin (as adjunctive therapy) are the main agents available for systolic HF. In addition, non-dihydropyridine calcium channel antagonists (verapamil, diltiazem) can be used instead of beta-blockers in HF with preserved EF. Finally, amiodarone can be considered for rate control if combination of beta-blocker and digoxin is inadequate^[41]. A number of studies have demonstrated prognostic benefit of beta-blockers in AF with HF. A retrospective analysis of the US Carvedilol HF trial data focused categorically on patients who had AF at the time of enrolment. In comparison to the placebo arm, the beta-blocker group had improved LV ejection fractions and better physician-determined global assessment. Moreover, there was a tendency towards reduced combined cardio-

vascular mortality and hospitalisation^[42]. The Digitalis Investigation Group trial showed that although digoxin did not affect mortality in HF, it reduced the number of hospital admissions. AF was among the exclusion criteria and as such these results may not be applicable to AF in HF^[43]. Moreover, digoxin loses its effect during periods of catecholamine excess and is not recommended as monotherapy. Of note, a recent post-hoc analysis of the the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) trial has cast doubt on the safety of digoxin in HF patients^[44]. It was shown that digoxin is associated with increased all-cause mortality including a 41% increased risk of death in patients with CHF or LVEF of less than 40%. This should, however, be interpreted with caution as AFFIRM was designed to compare rate and rhythm control and patients were not randomised to digoxin therapy. Moreover, only 25% of the AFFIRM cohort had HF. Moreover, a propensity matched analysis of the same cohort failed to demonstrate any increase in mortality with digoxin. It is likely that the patients on digoxin in the study had higher risk of mortality^[45]. Finally, data on the use of verapamil and diltiazem in HF is limited^[46]. Verapamil has been shown to be useful in HF patients with normal LV systolic function^[47] and current ESC guidelines recommend their use in HF with preserved ejection fraction as an alternative to beta-blockers^[41]. However, these should be avoided in HF with reduced ejection fraction due to negative inotropic effect on LV contractility^[41,48].

Another point that needs further clarification relates to the optimal target ventricular rate for permanent AF patients in HF. Rate control efficacy in permanent Atrial fibrillation: a Comparison between lenient *vs* strict rate control II (RACE II) trial looked at lenient (110 bpm) *vs* strict (< 80 bpm) ventricular rate control in patients with AF. The primary end-point was a composite of cardiovascular death, HF admission, bleeding and embolic events including stroke. No significant difference was observed in the two arms^[49]. Again less than 35% of the cohort had HF (15% in NYHA class 4) and results may not be generalizable to the HF patients. Routine versus Aggressive upstream rhythm Control for prevention of Early atrial fibrillation in HF (RACE III) is currently recruiting and will provide definitive answers for the HF population^[50].

Rhythm control: Amiodarone and dofetilide are the main anti-arrhythmic agents assessed in HF patients with AF. Survival trial of antiarrhythmic therapy in congestive heart failure (CHF-STAT) and atrial fibrillation and congestive heart failure (AF-CHF) trials have demonstrated the efficacy of amiodarone in cardioversion and maintenance of sinus rhythm in patients with moderate to severe LV systolic dysfunction^[51,52]. Its overall effect on mortality was shown to be neutral but long-term clinical use remains limited due to a risk of significant side effects. DIAMOND-CHF trial looked at the effect of dofetilide on a cohort of mainly ischaemic HF patients.

A pooled sub-study analysis incorporated 506 patients who were in AF. Dofetilide was shown to be safe with an overall neutral effect on mortality. It was superior to placebo in cardioversion and patients on the drug were more likely to be in sinus rhythm at one year as compared to placebo (79% *vs* 42%). Moreover, it was also associated with reduced HF admissions^[53]. Importantly, patients who converted to sinus rhythm had lower all-cause mortality (in the dofetilide as well as placebo arms) signifying the beneficial prognostic impact of sinus rhythm. However, torsade de pointes (1.6%) remains a cause for concern with dofetilide and requires initiation in hospital under close monitoring. Furthermore, it is not available in Europe. Subsequently, dronedarone (an iodine-free amiodarone derivative) was introduced with a promising adverse effect profile. A post hoc analysis of the ATHERNA (A Trial with dronedarone to prevent Hospitalization or death in patiENTS with Atrial fibrillation) looked at stable patients with LVEF less than 40% and NYHA 2-3 symptoms. It showed a reduced risk of all-cause mortality and/or hospitalisation due to cardiovascular events^[54]. However, ANtiarrhythmic trial with dronedarone in Moderate-to-severe congestive heart failure Evaluating morbidity Decrease (ANDROMEDA) trial (which looked at patients with severe HF in sinus rhythm and not AF) had to be terminated prematurely because dronedarone increased mortality in such patients^[55]. As a result, it is no longer licensed for use in patients with unstable/severe HF.

Rate *vs* rhythm control: There is no convincing scientific evidence so far to support a rhythm control strategy in preference to rate control. Given the negative impact of AF in HF, the concept of maintaining sinus rhythm appears attractive, yet a number of randomised trials have failed to demonstrate improved long-term outcomes with a rhythm control approach^[56-59]. The results are, however, limited by the fact that these trials were not exclusive to HF (for instance only 25% of the AFFIRM cohort had depressed LV function) and it may be difficult to apply these findings to the HF population. On the other hand, there have been trials looking exclusively at HF patients as well. AF-CHF enrolled 1376 patients with systolic HF. They were randomized to either rhythm or rate control and followed up for 3 years looking at prospective data for mortality, HF admissions and stroke^[52]. The difference in cardiovascular mortality observed in the two arms was not significant (27% in rhythm control *vs* 25% in rate control respectively). It is noteworthy, however, that only 80% of patients in the rhythm control arm remained entirely AF-free (65% when looking at overall 3 year follow up visits as well as the 21% who crossed over to rate control arm)^[11]. Interestingly, a post hoc analysis of the AFFIRM trial looked at the rhythm control arm of the trial. Sinus rhythm was associated with less severe NYHA symptomatic class and better functional capacity (assessed by 6-min walk test)^[60]. Similarly, in a subgroup analysis of CHF-STAT trial, Kaplan-Meier analysis of the survival

curves for those who converted to SR with amiodarone showed significantly better survival as compared to those who remained in AF^[51]. Same conclusion can be derived from the DIAMOND sub-study as well^[53]. However, these results are based on post-hoc subgroup analyses and should be applied with caution. A recent meta-analysis of the 4 main randomised control trials of AF rate *vs*. rhythm control in HF (incorporating 2486 patients) has demonstrated no significant difference in terms of mortality and thromboembolic events^[61].

Thromboprophylaxis: Although beyond the scope of this review, it would be amiss not to mention the enormous clinical, social and economic impact of stroke in HF patients with AF. Due to various co-morbidities, patients with HF have a significantly higher risk of thromboembolic events particularly stroke. Hence, oral anticoagulation is imperative unless there are equally binding contraindications. ACCF/AHA/HRS guidelines have kept the option of either aspirin or anticoagulation for patients with a CHADS₂ score of 1 while European Society of Cardiology (ESC) and Canadian Cardiovascular Society (CCS) guidelines indicate anticoagulation for such patients in preference to aspirin. Nevertheless, there is unanimous agreement in recommending long-term anticoagulation for all patients with a CHADS₂ score of 2 and above^[62]. Warfarin is well recognized in this regard and has been the mainstay of thromboprophylaxis in AF^[63] for the last 60 years. It has been shown to reduce the risk of stroke by as much as 65% and is thrice as efficacious as aspirin^[64]. Its clinical utility, however, is fraught with a variety of limitations (both real and perceived, by patients and physicians alike). These include a narrow therapeutic window, need for meticulous monitoring of INR levels, unreliable blood levels due to interaction with various drugs/food and risk of bleeding in an increasingly frail/ ageing population.

The last few years have witnessed the exciting development of a novel group of oral anticoagulants (NO-ACs) with the advantage of rapid onset of action, fewer drug/food interactions and predictable blood levels thus exonerating patients from laborious INR monitoring. They have been shown to carry a lesser risk of intracranial bleeding in comparison to warfarin while maintaining the same level of protection against stroke. However, widespread use is restricted by higher costs, unavailability of a reversal agent in the event of a major bleed and no validated lab markers of anticoagulant effect^[65]. The two main classes consist of direct thrombin inhibitors (dabigatran) and activated factor X inhibitors (apixaban, rivaroxaban, edoxaban) while several others are under development. Dabigatran was the first to be approved by Food and Drug Administration in 2010 for non-valvular AF following the Randomized Evaluation of Long-term anticoagulation therapy (RE-LY) trial^[66] which enrolled 18113 patients with AF. One-third of the study population had symptomatic HF or LVEF < 40%. Patients were randomized to receive either 150 or 110 mg twice daily

(blinded dose groups) of dabigatran or INR-guided warfarin therapy. In comparison to warfarin, 110 mg twice daily dose was non-inferior in efficacy and superior in safety while the 150 mg twice daily dose was superior in efficacy and had similar rates of major bleeding. Consequently, dabigatran has been recommended as an alternative to warfarin in recent ESC, AHA/ACCF as well as CCS guidelines^[67-69]. Similarly, Rivaroxaban was studied in the Rivaroxaban Once daily oral direct factor Xa inhibition Compared with vitamin K antagonism for prevention of stroke and Embolism Trial in Atrial Fibrillation (ROCKET-AF) looking at over 14000 patients. Data demonstrate non-inferiority to warfarin in terms of efficacy. It was associated with less intracranial haemorrhage as well albeit a higher risk of gastrointestinal bleed^[70]. Finally, Apixaban is the only one so far which has been shown to be superior to warfarin in reducing the primary end-point of thromboembolic events including stroke (annual event rate 1.27% *vs* 1.60%; $P < 0.001$ for noninferiority; $P = 0.01$ for superiority). This is derived from the Apixaban in Preventing Stroke and Systemic Embolism in Subjects With Nonvalvular Atrial Fibrillation trial which enrolled over 18000 patients. The 21% reduction in primary safety end-point was mainly derived from a lower likelihood of haemorrhagic strokes. There was no significant difference in the rates of ischaemic strokes between the two^[71]. All three NOACs available so far have been licensed for use in non-valvular AF.

Non-pharmacological therapy

Drug therapy is the mainstay of AF management. However, many patients are unable to achieve rhythm or rate control targets due to therapeutic inefficacy or side effects respectively. Consequently, device therapy and electrophysiological catheter interventions have gained importance.

“Pace and ablate” strategy: Atrio-ventricular node (AVN) ablation accompanied by a permanent pacemaker is often used as an extreme option for definitive rate control. However, AF is not eliminated per se and rate control with a regular RR length may not suffice in compensating for the haemodynamic detriment caused by A-V dys-synchrony and loss of atrial systole. Thus, arguably, the procedure may only be of symptomatic benefit^[72]. Moreover, there is a potential for progressive inter-ventricular dys-synchrony due to chronic RV pacing. Hence, cardiac resynchronisation therapy (CRT) has emerged as the pacing option of choice in all patients with systolic HF^[73,74] who require pacing for AVN ablation. On the other hand, it is well recognized that clinical response to CRT is hampered if adequate AF rate control cannot be achieved. This is likely to be due to a lower percentage of biventricular pacing and here AVN ablation can be very helpful. This has been demonstrated in a recent meta-analysis of 23 observational studies involving 7495 CRT patients (25% of the total had AF). When compared to patients in sinus rhythm, presence of AF conferred a

higher likelihood of CRT non-response and increased all-cause mortality (10.8% *vs* 7.1% per year, pooled RR = 1.50, 95%CI: 1.08-2.09, $P = 0.015$). In addition, there was a lesser improvement in quality of life, exercise capacity and LV end-systolic dimensions. On the other hand, in patients with AF, AVN ablation not only improved response to CRT (RR = 0.40, 95%CI: 0.28-0.58, $P < 0.001$) but was associated with a reduced risk of mortality as well^[75]. A number of other small, mostly single-centre, non-randomized studies of CRT (in HF patients with AF) have also shown improvement in soft end-points such as reduced mitral regurgitation, improved LV ejection fraction and better exercise capacity but clearly more data is required^[76-78]. For instance, a registry-based analysis of patients with severe HF compared 139 patients who had AF with 445 in sinus rhythm. One year follow up revealed comparable CRT-related improvement in NYHA symptom class and LV ejection fractions in the two cohorts. Of note, mortality was higher in the AF group (12% *vs* 7%; OR = 1.80, 95%CI: 0.95-3.4)^[78]. Although the results are encouraging, yet large scale placebo controlled randomised trials are still required to confirm long term prognostic benefit.

AF ablation: As noted above, “pace and ablate” strategy is effective in controlling the ventricular rate but it does not eliminate AF as such. Also, like all invasive procedures CRT is not free of potential complications. Consequently, radio-frequency catheter ablation (RFA) using pulmonary vein isolation (PVI) has gained momentum in the management of AF. A number of observational studies (albeit small) provide supportive data for such a strategy. The non-randomized observational study by Hsu *et al*^[79] compared 58 patients in HF with an equivalent number of age/sex matched controls without HF. All underwent RFA for AF. At the completion of one year, 78% of the HF cohort and 84% of controls remained in sinus rhythm (although 50% had required a second procedure due to recurrence of AF). RFA led to significantly improved LV function (mean increase 21%) in the HF cohort. In addition, significant improvement was seen in NYHA symptom class, quality of life (assessed by SF-36 QoL scores) and exercise capacity (assessed by bicycle-ergometer stress test) as well. The trial was, however, not powered to look at mortality trends. Similar results have been obtained in a number of other small non-randomized studies demonstrating improvement in LVEF and patient symptoms^[80-82]. Pulmonary vein Antrum isolation *vs* atrioventricular node ablation with Biventricular pacing for treatment of atrial fibrillation in patients with congestive heart failure (PABA-CHF) was a multi-centre study which prospectively randomized 81 drug-refractory AF patients (with a LVEF of 40% or less and NYHA functional class 2-3) to undergo PVI or AVN ablation with biventricular ICD implant. They were followed up at 6 mo. The composite primary end point consisted of LVEF, 6-min walk distance and Minnesota Living with Heart Failure score. PVI patients fared better in all

three components of the end point than the cohort who underwent AVN ablation and biventricular pacing^[83]. Recently, MacDonald *et al.*^[84] conducted a randomised controlled trial in HF patients comparing rhythm control by RFA ($n = 22$) to rate control by medical therapy ($n = 19$). RFA failed to show any significant improvement in radionuclide LV ejection fractions as compared to the rate control arm. Only 50% were able to retain sinus rhythm at the end of one year and a significant (15%) complication rate was observed. A meta-analysis of AF ablation trials in patients with moderate LV systolic dysfunction looked at 9 studies involving a total of 354 patients. RFA led to an overall improvement in LV systolic function. However, the results are limited by heterogeneous study cohorts and lack of long-term outcome data^[85]. Hence, large scale, multicentre, randomized controlled trials with longer follow up will be required for further definitive clarification. Finally, in patients undergoing cardiac surgery, surgical ablation techniques (variations of Cox Maze procedure) are available as a safe and effective alternative^[86] including for those with depressed LV function^[87].

FUTURE TRENDS

Selective AV nodal stimulation

Selective AV nodal vagal stimulation (AVN-VS) has emerged as a potentially viable therapeutic intervention for ventricular rate control in AF. Loss of vagal tone followed by sympathetic overstimulation is thought to contribute to the pathophysiology of HF. Epicardial AV nodal fat pad stimulation (using catheter electrodes) targets parasympathetic efferents in the vagal ganglia and confers negative chronotropic and dromotropic effects. This can then be potentially used to modulate AF rate control in patients with HF. Small-scale, randomised preclinical case-control studies have shown effective heart rate control along with improvement in LV function in acute^[88] as well as chronic settings^[89]. Investigators induced HF and AF in canine models using rapid ventricular pacing for 4 wk followed by continued rapid atrial pacing respectively. Similar reversible negative chronotropic effects have been demonstrated in a cohort of 25 patients who underwent efferent vagal nerve stimulation with a multipolar catheter in superior vena cava or coronary sinus^[90]. Although it is only hypothesis generating at this stage, yet it showed consistent slowing of the heart rate and this was associated with improved LV function. Larger trials are needed to ascertain the true potential of this technique.

Atrial-specific anti-arrhythmic agents

Currently available anti-arrhythmic agents used for AF act on multiple ion-channels located in the atria as well as ventricles. Consequently, there is a risk of ventricular pro-arrhythmia and this is a particular concern in patients with structural heart disease/HF. Development of atrial specific anti-arrhythmics with a reduced risk of ventricular pro-arrhythmia is indeed an attractive strategy^[91]. Vernakalant is a potassium-channel blocker

which has undergone successful phase II and III trials. It is different to the conventional class III agents in that it selectively delays atrial repolarization by blocking atrial specific potassium-channels. As a result it suppresses AF by prolonging the atrial refractory period and is not associated with ventricular pro-arrhythmic effects such as QT prolongation and torsades^[92]. A phase III superiority study of Vernakalant *vs* Amiodarone in Subjects With Recent Onset Atrial Fibrillation (AVRO) demonstrated superior efficacy of vernakalant as compared to amiodarone^[93]. However, only 20% of the patients in the cohort had HF. Also, there is no experience yet in advanced HF as patients with unstable congestive HF, NYHA class 4 symptoms, or HF requiring inotropes were excluded from the study.

Left atrial appendage occlusion devices

A significant minority of patients in AF are unable to benefit from oral anticoagulation-either due to contraindications (bleeding, allergy) or therapeutic failure (ischaemic stroke despite effective anticoagulation). Studies have shown that in non-rheumatic AF, left atrial appendage serves as the source of thromboemboli in around 90% of cases^[94]. Consequently, percutaneous devices for the occlusion/exclusion of the left atrial appendage have emerged as a potentially promising answer to this challenging conundrum^[95]. Results from the recent randomised WATCHMAN left atrial appendage system for embolic PROTECTION in patients with Atrial Fibrillation (PROTECT AF) trial have established the feasibility of this technique^[96] while demonstrating non-inferiority with warfarin therapy. The initially high rate of procedural complications has subsequently improved with greater operator experience^[97] and combination with PVI has been successfully carried out^[98] as well. Long term outcome data is not available yet. Trials are also underway assessing further devices such as the Amplatzer cardiac plug and LARIAT suture delivery system^[99].

Genomics

Despite the frequent coexistence of AF and HF, it is intriguing that more than half of even severe HF patients do not develop AF. It is postulated that there may be a genetic predilection for AF in certain HF patients. If such is the case, then modulating these factors may provide a potential therapeutic target. Indeed, familial clustering of AF is well recognized. Moreover, genome wide association studies have demonstrated several common AF-related mutations and polymorphisms^[100]. Recently, a large population study showed a strong genetic association between AF and a polymorphism in the *ZFHX3* gene (which encodes a cardiac transcription factor). This was associated with increased AF risk in HF patients when compared to the general population^[101]. The mechanism by which this translates into pathology is not known. Polymorphisms have also been identified in the beta1-adrenergic receptor gene in patients with systolic HF and AF^[102]. Again the exact significance is not clear yet but it may help risk stratify HF patients in terms of favourable response to beta blocker therapy^[103].

Upstream therapy

Apart from ion-channel blockers, other pharmacologic agents have been investigated for potential anti-AF effects with the hope that modification of the arrhythmogenic atrial substrate and neuroendocrine axis may be of benefit. Limited data is available for polyunsaturated fatty acids^[104], statin therapy^[105] and renin-angiotensin-aldosterone system blockade^[106,107]. At best, the findings have been inconclusive so far and larger randomized controlled trials are required^[108].

CONCLUSION

HF and AF have emerged as global cardiovascular epidemics. They commonly coexist accounting for an enormous clinical and economic burden on healthcare. Emerging evidence suggests that AF confers an adverse prognostic impact on HF. Despite the negative impact of AF in HF, to date there is no definite evidence that rhythm control is prognostically superior to a rate control strategy. Trials of AF ablation have been encouraging yet larger studies (looking at hard end-points) are required before it can be incorporated into mainstream clinical practice. Development of novel anticoagulants constitutes an important step towards minimizing the thromboembolic toll of AF. Genomics, pharmacological “upstream” modification of the atrial substrate and development of selective atrial anti-arrhythmic agents provide further insights into this exciting field. It is not clear yet whether these will translate into clinically tangible benefits for the HF patient.

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P- Reviewers Aronow WS, Chawla M, Di Bella G, Ng T
S- Editor Zhai HH **L- Editor** A **E- Editor** Lu YJ



Initial clinical presentation of Takotsubo cardiomyopathy with-a focus on electrocardiographic changes: A literature review of cases

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Received: April 4, 2013 Revised: May 12, 2013

Accepted: June 1, 2013

Published online: July 26, 2013

Abstract

AIM: To review the initial presentation and demonstrate the importance of Takotsubo cardiomyopathy.

METHODS: A PubMed search using the terms "Takotsubo cardiomyopathy (TC)" and "apical ballooning syndrome" yield 211 publications. Only those that were relevant were fully reviewed. The gender, age, precipitating stressor, main complaint at presentation, electrocardiogram (ECG) at admission and serum cardiac markers of patients diagnosed with TC, were extracted as available. The data were organized in tables and graphics, and the incidence of the disorder was calculated and analyzed.

RESULTS: A total of 250 clinical cases were examined. The predominant gender that was affected was female, with a prevalence of 87.5%. The mean age of presentation was 64 ± 14 years. The cases were divided by age into 10-year intervals. The age interval of 60-69 years showed the highest frequency of TC, accounting for 79 cases. The most common precipitating stressor was physical (50% of cases). Chest pain was

the primary complaint at presentation (58.8% of cases) followed by dyspnea (30% of cases). The ST segment changes category was the most common (60%), followed by T wave changes (39.6%). Of the 60% of cases with ST segment changes, 12% had concomitant T wave changes. This means that for 27.6% of the cases, the primary abnormality in the ECG was T wave changes; 87.6% of cases with TC had a change in the ST segment, in the T wave or in both. The percentage of ECGs presenting with changes in the anterior wall was 54.4% (35.6% of ST segment elevation + 1.6% of ST segment depression + 17.2% of T wave inversion). The percentage of patients presenting with changes in the lateral segment of the heart was 46.8%, while the percentage of patients with changes in the inferior heart was 21.6% and the percentage of patients with changes in the apical region was only 16%. The prevalence of elevated creatinine kinase and/or troponin on initial presentation was 89.3%.

CONCLUSION: It is essential that every physician consider Takotsubo cardiomyopathy as a possible differential diagnosis when a patient is classified with acute coronary syndrome. To do so, it is necessary to know the clinical presentation of this syndrome in its early stages.

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Key words: Apical ballooning syndrome; Broken heart syndrome; Stress cardiomyopathy; Takotsubo cardiomyopathy; Takotsubo syndrome

Core tip: Takotsubo cardiomyopathy is a syndrome that, while frequently not recognized, has a significant impact and represents a significant percentage of diagnosed acute coronary syndromes. The importance of its recognition by physicians should be stressed. There are no previously published articles that analyze a sig-

nificant number of reported cases of Takotsubo cardiomyopathy, nor are prior literature reviews available that examine all the points discussed by this author relative to the initial stages of the disease.

Sanchez-Jimenez EF. Initial clinical presentation of Takotsubo cardiomyopathy with-a focus on electrocardiographic changes: A literature review of cases. *World J Cardiol* 2013; 5(7): 228-241 Available from: URL: <http://www.wjgnet.com/1949-8462/full/v5/i7/228.htm> DOI: <http://dx.doi.org/10.4330/wjc.v5.i7.228>

INTRODUCTION

Takotsubo cardiomyopathy (TC), apical ballooning syndrome and stress cardiomyopathy have all been used to refer to a syndrome that was described for the first time in 1991 in Japan. Five such were shown to have left ventriculograms with transient akinesis in the apical diaphragmatic and/or anterolateral wall but hyperkinesis in the basal wall of the heart^[1].

Many hypotheses have been proposed to explain the pathophysiology of TC, including multivessel coronary vasospasm, abnormalities of coronary microvascular function, and catecholamine-mediated cardiotoxicity^[2]. Some authors consider estrogen an important factor because it changes the $\beta 1:\beta 2$ adrenoreceptor (AR) ratio in favor of the $\beta 2$ AR-Gi protein, which protects the myocardium from catecholamines in stressful situations^[3].

The typical initial presentation pattern as chest pain and/or dyspnea, the electrocardiographic changes and elevated serum cardiac markers observed in TC patients often result in the misdiagnosis of TC as acute coronary syndrome (ACS). For the diagnosis of TC, it is necessary to perform echocardiography to observe the wall motion abnormality and coronary angiography to confirm the absence of significant stenotic lesions^[2-4]. For some authors, cardiac magnetic resonance imaging (CMRI) (Figure 1) is very important due to its unique ability to assist diagnosis with noninvasive techniques; certainly, CMRI is very helpful in the differential diagnosis of TC and myocarditis, and with patient follow-up^[5].

Many authors mention that the electrocardiographic changes that are seen in the presentation of TC are similar to those of ACS, particularly ST segment elevation myocardial infarction (STEMI); the similarities may include ST segment changes, T wave changes and QT interval changes^[6].

This article analyzes the initial clinical presentation of a large number of cases of TC that have been describe in the literature and assesses various parameters with a focus on electrocardiographic changes.

MATERIALS AND METHODS

The reviewed articles were found on PubMed using the search terms “Takotsubo cardiomyopathy” and “api-

cal ballooning syndrome”. Three filters, namely “case reports”, “free text available” and “humans”, were used. After setting those filters, 211 articles were found. Of these, only those relevant to TC, which accounted for 197 articles, were fully reviewed. Of these, eight were eliminated because they did not include electrocardiograms or because the final diagnosis was not TC. Therefore, the study was conducted using 189 articles in total.

The criteria used to define TC, were those used by each author in each clinical case. One case of right ventricular Takotsubo^[7] and several cases of reverse Takotsubo, broken-heart syndrome and stress cardiomyopathy were also included.

The following data were extracted upon availability: gender, age, precipitating stressor, main complaint at presentation, electrocardiogram (ECG) at admission and serum cardiac markers.

There was no age restriction for inclusion of cases in the study. Cases were classified by age using intervals of 10 years for better management of information. Two patients, a 16-year-old and a 90-year-old, fell outside the first interval of 20-29 years and the last interval of 80-89 years. The median and mean age of the patients and the standard deviations of these values were calculated.

The precipitating stressors were grouped into four categories: physical (physical effort, organic disease or medical condition); emotional (psychological, anxiety or family situation); undetermined (unclear whether the precipitating stressor was emotional, physical or both); no stressor (no identifiable stressor in the history); and not available (not available in the review article). The prevalence of each precipitating stressor was then calculated.

Due to the variable nomenclature assigned by the authors to the main complaint at presentation, it was decided that this nomenclature should be merged into single terms that described all patients who showed similar symptoms. The term “chest pain” was used to include chest discomfort, chest tightness and retrosternal discomfort. “Dyspnea” was used to include respiratory distress, shortness of breath, orthopnea and pulmonary congestion. “Hypotension” included hemodynamic instability, right heart failure and cardiogenic shock. “Loss of consciousness” included ventricular fibrillation and cardiopulmonary arrest, and “palpitations” included tachycardia. After all signs and symptoms were classified, they were listed and their prevalence was calculated based on the total number of cases.

The presence of a minimum of one ECG description was set when choosing the articles. The first ECG was extracted and was preferred for every case. If the time at which the test was taken was not specified, the test made available in the article was assumed to be the first and only test performed and was used in this study. If multiple tests were performed during the initial case presentation, the test that was performed first was extracted. All electrocardiographic descriptions of each case were obtained. The ECG data were grouped into the following categories: ST segment changes, T wave changes, Q wave changes, QT prolonged, normal category and others. If

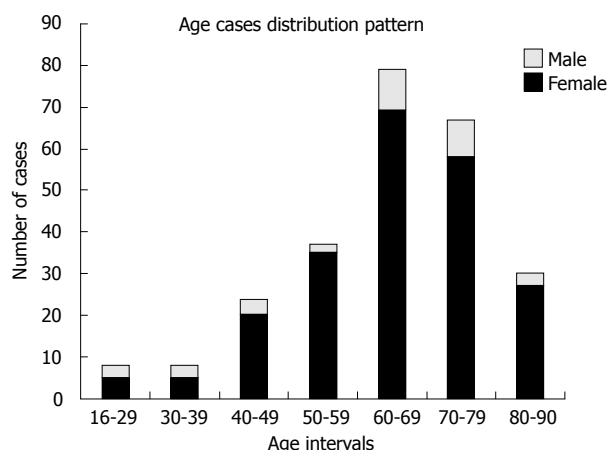


Figure 1 Graphic showing total cases grouped by age intervals.

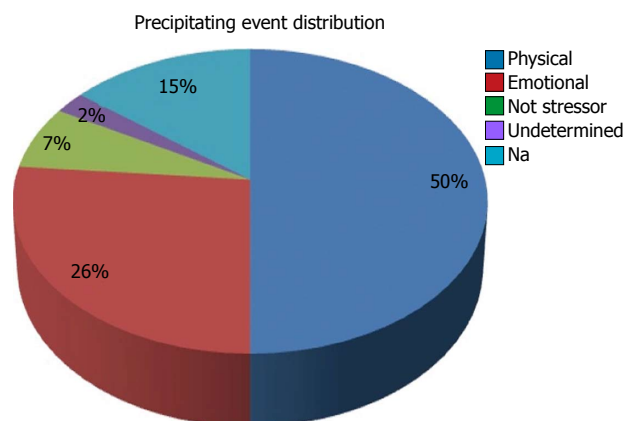


Figure 2 Graphic showing precipitating stressors grouped in categories for all cases studied.

Table 1 Electrocardiographic findings organized by frequency in presentation

Electrocardiogram description	Cases (n)	Incidence (%)
ST segment changes	150	60.00
T wave changes	99	39.60
Prolonged QT	26	10.40
Normal	16	6.40
Q wave	11	4.40
AV block	7	2.80
LBBB	6	2.40
RBBB	6	2.40
AF	5	2.00
VT	3	1.20
VF	3	1.20
Ventricular bigeminy	2	0.80
Other ¹	1	0.40

¹Other: U wave, Osborn wave, Torsade de Pointes, ventricular atrial retrograde conduction, ventricular pace rhythm, premature ventricular contractions, ventricular ectopic beats, multifocal ventricular contractions, ventricular asystole and escape junctional rhythm. AV block: First, second and third degree atria-ventricular block; LBBB: Left bundle branch block; RBBB: Right bundle branch block; AF: Atrial fibrillation; VT: Ventricular tachycardia; VF: Ventricular fibrillation.

the ECG showed documented long-standing changes such as LBBB (left bundle branch block) or AV block, the cases were not considered in this study. The incidence of each of these categories in the ECG data was calculated (Table 1).

The ST segment category was also divided into four groups based on the following specific changes: ST segment elevation, ST segment depression, flattened ST segment and non-specific ST segment changes (Table 2). The incidence of each based on the ST segment changes category and on the total population was calculated.

The analysis of the T wave changes was also divided into four groups: T wave inversion, hyperacute T wave, flattened T wave and non-specific T wave changes (Table 2), and the incidence of each based on both the T wave category and the total cases was calculated.

The ECG findings were classified by anatomical re-

gion of the heart into inferior, lateral, septal, anterior and non-specific, based on the altered leads^[8]. The incidence of abnormalities in each region was calculated and further analyzed (Table 3).

The serum cardiac markers creatinine kinase (CK-MB) and/or troponin were classified as normal or elevated; the latter category included mild, moderate and severe elevation. The results extracted were the first test during the admission or the first test result after suspecting a case. The prevalence of each marker elevation was calculated.

RESULTS

One hundred and eighty-nine case report articles, each of which included one or more individual clinical cases, were analyzed; in total, 250 clinical cases were examined (Table 4).

Gender

The predominant gender was female; it accounted for 219 cases with a prevalence of 87.5%.

Age

The age of the patients ranged from 16-90 years. The mean age at presentation was 64 ± 14 years, with a 95%CI of 64 ± 2 years and a median of 66 years. Figure 1 shows the number of cases grouped by 10-year intervals with respect to age. The age interval with the highest number of cases is 60-69 years; it includes 79 cases.

Precipitating stressor

Figure 2 shows the distribution of precipitating events among all cases. The 6 (2%) cases listed as “undetermined” were difficult to categorize. For example, a patient who had an operation was very stressed and anxious about the surgery results^[9]. In the cases where the stressor was not available, the author did not mention whether there was a precipitating factor.

Main complaint at presentation

Table 5 shows the frequency of presentation of all cases

Table 2 ST segment, T wave change categories organized by incidence

	Cases (n)	Category incidence ¹ (%)	Global incidence ² (%)
ST segment changes			
ST segment elevation	135	90.00	54.00
ST segment depression	11 ³ (21 ⁴)	7.30	4.40
ST segment non-specific changes	3	2.00	1.20
ST segment flattened	1	0.70	0.40
T wave changes			
T wave inversion	91	91.90	36.40
Hyperacute T wave	4	4.00	1.60
Flattened T wave	2	2.00	0.80
Non-specific T wave changes	2	2.00	0.80

¹Percentage calculated based on total ST segment changes cases (150); percentage calculated based on total cases with T wave changes (99);

²Percentage calculated based on total cases in the study (250); percentage calculated based on total cases in the study (250); ³Total number of cases presenting with ST segment depression alone (without concomitant ST segment elevation); ⁴Total number of cases presenting with ST segment depression.

Table 3 Incidence of electrocardiographic change categories shown by anatomical region

Category and Localization	Cases (n)	Category incidence ¹ (%)	Global incidence ² (%)
ST segment elevation			
Anterior	89	65.90	35.60
Lateral	66	48.90	26.40
Inferior	26	19.30	10.40
Septal (apical)	24	17.80	9.60
Not specified	22	16.30	8.80
ST segment depression ³			
Anterior	4	36.40	1.60
Lateral	6	54.50	2.40
Inferior	5	45.50	2.00
Septal (apical)	0	0.00	0.00
Not specified	2	18.20	0.80
T wave changes ⁴			
Anterior	43 (2 ⁵)	43.40	17.20
Lateral	45 (1 ⁵)	45.50	18.00
Inferior	23	23.20	9.20
Septal (apical)	16	16.20	6.40
Not specified	15	15.20	6.00

¹Percentage calculated based on the total number of cases in each category;

²Percentage calculated based on the total number of cases in the study (250); ³Only cases with ST segment depression as the main finding; ⁴Only cases with T wave changes as the main finding, does not include T wave changes accompanying ST segment elevation or ST segment depression;

⁵Only 3 cases that were not T wave inversions.

grouped with respect to symptoms and signs. Chest pain and dyspnea together were encountered in only 49 (20%) cases.

Electrocardiogram at admission

Table 1 shows the incidences of various types of electrocardiographic abnormalities in the TC cases. Of the 60% of cases with ST segment changes, 12% had concomitant

T wave changes, indicating that the main abnormality in the ECG for 27.6% of cases was T wave changes and that 87.6% of cases with TC had a change in the ST segment, in the T wave or both. Slow R progression was found in 3 cases, and tachycardia was found in 17 cases; one case of an anterior infarct of indeterminate age^[10] was classified into the normal category.

Table 2 shows the incidence of specific ST segment changes. The incidence of ST segment depression in the total population (250 cases) and in the ST segment category (150 cases) was 4.4% and 7.3%, respectively. These calculations are based on 11 cases that presented with ST segment depression alone without concomitant ST segment elevation. The total number of cases regarding ST segment depression was 21; thus, 10 cases had concomitant ST segment elevation changes in the ECG. Table 2 shows the incidence of the T wave changes by group.

Table 3 shows the relative frequency at which various anatomical regions were affected in the electrocardiogram. The percentage of ECGs that showed changes in the anterior wall was 54.4% (35.6% of ST segment elevation + 1.6% of ST segment depression + 17.2% of T wave inversion), and the percentage that showed changes in the lateral segment of the heart was 46.8%. The percentage of ECGs showing changes in the inferior heart was 21.6%, while the percentage that showed changes in the apical region was only 16%.

Serum cardiac markers

The prevalence of elevated serum cardiac markers or normal cardiac markers was calculated from the extracted data. The “not available” data cases were not considered in the calculation. The prevalence of elevated CK-MB and/or troponin in patients initially presenting with TC was 89.3%, and the prevalence of negative or normal levels of these cardiac enzymes at presentation was 10.7%.

DISCUSSION

After an exhaustive search of articles describing clinical cases of TC, with emphasis on those that provided the minimum electrocardiographic data, a large number of articles and cases were found. These were analyzed to obtain the data required for this research.

The data obtain in this study indicate a pyramidal trend in age of occurrence of TC. The peak of TC incidence occurs in the 60 s; from this point, there is a gradual decrease in TC incidence as age increases or decreases, with a steeper slope in the direction of the younger population. The high female prevalence of the disease and the age distribution of its occurrence provide support for at least one hypothesis of its pathophysiology, *i.e.*, that lack of estrogen is an important causal factor of this syndrome^[11].

A newly diagnosed disease, an upcoming operation, the induction of anesthesia, a new medication, a stress test or a major physical effort are only some of the physical stressors that can cause TC. This research show that

Table 4 Total number of cases analyzed tables

No.	Age (yr)	Ref.	No.	Age (yr)	Ref.	No.	Age (yr)	Ref.
1	30	Muller <i>et al</i> ^[8]	85	69	Haghi <i>et al</i> ^[70]	169	68	Lisi <i>et al</i> ^[140]
2	67	Yaoita <i>et al</i> ^[9]	86	69	Haghi <i>et al</i> ^[70]	170	71	Rotondi <i>et al</i> ^[141]
3	73	Izumi <i>et al</i> ^[10]	87	43	Haghi <i>et al</i> ^[70]	171	82	Kawano <i>et al</i> ^[142]
4	62	Kobayashi <i>et al</i> ^[11]	88	69	Haghi <i>et al</i> ^[70]	172	79	Hutchings <i>et al</i> ^[143]
5	65	Ker <i>et al</i> ^[12]	89	52	Di Valentino <i>et al</i> ^[71]	173	55	Hutchings <i>et al</i> ^[143]
6	78	Lau <i>et al</i> ^[13]	90	68	Stähli <i>et al</i> ^[72]	174	82	Zuhdi <i>et al</i> ^[144]
7	62	Hayashi <i>et al</i> ^[14]	91	65	Vivo <i>et al</i> ^[73]	175	45	Stout <i>et al</i> ^[145]
8	65	Peraira Moral <i>et al</i> ^[15]	92	81	Sacha <i>et al</i> ^[74]	176	76	Daly <i>et al</i> ^[146]
9	81	Wedekind <i>et al</i> ^[16]	93	53	Fiol <i>et al</i> ^[75]	177	78	Daly <i>et al</i> ^[146]
10	81	Davin <i>et al</i> ^[17]	94	61	Oberson <i>et al</i> ^[76]	178	65	Saito <i>et al</i> ^[147]
11	79	Teo ^[18]	95	29	Magno <i>et al</i> ^[77]	179	75	Silberbauer <i>et al</i> ^[148]
12	51	Arroyo <i>et al</i> ^[19]	96	82	Kim <i>et al</i> ^[78]	180	47	Biteker <i>et al</i> ^[149]
13	79	Consales <i>et al</i> ^[20]	97	71	Kume <i>et al</i> ^[79]	181	74	Merli <i>et al</i> ^[150]
14	64	Maruyama <i>et al</i> ^[21]	98	78	Kume <i>et al</i> ^[79]	182	72	Merli <i>et al</i> ^[150]
15	80	Nguyen <i>et al</i> ^[22]	99	77	Kume <i>et al</i> ^[79]	183	71	Merli <i>et al</i> ^[150]
16	84	Nishikawa <i>et al</i> ^[23]	100	74	Kume <i>et al</i> ^[79]	184	75	Merli <i>et al</i> ^[150]
17	53	Sakihara <i>et al</i> ^[24]	101	78	Kume <i>et al</i> ^[79]	185	57	Virani <i>et al</i> ^[151]
18	66	Ono <i>et al</i> ^[25]	102	78	Ahn <i>et al</i> ^[80]	186	64	Virani <i>et al</i> ^[151]
19	48	Daly <i>et al</i> ^[26]	103	55	Mahida <i>et al</i> ^[81]	187	44	Virani <i>et al</i> ^[151]
20	76	Iengo <i>et al</i> ^[27]	104	53	Bianchi <i>et al</i> ^[82]	188	64	Virani <i>et al</i> ^[151]
21	44	Pison <i>et al</i> ^[28]	105	61	Hwang <i>et al</i> ^[83]	189	69	Chia <i>et al</i> ^[152]
22	52	Pison <i>et al</i> ^[28]	106	55	Ikeda <i>et al</i> ^[84]	190	57	Yazdan-Ashoori <i>et al</i> ^[153]
23	81	Desmet <i>et al</i> ^[29]	107	75	Ikeda <i>et al</i> ^[84]	191	78	Shah <i>et al</i> ^[154]
24	78	Desmet <i>et al</i> ^[29]	108	64	Suzuki <i>et al</i> ^[85]	192	24	Volman <i>et al</i> ^[155]
25	65	Desmet <i>et al</i> ^[29]	109	88	Teraoka <i>et al</i> ^[86]	193	68	Salemi <i>et al</i> ^[156]
26	71	Desmet <i>et al</i> ^[29]	110	60	Hara <i>et al</i> ^[87]	194	50	Coutance <i>et al</i> ^[157]
27	48	Desmet <i>et al</i> ^[29]	111	89	Kurisu <i>et al</i> ^[88]	195	66	Salemi <i>et al</i> ^[158]
28	66	Desmet <i>et al</i> ^[29]	112	77	Kurisu <i>et al</i> ^[88]	196	81	Oe <i>et al</i> ^[159]
29	52	Desmet <i>et al</i> ^[29]	113	73	Verberne <i>et al</i> ^[89]	197	68	Fazal <i>et al</i> ^[160]
30	48	Desmet <i>et al</i> ^[29]	114	60	Subramanyam <i>et al</i> ^[90]	198	46	Afonso <i>et al</i> ^[161]
31	45	Desmet <i>et al</i> ^[29]	115	41	Sanchez-Recalde <i>et al</i> ^[91]	199	38	Afonso <i>et al</i> ^[161]
32	66	Desmet <i>et al</i> ^[29]	116	41	Barriaes-Villa <i>et al</i> ^[92]	200	52	Afonso <i>et al</i> ^[161]
33	57	Desmet <i>et al</i> ^[29]	117	60	Fuse <i>et al</i> ^[93]	201	54	Sacco <i>et al</i> ^[162]
34	60	Desmet <i>et al</i> ^[29]	118	80	Kawano <i>et al</i> ^[94]	202	73	Daly <i>et al</i> ^[163]
35	69	Desmet <i>et al</i> ^[29]	119	63	Wong <i>et al</i> ^[95]	203	55	Jabiri <i>et al</i> ^[164]
36	41	Manivannan <i>et al</i> ^[30]	120	54	Kimura <i>et al</i> ^[96]	204	58	Madaria Marijuan <i>et al</i> ^[165]
37	60	Prasad <i>et al</i> ^[31]	121	77	Varela <i>et al</i> ^[97]	205	50	Traullé <i>et al</i> ^[166]
38	65	Chandrasegaram <i>et al</i> ^[32]	122	55	Elkhateeb <i>et al</i> ^[98]	206	32	D'Amato <i>et al</i> ^[167]
39	84	Wang <i>et al</i> ^[33]	123	59	Kaushik <i>et al</i> ^[99]	207	44	Artukoglu <i>et al</i> ^[168]
40	73	Wani <i>et al</i> ^[34]	124	53	Uechi <i>et al</i> ^[100]	208	85	Shah <i>et al</i> ^[169]
41	54	Wani <i>et al</i> ^[34]	125	67	To <i>et al</i> ^[101]	209	61	Crivinel <i>et al</i> ^[170]
42	63	Wani <i>et al</i> ^[34]	126	72	To <i>et al</i> ^[101]	210	55	Lateef ^[171]
43	70	Schmidt <i>et al</i> ^[35]	127	46	Mehta <i>et al</i> ^[102]	211	70	Potter <i>et al</i> ^[172]
44	46	Zaman <i>et al</i> ^[36]	128	63	Oomura <i>et al</i> ^[103]	212	73	Agarwal <i>et al</i> ^[173]
45	73	Meimoun <i>et al</i> ^[37]	129	27	Volz <i>et al</i> ^[104]	213	72	Opolski <i>et al</i> ^[174]
46	22	Sasaki <i>et al</i> ^[38]	130	79	Miyazaki <i>et al</i> ^[105]	214	67	Y-Hassan <i>et al</i> ^[175]
47	86	Surapaneni <i>et al</i> ^[39]	131	83	Akashi <i>et al</i> ^[106]	215	87	Kurisu <i>et al</i> ^[176]
48	24	Park <i>et al</i> ^[40]	132	81	Wissner <i>et al</i> ^[107]	216	78	Kurisu <i>et al</i> ^[176]
49	85	Cherian <i>et al</i> ^[41]	133	47	Papanikolaou <i>et al</i> ^[108]	217	70	Gotyo <i>et al</i> ^[177]
50	41	Lee <i>et al</i> ^[42]	134	62	Bonnemeier <i>et al</i> ^[109]	218	79	Singh <i>et al</i> ^[178]
51	30	Lee <i>et al</i> ^[42]	135	60	Haghi <i>et al</i> ^[110]	219	44	Núñez <i>et al</i> ^[179]
52	89	Korlakunta <i>et al</i> ^[43]	136	78	Rau <i>et al</i> ^[111]	220	62	Núñez <i>et al</i> ^[179]
53	69	Magri <i>et al</i> ^[44]	137	53	Dahdouh <i>et al</i> ^[112]	221	52	Núñez <i>et al</i> ^[179]
54	65	Rahman <i>et al</i> ^[45]	138	69	Moriya <i>et al</i> ^[113]	222	69	Núñez <i>et al</i> ^[179]
55	63	Khallafi <i>et al</i> ^[46]	139	44	Hasdemir <i>et al</i> ^[114]	223	69	Núñez <i>et al</i> ^[179]
56	75	Demirelli <i>et al</i> ^[47]	140	53	Mariano <i>et al</i> ^[115]	224	29	Jayaraman <i>et al</i> ^[180]
57	75	Latib <i>et al</i> ^[48]	141	36	Sun <i>et al</i> ^[116]	225	71	Carvalho <i>et al</i> ^[181]
58	58	Altman <i>et al</i> ^[49]	142	75	Dandel <i>et al</i> ^[117]	226	78	Guttormsen <i>et al</i> ^[182]
59	65	Bagga <i>et al</i> ^[50]	143	65	Ionescu <i>et al</i> ^[118]	227	53	Mrdovic <i>et al</i> ^[183]
60	61	Buchholz <i>et al</i> ^[51]	144	16	Maruyama <i>et al</i> ^[119]	228	84	Auer <i>et al</i> ^[184]
61	61	Zhou <i>et al</i> ^[52]	145	70	Sato <i>et al</i> ^[120]	229	64	Auer <i>et al</i> ^[184]
62	74	Mittal <i>et al</i> ^[53]	146	63	Shah <i>et al</i> ^[121]	230	64	Auer <i>et al</i> ^[184]
63	47	Kim <i>et al</i> ^[54]	147	62	Lee <i>et al</i> ^[122]	231	82	Auer <i>et al</i> ^[184]
64	60	Doesch <i>et al</i> ^[55]	148	67	Merchant <i>et al</i> ^[123]	232	63	Arslan <i>et al</i> ^[185]
65	66	Lopes <i>et al</i> ^[56]	149	86	Merchant <i>et al</i> ^[123]	233	66	Arslan <i>et al</i> ^[185]
66	64	Lopes <i>et al</i> ^[56]	150	76	Merchant <i>et al</i> ^[123]	234	70	Arslan <i>et al</i> ^[185]
67	76	Lopes <i>et al</i> ^[56]	151	42	Merchant <i>et al</i> ^[123]	235	71	Arslan <i>et al</i> ^[185]

68	58	Lopes <i>et al</i> ^[56]	152	76	Nault <i>et al</i> ^[124]	236	76	Barriaes Vila <i>et al</i> ^[186]
69	51	Lopes <i>et al</i> ^[56]	153	62	Nault <i>et al</i> ^[124]	237	78	Barriaes <i>et al</i> ^[186]
70	63	Sealove <i>et al</i> ^[57]	154	71	Novo <i>et al</i> ^[125]	238	70	Barriaes <i>et al</i> ^[186]
71	82	Inoue <i>et al</i> ^[58]	155	68	Blázquez <i>et al</i> ^[126]	239	74	Guardado <i>et al</i> ^[187]
72	25	Maréchaux <i>et al</i> ^[59]	156	74	Ramanath <i>et al</i> ^[127]	240	45	Cho <i>et al</i> ^[188]
73	77	Arias <i>et al</i> ^[60]	157	70	Biswas <i>et al</i> ^[128]	241	68	Gallego Page <i>et al</i> ^[189]
74	76	Vasconcelos Filho <i>et al</i> ^[61]	158	61	Preti <i>et al</i> ^[129]	242	64	Sousa <i>et al</i> ^[190]
75	61	Margey <i>et al</i> ^[62]	159	59	Selke <i>et al</i> ^[130]	243	68	Jakobson <i>et al</i> ^[191]
76	67	Purvis <i>et al</i> ^[63]	160	74	Alves <i>et al</i> ^[131]	244	49	Jakobson <i>et al</i> ^[191]
77	59	Bilan <i>et al</i> ^[64]	161	83	Yeh <i>et al</i> ^[132]	245	74	Otomo <i>et al</i> ^[192]
78	53	Lentschener <i>et al</i> ^[65]	162	68	Kurisu <i>et al</i> ^[133]	246	75	Otomo <i>et al</i> ^[192]
79	61	Kyuma <i>et al</i> ^[66]	163	57	Rotondi <i>et al</i> ^[134]	247	55	Gomes <i>et al</i> ^[193]
80	76	Kyuma <i>et al</i> ^[66]	164	84	Guevara <i>et al</i> ^[135]	248	61	Furushima <i>et al</i> ^[194]
81	76	Kyuma <i>et al</i> ^[66]	165	69	Ukita <i>et al</i> ^[136]	249	84	Sakai <i>et al</i> ^[195]
82	81	Figueredo <i>et al</i> ^[67]	166	73	van de Donk <i>et al</i> ^[137]	250	64	Hakeem <i>et al</i> ^[196]
83	60	Naganuma <i>et al</i> ^[68]	167	66	Mawad <i>et al</i> ^[138]			
84	61	Láinez <i>et al</i> ^[69]	168	90	Xu <i>et al</i> ^[139]			

Table 5 Frequency of the main complaints reported in the cases studie

Main complaint	Presentation frequency (%)
Chest pain	58.80
Dyspnea	30.00
Hypotension	8.40
Nausea and/or vomiting	8.00
Syncope	6.40
Palpitations	5.20
Asymptomatic	4.80
Loss consciousness	5.20
Headache	3.60
Epigastric pain	2.00
Dizziness	2.00
Weakness	2.00
Cough	1.60
Back pain	1.60
Pedal edema	1.20
Seizure	0.80
Othersa	0.40

a physical stressor is by far the most common stressor reported in TC patients. Emotional stressors are reported in a quarter of all cases and can be as serious as the death of a relative^[12]; they may also be less serious, such as watching a soccer team losing^[13]. The asymptomatic presentations include patients undergoing anesthesia^[14] and/or medical procedures, for example, tracheal intubations^[15]. In these cases, the lack of symptoms can occur due to the sedation.

The chief complaint of the TC patients varied, depending on the causative factor, the trigger stressor and the presentation of each case. TC presents as an ACS; in the latter, the most common clinical presentation is chest pain and the second is dyspnea; this suggests that chest pain and dyspnea will be the most common presentation of stress cardiomyopathy^[16]. In this study, chest pain was the most common initial symptom of the cases presented, and dyspnea was the second most common symptom. Hypotension and cardiopulmonary arrest were relatively common findings, most likely because of the severity of presentation in those patients. Furthermore, the initial

symptoms of TC are often related to the factors causing stress cardiomyopathy. For example, a patient with a seizure^[17,18] or a stroke^[19] can only present neurological signs and symptoms.

A very important tool used by physicians in emergency departments and hospital settings to evaluate chest pain, ACS and preoperative patients is the electrocardiogram, which is very easy to perform and is associated with very low cost. Although percutaneous coronary intervention and CMRI are also sometimes useful tools, and the initial suspicion of the TC is usually confirm by echocardiography; it is very important for physicians to know how the TC present in terms of electrocardiography because these findings, together with the patient's clinical characteristics, should orient the physician to consider this syndrome as a differential diagnosis.

Notably, the definitive diagnosis of TC is confirmed by echocardiographic follow-up performed days or weeks after the initial presentation and showing normalization of the wall motion and left ventricular abnormalities. The CMRI has demonstrated value in the evaluation and follow-up of patients with TC; however, the test of choice is the echocardiography due to its low cost and accessibility^[20,21](Figure 3).

Changes in the ST segment of the ECG were the most common finding in all cases; these changes are typical of the presentation of ACS and are most likely the reason for the initial management of most TC cases as ACS^[22,23]. Changes in the T wave are the second most common finding in the study population. Again, changes in the T wave are very common in acute myocardial ischemia and infarction^[23], explaining the frequent initial diagnosis of ACS in patients with TC. Notably, for some authors, T wave changes are the most common findings among TC patients^[24]. The QT interval is prolonged in approximately 10% of patients, a substantially high incidence. There is perhaps a relationship between the QT interval measurement and TC; there is a need for more research into this possibility. The ischemic heart can present with increased QT dispersion, but this observation has not yet been proven to have any practical useful-

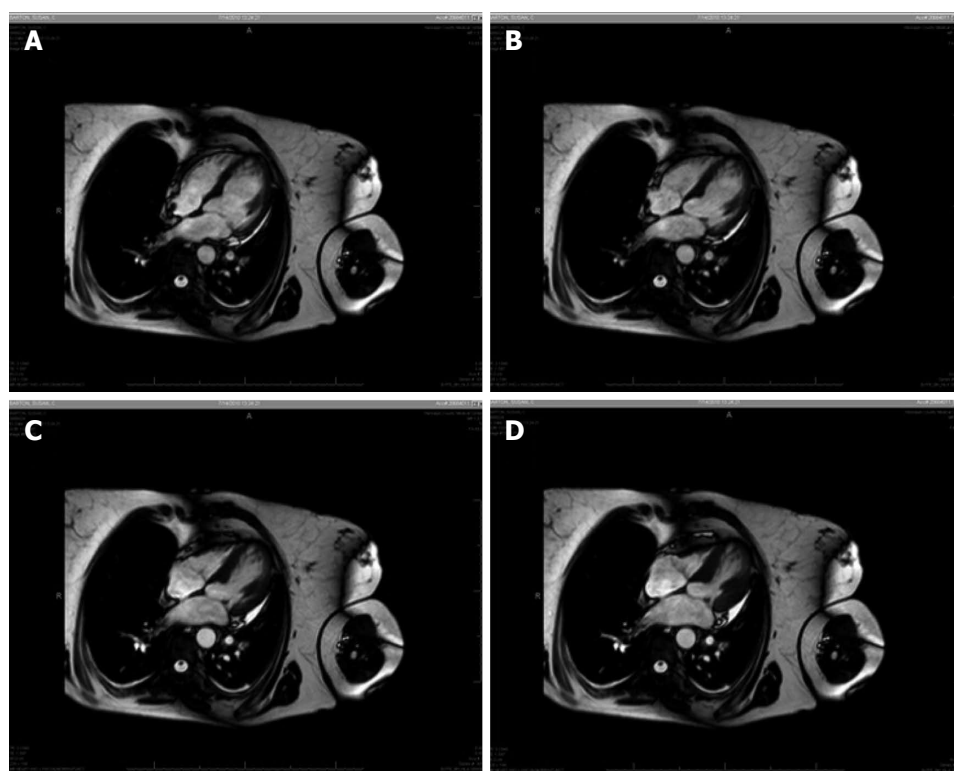


Figure 3 Cardiac magnetic resonance imaging for Takotsubo cardiomyopathy. A: Diastole: both ventricles are distended and full of blood; B and C: Systole: both ventricles contracting; D: End of systole: the right ventricle shows a normal pattern, while the left ventricle has a ballooning shape.

ness^[25]. For the physician, it is important to know that a small percentage (approximately 6%) of TC cases present with a normal ECG during admission. There were also a few cases of multiple presentations in the study; ventricular tachycardia or ventricular fibrillation, for example, can hide the expected electrocardiographic changes.

Among the ST segment changes, ST segment elevation was the most common finding, accounting for 90% of the ST changes. It is the most common presentation of a STEMI, and in this study it occurred in more than half of all cases. Although it was present in almost 10% of incidences, ST depression was not very prominent finding; in half of the cases in which it occurred, it was accompanied by other major findings such as ST segment elevation. Other ST segment presentations, such as flattened ST segments, were not commonly found in the initial ECG at admission.

T wave changes showed a distribution similar to that of ST segment changes. The incidence of the T wave inversion was very high, approximately 92% of all T wave changes. This pattern is very common in the ischemic heart. In fact, in this study, overall T wave presentation occurred in almost one third of the patients, a very significant number. When this type of electrocardiographic change is present, TC should be considered a probable diagnosis. Other T wave presentations, such as hyperacute T wave, flattened T wave and nonspecific changes, very uncommonly presented as the only finding in the ECG.

The anatomical site most commonly affected by stress cardiomyopathy is the left ventricle, but there have been cases with right ventricular akinesis^[7] and even cases in

which both ventricles are affected^[10]. Electrocardiographic presentations of this syndrome are highly variable. In this study, it was documented that in TC the ECG changes in frequency starting from the anterior region as the most commonly affected, followed by the lateral, the inferior and finally the septal region. The clinician must remember these patterns when making a differential diagnosis and never rule out the possibility of a TC based on the ECG.

During the initial presentation of TC patients, there is a very high prevalence of serum cardiac marker elevation, making this diagnosis consistent with ACS (specifically STEMI and NSTEMI). Some authors have indicated that the distinction between TC and ACS is reflected in the level of cardiac enzyme elevation^[26,27]. These findings contain important information that should raise the physician's clinical suspicions regarding this syndrome.

COMMENTS

Background

Takotsubo syndrome has the same presentation as acute coronary syndrome (ACS) but is usually associated with history of a trigger stressor, which can be emotional or physical. Although a number of ideas have been proposed to explain its pathophysiology, there is evidence that catecholamines and estrogen play an important role. Many physicians do not readily think of Takotsubo cardiomyopathy (TC) when presented with a patient with cardiac chest pain or even with a ST segment elevation myocardial infarction (STEMI), and other physicians are not even aware of the existence of the syndrome. For this reason, it is likely that many patients are misdiagnosed. The presentation similarities of TC with ACS include symptoms, electrocardiogram (ECG) changes and serum cardiac marker levels.

Research frontiers

In some health facilities, the initial management of a STEMI is based on intra-

venous fibrinolysis, which is performed without confirmation of coronary artery obstruction using percutaneous coronary intervention (PCI). Takotsubo patients can have the same presentation as STEMI patients but normal or clean coronary arteries. This and other evidence makes the PCI management of choice in STEMI patients.

Innovations and breakthroughs

Although this article does not focus on patient prognosis, it is important that future research addresses the relationship between initial presentation/initial electrocardiographic changes and prognosis. Cardiac magnetic resonance imaging is a new tool that may prove useful in both initial diagnosis and noninvasive follow-up of this syndrome.

Applications

The results of the study are important in clinical practice. They can help inform physicians to include TC in the differential diagnosis of patients who present to the emergency department with cardiac chest pain.

Terminology

TC is a condition that has acquired many names over time; these include Takotsubo syndrome, stress cardiomyopathy, apical ballooning syndrome and TC. ACS is a term applied to situations in which the blood supplied to the heart muscle is suddenly blocked; it includes unstable angina, STEMI and non-ST segment elevation myocardial infarction. Troponin and creatinine kinase (CK-MB) are cardiac markers used to classify and assist with the diagnosis of myocardial infarction. CK-MB is an isoenzyme composed of a muscle portion and a brain portion; it is very specific for myocardial muscle.

Peer review

It is necessary for every physician to know the clinical presentation of TC in its early stages. As mentioned above, this entity should be included in the differential diagnosis of "ACS" patients. The present work represents an interesting examination of value for clinical practice and stresses an important issue in the field of cardiology.

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P- Reviewers Hung MJ, Sakabe K, Xanthos T **S- Editor** Gou SX
L- Editor A **E- Editor** Lu YJ



Ibutilide and novel indexes of ventricular repolarization in persistent atrial fibrillation patients

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Received: February 10, 2013 Revised: May 15, 2013

Accepted: June 1, 2013

Published online: July 26, 2013

Abstract

AIM: To examine the effect of ibutilide on novel indexes of repolarization in patients with persistent atrial fibrillation (AF).

METHODS: We studied consecutive patients scheduled for elective electrical cardioversion. Intravenous ibutilide (1 + 1 mg) was administered before the electrical cardioversion while close electrocardiographic (ECG) monitoring was performed. ECG indexes such as corrected QT interval (QTc), the interval from the peak until the end of T wave (Tpe), and the Tpe/QT ratio were measured before ibutilide infusion and 10 min after the end of infusion.

RESULTS: The final study population consisted of 20 patients (mean age: 67.1 ± 9.9 years, 10 men). Six patients were cardioverted pharmacologically and did not proceed to electrical cardioversion. Two patients

developed short non-sustained episodes of torsades de pointes ventricular tachycardia. All but one of the aforementioned ECG indexes increased significantly after ibutilide administration. In specific, the QTc interval increased from 442 ± 29 to 471 ± 37 ms ($P = 0.037$), the Tpe interval in precordial leads from 96 ms (range 80-108 ms) to 101 ms (range 91-119 ms) ($P = 0.021$), the Tpe interval in lead II from 79 ms (range 70-88 ms) to 100 ms (range 87-104 ms) ($P < 0.001$), the Tpe/QT ratio in precordial leads from 0.23 ms (range 0.18-0.26 ms) to 0.26 ms (range 0.23-0.28 ms) ($P = 0.028$), and the Tpe interval dispersion from 25 ms (range 23-30 ms) to 35 ms (range 27-39 ms) ($P = 0.012$). However, the Tpe/QT ratio in lead II did not change significantly.

CONCLUSION: Ibutilide increases the duration and dispersion of ventricular repolarization. The prognostic value of Tpe and Tpe/QT in the setting of drug-induced proarrhythmia needs further study.

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Key words: Ibutilide; Ventricular repolarization; Arrhythmic risk; Proarrhythmia; Dispersion of repolarization; T peak-to-end; T peak-to-end/QT ratio

Core tip: In this pilot study we examined the effect of ibutilide on novel indexes of repolarization in patients with persistent atrial fibrillation scheduled for electrical cardioversion. Electrocardiographic (ECG) indexes such as corrected QT interval, the interval from the peak until the end of T wave (Tpe), and the Tpe/QT ratio were measured. We showed that ibutilide significantly increases the dispersion of ventricular repolarization as assessed by modern ECG markers such as Tpe interval and Tpe/QT ratio. These indexes may have a prognostic value with regard to drug-induced proarrhythmia.

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INTRODUCTION

Drug-induced proarrhythmia represents a significant problem that poses special risks in the implementation of drug therapy^[1]. Several antiarrhythmic drugs seem to have proarrhythmic potential^[2,3]. Ibutilide is a class III antiarrhythmic agent effective for pharmacological cardioversion of recent-onset atrial fibrillation (AF) or atrial flutter^[4,5]. It is administered intravenously and has a rapid onset of action^[5]. In addition, ibutilide pretreatment facilitates external electrical cardioversion of persistent AF^[6-8]. However, its QT-prolonging properties and the increased risk for torsades de pointes (TdP) ventricular tachycardia raise safety concerns and limit its widespread use^[5].

A well-known pathogenetic factor for malignant ventricular arrhythmias is the increased dispersion of repolarization which reflects the heterogeneity rather than the total duration of repolarization^[9]. The T peak-to-end (Tpe) interval and the Tpe/QT ratio represent novel electrocardiographic indexes of arrhythmic risk that possibly correspond to the spatial dispersion of ventricular repolarization^[9-11]. It has also been demonstrated that in the setting of acquired QT prolongation the Tpe/QT ratio is a better predictor of TdP compared to the corrected QT interval (QTc) interval and QT dispersion^[12]. Thus, in this pilot observational study we sought to investigate the impact of ibutilide pretreatment on the aforementioned electrocardiographic (ECG) indexes in the setting of persistent AF before electrical cardioversion.

MATERIALS AND METHODS

We screened consecutive patients with persistent AF scheduled for elective electrical cardioversion. Patients taking drugs or having conditions that affect the QT interval were excluded. In specific, exclusion criteria were recent acute coronary syndrome within the past 6 mo, recent percutaneous coronary intervention or cardiac surgery, congestive heart failure with New York Heart Association class > II, presence of nonsustained ventricular tachycardia on Holter monitoring, presence of bundle branch block, QRS duration > 120 ms, previous implantation of a pacemaker or a defibrillator, administration of antiarrhythmic drugs, administration of drugs that prolong the QT interval, thyroid dysfunction, renal failure, and electrolyte disturbances. All patients were on β -blockers and/or digoxin for rate control as well as on vitamin K antagonists for anticoagulation treatment.

The patients were admitted to the coronary care unit in the morning hours. After checking the laboratory examinations, intravenous ibutilide (1 mg for 10 min +

1 mg after 20 min if the patients were still in AF) was administered at a fasting state before the electrical cardioversion while close ECG monitoring was performed. ECG indexes such as QTc, the interval from the peak until the end of T wave (Tpe) and the Tpe/QT ratio were measured before ibutilide infusion and 10 min after the end of administration.

The ECG indexes were assessed at baseline in the supine position and calculated as described in our previous reports^[13-15]. Specifically, the QT and the QTpeak intervals were measured manually on ECG recordings at a paper speed of 50 mm/s. QT interval was assessed as the time between the first deflection of QRS and the point of return of the T wave to the isoelectric line. The Tpe interval was calculated as QT-QTpeak. The QT interval was measured in as many of the 12 leads as possible while Tpe interval was assessed in lead II and in the precordial leads^[10,13-15]. The Tpe interval and the Tpe/QT ratio were calculated using the corresponding values from each lead. The measurements were obtained in 5 consecutive complexes of each lead and the resulting average value was finally accepted. In order to avoid diurnal variations, all procedures were performed during the same time interval (from 9.00 am to 11.00 am). QT interval corrected for heart rate (QTc) was calculated using the Bazett's formula ($QTc = QT/RR^{0.5}$)^[16]. The Tpe and QTc reported values were the maximum obtained values. All measurements were performed by one experienced investigator (Korantzopoulos P) who was unaware of the clinical characteristics of the study participants. To identify intraobserver variability, the ECG tracings of 6 randomly selected patients were reexamined 10 d after the initial evaluation. Intraobserver variation was less than 5%.

Statistical analysis

Continuous variables are expressed as mean \pm SD, or as median (25th-75th percentile) if their values are not normally distributed. The examination of normality was performed by the Kolmogorov-Smirnov test. Categorical variables are presented as frequencies. Comparisons of the continuous variables performed using the paired *t*-test or the non-parametric Wilcoxon signed-rank test. A two-tailed *P* value < 0.05 was considered significant. All analyses were performed using the SPSS software (version 16.0; SPSS Inc., Chicago, IL, United States).

RESULTS

The final study population consisted of 20 patients (mean age: 67.1 ± 9.9 years, 10 men). The baseline clinical and demographic characteristics of the patients are presented in Table 1. The mean duration of persistent AF before the attempted electrical cardioversion was 3 mo while the patients had preserved left ventricular ejection fraction and marginally dilated left atria (Table 1).

Six patients were cardioverted pharmacologically and did not proceed to electrical cardioversion. Two patients

Table 1 Baseline and clinical characteristics of the study population

Patients' characteristics	Value
Age (yr)	67.1 ± 9.9
Men	50%
Duration of atrial fibrillation (d)	94 ± 51
Baseline heart rate (beats per minute)	87 ± 19
Hypertension	65%
Diabetes	30%
Coronary artery disease	25%
Left ventricular ejection fraction	58% ± 7%
Left atrial diameter (mm)	41.7 ± 4.3
Sodium (mEq/L)	139.0 ± 3.0
Potassium (mEq/L)	4.4 ± 0.4

developed short non-sustained episodes of TdP ventricular tachycardia a few minutes after the infusion of the second dose. All but one of the aforementioned ECG indexes increased significantly after ibutilide administration. In specific, the QTc interval, the Tpe interval in precordial leads, the Tpe interval in lead II, the Tpe/QT ratio in precordial leads, and the Tpe interval dispersion increased (Table 2). However, the Tpe/QT ratio in lead II did not change significantly (Table 2).

DISCUSSION

In this pilot study we demonstrated that ibutilide significantly increases the total duration of repolarization reflected by the QTc interval and more importantly the dispersion of ventricular repolarization as assessed by modern ECG markers such as Tpe interval and Tpe/QT ratio.

Ibutilide confers a high risk of TdP (up to 9% of cases), although most episodes are self-terminated and do not require electrical termination^[17]. However, its proarrhythmic potential may hamper its use in several clinical settings. Besides its use for pharmaceutical cardioversion of recent-onset AF or atrial flutter, ibutilide increases the success rates of electrical cardioversion of these arrhythmias, facilitates electrical cardioversion of refractory persistent AF, and lowers energy requirements during the procedure^[6-8,17,18]. Of note, ibutilide infusion must be followed by 3-4 h of ECG monitoring to exclude TdP^[5-8].

Ibutilide prolongs repolarization by inhibition of the rapidly activating component of the delayed rectifier potassium currents (I_{Kr}) and by selective enhancement of the slow inward sodium current^[19]. It should be pointed out that the heterogeneity of ventricular repolarization is a much more important parameter for proarrhythmia compared to the total duration of repolarization. For example, it is well known that amiodarone carries a very low risk for proarrhythmia despite its QT prolonging effects^[20]. This apparent paradox is explained by the fact that amiodarone prolongs the ventricular repolarization homogeneously and does not increase transmural dispersion of repolarization^[20].

Spatial dispersion of repolarization reflects the het-

Table 2 Electrocardiographic variables before and after ibutilide infusion

Variables	Before ibutilide	After ibutilide	P value
QTc (ms)	442 ± 29	471 ± 37	0.037
Tpe in lead II (ms)	79 (70-88)	100 (87-104)	< 0.001
Tpe in precordial leads (ms)	96 (80-108)	101 (91-119)	0.021
Tpe dispersion (ms)	25 (23-30)	35 (27-39)	0.012
Tpe/QT in lead II	0.22 (0.18-0.24)	0.24 (0.22-0.28)	0.12
Tpe/QT in precordial leads	0.23 (0.18-0.26)	0.26 (0.23-0.28)	0.028

The parameters are presented as means ± SD or as median values (25th-75th percentile). QTc: Corrected QT interval; Tpe: T peak-to-end.

erogeneity of repolarization which creates voltage gradients and thus promoting ventricular arrhythmias. Tpe interval represents a promising marker of total dispersion of ventricular repolarization (transmural, apicobasal, or global)^[10]. However, the Tpe/QT ratio appears to be a more sensitive arrhythmogenic index since it remains constant despite changes in the heart rate (dynamic changes in Tpe and QT interval occur in a proportional and parallel fashion)^[10,12,21]. Remarkably, an increased Tpe/QT ratio has been associated with arrhythmic events in patients with acquired long QT syndrome^[12], in patients with hypertrophic cardiomyopathy^[22], and in cardiac resynchronization therapy patients^[23]. Also, the Tpe interval is independently associated with sudden cardiac death in the general population^[24], as well as with mortality after acute myocardial infarction^[25]. In the setting of stable coronary artery disease where exercise-induced arrhythmias represent a specific problem, we recently demonstrated that Tpe/QT ratio significantly increases at peak exercise^[13]. Very recently we also showed that these novel indexes of dispersion of repolarization including Tpe/QT are increased in individuals with early repolarization^[14] and also after hemodialysis in patients with end-stage renal disease^[15].

Taking into account the aforementioned considerations we focused on the measurement of the novel indexes Tpe and Tpe/QT in order to investigate the effects of ibutilide administration on the dispersion of ventricular repolarization in patients with AF. Accumulating evidence suggests that the older index "QTc dispersion" does not actually reflect the dispersion of ventricular repolarization^[26] and therefore we did not assess this parameter. In experimental models such as in the rabbit left ventricular wedge preparation the estimation of transmural dispersion of repolarization represented by Tpe interval and Tpe/QT ratio proved to be a useful tool for the prediction of drug-induced QT prolongation and proarrhythmic potential^[27]. In this context, Yamaguchi *et al.*^[12] showed that Tpe/QT ratio is a better predictor of TdP compared to QTc interval and QT dispersion in the setting of acquired QT prolongation. With regard to ibutilide, Kannankeril *et al.*^[28] recently demonstrated that QT prolongation by the drug does not correlate to baseline QTc and does not differ between the 2 sexes. Given that

the QT prolongation by ibutilide is highly variable and does not accurately predict the occurrence of TdP the assessment of dispersion of ventricular repolarization may confer an advantage for this purpose.

Limitations

We feel that our study adds to the current knowledge of drug-induced proarrhythmia and its evaluation through novel ECG markers of dispersion of repolarization. However, some limitations are apparent. Firstly, the study population was small. Secondly, due to the limited number of patients it was not feasible to compare the indexes of repolarization between patients who suffered short episodes of TdP ($n = 2$) and patients who did not suffer any ventricular arrhythmia ($n = 18$). Thirdly, we have to acknowledge that our patients did not have significant comorbidities and especially they did not have significant LV dysfunction. The effect of ibutilide on ventricular repolarization may be more prominent in more advanced heart disease states. Finally, although we measurements of the ECG were obtained in 5 consecutive complexes of each lead and the resulting average value was finally accepted, we have to admit that the high variability of the RR intervals during AF poses specific problems in the accuracy of measurements.

In conclusion, ibutilide administration increases the duration and the dispersion of ventricular repolarization. Therefore, Tpe interval and Tpe/QT ratio may represent useful prognostic markers for the occurrence of TdP after ibutilide infusion. Undoubtedly, the prognostic role of these ECG indexes and their variations in the setting of drug-induced proarrhythmia needs further study.

COMMENTS

Background

Drug-induced proarrhythmia represents a significant problem that poses special risks in the implementation of drug therapy. Several antiarrhythmic drugs seem to have proarrhythmic potential. Ibutilide is a class III antiarrhythmic agent effective for pharmacological cardioversion of recent-onset atrial fibrillation (AF) or atrial flutter. It is administered intravenously and has a rapid onset of action. In addition, ibutilide pretreatment facilitates external electrical cardioversion of persistent AF.

Research frontiers

Electrocardiographic (ECG) indexes such as corrected QT interval, the interval from the peak until the end of T wave (Tpe), and the Tpe/QT ratio were measured.

Innovations and breakthroughs

In this pilot study authors examined the effect of ibutilide on novel indexes of repolarization in patients with persistent atrial fibrillation scheduled for electrical cardioversion. Authors showed that ibutilide significantly increases the dispersion of ventricular repolarization as assessed by modern ECG markers such as Tpe interval and Tpe/QT ratio. These indexes may have a prognostic value with regard to drug-induced proarrhythmia.

Peer review

According to this report 10% of the subjects developed short episodes of TdP and 30% were pharmacologically converted into sinus rhythm. It demonstrated the significant side effects and proarrhythmic profile of ibutilide. It has been nicely shown that the novel tools of Tpe interval and Tpe/QT are useful for the prediction of ibutilide-induced QT prolongation compared the classic QTc interval.

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P- Reviewers Kettering K, Liu T, Said S **S- Editor** Gou SX
L- Editor A **E- Editor** Lu YJ



Response of blood pressure after percutaneous transluminal renal artery angioplasty and stenting

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Received: April 15, 2013 Revised: May 20, 2013

Accepted: June 9, 2013

Published online: July 26, 2013

Abstract

AIM: To evaluate the short and intermediate term outcome of percutaneous transluminal renal artery angioplasty (PTRA) and stenting particularly on blood pressure (BP) control and renal function and to evaluate predictors of poor BP response after successful PTRA and stenting.

METHODS: We conducted a prospective analysis of all patients who underwent PTRA and stenting in our institute between August 2010 to September 2012. A total number of 86 patients were underwent PTRA and renal stenting. Selective angiography was done to confirm at least 70% angiographic stenosis. The predilatation done except few cases with critical stenosis, direct stenting was done in the rest of cases. All patients received aspirin 325 mg orally, and clopidogrel 300 mg orally within 24 h before the procedure. Heparin was used as the procedural anticoagulant agent. Optimal results with TIMI-III flow obtained in all cases. Follow-

ing stent placement, aspirin 150 mg orally once daily was continued for a minimum of 12 mo and clopidogrel 75 mg orally once daily for at least 4 wk. The clinical, radiological, electrocardiography, echocardiography and treatment data of all patients were recorded. The BP measurement, serum creatinine and glomerular filtration rate (GFR) were recorded before the procedure and 1 and 6 mo after PTRA.

RESULTS: A total of 86 patients were included in the study. The mean age of study population was 55.87 ± 11.85 years old and 67 (77.9%) of patients were male. There was a significant reduction in both systolic and diastolic BP at 1 mo after the procedure: 170.15 ± 20.10 mmHg vs 146.60 ± 17.32 mmHg and 98.38 ± 10.55 mmHg vs 89.88 ± 9.22 mmHg respectively ($P = 0.0000$). The reduction in BP was constant throughout the follow-up period and was evident 6 mo after the procedure: 144.23 ± 18.19 and 88.26 ± 9.79 mmHg respectively ($P = 0.0000$). However, no improvement in renal function was observed at any time during the follow-up period. After multivariate analysis, we found male sex, low GFR (< 60 mL/min) and higher baseline mean BP as a poor predictors of successful outcome on BP response after PTRA and stenting.

CONCLUSION: The PTRA and stenting can be considered as an effective therapeutic intervention for improving BP control with minimal effect on renal function. The male sex, higher baseline BP and low GFR are associated with poor BP response after successful PTRA and stenting.

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Key words: Percutaneous transluminal renal artery angioplasty; Hypertension; Glomerular filtration rate; Renovascular hypertension; Renal stent

Core tip: To evaluate the short and intermediate term

outcome of percutaneous transluminal renal artery angioplasty (PTRA) and stenting particularly on blood pressure (BP) control and renal function and to evaluate predictors of poor BP response after successful PTRA and stenting. The PTRA and stenting can be considered as an effective therapeutic intervention for improving BP control with minimal effect on renal function. The male sex, higher baseline BP and low glomerular filtration rate are associated with poor BP response after successful PTRA and stenting.

Prajapati JS, Jain SR, Joshi H, Shah S, Sharma K, Sahoo S, Virparia K, Thakkar A. Response of blood pressure after percutaneous transluminal renal artery angioplasty and stenting. *World J Cardiol* 2013; 5(7): 247-253 Available from: URL: <http://www.wjgnet.com/1949-8462/full/v5/i7/247.htm> DOI: <http://dx.doi.org/10.4330/wjc.v5.i7.247>

INTRODUCTION

Renovascular hypertension occurs in 1% to 5% of all patients with hypertension. Renovascular hypertension is the most common form of secondary hypertension. Renal artery stenosis (RAS) is caused often by atheromatous plaques (80% of the cases over 40 years), but can also be due to fibromuscular dysplasia (10% of the cases and more often in young patients), arteritis (Takayasu's disease), neurofibromatosis and post radiation injury^[1-4]. It can also occur in post renal transplant patients or after a renal bypass graft^[4].

RAS is associated with increased cardiovascular events and mortality. Its prevalence varies from 7% in individuals over 65 years of age to 20%-30% in high risk group of patients. It may affect up to 30% of patients with coronary artery disease and nearly 50% of those with significant peripheral vascular disease (PVD)^[5,3-7]. Atherosclerotic RAS is a progressive disease associated with loss of renal mass over time, despite control of hypertension. Progression of RAS to complete occlusion is more likely with more severe (> 60%) lesions and may occur at a rate of up to 20%/year^[4,8-10].

Atherosclerotic RAS is an important cause of renal insufficiency, refractory hypertension, and cardiac destabilization syndromes (unstable angina and flash pulmonary edema)^[11,12]. Unilateral RAS manifests clinically as a vasoconstrictor-mediated hypertension, whereas bilateral RAS causes hypertension caused by volume overload. Up to 20% of patients older than 50 years of age requiring renal dialysis have atherosclerotic RAS (ischemic nephropathy) as the cause of their renal failure. The treatment of RAS includes medical therapy, balloon angioplasty and surgery. Surgery has been replaced by percutaneous transluminal renal artery angioplasty (PTRA) and stenting and remains at high risk with a 2%-7% perioperative mortality rate, a 17%-31% morbidity, deterioration rate in renal function in 11%-31% of patients

and reocclusion and restenosis in 5%-18%. Indications for surgery are limited and include failed percutaneous approach, hostile aorta, infra-renal total occlusion and in association with aortic surgery^[4,13-15].

The PTRA technique has become the cornerstone for treatment of RAS and is now the first line treatment to be proposed. Balloon angioplasty alone was first proposed but several series reported the successful use of endovascular stents for treating suboptimal angioplasty results and as a primary intervention for atherosclerotic lesions and particularly ostial lesions with better immediate and long-term results than with balloon angioplasty alone^[16-21]. Despite many reports of clinical success in selected and carefully chosen patient groups, the enthusiasm for widespread treatment of mild or moderate renovascular disease has waned. Recent published data from the Angioplasty and Stenting for Renal Artery Lesions (ASTRAL) trial, in which patients were randomized to revascularization *vs* continued medical therapy alone, did not show a clear benefit of renal revascularization, although its design and conclusions have been criticized^[22]. We designed this study to evaluate the short and intermediate term outcome of PTRA and stenting particularly on blood pressure (BP) control and renal function and to evaluate predictors of poor BP response after successful PTRA and stenting.

MATERIALS AND METHODS

Study population

This study was carried out in the Department of Cardiology, UN Mehta Institute of Cardiology and Research, from August 2010 to September 2012. This institute is tertiary care center situated in Ahmedabad, Gujarat, India. A total number of 86 patients were underwent PTRA and renal stenting with following inclusion criteria: (1) significant renal artery stenosis (70% or more stenosis); (2) onset of hypertension before 30 years and after 55 years; (3) exacerbation of previously well controlled hypertension; (4) malignant hypertension and Refractory hypertension; (5) azotemia shortly after institution of therapy with ACE inhibitors or ARB blockers; (6) hypertension and atrophic kidney or discrepancy in kidney size (> 1.5 cm); (7) hypertension and recurrent episodes of acute pulmonary edema or unexplained heart failure; (8) hypertension and systolic-diastolic abdominal bruit that laterlize to one side; and (9) hypertension and progressive unexplained azotemia. The exclusion criteria were: (1) serum creatine value > 3 mg/dL; (2) small kidney; and (3) total renal artery occlusion.

Informed written consent was obtained from all patients before treatment. This study conducted in accordance with the International Conference on Harmonization guidelines Good Clinical Practices, Declaration of Helsinki, and medical ethics committee requirements.

All patients' systolic BP, diastolic BP, serum creatinine and GFR were measured at baseline, 1 mo and 6 mo respectively. The BP was measured in supine position in

Table 1 Baseline characteristics of study population: Clinical, laboratory and imaging data *n* (%)

Variables	<i>n</i> = 86
Male gender	67 (77.9)
Age (yr)	55.87 ± 11.85
Background diseases	
Stage-1 (malignant) hypertension	14 (16.3)
Stage-2 hypertension	65 (75.6)
Diabetes mellitus	34 (39.5)
Smoking	61 (70.9)
Clinical features of left ventricular dysfunction	23 (26.7)
Left ventricular hypertrophy	29 (33.7)
Coronary artery disease	72 (83.7)
Blood pressure	
Systolic (mmHg)	170.15 ± 20.10
Diastolic (mmHg)	98.38 ± 10.55
Antihypertensive drugs (<i>n</i>)	3.07 ± 0.69
Indication criteria	
Hypertension resistant to standard medication	71 (82.6)
Renal bruit	53 (61.6)
Serum creatinine (mg/dL)	20 (23.3)
Stenosis	
Bilateral	23 (26.7)
Coronary angiography	
Single vessel disease	25 (29.1)
Double vessel disease	14 (16.3)
Triple vessel disease	28 (32.6)
Normal vessel	19 (22.1)

Values are presented as percentage (%) and mean ± SD.

both upper limbs and lower limbs with mercury manometer with standard cuff size after adequate rest. Patients were not allowed to have tea, coffee, smoking and alcohol 1 h prior to procedure. Patients were allowed to continue their antihypertensive medicines. Patients were on primarily b blocker, diuretics, ace inhibitors/ARB or calcium channel blockers.

Procedure

All patients who underwent PTR A and stenting received anticoagulation as per hospital protocol. Selective angiography was done to confirm at least 70% angiographic stenosis. PTR A was performed with either 6/7 F RDC or JR 3.5 guiding catheter and work hoarse guidewire. The predilatation done except few cases with critical stenosis, direct stenting was done in the rest of cases. Post dilation was done if required. The study included bare metal stent (BMS) of 12, 15, and 18 mm lengths with diameters ranging from 4 to 7 mm.

All patients received aspirin 325 mg orally, and clopidogrel 300 mg orally within 24 h before the procedure. Heparin was used as the procedural anticoagulant agent. Optimal results with TIMI-III flow obtained in all cases. Following stent placement, aspirin 150 mg orally once daily was continued for a minimum of 12 mo and clopidogrel 75 mg orally once daily for at least 4 wk.

Statistical analysis

All collected data entered into the "IBM SPSS STAIST-ICS version 20". The quantitative data expressed as mean

Table 2 Blood pressure, antihypertensive medication, serum creatinine and glomerular filtration rate initial *vs* follow-up measurements

Time of follow-up	mean ± SD	<i>P</i> value
Systolic blood pressure (mmHg)	170.15 ± 20.10	< 0.0001
Baseline		
1 mo	146.60 ± 17.32	
6 mo	144.23 ± 18.19	
Diastolic blood pressure (mmHg)	98.38 ± 10.55	< 0.0001
Baseline		
1 mo	89.88 ± 9.22	
6 mo	88.26 ± 9.79	
Antihypertensive drugs (<i>n</i>)	3.07 ± 0.69	< 0.0001
Baseline		
1 mo	2.37 ± 0.84	
6 mo	2.25 ± 0.94	
Serum creatinine (mg/dL)	1.21 ± 0.66	0.964
Baseline		
48 h	1.29 ± 0.88	
1 mo	1.33 ± 1.27	
6 mo	1.21 ± 0.79	
GFR estimation (mL/min)	65.71 ± 25.20	0.546
Baseline		
6 mo	66.68 ± 25.03	

Values are presented as mean ± SD, *P* value compares baseline to 6 mo. GFR: Glomerular filtration rate.

and standard deviation (SD) where qualitative data expressed in percentage (%). The independent and dependent student's *t*-test have been used to carry out significant changes in paired and non-paired quantitative data. Also, χ^2 and Fisher exact test have been used to carry out significant change in qualitative data. The *P* value < 0.05 consider as a statistically significant. All statistically significant variables taken for univariate binary logistic regression and for univariate significant variables entered into multiple step wise logistic regression for further analysis of the variables.

RESULTS

Out of 86 patients, 6 patients were lost follow-up and 5 patients developed non procedural related mortality in follow-up. All baseline characteristics of study population were shown in Table 1. The BP, antihypertensive medication, serum creatinine and GFR data compared at pre-procedure and follow-up period in Table 2. There was no procedure related mortality. Two patients had local vascular complications which were managed conservatively. Out of 86 patients, 83 patients had atherosclerosis RAS and 3 patients takayasu arteritis.

The mean systolic BP was reduced from 170.15 ± 20.10 to 146.60 ± 17.32 mmHg and diastolic BP from 98.38 ± 10.55 to 89.88 ± 9.22 mmHg at one mo follow-up. This significant reduction in BP after PTR A was maintained at 6 mo follow up of 144.23 ± 18.19 systolic and 88.26 ± 9.79 diastolic BP respectively (Table 1). There was a statistically significant reduction in systolic BP compared to pre-intervention (paired *t* test: *P* <

Table 3 Levels of sIL-2R, alanine aminotransferase, and hepatitis B virus DNA in the sera of patients with chronic HBV infection (mean \pm SD)

Group ¹	n	mean \pm SD	P value
Age (yr)			0.51
A	26	56.81 \pm 13.87	
B	49	54.80 \pm 11.55	
Initial systolic BP (mmHg)			0.01
A	26	179.31 \pm 20.32	
B	49	166.00 \pm 18.76	
Initial diastolic BP (mmHg)			0.04
A	26	101.92 \pm 10.90	
B	49	96.79 \pm 10.14	
Initial mean BP (mmHg)			0.01
A	26	141.00 \pm 17.73	
B	49	129.00 \pm 16.76	
No. of medications			0.01
A	26	3.26 \pm 0.77	
B	49	2.87 \pm 0.57	
Creatinine (mg/dL)			0.07
A	26	1.38 \pm 0.48	
B	49	1.11 \pm 0.66	
Diameter of stent			0.23
A	26	5.76 \pm 0.94	
B	49	6.05 \pm 0.98	
Percent of renal artery stenosis (RAS)			0.05
A	26	87.65 \pm 7.71	
B	49	83.79 \pm 8.40	
GFR (mL/min)			0.01
A	26	54.03 \pm 24.22	
B	49	72.97 \pm 25.43	
Duration of HT (yr)			0.55
A	26	4.00 \pm 3.96	
B	49	3.40 \pm 3.32	

Values are presented as mean \pm SD. ¹Group A: Patients who did not show blood pressure reduction after percutaneous transluminal renal artery (PTR A) (26 patients); group B: Patients who showed blood pressure reduction after PTR A (49 patients). HT: Hormone Therapy; BP: Blood pressure; GFR: Glomerular filtration rate.

0.0001). The 65.33% of patients showed reduction in BP. There was no difference in the magnitude of systolic BP response among patients treated for bilateral RAS compared with those treated for unilateral RAS.

Mean intake of total number of medicines at baseline was 3.07 ± 0.69 . At 1 mo follow-up, number of medicines reduced to 2.37 ± 0.84 and at 6 mo to 2.25 ± 0.94 . There was statistically significant reduction in mean number of medicines intake ($P < 0.0001$).

At baseline, mean serum creatinine value was 1.21 ± 0.66 mg/dL. After PTR A and stenting, at 48 h there was mild elevation in serum creatinine to 1.29 ± 0.88 mg/dL. At 1 mo of follow up, serum creatinine was 1.33 ± 1.27 mg/dL and at 6 mo was 1.21 ± 0.79 mg/dL. There was no statistically significant difference in serum creatinine value after PTR A. At baseline mean GFR was 65.71 ± 25.20 mL/min. After PTR A and stenting at 6 mo of follow up, GFR was 66.68 ± 25.03 mL/min. There was no statistically significant difference in GFR at follow up after PTR A and stenting (Table 1).

PTR A and stenting to renal artery significantly lowers BP and mean number of drug intake but not cause signif-

Table 4 Clinical features of resistant hypertensive group: Responsive *vs* unresponsive to percutaneous transluminal renal artery *n* (%)

	Group A <i>n</i> = 26	Group B <i>n</i> = 49	P value
Male gender	24 (92.3)	33 (67.3)	0.016
Smoker	22 (84.6)	33 (67.4)	0.1
Ischemic heart disease	21 (80.8)	35 (71.4)	0.376
Diabetes mellitus	8 (30.8)	19 (38.8)	0.49
C/f of LVF	5 (19.2)	11 (22.4)	0.746
Smoking	22 (84.6)	33 (67.4)	0.1
Renal bruit	20 (76.9)	29 (59.2)	0.124
Refractory HT	23 (88.5)	37 (75.5)	0.182
LVH	14 (53.9)	14 (28.6)	0.031
LAD	19 (73.1)	34 (69.4)	0.733
TVD	12 (46.2)	13 (26.5)	0.08
Renal artery stenosis (unilat <i>vs</i> bilat)	15 (57.7)	40 (81.6)	0.026
Bilateral RAS	11 (42.3)	9 (18.4)	
LMCA disease	23 (88.5)	47 (95.9)	0.218
Absent			
Present	3 (11.5)	2 (4.1)	

Group A: Patients who did not show blood pressure reduction after percutaneous transluminal renal artery (PTR A) (26 patients); and group B: Patients who showed blood pressure reduction after PTR A (49 patients). HT: Hormone therapy; LVH: Left ventricular hypertrophy; TVD: Triple vessel disease; LAD: Left anterior descending; LVF: Left ventricular function; RAS: Renal artery stenosis; LMCA: Left main coronary artery.

icantly reduction in serum creatinine or change in GFR.

Prediction of BP reduction after PTR A among resistant hypertensive patients

In order to evaluate predictors of poor BP reduction after successful PTR A and stenting, we divided 75 patients into two groups: group A, the non-responsive group, which included patients without significant BP reduction after PTR A (26 patients), and group B, the responsive group, which included patients who showed significant BP reduction followed PTR A (49 patients) (BP reduction $< 140/90$ mmHg with or without drugs was considered significant reduction).

Higher baseline systolic and diastolic BP (number value < 0.01 and < 0.04 , respectively) and higher mean intake of no. of medications (P value < 0.01) for control of BP was associated with poor response of BP control after successful PTR A and stenting. Non-responsive group associated with higher mean baseline serum creatinine (1.38 mg/dL *vs* 1.11 mg/dL) but not statistically significant ($P = 0.07$). But baseline low GFR < 60 mL/min was associated with poor response after PTR A and stenting ($P < 0.01$). Higher initial % of RAS was also associated with poor response ($P = 0.05$). Between these groups, neither duration of Hormone Therapy nor diameter of stent used was significantly different (Table 3).

Clinical features in the resistant hypertensive group

Comparing various characteristics between both groups reveals male sex ($P = 0.016$), left ventricular hypertrophy ($P = 0.031$), presence of triple vessel disease ($P = 0.08$)

Table 5 Multivariate analysis: The independent predictors for poor blood pressure response after percutaneous transluminal renal artery

Variables	Univariate <i>P</i> value	Multivariate analysis			95%CI
		<i>P</i> value	β	Exp β	
Male sex	0.02	0.046	1.797	6.032	1.028–35.380
High mean SBP	0.01	NS			
High mean DBP	0.05	NS			
High mean BP	0.09	0.013	-0.044	0.957	0.925–0.991
Low GFR (< 60 mL/min)	0.01	0.015	1.377	3.965	1.308–12.020
LVH	0.03	NS			
Drugs (<i>n</i>)	0.01	NS			
Bilateral <i>vs</i> unilateral RAS	0.02	NS			
Percent of stenosis	0.06	NS			
Presence of TVD	0.09	NS			
Constant			2.365	10.65	

TVD: Triple vessel disease; BP: Blood pressure; RAS: Renal artery stenosis; GFR: Glomerular filtration rate; LVH: Left ventricular hypertrophy; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; NS: Not significant.

and presence of bilateral RAS ($P = 0.026$) were associated with poor outcome after PTRA and stenting (Table 4).

DISCUSSION

In the current study we demonstrated that in patients with significant RAS, PTRA improved BP control and decreased mean number of drug intake significantly and this improvement was maintained during the entire follow-up period of 6 mo. PTRA and stenting did not cause significant improvement in renal function (P value for both serum creatine and GFR was not significant).

In recent years, role of PTRA and stenting in management of RAS has been questioned. In the early 1980s the concept was that revascularization of the stenotic atherosclerotic renal artery will salvage the ischemic kidney and will cure hypertension^[23]. Revascularization methods and medication have improved considerably over the past 20 years and the aims of managing patients with atherosclerotic renal artery stenosis (ARAS) have progressed from focusing on BP control to stabilizing renal function and finally to preventing clinical events. However, as the procedure became broadly applied during the 1990s mixed results emerged. Some patients showed major benefit after PTRA, while others experienced further deterioration of renal function and major morbidity^[24]. Today it is acknowledged that ARAS is a complex clinical entity that ranges from asymptomatic disease discovered incidentally on imaging to high grade bilateral disease complicated by recurrent pulmonary edema, severe hypertension, and progressive renal failure. RAS is generally associated with high incidence of associated CAD and target organ damage. Mortality in these patients is high and mostly related to cardiovascular events regardless of whether renal revascularization was performed^[25].

In recent years several controlled trials were designed

to evaluate the effectiveness of PTRA *vs* medical treatment in patients with severe ARAS. The DRASTIC study included a cohort of 106 hypertensive subjects with ARAS. The patients were randomly assigned to revascularization or medical treatment, but after 12 mo of follow-up no difference in BP control or renal function was demonstrated between the groups^[26]. The STAR study, which included 140 patients with creatinine clearance < 80 mL/min per 1.73 m² and ARAS $\geq 50\%$, also failed to show benefit of the invasive approach *vs* medical treatment^[27].

The largest randomized trial, the ASTRAL study, comparing revascularization to medical treatment for ARAS, examined 806 subjects who were followed for 5 years. This study concluded that revascularization for ARAS has more risk than benefit^[23]. But important limitation of the trial was the selected population. Patients were enrolled in the trial only if their own physician was uncertain as to whether revascularization would provide a worthwhile clinical benefit. Patients with symptomatic ARAS such as uncontrolled hypertension despite optimal medical treatment, or with recurrent episodes of flush pulmonary edema were not included in the study^[23]. This study is at the top of the list with ASTRAL, raised considerable debate regarding the management of patients with ARAS^[28]. The main claim of the ASTRAL critics was that the success of PTRA for ARAS is strongly dependent on the selection of the right patients for this procedure.

In our study, we found PTRA and stenting associated with significant improvement in BP control with reduced mean intake of drugs without improvement in renal function. We also sought predictors of poor BP control after successful PTRA and stenting.

The predictors of poor response to BP control after PTRA and stenting by univariate analysis were male sex, high baseline systolic, diastolic and mean BP, low GFR, presence of LVH, high baseline mean intake of number of drugs, presence of bilateral stenosis, higher angiographic % diameter of stenosis and presence of TVD. But on multivariate analysis; the independent predictors for poor BP response after PTRA were male sex ($P = 0.046$), higher baseline mean BP ($P = 0.013$) and low GFR (< 60 mL/min) ($P = 0.015$) (Table 5).

Patients with poor BP response (34.66%) may be considered for renal sympathetic denervation therapy. As early studies in animals and in humans suggested that the renal nerves play a role in BP regulation. A series of pilot studies as well as a clinical trial (symplicity HTN-2) involving patients with uncontrolled hypertension then showed that a catheter-based system can safely denervate the kidney and produce notable and sustained reductions in BP. Ongoing symplicity HTN-3: Renal Denervation in Patients With Uncontrolled Hypertension trial will help us to establish whether therapeutic renal denervation using a catheter-based approach is a safe and effective therapy for patients with uncontrolled hypertension.

Study limitations

Given that the majority of patients were Asian, the find-

ings in our trial may not be generalized among other ethnic and racial populations. Another limitation of this study is that we have not used any emboli protection device. As atheroembolism is major concern in percutaneous intervention of renal artery and associated with different degree of renal impairment. Atheroembolism may impair outcome of PTRAs and stenting particularly on renal function. Use of distal embolic protection device may be associated with improved outcome. We have not used FFR to evaluate lesion severity in our study. FFR can predict individual response to renal artery stenting and improve outcome of PTRAs and stenting.

In conclusion, considering the results of our study and previous works it appears that the main effect of renal artery revascularization in ARAS is on BP control in patients with resistant hypertension, with minimal influence on renal function. Male sex, higher baseline BP and low GFR (< 60 mL/min) are associated with poor BP response after successful PTRAs and stenting. Further studies with emboli protection devices and FFR to assess severity of lesion may be helpful to validate this observation.

COMMENTS

Background

Percutaneous transluminal renal artery angioplasty (PTRAs) and stenting is an established procedure for the treatment of renovascular hypertension caused by renal artery stenosis (RAS). Recently published trials have questioned the efficacy of PTRAs and stenting of renal artery.

Research frontiers

The PTRAs technique has become the cornerstone for treatment of RAS and is now the first line treatment to be proposed. Balloon angioplasty alone was first proposed but several series reported the successful use of endovascular stents for treating suboptimal angioplasty results and as a primary intervention for atherosclerotic lesions and particularly ostial lesions with better immediate and long-term results than with balloon angioplasty alone.

Innovations and breakthroughs

They found PTRAs and stenting associated with significant improvement in blood pressure (BP) control with reduced mean intake of drugs without improvement in renal function. Authors also sought predictors of poor BP control after successful PTRAs and stenting.

Peer review

This is a study on percutaneous transluminal renal artery dilatation and stenting in a cohort of 86 patients with significant renal artery stenosis.

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P- Reviewers Biondi-Zoccai G, Cheng XS, Castillo R, Durandy Y
S- Editor Gou SX **L- Editor** A **E- Editor** Lu YJ



Hypoxemia without persistent right-to-left pressure gradient across a patent foramen ovale: A clinical challenge

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Received: February 9, 2013 Revised: April 25, 2013

Accepted: June 1, 2013

Published online: July 26, 2013

left shunt; Shunt closure; Pulmonary embolism; Atrial septal defect

Core tip: Patent foramen ovale (PFO) is a common, yet benign entity most of the time. Rarely, it is known to play role in causation of stroke, migraine and even rarely, profound hypoxemia. We report a rare case of severe hypoxemia due to PFO where the shunting is not persistent. We also review the sparse literature on PFO closure for this indication and discuss how the decision making for such indication needs to be individualized.

Pant S, Hayes K, Deshmukh A, Rutlen DL. Hypoxemia without persistent right-to-left pressure gradient across a patent foramen ovale: A clinical challenge. *World J Cardiol* 2013; 5(7): 254-257 Available from: URL: <http://www.wjgnet.com/1949-8462/full/v5/i7/254.htm> DOI: <http://dx.doi.org/10.4330/wjc.v5.i7.254>

Abstract

Patent foramen ovale (PFO) closure for systemic hypoxemia is controversial. The first systematic, albeit retrospective, study was recently presented which showed good procedural and clinical success for PFO closure for this indication. We present a case of acute right to left intra-cardiac shunt across PFO where the shunting is not persistent. Hence making a decision on PFO closure based on the aforementioned promising trial may not have been the right decision for the patient. This case highlights that the decision on PFO closure for such indication needs to be individualized. We also review the sparse literature on PFO closure for this indication and discuss how the decision making for such indication needs to be individualized.

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Key words: Patent foramen ovale; Hypoxemia; Right-to-

INTRODUCTION

Patent foramen ovale (PFO) closure for systemic hypoxemia is controversial. The first systematic, albeit retrospective, study was recently presented which showed good procedural and clinical success for PFO closure for this indication.

CASE REPORT

A 83-year-old female was transferred from an outside facility after an extensive evaluation for acute hypoxemia. She initially presented with worsening shortness of breath over a few days, aggravated by exertion but without any orthopnea or paroxysmal nocturnal dyspnea. She denied cough or chest pain. Her past medical history was significant for hypertension, osteoarthritis, transient ischemic attacks, gastroesophageal reflux disease, osteoporosis and coronary artery disease. During the recent admis-

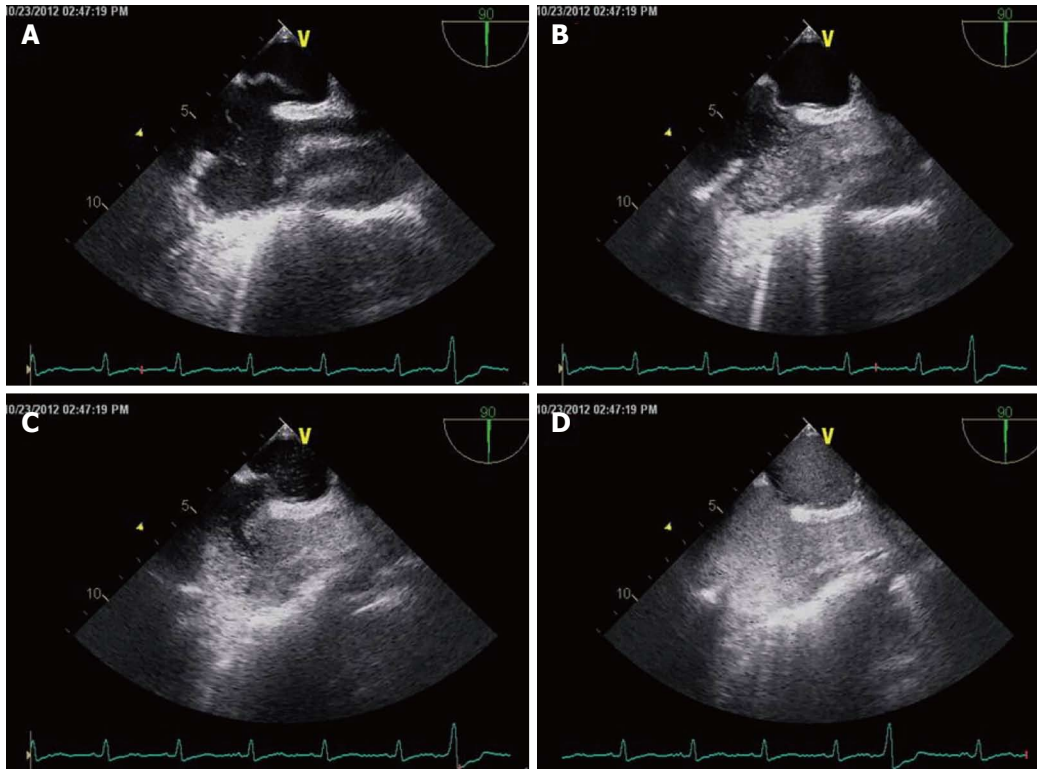


Figure 1 Transesophageal echocardiography with bubble study. A: Transesophageal echocardiography (TEE) of the patient with a patent foramen ovale (PFO) showing a wide separation in the inter-atrial septum; B: TEE with injected agitated saline showing the presence of bubbles in the right atrium; C: TEE of the patient within the same cardiac cycle showing jet of bubbles crossing the inter-atrial septum through the PFO; D: Opacification of entire left atrium as the jet of bubbles gushes through the PFO.

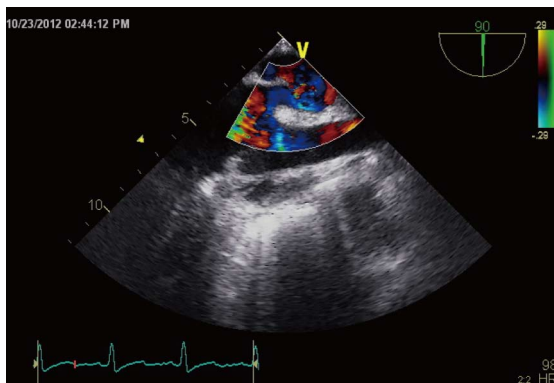


Figure 2 Transthoracic echocardiography with Doppler showing significant flow of blood across the inter-atrial septum.

sion to the outside facility, she had undergone a left heart catheterization (LHC) with stenting of the left circumflex and obtuse marginal arteries. The right coronary was chronically totally occluded and attempt to revascularize it was unsuccessful. The pressure and oxygen saturation data is presented in Table 1. Ventilation/perfusion scan showed low probability for pulmonary embolism (PE). Lung perfusion scintigraphy demonstrated increased uptake underlying the calvarium suspicious for right to left shunt.

At presentation to our facility, her blood pressure was 139/73 mmHg, heart rate 113 beats per minute, respira-

tory rate 23 and oxygen saturation was 90% on nasal canula oxygen of 15 L/min. Systemic examination was unremarkable. Arterial blood gas on admission was pH 7.5, $p\text{CO}_2$ 25 mmHg, $p\text{O}_2$ 54 mmHg and HCO_3^- 19.5 mEq/L. Chest roentgenogram was normal. Computed tomography angiogram chest PE protocol was negative. The possibility of intra-cardiac shunt was initially thought less likely in the absence of a right-to-left pressure gradient on recent heart catheterization. The patient continued to remain hypoxemic. Blood gas evaluation performed with and without oxygen revealed no significant improvement in PaO_2 with oxygen, suggesting right to left shunting at the intracardiac or intrapulmonary level. A transesophageal echocardiogram with bubble and doppler studies was subsequently done (Figures 1 and 2). Significant right to left shunting across a PFO was observed. The inter-atrial septum was markedly deviated to the left atrial side during systole and represented an atrial septal aneurysm. QP (pulmonary flow): QS (systemic flow) ratio could not be precisely estimated due to limited views of the right ventricular outflow tract but was approximately 0.7. This observation suggested significant right to left shunting. She was also found to have healthcare associated pneumonia during that time which was adequately treated with antibiotics. PFO closure was considered but it was thought that the large right to left shunting at the atrial level observed earlier was likely related to pulmonary vasoconstriction related to her pneumonia. After a few days, her oxygen re-

Table 1 Pressure and oxygen saturation in various chambers measure on cardiac catheterization

Location	Pressure (mmHg)	Oxygen saturation
Right atrium	2	
High		65%
Medium		63%
Low		67%
Right ventricle	2/18	60%
Pulmonary artery	20/6	61%
Left atrium	3	95%
Aorta		95%
Inferior venacava		73%
Superior venacava		70%

quirement decreased. Blood gas evaluation was performed with (pH 7.3, pCO₂ 37 mmHg, pO₂ 68 mmHg and HCO₃⁻ 22 mEq/L) and without oxygen (pH 7.4, pCO₂ 34 mmHg, pO₂ 56 mmHg and HCO₃⁻ 21 mEq/L). Repeat echocardiogram showed persistent but decreased shunting. She was subsequently discharged to a nursing home on 2 L oxygen.

DISCUSSION

PFO occurs in nearly 30% of the adult population^[1]. During the last decade, PFO and right-to-left shunting of venous blood has been linked to a number of disorders including cryptogenic headache, migraine and vascular headache, and decompression sickness with air embolism^[2-4]. Recent reports have documented that acute right-to-left inter-atrial shunt (ARLIAS) across PFO may cause profound and difficult-to-treat hypoxemia^[5-7]. This is often diagnosed unexpectedly during investigation for other causes of acute hypoxia. Echocardiography with bubble contrast remains the most sensitive, non-invasive and first line investigation for detection of ARLIAS^[5]. The data on closure of PFO for hypoxemia derives mainly from case reports and series. Successful closure in these cases demands not only an acceptable peri-procedural and long term risk (known as “procedural success”) but also a complete reversal of the shunt and resolution of hypoxemia (known as “clinical success”). A systematic review by Khairy *et al*^[7] in 2003 found that the incidence of major and minor complications of PFO closure was 1.5% and 7.9% respectively. Cardiac arrhythmias, device embolization, hemopericardium, right heart failure, transient ischemic attack and residual moderate to severe shunt are the known complications of device closure^[7-9]. The indication for transcatheter closure of PFO reviewed by Nguyen *et al*^[10] was for presumed paradoxical emboli. Over the last decade, there has been significant progress made in PFO closure terms of device technology, as well as the technique. Recently, a single-center, retrospective study of 104 patients undergoing PFO closure for systemic hypoxemia showed a good clinical safety as well as mechanical effectiveness of PFO closure using Amp-latzer Cribiform atrial septal defect Occluder or Helex

Septal Occluder.

The two prerequisite for development of ARLIAS are presence of an interatrial shunt such as PFO or less commonly, atrial septal defect and a functional component that promotes abnormal shunting of the blood through the shunt. This includes various cardiac or pulmonary insults such as pulmonary embolus, severe asthma and right ventricular infarction or coronary artery bypass grafting that raises right atrial pressure above left atrial pressure. Treatment of such precipitating factors may cause resolution of hypoxemia as evident in our patient. Hence, the shunting process may not be persistent, as a result of which, the atrial chamber pressures could have been normal in our patient at the time of catheterization. A similar case of hypoxemia, without a persistent right-to-left pressure gradient has been reported by Marples *et al*^[6]. As the underlying process progresses, a pressure gradient may develop across the PFO leading to right-to-left shunting. The process of shunting further worsens the hypoxia. This may tempt physicians to decide on PFO closure to correct the hypoxemia. However, such decision would have only invited more complications to our patient (such as right ventricular failure) and may not have been the right therapy for the patient's hypoxemia. Hence, it is necessary to carefully consider the risk-to-benefit ratio and give due importance to physiological considerations before deciding on percutaneous device closure as a treatment modality for hypoxemia. If a reversible trigger for development of acute right-to-left shunting exists, appropriate management of that process may alleviate the need for device closure and related complications as seen in our patient.

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P-Reviewer Vermeersch P **S-Editor** Gou SX
L-Editor A **E-Editor** Lu YJ



Multi-vessel percutaneous coronary intervention in a patient with a type B aortic dissection-transradial or transfemoral?

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Received: March 19, 2013 Revised: June 17, 2013

Accepted: July 4, 2013

Published online: July 26, 2013

nary intervention (PCI) in a patient with a chronic aortic dissection. There is a paucity of literature on this subject. This case discusses the possible mechanisms of dissection propagation with a transfemoral approach and highlights the need for training in both approaches. Decision making in choosing arterial access for PCI in patients with aortic dissection.

Hamid T, Choudhury TR, Fraser D. Multi-vessel percutaneous coronary intervention in a patient with a type B aortic dissection-transradial or transfemoral? *World J Cardiol* 2013; 5(7): 258-260
Available from: URL: <http://www.wjgnet.com/1949-8462/full/v5/i7/258.htm> DOI: <http://dx.doi.org/10.4330/wjc.v5.i7.258>

Abstract

Patients with chronic aortic dissections are at high risk of catheter-induced complications. We report a 41-year-old patient with a type B aortic dissection (Stanford) who underwent successful three-vessel percutaneous coronary intervention *via* the right radial artery approach following a non-ST elevation myocardial infarction. The patient remained asymptomatic at 6 mo follow-up. Trans-radial approach for coronary interventions can be used safely in patients with Stanford type B aortic dissection without increasing the risk of procedure-related complications in this high-risk group of patients.

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Key words: Aortic dissection; Type B; Percutaneous coronary intervention; Transfemoral

Core tip: The case highlights the use of a transradial approach to carry out multivessel percutaneous coro-

INTRODUCTION

A 41-year-old male patient was admitted with cardiac chest pain and elevated troponin. His 12 lead electrocardiogram showed widespread T wave inversion. A diagnosis of non-ST elevation myocardial infarction (NSTEMI) was made. He was known to have a chronic Stanford type B aortic dissection, extending in the descending aorta from beyond the left subclavian artery down to the abdominal aorta, and was under regular medical surveillance.

CASE REPORT

His cardiovascular risk factors included hypertension, hypercholesterolemia and smoking. He had been given standard NSTEMI treatment with dual antiplatelets (aspirin 300 mg and clopidogrel 300 mg) and low-molecular weight heparin (weight adjusted) at admission. While an inpatient, he had further cardiac chest pains and therefore, was transferred to the catheter-lab for cardiac catheterisation. Prior to

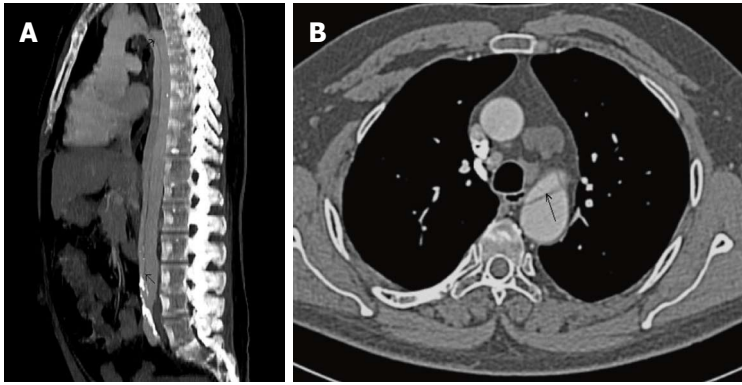


Figure 1 Computed tomography aorta. A: Sagittal view; B: Transverse view. Computed tomography aorta showing the chronic aortic dissection extending from the upper descending aorta down to the abdominal aorta. Arrows indicate dissection flap entry and exit points (A) and flap (B).

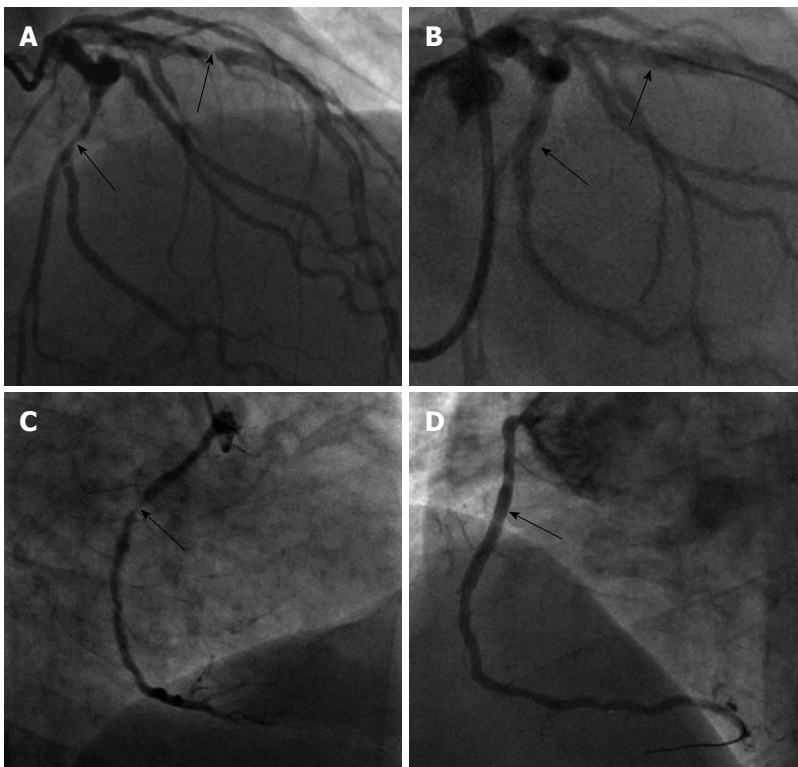


Figure 2 Coronary angiogram image. A: Lesions in left anterior descending (LAD), left circumflex (LCx). Coronary angiogram image showing severe lesions in LAD and LCx arteries (arrows); B: Percutaneous coronary intervention to LAD and LCx. Post-percutaneous coronary intervention (PCI) images showing successful PCI to lesions in LAD and LCx (arrows); C: Lesion in right coronary artery (RCA). Coronary angiogram image showing tight lesion in RCA (arrow); D: PCI to RCA. Successful PCI to RCA with a DES (arrow).

the procedure, he received further loading with clopidogrel 300 mg. During the procedure, he received weight adjusted unfractionated heparin intravenously. The decision to use standard acute coronary syndrome (ACS) peri-procedural therapy was made in view of the fact that the patient had been stable from his chronic aortic dissection and that his recent electronic computer X-ray tomography technique (CT) of the aorta showed no extension of his dissection (Figure 1). Informed consent was obtained prior to the percutaneous coronary intervention.

The coronary diagnostic procedure was performed *via* the right radial artery approach. Five French JR4[®] and JL 3.5[®] diagnostic catheters were used for the right and left coronary systems respectively. This confirmed a normal left main stem. The left anterior descending (LAD), left circumflex (LCx) and right coronary artery (RCA) had severe mid-vessel lesions (Figure 2A and C). Due to the complexity of the case, it was decided to treat all three lesions at the same procedure.

A Medtronic Launcher EBU 5.0 (6F)[®] (Medtronic) guide catheter was used to cannulate the left system. Two 0.014" BMW[®] guidewires (Abbott Vascular) were advanced to the distal LAD and LCx. The lesion in the LAD was directly stented using a 4.0 mm × 15 mm Resolute Integrity[®] drug eluting stent (DES) (Medtronic). The LCx lesion was pre-dilated using a 2 mm × 15 mm Maverick Balloon[®] (Boston Scientific), followed by a 2.75 mm × 22 mm Resolute Integrity[®] DES.

An Amplatz (AL2) guide catheter was used to cannulate the RCA. A 0.014" BMW[®] guidewire was advanced to the distal RCA. The lesion was pre-dilated with a 2.0 mm × 15 mm Maverick Balloon[®] followed by a 3.0 mm × 22 mm Resolute Integrity[®] DES. Excellent final angiographic results were obtained (Figure 2B and D). A Terumo TR band[®] (Terumo) was deployed to the radial access site at the end of procedure. There were no peri or post procedure complications. A total of 300 mL contrast (Visipaque[®]) and 7000 units heparin were given. His

repeat blood tests including haemoglobin, urea, creatinine and electrolytes were normal post-procedure. The patient made an uneventful recovery and was discharged a few days later on dual antiplatelets (aspirin 75 mg and clopidogrel 75 mg daily) and standard secondary prevention. He was instructed to continue on dual antiplatelets for 1 year and aspirin for lifelong thereafter.

DISCUSSION

Aortic dissection can be classified according to the location of the dissection and the relevance to patient management. The commonly used Stanford classification distinguishes aortic dissections by whether the ascending aorta is involved (type A) or not (type B)^[1]. The incidence of aortic dissection in the general population is approximately 2.6-3.5 per 100000 person-years^[2,3]. In a study by Islamoglu *et al*^[4], 11 of 76 patients with aortic dissection (acute and chronic) ie 14.5% had concomitant coronary artery disease. However, none of the chronic type B dissection patients who underwent coronary angiography had coronary artery disease. CT angiography allows the fast and reliable detection of aortic dissections and delineation of the dissection flap anatomy.

Since the introduction of trans-radial coronary angioplasty^[5], procedural success rates have evolved remarkably and complex coronary artery lesions can be treated with minimal complications. Our patient had a chronic Stanford type B aortic dissection. A transfemoral approach would carry a high risk of complicating the existing dissection. Hildick-Smith *et al*^[6] published a large case series looking at transradial coronary angiography in patients with contraindications to a femoral approach. Of 500 patients in that series, 10 patients had aortic dissection and had a transradial approach. However, there is no series looking solely at patients with aortic dissection and the best approach for PCI. Furthermore, there is a paucity of literature discussing the possible mechanisms of catheter-related complications in relation to aortic dissections in cases similar to ours. Mechanisms would include entry of the catheter tip into the false lumen. Using a femoral approach, this could happen at the exit site of the existing dissection. Continued advancement of the catheter would then risk propagation of the dissection into the ascending aorta as well as rupture of the vessel. Additional risks would include catheter entry into the false lumen *via* puncturing the wall between the true and false lumens. In our patient, to avoid these potential complications, we safely used the right trans-radial approach for three-vessel PCI without any procedural complications. This would appear to be the ideal approach in patients with Stanford type B aortic dissections as it avoids the descending aorta and thus, the potential to worsen an existing dissection. However, a radial approach is not without risk of aortic

dissections. Indeed, there are case reports of iatrogenic aortic dissections due to aggressive catheter manipulation during PCI *via* a radial approach^[7]. Furthermore, in patients with aberrant right subclavian artery (arteria lusoria), PCI *via* a right radial approach can be extremely difficult and there are reports of iatrogenic aortic dissections during such procedures^[8].

This case highlights the importance of choosing the right access approach in patients with a complicated background like ours. It also highlights the importance of training interventionalists in both the transradial and transfemoral approaches as each has its own merits and is sometimes the only feasible approach in certain patient groups.

In conclusion, trans-radial approach for coronary interventions can be used safely in patients with Stanford type B aortic dissection without increasing the risk of procedure-related complications in this high-risk group of patients.

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P- Reviewers Abdel razek AAK, Hung MJ, Panduranga P, Said S, Vermeersch P **S- Editor** Gou SX **L- Editor** A **E- Editor** Lu YJ



Berberine behind the thriller of marked symptomatic bradycardia

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Received: April 23, 2013

Revised: June 7, 2013

Accepted: June 18, 2013

Published online: July 26, 2013

Abstract

Berberine is used in traditional Chinese medicine for the treatment of congestive heart failure, hypertension, diabetes, and dyslipidaemia and has a good safety profile. We report a case of a 53-year-old sportsman referred to our hospital for the onset of fatigue and dyspnoea upon exertion after he started berberine to treat hypercholesterolaemia. An electrocardiogram showed sinus bradycardia (45 bpm), first-degree atrioventricular block, and competitive junctional rhythm. An ergometric stress test showed slightly reduced chronotropic competence and the presence of runs of competitive junctional rhythm, atrial tachycardia, and sinus pauses in the recovery. After 10 d of wash-out from berberine, the patient experienced a complete resolution of symptoms, and an ergometric stress test showed good chronotropic competence. An electrocardiogram Holter

showed a latent hypervagotonic state. This is the first case report that shows that berberine could present certain side effects in hypervagotonic people, even in the absence of a situation that could cause drug accumulation. Therefore, berberine's use should be carefully weighed in hypervagotonic people due to the drug's bradycardic and antiarrhythmic properties, which could become proarrhythmic, exposing patients to potential health risks.

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Key words: Berberine; Bradyarrhythmia; Side effect; Hypervagotonia; Hypercholesterolaemia; Electrocardiogram

Core tip: Berberine is widely used in traditional Chinese medicine for the treatment of congestive heart failure, hypertension, diabetes, and dyslipidaemia. We report a case of marked symptomatic sinus bradycardia with competitive junctional rhythm caused by berberine, showing that berberine, due to its antiarrhythmic properties, can cause the onset of bradyarrhythmia. In this case report, we focus on the possible side effects of so-called natural medicine based on holistic, home, and herbal remedies, which is considered to be safe only because the treatment is natural. However, under certain conditions, natural medicine can lead to potential health risks in patients.

Cannillo M, Frea S, Fornengo C, Toso E, Mercurio G, Battista S, Gaita F. Berberine behind the thriller of marked symptomatic bradycardia. *World J Cardiol* 2013; 5(7): 261-264 Available from: URL: <http://www.wjgnet.com/1949-8462/full/v5/i7/261.htm> DOI: <http://dx.doi.org/10.4330/wjc.v5.i7.261>

INTRODUCTION

Berberine is an alkaloid from *Hydrastis canadensis* L., the

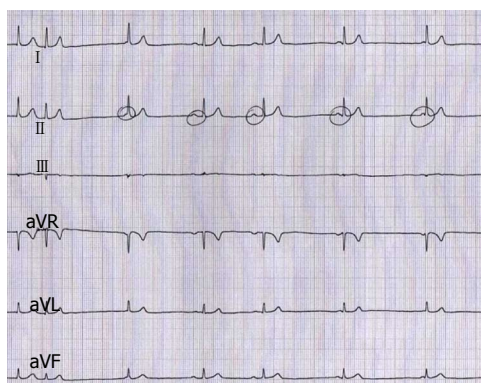


Figure 1 Competitive junctional rhythm.

Chinese herb Huang Lian, and many other plants. Berberine is widely used in traditional Chinese medicine for the treatment of congestive heart failure^[1-3], hypertension^[3], diabetes, and dyslipidaemia^[4-5]. Berberine has multiple cardiovascular effects, including negative chronotropic, antiarrhythmic and vasodilatory properties^[1,2] and an anti-inflammatory effect^[6]. Several cardiovascular effects of berberine are attributed to the blockade of K⁺ channels [delayed rectifier and K(ATP)], the stimulation of Na⁺-Ca⁽²⁺⁾ exchangers^[2,7], and the activation of cardiac M2 muscarinic cholinergic receptors^[8].

Berberine has been tested in acute coronary syndrome patients following percutaneous coronary intervention (PCI)^[6], in congestive heart failure secondary to ischemic or idiopathic dilated cardiomyopathy^[3], in menopausal women^[9], in elderly hypercholesterolaemic patients^[10], and in patients with metabolic syndrome^[11], offering various therapeutic strategies without evidence of side effects.

CASE REPORT

We report a brief case that shows that berberine could cause side effects under specific conditions.

A 53-year-old man was referred to the emergency room of our hospital after the onset of fatigue and dyspnoea upon exertion, with evidence of bradycardia. He was overweight and hyperlipidaemic and used to swim three times per week. His medical history was unremarkable, except that he had started berberine 6 d before to treat hypercholesterolaemia. Upon physical examination, the patient presented a normal blood pressure and oxygen saturation but an irregular heart rate of 50 bpm. He did not present signs of heart failure, and cardiac, pulmonary, and vascular examinations were normal. The electrocardiogram (ECG) showed sinus bradycardia with a heart rate of 45 bpm, first-degree atrioventricular block (PR interval of 280 ms), and a competitive junctional rhythm at 55 bpm (Figure 1). Both blood analysis and echocardiography did not show any justification for the marked bradycardia. An overdose of berberine was ruled out because the patient consumed the correct daily dose. Because berberine excretion is hepatobiliary^[12], the presence of any predisposing factor for reduced excretion,

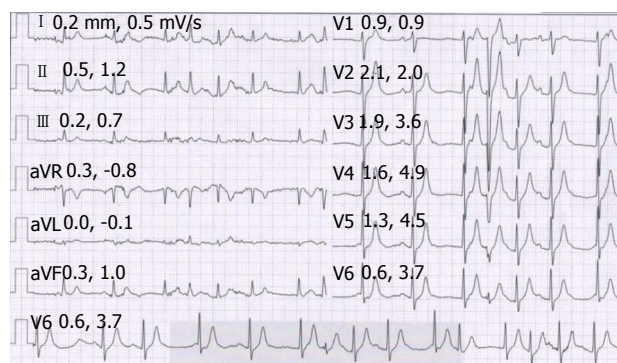


Figure 2 Junctional beats, premature supraventricular beats, sometimes aberrant starting brief runs of atrial tachycardia.

such as hepatic or biliary disease, was examined and ruled out.

Given the bradycardic and antiarrhythmic properties of berberine, we decided to discontinue the drug, and based on the presence of dyspnoea upon exertion, an ergometric stress test was performed to evaluate chronotropic competence. A 24-h wash-out from berberine was sufficient before the test, as berberine's half-life is less than 30 min^[12]. The ergometric stress test showed slightly reduced chronotropic competence, with an increase in the heart rate from 45 bpm to 127 bpm, equivalent to 76% of the maximal prediction. The test also showed a reduction in the atrioventricular conduction delay, with a PR that reached 180 ms for a heart rate of 127 bpm. The patient presented a good functional class (the test was stopped at the second minute of the step second Bruce protocol, METs 13.5). The recovery was characterised by the presence of runs of competitive junctional rhythm; premature supraventricular beats that were occasionally aberrant, sporadically starting brief runs of atrial tachycardia (Figure 2); and a sinus pause with an RR of a maximum of 1.7 s (Figure 3A). Most likely, the patient's symptoms were not closely related to bradycardia at rest but rather to the loss of AV synchronisation during the junctional rhythm and to the reduction in chronotropic competence during stress.

Over the following days, the patient experienced a complete resolution of symptoms and performed normal life activities and his usual sport activity (swimming) without experiencing dyspnoea or fatigue. After 10 d of wash-out from berberine, he underwent a new ergometric stress test and an ECG Holter. The ergometric stress test was normal. The ECG at rest was characterised by the presence of sinus bradycardia with a heart rate of 43 bpm and first-degree atrioventricular block (PR at rest of 280 ms), as presented several days before. However, the test presented better chronotropic competence. The test was maximal (86% of the predicted heart rate), despite the patient having reached the same workload as in the first test. The presence of first-degree atrioventricular block was consistent with a PR interval normalised at a high rate.

During the ECG-Holter monitoring, we observed a

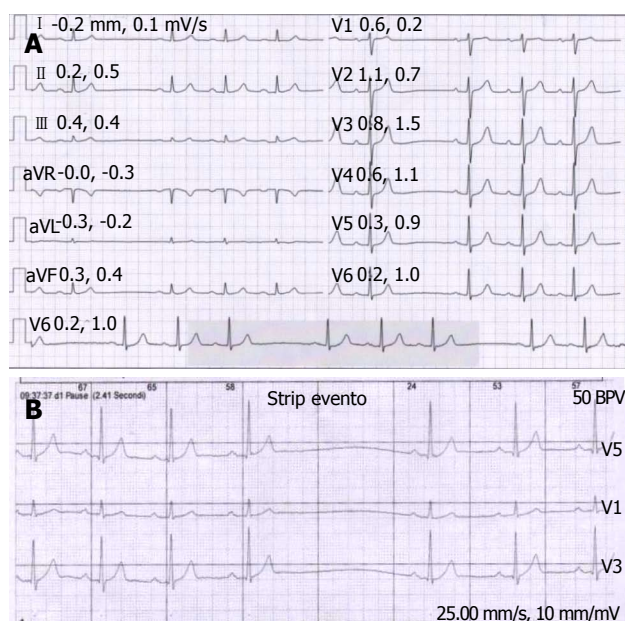


Figure 3 Sinus pause. A: With an RR of max 1.7 s; B: With an RR 2.4 s.

sight typical of a hypervagotonic state: bradycardial sinus rhythm with normal variation of the heart rate with a circadian cycle and physical activity (FC maximum 104, average 56, minimum 40 bpm); several nocturnal runs of sinus bradycardia at 30 bpm; and several, especially nocturnal sinus pauses, with an RR interval of 2.4 s (Figure 3B).

The patient continued to be asymptomatic and to practice his normal life and sport activities and treated his dyslipidaemia with diet.

DISCUSSION

This is the first case report that shows that berberine could present certain side effects in hypervagotonic people, even in the absence of a situation that could cause drug accumulation. Indeed, berberine has been found to have a good safety profile^[2,3,5,6,9-11] in patients with pathological conditions characterised by a hyperadrenergic state, such as acute coronary syndrome^[13], heart failure^[14,15], diabetes^[16], hypertension^[17], and menopause^[18]. In a murine model, it has been proven that berberine reduces plasma adrenaline and noradrenaline levels^[19]. We do not know whether the bradycardic and antiarrhythmic properties of berberine are vagally mediated by the activation of muscarinic receptors, as shown by Salehi *et al.*^[8], or are not vagally mediated, as reported by Shaffer^[20]. However, it is possible that in hypervagotonic people with marked sinus bradycardia, berberine's bradycardic effect can induce the onset of competitive junctional rhythm, causing a loss of atrioventricular synchronisation, and can reduce chronotropic competence with the onset of symptoms upon exertion. Therefore, berberine's use should be carefully weighed in hypervagotonic people due to the drug's bradycardic and antiarrhythmic proper-

ties, which could become proarrhythmic, exposing patients to potential health risks.

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P- Reviewers De Ponti R, Alzand BSN **S- Editor** Wen LL
L- Editor A **E- Editor** Lu YJ



Non-coronary myocardial infarction in myasthenia gravis: Case report and review of the literature

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Received: April 17, 2013 Revised: June 10, 2013

Accepted: July 4, 2013

Published online: July 26, 2013

Key words: Myasthenia gravis; Myocardial infarction; Pyridostigmine

Core tip: Cardiovascular adverse events in patients with myasthenia gravis (MG) are rare, but the early recognition of such events is crucial. We describe a case of a non-coronary myocardial infarction during the initial treatment period with pyridostigmine bromide in a female patient with MG. In this case report possible causes of myocardial adverse events in the context of MG, which may occur during the ongoing treatment and the clinical course of the disease, are discussed.

Zis P, Dimopoulos S, Markaki V, Tavernarakis A, Nanas S. Non-coronary myocardial infarction in myasthenia gravis: Case report and review of the literature. *World J Cardiol* 2013; 5(7): 265-269
Available from: URL: <http://www.wjgnet.com/1949-8462/full/v5/i7/265.htm> DOI: <http://dx.doi.org/10.4330/wjc.v5.i7.265>

Abstract

Cardiovascular adverse events in patients with myasthenia gravis (MG) are rare, but the early recognition of such events is crucial. We describe a case of a non-coronary myocardial infarction (MI) during the initial treatment period with pyridostigmine bromide in a female patient with MG. Clinicians should be cautious about the appearance of potential MI in patients with MG. A baseline electrocardiogram is advocated, when the early recognition of the MI clinical signs and the laboratory findings (myocardial markers) are vital to the immediate and appropriate management of this medical emergency, as well as to prevent future cardiovascular events. In this case report possible causes of myocardial adverse events in the context of MG, which may occur during the ongoing treatment and the clinical course of the disease, are discussed.

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INTRODUCTION

Myasthenia gravis (MG) is a neuromuscular disorder characterized by weakness and fatigability of skeletal muscles. The number of available acetylcholine receptors at the neuromuscular junction is decreased because of an antibody-mediated autoimmune attack. Anticholinesterase medications are widely used to treat MG as they act by blocking hydrolysis of acetylcholine by acetylcholinesterase, consequently allowing acetylcholine to interact repeatedly with the limited number of acetylcholine receptors^[1]. Apart from their muscarinic side effects, it has been shown that they can rarely cause cardiovascular side effects^[2,3].

CASE REPORT

A 71-year-old female patient presented with a 4-wk his-

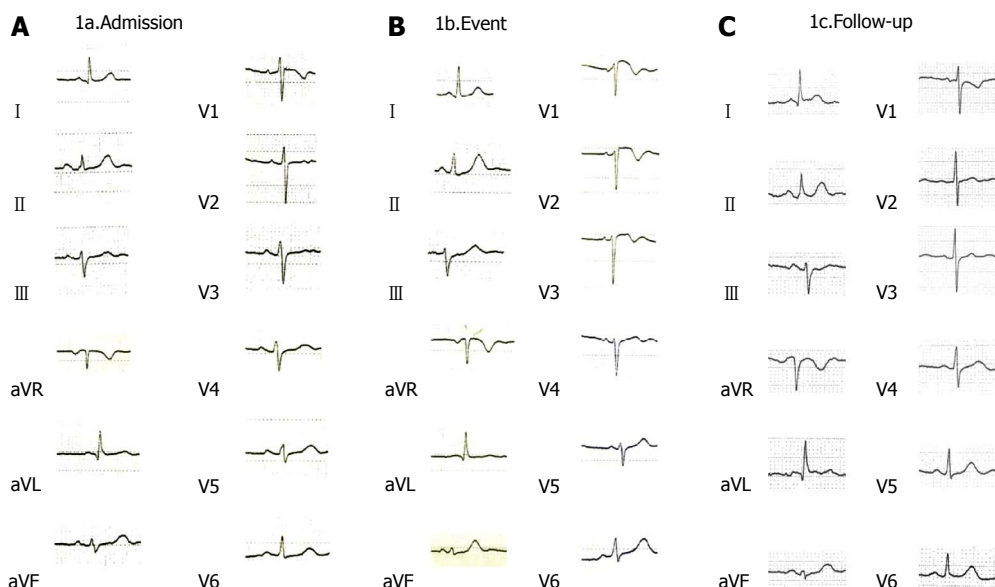


Figure 1 The electrocardiogram. A: A 12-lead standard electrocardiogram (ECG) of the patient at hospital admission; B: At 10th day after admission. An ST elevation in leads V1-V2 and T-wave abnormalities can be noted; C: In the repeat ECG, all changes noted in the abnormal ECG have resolved, as can be noted.

tory of worsening dysphagia and dysarthria. The edrophonium test that was performed in the emergency department was positive and therefore she was admitted to the Department of Neurology for further investigation and management. Past medical history included arterial hypertension well controlled on carvedilol and diet controlled dyslipidaemia. There was no history of diabetes, smoking or alcohol abuse. The rest of the medical history included a hip replacement surgery 12 mo prior to the current admission, which was complicated by deep venous thrombosis for which she received oral anticoagulant therapy for 12 mo. Finally, she was receiving a low-dose benzodiazepine on an as-required basis for anxiety disorder.

On admission the patient was alert and orientated with normal observations (blood pressure 140/74 mmHg, pulse 94/min, saturation 96% on FiO₂ 21%). The electrocardiogram (ECG) revealed no signs of ischemia (Figure 1) and routine blood and biochemical tests were within normal values [haemoglobin 15.0 g/dL, serum glucose 83 mg/dL, urea 47 mg/dL, creatinine 0.76 mg/dL, aspartate aminotransferase (AST) 32 IU/L, alanine aminotransferase 16 IU/L, potassium 5.0 mmol/L, sodium 136 mmol/L]. Thyroid hormones were within normal limits. Neurological examination revealed mild proximal weakness in all four limbs, dysphagia and nasal speech. Physical examination was otherwise unremarkable.

A diagnosis of MG was confirmed by positive rapid decremental responses of muscle action potentials to repetitive nerve stimulation and an elevated anti-acetylcholine receptor antibody count (titer 135 nmoles/L, normal values < 0.5 nmoles/L). Pyridostigmine bromide 60 mg tds and prednisolone, 10 mgs OD were commenced to treat MG.

Three days later muscarinic side effects such as diarrhea, abdominal cramps and salivation appeared while

there was a significant improvement in neurological examination with regards to dysarthria and dysphagia. On the 4th day the patient complained of chest pain (with a duration of less than 30 min) accompanied by an intense sense of discomfort (emotional stress similar to an acute panic attack). There were no changes in the ECG and serial measurements of troponin, creatine kinase (CK), CK-MB, AST, lactate dehydrogenase (LDH) and ProBNP levels were normal.

However, the frequency of such episodes of chest pain was increased from one every two days to twice a day and on day 10th the ECG revealed ST elevation in leads V1-V2 and T-wave abnormalities (Figure 1) with a subsequent significant elevation in troponin and ProBNP level (Figure 2). At that point blood pressure was 160/80 mmHg, pulse 69/min and oxygen saturation 96% (on oxygen nasal cannula, 2 L/min). Chest radiography was within normal limits, D-dimers were within normal values and the arterial blood gases did not show hypoxaemia and hypocapnia consistent with pulmonary embolism, therefore the latter was highly unlikely in our differential diagnoses. A subsequent spiral chest CT, with intravenous contrast, performed a few days later confirmed that there was no evidence of pulmonary embolism.

Based on the ECG and the increase in troponin and ProBNP levels a diagnosis of myocardial infarction (MI) was made and the patient was transferred to the intensive coronary care unit where treatment with nitrates, aspirin, clopidogrel and heparin was initiated. The cardiac ultrasound showed concentric hypertrophy of the left ventricle (left ventricle ejection fraction 55%) with anteroseptal hypokinesia and type I diastolic dysfunction.

The chest pain resolved within hours. The patient underwent coronary angiography a few days later (as she did not consent to the procedure in the acute phase), which

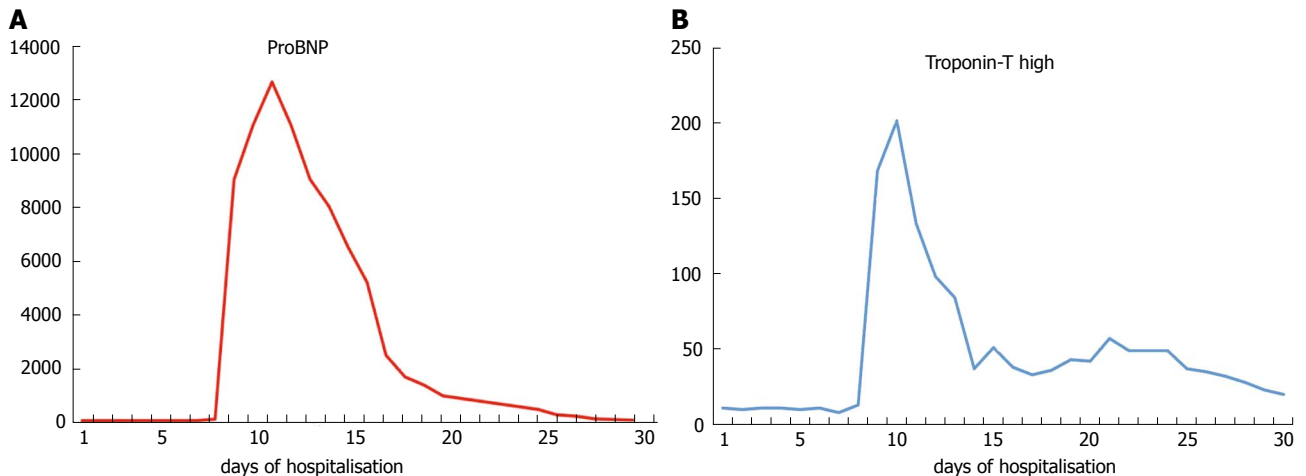


Figure 2 The frequency of such episodes of chest pain was increased. A: ProBNP; B: Troponin-T. ProBNP, troponin-T high levels during clinical presentation of patient's symptomatology. In Y axis, both ProBNP and troponin are measured in pg/mL (normal values; ProBNP < 150 pg/mL, troponin < 14 pg/mL).

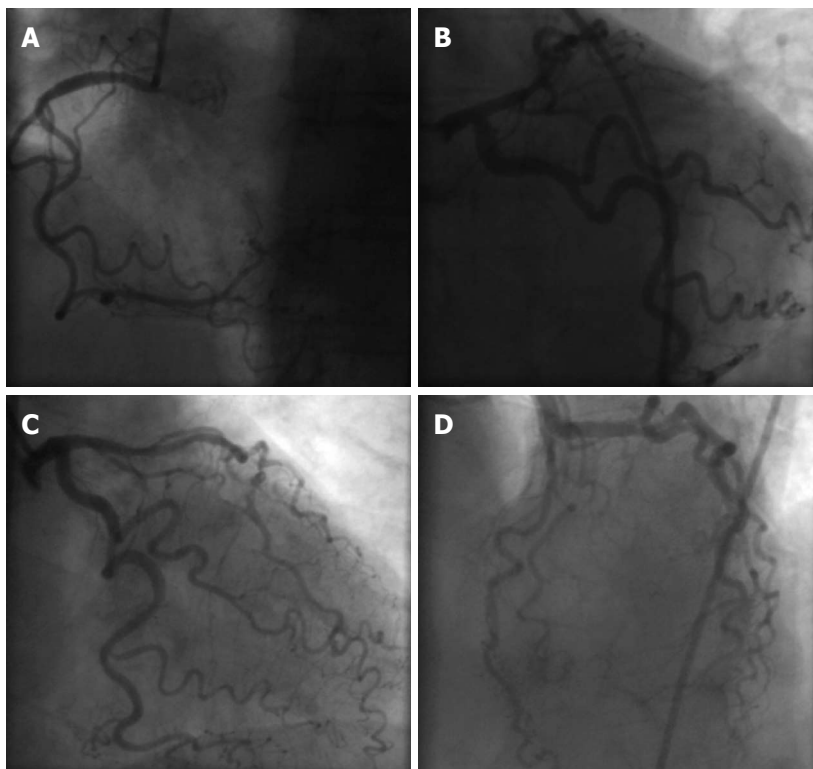


Figure 3 A normal coronary angiography performed at the patient. A: Right coronary artery; B: Left coronary artery; C: Left coronary artery-right anterior oblique; D: Left coronary artery-left anterior oblique.

revealed a normal right coronary artery and a narrowing of less than 30% in the left anterior descending (Figure 3). Moreover, serial measurements of CK, AST and LDH did not show significant variation. The patient remained afebrile and the C-reactive protein and erythrocyte sedimentation rate values were normal.

During her hospital stay the patient was further investigated with chest axial computed tomography, which revealed a type A thymoma (N1M0) that was successfully surgically removed. Because of the initial difficulty in weaning from the mechanical ventilation a tracheostomy was performed and she was transferred to the medical intensive care unit. Her pyridostigmine dose was gradually

reduced and was eventually stopped. The patient continued to receive only prednisolone in a high dose (75 mg/d), which was gradually reduced to 30 mg once daily.

The patient presented with weakness acquired during the intensive care unit (ICU) stay, which was gradually improved, tracheostomy was removed and she was discharged from the hospital in a generally good clinical condition. The neurological examination for MG was unremarkable at hospital discharge.

However, one month later, while she was in a sitting position, talking with her relatives she had a sudden cardiac death as reported from the last phone follow-up communication.

DISCUSSION

We present a case of a non-coronary MI in a patient with MG. A non-coronary MI, defined alternatively as a MI with normal coronary arteries, is a medical condition, which has been described in the literature for more than 30 years^[4]. Its prevalence varies between 1% and 12% depending on the definition of “normal” coronary arteries, which usually includes no luminal irregularities (strict definition) or arteries with some degree of stenosis (less than 30%)^[5-7].

Patients with MG under treatment complain frequently of the anticholinesterase medications muscarinic side effects, including diarrhea, abdominal cramps, salivation and nausea. However, cardiovascular adverse events in MG are rare. They occur mainly as a consequence of the MG treatment and less frequently in the context of a MG crisis through a possible immunological mechanism.

To the best of our knowledge three cases of cardiovascular side effects in patients with myasthenia gravis induced by anticholinesterase medication have been reported so far; a case of coronary spastic angina induced by ambenonium chloride^[2], a case of coronary spastic angina induced by distigmine bromide^[3] and a case of coronary vasospasm secondary to hypercholinergic crisis caused by pyridostigmine^[8]. Cases of coronary vasospasm have also been described in anaesthetic practice where anticholinesterases are used to reverse the action of non-depolarizing muscle relaxants^[9].

The exact mechanism under which cardiovascular side effects during treatment with acetylcholinesterase inhibitors occur remains unknown. However, it is well recognized that the coronary artery response to acetylcholine is very sensitive, constricting abnormally when the endothelium is damaged, in contrast to normal coronary arteries showing coronary vasodilation by acetylcholine^[2]. One possible mechanism is that since pyridostigmine inhibits acetylcholinesterase in the synaptic cleft, thus slowing down the hydrolysis of acetylcholine and increasing the attachment of acetylcholine to the limited acetylcholine receptors, the exposure of coronary artery to acetylcholine might be increased. Furthermore, the use of prednisone decreases the anti-acetylcholine receptor antibody and enhances the effect of pyridostigmine^[2].

In MG cardiovascular side effects can also occur during intravenous immunoglobulin infusion (IVIg). IVIg has been associated with several possible adverse reactions including induction of a hypercoagulable state. IVIg-induced hypercoagulability has been associated with both non-ST elevation myocardial infarction^[10] and ST elevation myocardial infarction^[11]. The risk of acute MI seems to be increased with the use of high-dose IVIg in older individuals as well, especially those with at least one cardiovascular risk factor^[12,13]. Takotsubo cardiomyopathy has also been observed in a patient during plasmapheresis treatment for myasthenic crisis^[14]. In our case, the cardiac ultrasound during the MI did not show any contractile dysfunction suggestive of Takotsubo cardiomyopathy.

Moreover, in our case the patient neither received IVIg nor did she undergo plasmapheresis.

Previous case studies have indicated a possible link between MG and cardiovascular disorders^[15-18]. It has also been suggested that myocarditis may occur in MG through the effects of striational muscle antibodies that cross-react with both skeletal muscles and myocardial tissue^[16]. However, our patient remained afebrile, C-reactive protein and CK levels were normal and ECG did not show diffuse T-wave inversion. For these reasons myocarditis was an extremely unlikely diagnosis of our case.

In a recent case report it was shown that acute emotional stress may be a triggering factor for both Takotsubo cardiomyopathy and MG crisis^[19], the mechanisms, however, remain unclear. In our case report acute emotional stress was involved in myocardial infarction presentation and might also have been a triggering factor even though contrary to that case report^[19] a MG crisis was not manifested. The exact role of emotional stress is unclear in our case presentation as emotional stress can be both a precipitant and a consequence of the MI itself in a patient with a history of an anxiety disorder.

As our patient was haemodynamically stable with normal arterial blood gases, no evidence of sepsis and no anaemia, we believe that her MI did not occur because of demand ischemia but due to coronary vasospasm. The time interval between treatment initiation with pyridostigmine bromide and the myocardial infarction suggests that there may be a link between the two events. Moreover, apart from the pyridostigmine and the prednisolone there were no other changes in our patient's drug regime. The subsequent sudden death of the patient, however, occurred while she was not on pyridostigmine and is, therefore, against this hypothesis.

The coronary slow flow phenomenon is characterized by angiographically normal coronary arteries with delayed opacification of the distal vasculature^[20]. Although slow coronary flow can induce abortive sudden death^[21] our patient did not have risk factors such as smoking that could have caused endothelial dysfunction. Further studies are needed to explore a possible pathophysiological link between MG and non-coronary MI.

Limitations

Our patient suffered a sudden cardiac death a few months after the first MI while she was not on pyridostigmine bromide but only on prednisolone. Unfortunately, autopsy was not performed to identify the exact cause of death and to identify whether the two incidents, the MI and the cardiac death, share a common pathophysiological mechanism. However, being on prednisone, which decreases the antiacetylcholine receptor antibody levels, might have still induced an iatrogenic hypercholinergic crisis. Another possible explanation is that a sudden arrhythmic cardiac event (ventricular fibrillation/ventricular tachycardia) may be the cause of sudden death due to the recent history of MI.

We excluded Takotsubo cardiomyopathy based on the cardiac ultrasound, which did not show any relevant con-

tractile dysfunction. However, we did not perform a ventriculography to confirm this. Moreover, we have ruled out pulmonary embolism based on the normal arterial blood gases and D-dimers titer, which was normal. The spiral chest CT, with intravenous contrast, that took place few days later was normal.

Finally, we did not measure anti-striatal antibodies and we did not perform a magnetic resonance scan of the heart, so we cannot rule out the possibility that MG had an indirect autoimmune adverse effect in the myocardial tissue of our patient; however, the presence of these antibodies have not been associated with an isolated myocardial infarction so far. Despite the fact that we cannot exclude that the MG itself has been involved with the non-coronary MI, the patient, at the time of the MI, was stable with regards to the MG symptoms and as she was not in MG crisis, and therefore the link between MG and MI is less likely.

In conclusion, we describe a case of a non-coronary MI during the initial treatment period with pyridostigmine bromide in a female patient with MG. Clinicians should be cautious about the appearance of potential MI in patients with MG. A baseline ECG is advocated, when the early recognition of the MI clinical signs and the laboratory findings (myocardial markers) are vital to the immediate and appropriate management of this medical emergency, as well as to prevent future cardiovascular events.

ACKNOWLEDGEMENTS

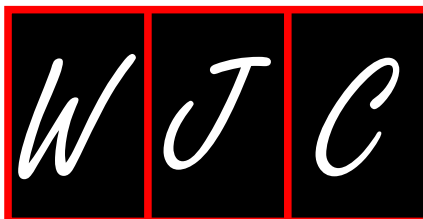
We express gratitude to the patient's family. We would also like to thank Dr. Elli Kontogeorgi and Dr. Dimitrios Karakalos for their helpful contribution to the clinical management of the patient. Finally, we are sincerely thankful to Dr. Rosie Rogers, for the language revision of the manuscript.

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Name of journal

World Journal of Cardiology

ISSN

ISSN 1949-8462 (online)

Launch date

December 31, 2009

Frequency

Monthly

Instructions to authors

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Publisher

Baishideng Publishing Group Co., Limited

Flat C, 23/F, Lucky Plaza, 315-321 Lockhart Road,

Wan Chai, Hong Kong, China

Fax: +852-65557188

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Acknowledgments

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Format

Journals

English journal article (list all authors and include the PMID where applicable)

- 1 **Jung EM**, Clevert DA, Schreyer AG, Schmitt S, Rennert J, Kubale R, Feuerbach S, Jung F. Evaluation of quantitative contrast harmonic imaging to assess malignancy of liver tumors: A prospective controlled two-center study. *World J Gastroenterol* 2007; **13**: 6356-6364 [PMID: 18081224 DOI: 10.3748/wjg.13.6356]

Chinese journal article (list all authors and include the PMID where applicable)

- 2 **Lin GZ**, Wang XZ, Wang P, Lin J, Yang FD. Immunologic effect of Jianpi Yishen decoction in treatment of Pixu-diarhoea. *Shijie Huaren Xiaobua Zazhi* 1999; **7**: 285-287

In press

- 3 **Tian D**, Araki H, Stahl E, Bergelson J, Kreitman M. Signature of balancing selection in Arabidopsis. *Proc Natl Acad Sci USA* 2006; In press

Organization as author

- 4 **Diabetes Prevention Program Research Group**. Hypertension, insulin, and proinsulin in participants with impaired glucose tolerance. *Hypertension* 2002; **40**: 679-686 [PMID: 12411462 PMID:2516377 DOI:10.1161/01.HYP.0000035706.28494.09]

Both personal authors and an organization as author

- 5 **Vallancien G**, Emberton M, Harving N, van Moorselaar RJ; Alf-One Study Group. Sexual dysfunction in 1, 274 European men suffering from lower urinary tract symptoms. *J Urol* 2003; **169**: 2257-2261 [PMID: 12771764 DOI:10.1097/01.ju.0000067940.76090.73]

No author given

- 6 21st century heart solution may have a sting in the tail. *BMJ* 2002; **325**: 184 [PMID: 12142303 DOI:10.1136/bmj.325.7357.184]

Volume with supplement

- 7 **Geraud G**, Spierings EL, Keywood C. Tolerability and safety of frovatriptan with short- and long-term use for treatment of migraine and in comparison with sumatriptan. *Headache* 2002; **42** Suppl 2: S93-99 [PMID: 12028325 DOI:10.1046/j.1526-4610.42.s2.7.x]

Issue with no volume

- 8 **Banit DM**, Kaufer H, Hartford JM. Intraoperative frozen section analysis in revision total joint arthroplasty. *Clin Orthop Relat Res* 2002; (**401**): 230-238 [PMID: 12151900 DOI:10.1097/00003086-200208000-00026]

No volume or issue

- 9 Outreach: Bringing HIV-positive individuals into care. *HRS-A Careaction* 2002; 1-6 [PMID: 12154804]

Books

Personal author(s)

- 10 **Sherlock S**, Dooley J. Diseases of the liver and biliary system. 9th ed. Oxford: Blackwell Sci Pub, 1993: 258-296

Chapter in a book (list all authors)

- 11 **Lam SK**. Academic investigator's perspectives of medical treatment for peptic ulcer. In: Swabb EA, Azabo S. Ulcer disease: investigation and basis for therapy. New York: Marcel Dekker, 1991: 431-450

Author(s) and editor(s)

- 12 **Breedlove GK**, Schorheide AM. Adolescent pregnancy. 2nd ed. Wiczorek RR, editor. White Plains (NY): March of Dimes Education Services, 2001: 20-34

Conference proceedings

- 13 **Harnden P**, Joffe JK, Jones WG, editors. Germ cell tumours V. Proceedings of the 5th Germ cell tumours Conference; 2001 Sep 13-15; Leeds, UK. New York: Springer, 2002: 30-56

Conference paper

- 14 **Christensen S**, Oppacher F. An analysis of Koza's computational effort statistic for genetic programming. In: Foster JA, Lutton E, Miller J, Ryan C, Tettamanzi AG, editors. Genetic programming. EuroGP 2002: Proceedings of the 5th European Conference on Genetic Programming; 2002 Apr 3-5; Kinsdale, Ireland. Berlin: Springer, 2002: 182-191

Electronic journal (list all authors)

- 15 Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis serial online, 1995-01-03, cited 1996-06-05; 1(1): 24 screens. Available from: URL: <http://www.cdc.gov/ncidod/eid/index.htm>

Patent (list all authors)

- 16 **Pagedas AC**, inventor; Ancel Surgical R&D Inc., assignee. Flexible endoscopic grasping and cutting device and positioning tool assembly. United States patent US 20020103498. 2002 Aug 1

Statistical data

Write as mean \pm SD or mean \pm SE.

Statistical expression

Express *t* test as *t* (in italics), *F* test as *F* (in italics), chi square test as χ^2 (in Greek), related coefficient as *r* (in italics), degree of freedom as *ν* (in Greek), sample number as *n* (in italics), and probability as *P* (in italics).

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