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Original article

Effect of spironolactone on ventricular arrhythmias in patients with left ventricular systolic dysfunction and implantable cardioverter defibrillators

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ABSTRACT

Aims/objectives: Patients with implantable cardioverter defibrillators (ICD) often receive an adjunctive anti-arrhythmic therapy. We propose that an addition of spironolactone will reduce the number of clinically significant ventricular arrhythmias and ICD-related therapies.

Methods and results: In a multicentre retrospective study, 64 patients with ischaemic and non-ischaemic dilated cardiomyopathy whose left ventricular ejection fraction (LVEF) was <35% and with ICD were selected. Amongst these patients, 28 patients were on spironolactone and 36 were not taking spironolactone. The ICD interrogation data were analysed for a maximum of 12 months. Wilcoxon Rank Sum test was used to compare the study and control groups. The outcomes were: (1) the number of shocks/anti-tachycardia pacing (ATP) episodes and (2) the number of episodes of ventricular tachycardia (VT) requiring ATP, non-sustained VT (NSVT), and ventricular fibrillation (VF) over the study period. The spironolactone group had fewer monthly VTs (P=0.027) (requiring ATP). The two groups did not differ in the number of NSVT or VF per month.

Conclusion: Addition of spironolactone as an adjunct to ICD therapy in patients with congestive heart failure (CHF) reduces VT requiring ATP, but does not affect NSVT or VF per month.

KEYWORDS

Aldosterone antagonists
ICD shocks
Implantable cardioverter defibrillators (ICDs)
Spironolactone
Ventricular tachycardia (VT)

Introduction

The addition of aldosterone receptor antagonists to standard therapy for congestive heart failure (CHF) in ischaemic or non-ischaemic cardiomyopathy (CMP) is a Class I recommendation (as per the ACC/AHA guidelines) in patients with moderately severe to severe heart failure (HF) symptoms (New York Heart Association [NYHA] III/IV) and left ventricular ejection fraction (LVEF) <35% in the absence of renal failure and hyperkalaemia. The addition of aldosterone antagonists [AA] to standard therapy reduced morbidity and mortality in the HF population. It is also known that spironolactone reduces the number of ventricular arrhythmias in patients with CHF secondary to idiopathic dilated, or to ischaemic CMP. The incidence of sudden cardiac death decreased in the patients receiving AA in large randomised prospective multicentre trials (Randomised ALdactone Evaluation Study [RALES], Eplerenone Post-AMI Heart failure Efficacy and SURvival Study [EPHESUS]). The addition of AA in EPHESUS proved to be a cost saving strategy due to a significant decrease in mortality. In a subgroup of patients in the EPHESUS trial with LVEF <30%, the relative risk reduction for sudden cardiac death and all-cause mortality was significantly incremental with the use of a selective AA (Eplerenone). Systematic reviews of clinical trials studying the efficacy of AA in HF revealed a significant reduction in all-cause mortality and sudden cardiac death. Mortality and morbidity was improved in a randomised clinical trial among patients with mild chronic systolic HF (NYHA Class II) and LV dysfunction.

Implanted cardioverter defibrillators (ICDs) effectively treat sustained ventricular arrhythmias and thereby prolong...
life compared with anti-arrhythmic drug therapy (or no anti-arrhythmic drug therapy) in patients at risk for sustained ventricular tachyarrhythmias.\textsuperscript{11–15} However, many patients with an ICD have ventricular tachyarrhythmias that may cause transiently disabling symptoms and may lead to painful ICD shocks. In patients implanted with defibrillators after sustained ventricular tachyarrhythmias, quality of life improves in many but not in those who require multiple ICD therapies. Frequent shocks are associated with a higher mortality and frequent, expensive hospitalisations.\textsuperscript{16} Over time, 30–50% of ICD recipients receive anti-arrhythmic drug therapy to prevent symptomatic tachyarrhythmias and to reduce the number of device therapies. Moreover, defibrillator therapies often occur in clusters which suggest that recurrences of ventricular tachyarrhythmias do not occur randomly.

The anti-arrhythmic drugs availability for these patients is limited largely due to their proarrhythmic effects. Drugs with Class I actions are contraindicated in patients with coronary artery disease (CAD) or left ventricular (LV) dysfunction. Sotalol a Vaughn Williams Class III anti-arrhythmic drug, a potassium channel-blocking agent with β-blocking properties it has been shown to be effective as an adjunctive therapy in patients with an ICD.\textsuperscript{17} It can cause \textit{Torsade des pointes} and complicates concomitant therapy with β-blockers for many ICD patients who also have CHF. Similarly, azimilide, which is a pure K channel blocker, in a randomised placebo-control trial has shown to reduce the number of total appropriate therapies (both ventricular tachycardia [VT] and ventricular fibrillation [VF]),\textsuperscript{18} (hazard ratio $=0.52$, 95% confidence interval [CI] 0.30–0.89, $P=0.017$). About 1% patients developed TdP related to azimilide use and the incidence was not increased among those with diminished LVEF or women. One patient developed neutropenia. In a post hoc analysis, azimilide has also shown to be effective in reducing emergency room visits as well as hospitalisation amongst patients with ICD. Unfortunately, the drug did not get Food and Drug Administration (FDA) approval. The use of amiodarone is similarly limited by multiple serious adverse effects which include irreversible and sometimes fatal pulmonary toxicity, hypothyroidism, hyperthyroidism, and neurologic side effects such as tremors, ataxia, and hepatic toxicity. Amiodarone use may also increase the defibrillation thresholds. Additionally, amiodarone usage may also cause drug-drug interaction with many cardiac and non-cardiac drugs due to its effect on cytochrome P 450 system.

Aldosterone has an important role in the pathophysiology of HF.\textsuperscript{4} It promotes the retention of sodium, loss of magnesium and potassium, sympathetic activation, parasympathetic inhibition, myocardial fibrosis, baroreceptor dysfunction, and vascular damage and impairs arterial compliance. It also prevents the uptake of norepinephrine by myocardium.\textsuperscript{19–22} Spironolactone is a non-selective aldosterone receptor blocker. The effect of aldosterone receptor blockers on plasma volume and electrolyte balance is well-known. In addition, the aldosterone receptor blockade decreases sympathetic drive and improves norepinephrine uptake in patients with HF and heart rate variability. It improves ventricular remodelling by decreasing myocardial fibrosis. Aldosterone receptor blockers also reduce coronary vascular inflammation, reduce oxidative stress, improve endothelial dysfunction, attenuate platelet aggregation, decrease activation of matrix metalloproteinases, and improve ventricular remodelling.

We propose that the addition of AAs to the standard therapy for CHF in patients with ICDs will reduce the number of clinically significant ventricular arrhythmias, thereby reducing the number of times anti-tachycardia pacing (ATP) and shocks delivered, as detected by ICD interrogation.

\section*{Methods}

\subsection*{Patient sample}

This was a retrospective study. Patients were enrolled from three different medical centres. The study group consisted of patients with ICDs with an ejection fraction (EF) $<35\%$ and receiving spironolactone. The control group consisted of patients with ICDs and an EF $<35\%$ who were not on spironolactone therapy. The aetiology of ventricular dysfunction could be ischaemic, non-ischaemic, or idiopathic dilated CMP. The enrollment period was from January 2000 through December 2002. To be eligible for inclusion, the ICD had to be placed for at least 12 months.

\subsection*{Study baseline characteristics and outcomes}

Baseline demographic and clinical characteristics were collected for the two groups. Patients in the treatment group were followed from the time they started receiving spironolactone. Control group patients were followed from the time of ICD placement. The outcomes were (1) the monthly shocks/ATP episodes and (2) monthly episodes of VT, non-sustained VT (NSVT), and VF.

\subsection*{Statistical analysis}

Fisher’s exact test was used for comparisons involving categorical variables while the independent sample $t$-test was used for continuous variables. Inferences were made at the 0.05 level of significance with no adjustment for multiple comparisons.

\section*{Results}

Twenty-eight patients were in the study group, ICD patients with an LVEF $<35\%$ and receiving spironolactone while 36 patients with ICDs composed the control group, ICD patients with an LVEF $<35\%$ but not taking spironolactone. Table 1 shows the baseline characteristics of the two groups. The two groups differed only on digoxin, with 71% of treatment patients versus 36% of control patients using this medication ($P=0.006$).

Table 2 shows that the control group was followed for a longer period than the treatment group (mean $=17.5$ months...
Ventricular arrhythmias are common in LV dysfunction and CHF. The incidence of ventricular arrhythmias is lower in patients with CHF who received spironolactone. The VT rate was significantly lower among patients treated with AA in a small retrospective study by Dimas et al.\textsuperscript{23}

We postulated that ICD patients with CHF, LV dysfunction, and EF <35% would benefit from treatment with spironolactone. Ventricular tachycardia/month in the group on spironolactone were lower in patients who did not receive this drug. While NSVTs were notably lower in the treatment group and VF were notably lower in the control group, these differences did not reach the statistical significance due to small sample sizes, patient variability, and large standard deviations in relation to means. A slightly lower rate of monthly shocks was found in the treatment group, but this difference was also not significant.

There was a reason to believe that spironolactone would decrease the number of episodes of ventricular arrhythmias and possibly sudden cardiac death. The mechanism of action is due to anti-arrhythmic actions that include inhibition of electrical and structural cardiac remodelling, inhibition of neurohumoral activation, reduction of blood pressure and stabilisation of electrolyte disturbances.

Aldosterone receptor blockers work at different levels via different mechanisms to improve outcomes in patients with CHF. The most well-known mechanisms of these are through blockade of aldosterone thus promoting natriuresis, preserving potassium and magnesium in the body. Aldosterone blockers also decrease cardiac fibrosis and improve cardiac sympathetic activity, norepinephrine uptake, heart rate variability, and ventricular remodelling.

Ventricular arrhythmias are common in LV dysfunction and CHF. These are frequently associated with a poor prognosis in this population. Anti-arrhythmic drugs, such as Class I

### Discussion

The beneficial effects of aldosterone receptor blockers are well-known in patients with CHF both due to ischaemic or secondary to non-ischaemic CMP. It is also known that sudden cardiac death is significantly higher in patients with LV dysfunction who are not receiving aldosterone receptor blockers. The incidence of ventricular arrhythmias is lower in patients with CHF who received spironolactone. The VT rate was significantly lower among patients treated with AA in a small retrospective study by Dimas et al.\textsuperscript{23}

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Baseline characteristics of the treatment and control groups.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Treatment group</td>
</tr>
<tr>
<td>Age</td>
<td>(n=28) (%)</td>
</tr>
<tr>
<td>Mean</td>
<td>64.61</td>
</tr>
<tr>
<td>SD</td>
<td>11.37</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>22 (78.6)</td>
</tr>
<tr>
<td>Female</td>
<td>6 (21.4)</td>
</tr>
<tr>
<td>Institution</td>
<td></td>
</tr>
<tr>
<td>Good Sam</td>
<td>12 (42.9)</td>
</tr>
<tr>
<td>Dayton Card</td>
<td>7 (25)</td>
</tr>
<tr>
<td>DCEP</td>
<td>9 (32.1)</td>
</tr>
<tr>
<td>Beta-blockers</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>24 (85.7)</td>
</tr>
<tr>
<td>No</td>
<td>4 (14.3)</td>
</tr>
<tr>
<td>ACEIs</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>21 (75)</td>
</tr>
<tr>
<td>No</td>
<td>7 (25)</td>
</tr>
<tr>
<td>ARBs</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>3 (10.7)</td>
</tr>
<tr>
<td>No</td>
<td>25 (89.3)</td>
</tr>
<tr>
<td>CAD</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>23 (82.1)</td>
</tr>
<tr>
<td>No</td>
<td>5 (17.9)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td></td>
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<tr>
<td>Yes</td>
<td>8 (28.6)</td>
</tr>
<tr>
<td>No</td>
<td>20 (71.4)</td>
</tr>
<tr>
<td>Amiodarone</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>6 (21.4)</td>
</tr>
<tr>
<td>No</td>
<td>22 (78.6)</td>
</tr>
<tr>
<td>Sotalol</td>
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</tr>
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<td>Yes</td>
<td>1 (3.6)</td>
</tr>
<tr>
<td>No</td>
<td>27 (96.4)</td>
</tr>
<tr>
<td>Digoxin</td>
<td></td>
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<td>Yes</td>
<td>20 (71.4)</td>
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<td>No</td>
<td>8 (28.6)</td>
</tr>
<tr>
<td>Ejection fraction</td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>21.32</td>
</tr>
<tr>
<td>SD</td>
<td>6.74</td>
</tr>
</tbody>
</table>


and median = 16 months for the control group versus mean = 11 months and median = 7 months for the treatment group, P = 0.026. The two groups did not differ on monthly shocks for any cause (P = 0.83), monthly NSVTs (P = 0.33), or monthly VFs (P = 0.24), but the treatment group has fewer monthly VTs (P = 0.027) requiring ATP.

## Table 2

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Treatment group</th>
<th>Control group</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of follow-up months</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>11.04</td>
<td>17.50</td>
<td>0.026</td>
</tr>
<tr>
<td>SD</td>
<td>10.81</td>
<td>11.57</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>7</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>Shocks (per month)**</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>0.24</td>
<td>0.29</td>
<td>0.83</td>
</tr>
<tr>
<td>SD</td>
<td>1.14</td>
<td>0.66</td>
<td></td>
</tr>
<tr>
<td>VT (per month)†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>0.0020</td>
<td>0.1957</td>
<td>0.027</td>
</tr>
<tr>
<td>SD</td>
<td>0.0108</td>
<td>0.4523</td>
<td></td>
</tr>
<tr>
<td>NSVT (per month)‡</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>0.3539</td>
<td>5.5938</td>
<td>0.33</td>
</tr>
<tr>
<td>SD</td>
<td>1.2432</td>
<td>28.3622</td>
<td></td>
</tr>
<tr>
<td>VF (per month)#</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>0.2393</td>
<td>0.0139</td>
<td>0.24</td>
</tr>
<tr>
<td>SD</td>
<td>1.1360</td>
<td>0.0833</td>
<td></td>
</tr>
</tbody>
</table>

and exercise stress tests. Animal studies have shown that number ventricular arrhythmia assessed by Holter monitoring were placed in high-risk patients, they reduce mortality. Randomised prospective trials using eplerenone and spironolactone in the RALES3 and EPHESUS2 trials respectively showed that sudden cardiac death improved in patients in the treatment groups. Ramires et al. and others also showed the treatment with spironolactone in patients with CHF decreases the number ventricular arrhythmia assessed by Holter monitoring and exercise stress tests. Animal studies have shown that chronic aldosterone-overload induces structural and electrical remodelling of the myocardium increasing the risk for malignant ventricular arrhythmia2,25 and the use of AA attenuated electrical remodelling and suppressed the inducibility of ventricular arrhythmia.2,25,26 The use of AA causes a delay or reversal of myocardial fibrosis as noted by a decreased turnover of extracellular markers in the treatment arm of RALES trial.27 Spironolactone has also been shown to reduce plasma levels of metalloproteinases in ischaemic HF indicating its role in reversing collagen dysregulation that plays a role in cardiac remodelling.28 Other potential causes for decrease in arrhythmia could be due to reduction in heart rate, heart rate variability, alteration in QT dispersion, myocardial collagen turnover, magnesium efflux and an early morning rise in heart rate among heart failure patients.5,29,30 The selective aldosterone receptor blocker eplerenone has been shown to improve impulse propagation, reduce the incidence of cardiac arrhythmias and minimised myocardial fibrosis in the setting of CMP.31

Our study had some inherent shortcoming due to retrospective data analysis and small sample size. Unlike other monitoring modalities, ICDs were capable of storing all VT and VF events which could unequivocally demonstrate the beneficial effect of AA on suppression of VT/month.

We showed that the spironolactone is a useful and potent anti-arrhythmic drug for patients with LV dysfunction and CHF by decreasing VT episodes. However, further prospective, double-blind, placebo-controlled studies are needed among HF patients who are undergoing biventricular ICD implantation, where the arrhythmias and therapies delivered by ICDs can be retrieved and documented based on stored electrograms.

References


Prevalence of hypertension in Nepalese community triples in 25 years: a repeat cross-sectional study in rural Kathmandu

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ABSTRACT

Aim/Objectives: The objective of the study was to examine if there has been any change in the prevalence of hypertension (HTN) in the Nepalese population in the last two and half decades.

Methods: A population-based cross-sectional study was done in Bhadrabas village area of Kathmandu valley to estimate the prevalence of HTN and the findings were compared to the study done in the same location 25 years ago.

Findings: The study shows that there has been a three-fold increment in the prevalence of HTN in the same location. The major causes behind this increment appear to be increased salt intake and increased body mass index (BMI).

Conclusion: This is the first repeat cross-sectional study on blood pressure (BP) in a Nepalese population. There is a very high prevalence as well as a sharp rise in HTN prevalence in this society largely because of changing lifestyle which is most likely because of socio-economic transition.

KEYWORDS

Hypertension    Kathmandu    Repeat cross-sectional

Introduction

Hypertension (HTN) is a global public health problem with 1/4 adults worldwide estimated to have high blood pressure (BP).¹ The first scientific HTN survey in Nepal was done in 1981 by Mrigendra Samjhana Medical Trust.² The prevalence of HTN according to the then used World Health Organization (WHO) criteria (160/95 mmHg)³ in the various parts of the country was as follows: 5.3% in Mountains (Jumla), 6% in rural Kathmandu (Bhadrabas and Alapot), 8.1% in Terai plains (Parsauni), and 9.9% in urban Kathmandu.⁴ Since then, there has been a few studies done in various parts of Nepal.⁵ These studies done in different geographical settings indicate towards a high prevalence of HTN in the Nepalese population. For example, a BP study in Dharan town of Eastern Nepal in 2005 found a prevalence of almost 23% according to the Jet Navigation Chart (JNC) VII guidelines.⁶

Because all these were one-time cross-sectional studies, these studies cannot show any trend, i.e. if there is a rise in the prevalence of HTN in these populations in the last few years or decades. A robust evidence of HTN trend can only be produced if a methodologically comparable study on HTN in the same location after a certain period yields a rising trend. To fill this particular gap in information regarding HTN in Nepal, a repeat cross-sectional study was planned. Thus, after 25 years since the initial study, a repeat survey was done in 2006 in the Bhadrabas area (consisting of adjoining Bhadrabas and Alapot villages) in the outskirts of Kathmandu valley. The main objectives of the study were to find out the prevalence of HTN in the urbanising area of a developing country and to compare the findings with the 1981 study done in the same location.⁷

Methods

Bhadrabas and Alapot are villages in Kathmandu valley located approximately 15 Km Northeast of the Kathmandu city. The details of the methodology used in the 1981 study were published a long-time back in Indian Heart Journal.⁸ In brief, the survey was carried out from the beginning of March to the end of April 1980. The study population included 1405 individuals (639 males and 766 females) of the total 1547 people, aged ≥21 years. A single casual BP, using a mercury manometer was recorded. The criteria for diagnosing HTN were those recommended by the WHO Expert Committee, 1978 (systolic
BP [SBP] ≥ 160 mmHg and/or diastolic BP [DBP] ≥ 95 mmHg.\(^3\)

Physical activity was classified arbitrarily into three broad groups: light (mainly sedentary, no regular physical exercise), moderate (manual farming or regular exercise like walking, cycling) and heavy (heavy manual work like carrying heavy loads). Determination of overweight was done with Broca’s index (weight [kg] × 100/height [cm]\(^2\) – 100).

For the 2006 study, the latest JNC-7 guideline for diagnosis of HTN was used (SBP ≥140 mmHg and/or DBP ≥ 90 mmHg).\(^9\)

However, for appropriate comparison with the 1981 study, the higher cut-off of 160/95 was also used. Similarly, though body mass index (BMI) of >23 kg/m\(^2\) was considered as overweight for the 2006 study as per the cut-off recommended for South Asians,\(^10\) Broca’s index was also calculated for making comparison with the 1981 study.

To determine the amount of daily salt consumption at the household level, the enumerators carried small sachets with 5 g, 10 g, 20 g, 50 g, and 100 g of salt. They were shown to the respondent to determine which sachet-size matched their per capita consumption. The per capita consumption was then calculated by taking into account all the family members of the household and presuming that children aged 0 – 2 years consumed zero units, those aged 2 – 12 years consumed half unit while those aged ≥ 12 years consumed one unit. Besides home-cooked food, the enumerators took into calculation the salt consumed in pickles and other high salt-containing fast food items such as chips and noodles etc. taken outside.

To determine the amount of daily salt consumption at the household level, the enumerators carried small sachets with 5 g, 10 g, 20 g, 50 g, and 100 g of salt. They were shown to the respondent to determine which sachet-size matched their daily salt used for cooking. The per capita consumption was then calculated by taking into account all the family members of the household and presuming that children aged 0 – 2 years consumed zero units, those aged 2 – 12 years consumed half unit while those aged ≥ 12 years consumed one unit. Besides home-cooked food, the enumerators took into calculation the salt consumed in pickles and other high salt-containing fast food items such as chips and noodles etc. taken outside, which have become popular in Nepal during the last decade or so. Other measurements and variables were similar to the 1981 study.

For both the studies, a door-to-door visit to all the households present in the area was done with the intention of including all the adults aged ≥ 21 years. Those who consented to participate were enrolled. The response rate was 91% in the 1981 study whereas in 2006, 84% out of the total eligible 1450 adults consented to get enrolled for the study.

Ethical clearance was taken and informed consent was obtained from the participants. Data for the 2006 study was analysed with SPSS version 13.0. Comparisons with the 1981 study were based on the results published in a monograph\(^11\) as well as in the Indian Heart Journal.\(^12\) Multivariate logistic regression analyses were performed to study the strength of association of HTN with the following five risk factors: high salt intake, physical inactivity, tobacco consumption, high waist circumference, and BMI (>23 kg/m\(^2\)). For each multivariate logistic regression analysis, the other four variables along with age and sex were adjusted.

### Results

#### Description of the study population

A total of 1218 adults aged 21 years were enrolled; 527 of them were males while the remaining 691 were females (Table 1). The demographic characteristics of the 2006 study are described and compared with the 1981 population in Table 1. The mean age of the study population in 2006 was 40.54 (±16) years (41.48 ± 15.24 for males and 39.83 ± 16.53 for females).

#### Prevalence of hypertension

The prevalence of HTN in Bhadrabas in 2006, according to the JNC VII classification was found to be 33.8% (males: 38.3%, females: 30.8%).

#### Association of various risk factors with hypertension

Multivariate logistic regression analysis of the common risk factors is shown in Table 2. All risk factors particularly physical inactivity, high salt intake and obesity were associated with high BP. All the variables in the table: high salt intake, physical inactivity, tobacco, high waist circumference, BMI (>23 kg/m\(^2\)) have been adjusted for age and sex, and then with one another. For example, for high salt intake: age, sex, physical activity, tobacco, high waist, and BMI were adjusted.

### Table 1

<table>
<thead>
<tr>
<th>Year</th>
<th>Sample size</th>
<th>Male/female (ratio)</th>
<th>Mean age (SD)</th>
<th>Age distribution (yr)</th>
<th>Male n (%)</th>
<th>Female n (%)</th>
<th>Total n (%)</th>
<th>Male n (%)</th>
<th>Female n (%)</th>
<th>Total n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1981</td>
<td>1405</td>
<td>639/766 (1:1.2)</td>
<td>39.61 (14.76)</td>
<td>21–30</td>
<td>232 (36.3)</td>
<td>253 (33)</td>
<td>485 (34.5)</td>
<td>135 (25.6)</td>
<td>233 (33.7)</td>
<td>368 (30.2)</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>31–40</td>
<td>115 (18)</td>
<td>187 (24.4)</td>
<td>302 (21.5)</td>
<td>148 (28.1)</td>
<td>153 (22.1)</td>
<td>301 (24.7)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>41–50</td>
<td>109 (17.1)</td>
<td>155 (20.2)</td>
<td>264 (18.8)</td>
<td>85 (16.1)</td>
<td>110 (15.9)</td>
<td>195 (16)</td>
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<td></td>
<td></td>
<td>51–60</td>
<td>91 (14.2)</td>
<td>86 (11.2)</td>
<td>177 (12.6)</td>
<td>73 (13.9)</td>
<td>86 (12.4)</td>
<td>159 (13.1)</td>
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<td></td>
<td></td>
<td></td>
<td>61–70</td>
<td>60 (9.3)</td>
<td>63 (8.2)</td>
<td>123 (8.7)</td>
<td>57 (10.8)</td>
<td>57 (8.2)</td>
<td>114 (9.4)</td>
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<td></td>
<td></td>
<td>&gt;70</td>
<td>32 (5)</td>
<td>22 (2.9)</td>
<td>54 (3.8)</td>
<td>29 (5.3)</td>
<td>52 (7.5)</td>
<td>81 (6.7)</td>
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<tr>
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<td></td>
<td></td>
<td></td>
<td>Total</td>
<td>639 (100)</td>
<td>766 (100)</td>
<td>1405 (100)</td>
<td>527 (100)</td>
<td>691 (100)</td>
<td>1218 (100)</td>
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<tr>
<td>2006</td>
<td>1218</td>
<td>527/691 (1:1.3)</td>
<td>40.54 (16)</td>
<td>21–30</td>
<td>135 (25.6)</td>
<td>233 (33.7)</td>
<td>368 (30.2)</td>
<td>135 (25.6)</td>
<td>233 (33.7)</td>
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<td></td>
<td>&gt;70</td>
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<td>81 (6.7)</td>
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<td></td>
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<td></td>
<td></td>
<td>Total</td>
<td>527 (100)</td>
<td>691 (100)</td>
<td>1218 (100)</td>
<td>527 (100)</td>
<td>691 (100)</td>
<td>1218 (100)</td>
</tr>
</tbody>
</table>

DBP: diastolic blood pressure, SBP: systolic blood pressure, SD: standard deviation.
Table 3

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>Year</th>
<th>$n$ (%)</th>
<th>Year</th>
<th>$n$ (%)</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HTN ($\geq 160/95$ mmHg)</td>
<td>1981</td>
<td>84 (6)</td>
<td>2006</td>
<td>225 (18.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Salt intake ($\geq 5$ g)</td>
<td>1981</td>
<td>785 (55.9)</td>
<td>2006</td>
<td>1090 (89.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Overweight (Broca’s index)</td>
<td>1981</td>
<td>169 (12)</td>
<td>2006</td>
<td>526 (43.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Physical inactivity</td>
<td>1981</td>
<td>157 (11.2)</td>
<td>2006</td>
<td>123 (10.1)</td>
<td>0.37</td>
</tr>
</tbody>
</table>

Note: *For each of the five multivariate logistic regression analyses, the other four variables along with age and sex were adjusted. BMI: body mass index; CI: confidence intervals.

**Comparison of prevalence of hypertension in the Bhadrabas community in the 1981 and 2006 studies**

To make a rational comparison between the 1981 and 2006 data, same cut-off points for defining HTN should be used for both the data. So, when the 2006 data was re-analysed using the old criteria of 1981, i.e. 160/95 mmHg, the prevalence of HTN in 2006 was calculated to be 18% which is still very high compared to the 6% prevalence in 1981 (Table 3). In other words, HTN had tripled (from 6% to 18%) in the same place in a span of 25 years. Comparisons in terms of age and sex in Figures 1 and 2, respectively show the trend to be similar for both sexes and all age groups.

**Patient’s awareness of hypertension status and treatment status in the 1981 and 2006 studies**

In 1981, only 4 (4.8%) of the hypertensive people were aware of their high BP status while almost one-third (31.8%) of hypertensives in 2006 were aware. All four aware cases in 1981 and 97 (23.5%) of the hypertensives in 2006 were getting treatment. In 2006, BP was under control in 39 (9.5%) of the hypertensives.

**Discussion**

The study has shown that the prevalence of HTN has indeed increased in the last quarter century in the rural Bhadrabas and Alapot community in the outskirts of Kathmandu. Given
the similar socio-developmental transition in many other parts of the country—particularly in the rapidly urbanising regions—it may be said that this rise in HTN could well be true for various other urbanising areas of Nepal.

The prevalence of HTN given by this study is marginally higher than other contemporary studies from Nepal on HTN. Important contributors for this rise seem to be increased salt intake and rising level of obesity (Table 3). A well-designed study in 1998 has already established the role of salt in genesis of HTN in the Nepalese population. Since physical inactivity level has remained the same at least in this community, change in the dietary habit appear to be the key factor.

Rise in the awareness level regarding the HTN status from <5% to almost a third is a large increase. This may be partly attributed to increasing general and cardiovascular literacy as well as the health programmes run in the community by Mrigendra Samjhana Medical Trust. The awareness, treatment, and control rates of the 2006 study are comparable to another suburban Kathmandu study in 2005 (31.8% vs 41.1%, 23.5% vs 26%, 9.5% vs 6%). In a study conducted in an Eastern Hilly town of Nepal called Dharan, almost 60% of the hypertensives were aware of their disease with 50% of the hypertensives having their BP under control. Presence of a tertiary care academic hospital with community-oriented programmes is a possible reason for this better awareness and control rates in Dharan.

This is the first published repeat cross-sectional study on HTN in Nepal. In fact, there are not many such studies in the other parts of the world too. The intention of seeing a trend of BP in the population has been fulfilled often with longitudinal cohort studies. The merits and demerits of both the options can be debated. In a resource-limited setting like ours, a repeat cross-sectional study may be cost-beneficial as well as adequately effective. Such studies can in fact also be employed to observe effects of intervention over a certain period of time in a community.

Certain limitations of the study can put the result under scrutiny. The difference in the prevalence can be argued to be because of various confounders. But given the fact that the demographic structure of the community has remained more or less the same except for some possibility of out-migration among the youth, and similarity in data collection methods including the similarity in the age–sex structure of the sampled population in the two studies, the increase in HTN prevalence does seem real. Measurement of salt consumption had to be arbitrarily done because of lack of accurate technicality to measure urinary sodium output in Nepal in 1981 and we wanted to do both the estimations by the same method. Nonetheless, renowned studies such as National Health and Nutrition Examination Surveys (NHANES) have also used 24-hour recall method to estimate salt intake, and causal associations with cardiovascular events based on such estimations have been reported as well.

This repeat cross-sectional study has shown that prevalence of HTN has increased three-fold in a rural community of Nepal. It shall be important to follow this population in the future to see the trend of BP in the Nepalese population. The study also has indirectly pointed out there is inadequacy from the perspective of public health and that we have not been able to do enough to prevent the problem. So, Nepal needs to seriously implement programmes to address HTN and its consequences.

Acknowledgement

The authors would like to thank Ms. Amsuka Rajopadhyaya and Ms. Sangita Shrestha for their help in the research work.

References

Editorial
Trends in hypertension
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Non-communicable diseases, especially cardiovascular diseases are major cause of death and disability in the world, even in the low and middle income countries. The International Case Control Studies—INTER HEART1 and INTER STROKE2 involving 52 countries, including those of low income reported that standard 10 risk factors account for >90% of vascular events. But the population attributable risks are different in INTER HEART and INTER STROKE, with greater importance of lipids (49.2%), diabetes (9.9%) in INTER HEART and of hypertension (HTN) (34.6%) in INTER STROKE.

The level of blood pressure (BP) at which to intervene is still debated by HTN experts. The suggested levels at which to intervene has changed from 120/80 in 1942, to 180/100 in 1948, and 150/90 in 1952. In 1959, World Health Organization (WHO) published a report about technique of measurement of BP and cut-off value of 160/95 which became a standard dividing line between normotension and HTN. Norman Kaplan stated that the dividing line be established on some rational basis and defined HTN as that level of BP at which benefits of action exceed the risks of inaction. This level can only be determined by longitudinal studies of cohort of patients over a long period of time (for identifying level at which cardiovascular risk occurs) and by intervention trials demonstrating benefits from BP reduction. Stamler et al.3 analysed all the US studies of correlation of level of BP with cardiovascular events and showed that both systolic BP (SBP) and diastolic BP (DBP) have continuous, graded, independent relationship to the clinical outcome variables of cardiovascular mortality and total mortality. The longitudinal study of Framingham reported continuum of risk of stroke and coronary artery disease with DBP, with no cut-off value at which risk was not present. Further intervention trials like Treatment Of Mild Hypertension Study (TOMHS) (BP = 140–159/90–95 mmHg) have shown better vascular outcome compared to placebo. Similar data was reported in Multiple Risk Factor Intervention Trial (MRFIT) with excess mortality above SBP of 120 mmHg.

No prospective longitudinal study of correlating level of BP with clinical events exists in Asian countries. Most of the studies have been one time cross-sectional studies and in a few at different points of time showing trend of HTN prevalence over decades of time like in a paper published in this journal from Nepal. Striking feature of various prevalence studies has been progressive rise in SBP throughout life, with a difference of 20–30 mmHg between early and late adulthood with less striking increase in DBP. In later years, the DBP may level off or slightly decline. The mean level of SBP and DBP are higher in men than women in early adulthood, but the difference narrows progressively and may even be reversed by the sixth or seventh decade.

Studies evaluating the prevalence of HTN in the same geographical area over decades have not been many in India. In an attempt to evaluate the changing trends of prevalence of HTN in India, Gupta et al.4 analysed epidemiological studies done in India from 1950 onwards till 1998. Most of these studies used WHO criteria (>160/95 mmHg) for diagnosis of HTN, which showed increasing trend from 4.35% in Agra (Mathur 1963), 6.4% in Rohtak (Gupta 1978) and 15.52% in Bombay (Dalal 1980). Using Joint National Council (JNC) V criteria (>140/90 mmHg) also showed steep increase in prevalence of HTN from 6.2% (Delhi 1959), 30.9% (Jaipur 1995), 44% (Mumbai 1999), and 36% (Chennai 2001). Bhopal et al.5 compared HTN prevalence rates in Indians, Pakistanis, and Bangladeshis in Britain and reported that HTN was more in Indians compared to other South Asian groups. In SHARE6 study, the prevalence of self-reported HTN amongst South Asians (12.5%) was similar to Europeans (11%) but lower than Chinese (15.9%). Ahlawat et al.7 reported trends in HTN in Chandigarh—Urban North Indian—population over a 30-year period. The prevalence in 1968 was 19.99% in men and 24.8% in women which increased to 43.7% in men and 45.8% in women in 1997. Similar study was done in Jaipur; once in 1995 (Jaipur Heart Watch 1—JHW18) and subsequently in 2002 (JHW28). In JHW1, HTN was present in 29.5% men and 33.5% women as compared to 36.4% men and 37.5% women in JHW2, but age-adjusted prevalence rates are not significantly

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doi: 10.1016/S0019-4832(12)60046-7
different in the two studies. Further, the age-adjusted prevalence of prehypertension (high normal BP 120–139/80–89) was not significantly different between the two studies. In this journal, cross-sectional study of prevalence of HTN in Nepal over a period of three decades showed tripling of prevalence even by WHO definition (> 160/95 mmHg). Further, there was good correlation of increased prevalence of HTN with obesity (body mass index) and salt consumption which emphasises the importance of lifestyle changes in prevalence of HTN.

This study from Nepal is done in rural Kathmandu (Bhadrabas and Alapot) in a small number of subjects using only single casual measurement BP using mercury manometer. Further, the study used different criteria for HTN at different points of time (WHO definition of 160/95 in 1980 and JNC criteria of 140/90 in 2006) and thus making the interpretation difficult. But comparison of mean SBP reveals an increase from 118.4 mmHg in 1980 to 120.82 mmHg in 2006 and an increase in mean DBP of 74.6 mmHg to 80.14 mmHg. Although, these differences of 1–2 mmHg may appear small, they have good correlation with changes in prevalence of HTN. An increase in mean BP is associated with increase in prevalence. In various cohorts of seven countries study, the trends in prevalence of HTN changed with changes in mean BP. In Dutch cohort, during the period 1974–1980, the average SBP increased by 2 mmHg and DBP by 4 mmHg and prevalence of HTN increased from 12.7% in 1974 to 17.8% in 1980. Similar trends in prevalence of HTN were seen in Yugoslavian cohort. The Framingham study reported a decline in mean SBP and DBP over a period of 40 years that was associated with declining HTN prevalence. This study from Nepal also showed an increase in mean SBP and DBP with increased prevalence of HTN over a period of three decades.

Prevalence studies in USA between late 1970 and early 1990, declined from 32% to 25%, but the most recent survey data shows steady increase between 1988–1994 (23.9% men and 26% in women) and 1999–2000 (27.1% men and 30.1% women) with prevalence of 28.6% in 2005. There are ethnic differences observed in USA with almost 50% higher prevalence in African American adults compared with their white counterparts. International data indicate even higher prevalence of HTN in adults in some developed countries. Whereas the prevalence of HTN in Canada in adults (35–74 years) is 28%, similar to USA in 1990, concurrent data from six European countries revealed an overall prevalence rate of 44% with lowest prevalence in Italy 38% and highest in Germany 55%. Meta analysis of various studies of prevalence of HTN across the globe revealed that an overall 26.4% of adult population in 2000 had HTN (26.6% men and 26.1% women) and the number projected by 2025 will be 29.2%. The estimated total number of adults with HTN in 2000 was 972 million–333 million in developed and 639 million in developing countries and the predicted number by 2025 is 1.56 billion. This study reveals important public health challenge and the potential for preventive and therapeutic strategies.

Essential HTN is considered to be due to interaction of genetic susceptibility and adverse environmental factors resulting in obesity (specially truncal), higher dietary salt intake, poor intake of potassium and fibre and physical inactivity. These environmental factors not only explain the ethnic differences and increase in prevalence of BP but are also targets for prevention of HTN, an important risk factor for vascular disease.

References
Original article
A look into Lee’s score—peri-operative cardiovascular risk assessment in non-cardiac surgeries—usefulness of revised cardiac risk index
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ABSTRACT
Objective: The revised cardiac risk index (RCRI/Lee’s score) was designed for peri-operative risk assessment before elective major non-cardiac surgeries. Through this article, we report the usefulness of RCRI in our daily practice, while evaluating patients undergoing surgeries of varying risk.

Methods: Only referred patients, aged ≥ 40 years, were included. Risk stratification was done using RCRI scoring system. Patients were categorised into 4 classes depending on 0, 1, 2, and ≥3 risk predictors (risk predictors were high-risk surgery, history of ischaemic heart disease (IHD), diabetes on insulin, history of stroke (cerebrovascular accident [CVA]), history of congestive heart failure (CHF) and serum creatinine of >2 mg%). Electrocardiograms (ECG) were done in all patients, while troponin I in intermediate and high-risk patients, and in others if symptomatic. Peri-operative cardiovascular events were managed appropriately.

Results: Of the 920 patients included, only 853 patients were analysed as 67 patients were not operated upon. The mean age was 59 ± 11 years and 46% of the patients were women. Two hundred and ninety-two underwent high-risk surgeries, 97 patients had history of IHD, 89 had history of CHF, 36 gave history of CVA, 269 patients were diabetics on insulin and 68 had serum creatinine >2 mg%. Number of patients in Lee’s classes I, II, III, and IV were 311, 347, 150, and 52, respectively. 26 out of 853 patients had peri-operative events. Of the six variables in RCRI, only history of IHD was an independent predictor of events. Event rates increased as the RCRI class increased, i.e. 1.7%, 2.0%, 6.7%, and 7.7% for classes I–IV, respectively. Age >70 years, poor general medical condition, emergency surgery and left bundle branch block (LBBB) on ECG, were significantly associated with peri-operative events.

Conclusion: The RCRI is a useful tool in pre-operative risk stratification. It should perhaps be further updated to improve its predictive accuracy.

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KEYWORDS
Non-cardiac surgeries
Peri-operative evaluation
Revised cardiac risk index

Introduction
The peri-operative period provides a physician with a golden opportunity to assess the cardiac status of patients undergoing surgery. Many patients with risk factors undergoing non-cardiac surgery could have underlying silent coronary heart disease. As cardiovascular complications are an important cause of morbidity and mortality with major non-cardiac procedures, it is imperative that patients need to be evaluated and peri-operative coronary risk be reduced. Many scoring systems are described in literature. Goldman’s pioneering work in 1977 led to a methodical assessment of peri-operative cardiac risk.1 Workup for cardiac disease is most helpful in patients at intermediate risk of the peri-operative events. No pre-operative cardiovascular testing should be performed if the results do not change peri-operative management and outcome.

Revised cardiac risk index2 by Lee et al. (RCRI/Lee’s score) was proposed in 1999, and comprises six independent risk factors. These six factors are high-risk type of surgery, history of ischaemic heart disease (IHD), history of congestive heart failure (CHF),
history of cerebrovascular disease, pre-operative treatment with insulin, and pre-operative serum creatinine > 2.0 mg/dL. In their study, the rates of major cardiac complication with 0, 1, 2, or ≥3 of these factors were 0.4%, 0.9%, 7%, and 11%, respectively. Through this study, we aimed to assess the utility of RCRI in peri-operative risk assessment of patients undergoing non-cardiac surgeries of varying risk, as in daily practice.

Methods

All patients over 40 years of age, referred to the Cardiology Department for pre-operative risk stratification, were included in the study during the period 2006–2007. The study population included 920 patients who were risk stratified for various surgeries. Sixty-seven patients were not operated upon, hence, only 853 patients were considered for the analysis (Figure 1).

Pre-operative evaluation included a detailed medical history including risk factors, prior cardiovascular disease, other major systemic diseases and treatment history. Objective assessment included an electrocardiogram (ECG), echocardiogram, and exercise stress test when feasible. Risk stratification was done using Lee’s scoring system, and patients were categorised into four classes, namely I, II, III, and IV depending on the presence of 0, 1, 2, and ≥3 risk predictors, respectively. All patients had ECGs done pre-operatively, immediate post-operative, and on day 1 after surgery. Troponin I was estimated in intermediate and high-risk patients, and in others if symptomatic.

Statistical methods

Descriptive statistical analysis was carried out in the present study. Results on continuous measurements are presented as mean± SD (min–max) and results on categorical measurements are presented as number (%). Significance was assessed at 5% level of significance. Student t-test (two tailed, independent) was used to find the significance of study parameters on continuous scale between the 2 groups. Inter-group analysis χ²/Fisher exact test was used to determine the significance of the study parameters on the categorical scale between the 2 groups. Receiving operating curve (ROC) analysis was performed to find the diagnostic performance of Lee’s score. Statistical software, namely SPSS 15.0 was used for the analysis.

Results

The baseline characteristics are outlined in Table 1. The mean age of the patients was 59.9±11 years and 46% were women. Two hundred and ninety-two patients (34.2%) underwent high-risk surgeries, 97 (11.7%) had history of IHD, 89 (10.4%) had history of CHF, 36 (4.2%) gave history of cerebrovascular accident (CVA), 269 (31%) were diabetics on insulin, and 68 patients (8%) had serum creatinine > 2 mg%.

The number of patients in Lee’s classes I, II, III, and IV were 304 (36%), 347 (41%), 150 (17%) and 52 (6%), respectively (Figure 1). The various surgeries done are listed in Table 2.
End points

Twenty-six (∼3%) patients suffered from a peri-operative event. The events were as shown in Figure 2. Non-ST-elevation myocardial infarction (NSTEMI) was the most common type of acute coronary syndrome followed by unstable angina. One patient developed ST-elevation myocardial infarction (STEMI) and succumbed to refractory arrhythmia. Two patients had acute pulmonary oedema, 1 each due to pre-existing LV dysfunction and NSTEMI. There were three deaths in total, one due to STEMI and the other two were sudden cardiac deaths in a patient suffering from hypertrophic obstructive cardiomyopathy (HOCM) on dual chamber pacemaker and the other a case of triple vessel disease.

On univariate analysis, age >70 years, history of IHD, history of MI, pathological Q waves, left bundle branch block (LBBB) on ECG, poor general medical condition (defined by hypoxia, hypercarbia, hypokalaemia, renal failure, bedridden state) and emergency surgeries, all correlated independently with peri-operative events ($P$ values 0.01, <0.001, 0.015, 0.005, 0.001, <0.001, respectively). Unstable angina within the past 6 months tended to be associated with higher peri-operative event rate ($P=0.059$).

Only one among the 6 factors of RCRI was an independent correlate of peri-operative cardiac event, i.e. IHD (Adj OR 4.98 95% CI [2.04–12.16], $P<0.001$) (Table 3).

The event rates in classes III and IV were significantly higher than class II (6.7% and 7.7% vs 2%, $P=0.009$, and 0.04, respectively). The difference between class IV and class III in event rates was not very different (7.7% vs 6.7%, $P=0.759$) (Table 4).

Event rates increased as the RCRI class increased, 1.6%, 2.0%, 6.7%, and 7.7% for classes I–IV, respectively (Figure 1). Area under the ROC curve for RCRI was 0.65.

Performance by procedure type

Analysis of the performance of the RCRI within types of procedures showed that only peripheral vascular surgeries showed trend towards higher cardiac complication rates (OR 4.58, $P=0.090$).

Protective effects of drugs on outcomes were not obvious (Table 5).

Figure 2 Types of events. NSTEMI: non-ST-elevation myocardial infarction, STEMI: ST-elevation myocardial infarction.

### Table 3
Rates of major cardiac complications and multivariate ORs* among patients with individual risk factors.

<table>
<thead>
<tr>
<th>Revised cardiac risk index variables</th>
<th>Events/pop (%)</th>
<th>OR</th>
<th>Adj OR</th>
<th>95% CI</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HRS$^a$</td>
<td>10/292 (3.4)</td>
<td>1.08</td>
<td>-</td>
<td>0.43, 2.3</td>
<td>0.92</td>
</tr>
<tr>
<td>IHD$^b$</td>
<td>10/97 (10.3)</td>
<td>5.32</td>
<td>4.98</td>
<td>2.04, 12.16</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CHF$^c$</td>
<td>4/89 (4.5)</td>
<td>1.58</td>
<td>1.09</td>
<td>0.13, 9.52</td>
<td>0.94</td>
</tr>
<tr>
<td>CVA</td>
<td>0/36 (0)</td>
<td>1.7</td>
<td>1.26</td>
<td>0.39, 4.11</td>
<td>0.69</td>
</tr>
<tr>
<td>Pre-operative insulin therapy</td>
<td>11/269 (4)</td>
<td>1.62</td>
<td>1.07</td>
<td>0.44, 2.57</td>
<td>0.88</td>
</tr>
<tr>
<td>Serum creatinine &gt;2mg%</td>
<td>4/68 (5.8)</td>
<td>1.7</td>
<td>1.26</td>
<td>0.39, 4.11</td>
<td>0.69</td>
</tr>
</tbody>
</table>

*Based on logistic regression models including these six variables.
$^a$Intraperitoneal, intrathoracic and suprainguinal vascular surgeries.
$^b$History of angina, history of myocardial infarction not revascularised, TMT positive for inducible ischemia, pathological Q waves.
$^c$History of CHF, CXR evidence of pulmonary venous hypertension, LV S3, rales suggestive of pulmonary oedema.

### Table 4
Major cardiac complication rates and 95% confidence interval in the study cohorts stratified by Lee’s class.

<table>
<thead>
<tr>
<th>Lee’s class</th>
<th>Event group</th>
<th>Non-event group</th>
<th>OR</th>
<th>95% CI</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>5 (19.2)</td>
<td>299 (36)</td>
<td>1</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>II</td>
<td>7 (26.9)</td>
<td>340 (41.3)</td>
<td>1.22</td>
<td>0.38–3.88</td>
<td>0.74</td>
</tr>
<tr>
<td>III</td>
<td>10 (38.5)</td>
<td>140 (17)</td>
<td>4.23</td>
<td>1.42–12.6</td>
<td>0.01</td>
</tr>
<tr>
<td>IV</td>
<td>4 (15.4)</td>
<td>48 (5.8)</td>
<td>4.93</td>
<td>1.28–19.02</td>
<td>0.02</td>
</tr>
</tbody>
</table>

CI: confidence interval, OR: odds ratio.

### Table 5
Impact of drugs in patients who were already on them.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Total number of patients taking the drug</th>
<th>Patients taking drugs in the event group</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td>126/842</td>
<td>9/26</td>
<td>0.09</td>
</tr>
<tr>
<td>Beta-blockers</td>
<td>191/840</td>
<td>8/24</td>
<td>0.10</td>
</tr>
<tr>
<td>ACEI</td>
<td>116/841</td>
<td>9/23</td>
<td>0.10</td>
</tr>
<tr>
<td>Statins</td>
<td>124/841</td>
<td>4/23</td>
<td>0.16</td>
</tr>
</tbody>
</table>

ACEI: angiotensin-converting enzyme inhibitor.
Discussion

Only patients undergoing elective, major non-cardiac surgeries were studied by Lee et al. We considered patients undergoing various non-cardiac surgeries of differing surgical risks, and both elective and emergency procedures. This we believe is more real world. The presence of 2 or more of the 6 risk predictors in the RCRI is associated with high complication rates like in the original study. This is also in line with various studies which indicate that risk of surgery increases as the number of co-morbidities increase.

The event rate in our study was 3% which is much higher than the reported 1%.3 This could be due to the fact that we considered unstable angina and NSTEMI also as peri-operative events and not just MI, which was considered as a major cardiac complication in Lee's study. Additionally we also measured troponin I in all intermediate and high-risk patients, unlike creatinine kinase-MB which was relied upon for a diagnosis of MI in the original study. This explained the higher event rate in view of the increased sensitivity of troponin.

Certain conditions like diabetes mellitus, impaired renal function, and prior strokes are known to be associated with higher peri-operative cardiovascular events. But, these factors were not independently predictive of coronary events in our study.

A third heart sound or signs of heart failure portend worse cardiac outcomes after major surgeries.1,4 Again, heart failure was not an independent predictor in our study. Conflicting evidence exists regarding the risk in patients with hypertrophic cardiomyopathy. A retrospective study had shown higher peri-operative events in these patients.5 We had 4 patients with HCM (two were obstructive), and one of them (HOCM) had a sudden cardiac death following hip replacement under spinal anaesthesia. General anaesthesia may be better in these patients.

Advanced age is found to be a significant predictor of cardiac events.6 In our study too, we found the mean age in the event group to be significantly higher than the non-event group, and age >70 years was a significant risk factor for peri-operative complications. Severe aortic stenosis is classified as an active cardiac condition in the American College of Cardiology (ACC)/American Heart Association (AHA) guidelines,7 while some studies have not shown severe AS to be a risk predictor.8–10 We had only 2 patients with severe aortic stenosis but none had an event. Left bundle branch block is associated with higher peri-operative events.11 Of the 12 patients with LBBB, 3 (25%) developed an event (P=0.005). Traditionally, cardiac risk stratification and further testing is advised for patients undergoing intermediate and high-risk surgeries as they benefit most, which does not make low-risk surgeries cardiac risk free. We found that even patients undergoing low-risk procedures can develop peri-operative cardiac event if their risk level is high. In our study, four of the 26 patients who had an event, underwent low-risk surgeries, but were classified as intermediate and high-risk by RCRI. There was a tendency towards significant association between cardiac complications and peripheral vascular surgery.

Hypertensive patients are at twice the risk of developing postoperative myocardial ischaemia and higher risk of peri-operative death.12,13 Hypertension if <180/110mmHg is not found to be associated with cardiac complications.13 Blood pressure was well controlled pre-operatively in our patients and was not a predictor of CV events.

Bodenheimer,14 suggested improved outcomes are more likely to result from controlling postoperative oxygen demand than additional risk stratification. Beta-blockers were not protective in those patients with new wall motion abnormalities in greater than five segments on dobutamine stress echo.15 This group with risk factors and extensive wall motion abnormalities on pre-operative stress echo may be the group to consider for prophylactic coronary revascularisation. We did not do dobutamine stress echo in our study. We found no significant protection provided by beta-blockers. The possible explanations could be many. First, our cases did not include many very high-risk cases in which this class of drug is proven to benefit.16–18 Second, the average heart rate (81 bpm) between those who were and those who were not on beta-blockers was no different. Third, the duration of beta-blockade before surgery was short in a significant number of patients and evidence points to the probable benefit in patients who are on these drugs for longer period of time before major surgery.18

In our study, history of IHD was the only factor independently associated with complications. Unstable angina within 6 months showed trend towards more peri-operative events. Patients undergoing non-cardiac surgery within a year of coronary intervention are at high-risk of morbidity and mortality due to stent thrombosis and its consequences. We had 4 patients who had undergone percutaneous coronary intervention (PCI) within the last year and none had an event.

In patients undergoing elective, intermediate or high-risk surgeries and not having active cardiac conditions, further testing is decided upon the effort tolerance.19 Patients with poor effort tolerance need further cardiac testing as it is a predictor of poor cardiac outcomes after major surgeries.1 In our study, poor effort tolerance was not associated with increased peri-operative complications.

It is our belief that better management of patients before surgery, newer drugs in the armamentarium to treat CHF, diabetes, dyslipidaemia, drugs to retard progression of renal failure could be a major factor in decreasing the impact of these factors on outcomes. Refinement in anaesthetic techniques has its own impact. Many other factors like duration of diabetes, renal failure being more often acute than chronic and CVAs being mostly minor in our study could have led to discrepancies with what is known. Thus, one factor was the only independent predictor in our study compared to four in Lee’s study.

Though only IHD is an independent risk predictor, it can still be found that Lee’s index is useful in risk stratification. This is obvious as we see the graded relationship between increasing Lee’s class and peri-operative cardiac complications: 1.6%, 2%, 6.7%, and 7.7% for Lee’s classes I, II, III, and IV, respectively.

Our study is the largest prospective study in our country. We believe Lee’s score is useful in peri-operative risk stratification.
in patients undergoing surgeries of varying risks. We feel that its predictive accuracy increases with the addition of factors like age, general medical condition, urgency of surgery, and LBBB.

**Study limitations**

Long-term follow-up of patient was not done. Only cases deemed at risk by the surgeons or anaesthetists were referred, which included a fraction of cases operated upon in our institute.

**Conclusion**

The Revise Cardiac Risk Index by Lee et al. is useful in the risk stratification of patients scheduled to undergo non-cardiac surgery. Its accuracy can be improved by the addition of age >70 years, poor general medical condition, emergency surgery, and LBBB on ECG as further risk predictors.

**Acknowledgements**

I gratefully acknowledge the help of Dr. Srikumar Nair from KMC, Manipal and Dr. K.P. Suresh from NIANP, Bengaluru for their inputs on statistics. I would also like to acknowledge the cooperation of the patients, surgeons and anaesthetists.

**References**

Patients subjected to non-cardiac surgery are at a significant risk to develop cardiac complications. With aging populations and improved surgical and anaesthesia techniques, even elderly populations are frequently considered for non-cardiac surgery today. It is estimated that about 40 million non-cardiac surgeries are performed in Europe annually and the perioperative myocardial infarction (MI) occurs at a rate of 1% causing 400,000 myocardial infarcts. Further, the cardiovascular mortality rate of 0.3% gives mortality of 133,000 annually related to non-cardiac surgery. It is also a well-known fact that the peri-operative complications are more frequent following vascular surgery. Number of risk assessment algorithms have been developed and tested, however the revised cardiac risk index (RCRI) described by Lee et al. in 1999, remains the most used risk assessment model. These indices are predominantly based on history and simple clinical tools. Patients with active cardiac conditions like, unstable angina or severe angina, recent MI (within 30 days), significant arrhythmias (advanced heart blocks, atrial fibrillation with uncontrolled ventricular rate, symptomatic ventricular arrhythmias, and symptomatic bradycardia), and severe valvular disease undergoing planned non-cardiac surgery, need to be evaluated extensively, and at times, this may lead to postponement or cancellation of the planned surgery. Patients with risk factors as indicated by the risk scores but without active cardiac conditions need to be evaluated further to prevent postoperative cardiovascular events. A pooled analysis of several studies found a 30-day incidence of cardiac events (postoperative MI and death) of 2.5% in unselected patients >40 years of age. Incidence of postoperative cardiac events varies widely depending upon the tools used to detect myocardial damage as the events may occur silently. Use of sensitive markers like troponins, can detect largely asymptomatic cardiac events. Such patients have higher 6-months event rates as compared to those who do not show elevation of troponins following non-cardiac surgery. Risk assessment prior to planned non-cardiac surgery can help in predicting the postoperative events. It also helps the physician and anaesthesiologist to take necessary precautions to minimise the postoperative events.

In this issue of the journal Jayakeerthi et al. have reported their experience of pre-operative risk evaluation on 920 patients referred for cardiac assessment. They used RCRI proposed by Lee et al. in 1999 for prediction of cardiac events following surgery in 853 patients. The RCRI was described for planned non-cardiac surgery patients, whereas, the cohort described in the current report includes emergent surgical procedures in addition to elective surgeries, which the authors believe reflects the real world. The number of emergency surgeries was relatively small (40/853). Electrocardiogram (ECG) monitoring was done for all patients (pre-operative, immediate postoperative and 1st postoperative day) in addition to troponin estimation in intermediate and high-risk patients. This resulted in event rate of 3% which comprised primarily of non-ST-segment elevation MI (NSTEMI) (63% of the events). Inclusion of troponin positivity as a postoperative event might have lead to high overall event rate of 3%. Similar observations were made by Poldermans et al. The event rate increased markedly as the RCRI class increased, which confirms with the earlier studies and clinical experience. Further, analysis done by the authors show that the postoperative events were more common in older individuals, in patients with history of ischaemic heart disease, in patients undergoing emergency surgery and in patients with poor general medical status at surgery. Overall, RCRI was found to be a useful tool and the authors suggest addition of age, emergency surgery, and general medical condition to improve upon the risk prediction.

Although, this seems to be the first large experience of risk assessment from our country, number of large scale data is available from Europe and North America. Boersma et al. reviewed the records of 108,593 patients undergoing non-cardiac surgery at Erasmus University database from 1991–2000 and found that RCRI was a good predictive tool and the
accuracy could be improved by adding age and type of surgery to the RCRI. The American College of Surgeons’ National Surgical Quality Improvement Programme (NSQIP) database was used to determine risk factors associated with intra-operative/postoperative MI or cardiac arrest (MICA). The model was developed from a database of >200,000 non-cardiac surgeries performed in 2007 and validated on 2008 dataset.7 On multivariate logistic regression analysis, type of surgery, dependent functional status, abnormal creatinine, American Society of Anesthesiologists’ class and increased age were identified as predictors of MICA. The risk model developed from these indicators was found to outperform the RCRI (c statistics of 0.87 vs 0.74 for RCRI). An easy to use calculator is developed from this model and is available on the web (www.surgicalriskcalculator.com). This calculator is the most recent which reflects the peri-operative cardiovascular risk in the current era.

In summary, the author’s effort to document the postoperative cardiac events in a large database needs to be applauded. It is noteworthy that they have used ECG surveillance and troponin monitoring to detect the postoperative cardiac events, which albeit has given a higher event rate as compared to the standard existing literature. However, it is important to recognise silent myocardial injury in postoperative patients, as it has a significant impact on intermediate term outcome. This article highlights the importance of using appropriate risk models, especially in countries like India, where the medical practice is nursing home-based. Once patient is identified as higher risk (RCR class > 3), appropriate care can be taken to manage such a patient, including shifting such patients to a tertiary care centre for the required surgery. Such simple actions can help all of us to manage postoperative more effectively reducing morbidity and mortality.

References

Original article
Pregnancy associated plasma protein-A (PAPP-A) as an early marker for the diagnosis of acute coronary syndrome
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A B S T R A C T
Aims and objectives: Pregnancy associated plasma protein-A (PAPP-A), a metalloproteinase plays a pivotal role in the pathogenesis of atherosclerosis. Recent studies have reported that elevated levels of PAPP-A, signal the onset of acute coronary syndrome (ACS). We, therefore, proposed to study the analytical competence of PAPP-A in patients admitted to the emergency department with chest pain and finally diagnosed as ACS.

Methods and results: Pregnancy associated plasma protein-A was measured using enzyme-linked immunosorbent assay (ELISA) in 485 patients admitted to emergency care unit, of which 89 patients were diagnosed as Non-cardiac chest pain (NCCP). Elevated levels of PAPP-A were observed in patients diagnosed as ACS on comparison with the controls. Receiver operator characteristic (ROC) curve analysis showed PAPP-A to be a good discriminator between ischaemic and non-ischaemic patients. The area under the curve was found to be 0.904, 95% CI (0.874–0.929) with 90% sensitivity and 85% specificity (P<0.0001). The cut-off value from the ROC curve was 0.55 μg/mL above which PAPP-A was considered to be positive.

Conclusion: Pregnancy associated plasma protein-A seems to be a promising biomarker for identification and risk stratification for patients with ACS.

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K E Y W O R D S
Acute coronary syndrome—Biomarker
Atherosclerosis
PAPP-A-metalloproteinase

Introduction
Diagnosis of patients with acute coronary syndrome (ACS) is a major challenge for the clinicians at the emergency unit. Despite the success of cardiac troponins as gold standard, the search for a biomarker which precedes necrosis is still on. Recent studies have suggested that pregnancy associated plasma protein-A (PAPP-A) is an emerging biomarker in the category of markers of inflammation and plaque instability.1–3 Pregnancy associated plasma protein-A is a zinc binding metalloproteinase which was originally identified as a circulating protein in the serum of women in advanced stages of gestation. In 2001, Bayes-Genis et al4 described PAPP-A as a potent marker for coronary artery disease (CAD) and ACS. The demonstrated elevated levels of PAPP-A are found in unstable plaques than in stable plaques. Later, several studies have reported that circulating (elevated) levels of PAPP-A, independently predict the risk of an ischaemic event.5,6 Uncomplexed form of PAPP-A is elevated in ACS. Binding of pro major basic protein (MBP) to PAPP-A molecule is hindered due to oxidative stress in the microenvironment of the plaque. Unbound PAPP-A acts as a metalloproteinase causing rupture of the plaques. To the best of our knowledge, no study demonstrating PAPP-A as a sensitive biomarker for ACS in Indian population has been carried out. Therefore, we evaluated the circulating PAPP-A concentrations to detect the onset of ACS.
Methods

Patients

The study was carried out at the Department of Biochemistry and Clinical Lab, International Centre for Cardiothoracic and Vascular Diseases, Frontier Lifeline & Dr. KM Cherian’s Heart Foundation, Chennai, India. The study was approved by the Institutional Ethics Committee and written informed consent was obtained from all the patients.

The study group included 485 consecutive patients admitted to critical care unit (CCU) with manifestations suggestive of acute myocardial ischaemia including those with chest pain with or without radiation, compressing chest discomfort, palpitations, shortness of breath, lower jaw pain, left arm pain, epigastric pain, hypotension and other symptoms suggestive of angina. 12-lead electrocardiogram and all demographic details of the patients were recorded.

Of the 485 consecutive patients admitted to CCU, 297 patients had ACS (98 patients with ST-segment elevation, 99 patients without ST-segment elevation and 100 patients with unstable angina) with a mean age of 55 ± 11 years and 76% of them being males. Remaining patients were diagnosed as non-cardiac chest pain (NCCP) with a mean age of 52 ± 11 years and 67% being males.

Among 99 healthy volunteers with no clinical evidence of heart disease, a mean age of 50 ± 12 years and proportion of males being 63% were observed. Patients with liver, kidney disorders, brain ischaemia, tumour, and pregnant women were excluded from the study.

Blood sampling

Venous blood was drawn from patients admitted to CCU within 4–6 hours after symptom onset into plain tubes (without anticoagulants) and allowed to clot for half-an-hour, before centrifugation. Serum was separated and stored at −40°C until analysis and the samples were thawed only once.

Detection of pregnancy associated plasma protein-A, troponin I, and creatine kinase-MB fraction

Levels of PAPP-A were determined using Demeditec Diagnostics (Germany), according to the manufacture’s instructions. The concentrations of troponin I and creatine kinase-MB fraction (CK-MB) were determined by microparticle enzyme immunoassay (MEIA) (Abbott Axsym) and International Federation of Clinical Chemistry (IFCC) methods respectively. Troponin I levels above > 0.1 ng/mL and CK-MB levels > 25 U/L were considered to be positive.

Statistical analysis

Statistical evaluations were performed using Statistical Package for the Social Sciences (SPSS) software 9.0. Receiver operator characteristic curve analysis was performed using MedCalc 9.6. Data are expressed as mean ± SD. Significance between subgroups were analysed using Kruskal Wallis test. P values < 0.05 were considered to be statistically significant.

Results

The biochemical, haematological parameters and risk factors of the study groups are summarised in Table 1. Mean PAPP-A values (µg/mL) in the ST-segment elevated myocardial infarction (STEMI), non-STEMI (NSTEMI) and unstable angina (UA) patients were 1.13 ± 0.25, 0.90 ± 0.29, and 0.84 ± 0.26, respectively (Table 2). The differences were found to be significantly higher in patients than in controls (0.31 ± 0.33) (P < 0.001). The levels in NCCP were (0.43 ± 0.49) (P < 0.001) also found to be lower in comparison with patients. Figure 1 depicts the levels of mean PAPP-A in different study groups. Figure 2 shows the PAPP-A values in cases and controls. Intercomparison of groups revealed no significant differences between controls and NCCP & STEMI and NSTEMI. All other group comparisons were found to be highly significant (P < 0.001).
Table 1
Baseline characteristics of patients with acute coronary syndrome and control subjects.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Control (n=99)</th>
<th>NCCP (n=89)</th>
<th>STEMI (n=98)</th>
<th>NSTEMI (n=99)</th>
<th>UA (n=100)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>45±12</td>
<td>53±12</td>
<td>55±12</td>
<td>56±13</td>
<td>55±11</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Male (n)</td>
<td>63</td>
<td>67</td>
<td>89</td>
<td>71</td>
<td>67</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Serum glucose (mg/dL)</td>
<td>108.34±23.93</td>
<td>142.18±47.77</td>
<td>214.54±91.88</td>
<td>170.27±75.03</td>
<td>184.23±81.34</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Serum total cholesterol (mg/dL)</td>
<td>168.8±18.39</td>
<td>170.18±23.56</td>
<td>186.19±40.86</td>
<td>194.23±43.11</td>
<td>183.8±39.24</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Serum triglycerides (mg/dL)</td>
<td>148.14±33.20</td>
<td>148.95±45.87</td>
<td>157.67±63.20</td>
<td>151.26±53.17</td>
<td>157.49±67.10</td>
<td>NS</td>
</tr>
<tr>
<td>Serum LDL-cholesterol (mg/dL)</td>
<td>82.04±24.07</td>
<td>109.16±29.94</td>
<td>118.23±34.96</td>
<td>118.97±37.82</td>
<td>126.86±39.77</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Serum HDL-cholesterol (mg/dL)</td>
<td>47.42±7.86</td>
<td>38.02±5.60</td>
<td>37.89±5.77</td>
<td>37.41±4.47</td>
<td>37.31±3.70</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Serum urea (mg/dL)</td>
<td>26.76±5.06</td>
<td>25.77±4.27</td>
<td>27.49±4.77</td>
<td>27.35±4.67</td>
<td>25.33±4.67</td>
<td>NS</td>
</tr>
<tr>
<td>Serum creatinine (mg/dL)</td>
<td>0.83±0.14</td>
<td>0.80±0.11</td>
<td>0.84±0.14</td>
<td>0.82±0.13</td>
<td>0.81±0.11</td>
<td>NS</td>
</tr>
<tr>
<td>Serum total protein</td>
<td>6.04±0.76</td>
<td>5.94±1.01</td>
<td>6.06±0.67</td>
<td>6.09±0.91</td>
<td>6.05±0.84</td>
<td>NS</td>
</tr>
<tr>
<td>Total WBC count (cells/cmm)</td>
<td>7812.36±1488.50</td>
<td>8224.44±1980.94</td>
<td>11783.67±3645.91</td>
<td>9676.77±3205.53</td>
<td>9771.00±2857.78</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Haemoglobin (g/dL)</td>
<td>14.09±1.58</td>
<td>13.66±1.60</td>
<td>14.16±1.55</td>
<td>13.66±1.54</td>
<td>13.55±1.52</td>
<td>NS</td>
</tr>
<tr>
<td>Diabetes mellitus (%)</td>
<td>20</td>
<td>36</td>
<td>61</td>
<td>58</td>
<td>62</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>2</td>
<td>21</td>
<td>47</td>
<td>54</td>
<td>55</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Family history of CAD (%)</td>
<td>19</td>
<td>15</td>
<td>46</td>
<td>48</td>
<td>49</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Smoking (%)</td>
<td>21</td>
<td>35</td>
<td>41</td>
<td>40</td>
<td>27</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Food habits (%)</td>
<td>56</td>
<td>79</td>
<td>77</td>
<td>66</td>
<td>76</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>(non-vegetarian) (%)</td>
<td>79.95±1.13</td>
<td>83.71±8.97</td>
<td>87.15±13.75</td>
<td>88.01±13.49</td>
<td>87.40±12.51</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>25.79±3.82</td>
<td>26.05±3.54</td>
<td>25.84±4.95</td>
<td>25.39±3.56</td>
<td>27.06±3.60</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Data are expressed as mean±SD for continuous variables and percentage (%) for categorical variables. CAD: coronary artery disease, HDL: high density lipoprotein, LDL: low density lipoprotein, NCCP: non-cardiac chest pain, NS: non-significant, NSTEMI: non-ST segment elevation myocardial infarction, STEMI: ST segment elevation myocardial infarction, UA: unstable angina, WBC: white blood cell.

Table 2
Serum levels of pregnancy associated plasma protein-A in the sub groups of acute coronary syndrome on comparison with goal standards.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Control</th>
<th>NCCP</th>
<th>STEMI</th>
<th>NSTEMI</th>
<th>UA</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PAPP-A (µg/mL)</td>
<td>0.31±0.33</td>
<td>0.43±0.49</td>
<td>1.13±0.25</td>
<td>0.90±0.29</td>
<td>0.84±0.26</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Troponin I (µg/mL)</td>
<td>0.02±0.04</td>
<td>0.84±0.42</td>
<td>6.65±8.30</td>
<td>2.34±5.46</td>
<td>0.44±2.23</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CK-MB (IU/L)</td>
<td>19.47±7.31</td>
<td>20.17±8.56</td>
<td>94.24±87.84</td>
<td>62.61±74.53</td>
<td>29.63±25.00</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>


Table 3
Sensitivity, specificity, area under the curve and 95% confidence interval of Troponin I, creatine kinase-MB fraction and pregnancy associated plasma protein-A at the optimum cut-off value obtained from the receiver operator characteristic curve.

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>AUC</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Troponin I</td>
<td>54</td>
<td>95</td>
<td>0.765</td>
<td>0.725–0.802</td>
</tr>
<tr>
<td>CK-MB</td>
<td>57</td>
<td>93</td>
<td>0.789</td>
<td>0.760–0.833</td>
</tr>
<tr>
<td>PAPP-A</td>
<td>90</td>
<td>85</td>
<td>0.804</td>
<td>0.874–0.929</td>
</tr>
</tbody>
</table>

CI: confidence interval, CK-MB: creatine kinase-MB fraction, AUC: area under the curve, PAPP-A: pregnancy associated plasma protein-A.

From the ROC curve, the optimum cut-off value for PAPP-A was found to be 0.55µg/mL (Figure 3). The area under the curve was found to be 0.904, 95% CI (0.874 – 0.929) (P < 0.0001) with 90% sensitivity and 85% specificity (Table 3). Figure 4 shows the comparison of ROC curves of PAPP-A with gold standards namely troponin and CK-MB, and PAPP-A was found to be highly significant.

Discussion

Pregnancy associated plasma protein-A, a zinc binding metalloproteinase is abundantly expressed in plaque cells and extracellular matrix of eroded and ruptured plaques. During the evaluation of unstable plaques in patients who have died suddenly of cardiac causes, an association between PAPP-A and atherosclerotic plaque was confirmed using histological evidence. Pregnancy associated plasma protein-A was originally used to determine the foetal diagnosis of Down syndrome. However, circulating concentrations of PAPP-A were shown
to be present in lower concentrations in both men and non-pregnant women.

Our study results show that circulating concentrations of PAPP-A in serum of patients with both UA and acute MI were higher than controls and NCCP. These were in agreement with Bayes-Genis et al.7 who observed increased PAPP-A concentrations even in patients with negative cardiac troponin. Pregnancy associated plasma protein-A appeared to be an independent predictor of future ischaemic events as well as the need for percutaneous coronary intervention (PCI) or coronary artery bypass graft surgery.5

Similar findings were reported by Heeschen et al.6 who observed raised PAPP-A in ACS than stable angina and patients without evidence for CAD. Mean PAPP-A levels in NSTEMI patients did not significantly differ from mean PAPP-A levels in UA.

The current study also observed no significant difference between NSTEMI and UA. But STEMI levels were found to be elevated than NSTEMI and UA. Similar results were observed by Iversen et al.8 where PAPP-A levels at admission were significantly higher in patients with STEMI than those with NSTEMI and UA. Elseber et al.9 reported a significant difference in mean PAPP-A levels between NCCP and ACS patients which were in very good agreement with our results. But there was an overlap in the serum PAPP-A levels due to a very small sample size in the study by Elseber et al.9 Prior reports, however, have clearly documented the prognostic utility of PAPP-A levels in similar populations. Iversen et al.10 have reported low levels of PAPP-A in patients without heart disease and confirm the association of elevated PAPP-A levels with the diagnosis of ACS. Our results also showed a significant difference between the mean PAPP-A levels in ACS patients when compared to NCCP.

Receiver operator characteristic curve analysis of our study population reported first in Indian population showed the area under the curve to be 0.904 with 90% sensitivity and 85% specificity (Table 2) at a cut-off value of 0.55μg/mL. In patients with samples drawn <6 hours after the onset of symptom, PAPP-A seemed to be more sensitive than CK-MB and troponin.8 Our results are highly significant when compared with the study by Laterza et al.11 who reported a cut-off value of 0.22mIU/L, with a sensitivity of 66.7% and a specificity of 51.1%.

Laterza et al.11 concluded PAPP-A to be a modest predictor of adverse events at 30 days. Heeschen et al.5 in a similar study showed PAPP-A was a powerful predictor both in patients with low and high troponin levels.

Other studies have demonstrated that in asymptomatic male subjects whose carotid intima media thickness and lesion status were evaluated by non-invasive ultrasonography, the presence of hyperlipidaemia and hyperchoic or isoechoic and echogenic lesions were associated with significantly higher PAPP-A levels.12

The exact role of PAPP-A in the pathophysiology of PAPP-A remains unclear but PAPP-A activates insulin-like growth factor-1 (IGF-I), a potent mediator of atherosclerosis.13 Pregnancy associated plasma protein-A may be involved in the process of plaque rupture and destabilization and hence plays an important role as significant predictive factor for diagnosis of patients presenting to CCU with acute chest pain.14 Furthermore, the prior reports have suggested the use of serum samples for PAPP-A to be highly beneficial than other sample types.15

In a substudy of the CAPTURE trial, elevated PAPP-A levels (>12.6mIU/L) in patients with ACS indicated an increased risk of death or MI at 30 days and 6 months, even in patients with negative troponin results.6 To date, the main problem is the standardisation due to the variation of complexed/uncomplexed PAPP-A epitopes. Ultra-sensitive assays have been identified but these assays are not equivalent in diagnostic value in non-pregnant patients. Adoption of PAPP-A as a clinical cardiac biomarker will require assay standardisation
and finding an optimal cut-off accordingly in addition to further clinical investigations. Elucidation of the actions of PAPP-A in the unstable plaque may hold the promise of leading to the development of specific plaque-directed therapies for the treatment of both stable and unstable coronary syndromes. In conclusion, PAPP-A elevations in circulation plays an important role in the diagnosis of ACS. Although, the study has been conducted on a reasonably good sample size, it is felt that further larger clinical trials would enhance the diagnostic capability of this novel biomarker.

References

Original article
Assessment of left ventricular systolic function by velocity vector imaging
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¹Associate Professor, ²Professor, Department of Cardiology, ³Professor, Department of Nuclear Medicine, Christian Medical College, Vellore – 632004, Tamilnadu, India.

ABSTRACT

Objectives: To study the usefulness of a novel echocardiographic technique, velocity vector imaging (VVI) in the measurement of left ventricular ejection fraction (LVEF).

Background: Ejection fraction measured by echocardiography forms the cornerstone in the assessment of LV systolic function. Errors in measurement of EF by routine two-dimensional echocardiography (2D ECHO) limit its utility. The VVI is a new technology which uses speckle tracking and other algorithms to track the endocardial border. This may help in more accurate assessment of EF.

Methods: Global and regional LVEF was measured in 49 patients using VVI, 2D ECHO and radionuclide-gated single photon emission computed tomography (SPECT). Results were categorised as normal, mild, moderate, or severe LV systolic dysfunction based on American Society of ECHO classification. The results were analysed by appropriate statistical tests for correlations.

Results: The mean EF was $35 \pm 12.08\%$ by VVI, $54.2 \pm 19.51\%$ by SPECT ($P < 0.001$ vs VVI) and $50.3 \pm 8.92\%$ by 2D ECHO ($P < 0.001$ vs VVI). There was weak linear positive correlation between EF measured by VVI and the other modalities (Pearson’s correlation coefficient 0.577 for SPECT and 0.573 for 2D; $P = 0.01$). The VVI systematically underestimated the EF compared to SPECT. Greater number of patients had moderate or severe LV systolic dysfunction by VVI (37; 74.5%) than by SPECT (17; 34.7%; $P = 0.037$). We derived a correction factor to calculate SPECT EF from VVI EF as follows: $\text{EF (SPECT)} = \text{EF (VVI)} \times 0.9 + 21$ or approximately VVI (EF) + 20.

Conclusion: Measurement of EF by VVI is feasible. The VVI underestimated the EF when compared to nuclear-gated SPECT in this study. The accuracy of this technology and the need for a correction factor needs to be assessed in future studies.

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KEYWORDS
Ejection fraction
Velocity vector imaging
Single photon emission computed tomography

Introduction

Left ventricular (LV) function is a useful measure in the assessment and prognostication of heart disease. The LV ejection fraction (EF) continues to be the principal method used in the assessment of LV systolic function despite its limitations.¹–³ Measurement of EF by routine two-dimensional echocardiography (2D ECHO) is highly operator-dependent and therefore may be prone to errors and have less reproducibility.⁴ Recent technological advances have resulted in the development of new modalities that have increased the value of ECHO as a diagnostic tool. This is important, given the lesser cost and ease of performance of ECHO.

Velocity vector imaging

Speckle tracking echocardiography (STE) tracks movement of the myocardium using acoustic markers where ultrasonic energy is altered based on the structure of the myocardium.⁵ Velocity vector imaging (VVI) is a unique technology that uses a complex tracking algorithm for assessing myocardial velocities. The VVI extracts cardiac motion by tracking a user-defined interface, which is typically drawn along a border. The trace is tracked through one or more cardiac cycles by application of a series of tracking steps which include speckle tracking, global motion coherence, consistency of periodicity between cardiac cycles and other techniques. Motion of tissue, both perpendicular (inward-outward border motion) and parallel to the trace (tissue strain) is tracked to give robust estimates of myocardial movement. Modifications are made to the tracking...
algorithm depending on the user-selected trace (e.g., apical vs short axis views).\textsuperscript{6} Yellow velocity vectors placed on the 2D image indicate the direction and relative speed of the tissue with longer arrows indicating proportionally higher velocities. Using VVI requires a good quality 2D image and at least one full R–R wave must be contained as the VVI algorithm uses the periodicity of cardiac motion in tracking and analysis.

Velocity vector imaging is useful in calculating global and regional EF and has potential in assessing ventricular dyssynchrony,\textsuperscript{7} right ventricular (RV) function, left atrial mechanics etc.\textsuperscript{8}

In this study, we assessed the LVEF using VVI and compared it with that obtained by nuclear single photon emission computed tomography (SPECT) and routine 2D ECHO.

**Methods**

The study was performed among patients from the Cardiology outpatient area of Christian Medical College, Vellore; a tertiary care institution in South India. All patients presenting for evaluation of suspected ischaemic heart disease (IHD) were eligible to participate. Patients with poor ECHO window were excluded. Baseline clinical data was collected in all patients. All patients underwent a 12-lead electrocardiogram (ECG) and 2D ECHO. The EF was calculated as per Simpsons rule. Patients were categorised as normal or having mild, moderate or severe LV dysfunction (LVD) based on American Society of Echocardiography Classification (normal $\geq 55\%$, mild LVD $45–54\%$, moderate LVD $30–44\%$, severe LVD $<30\%$).\textsuperscript{9} All patients gave informed consent for participation in the study.

**Velocity vector imaging analysis**

Velocity vector imaging analysis was performed using the Siemens Sequoia 512 machine (Siemens Medical Solutions, USA, Inc.) by a single operator who did not know the EF measured by the other modalities. The LV endocardium was traced manually in the apical 4-chamber view to provide the basic trace. The VVI software was then used to automatically track endocardial border movement. The LV volume was calculated based on the volume of 64 disks whose diameters fit between opposing sides of the trace and are parallel to the plane defined by the trace endpoints (mitral plane).\textsuperscript{10} Regional EF was computed by dividing each side of the trace into three segments of equal length, then dividing the disks into two portions using a line from the apex to the centre of the base. A regional EF of $<35\%$ was considered low.\textsuperscript{11}

**Nuclear imaging**

Each patient also underwent nuclear-gated SPECT from which regional ischaemia was analysed and EF calculated. In addition, SPECT EF was calculated by another observer independently in 12 randomly selected patients to assess inter-observer variability.

**Table 1**

Demographic characteristics (percentages in parentheses).

<table>
<thead>
<tr>
<th>Age (mean±SD)</th>
<th>55.04±8.78</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>43 (87.8)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>21 (42.9)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>20 (40.8)</td>
</tr>
<tr>
<td>Smoker</td>
<td>15 (30.6)</td>
</tr>
<tr>
<td>Dyslipidaemia</td>
<td>30 (61.2)</td>
</tr>
<tr>
<td>Angina</td>
<td>25 (51)</td>
</tr>
<tr>
<td>Dyspnorea</td>
<td>22 (44.9)</td>
</tr>
<tr>
<td>NYHA</td>
<td></td>
</tr>
<tr>
<td>Class I</td>
<td>13 (26.5)</td>
</tr>
<tr>
<td>Class II</td>
<td>33 (67.3)</td>
</tr>
<tr>
<td>Class III</td>
<td>3 (6.3)</td>
</tr>
<tr>
<td>Previous STEMI</td>
<td>20 (40.8)</td>
</tr>
<tr>
<td>Previous ACS (other than STEMI)</td>
<td>14 (28.6)</td>
</tr>
<tr>
<td>Q waves on ECG</td>
<td>15 (30.6)</td>
</tr>
<tr>
<td>RWMA by ECHO</td>
<td>17 (34.7)</td>
</tr>
<tr>
<td>Ischaemia on SPECT</td>
<td>13 (26.5)</td>
</tr>
<tr>
<td>Aspirin</td>
<td>32 (65.3)</td>
</tr>
<tr>
<td>Beta-blocker</td>
<td>28 (57.1)</td>
</tr>
<tr>
<td>Statin</td>
<td>35 (71.4)</td>
</tr>
<tr>
<td>ACEI/ARB</td>
<td>25 (51.1)</td>
</tr>
<tr>
<td>Nitrate</td>
<td>22 (44.9)</td>
</tr>
</tbody>
</table>


**Statistics**

Pearson's correlation coefficient was used to analyse the correlation between EF calculated by VVI, SPECT, and 2D ECHO. Paired $t$-test was used to analyse continuous variables and $\chi^2$-test or Fisher's exact test was used to assess categorical variables. Significance was considered at a $P$ value of $\leq0.05$.

**Results**

A total of 49 patients were studied. Table 1 shows the demographic characteristics of the patients studied.

**Measurement of ejection fraction**

The mean EF calculated by VVI was $35\pm12.08\%$, as compared to $54.2\pm19.51\%$ with SPECT ($P<0.001$ vs VVI) and $50.3\pm8.92\%$ with 2D ECHO ($P<0.001$ vs VVI). The mean EF measured by VVI was significantly less than that measured by the other modalities. Thirty four out of 49 patients (69.3%) had reduced segmental EF in one or more regions as measured by VVI.

There was a positive linear correlation between the VVI EF and SPECT EF (correlation coefficient 0.577; $P=0.01$) as well as 2D EF (correlation coefficient 0.573; $P=0.01$).
Table 2
Left ventricular dysfunction by two-dimensional echocardiography, single photon emission computed tomography, and velocity vector imaging (percentages in parentheses).

<table>
<thead>
<tr>
<th>LV Function</th>
<th>2D</th>
<th>SPECT</th>
<th>VVI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>27 (55.1)</td>
<td>28 (57.1)</td>
<td>2 (4.1)</td>
</tr>
<tr>
<td>Mild</td>
<td>6 (12.2)</td>
<td>4 (8.2)</td>
<td>10 (20.4)</td>
</tr>
<tr>
<td>Moderate</td>
<td>16 (32.7)</td>
<td>10 (20.4)</td>
<td>22 (44.9)</td>
</tr>
<tr>
<td>Severe</td>
<td>0</td>
<td>7 (14.3)</td>
<td>15 (30.6)</td>
</tr>
</tbody>
</table>

2D: two-dimensional, LV: left ventricular, SPECT: single photon emission computed tomography, VVI: velocity vector imaging.

Assessment of left ventricular dysfunction

Table 2 shows the relative proportion of patients with normal LV function, mild, moderate, or severe LVD with the different modalities of measurement. There were significantly greater proportion of patients having moderate or severe LVD by VVI (75.5%) when compared to SPECT (34.7%; P = 0.037 vs VVI).

Inter-observer correlation for measurement of ejection fraction by gated single photon emission computed tomography

Excellent agreement was seen for measured EF by SPECT (correlation coefficient 0.992, P = 0.01) between two observers, reflecting good reliability of measurement.

Correction factor for velocity vector imaging ejection fraction

A numerical equation giving the relationship between SPECT EF and VVI EF was obtained from a linear regression scatter plot. The SPECT EF can be calculated from the VVI EF as given by the equation: 
\[ \text{EF (SPECT)} = \text{EF (VVI)} \times 0.9 + 21 \]  
or approximately VVI (EF) + 20.

Discussion

In this study, we have evaluated the new ECHO modality of VVI in the assessment of LV systolic function by EF. As per the results obtained from this study, EF measured by VVI does not appear to be accurate. There was weak positive linear correlation between the EF measured by VVI and the other modalities, i.e., SPECT and 2D ECHO. The mean EF as measured by VVI was significantly less than that measured by either SPECT or 2D ECHO. Taken together, the above facts suggest that VVI systematically underestimates the EF as compared to gated SPECT.

In addition to showing that this difference is significant in absolute terms, we also analysed whether it affects classification into different categories of LVD as this is more likely to directly affect therapy. A significantly greater proportion of patients were classified as having moderate or severe LVD by VVI as compared to SPECT. Thus, the underestimation of EF by VVI is clinically significant.

As SPECT was used as the gold standard for EF in this study, reliability of measurement was checked by looking for any variation in measurement between two independent observers. The inter-observer correlation was excellent showing that measurement error was not a significant issue in calculating EF from gated SPECT.

Finally, we looked at the numerical relationship between the calculated VVI EF and SPECT EF and found that the VVI EF was numerically about 20% SPECT EF. In other words, the ‘correct’ SPECT EF can be found by adding 20 to the VVI EF. This can be potentially incorporated as a correction factor in the VVI algorithm to improve its accuracy. This will need to be prospectively validated.

There are few studies in literature assessing the use of VVI for assessment of myocardial systolic function. Chen et al. measured regional EF in subject’s post myocardial infarction and concluded that VVI reflects impairment in regional systolic function. Pirat et al. have shown that global and regional RV EF measured by VVI correlated well with that measured by 2D ECHO. Most studies have used VVI for measurement of myocardial deformation parameters and assessment of dyssynchrony. Zeng et al. showed decreased strain and strain rate to be indicators of reduced systolic function in patients with dilated cardiomyopathy. Vannan et al. have shown that assessment of circumferential strain using VVI can help explain non-response after cardiac resynchronisation therapy.

It is difficult to speculate as to why there was a significant underestimation of EF by VVI. To our knowledge, this is the first study to attempt to validate LVEF measured by VVI against an existing standard. Bansal et al. found that longitudinal and radial strain were significantly underestimated by VVI in comparison to tagged magnetic resonance imaging (MRI). As VVI is a new and still evolving technology, the software and tracking algorithm may need to be ‘fine tuned’ as data from more clinical studies become available.

Limitations

The present study is limited by the small patient numbers; hence its findings will need to be validated in larger studies. We also did not assess regional contractility or other parameters such as strain and strain rate using VVI which would have given more detailed information. There is no doubt that VVI is a conceptually sound technology with good future potential. Further studies assessing the use of VVI to measure parameters of myocardial function in a variety of patient populations will shed further light on the performance of this technology.

Conclusion

In conclusion, measurement of EF by VVI is simple and feasible for use in clinical practice. The accuracy of this technology
in comparison with current standards and the need, if any, for a correction factor in the VVI algorithm needs to be further assessed in future studies.

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Editorial

Muscle mechanics by velocity vector imaging—questioning the questions themselves!

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For decades, assessment of left ventricular (LV) ejection fraction (EF) has been the predominant parameter for assessing LV systolic function. In recent years, there is broadening of understanding of myocardial myofibre structure, which has paved the way for more comprehensive understanding of myocardial mechanics. The deformation characteristics of myocardium or strain, and its quantitation is complex. The enthusiasm of studying myocardial mechanical function using tissue Doppler-derived strain, faced criticisms with regard to angle dependency, noise interference, and inter as well as intra-observer variability.¹ Speckle tracking echocardiography (ECHO) emerged as an alternative technique, that analyses tissue motion, by tracking natural acoustic reflections, and resolved angle dependency of tissue Doppler-derived strain.² As echocardiographers across the globe were trying to decipher the differences between ‘Lagrangian’ and ‘Eulerian’ strain, and conceptualise the LV mechanical function in three-dimensions (3D), there was a ‘twist’ to the tale. The concept of ‘rotation’, ‘twist’, and ‘torsion’ came to the fore-front.³ While some used the terms interchangeably, others emphasised the subtle differences. Another major highlight was the concept of ‘wringing’ motion of the heart in systole with storage of potential energy. This potential energy is released back like a spring uncoiling and generating suction force for a rapid early diastolic filling. With stiffness of myocardial fibres, delayed untwisting attenuates LV filling with concomitant rise in LV filling pressures. The sub-endocardial region which is the most vulnerable region to ischaemia, governs LV longitudinal mechanics. Hence, circumferential and radial strain may remain normal or even exaggerated to compensate for preserving LV systolic function.⁴ In other words, LVEF may be a poor indicator of LV systolic function.

Velocity vector imaging (VVI) is a novel imaging technique based on detecting speckles from the myocardium with two-dimensional (2D) ECHO analysing motion in different directions and is angle independent.⁵ It can be used to study cardiac mechanics and quantify global and regional cardiac function. In this issue, Narayanan et al.,⁶ in the article ‘Assessment of LV systolic function by VVI have compared global LVEF assessed by VVI, 2D ECHO and single photon emission computed tomography (SPECT). The results question the accuracy of VVI tracking algorithm as it underestimated LVEF as compared to SPECT. It would have been interesting to see the results of regional function in this study. Unfortunately, the authors failed to address this issue which is a limitation of this study. However, the authors deserve appreciation for boldly declaring the results which is not aligned to the existing belief.

While eulogies pertaining to new imaging technologies are easier to sight in the literature, negative studies are often ignored. This brings to fore-front a study which used 2D and 3D speckle tracking technique.⁷ There was underestimation of LV volumes with 2D speckle tracking ECHO as compared to 3D speckle tracking. The advantage of 3D speckle tracking is the evaluation of the motion of all myocardial segments in a single analysis step. In a single beat, the rotational mechanics of LV can be performed more accurately. However, the data on muscle mechanics with 3D ECHO is small and needs further elucidation.

At present, there are more questions than answers and questions questioning the questions themselves with regard to assessment of muscle mechanics by ECHO. Definitely, we will have more answers tomorrow, but understanding tomorrow, a day ahead, is not a contradiction of terms.

References


CardioSiteIndia

There has been a long standing need for an online portal for the Cardiologists and Internists in India that would help in keeping them updated about the recent happenings in the field of cardiology. Keeping this in mind, the website CardioSiteIndia (www.cardiositeindia.com) has been launched.

CardioSiteIndia is unique in terms of its offerings. It is a highly activity-driven forum that provides its members with an opportunity to network upload PPTs and videos, share journal reviews and receive the latest updates in the field of cardiology from all over the world.

Following are the salient features of CardioSiteIndia:

- Journal reviews and views of the cardiology community of India.
- Case of the month.
- Hot topic of the week and burning issues.
- Quick fire diagnostic quiz: ECG, Echo, Angio, etc.
- Latest news in cardiology from India and the world.

Apart from the above features, CardioSiteIndia provides its members with a social networking feature so as to enable the cardiologists of India to conveniently connect with each other and express their opinions. It also has a separate section for the lay population that would help the enormous number of people seeking heart-related information.

The Editor-in-Chief of the portal is Dr. Dev Pahlajani, an eminent cardiologist who pioneered invasive and interventional cardiology in India. He would be providing all the academic inputs for the portal along with a team of cardiologists of preeminence from all over the country.

The portal is being developed by Hansa MedCell which is a leading independent provider of Continuing Medical Education (CME), medical information, and pharma marketing strategy services.
Original article
Percutaneous coronary intervention in cardiogenic shock complicating acute ST-elevation myocardial infarction—a single centre experience
Vijayakumar Subban, Anand Gnanaraj, Balashankar Gomathi, Ezhilan Janakiraman, Ulhas Pandurangi, Latchumanadhas Kalidoss, S. Mullasari Ajit

ABSTRACT
Background: Mortality in acute myocardial infarction (AMI) complicated by cardiogenic shock (CS) approaches 70–80%, regardless of the type of pharmacological treatment. Early revascularisation improves survival in AMI with CS. Our aim is to assess the predictors of mid-term outcome after percutaneous coronary intervention (PCI) in patients with ST-segment elevation myocardial infarction (STEMI) and CS.

Methods: Forty-one patients who underwent primary or rescue PCI for CS were analysed comparing their baseline, angiographic, PCI data, 30-day and 1-year survival.

Results: There were no significant differences between survivors and non-survivors in baseline characters, except for more number of transfer admissions (P=0.0005), and cardiopulmonary resuscitations (P=0.015) in the later group. The mean time between myocardial infarction (MI) onset to shock and MI onset to revascularisation were 12.8±12.9 hours and 17.0±16.8 hours, respectively. Patients with better pre-procedure thrombolysis in myocardial infarction (TIMI) flow in the infarct-related artery (IRA) had better survival (P=0.0005). Successful PCI was achieved in 48.8% of patients. The 30-day mortality was 56.1% and all were prior to hospital discharge. Patients with successful PCI had better short-term survival in comparison with patients with failed PCI (80% vs 9.6%). Eighteen patients who survived at 30 days were followed up for 12–72 months (mean 28.5±5.4 months). Fifteen patients survived at 1 year after PCI and all were in good functional status.

Conclusion: Mortality remains high even with PCI. Achieving IRA patency with TIMI 3 flow is the main determinant of survival. Survival and functional status are good in patients who are discharged from hospital.

KEYWORDS
Acute myocardial infarction
Cardiogenic shock
Primary angioplasty

Introduction
Cardiogenic shock (CS) is the leading cause of death in the setting of acute myocardial infarction (AMI). It complicates 5–10% of the patients with AMI. With conservative management, 70–80% of the patients with CS succumb to this illness. The incidence of shock remained constant over the past two decades with a declining trend in the recent years with increasing use of primary percutaneous coronary intervention (PCI) for AMI. Pathological studies have established that myocardial dysfunction either from ischaemia or necrosis constitutes the major cause of CS. Restoration of perfusion to the ischaemic myocardium is the definitive way of improving survival in AMI with CS. Even though there was intensive medical management with inotropic support, thrombolysis and intra-aortic balloon pump (IABP) support has shown some improvement in survival, this modality is less effective in CS. Non-randomised studies have reported marked lowering of mortality with early revascularisation. In the randomised SHOCK (SHould we emergently revascularise Occluded Coronaries for cardiogenic shock?) trial, there were 132/1000 lives of patients saved, treated with early revascularisation as compared with medical therapy. This paper reviews our hospital PCI experience in AMI complicated by CS.
Materials and methods

This study was conducted between January 2001 and June 2007. Consecutive patients with acute ST-elevation myocardial infarction (STEMI) who underwent primary or rescue PCI were prospectively enrolled in a database. Patients who had PCI for CS were selected for our study. This population included patients directly admitted to our coronary care unit and those referred from peripheral hospitals without PCI facilities.

To obtain a more homogeneous population, only patients with CS due to predominant left ventricular failure (LVF) were included in the analysis. Patients with mechanical complications such as severe mitral regurgitation (MR), ventricular septal rupture, free wall rupture with tamponade, isolated right ventricular infarction and CS resulting from excess beta or calcium channel blockade or as a complication of a cardiac catheterisation were excluded.

The diagnosis of AMI was made if at least two of the following three elements were present: chest pain; ST-segment elevation of at least 0.1 mV in limb leads or 0.2 mV in precordial leads or a new onset left bundle branch block; serum creatinine phosphokinase-myocardial band isoenzyme (CPK-MB) elevation above twice the upper limit of normal.

The CS was defined as a compatible clinical presentation associated with a systolic blood pressure of 90 mmHg for at least 30 minutes despite inotropic and volume support as needed.

After admission to the coronary care unit, patients received inotropic and ventilator support as needed. They, then, underwent coronary angiography and angioplasty of the infarct-related artery (IRA) after IABP insertion. Patients were pre-loaded with 325 mg of aspirin and 50–70 units/kg of heparin. Glycoprotein (GP) IIb–IIIa inhibitor was administered as an adjunct in most of the patients. Periprocedural activated clotting time was maintained >200 seconds (HemoTec device). All suitable lesions in the IRA were stented. Multi-vessel PCI was done, when persistent haemodynamic instability was assumed to be related to the critical lesions in the non-IRAs.

Successful PCI was defined as a residual diameter stenosis of <50% and a thrombolysis in myocardial infarction (TIMI) 3 flow in the culprit vessel after the procedure.

All surviving patients were followed up clinically after hospital discharge for a mean of 28.5 ± 3.4 months.

Results

Between January 2001 and June 2007, 41 patients underwent primary or rescue PCI for AMI complicated by CS in our institution.

Baseline data

There were 31 (75.6%) men and 10 (24.4%) women. Their mean age was 58.2 ± 10.4 years. The baseline characteristics of these patients are shown in Table 1.

Anterior wall myocardial infarction (AWMI) occurred in 25 (61%) patients. Remaining patients 16 (39%) had non-anterior wall myocardial infarction (inferior wall and posterior wall) infarction.

Mechanical ventilator support was given in 29 (70.8%) patients. All the patients received catecholamine support and IABP. Ten patients (24.4%) required temporary transvenous pacing. The MR (<Grade II) was present in 10 (24.4%) patients. Post PCI, two patients developed severe MR, two had ventricular septal rupture and free wall rupture occurred in one patient. All these patients underwent emergency coronary artery bypass surgery. Renal dysfunction requiring peritoneal dialysis occurred in 12 (29.2%) patients. Multi-organ dysfunction developed in 19 (46.3%) patients. Two patients had re-infarction.

Angiographic data (Table 2)

Coronary angiography showed single vessel disease in 15 (36.6%) patients. Double vessel disease was present in 12 (29.3%) and triple vessel disease in 11 (26.8%) patients. Left main coronary artery (LMCA) disease was present in 3 (7.3%) patients.

The IRA was the left anterior descending in 27 (65.79%), the circumflex in 7 (17.1%) and the right coronary artery in 7 (17.1%). Before the intervention, an occluded IRA (TIMI 0/1 flow) was observed in 35 (85.4%), a TIMI 2 flow in 6 (14.6%) and none of the patients had TIMI 3 flow.

Percutaneous coronary intervention data (Table 3)

Most of the patients underwent percutaneous transluminal coronary angioplasty (PTCA) to the IRA. Three patients had multivessel PCI. The LMCA stenting was done in one patient after right coronary artery distribution (RCA) stenting for persistent shock. Two patients underwent left anterior descending (LAD) stenting (90% stenosis) after RCA stenting.

The intervention resulted in TIMI 3 flow in 20 (48.8%) and TIMI 2 flow in 16 (39%) patients, while 5 (12.2%) had TIMI 1 flow in the IRA. A PCI success was achieved in 20 (48.8%) patients.

A stent was implanted in 37 (90.2%) patients. Totally, 43 stents were implanted, 26 (60.4%) bare metal stents and 17 (39.6%) drug-eluting stents. The GP IIb/IIIa inhibitor was
Table 1
Cardiogenic shock complicating acute myocardial infarction: baseline characteristics.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>All PCI patients (n=41)</th>
<th>Survivors (n=18)</th>
<th>Non-survivors (n=23)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>58.2 ± 10.4</td>
<td>55.3 ± 10.7</td>
<td>60.4 ± 9.9</td>
<td>0.300</td>
</tr>
<tr>
<td>Male gender (%)</td>
<td>31 (75.6)</td>
<td>16 (88.9)</td>
<td>15 (65.2)</td>
<td>0.081</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>22 (53.7)</td>
<td>10 (55.6)</td>
<td>12 (52.2)</td>
<td>0.540</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>15 (36.6)</td>
<td>8 (44.4)</td>
<td>7 (30.4)</td>
<td>0.275</td>
</tr>
<tr>
<td>Smoking (%)</td>
<td>16 (39)</td>
<td>9 (50)</td>
<td>7 (30.4)</td>
<td>0.171</td>
</tr>
<tr>
<td>Dyslipidaemia (%)</td>
<td>9 (22)</td>
<td>4 (22.2)</td>
<td>5 (21.7)</td>
<td>0.630</td>
</tr>
<tr>
<td>Family history (%)</td>
<td>16 (39)</td>
<td>8 (44.4)</td>
<td>8 (34.8)</td>
<td>0.397</td>
</tr>
<tr>
<td>Previous MI (%)</td>
<td>8 (19.5)</td>
<td>3 (16.7)</td>
<td>5 (21.7)</td>
<td>0.300</td>
</tr>
<tr>
<td>Previous PCI (%)</td>
<td>5 (12.2)</td>
<td>2 (11.1)</td>
<td>3 (13)</td>
<td>0.581</td>
</tr>
<tr>
<td>Lowest SBP (mmHg)</td>
<td>68.8 ± 11.8</td>
<td>69.9 ± 10.5</td>
<td>68 ± 12.9</td>
<td>0.252</td>
</tr>
<tr>
<td>HR (bpm)</td>
<td>112.5 ± 3.5</td>
<td>118.4 ± 27.2</td>
<td>107.9 ± 32.7</td>
<td>0.533</td>
</tr>
<tr>
<td>Creatine kinase total</td>
<td>4704.9 ± 3215.3</td>
<td>5206.28 ± 3274.2</td>
<td>4312.3 ± 3185.3</td>
<td>0.426</td>
</tr>
<tr>
<td>EF (%)</td>
<td>29.4 ± 7.7</td>
<td>29.8 ± 5.6</td>
<td>29.1 ± 9.1</td>
<td>0.475</td>
</tr>
<tr>
<td>Mean time from MI to Shock (hr)</td>
<td>12.2 ± 12.9</td>
<td>12.6 ± 15</td>
<td>11.8 ± 11.4</td>
<td>0.348</td>
</tr>
<tr>
<td>CPR (%)</td>
<td>18 (43.9)</td>
<td>4 (22.2)</td>
<td>14 (60.9)</td>
<td>0.015*</td>
</tr>
<tr>
<td>Transfer admission (%)</td>
<td>24 (58.5)</td>
<td>4 (22.2)</td>
<td>20 (87)</td>
<td>0.0005*</td>
</tr>
<tr>
<td>Thrombolytic eligibility (%)</td>
<td>31 (75.6)</td>
<td>13 (72.2)</td>
<td>18 (78.2)</td>
<td>0.655</td>
</tr>
<tr>
<td>Thrombolytic administered (%)</td>
<td>15 (36.6)</td>
<td>5 (27.8)</td>
<td>10 (43.4)</td>
<td>0.300</td>
</tr>
<tr>
<td>GP IIb/IIIa inhibitor (%)</td>
<td>35 (85.4)</td>
<td>15 (83.3)</td>
<td>20 (87)</td>
<td>0.542</td>
</tr>
<tr>
<td>Inotropes/vasopressors (%)</td>
<td>41 (100)</td>
<td>18 (100)</td>
<td>23 (100)</td>
<td>–</td>
</tr>
<tr>
<td>IABP (%)</td>
<td>41 (100)</td>
<td>18 (100)</td>
<td>23 (100)</td>
<td>–</td>
</tr>
<tr>
<td>IABP duration (hr)</td>
<td>51.5 ± 43</td>
<td>57.4 ± 40.4</td>
<td>46.9 ± 45.3</td>
<td>0.260</td>
</tr>
<tr>
<td>Stent in IRA (%)</td>
<td>35 (70.8)</td>
<td>12 (66.7)</td>
<td>23 (100)</td>
<td>0.745</td>
</tr>
</tbody>
</table>


Table 2
Cardiogenic shock complicating acute myocardial infarction: angiographic characteristics.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>All PCI patients (%)</th>
<th>Survivors (%)</th>
<th>Non-survivors (%)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diseased vessels</td>
<td>0.505</td>
<td>0.505</td>
<td>0.505</td>
<td></td>
</tr>
<tr>
<td>SVD</td>
<td>15 (36.6)</td>
<td>7 (38.9)</td>
<td>8 (34.8)</td>
<td></td>
</tr>
<tr>
<td>DVD</td>
<td>12 (29.3)</td>
<td>6 (33.3)</td>
<td>6 (26.1)</td>
<td></td>
</tr>
<tr>
<td>TVD</td>
<td>11 (26.8)</td>
<td>4 (22.2)</td>
<td>7 (30.4)</td>
<td></td>
</tr>
<tr>
<td>LMD</td>
<td>3 (7.3)</td>
<td>1 (5.6)</td>
<td>2 (8.7)</td>
<td></td>
</tr>
<tr>
<td>Culprit vessel</td>
<td>0.557</td>
<td>0.557</td>
<td>0.557</td>
<td></td>
</tr>
<tr>
<td>LAD</td>
<td>27 (65.8)</td>
<td>12 (66.7)</td>
<td>15 (65.2)</td>
<td></td>
</tr>
<tr>
<td>LCX</td>
<td>7 (17.1)</td>
<td>4 (22.2)</td>
<td>3 (13.1)</td>
<td></td>
</tr>
<tr>
<td>RCA</td>
<td>7 (17.1)</td>
<td>2 (11.1)</td>
<td>5 (21.7)</td>
<td></td>
</tr>
<tr>
<td>Pre-PCI TIMI flow</td>
<td>0.001*</td>
<td>0.001*</td>
<td>0.001*</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>12 (29.3)</td>
<td>0</td>
<td>12 (52.2)</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>23 (56.1)</td>
<td>13 (72.2)</td>
<td>10 (43.5)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>6 (14.6)</td>
<td>5 (27.8)</td>
<td>1 (4.3)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>


Table 3
Cardiogenic shock complicating acute myocardial infarction: percutaneous coronary intervention details.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>All PCI patients (%)</th>
<th>Survivors (%)</th>
<th>Non-survivors (%)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post-PCI TIMI flow</td>
<td>0.0005*</td>
<td>0.0005*</td>
<td>0.0005*</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>5 (12.2)</td>
<td>0</td>
<td>5 (21.7)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>16 (39)</td>
<td>2 (11.1)</td>
<td>14 (60.9)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>20 (48.8)</td>
<td>16 (88.9)</td>
<td>4 (17.4)</td>
<td></td>
</tr>
<tr>
<td>PCI success</td>
<td>0.0005*</td>
<td>0.0005*</td>
<td>0.0005*</td>
<td></td>
</tr>
<tr>
<td>Successful</td>
<td>20 (48.8)</td>
<td>16 (88.9)</td>
<td>4 (17.4)</td>
<td></td>
</tr>
<tr>
<td>Unsuccessful</td>
<td>21 (51.2)</td>
<td>2 (11.1)</td>
<td>19 (82.6)</td>
<td></td>
</tr>
</tbody>
</table>

*Statistically significant. PCI: percutaneous coronary intervention, TIMI: thrombolysis in myocardial infarction.

Survival

The 30-day mortality rate was 56.1%. Of all the parameters analysed, only three variables were significantly different between survivors and non-survivors. Patients who were transferred from peripheral centres to our institution after shock onset (P=0.0005) and those who underwent cardiopulmonary resuscitation prior to angioplasty (P=0.015) fared less well in our series. The 30-day survival rate was better in patients with higher pre- and post-TIMI flow grades (P=0.0005).
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With successful PCI, the survival was 80%. In contrast, with failed PCI, the survival was only 9.6%. Of the five patients who underwent emergency surgery, four died during the postoperative period.

Follow-up data

Eighteen patients survived at 30 days and were followed up for 12–72 months (mean 28.5 ± 5.4 months). Elective repeat PCI was done in two patients for diseased non-IRAs. Two patients underwent implantable cardioverter defibrillator (ICD) implantation for ventricular tachycardia and one patient had cardiac resynchronisation therapy. Three patients died during first year follow-up, one from heart failure and other two from ventricular arrhythmias (Figure 2). Another three patients died after 1 year follow-up. Remaining 12 patients are on follow-up till date. Most of these patients are in New York Heart Association (NYHA) I/II functional status.

Table 4
Comparison of percutaneous coronary intervention in SHOCK trial data and our data.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>SHOCK trial data</th>
<th>Our data</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>82</td>
<td>41</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>65 ± 10</td>
<td>58.2 ± 10.4</td>
</tr>
<tr>
<td>Diabetes mellitus (%)</td>
<td>25</td>
<td>53.7</td>
</tr>
<tr>
<td>Mean time from MI to shock (hr)</td>
<td>NA</td>
<td>12.2 ± 12.9</td>
</tr>
<tr>
<td>Mean time from MI to revascularisation (hr)</td>
<td>NA</td>
<td>17 ± 16.8</td>
</tr>
<tr>
<td>Thrombolysis (%)</td>
<td>49</td>
<td>36.6</td>
</tr>
<tr>
<td>Multivessel disease (%)</td>
<td>81</td>
<td>65</td>
</tr>
<tr>
<td>IABP (%)</td>
<td>89</td>
<td>100</td>
</tr>
<tr>
<td>Stents (%)</td>
<td>34</td>
<td>90.2</td>
</tr>
<tr>
<td>GP IIb/IIIa inhibitors (%)</td>
<td>32</td>
<td>85</td>
</tr>
<tr>
<td>TIMI-3 flow (%)</td>
<td>61</td>
<td>48.8</td>
</tr>
<tr>
<td>30-day survival (%)</td>
<td>54</td>
<td>45</td>
</tr>
<tr>
<td>1 year survival (%)</td>
<td>51</td>
<td>36</td>
</tr>
</tbody>
</table>


Discussion

The CS in the setting of AMI occurs most commonly due to abrupt dysfunction of >50% of the ventricular myocardium. This results either from extensive myocardial infarction (MI) per se, or from a less extensive infarction in the presence of a previous infarction or severe triple vessel disease. Myocardial infarction or ischaemia initiates cardiac dysfunction in patients with CS. The resulting myocardial dysfunction further worsens ischaemia creating a downward spiral. This vicious cycle if not quickly interrupted, may result in irreversible myocardial dysfunction. Thus, mortality in established shock without intervention is very high. The outcome of CS is closely related to the patency of the IRA. Even though thrombolytic therapy reduced the incidence of CS in the GISSI trial, the benefit of thrombolytic therapy in the presence of CS was disappointing. The lack of benefit might be due to reduced lysis of thrombi in patients with low perfusion pressures.

Many non-randomised studies have shown improvement in survival with early revascularisation. However, there are only two randomised trials that compared medical therapy with early revascularisation and not much data is available on PCI in the setting of CS.

Swiss multicentre angioplasty for SHOCK (SMASH) trial, the first randomised trial to compare intensive medical treatment and invasive treatment showed a non-significant mortality difference (69% vs 78%; relative risk 0.88, 95% confidence interval, 0.6–1.2). This trial was terminated prematurely due to inadequate enrollment. In the SHOCK trial, 302 patients were randomly assigned to initial medical stabilisation (n = 150) or to early revascularisation (n = 152) within 6 hours of randomisation. Patients underwent revascularisation if CS began within 36 hours of the onset of MI. Mortality at 30 days was 46.7% in the revascularisation arm and 56% in the medical stabilisation arm which was not statistically significant. Nevertheless, at 6 months, the mortality was significantly lower in the revascularisation group (50.3% vs 63.1%, \( P = 0.03 \)), resulting in 128 lives saved per 1000 patients.
treated. At the end of 1 year, there was a 13.2% reduction in mortality in the revascularisation arm, representing 132 lives saved per 1000 patients treated. In the PCI arm of SHOCK trial, the overall survival in the 82 patients who underwent angioplasty was 54% \((n=44)\) at 30 days and 50% \((n=41)\) at 1 year. In the large primary PCI registry of the Arbeitsgemeinschaft Leitende Kardiologische Krankenhausarzte (ALKK), 1333 patients with CS underwent PCI. Total in-hospital mortality was 46.1%. Sutton et al. has reported in-hospital mortality of 51% in 113 patients who underwent PCI for CS.

Various clinical and procedural characteristics have been shown to be associated with poor outcomes in different studies. In the SHOCK trial and other observational studies, advanced age with its associated co-morbidities, was an important predictor of mortality in patients undergoing PCI for CS. Mean age in our patients was 58.2 ± 10.4 years, slightly younger than other studies. However, age was not a predictor of mortality in our population.

Timings of shock from chest pain onset and time to revascularisation were also important determinants of outcome in major trials and registries. In SHOCK Trial Registry, patients who developed early shock (<24 hours) fared less well than those with late onset shock (after 24 hours). The mean time from MI to shock in our study was 12.8 ± 12.9 hours. Of the 41 patients, 20 (48%) developed shock within 6 hours of MI and 31 (76%) within 24 hours. Late shock occurred only in 10 (24%) patients. There was no relationship between timing of shock and mortality. In the randomised SHOCK trial and other registries, there was a trend towards improved survival in those who had early revascularisation (<6 hours). However, SHOCK trial also has shown survival benefit for as long as 48 hours after MI and 18 hours after shock onset. The mean time from MI onset to revascularisation in our study was 17 ± 16.8 hours. It is relatively longer compared to other studies. Most of our patients were transferred from other hospitals, which could explain the delay in PCI. This delay might have contributed to the higher mortality among our patients. We did not find any difference in mortality between those receiving revascularisation within 12 hours of MI and those revascularised later. As with SHOCK trial data, our study also suggests that late revascularisation (outside the traditional 12-hour window) is also useful in patients with CS.

In the SHOCK trial, 60% of the patients were transferred from centres without PCI facilities. This variable did not influence survival following PCI in the SHOCK study. Transfer admission was an important predictor of mortality in our study. Twenty-four (58%) patients were transferred from peripheral centres without PCI facilities. Most of the transferred patients (80%) succumbed to CS in spite of PCI. These patients were haemodynamically more unstable than patients directly admitted in our institution. Infrequent use of IABP, mechanical ventilation, inotropic support and long delay from MI to revascularisation in the transfer admissions might have contributed to higher mortality in this group of patients.

In the SHOCK Trial Registry, administration of thrombolytic therapy before PCI did not affect survival in patients undergoing PCI for CS. However, in a series of 171 patients who underwent PCI for CS, rescue angioplasty was associated with lower final TIMI 3 flow and higher 1-year mortality. Even patients with a successful rescue PCI procedure had higher 1-year mortality than those with a successful primary PCI.

In our series, 15 (36.6%) patients underwent rescue angioplasty. As in the SHOCK Trial Registry patients, rescue angioplasty did not significantly influence survival in our patients.

In SHOCK trial and other observational studies, procedural success with establishment of TIMI 3 flow in the IRA was the strongest predictor of survival. We could achieve TIMI 3 flow in 48.8% of the patients only, though we had established IRA patency (<50% stenosis) in 87.8% of the patients. The 30-day mortality in 18 patients who had procedural success was only 20% in contrast to 90.4% in failed PCI.

It has been shown in the primary PCI studies that usage of stent and other adjuncts was associated with improved IRA patency rate and TIMI flow. Even though there was no large randomised data in the setting of CS, subgroup of patients in SHOCK trial, ALKK registry and small observational studies achieved better procedural success with stenting. We used stent in the IRA whenever the lesion was suitable for stenting (>2.5 mm). In our study, 37 (90.2%) patients underwent stenting in the IRA. In the REO SHOCK study and other observational studies, use of GP IIb–IIIa inhibitors was associated with improved TIMI 3 flow in the IRA in patients undergoing PCI for CS. We have used GP IIb–IIIa inhibitors in 35 (85.4%) of our patients. However, neither stenting nor GP IIb–IIIa inhibitors influenced the outcome in our series. Mechanical ventricular support as a bridge to recovery might improve outcome in CS. Even though IABP is the commonly employed assist device, the results in the setting of CS are conflicting. As a policy, we used IABP in all CS patients and hence we did not assess influence of IABP on mortality. Ongoing studies with IABP and other assist devices might shed more light on this issue. Although, most of our patients received IABP support, GP IIb–IIIa inhibitors and stenting, PCI success was less in our series than in SHOCK study and other registries. This could be due to long delay between shock onset and PCI.

Data for long-term outcome in CS is now available. In the SHOCK trial cohort, the 6 year survival rates for the hospital survivors were 62.4% vs 44.4% in the early revascularisation and initial medical stabilisation groups respectively. In the GUSTO-I trial, 55% hospital survivors were alive at 11 years. Furthermore, annual mortality rates after 1 year (2–4%) were similar for those with and without shock. Most of these patients were in good functional status. Patients who survived the initial crisis did well in our series also. This also emphasises the importance of aggressive revascularisation in patients with CS.

**Limitations**

Small sample size was the main limitation of the study. The CS was not confirmed invasively in all patients. Only 1-year follow-up was available in all patients. Mechanical causes of CS were excluded from analysis. Shock due to non-STEMI was not included in our study.
Conclusion

The CS remains the leading cause of death in AMI. By preserving ischaemic myocardium, PCI reduces the in-hospital mortality which was maintained in the long-term. Establishment of TIMI 3 flow is of paramount importance. In AMI with CS, even with best available treatment, survival is <50% in our study. This could be due to longer delay between shock onset and PCI. Transfer admissions were the main contributors to this delay. Early risk stratification, better referral systems, optimal use of adjunctive therapies and assist devices could improve the survival in future.

Acknowledgement

The authors sincerely thank Ms. Devapriya and Ms. Anitha for their valuable contribution in data collection.

References

Cardiogenic shock continues to be the most common cause of death in patients with acute myocardial infarction (MI), occurring in 5–10% of ST-elevation MIs (STEMI) and 2–3% of non-ST-elevation acute coronary syndromes (ACS). A complex, degenerating clinical spiral of multiorgan dysfunction, cardiogenic shock begins when the heart is no longer able to provide sufficient resting pressure and flow.¹ Without effective intervention, progression of cardiogenic shock is rapid and fatal.²

Over the past decade, although the rates of cardiogenic shock present on hospital admission have remained constant, the overall incidence has decreased. This may be attributed to the increased global frequency of revascularisation for ACS. The AMIS Plus Registry³ of 23,696 patients with ACS provides good proof for this. The overall incidence of cardiogenic shock from 1997 to 2006 fell from 12.9% to 5.5% (P < 0.001), while the use of primary percutaneous coronary intervention (PPCI) during the same period in patients with cardiogenic shock increased from 7.6% to 65.9% (P = 0.01) and was associated with a lower hospital mortality (odds ratio 0.47, 95% confidence interval 0.30–0.73, P = 0.001). The rates of cardiogenic shock on admission remained constant (28.5% of all cases; 2.3% of those with ACS). However, the incidence of shock developing in patients with MI after admission fell from 10.6% to 2.7% (P < 0.001) and in-hospital shock mortality fell from 62.8% to 47.7% (P = 0.010).

Despite advances and innovations in the management of cardiogenic shock, the rates of mortality, although improved to an extent in the recent decades, remain strikingly high. In the 1970s, the outlook of survival for patients with cardiogenic shock was dismal, with rates of in-hospital mortality exceeding 80%. For the past two decades, rates of survival have improved; however, approximately 50% of patients with cardiogenic shock still do not survive to hospital discharge. In this issue of the journal, Mulasari et al. studied 41 patients who underwent PPCI or rescue PCI for acute MI complicated by cardiogenic shock.⁴ The 30-day mortality rate of this group of patients was 56.1%. Such substantial figures are shared by other studies too. In the Arbeitsgemeinschaft Leitende Kardiologische Krankenhausarztretry with 1333 patients with cardiogenic shock, total in-hospital mortality was 46.1%.⁵ Similarly, the overall survival in the PCI arm of the (Should we emergently revascularise occluded coronaries for cardiogenic shock?) SHOCK trial was 54% at 30 days and 50% at 1 year.⁶

Although, early shock-related mortality remains significant with improving medical and interventional therapy, the outlook for survivors of ACS may be increasingly optimistic.⁷,⁸ In the SHOCK trial, the mortality rates in the two groups of revascularisation and medical treatment were not statistically significant at 30 days (46.7% vs 56%, respectively, P = 0.11), but by 6 months there was difference in benefit, and significantly increased survival rates were observed in patients treated with revascularisation (50.3% vs 63.1%, P = 0.027).⁶ Since, the SHOCK trial, hospital mortality has decreased gradually, now falling to <50% in few studies.⁹ This improvement may be ascribed to the increased rates of PPCI for ACS, which logically might prevent progression to cardiogenic shock in those at risk.

How effective are predictive models for the early prediction of shock and its eventual outcome? Considering the need for specialised multidisciplinary input, including surgical backup, early prediction of shock is of paramount importance. In the GUSTO-I¹⁰ and GUSTO-III¹¹ trials, patient’s age, systolic blood pressure, heart rate, or presenting Killip class predicted 85–95% of cases of shock. In the Global Registry of Acute Coronary Events, Jolly et al. showed that the degree of troponin elevation was predictive of post-infarction shock, cardiac arrest, and heart failure in 16,318 non-STEMI patients.¹² Sutton et al. in a single-centre UK experience of 113 patients with shock undergoing emergency PPCI, identified age >70 years, previous infarction, shock complicating failed thrombolysis treatment, and multivessel disease to be associated with adverse outcomes.¹³ Coronary angiographic findings at presentation have been found to have strong predictive value for mortality. In the SHOCK Trial Registry,¹⁴ in patients with left main

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doi: 10.1016/S0019-4832(12)60053-4
stem occlusion, the in-hospital mortality was 79%; while for isolated occlusion of the left anterior descending, left circumflex, and right coronary arteries, in-hospital mortality was 42%, 42%, and 37%. In the current study, patients who transferred from peripheral centres and underwent cardiopulmonary resuscitation fared worse. Also, expectedly, higher pre and post-procedure thrombolysis in MI flows were associated with better 30-day survival. A universal and effective prediction model for the development of cardiogenic shock is lacking and therefore very essential.

Is coronary angioplasty and revascularisation the end-of-the-road in the management of ACS with cardiogenic shock? Mechanical circulatory support systems are capable of sustaining life during profound post-infarction cardiogenic shock and are an important adjunct to coronary angioplasty in rapidly deteriorating patients. Options available for advanced circulatory support include the intra-aortic balloon pump (IABP), percutaneously inserted left ventricular assist devices (LVADs), extra-corporeal membrane oxygenation (ECMO), surgically inserted blood pumps and urgent cardiac transplantation.\(^\text{15}\) Although, counter-intuitive, no study has shown a survival benefit for the IABP in patients with established cardiogenic shock. Nevertheless, the ACC/AHA and ESC guidelines strongly recommend the use of IABP in the management of cardiogenic shock not reversed by pharmacological therapy. Percutaneously implantable blood pumps that are available to the cardiologist without the need for intervention by surgeons or perfusionists are the Impella Recover (Abiomed, Aachen, Germany) and Tandem Heart (Cardiac Assist, Inc., Pittsburgh, PA, USA). In a meta-analysis of three randomised studies with post-infarction cardiogenic shock, in which the IABP was directly compared with the Tandem Heart or the Impella Recover, it was found that, the LVAD resulted in greater cardiac index, mean arterial pressure, and reduced pulmonary capillary wedge pressure in comparison with the IABP, however, these findings did not translate into survival benefit. Although, disappointing, in established cardiogenic shock, percutaneous LVADs still have an important role in patients with haemodynamic instability undergoing high-risk PCI.\(^\text{16}\) By contrast, both ECMO and surgically implanted blood pumps show great promise to rescue more than half of those patients who would otherwise be destined to die. Extra-corporeal membrane oxygenation has been used as support in various scenarios in high-risk PCIs in cardiogenic shock including transradial PCI and left main occlusions, with survival benefits.\(^\text{17,18}\) These have also been used as bridges to LVADs or eventual cardiac transplantation. Urgent transplantation also provides an effective solution for rapidly deteriorating patients. This has been made possible in countries like Spain, which has one of the highest organ donation rates in Europe.

The scope for the aggressive management of cardiogenic shock is immense, but the resources limited. Mechanical circulatory support devices usually are either unavailable, or are limited only to heart transplant facilities. Financial constraints, especially in developing countries, pose another major hurdle in the utility of such support systems. Apart from prompt and efficient revascularisation, the need of the day is to broaden the horizons of advanced circulatory care and usher in the concept of the multidisciplinary team, which includes the cardiac surgeon, perfusionist, anaesthesiologist, and intensivist, in the management of the unstable and deteriorating patient with cardiogenic shock.

...The woods are lovely, dark, and deep,  
But I have promises to keep,  
And miles to go before I sleep.  
And miles to go before I sleep.  
—Robert Frost

References


Original article

Inferior vena cava obstruction: long-term results of endovascular management

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ABSTRACT

Background: Hepatic venous outflow obstruction (HVOO) can have acute or chronic presentation. In the chronic variety of inferior vena cava (IVC) obstruction, endovascular management with balloon angioplasty and stent implantation has emerged as a feasible, safe alternative to surgery which has high incidence of mortality and morbidity.

Aims and objectives: To study the feasibility and long-term follow-up of endovascular management of chronic IVC obstruction.

Methods: We studied 12 cases of HVOO who underwent endovascular management (balloon dilatation ± stenting). In most of the cases, the cause of obstruction was not obvious, but one case had metastatic hepatic nodules compressing on IVC. Diagnosis was established by clinical examination, venous Doppler and was confirmed by venography and/or computed tomography (CT) angiography. Cases underwent balloon dilatation and/or stenting.

Results: Out of 12 cases, six had membranous obstruction (four complete and two incomplete), five cases had segmental stenosis and one case had tumour compression. The lesion was crossed with either guide wire or Brockenbrough needle with Mullins sheath assembly and balloon dilatation was done with Inoue or Mansfield balloon. Seven cases underwent balloon dilatation alone while five cases underwent stenting. There was procedural success in all cases with reduction of gradient by 84%, disappearance of collaterals and clinical improvement. During the follow-up of 13 years, one case had restenosis, which was managed by stenting.

Conclusion: Endovascular management of IVC obstruction is safe with good long-term patency rates.

Original article

Indian Heart Journal 6402 (2012) 162–169

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KEYWORDS

Balloon dilatation
IVC obstruction
IVC stenting
IVC venography
Restenosis

Introduction

Inferior vena cava (IVC) obstruction can result from thrombosis secondary to hypercoagulable disorders, extrinsic compression by tumours, infective phlebitis, inflammation, trauma, surgery, or in many number of cases, idiopathic.1,2 In long-standing cases, it results in swelling of extremities, pain, venous ulceration and impaired liver and renal functions. The course of the disease can be rapidly fatal, or at times it may be confused with other causes of cirrhosis and portal hypertension. This form of chronic IVC obstruction is common in developing countries.1

Morphologically, IVC obstruction can be segmental, diffuse, discrete complete membranous or incomplete membranous obstruction. Discrete membranous obstruction now is believed to be a sequel of thrombosis and subsequent partial recanalisation.1

Diagnosis can be established by clinical examination, colour Doppler sonography, contrast-enhanced computed tomography (CECT), magnetic resonance imaging (MRI), and venography.

In the past, surgical created shunts were the options for managing hepatic venous outflow obstruction (HVOO). It had high mortality and morbidity, as the patients were very sick and surgery was involving thoracoabdominal approach in a highly congested patient.4,14 The percutaneous management has emerged as a very promising modality of management of HVOO. Balloon dilatation with or without stenting of hepatic veins (HV) and/or IVC has been reported earlier by various authors.15,16 The feasibility and long-term patency of IVC stenting is not very clear, especially in this part of the world, where membranous obstruction is commoner than in the West.
The purpose of this study is to evaluate the clinical presentation, diagnosis and modalities of endovascular management of IVC obstruction.

**Materials and methods**

From 1996–2009, we studied 12 cases of HVOO who underwent endovascular management.

In our study, only chronic occlusion of IVC is considered which is defined as symptoms and objective imaging evidence of occlusion >3 months.

Age of presentation was 28–55 years (mean 35 years). There were seven males and five females.

In most of the cases, the causes of IVC obstruction were not known, except in one, which had metastatic carcinoma (adenocarcinoma stomach) with multiple secondary nodules on the liver with IVC compression.

Baseline characteristics and clinical presentation is given in Table 1 and Figures 1 and 2.

Diagnosis was established by clinical examination, ultrasound Doppler study and confirmed by angiography and/or spiral CT angiography.

The details of the procedure, risks and benefits were explained to all patients and a written consent was obtained. The procedure was done under local anaesthesia with mild sedation whenever needed (either fentanyl citrate or midazolam hydrochloride).

Seven cases had acute-on-chronic obstruction of IVC and were treated with 24-hour infusion of either streptokinase or urokinase (100,000 U/hr), before taking up the procedure.

Angiographic profile of 12 cases who underwent balloon angioplasty with or without stenting is as follows.

1. Membranous (complete) obstruction—four cases.
2. Membranous (incomplete) obstruction—two cases.
3. Segmental obstruction—five cases.
4. External compression by tumour—one case.

All the cases had IVC obstruction; there was no involvement of HVs in our series. Out of 12 cases, six cases underwent balloon dilatation alone whereas six cases underwent stenting of IVC. One case who underwent balloon dilatation alone, presented with restenosis twice and treated with stent implantation.

**Procedural details**

In all cases, IVC obstruction was confirmed by angiography. In two cases of incomplete membranous obstruction of IVC (MOVC), the lesion was crossed with guide (0.032″ Terumo)

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Baseline characteristics of patients with chronic inferior vena cava obstruction.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>35 ± 6.1 yr</td>
</tr>
<tr>
<td>Sex</td>
<td>Female/male 7/5</td>
</tr>
<tr>
<td>Oedema of lower extremities</td>
<td>12/12 cases</td>
</tr>
<tr>
<td>Abdominal swelling and ascites</td>
<td>12/12 cases</td>
</tr>
<tr>
<td>Prominent veins on abdomen and back</td>
<td>12/12 cases</td>
</tr>
<tr>
<td>Hepatomegaly</td>
<td>10/12 cases</td>
</tr>
<tr>
<td>Hepatomegaly with nodules on liver (metastatic nodules from adenocarcinoma of stomach)</td>
<td>1/12 cases</td>
</tr>
<tr>
<td>Splenomegaly</td>
<td>4/12 cases</td>
</tr>
<tr>
<td>Impaired hepatic function</td>
<td>10/12 cases</td>
</tr>
</tbody>
</table>

**Figure 1** A case of membranous obstruction of inferior vena cava presenting with ascites and spider nevi on the abdominal wall.

**Figure 2** Inferior vena cava compression by metastatic nodules—note the nodular appearance of liver (A) and oedema feet (B).
wire and angioplasty using Inoue balloon was done with good result.

In four cases with complete membranous obstruction, the lesion was crossed with Brockenbrough needle (straightened)-Mullins sheath assembly which was exchanged to steel-coiled guide wire. Then, the IVC obstruction was dottered using the septal dilator (used to dilate the interatrial septum during mitral valvuloplasty). The lesions were dilated with Inoue balloon (18–22 cc volume) and achieved good result in all cases (Figure 3).

Segmental IVC obstruction was crossed with guide wire (Terumo 0.035 ″ 135 cm/7 F multipurpose catheter assembly). In few cases, lesions were dottered with septal dilator and then balloon angioplasty was done using Mansfield balloon or Inoue balloon. One case underwent balloon angioplasty alone and five cases of segmental IVC obstruction were stented primarily (a total of nine stents were used, seven—self-expanding, two—balloon mounted) (Figure 4).

The case who had undergone balloon dilatation alone for segmental IVC obstruction (in March 1995) came with restenosis 7 months after the index procedure. He was treated with repeat angioplasty and stent implantation. While deploying (from femoral vein), self-expanding wall stent (18 mm × 80 mm) slipped proximally and got deployed in the IVC across the renal veins. The second stent (balloon crimped Palmaz Schatz) also missed the intended site (hepatic segment of IVC close to RA-IVC junction) of deployment and had to be deployed in the hepatic segment of IVC proximal to the HV entry. A wall stent (third stent 18 mm × 40 mm) was deployed accurately at the site of the lesion. The same patient presented with re-restenosis at the proximal part of the third stent and adjacent IVC, 8 years later, which was dilated with balloon and stented successfully (Palmaz Schatz stent). Subsequently, after 5 years follow-up, he is asymptomatic with patent IVC.

One patient who had tumour compression of IVC (hepatic tumour metastasis from adenocarcinoma stomach), palliation was done by stenting the IVC with self-expandable Wall stent (22 mm × 70 mm) (Figure 5). It was post dilated with Inoue balloon. Two months later, he died of hepatocellular failure (due to extensive metastasis), but remained free of IVC obstruction till death.

Procedural success was defined as venographic evidence of rapid flow through created lumina and disappearance of collaterals and absence of significant gradients across the level of obstruction.

All patients received anticoagulation with unfractionated heparin during the procedure and oral anticoagulation so as to maintain international normalised ratio (INR) of 2–3 indefinitely.

Follow-up was done at 1st month, 3rd month and every 6 months subsequently. A thorough clinical examination was

Figure 3  Image reveals complete obstruction of IVC simultaneous contrast injection from upper and lower limb approach revealing membranous obstruction (A and B). Lesion crossed with Brockenbrough needle puncture/coiled guide wire through Mullins sheath in right atrial. (C) MVOC dilated with Inoue balloon (C). Final post balloon angioplasty image (D) reveals no residual obstruction. IVC: inferior vena cava, MOVC: membranous obstruction of IVC.
Results

The procedure was successful in all 12 cases. There was no gradient across the lesion in the cases that underwent stenting for segmental IVC obstruction. Gradients decreased by 84% (22±5 mmHg to 4±3 mmHg) in MOVC who underwent isolated balloon angioplasty. The IVC venogram revealed IVC obstruction was adequately dilated (<30% residual lesion in isolated balloon angioplasty in MVOC, no residual lesion in the stented group). Antegrade runoff was normal in all cases. Collaterals disappeared in all cases immediately. Oedema, ascites and hepatomegaly gradually decreased over 1 week. Hepatic impairment improved in most cases by 1 month, it persisted in two cases.

Stents were placed in seven cases (five cases during the first procedure and two cases during follow-up, as they had restenosis). Details of the procedure are given in Table 2.

Late results and follow-up

Follow-up varies from 15 months to 14 years. One patient presented with restenosis 8 months after balloon angioplasty which was treated with stent implantation and 8 years later, he presented with re-restenosis at the proximal end of stent and adjacent IVC (Figure 6) which was subsequently dilated and stented. Fourteen years follow-up of this patient revealed patent stents.

Two cases died because of hepatocellular failure (1 and 3 months after the procedure), unrelated to the procedure. Both patients had patent IVC till death.

The other cases (both membranous and segmental IVC obstruction), have maintained patent IVC, on follow-up, by ultrasound Doppler studies.

Discussion

In 1845, Budd described three cases of HV thrombosis (HVT) due to infectious phlebitis.

Chiari described in 1899 three additional cases of HV occlusion due to phlebitis, IVC involvement was present in one of the cases. Since Pleasants’ literature review in 1911 of 296 cases, the Budd-Chiari syndrome (now termed as HVOO) has included both HV and IVC obstruction/stenosis.

Okuda in 2001 emphasised that the classic HVOO also called HVT and MOVC, also called primary thrombosis of the IVC, are epidemiologically, pathologically, and clinically different and should be treated as two different clinical entities.
Figure 5 Image reveals obstruction to inferior vena cava (IVC) (haepatic portion—A and B). There is significant gradient between IVC and right atrial, across the obstruction which was relieved following stenting (C and D). Guide wire is passed across the obstruction (E), stent positioned (F), deployed (G), post dilated with Inoue balloon (H and I). At the end, no residual obstruction (J).
The HVT and MOVC have a different onset, clinical manifestations and natural history. Whereas HVT is a severe disease with an acute onset, MOVC presents as a mild disease at the onset, which can eventually turn into a fibrous occlusion of the IVC.

According to Pant and Punamia,17 HVOO can be identified into following categories:

Type A: IVC obstruction.

Type B: Pure HV obstruction with short segment stenosis.

Type C: Combined short segment HV and IVC occlusion.

Type D: Extensive intrahepatic occlusion of HVs with no identifiable main HV.

These can be differentiated on the basis of cross-sectional imaging and catheter angiography. Type A or isolated IVC obstruction is common in the Indian subcontinent. Our study is restricted to this form of HVOO.

Table 2
Results of endovascular management of inferior vena cava obstruction.

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Type of obstruction</th>
<th>Endovascular management</th>
<th>Stenting</th>
<th>Technical success</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Complete membranous</td>
<td>Balloon dilatation only</td>
<td>None</td>
<td>Yes</td>
</tr>
<tr>
<td>2</td>
<td>Complete membranous</td>
<td>Balloon dilatation only</td>
<td>None</td>
<td>Yes</td>
</tr>
<tr>
<td>3</td>
<td>Segmental</td>
<td>Initial balloon dilatation, restenosis, one stent placement which got displaced, needed two stents. Re-restenosis, balloon dilatation and stented</td>
<td>A. 16 × 80 mm wall stent</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>B. 16 × 40 mm wall stent and 14 × 40 mm Palmaz Schatz stent</td>
<td>Yes</td>
</tr>
<tr>
<td>4</td>
<td>Segmental</td>
<td>Balloon dilatation + stenting</td>
<td>18 × 60 mm self-expanding wall stent</td>
<td>Yes</td>
</tr>
<tr>
<td>5</td>
<td>Complete membranous</td>
<td>Balloon dilatation only</td>
<td>None</td>
<td>Yes</td>
</tr>
<tr>
<td>6</td>
<td>Incomplete membranous</td>
<td>Dilatation with Inoue balloon</td>
<td>None</td>
<td>Yes</td>
</tr>
<tr>
<td>7</td>
<td>Segmental</td>
<td>Balloon dilatation + stenting</td>
<td>14 × 50 mm precise self-expanding stent</td>
<td>Yes</td>
</tr>
<tr>
<td>8</td>
<td>Tumour compression</td>
<td>Stenting post dilatation with Inoue balloon</td>
<td>22 × 70 mm wall stent</td>
<td>Yes</td>
</tr>
<tr>
<td>9</td>
<td>Segmental</td>
<td>Dilatation with Inoue balloon</td>
<td>None</td>
<td>Yes</td>
</tr>
<tr>
<td>10</td>
<td>Complete membranous</td>
<td>Balloon dilatation only</td>
<td>None</td>
<td>Yes</td>
</tr>
<tr>
<td>11</td>
<td>Segmental</td>
<td>Balloon dilatation + stenting</td>
<td>14 × 80 mm precise and 14 × 60 mm precise</td>
<td>Yes</td>
</tr>
<tr>
<td>12</td>
<td>Incomplete membranous</td>
<td>Balloon dilatation only</td>
<td>None</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Figure 6 Image reveals restenosis at the proximal end and adjacent part of the stent (A). Lesion was crossed (B) and predilated (C), lesion did not yield but balloon gave away (D). It was then predilated with Inoue balloon (E) and stented with Palmaz Schatz stent, mounted on Tyshak balloon (F). Post dilated with Inoue balloon subsequently (G). End result was excellent with patent Inferior vena cava (H).
Membrane like obstruction commonly found angiographically, has been found to consist of organised old thrombus arranged in layers of different ages. The clinical onset is mild and causes liver damage by congestion. A distinct pattern of subcutaneous venous collaterals typically develops together with retroperitoneal collaterals through the ascending lumbar and the iliolumbar veins into the hemiazygos and azygos veins. This type of the disease is more common in Asia and Africa.

The HVT has an acute onset with severe liver damage often requiring urgent portocaval decompression and might even require liver transplantation depending on the extent of venous involvement. The collateral venous pathways are similar to those seen in portal hypertension. This type of the disease is more common in Western countries. In our study, we did not come across hepatic venous involvement either in isolation or in combination with IVC obstruction.

The diagnosis of HV outflow block is established by the clinical history and physical examination. Clinically, it is recognised by hepatomegaly, portal hypertension, impaired liver function, and formation of communicating channel, and oedema or ulcer in the lower extremities. The clinical signs of ascites, abdominal pain, and hepatomegaly are the typical triad of HVOO.

The best imaging methods are ultrasound, computed tomography (CT) and MRI.

Once the diagnosis is established, inferior vena cavaography is needed to guide endovascular techniques.

Goal of treatment is to give a long-term patency of IVC with minimal mortality and morbidity. In case of tumour compression, it is restricted to palliation to relieve symptoms.

Treatment of IVC obstruction includes surgical (direct visualisation of obstruction and removal or venous bypass grafts) or interventional (balloon dilatation ± stenting). Surgery though successful, carries higher risk of complications in patients who already had impaired liver function.3–5 Mortality in surgical group is higher—33–40% (Kimura et al. & Iwaragi et al.).4

Gloviczki et al.18 recommended spiral venous grafts or polytetrafluoroethylene (PTFE) grafts to bypass the obstruction. In their series, 43% needed additional surgeries later and only 29% of cases maintained graft patency at 2 years. Seven out of 11 cases had PTFE patent graft at 9 months.

Angioplasty using balloon is a technique developed in the early 1990s which carries higher chances of success with minimal complications. Results of angioplasty are good in cases of discrete membranous obstruction, but disappointing in cases of segmental obstruction.19,20 This can be attributable to venous recoil, low flow states and thrombogenicity of IVC. Stents have revolutionised the endovascular management and to maintain long-term patency of IVC.21–24 There is a paucity of studies utilising stents in IVC obstruction especially in chronic setup. Most of the studies were conducted in acute form of the disease.21

Different balloons were used by different interventionists. In our study, we used Inoue balloon in many cases. Use of Inoue balloon was popularised by Yang et al. in 1992, it carries clear advantages13 which can be summarised as follows:

1. Adult IVC measures 20–22 mm, thus single Inoue balloon is ideal to dilate. Balloon to IVC ratio should be 1:1–1.1:1.
2. Balloon diameter is ideal for dilating membrane, as the waist of the balloon locks the centre of the membrane and dilates.
3. Lower inflation pressure is required (1–2 atm), for a shorter period of time (3 seconds).
4. Rubber-Nylon micromesh of IB has stronger build, thus ideal to dilate tough membrane.
5. Balloon size can be altered, thus it can be tailor made, suiting each type of lesion.

We were successful in re-establishing the patency of IVC in all 12 cases. During the long-term follow-up, 11/12 cases maintained patency, the one case that earlier had undergone stenting was re-intervened and additional stent placement was possible.

All the cases received anticoagulation for an indefinite period. We did not come across any case of stent thrombosis.

The procedure was safe and well tolerated in all our cases with no evidence of pulmonary embolisation, bleeding, infection, or haematoma formation. However, we recommend use of thrombolytic therapy for 24 hours, before undertaking intervention, in cases where acute-on-chronic thrombosis is suspected. This is to prevent pulmonary embolisation.

**Current status of stenting**

The decision of stenting the IVC is often individualised. However, it is particularly useful in the following cases:

1. Long segment of obstruction or multiple segments of obstruction.
2. Restenosis after balloon angioplasty.
3. Enlarged caudate lobe of liver or nodular compression on IVC (e.g. haepatoma).

**Conclusion**

Balloon angioplasty is efficacious in relieving IVC obstruction with minimal morbidity. Inoue balloon is ideal to dilate membranous obstruction. Stents should be used whenever there is residual obstruction after balloon angioplasty, segmental obstruction, restenosis following balloon angioplasty and extrinsic compression of IVC. Follow-up results are favourable for balloon angioplasty ± stenting with minimal re-stenosis rates.

**References**


Original article

Left atrial myxoma—influence of tumour size on electrocardiographic findings


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ABSTRACT

Objective: The data of 51 patients (33 females) who underwent excision of left atrial (LA) myxoma were retrospectively reviewed for correlation of tumour size and electrocardiographic (ECG) findings.

Methods and results: Mean age was 39.1 ± 15 years (range 9–53 years). The LA enlargement (LAE) on ECG was defined by standard criteria. The LAE in ECG in these patients did not correlate with echocardiographic LA dimensions or with the degree of left ventricular (LV) inflow obstruction. But it was found that the presence of LAE in ECG predicted maximum tumour dimension of >5 cm and correlated with the degree of mitral regurgitation (MR). The LAE in ECG disappeared following surgery in 87.5% of patients.

Conclusion: The LA enlargement on ECG in a patient with LA myxoma signifies larger tumour size or the presence of significant MR but is not necessarily associated with an increased LA size or LV inflow obstruction.

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KEYWORDS

Electrocardiography
Left atrium
Myxoma

Introduction

Myxomas are the most frequent benign primary tumour of the heart, and are most commonly located in the left atrium. There are very few reports describing usefulness of electrocardiograms (ECGs) in left atrial (LA) myxoma.1,2 In this study, we retrospectively reviewed the ECGs of patients who underwent excision of LA myxoma in our institution. We analysed the effect of the tumour size and the effect of tumour removal on the ECG features.

Materials and methods

We retrospectively reviewed the records of all patients who underwent excision of LA myxoma and had a 12-lead ECG in sinus rhythm available for analysis before surgical excision of the tumour. All patients were evaluated preoperatively by echocardiography (ECHO) (two-dimensional, Doppler studies, and colour flow imaging) and many of the patients underwent coronary angiography.

All tumours were excised successfully through a septal incision during cardiopulmonary bypass with cardioplegic arrest. In some cases, the part of the atrial septum, where the tumour was attached was also excised and the residual defect was closed with a pericardial patch.

Standard 12-lead ECGs which were recorded at a paper speed of 25 mm/s, a sensitivity of 1 mV/cm and filter settings of 0.05–40Hz. P-waves were analysed after photocopying the ECGs enlarging it to 200% size. The ECG intervals, including PR, QRS, and rate-corrected QT, were determined by averaging five consecutive beats from the rhythm strip record.

The P-wave duration in lead II (PDII) was defined as the time from the earliest onset of P-wave activity to the last activity. Lead V1 was used to measure the P-terminal Force (PTVF1), which was defined as the algebraic product of the terminal portion of the P-wave (seconds) and the negative deflection of the terminal portion of the P-wave (mV).3,4 We used the generally accepted criteria of ECG LA enlargement (LAE), i.e. >0.11 s of PDII and 0.004mVs or more of PTFV1.5,6 Only patients who satisfied both the ECG criteria were considered to have LAE. Another experienced investigator who was blinded to the clinical data repeated the ECG analysis. If there was a difference of opinion, then a third
electrocardiographer analysed the tracings (this was done in 7/85 ECGs).

The ECHO records of the patients were retrieved. Left atrial dimension (LAD) was obtained by routine M-mode ECHO in the parasternal long-axis view. Left ventricular (LV) inflow gradient was obtained by Doppler evaluation by calculating velocity time integral of mitral inflow velocities. Mitral regurgitation (MR) was graded by standard Doppler criteria. Tumour dimensions were measured in three different planes. The maximum diameter in any of the plane was taken as a reference of size of the tumour in that plane. By calculating the average radius of the tumour in three different planes, on ECHO, the approximate volume was calculated using the formula \( \frac{4}{3}\pi r^3 \). The ECHO recordings were also analysed by two echocardiographers blindly and the opinion of a third person taken if there was disagreement.

As a routine, ECG and ECHO were repeated before discharge and the patients were reviewed at 3 months from the surgery. The significance of the difference in mean values for the various parameters before and after surgery was determined with Student's paired t-test. Results were considered significant if \( P<0.05 \). Statistical analysis was done using SPSS software version 10.

Results

There were 82 patients with LA myxoma, who were surgically treated in our institution between 1994 and 2003. Out of them, 51 patients (age 9–53 years) had a 12-lead ECG in sinus rhythm available for analysis preoperatively.

Of the total of 51 patients included in the study, 26 patients presented with symptoms of mitral inflow obstruction, nine patients with cerebrovascular accident, and seven patients presented with systemic symptoms such as fever and weight loss. Two patients presented with myocardial infarction and two patients were accidentally detected to have atrial myxoma.

The most common site of attachment of tumour was to the interatrial septum near fossa ovalis (n = 39). Other sites of attachment were, to the LA roof in 9, posterior LA wall in 2, and to the posterior mitral leaflet in one patient. The latter patient underwent mitral valve replacement also.

Out of the 51 patients, there were 34 patients who had a tumour diameter in any given dimension >5 cm (Group I) and 17 had a maximum dimension of <5 cm (Group II). The mean PR interval in the ECG of patients in Group I was 0.18 ± 0.02 s (range 0.14–0.22) and in Group II was 0.17 ± 0.02 s (range 0.14–0.20). \( P \) not significant. 28 patients out of 34 who had tumour size >5 cm, had LAE on ECG, while only 5/17 patients with tumour size <5 cm had LAE (Table 1). Thus, maximum tumour dimension of >5 cm correlated with LAE on ECG. When we analysed patients with and without LAE in ECG, more patients had tumour size >5 cm in the group with LAE. But the presence of LAE in ECG did not correlate with LA size on ECHO (Table 2).

The tumour volume of the patients ranged from 42.5 cm\(^3\) to 209 cm\(^3\) (mean value 95.6 cm\(^3\)). The LAE in the ECG correlated with the average tumour volume which was 112.9 cm\(^3\) in patients with tumour size >5 cm, as compared to 59.9 cm\(^3\) in tumours <5 cm (\( P<0.05 \)) (Table 1).

There was no significant difference in transmitral gradient in patients with larger or smaller tumours. The tumour size did not correlate with LV inflow obstruction.

A total of 22 patients in Group I had mild or more (2+ or more) MR, while only four patients in Group II had significant MR (Table 1). The mean grade of MR in patients who demonstrated LAE in ECG was 2.3 ± 0.8 compared to 1.3 ± 0.9 in patients who did not have LAE (\( P=0.04 \)) (Table 2).

The ECG was available in 34 patients after surgery at 3 months follow-up. It was observed that LAE disappeared in the post surgical ECG in 21/24 patients who originally had LAE. The MR disappeared in 15 patients in Group I and in two patients in Group II after surgery, but none of the patients demonstrated more than mild MR after surgery.

Discussion

There are three commonly used criteria to define LAE in ECG. They are, total PD II >110 ms; PTFV1 >-0.04 ms, and P-wave notching in leads II with a peak-to-peak interval >40 ms.\(^3\)

We used two of the above criteria combined together—prolonged P-wave and an increase of PTFV1, which are more sensitive and specific for LAE.\(^3\) Jin et al.\(^4\) reported that combination of the two criteria identifies patients most likely to have cardiovascular disease.

Table 1

<table>
<thead>
<tr>
<th></th>
<th>Tumour size &gt;5 cm</th>
<th>Tumour size &lt;5 cm</th>
<th>( P ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LAE by ECG</td>
<td>28</td>
<td>5</td>
<td>&lt;0.02</td>
</tr>
<tr>
<td>PR interval (sec)</td>
<td>0.18 ± 0.02</td>
<td>0.17 ± 0.02</td>
<td>0.7</td>
</tr>
<tr>
<td>LA size by ECHO</td>
<td>38.8 ± 6.5</td>
<td>40.6 ± 7.3</td>
<td>0.8</td>
</tr>
<tr>
<td>Tumour volume (cm(^3))</td>
<td>112.9 ± 63</td>
<td>59.9 ± 12.9</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>More than mild (2+) MR</td>
<td>22</td>
<td>4</td>
<td>&lt;0.02</td>
</tr>
<tr>
<td>Mitral inflow gradient by ECHO (mmHg)</td>
<td>12.9 ± 9</td>
<td>11 ± 6</td>
<td>0.8</td>
</tr>
</tbody>
</table>


Table 2

<table>
<thead>
<tr>
<th>Tumour size</th>
<th>LAE by ECG (n=33)</th>
<th>No LAE by ECG (n=18)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;5 cm</td>
<td>28*</td>
<td>6*</td>
</tr>
<tr>
<td>&lt;5 cm</td>
<td>5*</td>
<td>12*</td>
</tr>
<tr>
<td>LA size by ECHO (mm)</td>
<td>39 ± 5**</td>
<td>39.3 ± 6.6**</td>
</tr>
<tr>
<td>MR (mean grade=ECHO)</td>
<td>2.3 ± 0.8</td>
<td>1.3 ± 0.9</td>
</tr>
</tbody>
</table>

\( *P<0.05, **P=0.05 \) not significant. ECG: electrocardiography, ECHO: echocardiography, LA: left atrium, LAE: left atrial enlargement, MR: mitral regurgitation.
The LAE on ECG is produced by many factors like increase in LA size or intra-atrial pressure and intra-atrial conduction defects.

Fragola et al. in a study of 1000 patients with LAE of different pathologies, found that in only 34% of the patients there was an agreement between LAE in ECG and LAE by ECHO. Also in a study by Scott et al. in patients with mitral stenosis there was no direct correlation between LA size and LAE in ECG. In another study, Jin et al. found that LAE on ECHO was present only in less than a third of the patients with LAE on ECG. Aggarwal et al. in a large series of patients with myxoma found only 35% of them demonstrating LAE on ECG.

Josephson et al. reported that the ECG pattern termed LAE appears to represent an interatrial conduction defect that can be produced by a variety of factors. They also opined that, considering cases of different aetiologies, only prolongation of interatrial conduction time was consistently related to the ECG pattern of LAE. The LA size or pressure was not predictably abnormal in patients with this pattern. They demonstrated that LAE in ECG correlated with ECHO LAE only in cases of mitral stenosis. In cases of cardiomyopathy, only LA pressure correlated with LAE in ECG, but not LA size. In cases of coronary artery disease, there was no correlation either with LA pressure or LA volume overload with LAE in ECG.

In a recent study Lee et al. have found no correlation with LAE in ECG and ECHO, LA volume > 32 mL/m². Aggarwal et al. also found there is no correlation between tumour size and LAE.

One of the two studies which correlated size of myxoma and ECG changes, found that LAE in ECG disappears on removal of the tumour. It is reported that large myxomas can produce LAE in the ECG. In a study of 15 patients, Komiya et al. reported the correlation of tumour weight to the presence of LAE in ECG. They found that tumours weighing > 16 g produced LAE in ECG. Another study found correlation with size of the myxoma and pulmonary artery pressure. The size of the tumour rather than the weight may be having more influence on LA pressure and intracavitary blood mass. So, we analysed the tumour volume and correlated with LAE. We found that the larger tumours with a maximum dimension > 5 cm and having a higher tumour volume produced LAE. But LA dimension as measured by ECHO was not different in patients with and without LAE in ECG.

In both groups with small and large tumours, we found that LA pressures were higher, indirectly, as indicated by the increase in transmitial gradient. There was significantly more MR in Group I which also might have contributed to the LAE. It is reported that mitral annular dilatation can be produced by LA myxomas, which can contribute to MR. Annular dilatation can resolve after surgery due to remodelling. It is also reported that MR may be underestimated in the presence of myxoma, though in our population none of the patients had significant MR after surgical excision.

Also increased intracavitary blood mass, which is supposed to affect heart-lead relationship, may have an effect in development of LAE in patients with larger tumours. Whether the LAE correlates with intra-atrial conduction defect due to attachment of the tumour cannot be established.

We found that ECG evidence of LAE disappeared in most patients after excision of the tumour. This could be due to the relief of obstruction and decrease in transmitial gradient, decrease in MR, and removal of the tumour itself which might have decreased the intracavitary blood mass.

As the LA dimension by ECHO was not significantly different between the two groups, either the higher degree of MR or increased intracavitary mass may be the reasons for LAE in ECG in patients with LA myxoma.

**Limitations of the study**

1. Tumour volume was calculated in the assumption that the tumour is a sphere. But actually, the shape may vary from patient to patient and many times it may be different from a sphere.
2. It was a retrospective study and hence the recorded dimensions in some planes may be inaccurate.
3. The number of patients who had analysable ECGs after surgery were only 34/51 cases.
4. The LA size was measured by M-mode in parasternal long-axis view, which may not be accurate.

**References**

Original article
Serum ferritin—a novel risk factor in acute myocardial infarction
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ABSTRACT

Background: A possible association between body iron status and risk of coronary heart disease (CHD) has been found to be controversial from the data obtained from various studies.

Objectives: To study the relationship of serum ferritin with acute myocardial infarction (AMI) in univariate and multivariate analysis and to assess the relationship of high serum ferritin with established conventional risk factors.

Methods: Hospital based case-control study of 75 cases of AMI, and 75 age and equal number of age, and gender-matched controls without having AMI in the age group of 30–70 years.

Results: Median serum ferritin levels were significantly higher in cases (220 \( \mu \)g/L) than controls (155 \( \mu \)g/L) \((P \leq 0.0001)\). In univariate analysis in addition to ferritin > 200 \( \mu \)g/L (odds ratio [OR] 6.71, 95% confidence interval [CI] = 3.22–12.89, \( P < 0.05 \)), diabetes (OR = 7.68, 95% CI = 2.95–19.13, \( P < 0.05 \)), hypertension (HTN) (OR = 2.36, 95% CI = 1.02–5.14, \( P < 0.05 \)) high-density lipoprotein (HDL) < 35 mg/dL (OR = 11.9, 95% CI = 2.66–52.57, \( P < 0.05 \)) and smoking (OR = 2.17, 95% CI = 1.12–3.87, \( P < 0.05 \)) were found to be significantly associated with AMI. After controlling for all conventional risk factors, in multiple logistic regression analysis, high ferritin was significantly associated with AMI. (adjusted OR = 5.72, 95% CI = 2.16–15.17, \( P < 0.001 \)). Serum ferritin was significantly higher in diabetics than non-diabetics \((P < 0.01)\).

Conclusion: High serum ferritin is strongly and independently associated with AMI.

KEYWORDS
Acute myocardial infarction (AMI)
coronal heart disease (CHD)
conventional risk factors
Serum ferritin

Introduction

Over the past several years, observational and epidemiological studies have identified a host of new and potential risk factors for atherothrombotic vascular diseases. In this growing list of new and emerging risk factors, the entities like elevated blood levels of homocysteine, fibrinogen, inflammation and infection, atherogenic lipoprotein, elevated triglyceride, and number of genetic polymorphism are of particular interest. Apart from these, there is strong evidence that oxidative free radicals have a role in the development of degenerative diseases including coronary heart disease (CHD). Oxidative free radicals increase the peroxidation of low-density lipoprotein (LDL), thereby increasing its uptake by macrophages with increased foam cell formation and atherosclerosis. Iron, a dietary constituent, is a pre-oxidant and a high concentration of blood ferritin, which measures stored iron, is a potential novel risk factor for CHD. Free iron which acts as a catalyst for the production of free radicals has been implicated in lipid peroxidation and atherosclerosis leading to myocardial infarction (MI). Serum ferritin concentrations are directly proportional to intracellular ferritin concentration and considered to be the best clinical measure of body iron stores and most feasible to use in epidemiological studies.

The role of ferritin in pathogenesis of coronary artery diseases (CAD) like acute MI (AMI), has generated considerable interest in recent times. There is a plethora of articles reporting the relationship between serum ferritin and AMI but with conflicting and contradictory results. Sullivan JL (1981) was the first to observe that high level of stored iron is a risk factor for heart disease. Subsequently, results of the various studies showed statistically significant association of high serum ferritin and AMI. However, some authors did not find any significant association of high ferritin and AMI. The main objective of our study was to compare the ferritin levels in cases and controls, in order to assess the relationship of serum ferritin with AMI, in both univariate and also in multivariate analysis, after controlling for established...
conventional risk factors (like diabetes mellitus [DM], HTN, lipids, body mass index [BMI], smoking, and alcohol intake).

Materials and methods

Inclusion and exclusion criteria

In this hospital based case-control study, 75 consecutive cases of AMI admitted to the Coronary Care Unit of Indira Gandhi Government Medical College, Nagpur, were enrolled. The diagnosis of AMI was based on fulfilling any two of the following criteria.\(^\text{14}\) (1) Chest pain of \(<12\) hours duration, (2) ST elevation \(>1\) mm in at least two consecutive leads, (3) increased cardiac markers (creatinine phosphokinase-MB (CPK-MB) two times the upper limit of normal), and (4) presumably new onset bundle-branch block. Cases with high ferritin levels like haemochromatosis, liver disease, tuberculosis, chronic inflammatory diseases, those on iron therapy and those having past history of AMI or CHD were excluded from the study.

One age (±5 years), gender and haemoglobin-matched control was recruited for each case, irrespective of presence of risk factors (HTN, DM, smoking and alcohol intake) but without having AMI (in the past or present) or any evidence of CHD (assessed by symptoms, clinical examination and normal electrocardiogram [ECG]). Controls were selected randomly from subjects attending outpatient department of hospital for minor ailments or routine medical check-up, subjects accompanying patients or amongst office working staff from various departments of this institution without having any evidence of AMI/CHD. The other exclusion criteria were same for controls as that for cases.

All the subjects were assessed by clinical examination ECG, serum creatine kinase-MB fraction (CK-MB). Height and weight were recorded. Body mass index was calculated by formula, weight in kg/height\(^2\) in m. Body mass index \(>25\) was considered as a risk factor for AMI.

Cases and controls were investigated for conventional risk factors (BMI, blood sugar, lipid profile). History of smoking and alcohol consumption was noted in details. Estimation of lipids was done by enzymatic method using autoanalyzer while glucose oxidase and peroxidase (GOD-POD) method was used for measurement of blood sugar. Serum ferritin was done in all the subjects and was estimated by using Genix ferritin enzyme-linked immunosorbent assay (ELISA) test which is based on a solid phase ELISA using ELISA reader.\(^\text{15}\) Since serum ferritin is a sensitive marker of body iron store, estimation of serum iron and total iron binding capacity (TIBC) was not considered in the present study.

Data analysis

Statistical analysis included the usual descriptive and univariate analysis. Discrete (categorical) variables were compared by \(\chi^2\)-test and for continuous variable, Students \(t\)-test was used. Since, the distribution of serum ferritin values in cases was slightly skewed, and the assumption of normality was not met, we used the non-parametric test (Mann–Whitney test) to compare the median values of ferritin in cases and controls. Unadjusted odds ratio with 95% CI were calculated and \(P\) values were computed. All \(P\) values were two-tailed and values \(<0.05\) were considered statistically significant.

To determine the independent association of serum ferritin with AMI, multivariate analysis was carried out by performing multiple logistic regression analysis, with AMI as a dichotomous independent outcome variable and serum ferritin and other conventional risk factors as dependent predictor variables and adjusted odds ratio (ORs) and 95% CIs were computed using Minitab statistical package Minitab II on personal computer.

The study was approved by Medical Ethic Committee of the Institution and written informed consent was obtained from all participants.

Results

A total of 75 cases and an equal number of controls were studied. The mean age of controls and cases was similar (50.6 ± 7.8 years and 51.16 ± 8.0 years) respectively (age range 30–70 years). Males outnumbered females with a ratio of 2.4:1. Mean haemoglobin in cases and controls was similar (13.29 g% and 13.39 g%, respectively), since they were matched for haemoglobin.

The median serum ferritin values were significantly higher in cases (220 \(\mu\)g/L) as compared to controls (155 \(\mu\)g/L). \((P<0.0001)\) (Table 1). The mean value of serum ferritin (\(\mu\)g/L) in controls and cases were found to be 155.65 ± 79.76 and 324.4 ± 256.8, respectively \((P<0.001)\). The distribution of serum ferritin for cases and control subjects indicated a shift towards higher concentration in patients with AMI (Figure 1). Correspondingly, more patients with AMI (62.66%) than control subjects (20%) had concentrations above the cut-off of

<table>
<thead>
<tr>
<th>Table 1</th>
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<tbody>
<tr>
<td>Comparison of median serum ferritin levels in cases and controls (by non-parametric Mann–Whitney test).</td>
</tr>
<tr>
<td>Cases ((n=75))</td>
</tr>
<tr>
<td>Median serum ferritin ((\mu\text{g/L}))</td>
</tr>
</tbody>
</table>

\(^\ast\)Statistically significant.

<table>
<thead>
<tr>
<th>Table 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Association of acute myocardial infarction with high serum ferritin.</td>
</tr>
<tr>
<td>Serum ferritin ((\mu\text{g/L}))</td>
</tr>
<tr>
<td>(\geq 200) (\mu\text{g/L})</td>
</tr>
<tr>
<td>&lt;200 (\mu\text{g/L})</td>
</tr>
<tr>
<td>OR 6.71</td>
</tr>
</tbody>
</table>

\(^\ast\)Statistically significant. CI: confidence interval, OR: odds ratio.
In univariate analysis, DM, hypertension, serum cholesterol, high-density lipoprotein (HDL) < 35 and smoking were found to be significantly associated with AMI (Table 3).

In multivariate analysis, high serum ferritin (> 200 μg/L) (P < 0.001, OR = 5.72, 95% CI 2.16–15.17), DM (P = 0.001, OR = 7.64, 95% CI 2.37–24.58), low HDL (< 35 mg%) (P < 0.001, OR = 0.86; 95% CI 0.79–0.93) are found to be independently associated with AMI (Table 4). When ferritin, cholesterol, BMI and HDL were taken as continuous variables, then also mean serum ferritin (P = 0.001) was found to be significantly associated with AMI.

We also assessed the relationship of serum ferritin with other risk factors. Mean serum ferritin was significantly higher in diabetics (346 ± 275.19) than non-diabetics (206.31 ± 169.04) (P = 0.01). There was no statistically significant relationship of ferritin with HTN, serum cholesterol, HDL, BMI, smoking and alcohol.

Discussion

We found serum ferritin to be significantly higher in cases of AMI as compared to controls. Epidemiological studies have shown that high ferritin levels are associated with an increased risk of cardiovascular disease. Our findings support this observation, as high serum ferritin levels were found to be significantly associated with AMI in both univariate and multivariate analyses.

Table 3

Comparison of conventional risk factors for myocardial infarction in cases and controls (univariate analysis).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Cases (%) (n=75)</th>
<th>Controls (%) (n=75)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (±SD) yr range</td>
<td>51.16 ± 8.002 (37–69)</td>
<td>50.6 ± 8.006 (33–64)</td>
<td>t = 0.43 P = NS</td>
</tr>
<tr>
<td>Diabetes mellitus*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Present</td>
<td>30 (40)</td>
<td>6 (8)</td>
<td>χ² = 21.05</td>
</tr>
<tr>
<td>Absent</td>
<td>45 (60)</td>
<td>69 (92)</td>
<td>OR = 7.68; 95% CI = 2.16–15.17; P &lt; 0.05*</td>
</tr>
<tr>
<td>Hypertension*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Present</td>
<td>20 (26.66)</td>
<td>10 (13.33)</td>
<td>χ² = 25.35</td>
</tr>
<tr>
<td>Absent</td>
<td>55 (73.33)</td>
<td>65 (86.66)</td>
<td>OR = 2.36</td>
</tr>
<tr>
<td>Mean serum cholesterol (±SD)*</td>
<td>182.77 ± 49.8</td>
<td>160.29 ± 43.5</td>
<td>t = 2.94</td>
</tr>
<tr>
<td>mg/dl range</td>
<td>2 (105–330)</td>
<td>3 (100–300)</td>
<td>P &lt; 0.001</td>
</tr>
<tr>
<td>Serum cholesterol mg%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 200</td>
<td>24 (32)</td>
<td>14 (18.66)</td>
<td>χ² = 3.52</td>
</tr>
<tr>
<td>&lt; 200</td>
<td>51 (68)</td>
<td>61 (81.33)</td>
<td>OR = 2.05</td>
</tr>
<tr>
<td>Mean HDL (±SD) mg/dl range*</td>
<td>39.76 ± 5.96</td>
<td>40.49 ± 5.63</td>
<td>t = 0.05</td>
</tr>
<tr>
<td>&gt; 25</td>
<td>31–55</td>
<td>33–64</td>
<td>P &lt; 0.001</td>
</tr>
<tr>
<td>BMI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 25</td>
<td>26 (34.66)</td>
<td>16 (21.33)</td>
<td>χ² = 3.30</td>
</tr>
<tr>
<td>&lt; 25</td>
<td>49 (65.33)</td>
<td>59 (78.66)</td>
<td>OR = 1.9595%</td>
</tr>
<tr>
<td>Smoking*</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Present</td>
<td>39 (52)</td>
<td>25 (66.66)</td>
<td>χ² = 6.10</td>
</tr>
<tr>
<td>Absent</td>
<td>36 (48)</td>
<td>50 (66.66)</td>
<td>OR = 2.17</td>
</tr>
<tr>
<td>Alcohol intake</td>
<td></td>
<td></td>
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<tr>
<td>Present</td>
<td>32 (42.66)</td>
<td>22 (29.33)</td>
<td>χ² = 5.2</td>
</tr>
<tr>
<td>Absent</td>
<td>43 (57.33)</td>
<td>53 (70.66)</td>
<td>OR = 1.79</td>
</tr>
</tbody>
</table>

*Statistically significant. BMI: body mass index, CI: confidence interval, HDL: high-density lipoprotein, NS: non-significant, OR: odds ratio, SD: standard deviation.
found a positive relationship between body iron stores and CAD.\textsuperscript{16,17} Subsequently, evidence of an association of elevated serum ferritin and increased risk of AMI came from various authors\textsuperscript{9,18,19} which is similar to our findings. However, the results of some other studies did not show significant correlation between high ferritin and risk of AMI.\textsuperscript{10,11,13} High ferritin was observed as a strong indicator of presence of carotid artery atherosclerosis (assessed sonographically). Iron induced lipid peroxidation, involved in the early steps of the human atherogenesis which was the proposed underlying pathogenic mechanism.\textsuperscript{20} Blood donation has also been reported to be associated with decreased risk of cardiovascular (CV) events.\textsuperscript{21} High ferritin levels have been associated with established conventional risk factors like DM and HTN by various authors.\textsuperscript{22–24} Reduced extraction of hepatic with increasing iron stores leading to peripheral hyperinsulinemia was the proposed mechanism for DM\textsuperscript{25} and pronounced metabolic alteration is the proposed mechanism for high ferritin in hypertensives.\textsuperscript{24} Significant association of LDL cholesterol and ferritin was also reported previously.\textsuperscript{9,26} Presence of iron accelerates oxidation of polyunsaturated fatty acids in LDL and it is the possible explanation given by authors. High ferritin levels have been observed in smokers. Cigarette smoke mediated iron mobilisation from ferritin and it represents specific pro-oxidant mechanism related to smoking.\textsuperscript{27,28}

Thus, our study found a strong and independent relationship of high serum ferritin with AMI, and serum ferritin was significantly high in diabetics.

**Study limitations**

Sample size in the present study was small but adequate to show the association of high serum ferritin with AMI. Since, the case-control studies are retrospective studies, they have their own limitations in assessing the causal relationship of risk factors with AMI. Larger prospective studies in Indian population are needed to support the results of the present study.

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**Table 4**

Multiple logistic regression showing association of various risk factors with myocardial infarction (serum ferritin, serum cholesterol, body mass index, were taken as categorical variables).

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>Adjusted OR</th>
<th>95% CI</th>
<th>Z value</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>High serum ferritin (&gt;200 μg/L)*</td>
<td>5.72</td>
<td>2.16–15.17</td>
<td>3.5</td>
<td>0.000*</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0.91</td>
<td>0.27–3.08</td>
<td>−0.15</td>
<td>0.877</td>
</tr>
<tr>
<td>DM*</td>
<td>7.64</td>
<td>2.37–24.58</td>
<td>3.14</td>
<td>0.001*</td>
</tr>
<tr>
<td>Hypercholesterolemia (&gt;200 mg/dL)</td>
<td>1.01</td>
<td>0.98–1.04</td>
<td>0.76</td>
<td>0.446</td>
</tr>
<tr>
<td>BMI &gt; 25</td>
<td>0.99</td>
<td>0.86–1.15</td>
<td>−0.10</td>
<td>0.921</td>
</tr>
<tr>
<td>Smoking</td>
<td>2.04</td>
<td>0.72–5.81</td>
<td>1.33</td>
<td>0.183</td>
</tr>
<tr>
<td>Alcohol</td>
<td>1.07</td>
<td>0.38–3.01</td>
<td>0.12</td>
<td>0.905</td>
</tr>
<tr>
<td>TG (&gt;150 mg/dL)</td>
<td>0.88</td>
<td>0.73–1.06</td>
<td>−1.30</td>
<td>0.193</td>
</tr>
<tr>
<td>HDL (&lt;35 mg/dL)*</td>
<td>0.86</td>
<td>0.79–0.93</td>
<td>−3.50</td>
<td>0.000*</td>
</tr>
<tr>
<td>LDL (&gt;130 mg/dL)</td>
<td>0.99</td>
<td>0.96–1.03</td>
<td>−0.36</td>
<td>0.719</td>
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<tr>
<td>VLDL (&gt;40 mg/dL)</td>
<td>1.97</td>
<td>0.77–5.03</td>
<td>1.42</td>
<td>0.157</td>
</tr>
</tbody>
</table>

*Statistically significant. BMI: body mass index, CI: confidence interval, DM: diabetes mellitus, HDL: high-density lipoprotein, LDL: low-density lipoprotein, OR: odds ratio, TG: transaction gateway, VLDL: very-low-density lipoprotein.

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**Acknowledgement**

We acknowledge Dean, Indira Gandhi Government Medical College, Nagpur, for helping us in publication of this original article. We are also thankful to Dr. PP Joshi, Associate Professor, Medicine, Indira Gandhi Government Medical College, Nagpur, and Master of Clinical Epidemiology, Newcastle University, Sydney, Australia, for his valuable guidance in preparation of this original article.

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Biomarker-guided therapy for heart failure

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ABSTRACT

Although, there have been significant advances in the management of heart failure (HF), one of the important problems faced by the clinician treating these patients is the significant recurrence of HF with consequent need for readmission. In this article, a discussion is made about the role of natriuretic peptides for monitoring long-term treatment of these patients and different trials done in this regard.

KEYWORDS

BNP
Heart failure
Monitoring
NT-proBNP

Heart failure (HF) has become an important problem in cardiology practice both in India and abroad with increasing age of the population. The other reason for the rising prevalence of HF is the epidemic of diabetes with its associated coronary artery disease and chronic kidney disease.

The medical management of HF has become fairly standardised with a generally good agreement about evidence-based medical therapies namely angiotensin-converting-enzyme inhibitor (ACEIs), angiotensin receptor blockers (ARBs), beta blockers and aldosterone antagonists. However, despite these advances in HF therapy, these patients continue to get recurrence of HF with need for readmission frequently, the so-called acute decompensated HF (ADHF), so much so that readmission for HF is a part of primary end point in most HF trials.

One of the ways of monitoring patients of HF is to keep a close watch of patient’s body weight. However, it is a crude method and often by the time the weight increases, patient is already in pulmonary oedema or in the hospital. Hence, the need for sensitive and reliable biomarkers that can predict impending HF, and also to monitor and guide the treatment.

Natriuretic peptides serve this purpose to a large extent. They are excellent surrogates for wedge pressure, better at prognosis than left ventricular ejection fraction (LVEF) and correlate well with New York Heart Association (NYHA) class.1–4 Before discussing the weight of evidence in this regard, one needs to recapitulate the biochemistry of natriuretic peptides (Figure 1). There is a pre-proB-type natriuretic peptide (BNP) which is broken into proBNP which further breaks into BNP and N-terminal (NT) proBNP. The BNP is the active component and the NT-proBNP is the inactive component. The NT-proBNP rises more linearly with decrease in renal function, the probable reason for most of the important and the recent trials for measuring NT-proBNP.

Differences between BNP and NT-proBNP: Although, both molecules rise significantly with HF, there are basic differences between them (Table 1). Hence, one should avoid using both these measurements in the same institute, and instead, concentrate on one.

An important controversy in this area is whether during the follow-up of HF patients, one should aim at a fixed target

Figure 1 Basic biochemistry of natriuretic peptides. BNP: B-type natriuretic peptide, NT-proBNP: N-terminal proB-type natriuretic peptide.
by tailoring the dosages of various drugs particularly diuretics or depend only on clinical judgement. A number of trials have been done with this objective with variable results. Let us examine the data of some of the leading trials in this arena.

**PRIMA study:** The PRIMA study randomised 345 patients to NT-proBNP-guided therapy versus clinically-guided therapy and followed up for 1 year. The primary end point was number of days alive outside the hospital. Median age of the patients was 71 years. The NT-proBNP level at the time of admission was 8034 pg/mL and fell to 2958 pg/mL at discharge. There was no significant difference in primary end point/mortality between the two groups. However, when they looked at the figures of mortality and number of days alive outside the hospital in the group of patients who achieved and maintained target NT-proBNP in >75% of the visits, this group of patients had a significant advantage (Figure 2). The mortality was 10.9% compared to 33% in clinically-guided group (Figure 3). This fact highlights the importance of not only achieving the target but also maintaining it throughout. One important criticism against PRIMA study is the relatively high NT-proBNP target during follow-up as a result of which the threshold to hike the treatment was high. It was nearly 3 times higher than required in the biomarker-guided arm of BATTLE SCARRED study and 4–8 times higher than the TIME CHF. This particular drawback of PRIMA study may have diluted the effect.

**BATTLE SCARRED study:** The 3-year follow-up of this study was published in 2010 in the Journal of the American College of Cardiology (JACC). They had three groups in this trial. A total of 364 patients were randomised to NT-guided therapy or intensive clinical treatment or usual care group. The 3-year mortality was selectively reduced in patients <75 years of age in the NT-proBNP-guided therapy group compared to other two groups.

**TIME CHF study:** This study was done in patients >60 years of age with about 250 patients in each arm. There were 250 patients in 60–74 age group and 289 in >75 years of age group. 30% were in atrial fibrillation (AF). It is considered as a negative trial as the primary end point (18 months survival free of any hospitalisation) did not differ between the two groups. However, survival free of hospitalisation for HF is better with hormone-guided therapy among those patients <75 years of age.

Both TIME CHF and BATTLE SCARRED trials failed to show benefit in patients >75 years of age.

**PROTECT study:** This is one of the most recent studies. These authors attempted an aggressive reduction of NT-proBNP to <1000 pg/mL. The number of patients was 75 in each arm. The NT-proBNP levels were 1946 pg/mL at baseline which came down to 1842 pg/mL in the standard treatment arm, while they came down from 2344 pg/mL to 1125 pg/mL in the hormone-guided arm. Unlike the TIME CHF study, this study showed equal or more impressive results in patients >75 years with hormone-guided therapy (Figures 4 and 5). They also demonstrated reduction in heart size and increase in EF with hormone-guided therapy (Figure 6).

A meta analysis of the patients included in TIME CHF, STAR BRIGHT, and STARS BNP studies was published in 2008.

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### Table 1

<table>
<thead>
<tr>
<th></th>
<th>BNP</th>
<th>NT-proBNP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amino acids</td>
<td>32</td>
<td>76</td>
</tr>
<tr>
<td>Molecular weight (d)</td>
<td>3.5</td>
<td>8.5</td>
</tr>
<tr>
<td>Half-life (min)</td>
<td>22</td>
<td>60–120</td>
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<tr>
<td>Clearance</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary mechanism</td>
<td>Endopeptidase</td>
<td>Renal</td>
</tr>
<tr>
<td>Clearance receptor</td>
<td>NPRC</td>
<td>Renal</td>
</tr>
<tr>
<td>Haemodialysis</td>
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<td>No</td>
</tr>
<tr>
<td>Point-of-care</td>
<td>Yes</td>
<td>Pending</td>
</tr>
<tr>
<td>GFR correlation</td>
<td>Moderate</td>
<td>Strong</td>
</tr>
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<td>Biologic activity</td>
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</tr>
<tr>
<td>Range (pg/mL)</td>
<td>0–5000</td>
<td>0–35,000</td>
</tr>
</tbody>
</table>

BNP: B-type natriuretic peptide, GFR: glomerular filtration rate, NPRC: natriuretic peptide clearance receptor, NTproBNP: N-terminal proB-type natriuretic peptide.

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**Figure 2** PRIMA-study on NT-proBNP target analysis: primary end-point. NT-proBNP: N-terminal proB-type natriuretic peptide.

**Figure 3** PRIMA-study on NT-proBNP target mortality (%). NT-proBNP: N-terminal proB-type natriuretic peptide.
During an admission for acute HF (AHF), one should take a blood sample immediately after admission before any therapy is started, as in our experience, the natriuretic peptide (NP) levels come down very quickly in some patients. The next testing should be 24–48 hours later to look at the response and once again before discharge. After discharge, the BNP levels should be monitored once in a week or 2. Later, as the patient becomes stable, the frequency may be reduced.

**Establishing a steady state level of B-type natriuretic peptide for a given patient**

In a given patient once a stable clinical state is achieved, the NT-proBNP levels tend to become relatively stable. Once this is achieved, these levels can be used for monitoring over course of time.

**Target during chronic therapy**

As can be seen from the PROTECT study which gave the best possible results, for NT-proBNP a reasonable target is < 1000 pg/mL while at the same time a close watch should be kept on clinical condition, blood pressure, renal function, and electrolytes.

**Significance of non drop of B-type natriuretic peptide during acute admission**

These patients certainly carry a poor prognosis. Elevated pre-discharge levels predict high-risk of early readmission.

**New molecules:** A new emerging biomarker in the treatment of AHF is high-sensitivity Troponin. There is now evidence that patients with ADHF who have elevated Troponins have worse prognosis.10–12 This could be due to myonecrosis from subendocardial ischaemia. The availability of highly sensitive Troponin assays capable of detecting Troponins in the range of ng/L represents a new opportunity. In a recent trial in which serial sampling of high-sensitivity Troponin I in AHF was done, those patients with rapidly rising levels during hospitalization had worse outcome than those who had little
or no increase. Obviously, acute coronary syndrome has to be ruled out in such patients.

**Copeptin:** In patients with HF, it has been shown that increased arginine vasopresin (AVP) concentrations are associated with more severe disease. However, AVP is difficult to measure because of in vitro instability and rapid clearance. Copeptin, the C-terminal segment of prepro-vasopresin is a stable and reliable surrogate for AVP concentrations. In the BACH study (Biomarkers in AHF) increased 90-day mortality and readmission were seen in patients with elevated Copeptin levels. Thus, increased Copeptin levels may be used to decide about the treatment of hyponetrimia.

**Future studies:** The ACTIVATE Study is a multicentre study that will randomise patients admitted for AHF to Tolvaptan versus Placebo-based on the Copeptin levels. The HABIT trial is testing the feasibility of finger-stick NP tests at home which can avoid unwanted hospital visits.

Thus these are exciting times for biomarker-guided therapy.

**Concluding remarks:** Although, there is some controversy with some trials like TIME CHF showing negative results, a close examination of the data particularly from the PROTECT Study suggests improved outcomes both in terms of mortality and admission free survival with natriuretic peptides-guided therapy. This is the era of biomarkers and evidence-based medicine. Further, fine tuning of treatment of HF is required. The BNP-targeted therapy appears to go a long way in achieving this goal.

**References**

Review article

Dronedarone—current status in management of atrial fibrillation

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ABSTRACT

Atrial fibrillation (AF) is the most common of the serious cardiac rhythm disturbances and is responsible for substantial morbidity and mortality. Available drug therapy for AF has modest efficacy and is associated with the risk of life-threatening pro-arrhythmic complications. Dronedarone is a newer therapeutic agent with a structural resemblance to amiodarone and a better side effect profile. It is a multichannel blocker with antiadrenergic properties and has been evaluated in both rate and rhythm control strategies in the management of AF. In this review, we discuss the current role of dronedarone in the contemporary management of AF.

KEYWORDS

Antiarrhythmic drug
Atrial fibrillation
Dronedarone

Introduction

Atrial fibrillation (AF) is a common arrhythmia in clinical practice contributing to significant cardiovascular morbidity and mortality. The prevalence of AF increases with age and adversely impacts the healthcare resources. Major trials have shown the adequacy of rate-control in the management of AF, nevertheless the achievement of sustained sinus rhythm has been shown to improve quality of life and exercise performance. Current antiarrhythmic agents employed in the treatment of AF are limited by their modest efficacy, pro-arrhythmic effects, and long-term toxicity. Dronedarone is a new anti-arrhythmic agent which has been evaluated in many multicentre trials (Table 1).

Dronedarone

Dronedarone is a newer benzofuran derivative having a structural resemblance to amiodarone with two important molecular changes: it lacks the iodine moiety responsible for thyroid dysfunction and it has a methane sulfonyl group that decreases lipophilicity, resulting in a shorter half-life leading to lower tissue accumulation and less long-term toxicity. It is an orally administered drug cleared by non-renal mechanism and a steady-state serum level is achieved in 5–7 days. The bioavailability is relatively low (15%) because of extensive hepatic first-pass metabolism by cytochrome P450 (CYP) 3A4 and CYP2D6, thus requiring twice daily dosing to achieve steady-state serum levels. Dronedarone is a multichannel blocker with electrophysiological properties similar to those of amiodarone. It decreases slowly activating delayed-rectifier K+ current (I Kr), and inward rectifier potassium current I (K1), L-type Ca2+ current I (Ca [L]) and maximum rate of rise of action potential (dV/dt max) with a concentration and frequency-dependent relationship (I [Na]). The drug has very little effect on the QT interval, and proarrhythmia has not been observed. In vitro studies have shown a more efficient inhibition of (I [Na]) in atrial myocytes compared to amiodarone showing atrial selective antiarrhythmic properties. Dronedarone is an approximately 100 times more potent inhibitor on muscarinic acetylcholine receptor-operated K+ current IK (ACh) than amiodarone. This property may be involved, at least in part, in its anti-arrhythmic action against AF, as vagal activation is known to play a role in the pathophysiology of AF. Like amiodarone, dronedarone can partially inhibit the effects of stimulation of the beta 2 and alpha adrenoceptor system that may play a pivotal role in the onset of severe ventricular rhythm disturbances.
In patients with paroxysmal or persistent AF/AFL who had additional risk factors like hypertension, diabetes, age ≥70 years, previous stroke or transient ischaemic attack (TIA), systemic embolism, and left ventricle (LV) dysfunction. This was the largest trial assessing efficacy of an anti-arrhythmic drug in AF population in reduction of cardiovascular outcomes. In the treatment arm, there was a significant reduction in hospitalisations related to cardiovascular events (36.9% vs 29.3%) particularly due to reduction in hospital admissions for AF. There was, however, no benefit in hospitalisations due to heart failure (HF), ventricular arrhythmias and non-fatal cardiac arrest. Numerically there were fewer deaths in the dronedarone arm compared to placebo (139 vs 116). Overall, there was 30% reduction in cardiovascular deaths and 45% decrease in arrhythmia-related deaths. ATHENA specifically excluded patients who had either haemodynamic instability or severe (New York Heart Association [NYHA] Class IV) HF. An interesting observation in this trial was that there was lesser number of ischaemic strokes with the drug though the frequency of haemorrhagic strokes was similar. This decrease in strokes was particularly impressive in those with ≥2CHADS2 score.

**Dronedarone in permanent atrial fibrillation**

Achievement of adequately controlled ventricular rates is the principal objective in the management of permanent AF. The possibility that dronedarone could have rate-control properties was suggested by the fact that patients in EURIDIS and ADONIS trials which were placebo-controlled and identical in design, conducted in European, and non-European centres (USA, Argentina, Canada, South Africa, and Australia), respectively. Both these pivotal trials aimed at assessing the efficacy of dronedarone in the maintenance of normal sinus rhythm after electrical, pharmacological, or spontaneous conversion of paroxysmal AF or atrial flutter (AFL). It was shown that dronedarone reduced the 1 year symptomatic recurrences (77.5% vs 67.1% in the European trial; 72.8% vs 61.1% in the non-European trial) and prolonged the median time to recurrence (41–96 days in the European trial; 59–158 days in the non-European trial). Further, in both the trials, when the recurrence occurred, the mean ventricular rates were much slower compared to placebo (117 beats/min [bpm] vs 102 bpm and 116 bpm vs 104 bpm, respectively). In the period of 1 year, toxic effects related to lung, thyroid and liver were not significantly increased in the dronedarone group. Though, not an intended end point of the study, post hoc analysis showed a decrease in the combined outcome of hospitalisation and mortality. This observation led to the design of the ATHENA trial to evaluate the effect of treatment on all-cause mortality and morbidity in patients with paroxysmal and persistent AF or AFL. It was a prospective, randomised, placebo-controlled, double-blind, trial evaluating the effects of dronedarone versus placebo (ratio 1:1)
ADONIS trials who suffered recurrences had lower ventricular rates compared to placebo. ERATO trial specifically assessed the efficacy of dronedarone in the control of ventricular rate in patients with permanent AF, when added to standard rate-control therapy which included beta-blockers, calcium antagonists, and digoxin. In this prospective study, 174 elderly patients with permanent AF were randomised to treatment for 6 months with dronedarone (n = 85), or matching placebo (n = 89). The change in the mean ventricular rate between baseline and day 14 was objectively documented by 24-hour Holter. In addition, ventricular rate was also assessed during sub-maximal and maximal exercise.

Dronedarone achieved a significant decrease in the mean 24-hour ventricular rate at 14 days (11.7 bpm, P < 0.0001) which was sustained at 6 months. During maximal exercise compared to placebo, there was a mean reduction of 24.5 bpm (P < 0.0001), without any compromise in exercise tolerance. The effects of dronedarone were not influenced but were additive to other rate-control agents used in the study. Results of the ATHENA trial showed that the benefit of improved cardiovascular outcomes with dronedarone was also perceived in the subset of patients who progressed to permanent AF. This indicated that the benefits of dronedarone possibly extended beyond those that were obtained by rhythm control alone. The PALLAS was an ambitious study intending to demonstrate this hypothesis in patients with permanent AF having additional cardiovascular risk factors.

This trial was terminated for safety reasons 1 year after enrolment commenced achieving a mean follow-up of just 3.5 months. There was a highly significant increase in strokes, hospitalisations, and mortality related to cardiovascular causes in the dronedarone arm. There was an increase in HF-related hospitalisations and mortality. Surprisingly, in contrast to ATHENA study, there was a three-fold increase in arrhythmic deaths contributing to the cardiovascular mortality. The PALLAS generated a very sound evidence of harmful effects of dronedarone in permanent AF patients with cardiovascular risk factors.

Dronedarone versus amiodarone

Historically, amiodarone has been the most effective anti-arrhythmic agent in maintaining sinus rhythm in patients with AF and has been shown to be superior to sotalol and propafenone as a rhythm control agent. Its usage has been limited due to its cumulative and frequently irreversible toxicity. Dronedarone is an amiodarone congener with similar electrophysiological properties without the toxic and pro-arrhythmic effects. There exist some important differences between the two drugs. Amiodarone has a slow onset of action and requires 1–3 weeks to achieve therapeutic response and has a long half-life of 40–55 days. In contrast, dronedarone has a half-life of 13–19 hours and reaches a steady-state plasma concentration in 4–8 days.

The relative effectiveness of amiodarone and dronedarone achieving rhythm control in 504 patients with persistent AF was assessed by DIONYSOS trial. Patients were included if they had a need for cardioversion and needed to be on anti-arrhythmic drugs. They were randomised to receive amiodarone 600 mg once daily for 28 days followed by 200 mg once daily or 400 mg twice daily of dronedarone with median treatment duration of 7 months. The rate of AF recurrence was higher in the dronedarone group (63.5% vs 42%, P < 0.0001). The rate of discontinuation of the drug due to intolerance was lower with dronedarone (10% vs 13.3%) and so was the frequency of thyroid disorders (1.2% vs 7.8%). Discontinuation of dronedarone was predominantly due to gastrointestinal side effects. Dronedarone thus was shown to be less effective than amiodarone in maintaining sinus rhythm but demonstrated to have better safety profile.

Choice of dosage

The evidence for appropriate therapeutic dosage of dronedarone (800 mg daily) is derived solely from the DAFNE study.

**Dronedarone in heart failure**

Amiodarone is a popular anti-arrhythmic agent in clinical practice used frequently for suppression of atrial and ventricular arrhythmias in patients with HF; it has however not shown survival benefit in this population. The inability of amiodarone to reduce mortality in this vulnerable subset was attributed to its pro-arrhythmic effects. Similar lack of mortality benefit was seen with sotalol. As dronedarone was known to be a drug with electrophysiological properties similar to amiodarone and being devoid of its side effects, it was hypothesised that it would show mortality benefit in HF patients. In the ATHENA study, the dronedarone group, stable HF patients with LV dysfunction did as well as those with preserved LV function. The ANDROMEDA trial was a multicentre, double-blind, parallel-group, placebo-controlled study designed on the background of these facts to evaluate the effect of dronedarone on reduction in hospitalisations for worsening HF or death, in a high-risk population of patients with recently decompensated congestive heart failure (CHF). This study did not require patients to have AF.

After inclusion of 627 patients (310 in the dronedarone group and 317 in the placebo group), the trial was prematurely terminated for safety reasons. During a median follow-up of 2 months, 25 patients in the dronedarone group (8.1%) and 12 patients in the placebo group (3.8%) died (hazard ratio in the dronedarone group, 2.13; 95% confidence interval [CI], 1.07–4.25; P = 0.03). The excess mortality was predominantly related to worsening of HF—10 deaths in the dronedarone group and two in the placebo group. The primary end point which was the composite of death from any cause or hospitalisation for HF did not differ significantly between the two groups; there were 53 events in the dronedarone group (17.1%) and 40 events in the placebo group (12.6%) (hazard ratio, 1.38; 95% CI, 0.92–2.09; P = 0.12). It was concluded from this study that in patients with severe HF and LV systolic dysfunction, treatment with dronedarone was associated with increased early mortality related to the worsening of HF.
which was designed to compare three different doses of this drug with placebo for the maintenance of sinus rhythm following electrical cardioversion in patients with AF. The primary objective was to assess the efficacy of several doses of dronedarone for the maintenance of sinus rhythm for 6 months in patients undergoing cardioversion for AF. Patients fulfilling the entry criteria for the study were randomly assigned to either 400 mg twice daily, 600 mg twice daily, 800 mg twice daily or placebo, which were continued for 6 months. The primary end point was the time to first recurrence of AF after conversion to sinus rhythm. Secondary study endpoints were spontaneous conversion of AF following randomisation, heart rate in case of AF recurrence and the incidence of side effects.

Within a 6-month follow-up, the time to AF relapse increased on dronedarone 800 mg, with a median of 60 days versus 5.3 days in the placebo group (relative risk reduction 55% [95% CI, 28–72%] \(P = 0.001\)). No significant effect was seen at higher doses. Spontaneous conversion to sinus rhythm on dronedarone occurred in 5.8–14.8% of patients (\(P = 0.026\)). There were no pro-arrhythmic reactions. Drug-induced QT prolongation was only noticed in the 1600 mg group. Precipitate drug discontinuations affected 22.6% of subjects given 1600 mg dronedarone versus 3.9% on 800 mg and were mainly due to gastrointestinal side effects. No evidence of thyroid, ocular or pulmonary toxicity was found. Thus, dronedarone, at 800 mg daily dose appears to be effective and safe for the prevention of AF relapses after cardioversion.

We, however, have no data on the lower doses of the drug particularly to assess if the safety profile improves in permanent AF patients. The HARMONY is a new pacemaker-patient-based trial to examine the efficacy and safety of a low dose of 150–225 mg of dronedarone with 750 mg ranolazine on AF burden. About 150 patients will be enrolled at 45 sites in North America and Europe, starting January 2012.

**Dronedarone—present status in atrial fibrillation management**

The data generated by clinical experience with dronedarone clearly demonstrates that our quest for an ideal anti-arrhythmic agent suitable for all subsets of AF population is far from complete. Advantages in favour of this new antiarrhythmic drug are ease of initiation with a single dose as an outpatient, decreased requirement for monitoring end organ toxicity and no significant interaction with warfarin. Post drug initiation surveillance is limited to periodic electrocardiograms and liver function tests due to reports of rare hepatocellular injury. Though, less effective than amiodarone in the prevention of AF, it is comparatively safer and well tolerated in patients with preserved LV function. In paroxysmal and persistent AF/AFL it has been associated with decreased hospitalisations and cardiovascular mortality driven by its favourable effect on AF. This evidence from ATHENA, the largest anti-arrhythmic drug trial in AF, resulted in approval by the Federal Drug Administration in the USA and incorporation into the European and American guidelines for this indication. In patients with advanced HF and with severely impaired ventricular dysfunction, use of dronedarone increased mortality due to worsening HF and patients with permanent AF/AFL with risk factors for vascular events had increased rates of stroke, HF, and cardiovascular deaths. Similarly, outcomes are poor in patients with permanent AF and risk factors for vascular disease. Clearly, this drug is harmful in these groups of patients and should not be used. In AF patients who require amiodarone but have experienced drug toxicity, dronedarone provides a useful substitution.

**References**


Review article

Dedicated bifurcation stents

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KEYWORDS
Bifurcation
Final kissing inflation
Main-branch stent
Side-branch

ABSTRACT
Bifurcation percutaneous coronary intervention (PCI) is still a difficult call for the interventionist despite advancements in the instrumentation, technical skill and the imaging modalities. With major cardiac events relate to the side-branch (SB) compromise, the concept and practice of dedicated bifurcation stents seems exciting. Several designs of such dedicated stents are currently undergoing trials. This novel concept and pristine technology offers new hope notwithstanding the fact that we need to go a long way in widespread acceptance and practice of these gadgets. Some of these designs even though looks enterprising, the mere complex delivering technique and the demanding knowledge of the exact coronary anatomy makes their routine use challenging.

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Introduction
Coronary bifurcations vary not only in basal anatomy (plaque burden, plaque location, angle, branch diameter, and site) but also in dynamic anatomical changes during treatment (plaque shift, dissection, and carina modification). The search for an optimal approach to treat this subset of lesions has resulted in the introduction of different techniques (each with its own advantages and disadvantages). However, no two bifurcations are identical and no single strategy exists that can be applied to every bifurcation. In the past few years, significant advancements have occurred in our understanding and treatment of bifurcation lesions.¹ These may include:
1. Introduction of drug-eluting stents (DES).
2. Use of single stent strategy more often than double stents.
3. Acceptance of a suboptimal result in the side-branch (SB).
4. Performance of high pressure post dilation, kissing inflation, and use of intravascular ultrasound (IVUS).
5. Introduction of drug-eluting balloons especially for SB ostium.

Bifurcation percutaneous coronary intervention (PCI) has moved past an important milestone in accepting single stent strategy being the best for most of the bifurcations. The adoption of two stent strategy may be considered in the case of a large SB with ostial lesion, dissection of SB, significant pinching with decreased flow, etc. The different stenting techniques have been boiled down to largely provisional T-stenting.Whatever may be the strategy, the outcomes of bifurcation have largely improved thanks to the above mentioned advancements.

Recent studies on bifurcation percutaneous coronary intervention
In the last few years the optimal stenting strategy has been an area of considerable debate in bifurcation PCI. In order to clarify the best bifurcation PCI approach between ‘provisional’ T-stenting of implanting only one-DES (1 DES) in the main-branch (MB) vs a two-DES approach with routine stenting of both bifurcation branches (MB and SB), a number of studies and randomised controlled trials (RCT) have been performed.¹–³ The ‘Randomised Study of the Crush Technique Versus Provisional Side-Branch Stenting in True Coronary Bifurcations (CACTUS Study)’ was a prospective, randomised, multicentre study enrolling 350 patients was designed to assess whether elective stenting of both branches (by the use of Crush technique), which can be more technically demanding, provides greater benefits than the simple approach of stenting only the MB (provisional T-stenting) with additional stenting on the SB only in the case of unsatisfactory result at that site. Of the 350 patients, 177 were enrolled in the Crush arm while 173 in the provisional group. The true bifurcation
lesions were 94% of which 75% were type 1,1,1 according to the medina classification. The two groups were well matched for clinical characteristics and no differences were found in the distribution of true and non-true bifurcations. Of interest, is the fact that in the provisional group an additional stent implantation in 31% of cases was required for the following reasons: thrombolysis in myocardial infarction (TIMI) flow <3 (1.9%); significant residual stenosis (72%), and flow limiting dissection in the SB (39%). At 6-months follow-up no significant differences were found regarding the primary endpoint: cumulative major adverse cardiac event (MACE) rate was 15.8% in the Crush group vs 15% in the provisional group (P=0.95). Of interest the performance of final kissing balloon inflation (FKI) compared with no FKI was associated in both groups with: significantly lower incidence of in-hospital and follow-up myocardial infarction (MI) (7.5% FKI vs 29% no FKI, P<0.001) and angiographic restenosis in the MB (4.7% FKI vs 16% no FKI, P=0.03) and in the SB (11.9% vs 36%, P<0.001).

This study has demonstrated that in most true bifurcations, a provisional strategy is effective with the necessity to implant a second stent in the SB in about one-third of cases. The Crush technique did not appear to be associated with higher incidence of adverse events despite the limited follow-up time of 6 months. Data from the CACTUS study and other randomised trials supports at present that the general recommended strategy in coronary bifurcation treatment is provisional SB stenting. However, a number of coronary bifurcation lesions need stent implantation in both the SB and MB. Many techniques are used during the everyday clinical practice of which the Crush7 and Culotte8 outcomes.

More definitive data regarding the use of one stent or two stent stagey in bifurcation angioplasty with DESs has come from the prospective randomised NORDIC study. This was a landmark trial in which strategy of stenting both the main vessel (MV) and the SB was compared with a strategy of stenting the MV only, with optional stenting of the SB (MV), with sirolimus-eluting stents. In the MV group, the main treatment principles were (1) stenting of MV; (2) SB dilation if there was TIMI flow <3 in the SB; and (3) SB stenting if TIMI flow 0 in the SB after dilation. In the MV/SB group, the main treatment principles were stenting of both the MV and the SB by application of the Crush or Culotte technique. In all cases of SB stenting, the operator was required to attempt ‘kissing balloon’ dilation at the end of the procedure. A total of 413 patients with a bifurcation lesion were randomised. The primary end-point was a MACE: cardiac death, MI, target vessel revascularisation (TVR), or stent thrombosis after 6 months. At 6 months, there were no significant differences in rates of MACE between the groups (MV/SB 3.4%, MV 2.9%; P=NS). In the MV/SB group, there were significantly longer procedure and fluoroscopy times, higher contrast volumes, and higher rates of procedure-related increases in biomarkers of myocardial injury. A total of 307 patients had a quantitative coronary assessment at the index procedure and after 8 months. The combined angiographic end point of diameter stenosis >50% of MV and occlusion of the SB after 8 months was found in 5.3% in the MV group and 5.1% in the MV/SB group (P=NS). Independent of stenting strategy, excellent clinical and angiographic results were obtained with percutaneous treatment of de novo coronary artery bifurcation lesions with sirolimus-eluting stents. The simple stenting strategy used in the MV group was associated with reduced procedure and fluoroscopy times and lower rates of procedure-related biomarker elevation. Therefore, this strategy can be recommended as the routine bifurcation stenting technique. The study again underscoring the fact that most of the bifurcations can be managed with a provisional stenting stagey with optional second stent. However, there are lesions with a large SB (like left main bifurcation) where a planned two stent strategy should be selected.

The study by Erglis et al. is the first randomised clinical and angiographic comparison of 2-DES bifurcation techniques: Crush vs the Culotte. A total of 424 patients were randomised to Crush (n=209) and Culotte (n=215) stenting. The 2 groups were well balanced regarding baseline clinical characteristics while there were more patients with ‘true’ bifurcation lesions (as type 1,1; 1,0,1; 0,1,1) in the Culotte group (82.3% vs 73.3%, P<0.03). No differences were found in procedure time, fluoroscopy time, and volume of contrast used while FKI was performed in significantly less patients in the Crush group (85% vs 92%, P=0.03). At 6-months follow-up there were no differences regarding cumulative MACE rate: 4.3% in Crush vs 3.7% in Culotte; P=0.87. There were no differences in the other clinical event rates either: cardiac death 1% vs 0.5%, MI 1.9% vs 1.4%, TVR 2.4% vs 2.8% and ST 1.4% vs 1.9%). Complete angiographic follow-up was available in 88% of patients and there was a trend to less in segment restenosis at 8-months follow-up because of significantly reduced SB in-stent restenosis in Culotte treated patients (9.8% Crush vs 3.8% Culotte, P=0.04). These results showed that both Culotte and Crush were associated with excellent clinical and angiographic results and even though Culotte tended to have lower angiographic restenosis rates, neither of the 2 techniques can be claimed to be absolutely superior to the other. Data from NORDIC II Stent Study have demonstrated that a 2-DES strategy (Crush or Culotte) is associated with excellent clinical and angiographic results and should be considered in the treatment of large SBs where suboptimal angiographic results could be associated with subsequent clinical problems.

The importance of FKI in reducing late loss and restenosis, especially at the SB, has been repeatedly demonstrated and has now become standard in the performance of all two stent techniques. However, whether FKI is mandatory with provisional stenting is still unsettled. The ‘Nordic-Baltic Bifurcation III Study: A Prospective Randomised Trial of Side-Branch Dilatation Strategies in Patients with Coronary Bifurcation Lesions Undergoing Treatment with a Single Stent’ was presented by Niemela at transcatheter cardiovascular therapeutics (TCT) 2009 conference. This study had the purpose of evaluate the outcome of two SB strategies (no-FKI vs FKI) in coronary bifurcation lesions treated with MB stenting using sirolimus-eluting stents (SES). A total of 477 patients were randomised to no-FKI (n=239) and FKI (238). The groups were well matched in terms of clinical and angiographic baseline characteristics. However, it should be noted that only about half of the bifurcations treated were true bifurcations (51.8% no-FKI group
vs 54.6% FKI group) and the SB stenosis was not severe (39.4±34.4% no-FKI vs 40.3±34.4% FKI group). At 6-months follow-up, no differences were found in the primary endpoint of cumulative MACE (2.9% vs 2.9%) between the two groups (cardiac death: 0% vs 0.8%, index lesion MI: 2.2% vs 0%, target lesion revascularisation (TLR) 2.1% vs 1.3% and ST 0.4% vs 0.4%, in the no-FKI and FKI groups, respectively). These results showed that in bifurcation lesions, a strategy of routine FKI of the SB through the MB stent did not improve the 6-months clinical outcomes as compared to a strategy of no FKI. The recently published Korean CORRIBS registry also has shown routine final kissing inflation with single stent technique do more harm than good.11 ‘TIMI Flow-Guided Concept to Treat Side-Branches in Bifurcation Lesions—A Prospective Randomised Clinical Study (Thueringer Bifurcation Study, The THUEBIUS as Pilot Trial)’ was designed to assess whether treating the SB only when TIMI flow was 0 or 1 and/or the patient had angina was not inferior to routine FKI-PCI. One hundred and ten patients with bifurcation lesions undergoing provisional-T-stenting were randomly assigned to two arms: (A) stenting of the MB and FKI-PCI (simultaneous or sequential balloon angioplasty) in 56 patients; and (B) stenting of the MB and SB dilatation only if there was SB TIMI flow 0 or 1 or if the patient complained angina after deployment of the MB stent (54 patients). In both groups, inserting a guide wire in the SB was mandatory. The bifurcation site most often treated was left anterior descending artery-diagonal (81%) while most of patients had true bifurcation at visual assessment. According to the study protocol, PCI of the SB was performed in 82.1% in A group vs 16.7% in B group (P<0.05). No difference in periprocedural MI were found (4.6% group A vs 2.9% group B, P=0.52). At 6-months follow-up no significant differences were found in: TLR (primary endpoint) 17.9% vs 14.8% (P=0.67); MACE 23.2% vs 24.1% (P=0.92) and ST 3.6% vs 3.7% (P=0.97), in groups A and B, respectively.

These results showed no differences between the two treatment approaches and suggested a simple strategy with only ‘keep it open’ of the SB if the final SB TIMI flow was 2 and the patient is asymptomatic.21 However, it must be acknowledged that this study was markedly underpowered for detecting differences in clinical endpoints. As we have seen SB ostium is still a central point in the debate of bifurcation lesions PCI while it is the most common restenotic site in this subset of lesion. The specific mechanism underlying restenosis at SB ostium is at the moment not completely clear and presumably many factors are involved.1,8,11–13

The British Bifurcation Coronary study14 randomised 500 patients with coronary bifurcation lesion for simple or complex strategy using Paclitaxel DES. The simple group had provisional stenting where as the complex group had crush or Culotte technique with two DES. In the simple group (n=250), 66 patients (26%) had kissing balloons in addition to MV stenting, and 7 (3%) had T stenting. In the complex group (n=250), 89% of Culotte (n=75) and 72% of Crush (n=169) cases were completed successfully with final kissing balloon inflations. The primary end-point (a composite at 9 months of death, MI, and target vessel failure) occurred in 8% of the simple group versus 15.2% of the complex group (hazard ratio 2.02, 95% CI 1.17–3.47, P=0.009). The MI occurred in 3.6% vs 11.2%, respectively (P=0.001), and in-hospital major adverse cardiovascular events occurred in 2% vs 8% (P=0.002), respectively. The study concluded with recommending provisional stenting for majority of bifurcations.

The rationale for dedicated bifurcation stents

The conventional approach to bifurcation PCI (with either single or double stents) still has a number of limitations such as the following15–20:

1. Maintaining access to SB throughout the procedure.
2. MB stent struts jailing SB resulting in difficulty in re-wiring SB or passing balloon/stent into SB through the stent struts.21,22
3. Distortion of MB stent by SB dilatation; inability to fully cover and scaffold ostium of SB.
4. Inability of stent structure to withstand SB balloon dilatation and deformation.
5. Operator skills and technical experience.

Clearly bifurcation PCI is technically challenging and time-consuming especially in order to achieve an optimal long-term result.23 As a result, several stents have been specifically designed for bifurcations with the intention of addressing these shortcomings. However, the first generation of these dedicated bifurcation stents were difficult to deploy as they were stiff and accurate positioning of the stent at the SB ostium was tricky. Many also had larger crossing profiles and less flexibility compared with conventional stents, so that they were difficult to deliver in tortuous or calcified arteries.

It is hoped that the newer generation of bifurcation stents will overcome these drawbacks.

The design and technique

The currently available (or under investigation) dedicated bifurcation stents can be broadly divided into:

1. Stents for provisional SB stenting that facilitate or maintain access to the SB after MB stenting and do not require re-crossing of MB stent struts—Petal (Boston Scientific, Natick, MA, USA); Invatec (Invatec S.r.l., Brescia, Italy); Antares (Trireme Medical Inc, CA, USA); Y-med Sidekick (Y-med Inc, San Diego, CA, 142 USA); Nile Croco (Minvasys, Genevilliers, France); Multilink Frontier (Abbott Vascular Devices, Redwood City, CA/Guidant Corporation, Santa Clara, CA, USA). These stents allow the placement of a second stent on the SB if needed.

2. Side-branch stenting and then MB stent implanted in the bifurcation and requires re-crossing—Sideguard (Cappella Inc, MA, USA); Tryton (Tryton Medical, MA, USA); Axxess Plus (Devax, Irvine, California). The Tryton and Sideguard are designed to treat the SB first and require re-crossing into the SB after MB stenting for FKI. The Axxess Plus is the exception as it is planted in the proximal MB at the level of the carina and does not require re-crossing into the SB but may require the additional implantation of two further
stents to completely treat some types of bifurcation lesions. The stent delivery systems (SDS) of these dedicated bifurcation systems have a number of design features in common, which explains both their strengths and weaknesses:

a. Double balloons SDS has to be tracked over two wires and thus, wire wrap (twisting) is a common problem but the stent is implanted by simultaneous kissing inflation possibly resulting in shorter procedure times. However, these devices still tend to be bulkier than single balloon SDS requiring guide catheters larger than the standard 6F and limiting their use in calcified lesions and tortuous vessels.
b. Stents with a preformed SB aperture maintain access to the SB during MB stenting but successful implantation is dependent on accurate positioning with very little tolerance for incorrect placement.
c. The SDS with a side hole has axial and rotational self-positioning properties, i.e.
   - Axial: SDS has a ‘stopper’ to position the side cell at the SB level, closest to the carina.
   - Rotational: SDS automatically turns the side hole exactly towards SB.
d. The Nile, Frontier, Twin-Rail, Sidekick, and Stentys SDS have struts that only partially cover the ostium and thus, leave the potential for a gap and ostial restenosis.
e. Stents that have struts that can be expanded into SB ostium (Petal, Ariste) may be clinically advantageous as they provide complete coverage of the SB orifice and offer the possibility of delivering drug to the SB ostium.
f. Side-branch specific stents commit the operator to stenting both branches.
g. Unfortunately, most are still bare-metal stents (BMS) but with DES currently under development in the majority.

In this review, we will describe each of these devices in detail, including their unique design features, implantation technique, and available clinical results regarding their implantation in humans.

**Y-med Sidekick (Y-med Inc, San Diego, CA, USA)**

The Sidekick (Figure 1) is a low-profile 6F guide compatible SDS that integrates a MB fixed-wire platform with a rapid-exchange steerable SB guide wire designed to preserve SB access during bifurcation stenting. There are three models with different exit ports (proximal, mid, and distal) that are selected depending on the location of the disease in the bifurcation; e.g. proximal exit port for lesion distal to bifurcation or ostial lesion. When the device is close to the carina, a guide wire is passed through the SB exit port and MB stent struts into the SB, thus avoiding re-crossing into the SB. Various BMS designs and even a DES platform are currently under investigation. A first-in-man (FIM) clinical study has been performed by Dr. T. Ischinger and Dr. E. Grube has in 17 patients with 20 lesions.24 The device success rate was 80% and an additional stent was required in 40% of cases. During the short follow-up period (68–32 days), there was 1 MACE due to a subacute stent thrombosis.

**Figure 1 Y-med Sidekick stent.**

**Multilink Frontier (Abbott Vascular Devices, CA/Guidant Corporation, Santa Clara, CA, USA)**

The Multilink (ML) Frontier coronary stent system (Figure 2) is a balloon expandable stainless steel stent premounted on a dedicated delivery system with two balloons (monorail for MB and over-the-wire inner lumen for SB) and two guide wire lumens. To assist tracking and avoid guide wire crossing, the ML Frontier has an integrated-tip design that allows single tip delivery—the MB balloon tip includes a pocket on the distal sleeve for joining the MB and SB balloon tips with a mandrel. The ML Frontier is advanced into MB over a conventional wire. The joining mandrel is retracted, releasing the over-the-wire SB tip and a 300-cm wire is inserted into the SB balloon lumen and into the SB. The system is advanced to the carina and simultaneous kissing inflation of the two balloons is performed, using a single indeflator, to expand the stent into the MB and SB. The Frontier stent multicentre registry evaluated the safety and performance of this device in 105 patients.25 Device success was 91% and procedural success 93%. Two patients suffered an in-hospital MI secondary to SB occlusion. The late loss for the ML Frontier was 0.84–0.55 mm and the overall bifurcation restenosis rate (44.8%) was high (MB: 29.9%, SB: 29.1%). At 6-months follow-up, the TLR and MACE rates were 13.3% and 17.1%, respectively. The next-generation
of the ML Frontier will be a chromium cobalt stent with the Xience V drug-eluting stent platform (i.e. Everolimus on a non-erodable acrylic and fluoro polymer).

**The Invatec Twin-Rail (Invatec S.r.l., Brescia, Italy)**

The Invatec Twin-Rail (Figure 3) is a slotted tube, 316L stainless steel stent premounted on double balloons in its proximal portion, and only on the MB balloon in its distal portion. The stent has a closed cell type design with variable stent geometry. This 6F-compatible system consists of a single dual lumen catheter splitting into two distal balloons with a central stopper that prevents further advancement of the SDS when the carina is reached. The stent is deployed by simultaneous kissing inflation with a single indeflator. The Twin-Rail is similar to the ML Frontier double balloon system except that in the latter the SB balloon is a short tapered balloon while in the Twin-Rail there is a full dilatation balloon. In the DESIRE Trial, presented by Dr. Lefevre at TCT 2005, the Twin-Rail double balloon SDS was compared to a single balloon SDS in 20 patients. Although angiographic success was high, device success was only 75% with the Twin-Rail and there was a high rate of guide wire criss-cross with both devices. The TLR rate for the Twin-Rail was 14.3% at 7 months. In this small pilot study, there was also a trend for higher device success and better safety profile with the Twin-Rail compared to a single balloon SDS.

**Nile Croco (Minvasys, Genevilliers, France)**

The Nile Croco (Figure 4) is a double balloon SDS similar to the ML Frontier and Twin-Rail but unlike these latter SDS’s that are a single catheter with single inflation port, the Nile Croco has two independent yet joined catheters that require independent manipulation and pressure monitoring. The two parallel rapid-exchange catheters are premounted with a chromium cobalt stent crimped on the MB balloon and the tip of the SB balloon. The MB balloon has three markers with the central marker indicating the position of the SB aperture. After the stent is deployed into the MB, the SB balloon is advanced into the SB and a final kissing inflation is performed. The feasibility, safety and efficacy of bifurcation stenting using the Nile stent is currently being evaluated in the multicentre (10 European centres) Nile Registry. Preliminary results of the first 75 patients showed a procedural success rate of 94.7% and a MACE rate of 10.7% in the 45 patients in whom follow-up was available at 7 months.

**Advanced Stent Technologies SLK-view (AST, Pleasanton, CA)**

The SLK-view (Figure 5) is a stainless steel flexible slotted tube stent with a side aperture located between the proximal and distal section to facilitate access to the SB after deployment of the stent in the MB. The delivery system has a dual over-the-wire design with a proximal dual lumen shaft that separates into two catheters (a balloon and a side-sheath) at its distal segment. The stent is premounted in the distal segment of delivery system with the side-sheath running under the proximal segment of the stent and exiting through the side hole. There are total of three radio-opaque markers on the balloon, located at the centre, proximal and distal edges. The SLK-view system is placed over two wires simultaneously and advanced to the bifurcation until the centre marker band is aligned to the branch vessel and the side-sheath marker separates from the centre marker. The SLK-view stent is then deployed in the MB leaving the pre-formed side hole positioned at the ostium. Unlike the petal or Antares stents,
there are no stent struts protruding into and scaffolding the ostium. In a multicentre non-randomised study, Ikeno et al. report the 'Acute and Long-Term Outcomes of the Novel Side Access (SLK-view) Stent for Bifurcation Coronary Lesions' in 81 patients with 84 de novo bifurcation lesions. The study proved the feasibility of this stent with high procedural success rates (97.6%) while maintaining SB access in all treated lesions. However, the SLK-view bare-metal stent was associated with a high restenosis rate (MB: 28.3%, SB: 37.7%) and TLR rate (21%) at 6 months follow-up.

Petal (Boston Scientific, Natick, MA, USA)

The petal stent (Figure 6), with a side aperture located mid-stent and deployable struts (a 'sleeve') may be an attractive solution to prevent SB occlusion after MB stenting. A guide wire is placed in the MB and another in the SB. The dual side-exchange (double balloon) delivery system has a main lumen that guides the catheter to the primary lesion over the MB guide wire. The secondary lumen (side-sheath) facilitates proper alignment of the aperture to the SB ostium as it tracks over the SB guide wire. In addition to a conventional cylindrical-shaped balloon, there is a secondary elliptical balloon adjacent to the main balloon and connected to the same inflation lumen so that a single inflation device is needed. The petal stent is crimped over both balloons such that the elliptical balloon is under the side aperture and petal elements. Upon expansion, the main balloon deploys the stent into the MB, while the elliptical balloon deploys the petal elements into the SB ostium. The purpose of the 'petal' aperture is to retain access to the SB during and after deployment and to scaffold the SB ostium with outwardly-deploying strut elements that extend up to 2 mm into the branch during deployment. This unique feature has potential for delivery of anti-proliferative drug to the most common site of bifurcation restenosis. The 1st generation of this stent, called AST petal, developed by Advanced Stent Technologies was a 316L stainless steel slotted tube design. The FIM experience with the AST petal dedicated bifurcation stent has been reported by Ormiston et al. In this pilot study, the AST petal was successfully implanted in 12 of 13 patients. In nine patients, an additional stent was required in the bifurcation and the TLR rate was 15% at 6 months. The petal stent was acquired by Boston Scientific in 2004 and modified into the Taxus petal stent. This 2nd generation petal stent is a platinum chromium alloy stent which is coated with Paclitaxel on a Translate polymer [poly(styrene-b-isobutylene-b-styrene)]. The platinum chromium is superior to its stainless steel predecessor in that the new alloy allows even thinner stent struts with increased flexibility and radiopacity. In July 2007, the TAXUS PETAL I First Human Use (FHU) trial commenced with the successful implantation of the stent into the first patient by Dr. John Ormiston in Auckland, New Zealand. The TAXUS PETAL I FHU non-randomised trial will enrol a total of 45 patients in New Zealand, France and Germany to assess the acute performance and safety (death, MI, TVR) at 30 days and 6 months, as well as continued annual follow-up for 5 years.

Antares side-branch adaptive stent (Trireme Medical Inc, CA, USA)

The Antares side-branch adaptive stent (SAS) (Figure 7) with automatic SB support deployment consists of a single balloon expandable stainless steel stent. It has a SB support structure in the centre of the stent provided with four radiopaque tantalum markers for positioning and orienting at the bifurcation site. Stent deployment is achieved using a single rapid-exchange balloon catheter and a SB stabilising wire encased in a peel away lumen to minimise wire crossing. As the stent approaches the targeted bifurcation, the catheter is torqued to align the stent central opening with the SB ostium. The SB wire is advanced into the ostium thus assisting with accurate placement and facilitating access after MB stent deployment. Upon expansion of the main stent body, the ostial crown is automatically deployed with elements protruding approximately 2 mm into the SB to scaffold the ostium. The Antares is very similar to the petal stent but has the advantage of tracking over a single wire and unlike the petal that uses a balloon to expand the SB elements,
they expand automatically with this stent. A FIM study conducted by Dr. Alexander Abizaid is currently underway.

**Sideguard (Cappella Inc, MA, USA)**

The Sideguard (Figure 8) ostium protection device is a self-expanding trumpet shaped nitinol stent that is deployed using a special balloon release sheath system. It is currently a bare-metal stent but the next-generation will be drug-eluting with a biodegradable polymer. The Sideguard’s trumpet shaped design helps the stent conform to the ostium allowing for complete stent-to-wall apposition, optimizing scaffolding, and drug delivery. Its short length, self-expandable nitinol system, low-profile (<3.5 Fr) delivery system allows greater navigability even in very tortuous anatomy. Radio-opaque markers located at the distal and proximal ends of the Sideguard delivery system facilitate positioning of the stent at the SB ostium. The stent is deployed using a nominal pressure balloon, which helps tear a protective sheath that keeps the Sideguard in place until deployment. Once released, the Sideguard selfexpands into place. The delivery system and the guide wire are then removed from the SB. A conventional stent is then placed in the MB, the SB is re-accessed with a guide wire and the procedure is completed with a standard FKI. At TCT 2007, Dr. Grube presented the 6 months follow-up data from the first 16 patients enrolled in Cappella’s FIM multicentre clinical trial (SG-1). In 14 patients, the Sideguard was successfully implanted in the SB and a Cypher was implanted in the MB. At 6-months, the TLR rate was 12.5% (2/16) and there were no cases of stent thrombosis.29

**Tryton (Tryton Medical, MA, USA)**

The Tryton SB stent (Figure 9) is a slotted tube, cobalt chromium balloon expandable stent designed to be implanted in the SB of a bifurcation. The stent consists of three zones: a distal SB zone (that treats the disease in the SB); a transition zone (positioned at the SB ostium); and a MB zone. The central transition zone has a specific geometry, which contains three panels, each of which can be deformed in an independent fashion. The proximal MV zone is composed of three fronds that are connected proximally to the transitional panel and terminate in a circumferential band and the distal zone has the design characteristics of a standard slotted tube workhorse stent. Treatment of a bifurcation with the Tryton stent generally commits the operator to implanting two stents in the bifurcation and the technique is identical the approach when performing the Culotte technique. The Tryton stent is deployed across the SB ostium first. The initial FIM experience has shown that predilatation of the Tryton is essential to allow a MB stent to be advanced though the Tryton struts.30 A standard MV stent is then tracked through the proximal MV zone of the Tryton into the distal MV and deployed. The MB stent struts then have to be re-crossed in order to perform a FKI. In the ’Tryton I, FIM Study: acute and 30 day outcome’, Kaplan et al. report the results of the first 30 patients treated with the Tryton SB stent in conjunction with a standard DES.30 The Tryton was successfully implanted in all but one patient (96.7% angiographic success) and at 30 days follow-up two patients had experienced a MACE.

**Stentys (Stentys SAS, Clichy, France)**

The Stentys (Figure 10) bifurcated drug-eluting stent reported by Dr. Laborde and associates in the ‘Stentys coronary bifurcation stent’ the first of the next-generation bifurcation stents developed by Jacques Soguin the founder of the Devax Axxess stent. The Stentys is a self-expanding nitinol stent made of Z-shaped mesh linked by small interconnections.31 The stent is coated on the abluminal side with Paclitaxel on a durable polymer matrix (PESU), a polysulphone that permits controlled drug-elution.28 The unique feature of this stent is the ability to disconnect the stent struts with an angioplasty balloon. Thus, an opening for the SB can be created anywhere in the stent after it is implanted in the vessel while at the same time the disconnected struts scaffold the SB ostium. Thus, in comparison to the implantation of some of the other bifurcation stents such as the petal and the Antares, the procedural success is not dependant on accurate positioning of the stent and there is significant placement tolerance with
the Stentys. However, it would appear from the design that the disconnected struts only partially scaffold the ostium. The implantation procedure is performed in three steps: (1) Stentys is implanted in the MV with an approximate positioning, like a standard stent; (2) optimal location for the SB opening is chosen by inserting a balloon through the stent mesh; and (3) the balloon inflation disconnects the mesh and creates the opening. It is hoped that the self-expanding property of the stent will allow in situ modelling of the stent to fit the patient’s unique arterial anatomy. However, it is not known if the Stentys is more prone to stent fracture due to its disconnectable strut design. The FIM study with the Stentys bifurcation stent was initiated in September 2007 with the successful implantation of the Stentys by Dr. Eberhard Grube in a 56-year-old male patient at the HELIOS Heart Centre in Siegburg, Germany.32

**Axxess Plus (Devax, Irvine, California, USA)**

The Axxess Plus stent (Figure 11) is the first of these dedicated bifurcation stents designed to elute an *anti-restenotic drug*. It delivers *Biolimus-A9*, a sirolimus derivative via a bio-erodable polylactic acid polymer carrier. The Axxess Plus is a self-expanding, nickel-titanium, and conically shaped stent that is placed at the level of the carina. It has a rapid-exchange delivery system with hydrophilic coating with controlled deployment upon withdrawal of a cover sheath using the actuator. In the study, Six-Month Clinical and Angiographic Results of a Dedicated Drug-Eluting Stent for the Treatment of Coronary Bifurcation Narrowings, Grube et al. report the results of the prospective multicentre single-arm Axxess Plus trial that enrolled 139 patients.33 The Axxess stent was successfully implanted in the MB in 93.5% of cases with 80% of the patients receiving an additional stent to the MB or SB. At 6-months follow-up, the in-stent late loss was 0.09–0.56 mm and the overall TLR was 7.5% confirming the feasibility and efficacy of a dedicated bifurcation stent. In the multicentre AXXENT Trial, the safety and efficacy of the Axxess Plus stent in the left main coronary artery was evaluated in 33 patients using a 3 stent technique of implanting the Axxess in the distal left main and 2 Cypher stents in the left anterior descending and circumflex arteries. At 6-months follow-up, there was minimal late loss (0.043–0.32 mm) and no restenosis in the Axxess stent, whereas the restenosis rate was 6.9% for the left anterior descending artery and 16.1% for the circumflex artery. The overall TLR rate was 9.1% and there were no cases of stent thrombosis in this small pilot study. Currently, the Axxess Plus stent is being analysed in the DIVREGE Trial, a 600-patient study at 40 centres in the US.
Europe, Australia, and New Zealand. However, the Axxess stent is limited by the fact that it needs to be precisely nested at the carina to be effective and in majority cases will need another stent to fully treat the bifurcation.

Conclusion

The dedicated bifurcation stents open out a new array of highly innovative technology in to catheterisation laboratory, which requires skilful expertise to handle given the complexities in the design and technique. It is definitively a step forwards, but long-term large volume clinical trials are warranted before reaching a solid conclusion. Given the dynamicity and the individual variations in the coronary bifurcation anatomy, it is logical to think whether the dedicated stents do really dedicate themselves to all patients.

References

Case report
Aneurysmally dilated major aorto-pulmonary collateral in tetralogy of Fallot
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Introduction
Major aorto-pulmonary collateral arteries (MAPCAs) supply blood to the lungs when the native pulmonary circulation is underdeveloped. Instead of coming from the pulmonary trunk, supply develops from the aorta and other systemic arteries.¹ Major aorto-pulmonary collaterals arteries develop early in embryonic life but regress as the normal pulmonary arteries develop.² In certain cardiac conditions, the pulmonary arteries do not develop. The collaterals continue to grow, and can become the main supply of blood to the lungs.³

Case report
We came across an interesting patient, an 18-year-old girl, symptomatic since her early childhood with cyanosis and mild effort intolerance. She presented to us with recent onset dry irritating cough and right supra-clavicular pulsatile swelling. There was no history of cyanotic spells or squatting episodes. Clinically her heart rate was 78/min, blood pressure was 124/70 mmHg, mild central cyanosis and clubbing observed. Height was 159 cm and weight 35 kg, saturation was 70% at room air and haematocrit was 40%, with body surface area of 1.28 m². There was visible pulsatile (arterial pulsations) swelling seen in right supra-clavicular region approximately 2 cm in size. Cardiovascular examination revealed single second heart sound, aortic ejection click, and continuous murmur, which was heard all over supra-ternal area, right supra-clavicular, and back.

Trans-thoracic echocardiography (TTE) was consistent with diagnosis of tetralogy of Fallot (TOF) with pulmonary atresia. Additionally, there was severely dilated branch of aorta, probably arising from arch of aorta, proximal to the right innominate artery. However, it was difficult to differentiate whether it was the native arch vessel or a MAPCA. Hence, she underwent cardiac catheterisation which revealed presence of giant MAPCA (25 mm) arising from arch of aorta, proximal to the right innominate artery supplying hilar pulmonary arteries like a natural Blalock–Taussig shunt. Pulmonary arteries were confluent and were of adequate size (9.5 mm each) (Nakata index 116/Mcgoon index 1.40) and no additional significant MAPCAs were demonstrated (Figure 1). She opted for conservative management considering the major risk involving during the corrective surgery. However, a month later she suddenly died following a bout of massive haemoptysis.

Discussion
Major aorto-pulmonary collaterals are found in about 35–40% of patients with TOF with pulmonary atresia. An inverse relation was observed between the total number of aorto-pulmonary collaterals and the size and existence of central pulmonary arteries.⁴
Our patient was presented with pressure symptoms in the form of dry irritating cough due to aneurysmally dilated MAPCA.

There is only a single case report in the literature presenting with such a size of MAPCA causing pressure symptoms. The site of origin of MAPCAs are from the descending aorta (70%), the branch of aortic arch (15–20%), and the ascending aorta (10–15%).5 In our case, MAPCA was observed arising from the arch, as seen in approximately 15–20% of the cases.

However, three types of systemic collateral arteries were distinguished by their origin and a characteristic type of ‘anastomosis’ with a pulmonary artery by Rabinovitch et al.6 Type 1 the bronchial artery branches with intrapulmonary anastomoses, type 2 direct aortic branches with hilar anastomosis as seen in our case and type 3 indirect aortic branches with extra pulmonary anastomosis.

These aorto-pulmonary collaterals can sometimes lead to pressure symptoms on account of their size as described by Comerci et al. (aorto-pulmonary collaterals causing oesophageal indentations).7

Best modality of treatment in or patient would have been unifiocalisation of huge MAPCA to pulmonary artery and left Blalock–Taussig shunt at the same time. Considering the proximity of important arch vessels to the aneurysm, high likelihood of thromboembolic episode and major bleeding during the corrective surgery, conservative management was suggested.

Management was discussed with the surgeon. After explaining pros and cons of such a high-risk procedure to the relatives, they opted for medical management. Unfortunately, she died at home following about of massive haemoptysis. Autopsy could not be performed. The possible cause could be rupture of hypertrophied bronchial collaterals or direct erosion of large MAPCA in to the respiratory tract. There was an identical case report describing death due to mediastinal haemorrhage likely secondary to rupture of MAPCA described by Miyazaki et al.8

In conclusion, we should have high index of suspicion of aneurysmally dilated MAPCA in a patient of congenital cyanotic heart disease presenting with supra-clavicular pulsations and pressure symptoms.

References

Case report

Giant coronary artery aneurysm following implantation of Endeavour stent presenting with fever

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¹Professor and Head, ²Professor, ³Associate Professor, Department of Cardiology, CSM Medical University, ⁴Professor, Department of Cardiothoracic Surgery, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, UP, India.

ABSTRACT

Coronary artery aneurysms are a known but uncommon complication of percutaneous coronary intervention (PCI) probably related to effects of vessel wall trauma and possibly a combination of hypersensitivity and incomplete endothelisation associated with drug-eluting stents (DES). We present here a case of giant coronary artery aneurysm 3 months following implantation of a zotarolimus eluting endeavour stent presenting with fever.

KEYWORDS

Aneurysm
Angioplasty
Stents

Introduction

Development of coronary aneurysm following drug-eluting stent (DES) implantation has been increasingly reported in the past few years.¹ We report a case of giant aneurysm formation following implantation of a zotarolimus DES. This patient presented with systemic inflammatory manifestations along with chest pain, and was discovered to be having a giant aneurysm at the stent implantation site.

Case report

A 50-year-old male diabetic, hypertensive, non-smoker was admitted for elective percutaneous coronary intervention (PCI) to left anterior descending artery (LAD). The patient had a prior history of myocardial infarction. Recently, he was having worsening of angina despite full medical therapy. His two-dimensional (2D) echocardiography showed no wall motion abnormality with normal left ventricular ejection fraction. His coronary angiography showed a right coronary artery (RCA) total occlusion, and a mid LAD 99% lesion (Figure 1A). After an informed consent, a decision for revascularisation of the LAD with a DES was taken. A floppy wire was passed and the lesion predilated with a 2.5 mm × 15 mm SPRINTER Balloon (Medtronic, Minneapolis, USA), inflated at 10 atm and subsequently a 3.5 mm × 30 mm endeavour stent (Medtronic, Minneapolis, USA) was deployed at 14 atm pressure with good thrombolysis in myocardial infarction (TIMI) 3 flow (Figure 1B). The patient received standard care in terms of anticoagulant and anti-platelet medication and standard peri-procedure guidelines were followed. He was discharged on the 2nd day on dual anti-platelet therapy along with atorvastatin 80 mg, metoprolol 100 mg, along with oral antihyperglycaemic drugs. Three months later, the patient had an episode of high-grade fever with chills and pyrexia lasted for 7 days. He was prescribed oral antibiotics by his local physician. However, the fever continued, and no cause could be ascertained. He also started experiencing left precordial pain which was constant, dull ache and had a dragging character. On occasions, the pain was relieved with sublingual nitrates for which he was again sent to us for evaluation. In this background, a repeat angiography was planned. His glycaemic and renal status was normal throughout. The repeat angiography showed an aneurysmal dilation approximately 2.5 cm in size in the proximal part of the LAD where the stent had been deployed along with lesion proximal to the stent (Figure 2A). He was advised to undergo an emergent coronary artery bypass grafting (CABG) and resection of the aneurysmal sac. During surgery, a large aneurysm of the proximal LAD approximately 2.5 cm in diameter was noted. It was proximally...
ligated and a left internal mammary artery (LIMA) graft to LAD used to bypass the lesion (Figure 2B). He is now well on follow-up after 3 months.

Discussion

Coronary artery aneurysms after PCI are rare, with a reported incidence of 0.3–6.0%, and most ‘aneurysms’ are in fact pseudoaneurysms rather than true aneurysms.1 Aneurysms after PCI are more commonly reported after ablative techniques particularly excisional atherectomy, residual dissection and deep arterial wall injury caused by oversized balloons or stents, high-pressure balloon inflations, and laser angioplasty have all been associated.1,2 Dissection of the coronary artery during the time of balloon angioplasty has long been known as the major factor related to the occurrence of coronary artery aneurysm.3 As stents were used for the management of dissection, they also lead to restenosis which lead to the development of DES for the prevention of restenosis. The anti-proliferative mechanism of the anticancer drugs were thought to cause impaired healing effect, which ultimately may be counter-productive and lead to the formation of coronary artery aneurysm.4 In present case, the patient had a giant aneurysm, which was probably because of the zotarolimus eluting stent which had prevented proper healing along with an intense local and systemic inflammatory response. The patient presented with fever along with raised hsCRP at the time of the aneurysm formation. Intravascular ultrasound (IVUS) would be an essential tool in planning a therapeutic strategy. However, treatment of these cases has to be individualised using best clinical judgement. Simply stenting with a covered stent over the origin of the dilated segment will often cover the entrance of the dilated system resulting in closure of the aneurysm area. However, in our case, the patient was advised emergent bypass surgery with resection of the aneurysm as there was suspicion of infection and the aneurysm was large in size. Safety of DES in the long-term remains a cause of concern, and as newer stent technology becomes available which promote both healing and accelerate endothelialisation in the stented segments need to be explored, measures to decrease inflammation at the stent implantation site will also need to be utilised effectively.

References

Case report

Giant right atrial aneurysm presenting as right heart failure


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ABSTRACT

Idiopathic aneurysmal dilatations of the right atrium are rare anomalies. We report one such case of a young man presenting with fatigue, abdominal distension, pedal oedema, unremarkable cardiac examination except for raised jugular venous pressure, an electrocardiogram showing normal sinus rhythm with right bundle-branch block, and an radiograph of the chest showing cardiomegaly. The echocardiographic examination revealed a giant right atrium with low pressure tricuspid regurgitation. The computed tomography confirmed the findings of two-dimensional echocardiography. He was put on medical treatment and remained symptomatically controlled on follow-up.

KEYWORDS

Giant right atrium
Normal sinus rhythm
Right heart failure

Introduction

Giant right atrial (RA) aneurysm, also known as idiopathic dilatation of the right atrium and congenital enlargement of the right atrium, is a rare abnormality of unknown origin.\(^1\) This exceptional condition can be confused with other conditions that involve enlargement of the right atrium, such as Ebstein's anomaly and tricuspid hypoplasia.

We report a case of symptomatic giant RA aneurysm in sinus rhythm.

Case report

An 18-year-old boy presented with gradual onset abdominal distention and swelling of both legs and easy fatiguability which were gradually progressive over a period of 2 years. There was no history of fever. On examination, his blood pressure was 110/80 mmHg, heart rate was 100/min, jugular venous pulse was raised and the respiratory rate was 24/min. Cardiovascular system examination did not reveal any murmur. Respiratory system examination was normal. There was abdominal distention with hepatomegaly. Arterial oxygen saturation was 98%.

The chest radiograph posteroanterior view showed huge cardiomegaly (Figure 1). Electrocardiogram showed sinus rhythm with right axis deviation, right bundle-branch block, and tall R-wave with inverted T-waves in V1–V4. Two-dimensional echocardiography (ECHO) revealed aneurysmally

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Figure 1 Chest radiograph posteroanterior view showed huge cardiomegaly.
first to report the condition.3 which has later been identified under various headings like aneurysm, diverticulum or idiopathic dilatation.

Approximately, one-half (48%) of the patients with congenital enlargement of the right atrium have no symptoms. When they occur, symptoms include shortness of breath (28% of cases), palpitations (17%), and arrhythmia (12%) and rarely right heart failure (HF) and easy fatiguability. Our patient presented with symptoms of right HF. Sinus rhythm is observed in 53% of the patients. The major rhythm abnormality is atrial fibrillation or atrial flutter, seen in 28% of cases.2 Our patient had sinus tachycardia on presentation and remained in sinus rhythm with rate control.

Associated congenital heart defects consisting of atrial septal defect, ventricular septal defect and coronary sinus diverticula are not uncommon.4 It is obvious that there is a congenital structural defect in atrial wall which makes it prone to dilations even with modestly increased right-sided pressures. Lipomatous degeneration and reduction of muscular elements in the aneurysmal wall have been reported.2 The diagnosis of RA malformation can be established with ECHO, angiography, CT, or magnetic resonance imaging (MRI).1 Transthoracic ECHO is the most commonly used technique. However, additional imaging may be necessary. Computed
dilated RA measuring 14 cm × 10 cm (Figure 2). The tricuspid valve was not displaced. There was moderate low pressure tricuspid regurgitation and no stenosis. The RA wall was a kinetic without any intracavitary thrombus. The interatrial and interventricular septae were intact. The right ventricle (RV) and outflow tract were mildly dilated with preserved systolic function. The pulmonary arteries were normal and Doppler evaluation of the tricuspid leak indicated normal pressures. The left atrium and left ventricle were normal. Computed tomography (CT) scan showed aneurysmally dilated right atrium communicating with RV (Figure 3). Right ventricle and RV outflow tract were dilated with normal pulmonary arteries. Other laboratory investigations were within normal limits. The patient was advised a surgical intervention but did not give his consent. He remained in sinus rhythm and symptomatically controlled on medical management with diuretics, rate lowering drugs and limitation of activity.

Discussion

Aneurysm of right atrium is a quite uncommon condition, which has been reported as cases detected in age groups varying from neonates to late adulthood.2 Baily et al. were the first to report the condition.3 which has later been identified under various headings like aneurysm, diverticulum or idiopathic dilatation.

Approximately, one-half (48%) of the patients with congenital enlargement of the right atrium have no symptoms. When they occur, symptoms include shortness of breath (28% of cases), palpitations (17%), and arrhythmia (12%) and rarely right heart failure (HF) and easy fatiguability. Our patient presented with symptoms of right HF. Sinus rhythm is observed in 53% of the patients. The major rhythm abnormality is atrial fibrillation or atrial flutter, seen in 28% of cases.2 Our patient had sinus tachycardia on presentation and remained in sinus rhythm with rate control.

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tomography can provide good-quality anatomic information, and cardiac systolic function can be assessed, although not as precisely as with MRI because of limited temporal resolution.

Literature reports various ways to manage this condition like observational management, resection using cardiopulmonary bypass and correction of associated defects. Conservative management may not prevent atrial dilatation which could invite complications of thromboembolism. Fatal arrhythmias worsening tricuspid regurgitation and sudden death can occur. Arrhythmias necessitate and have been successfully treated by surgical excision of the aneurysm.5–7

**Conclusion**

Aneurysmal dilatation of the right atrium due to inherent defect in its wall can occur in the absence of other congenital defects or acquired heart disease. It usually presents with atrial, even ventricular arrhythmias and HF. Treatment ranges from conservative to surgical resection specially in the presence of arrhythmias.

**References**

Case report

Extra-adrenal phaeochromocytoma—a case report of refractory hypertension

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ABSTRACT

There are at least 5% of all hypertensive patients whose blood pressure (BP) remains elevated despite adequate treatment. In these cases, the clinician is forced to search for a secondary cause of the chronic BP elevation. Certain environmental factors are known to induce resistant-hypertension. Additionally, there may be pseudo-resistance occurring or the patient may be suffering from a secondary form of hypertension such as renovascular or endocrinological hypertension (phaeochromocytoma, Cushing’s syndrome, etc.).

We report a case of extra-adrenal phaeochromocytoma who was on adequate antihypertensive medications but remained refractory to treatment prior to the exact diagnosis.

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KEYWORDS

Extra-adrenal phaeochromocytoma
Phaeochromocytoma
Resistant-hypertension

Introduction

Refractory or resistant-hypertension is conventionally defined as systolic or diastolic blood pressure (BP) that remains uncontrolled despite adequate and sustained therapy with at least three classes of antihypertensive medications and affects 5–30% of the general population with hypertension. Although, resistant-hypertension affects a minority of treated hypertensive patients, the resulting target organ damage causes a disproportionately high-risk of cardiovascular events.1

The main reasons of hypertension being unresponsive to the standard antihypertensive treatment include incorrect diagnosis, inadequate antihypertensive drug therapy, non-compliance towards the treatment and secondary causes of hypertension.

The importance of diagnosing secondary hypertension lies in the fact that it may convert an incurable disease into a potentially curable one. Even if the underlying disease may not be curable, being able to offer disease specific treatment will often make BP control much easier.2

Case report

A 35-year-old female was admitted with complaints of holocranial headache and vomiting since 2 days and altered mental status since 1 day. There was no history of fever, seizures, head injury, or ear discharge. The patient had a history of repeated admissions with similar complaints of headache, vomiting, and altered sensorium. During each admission, the patient had increased BP recordings, which responded to conventional antihypertensive medications. There was no history of poor drug compliance. On examination, the patient was emaciated, afebrile, and dehydrated. Her pulse rate was 110/min which was equally palpated in all four limbs without any radiofemoral, radioradial, or apex pulse deficit. Blood pressure was 190/120 mmHg without any significant variation in all four limbs. Cardiovascular examination revealed a soft apical systolic murmur without thrill. There were no signs of meningeal irritation and her fundus examination was normal. 12-lead electrocardiogram (ECG) revealed left axis deviation and sinus tachycardia. Chest radiograph was normal. Non-contrast computed tomography (CT) scan brain was also normal. Patient was treated with enalapril (iv), nitro-glycerine (iv) in emergency ward and had marked improvement of her sensorium within three hours, but with...
persistent tachycardia. Later on, she was started upon enalapril, low-dose thiazide diuretic and beta-blockers in adequate dosage. Investigations revealed haemoglobin (Hb)—9.9 g%, total leucocyte count (TLC)—7600/mm³, blood urea—28 mg% and serum creatinine—0.8 mg%. Serum sodium and potassium were 144 and 4.4 mEq/L, respectively. During her stay in the hospital, the patient also gave a history of intermittent palpitations. Her thyroid profile was normal and 2-D echocardiography revealed mild mitral regurgitation. After 48-hours of admission, patient developed recurrent vomiting with increase in her BP readings. Conventional antiemetics failed to give any relief to the patient. Ultrasonography of abdomen revealed a 3 cm × 4 cm mass, a possible lymph node near head of pancreas located retroperitoneally. Upper gastrointestinal (GI)-endoscopy was normal. The patient's vomiting subsided spontaneously within 24 hours only to recur a day later. Serum cortisol levels were normal. 24-hours urinary vanillyl mandelic acid (VMA) level was done which came out to be 78 μmol/24 hours (normal <40). Contrast-enhanced computed tomography abdomen revealed a 3 cm × 5 cm mass in lesser sac with central necrosis abutting stomach and head of pancreas (Figure 1). Contrast-enhanced computed tomography chest and pelvis were normal. Correlating clinical, biochemical and radiological findings, the diagnosis of extra-adrenal pheochromocytoma was most likely. The patient was started on phenoxybenzamine 10 mg thrice daily orally and later on, metoprolol 50 mg twice daily was added to the regimen. The patient had marked clinical improvement as her pulse rate normalised and her BP got controlled. Expert surgical opinion was taken and the patient underwent exploratory laparotomy with removal of the tumour. Histopathology report showed a well-encapsulated tumour comprising of cells arranged in alveolar, trabecular, solid, and pseudopapillary pattern. Cells were mildly pleomorphic with round vesicular nucleus, granular chromatin, and abundant eosinophilic granular cytoplasm. Stroma was fibrovascular with no evidence of mitosis, necrosis, capsular, or vascular invasion (Figure 2).

Four weeks after surgery, repeat urinary VMA levels were 12 μmol/24 hours (normal <40). The patient was on 50 mg metoprolol/day and was entirely asymptomatic.

**Discussion**

Hypertension is one of the most common diseases, affecting approximately a quarter of the population worldwide. Secondary hypertension constitutes <5% of the causes of hypertension. However, recent studies showed a much higher prevalence. The most common endocrinological cause of secondary hypertension is primary hyperaldosteronism. Other causes are Cushing’s syndrome, phaeochromocytoma and acromegaly.

Phaeochromocytoma accounts for 0.2–0.6% of the hypertensive population. Diagnosis of phaeochromocytoma is important as catecholamine surges can cause cardiac arrhythmias, myocardial infarction, and even sudden death. Prolonged excess levels of catecholamines can lead to cardiotoxicity (catecholamine cardiomyopathy). Phaeochromocytoma follows the rule of 10, i.e. approximately 10% are bilateral, multiple, extra-adrenal, malignant, familial and occur in children. A small proportion are associated with genetic diseases such as MEN 2a, MEN 2b, neurofibromatosis and von Hippel-Lindau disease.

Typical clinical manifestations of phaeochromocytoma are hypertension, headache, palpitations, and paroxysms.
However, patient may present with atypical symptoms, such as nausea, vomiting, and weight loss. Hypotension may be a presenting feature of paragangliomas.\textsuperscript{6} As symptoms of phaeochromocytoma are non-specific, a high index of suspicion is required for correct diagnosis.

Extra-adrenal phaeochromocytomas are very rare (10\% of all phaeochromocytoma cases) and are usually seen in the second and third decades of life. There is no sex preponderance. Extra-adrenal phaeochromocytomas are often multicentric and are more likely to be malignant than those of adrenal origin.\textsuperscript{4,8}

Extra-adrenal phaeochromocytomas tend to be larger than their adrenal counterpart at the time of detection. Symptoms of extra-adrenal phaeochromocytoma can be divided into those caused due to excess catecholamines (similar to adrenal phaeochromocytoma) and those caused due to the location of the tumour, which can help in localising tumour site.\textsuperscript{4}

Several biochemical tests such as plasma free catecholamines, plasma and urine metanephrines, and urinary VMA levels can be used to demonstrate a state of catecholamine excess. Measurement of plasma free norepinephrine, epinephrine, or dopamine may be helpful in localisation of the tumour, as most adrenal tumours secrete only norepinephrine, extra-adrenal tumours secrete epinephrine and paragangliomas secrete dopamine which may be responsible for hypotensive manifestations.\textsuperscript{6}

Both anatomical and functional imaging should be carried out to determine the exact location, number of tumours and the presence of metastasis. Adrenal tumours >5 cm in diameter are more likely to metastasize.\textsuperscript{5} Ultrasound, CT scan, and magnetic resonance imaging (MRI) provides anatomical imaging. However, MRI is more sensitive as phaeochromocytoma usually has a distinct hyperintense signal on T2 weighted imaging which helps identify extra-adrenal tumours and metastatic disease. For functional imaging, scintigraphy is most commonly done with \textsuperscript{123}I- or \textsuperscript{131}I-Metaiodobenzylguanidine (MIBG). Recently, positron emission tomography (PET) scanning with (18F)-fluorodeoxyglucose (18-F-FDG), fluorine-18-L-dihydroxyphenylalanine (18F)-DOPA or (18F)-Dopamine have shown great promise. Out of these (18F)-Dopamine is best for imaging of phaeochromocytoma. When both MIBG scanning and PET scanning is negative, scintigraphy may be performed with radio-labelled octreotide (Octreoscan).\textsuperscript{6}

Meticulous pre-operative preparation of the patient with optimum alpha and beta adrenergic receptor blocking drugs is required. Correction of hypovolaemia and management of intra-operative and post-operative blood volume and blood glucose are of paramount importance.

When tumour is inoperable, alpha methyltyrosine (metirosine), which inhibits catecholamine synthesis can be used. Radiotherapy and chemotherapy have limited effectiveness in phaeochromocytoma.

Extra-adrenal phaeochromocytomas are more likely to recur and to metastasize than their adrenal counterparts, making lifelong follow-up with annual determinations of catecholamine production essential.\textsuperscript{7,9}

Acknowledgement

We are thankful to Professor N.K. Chaturvedi, Director PGIMER, Dr. Ram Manohar Lohia Hospital for granting permission to report this case. Departments of Surgery, Radiodiagnosis and Pathology at the Institute have also been associated with the diagnosis and management of this case and their contributions are gratefully accepted.

References

Case report

Foetal atrial flutter management—the role of electrical cardioversion

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ABSTRACT

We report a successful electrical cardioversion of a foetal atrial flutter (AFL) immediately post delivery. We describe the diagnostic tools, assessment and the management antenatally. Then, we review the literature and discuss the debate about management. We stress the point that if the flutter wave is not progressing, the foetal heart will tolerate till term and we can try electrical cardioversion with confidence after delivery.

KEYWORDS

Atrial flutter
Cardioversion
Foetal arrhythmias

Introduction

Foetal tachyarrhythmia may cause foetal hydrops and lead to foetal morbidity and mortality. Supraventricular tachycardia and atrial flutter (AFL) are mostly diagnosed. The most commonly used drug is still transplacental digoxin with an addition of either sotalol or flecainide. The outcome of foetal tachyarrhythmias depends on the presence or absence of hydrops foetalis but not on the type of arrhythmia. Treatment is required and primarily aimed at reaching an adequate ventricular rate and preferably conversion to sinus rhythm.

Case report

A 20-year-old primigravida female was referred to the foetal cardiac clinic because of foetal tachycardia with heart rate between 200–240 beats/min (bpm). The gestational age was 31 weeks and the mother felt excessive foetal movement. So, she was presented to our emergency room. The obstetrical ultrasound showed normal foetal organs with no evidence of pericardial effusion or hydrops foetalis signs.

The first foetal echocardiogram showed normal heart structure and function. The heart rate was 200 bpm using the outflow pulse Doppler (Figure 1). M-mode for apical 4-chamber view showed long ventriculoatrial (VA) tachycardia with a ratio of 2:1 atrioventricular (AV) conduction (Figure 2).

Figure 1 Outflow Doppler view showing ventricular rate of 200 bpm.

Figure 2 M-mode crossing both the atrium and the ventricle showing almost the ratio of 2:1 conduction.
The pregnant lady was admitted to the hospital for assessment and to start medications under supervision. We started oral digoxin 250 mg 3 times daily. Then, we added flecainide after 5 days observation of the heart rate which did not change. Sotalol was not started because of prolonged corrected QT interval in the mother’s electrocardiogram (ECG) which was 480 ms. Flecainide dose was initially 150 mg twice daily but we had to decrease the dose to 75 mg twice daily because of intolerable dizziness.

Upon subsequent foetal echocardiogram scanning, the ventricular rate went down to 170 bpm and the atrial rate to 360 bpm. The function was preserved but there was mild tricuspid valve regurgitation and mild right atrial enlargement. There were no signs of hydrops all through the observation course.

For the next 6 weeks, the mother was coming to the foetal clinic every week for assessment until she delivered spontaneously at 37 weeks using ventouse. She gave birth to a healthy term male baby weighing 3.5 kg. Initial ECG confirmed the diagnosis of AFL with ventricular rate of 196 bpm (Figure 3). Preparations were done to sedate the baby and we applied a direct shock of 6 joules only once with the strip running (Figure 4). There was immediate conversion to sinus rhythm with a rate of 135 bpm (Figure 5). The child was observed for 3 days in the hospital and the daily ECG plus Holter monitor did not show any recurrence of flutter waves. Transthoracic echocardiography was normal apart from small atrial septal defect with mild tricuspid valve regurgitation and normal ventricular function and dimensions. The baby was not put

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**Figure 3** 12-lead electrocardiogram immediately post delivery confirming the diagnosis of atrial flutter. The ventricular rate was 196 bpm.

**Figure 4** Electrocardiogram strip during DC shock showing the immediate cessation of the flutter wave.
on any prophylactic antiarrhythmic medication and showed normal ECG in the follow-up clinic visits.

Discussion

Foetal AFL accounts for approximately one-third of all clinically relevant tachyarrhythmia.2 Atrial flutter is the second most frequently observed foetal tachyarrhythmia. There is an increased incidence of about 6% of the association of an important underlying heart disease.2 There is a 2:1 AV block in >80% of cases of foetal AFL.1

Intrauterine treatment with digoxin combined with flecaïnidè, sotalol, or amiodarone, respectively, is required as first line treatment.2,3 Class III antiarrhythmic drugs showed potency against AFL at least to prevent the ratio of 1:1 conduction. Most foetuses with therapy-resistant AFL and absence of 1:1 AV conduction do not experience congestive heart failure and do not need to be delivered prematurely.2

Lisowski et al. reported successful electrical cardioversion in eight of nine patients who had AFL immediately post delivery. There was no recurrence after the neonatal period.3 When sinus rhythm has been established, recurrence of AFL is rare. Therefore, a wait-and-see policy is justifiable.1 We conclude that if AFL is maintained stable in utero with at least a ratio of 2:1 conduction will be safe to allow term pregnancy. Post delivery direct electrical shock is tempting with the advantage of no recurrence.

References

Case report

A case of reversible dilated cardiomyopathy due to acromegaly with partial empty sella

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ABSTRACT

Acromegaly has several cardiovascular manifestations of which cardiomyopathy (CMP) and hypertension (HTN) are important and contribute to the increased mortality associated with the disease. Both these manifestations are reversible with treatment. However, very advanced CMP with severe systolic dysfunction has low likelihood of reversal. The reversibility is higher in young population and decreases as age advances. Also, the time required for these manifestations to resolve is about 1 year. Here, we describe a case in which HTN and advanced heart failure resolved in an aged patient within a very short span of 2 months from the time of presentation.

KEYWORDS

Acromegaly
Partial empty sella
Reversible DCM

Introduction

Acromegaly is an endocrine disorder characterised by growth hormone (GH) excess. The usual presentation of the disease is with enlargement of soft tissues and coarsening of the facial features. The disorder has several cardiovascular manifestations including hypertension (HTN) and cardiac dysfunction. In a patient presenting with cardiac failure, it is important to recognise this condition as the underlying aetiology as it is potentially reversible. The cardiovascular system (CVS) manifestations of the disease are reversible, particularly so, if the patient is young and the condition is recognised and treated early. The magnetic resonance imaging (MRI) pituitary shows adenoma in about 98% of the patients.

Here, we present a case of acromegaly presenting as dilated cardiomyopathy (DCM), whose MRI pituitary showed partial empty sella suggesting that either the patient had primary partial empty sella with tumour overgrowth in sella or spontaneous intra-tumour infarct leading to formation of secondary partial empty sella. The patient, although elderly, had an unusual rapid resolution of HTN and improvement in cardiac functional status following starting of therapy.

Case report

A 60-year-old male patient presented with complains of breathlessness on exertion, oedema feet and orthopnoea for the last 1 month. There was no expectoration or chest pain. The past, personal and family histories were unremarkable. There was no past history of ischaemic heart disease. Examination of vitals showed a blood pressure (BP) of 210/110 mmHg in both upper limbs. General examination revealed coarse facial features, raised jugular venous pressure, and oedema feet. Tachycardia, S3 gallop and bibasilar rales were the findings on systemic examination. The electrocardiogram (ECG) showed sinus tachycardia and chest radiograph revealed cardiomegaly with pulmonary oedema. The routine biochemical investigations were normal except for a raised serum creatinine of 2.3 mg% (114.88 μmol/L). An echocardiographic evaluation was suggestive of DCM with an ejection fraction (EF) of 20%. Because of the presence of coarse facial features, the patient was evaluated for acromegaly with fasting and post-glucose GH levels. The fasting serum GH level was 2.1 ng/mL (2.1 μg/L) and post-glucose 1.2 ng/L (1.2 μg/L). Both the values were significant. Based on these biochemical findings, the patient was diagnosed as having acromegaly and was subjected to MRI pituitary. This was suggestive of partial empty sella. There was no clinical or other evidence of raised intracranial tension, pressure effects of tumour.
Considering acromegaly, the patient was treated with bromocriptine and drugs for HTN and cardiac failure (initially diuretics followed by diuretics with amlodipine once the pulmonary oedema resolved). During hospital stay, his BP never dropped below 160/100 mmHg but his symptoms of heart failure (HF) resolved. He was discharged with bromocriptine and other drugs. At 1 month follow-up, he had become normotensive and the doses of antihypertensive drugs were decreased. At 2 months, his BP was 100/68 mmHg and his serum creatinine reduced to 1.1 mg%. He was put off all drugs. At further follow-up, he was normotensive without any clinical signs or symptoms of HF.

Discussion

Acromegaly is an endocrine disorder characterised by excess secretion of GH. Most of the cardiovascular effects of this disorder are considered to be due to high circulating levels of IGF-1 (insulin-like growth factor). These effects are important because they are responsible for the majority of morbidity and mortality associated with this disorder. It is important to recognise this disorder because the CVS effects can be reversed or at least progression halted with effective treatment. Treatment with both, somatostatin analogues and GH receptor blockers has been reported to be effective. Usually the resolution of cardiac effects starts with regression of ventricular hypertrophy. The effect on cardiac mass is evident after about 1 year of treatment and this is followed by improvement in diastolic and systolic function. Young patients with short disease duration were more likely to reverse the acromegalic cardiac changes after 1 year of treatment. In this case, our patient had resolution of HTN and also of the symptoms and signs of HF in just 2 months of treatment with bromocriptine. This resolution persisted even after discontinuation of treatment suggesting that the disease had actually come under control. It is likely that the partial empty sella seen on MRI pituitary could represent a spontaneous intra-tumour infarct. Alternatively, it could represent a partial primary empty sella with tumour growth in the remaining tissue. The second possibility seems less likely because had it been the case, then discontinuation of bromocriptine would be likely to result in resurgence of disease activity. Also, spontaneous tumour regression due to tumour infarct would be more likely to achieve a biochemical control of the disease better than bromocriptine. Therefore, the first possibility seems more likely. Therefore, it is possible that regression of cardiovascular changes can occur quite rapidly even in elderly individuals with systolic dysfunction.

Conclusion

Through this case report, we would like to highlight the following aspects.
1. Rapid resolution of cardiac changes of acromegaly can occur.
2. Resolution is possible in elderly patients with systolic failure.

References

Case report

ST-segment elevation and ventricular tachycardia after ingestion of a common ornamental plant—a case report

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ABSTRACT

Japanese yew is a widely used ornamental plant. However, most people are unaware that it is also a poisonous plant. It has potent cardiac toxicities that can lead to sudden cardiac death.

A 37-year-old female patient presented to the emergency room with altered mental status and sustained ventricular tachycardia (VT). Electrocardiogram (ECG) after cardioversion showed profound QRS prolongation and ST-segment elevation suggestive of either hyperkalaemia, acute myocardial ischaemia, or Brugada syndrome. Her electrolytes and coronary angiography were normal.

After improvement of the patient’s mental status, she admitted that she has been consuming Japanese yew from her yard for several months. Few hours later, QRS duration normalised, but mild ST-segment elevation persisted in the right pre-cordial leads, making it more suspicious for Brugada syndrome. However, a procainamide challenge test and electrophysiology study failed to induce typical Brugada pattern ECG and VT. The absence of coronary artery disease and electrolytes disturbances points toward the fact that her arrhythmia and ECG changes are secondary to yew intoxication. The patient was monitored for a few days. She was haemodynamically stable and has not had any arrhythmia.

This case highlights the importance of public awareness of severe toxicity from Japanese yew or other yew plants. Yews contain taxines that are responsible for the ECG abnormalities due to its inhibitory effect on the cardiac sodium and calcium channels. They cause conduction abnormalities, VT, and ST-segment elevation that can resemble acute myocardial infarction, hyperkalaemia, and Brugada syndrome.

Keywords

Japanese yew
Ventricular tachycardia
ST-elevation
Procainamide challenge test

Case presentation

A 37-year-old Caucasian woman presented to the emergency room because of decreased level of consciousness and slurred speech. On physical examination, blood pressure was 76/40; heart rate was 170; oxygen saturation was 98% on room air. She was diaphoretic and had slurred speech. Laboratory investigations showed a normal cell count and chemistries, troponin was 0.03; creatine protein kinase (CPK), CPK-MB and liver function test were normal. Urine toxicology and alcohol level were negative.

Cardiac monitoring revealed ventricular tachycardia (VT) at a rate of 175/min. The patient promptly received electric cardioversion. The baseline electrocardiogram (ECG), 10 minutes after cardioversion, showed junctional rhythm with a rate of 62 beats/min and severe prolongation of the QRS complex (162 ms) with some Brugada-like pattern (Figure 1).

Further questioning of the patient revealed that she had been consuming Japanese yew leaves in the last 3–4 months, thinking that this plant might help with her flu. A coronary angiogram was performed and showed normal coronary arteries with normal left ventricular function.

Subsequent ECG showed almost normalisation of the QRS complex but V1 showed incomplete right bundle-branch block with coved type ST-segment elevation of about 1 mm, and PR prolongation of 274 ms. Serial 12-lead ECGs showed regression of the ST-segment elevation and normalisation of the QRS and PR interval.

Her ECG was suspicious for Brugada syndrome, although QRS prolongation was more profound than what is expected
in typical Brugada pattern. It was unclear if these changes were all due to the toxic effect of yew or, the yew merely unmasked a true Brugada syndrome. To determine this possibility, an electrophysiology study with procainamide challenge test was performed. Programmed ventricular extra stimulus testing, with up to triple extra stimuli failed to induce any tachycardia. Procainamide at 10 mg/kg was infused >10 minutes and there was no inducible ST-segment elevation in the right pre-cordial leads.

**Discussion**

Japanese yew (*Taxus cuspidata*) is an ornamental plant that is used as a garden tree and widely grown in eastern Asia and eastern North America. It is a member of the genus *Taxus*, which includes *Taxus Baccata* (European yew), *Taxus canadensis* (Canada yew) and many others. Historically, there is evidence of its previous use as a crude drug to treat diabetes, to promote diuresis, and as an emmenagogue. It is the source of paclitaxel, a chemotherapeutic agent used in the treatment of several cancers. However, it has also been associated with cases of animals and humans intoxications, including death, mainly due to its arrhythmogenic effect on the heart.

Chemical analysis of yew species leads to the isolation of several toxic alkaloids including taxine A and B. All parts of *Taxus* plants are toxic except the pulp, or aril, which contains very little taxine. Taxine B accounts for 30% of the total taxine fraction and taxine A represents only 1.8% of the taxine fraction. The taxines inhibit both the cardiac calcium channel (I_{Ca}) and the fast cardiac sodium channel (I_{Na}) in a dose-dependent manner. This can lead to suppression of cardiac contractility, sinoatrial node automaticity, atrioventricular (AV) node conduction and also depolarisation and repolarisation abnormalities.

The profound QRS prolongation in our case (Figure 1) is mainly due to the severe inhibition of the fast cardiac sodium channel by the taxines, during the phase 1 of the action potential. The degree of QRS prolongation depends on the severity of sodium channel inhibition.

The ST-segment elevation in the right pre-cordial leads few minutes after cardioversion (Figure 1) and in the lead V1, 8 hours after the event (Figure 2), resembles those seen in Brugada syndrome. It is secondary to the preferential sodium channel blockade of right ventricular epicardial cells leading to the loss of action potential dome in the right epicardium but not in the endocardium. This can also result in spatial dispersion of repolarisation that can lead to VT due to phase 2 re-entry.

Because an underlying congenital Brugada syndrome or other sodium channel susceptibility disorder could not be excluded, a procainamide challenge test was performed and it was negative, indicating that the ECG findings including VT and ST-elevation were purely caused by the toxic effects of yew.

**Conclusion**

Our case was suspicious of induced Brugada syndrome; however, it does not meet the criteria for Brugada phenotype. A case of Brugada ECG secondary to yew intoxication was previously reported in the literature. These two cases suggest that a combination of I_{Na} and I_{Ca} blockade could be more effective in reproducing the ECG pattern of Brugada syndrome. This was demonstrated in an in vitro study by Fish and Antzelevitch. However, the clinical value of this combined test has not been fully established. This case emphasizes again the importance of public awareness to the cardiac toxicity of yew plants.

**References**

Case report

Two cases of Pompe's disease: case report and review of literature

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ABSTRACT

Glycogen storage disease type II (also called Pompe's disease or acid maltase deficiency) is an autosomal recessive metabolic disorder which causes an accumulation of glycogen in the lysosomes due to deficiency of the lysosomal acid alpha-glucosidase enzyme. It is the only glycogen storage disease with a defect in lysosomal metabolism, and the first glycogen storage disease to be identified in 1932. The build-up of glycogen causes progressive muscle weakness (myopathy) throughout the body and affects various body tissues, particularly in the heart, skeletal muscles, liver, and nervous system.

We are presenting two cases of infantile form of Pompe's disease with secondary hypertrophic cardiomyopathy (CMP). The first case was a 1-year-old female child who presented with Ross Class III heart failure (HF) of 3 months duration. Echocardiography (ECHO) showed concentric left ventricular (LV) hypertrophy, with the posterobasal segment more hypertrophic than the interventricular septum and moderate pericardial effusion. The second case was a 2-month-old male child who presented with Ross Class II HF. His ECHO showed eccentric hypertrophy of the posterobasal left ventricle, with thickening of the mitral valve leaflets and the chordae with Grade I mitral regurgitation (MR). Both children were diagnosed to have Pompe's disease by blood alpha-glucosidase assay.

KEYWORDS

Alpha-glucosidase
Echocardiography
Hypertrophic cardiomyopathy
Left ventricular hypertrophy
Pompe's disease

Introduction

Pompe's disease or glycogen storage disease type II, is a lysosomal storage disorder in which deficiency of alpha-glucosidase leads to accumulation of glycogen and finally to destruction of muscle tissue.¹-² Complete deficiency of alpha-glucosidase causes a progressive lethal cardiac and skeletal muscle disorder known as infantile Pompe's disease. Partial deficiency leads to a milder late onset phenotype.³,⁴ The latter condition may present at any age and is subdivided into non-classical infantile, childhood, juvenile, and adult Pompe's disease. Infantile Pompe's disease is a rapidly progressive disease, characterised by prominent cardiomegaly, hepatomegaly, weakness and hypotonia, and death due to cardiorespiratory failure in the first year. Patients with the infantile variant form⁴ (non-classic infantile Pompe's disease) show slower progression and less severe cardiomyopathy (CMP) but present in the first year of life. Echocardiogram (ECHO) typically reveals a hypertrophic CMP with or without left ventricular (LV) outflow tract obstruction in the early stages of the disease. In the late stages of infantile disease, patients may have impaired cardiac function and a dilated CMP.

We present two cases of infantile Pompe's disease, both with ECHO features of hypertrophic CMP. In addition, the second case also showed thickening of mitral leaflets and chordae.

Case history

Case 1: The first case was a 1-year-old female child who had presented with features of Ross Class III heart failure (HF) at 9 months of age, treated at another hospital with diuretics and angiotensin-converting enzyme inhibitors (ACEI) and was referred to our hospital. She presented to us with cough of 10 days' duration. On examination, the patient was acyanotic and comfortable at rest. Her pulse rate was 110/min, respiratory rate was 30/min, with BP of 106/86 in the upper limbs and 120/86 in the lower limbs. Her cardiovascular system examination was clinically normal. She had mild hepatomegaly.

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ISSN: 0019-4832 Copyright © 2012. Cardiological Society of India. All rights reserved.
doi: 10.1016/S0019-4832(12)60067-4
Routine blood investigations were normal. Electrocardiogram (ECG) showed a PR interval of 0.10s and features of LV hypertrophy. The ECHO examination revealed concentric LV hypertrophy (Figures 1A, B) with Grade I diastolic dysfunction and no evidence of LV outflow tract obstruction. The assay for alpha-glucosidase from whole blood using dried blood spot filter paper was done. The activity of the alpha-glucosidase in the patient was 0.108 pmol/punch/hr (normal range: 0.75–7.23) and the ratio of neutral alpha-glucosidase/acid alpha-glucosidase (with inhibitor) was 76 (normal range: 9.8–43.37), consistent with the diagnosis of Pompe’s disease.

Case 2: The second case was a 2-month-old male child who presented with Ross Class II HF. On examination, the child was tachypnoeic and acyanotic. His cardiovascular system examination showed Grade II ejection systolic murmurs at the left second inter costal space. Wet lung signs were present. Moderate hepatosplenomegaly (HSM) was present. Serum aspartate transaminase and alanine transaminase were mildly elevated. Serum creatinine phosphokinase (total) was 1123 U/dL. The ECG showed short PR interval and features of LV hypertrophy. The ECHO examination revealed concentric LV hypertrophy, global hypokinesia of left ventricle, moderate LV systolic dysfunction and Grade II mitral regurgitation. Quantitative blood alpha-glucosidase level was 24 nmol/hr/mg (normal >60), suggestive of Pompe’s disease. Patient improved with diuretics and ACEIs. Ten months later, ECHO examination revealed eccentric LV hypertrophy involving posterobasal wall (Figure 2B).

Mitral valve leaflets and chordae were thickened (Figures 2A, C, D). Grade I MR (Figure 2E) was present. No evidence of LV outflow tract obstruction was observed.

Discussion

In infantile Pompe’s disease, the effects of glycogen accumulation are very pronounced in the heart. Lysosomal glycogen accumulation results in a significant amount of cardiac hypertrophy that may begin in utero and that is significant even at 4–8 weeks of age. The cardiac response to glycogen accumulation can result in hypertrophic or hypertrophic and dilated CMP. In the earlier phases of the disease, infants generally present with severe ventricular hypertrophy with or without LV outflow tract obstruction and normal or even hyperdynamic LV function. Both our cases had presented early in infancy with decompensated HF and improved with symptomatic treatment with diuretics and ACEIs. Both cases showed LV hypertrophy on ECHO. Neither of them showed evidence of LV outflow tract obstruction. Our second case, during the course of the disease also showed thickening of both mitral leaflets and chordae, which has not so far been described in literature.

Beyond infancy, there is variable involvement of the heart in Pompe’s disease, and a spectrum of disease among children with partial enzyme activity, ranging from unaffected to...
Moderate cardiac hypertrophy, and cardiac dysfunction has been described.\textsuperscript{4,5}

Interference with specialised conducting tissues produces a shortening of the atrio-ventricular (PR) interval on the ECG, seen in both our cases. The mechanism of accelerated atrio-ventricular conduction in Pompe's disease may be related to the insulator effect of glycogen in conduction tissue.\textsuperscript{9} The conduction abnormalities, in conjunction with the hypertrophic CMP, place these patients at a high-risk of tachyarrhythmia and sudden death, especially in situations of stress such as infection, fever, dehydration, and anaesthesia.\textsuperscript{9}

Thus, the diagnosis of hypertrophic CMP in infancy and childhood should be considered with the possibility of being a secondary form, and should be screened for Pompe's disease.

References

Journal review

1. Follow-up of CREST trial: no difference in restenosis rates between stenting and surgery
   doi: 10.1016/S0019-4832(12)60068-6

It should sound like music to interventionists. The new results from carotid revascularisation endarterectomy versus stenting trial (CREST) show that after 2 years of follow-up, restenosis rates are equal whether the patient underwent stenting or surgery. The data was presented at New Orleans recently during the International Stroke conference by Dr. Brajesh K. Lal. The rates of restenosis/occlusion were 6% and 6.3% in the stenting and surgery groups respectively (difference not statistically significant). The CREST trial is one of the recent and well-discussed trials in the area of carotid stenting and surgery that enrolled 2500 patients from 117 US and Canadian centres. The composite end-point was a combination of any stroke, myocardial infarction (MI), or death during the peri-procedural period and ipsilateral stroke during follow-up. Stenting was associated with a 7.2% event rate versus 6.8% with surgery, again non-significant difference. However, the stroke was higher with stenting while MI was higher with endarterectomy. The present analysis showed that during the follow-up by Doppler ultrasound, similar rates of restenosis (>70% diameter reduction)/occlusion were demonstrated between the stenting and surgery arms. The risk factors for restenosis in this analysis showed that women and patients with diabetes mellitus or dyslipidemia had double the risk.

2. The PROFI study (prevention of cerebral embolisation by proximal balloon occlusion compared to filter protection during carotid artery stenting). A prospective randomised trial.
   Bijuklic K, Wandler A, Hazizi F, Schofer J.
   doi: 10.1016/S0019-4832(12)60069-8

Background: Randomised trials comparing filter-protected carotid artery stenting (CAS) with carotid endarterectomy revealed a higher peri-procedural stroke rate after CAS. Proximal balloon occlusion may be more effective in preventing cerebral embolisation during CAS than filters.

Methods: Patients undergoing CAS with cerebral embolic protection for internal carotid artery stenosis were randomly assigned to proximal balloon occlusion or filter protection. The primary endpoint was the incidence of new cerebral ischaemic lesions assessed by diffusion-weighted magnetic resonance imaging (MRI). Secondary endpoints were the number and volume of new ischaemic lesions and major adverse cardiovascular and cerebral events (MACCE).

Results: Sixty-two consecutive patients (mean age: 71.7 years, 76.4% male) were randomised. Compared with filter protection (n = 31), proximal balloon occlusion (n = 31) resulted in a significant reduction in the incidence of new cerebral ischaemic lesions (45.2% vs 87.1%, P = 0.001). The number (median [range]): 2 [0–13] vs 0 [0–4], P = 0.0001) and the volume (0.47 [0–2.4] cm³ vs 0 [0–0.84] cm³, P = 0.0001) of new cerebral ischaemic lesions were significantly reduced by proximal balloon occlusion. Lesions in the contralateral hemisphere were found in 29% and 6.5% of patients (filter vs balloon occlusion, respectively, P = 0.047). The 30-day MACCE rate was 3.2% and 0% for filter versus balloon occlusion, respectively (P = non-significant).

Conclusion: In this randomised trial of patients undergoing CAS, proximal balloon occlusion as compared with filter protection significantly reduced the embolic load to the brain.

Perspective

Further strength for the use of the proximal protection device has been provided by the PROFI study. The distal protection devices have certain inherent disadvantages:
1. As the device crosses the lesion, in the beginning, there is a small risk of embolisation before deployment.
2. The distal protection devices (DPD) may not capture very tiny emboli.
3. If the DPD is not abutting the vessel wall, some emboli may still pass.
4. When there is large embolisation, the filter may clog which may lead to embolisation during retrieval.

A proximal balloon occlusion device like MO.MA does not have most of these disadvantages. However, there are issues like bulky design, higher cost and of course, the device is less operator-friendly. Also, it is contraindicated in cases of contralateral carotid occlusion.

The authors of PROFI study have demonstrated that the risk of embolisation is considerably reduced by using the MO.MA device. They randomised 62 patients to proximal versus distal protection (Emboshield, Abbott) devices and by using...
diffusion-weighted MRI, demonstrated that the incidence of new ischaemic lesions was 87% in the filter group versus 45% in balloon group. Clinically, although only one patient had a minor stroke in the filter group versus none in balloon group, it may not be practical to use a MO.MA device in every case. The study establishes the logic behind it.


doi: 10.1016/S0002-9149(12)60070-4

Objective: This study examined the clinical course of patients with asymptomatic severe aortic stenosis (AS) according to the new proposed aortic valve stenosis (AVS) grading classification.

Background: The management of patients with asymptomatic severe AS remains controversial. Moreover, under the same denomination of severe AS, several entities might be identified according to transvalvular flow rates and pressure gradients, resulting in four flow-gradient patterns.

Methods: Transthoracic echocardiography and measurement of B-type natriuretic peptide (BNP) level from venous blood sample were performed in 150 consecutive patients with asymptomatic severe AS and normal exercise test. Patients were classified in four groups, depending on left ventricular (LV) flow state (normal flow [NF] vs low flow [LF]: 35 mL/m²) and pressure gradient levels (low gradient [LG] vs high gradient [HG]: 40 mmHg).

Results: Patients with NF/LG had significantly lower BNP than those with LF/HG and LF/LG. The mean follow-up was 27–12 months. At 2 years, cardiac event-free survival was 83–6%, 44–6%, 30–12%, and 27–13% in NF/LG, NF/HG, LF/HG, and LF/LG groups, respectively (P = 0.0001). On multivariable analysis, LF/LG (hazard ratio [HR]: 5.26, 95% confidence interval [CI]: 2.04–14.3, P = 0.001) were identified as strong independent determinants of poor prognosis as compared with NF/HG. By limiting the multivariable analysis to patients with LF, LF/LG was an independent predictor of markedly reduced cardiac event-free survival when compared with LF/HG (HR: 5.4, 95% CI: 1.03–28.6, P = 0.046).

Conclusion: The use of the new proposed AS grading classification integrating valve area and flow-gradient patterns allows a better characterisation of the clinical outcome of patients with asymptomatic severe AS.

Perspective

This is a very elegantly done study involving asymptomatic patients with severe AS with ejection fraction (EF) >55%. The study goes on to prove that all these patients are not to be clubbed as one. The group which had LF and LG had the worst outcome and also the highest BNP levels (the so-called paradoxic LF/LG group with normal EF). The group which had HF and LG had the best outcome with lowest BNP levels. The other two groups with HGs had intermediate outcome. The study highlights the importance of taking all the parameters together including flow, gradient, and natriuretic peptide levels. The EF is just one of the many parameters that should be taken into consideration while determining the prognosis and further treatment.


doi: 10.1016/S0002-9149(12)60071-6

Context: Variants in the CYP2C19 gene influence the pharmacologic and clinical response to the standard 75 mg daily maintenance dose of the antiplatelet drug clopidogrel.

Objective: To test whether higher doses (up to 300 mg daily) improve the response to clopidogrel in the setting of loss-of-function CYP2C19 genotypes.

Design, setting, and patients: ELEVATE-TIMI 56 was a multicentre, randomised, double-blind trial that enrolled and genotyped 333 patients with cardiovascular disease (CVD) across 32 sites from October 2010 to September 2011.

Interventions: Maintenance doses of clopidogrel for four treatment periods, each lasting approximately 14 days, based on genotype. In total, 247 non-carriers of a CYP2C19*2 loss-of-function allele were to receive 75 mg and 150 mg daily of clopidogrel (two periods each), whereas 86 carriers (80 heterozygotes, six homozygotes) were to receive 75 mg, 150 mg, 225 mg, and 300 mg daily.

Main outcome measures: Platelet function test results (VASodilator-Stimulated Phosphoprotein [VASP] phosphorylation and verify now P2Y₁₂ assays) and adverse events.

Results: With 75 mg daily, CYP2C19*2 heterozygotes had significantly higher on-treatment platelet reactivity than did non-carriers (VASP platelet reactivity index [PRI]: mean, 70.0%; 95% CI, 66–74.0%, vs 57.5%; 95% CI, 55.1–59.9%, and verify now P2Y₁₂ reaction units [PRU]: mean, 225.6; 95% CI, 207.7–243.4, vs 163.6; 95% CI, 154.4–173.9; P < 0.001 for both comparisons). Among CYP2C19*2 heterozygotes, doses up to 300 mg daily significantly reduced platelet reactivity, with VASP PRI decreasing to 48.9% (95% CI, 44.6–53.2%) and PRU to 127.5 (95% CI, 109.9–145.2) (P < 0.001 for trend across doses for both). Whereas 52% of CYP2C19*2 heterozygotes were non-responders (≥230 PRU) with 75 mg of clopidogrel, only 10% were non-responders with 225 mg or 300 mg (P < 0.001 for both). Clopidogrel, 225 mg daily, reduced platelet reactivity in CYP2C19*2 heterozygotes to levels achieved with standard clopidogrel, 75 mg, in non-carriers (mean ratios of platelet reactivity, VASP PRI, 0.92; 90% CI, 0.85–0.99, and PRU, 0.94; 90% CI, 0.84–1.04). In CYP2C19*2 homozygotes, even with 300 mg daily of clopidogrel, mean VASP PRI was 68.3% (95% CI, 44.9–91.6%) and mean PRU, 287 (95% CI, 170.2–403.8).

Conclusion: Among patients with stable CVD, tripling the maintenance dose of clopidogrel to 225 mg daily in CYP2C19*2
heterozygotes achieved levels of platelet reactivity similar to that seen with the standard 75 mg dose in non-carriers; in contrast, for CYP2C19*2 homozygotes, doses as high as 300 mg daily did not result in comparable degrees of platelet inhibition.

**Perspective**

It is an established fact that those patients who have high platelet reactivity while on clopidogrel are at a higher risk of cardiovascular events including stent thrombosis. The reason for higher platelet reactivity includes importantly loss-of-function CYP2C19 allele. This gene decides the rate of conversion of clopidogrel pro-drug to active form. Platelet function testing has raised a lot of hope that we might by tailoring the dose overcome this problem. However, major trials which involved platelet function testing and gene testing failed to show improvement in clinical end-points. The GRAVITAS trial failed to show improvement in clinical end-points. The TRIGGER-PCI was halted midway for the same reason. However, the final word whether platelet function testing is useful or not has not been said. Further trials like TARGET-PCI are likely to clarify the issue. Newer P2Y12 inhibitors like prasugrel and ticagrelor by their more powerful action might make these tests redundant.

**1. Risk stratification in Brugada syndrome. Results of the PRELUDE (PRogrammed ELectrical stimUlation preDictive valuE) Registry.**

Priori SG, Gasparini M, Napolitano C, et al.
doi: 10.1016/S0019-4832(12)60072-8

**Study question:** Would inducibility of sustained ventricular tachycardia/ventricular fibrillation (VTs/VF) by programmed electrical stimulation (PES) accurately predict arrhythmic events in asymptomatic Brugada syndrome patients?

**Methods:** This was a prospective Italian registry of 308 patients (80% men, median age 44 years) with a spontaneous or drug-induced type 1 Brugada electrocardiogram (ECG) and without history of cardiac arrest. The PES was performed at enrolment, and patients were followed up every 6 months.

**Results:** During a median follow-up of 34 months, 14 arrhythmic events (4.5%) occurred (13 appropriate implantable defibrillator shocks, and one resuscitated cardiac arrest). History of syncope and spontaneous type 1 ECG (hazard ratio [HR]: 4.20), ventricular refractory period ≤200 ms (HR: 3.91), and QRS fragmentation (HR: 4.94) were significant predictors of arrhythmias. The PRELUDE was able to induce ventricular arrhythmias in 40% patients; however, arrhythmia inducibility was not a predictor of events at follow-up (9 of 14 events occurred in non-inducible patients).

**Conclusion:** Inducibility of VT/VF is unable to identify candidates for prophylactic implantable defibrillator therapy in Brugada syndrome patients who have not experienced arrhythmic events.

**2. Distinguishing ‘benign’ from ‘malignant early repolarization’: the value of the ST-segment morphology.**


**Study question:** Can the very common ‘benign early repolarization’ be distinguished from the very rare but malignant form associated with idiopathic ventricular fibrillation (VF)?

**Methods:** This was a case control study of 45 idiopathic VF patients, 124 controls matched for age and sex, and 121 young athletes. Patients with J-point elevation on ECG were taken and their ST-segment morphology was graded as either ‘horizontal’ or ‘scending’. ST-segment patterns were coded as ‘concave/rapidly ascending’ when there was ≥0.1 mV elevation of the ST-segment within 100 ms after the J-point or as ‘horizontal/descending’ when the ST-segment elevation was ≤0.1 mV within 100 ms after the J-point).

**Results:** J-waves were more prevalent among patients with idiopathic VF than among age- and sex-matched controls (42% vs 13%; P ≤ 0.001) or among young athletes (42% vs 22%; P ≤ 0.013). Of the 19 idiopathic VF patients with J-waves 13 (68.4%) had horizontal ST-segments; in contrast, only 4 (25%) of the 16 age-matched controls and 4 (14.3%) of the 28 young athletes with J-waves had a horizontal ST-segment.

**Conclusion:** The OR for having idiopathic VF for patients with J-waves was 4.0 (95% CI = 2.0–7.9), but having J-waves and horizontal ST-segment has an odds ratio of 13.8 (95% CI = 5.1–37.2). Despite the increased risk predicted by combination of J-point elevation and horizontal ST-segment, using Bayes Theorem of conditional probabilities, estimated odds for developing idiopathic VF for an individual in the age...
range of 35–45 years (even if he has both criteria) is only 34 in 100,000 or 0.03%.

**Perspective**

Previous studies by Tikkanen et al. (NEJM 2009;361:2529–37) reported that location of the early repolarisation pattern in the inferior leads and amplitude of the J-point elevation ≥0.2mV had adverse prognostic value. This study adds ST-segment morphology analysis to risk stratify people with J-point elevation on ECG to differentiate ‘benign’ from ‘malignant’ form of early repolarisation syndrome.

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1. **Randomised trial of ramipril in repaired tetralogy of Fallot and pulmonary regurgitation. The APPROPRIATE study (ACE inhibitors for potential prevention of the deleterious effects of pulmonary regurgitation in adults with repaired tetralogy of Fallot).**


Inter J Cardiol 2012;154:299–305.

doi: 10.1016/S0019-4832(12)60074-1

There is no consensus on optimal medical treatment and timing of pulmonary valve replacement for stable repaired tetralogy of Fallot (rTOF) patients with pulmonary regurgitation (PR) and consequent right ventricular (RV) dilatation. This randomised double-blind placebo study from United Kingdom aimed at studying the tolerability of the angiotensin-converting-enzyme (ACE) inhibitor, ramipril and its effect on cardiovascular function in rTOF patients. Clinically, stable rTOF patients with moderate/severe PR were included with 6 months follow-up. Cardiovascular magnetic resonance (CMR), echocardiography, neurohormonal analysis, and objective cardiopulmonary exercise testing were done at baseline and at follow-up.

Cardiovascular magnetic resonance-derived RV ejection fraction (EF) was considered the primary end-point. Seventy-two patients were enrolled of whom final analysis was performed on 64. Though, there was no difference in the primary end-point RV, i.e., EF, RV long-axis shortening improved significantly in the ramipril group compared to placebo (RV: 2.3 ± 3.8 vs 0.02 ± 2.7 mm; P = 0.017) as did left ventricular (LV) long-axis shortening (1.9 ± 4.5 vs −0.2 ± 3.7 mm respectively; P = 0.030). Other measurements did not differ in two groups. Patients on ramipril, compared to controls showed decrease in LV end-systolic volume index (−2.4 ± 5.0 vs 2.7 ± 3.6 mL/m²; P = 0.005) and increase in LVEF (2.5 ± 5.0 vs −1.3 ± 3.5%; P = 0.03) in subgroup with restrictive RV physiology. Ramipril did not cause adverse events and was well-tolerated. Authors concluded that ramipril is a well-tolerated therapy, improves biventricular function in patients with rTOF and may have a particular role in patients with restrictive RV physiology. Larger, longer term studies are needed to determine if ACE inhibitors can improve both ventricular remodelling and clinical outcomes.

**Comment**

Advances in diagnosis and management of congenital heart disease have resulted in an ever increasing adult cohort of rTOF patients. The PR subsequent to TOF repair though can be well-tolerated for several years, is a major cause of late morbidity in this population. Taking cues from beneficial effects of ACE inhibition in various conditions, authors undertook this randomised placebo-controlled study to look at tolerability, feasibility and efficacy of such therapy in these patients. Six months of ramipril therapy did not show improvement in RVEF. However, it was well-tolerated and did result in an increase in biventricular longitudinal systolic function. The ACE inhibition in patients with restrictive RV filling showed reduction in LVESVi and improvement in LVEF. Despite limited number of patients included, a relatively short follow-up and not so robust data to support benefit, this randomised trial has paved the path for future studies. This strategy of ACE inhibition, if found useful; can help deferring deleterious effects of PR in rTOF patients and thereby postponing pulmonary valve replacement.

2. **Impact of the permanent ventricular pacing site on left ventricular function in children: a retrospective multicenter survey.**

van Geldorp IE, Delhaas T, Gebauer RA, et al.

Heart 2011;97:2051–5.

doi: 10.1016/S0019-4832(12)60075-3

Chronic right ventricular (RV) pacing is associated with deleterious effects on cardiac function. This observational multi-centre study by Geldrop et al. looked at the importance of the ventricular pacing site on left ventricular (LV) function in children with isolated atrioventricular (AV) block receiving chronic ventricular pacing. Demographics, maternal autoantibody status, and echocardiographic measurements on LV end-diastolic and end-systolic dimensions and volumes at age <18 years were collected retrospectively from patients who have undergone ventricular pacing >1 year ago for isolated AV block. The LV contractility was assessed using LV Fractional Shortening (LVFS) and, if possible LV ejection fraction (LVEF) analysis. Linear regression analyses were adjusted for patient characteristics. Two-hundred and ninety-seven children from 27 centres were included, in whom pacing was applied at the RV epicardium (RVepi, n = 147), RV endocardium (RVendo, n = 113) or LV epicardium (LVepi, n = 37). LVFS was significantly affected by pacing site (P = 0.001), and not by maternal autoantibody status (P = 0.266). The LVEF in LVepi (39 ± 5%) was significantly higher than in RVendo (33 ± 7%, P < 0.001) and RVepi (35 ± 8%, P = 0.001; no significant difference between
RV-paced groups, \( P = 0.275 \). Subnormal LVFS (LVFS < 28%) was seen in 16/113 (14%) RVendo-paced and 21/147 (14%) RVepi-paced children, while LVFS was normal (LVFS ≥ 28%) in all LVepi-paced children \((P = 0.049)\). These results are supported by the findings for LVEF \((n = 122)\): LVEF was < 50% in 17/69 (25%) RVendo- and in 10/35 (29%) RVepi-paced patients, while LVEF was ≥ 50% in 17/18 (94%) LVepi-paced patients.

Authors conclude that in children with isolated AV block, permanent ventricular pacing site is an important determinant of LV function, with LVFS being significantly higher with LV epicardial pacing than with RV pacing.

**Comment**

The pacing-induced activation pattern is characterised by prolonged total activation duration and an abnormal sequence of activation (in both longitudinal and transverse directions) which may lead to dyssynchronous ventricular contraction. The degree of dyssynchrony varies with the site of pacing. The preservation of cardiac function during chronic ventricular pacing should be a high priority, especially in paediatric patients who are usually paced from an early age and may expect lifelong pacing. This study indicates that pacing site significantly influences LVFS, with better LVFS in patients with LV epicardial pacing compared to those with RV epicardial or endocardial pacing. The median follow-up of pacing in this study, as in other studies, was less than a decade, which is just a fraction of the life expectancy of a child receiving ventricular pacing for complete AV block. The index study, though retrospective, strengthens support to the use of LV pacing which incidently is technically easier with lateral thoracotomy or subxiphoid approach.

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Arrhythmia graphics
What is your diagnosis?

The electrocardiogram (ECG) of a 72-year-old gentleman who presented with a history of recurrent syncope is shown in Figure 1. What is the diagnosis from the ECG?

Commentary

Figure 1 shows sinus rhythm and right bundle branch block with intermittent blocked P waves suggesting a diagnosis of second degree atrioventricular (AV) block. Since the PR intervals do not seem to vary much, it appears to be of Mobitz type 2 variety especially since it also has wide QRS complexes. A close look at PR intervals especially in the P waves encompassing the blocked P waves indicates that the PR intervals are in fact varying. The PR interval in the beat after the blocked P wave is slightly shorter than in the beat just before the blocked P wave. Thus, it indicates a diagnosis of Mobitz type 1 block or Wenckebach AV block.

The intracardiac electrograms of the same rhythm are shown in Figure 2 with measured PR and HV intervals in milliseconds. It clearly shows that the PR intervals are slightly increasing before the block and this increase in PR interval is due to corresponding increase in the HV interval. Corresponding to the P wave that is blocked, the intracardiac His bundle electrograms show only A and H signals and no V signal indicating infra-hisian block. Thus, the right bundle branch is blocked and the intermittent AV block is occurring due to Wenckebach in the left bundle branch. In case of the commonly seen AV nodal Mobitz type 1 block, the intracardiac electrogram in the His bundle during blocked P wave will

![Figure 1](surface-electrocardiogram-showing-sinus-rhythm-second-degree-atrophicventricular-block-intermittent-blocked-p-waves-right-bundle-branch-block-lead-v5-missing-technical-problems.png)
show only A and no H or V signal. Also, AV nodal type 1 second degree block usually has narrow QRS complex, though it can also be associated with bundle branch block and wide QRS. In contrast, infra-hisian type 1 AV block cannot exist with narrow QRS complex.

Thus, the present ECG is a rare entity showing sinus rhythm with infra-hisian second degree Mobitz type 1 AV block with right bundle branch block.

**Figure 2** Intracardiac electrograms corresponding to the electrocardiogram (ECG) in Figure 1. From top to bottom are the surface ECG leads I, II, and V1, His Bundle electrogram (His) and right ventricular (RV) electrograms. The PR intervals are shown below lead II and HV intervals below the His bundle electrograms. Thick horizontal arrows depict the PR interval in beats encompassing the blocked P wave.

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Images in cardiology
A case of dyspnoea evaluated by cardiac computed tomography angiography
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A 1-year-old boy presented with failure to thrive and dyspnoea of 4 months duration. He was evaluated and found to be malnourished. His clinical examination revealed a pansystolic murmur at the left parasternal border with no jugular venous pressure (JVP) elevation or other features of heart failure.

Two-dimensional echo revealed a small ventricular septal defect (VSD) with left-to-right shunt and absent left pulmonary artery (LPA).

Figure 1 Origin of the left pulmonary artery (LPA) from right pulmonary artery (RPA).

Figure 2 Complete course of the left pulmonary artery (LPA).

Figure 3 Computed tomography angiography axial image showing the origin and posterior course of the left pulmonary artery (LPA).

Figure 4 Volume rendering technique image showing posterior view of the pulmonary arteries and the aorta. LPA: left pulmonary artery.
The cardiac computed tomography angiography imaging study showed all the characteristic features of an LPA sling with tracheal compression:

A. Normal size of main pulmonary artery (MPA), right pulmonary artery (RPA) and LPA.
B. Small perimembranous VSD.
C. There is anomalous origin of LPA just above tracheal bifurcation with a course posterior to the trachea and supplying the left lung (Figures 1–5).
D. There is mild tracheal compression between RPA anteriorly and LPA posteriorly.

Child underwent VSD closure and reimplantation of LPA to MPA anterior to trachea. Diffuse narrowing in proximal LPA improved as flow improved in LPA. There was gradual resolution of the dyspnoea.

**Figure 5** Volume rendering technique showing the MPA, RPA, and LPA origin. LPA: left pulmonary artery, MPA: main pulmonary artery, RPA: right pulmonary artery.
Instructions to authors

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