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The metabolic syndrome (MS) is a common phenotype associated with an increased risk for type 2 diabetes mellitus (T2DM) and cardiovascular disease (CVD). Although there is no universally accepted definition for the MS, affected individuals commonly have a cluster of features, including abdominal obesity, hypertension, dyslipidaemia and dysglycaemia.\textsuperscript{1-4}

The first formal definition of the MS was proposed by the World Health Organisation (WHO) in 1999. In the same year, the European Group for the Study of Insulin Resistance (EGIR) suggested a similar definition to that of the WHO, but excluded the microalbuminuria and diabetes components. In 2001, the United States National Cholesterol Education Program Adult Treatment Panel (NCEP ATP III) published a more practical definition for the MS, which eliminated insulin resistance as a criterion.\textsuperscript{1}

A few years later, in 2005, the cut-off point for fasting plasma glucose was lowered, resulting in the modified NCEP ATP III (modified ATP III) definition.\textsuperscript{2} In 2005, the International Diabetes Federation (IDF) proposed a new definition for the MS, which made abdominal obesity, classified by ethnic-specific cut-off points, a necessary condition for the MS. In 2007, the IDF presented a definition of the MS for use in children and adolescents, thus becoming the first major organisation to do so.

Throughout the Asia-Pacific region, there are differences in the prevalence of obesity and metabolic disturbances. People of Indian origin (PIO) are ethnically a particularly vulnerable group from the standpoint of metabolic abnormalities.\textsuperscript{3} Keeping this in mind, researchers in the Indian diaspora are now using South Asian Specific (SAS) cut offs to define the MS in people of Indian origin.

The SAS definition of the MS is otherwise similar to the modified ATP III with the exception of cut offs for waist circumference (WC) (lower vs modified ATP III) and triglycerides (higher vs modified ATP III). However, it is noteworthy to mention that whether using the modified ATP III or SAS definition of the MS, a large number of individuals may be misclassified due to lack of a common minimum platform required to better comprehend the problem in people of Indian origin.\textsuperscript{3,5}

Although widely used in epidemiological research, there has been ongoing concern that the WC cut-off points in the modified ATP III definition, which were predominantly intended for Americans, might not be appropriate for other ethnic groups, such as Asian Indians. South Asians (e.g. Asian Indians) have a more centralised distribution of body fat and a markedly higher mean waist–hip ratio (WHR) for a given level of body mass index (BMI) compared to Europeans.\textsuperscript{6} In Asian populations, morbidity and mortality is occurring in people with lower BMI and smaller WC. Therefore they tend to accumulate intra-abdominal fat without developing generalised obesity.\textsuperscript{6,7}

Although the IDF definition of the MS in most instances failed to identify a subgroup of subjects who had the highest risk for CVD, before the IDF’s definition of the MS, the effect of ethnicity on the individual criteria for diagnosing the MS was not considered. Recently, comparisons of the prevalence of the MS between different ethnic groups have raised concerns about the validity of the WHO, NCEP ATP III, modified ATP III and IDF definitions when applied across different ethnic groups. The originally accepted criteria for the MS were based on risk prediction in non-Asian populations.\textsuperscript{8} However, recent data from the Asian population, including Asian Indians, indicate that these definitions may not be satisfactory for risk prediction.\textsuperscript{9}

Although genetics most likely plays a crucial role in development of the MS, elucidating the exact genes involved has been hindered by the lack of a consistent definition of the MS,\textsuperscript{10} the varying combination of phenotypes even within a single definition, ethnic disparities, and gender influences. Recently, a large body of literature has emerged on early-life origins of the risk for the MS and associated diseases, such as coronary heart disease (CHD). Findings that experiences during the individual’s whole lifetime affect risk for disease highlight the need for an approach to understanding ethnic differences considering these early childhood conditions.

Moreover, research on the MS among children and adolescents and the implications of having the MS is limited. Because the roots of many adult chronic diseases originate in childhood, establishing a universally agreed definition of the MS in children and adolescents may help to identify children and adolescents who are at high risk for developing the MS, and allow for early prevention of possible adverse health events in early adulthood.

Differences in the prevalence of the MS and its components using the various definitions, both within and between populations, indicate that caution is required when comparing studies from different countries.\textsuperscript{1} Determining the clinical significance of these differences will require prospective outcome studies. Furthermore, to make the definition of the MS more sensitive, factors such as family history, habitual physical activity and smoking, along with region-specific cut offs for individual MS components are required to better comprehend the MS.\textsuperscript{6,7}

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Prevalence of asymptomatic left ventricular systolic dysfunction in hypertensive Nigerians: echocardiographic study of 832 subjects

OS OGAH, RO AKINYEMI, GD ADEGBITE, OI UDOFIA, SB UDOH, JO ADESINA, OS OJO, AA ALABI, T MAJEKODUNMI, JKL OSINFADE, RF OGUNDIPE, AO FALASE

Abstract

Background: We sought to determine the prevalence of echocardiographically determined left ventricular systolic dysfunction in asymptomatic hypertensive subjects seen in Abeokuta, Nigeria.

Methods: Echocardiography was performed in 832 consecutive hypertensive subjects referred for cardiac evaluation over a three-year period.

Results: Data were obtained in 832 subjects (50.1% women) aged 56.0 ± 12.7 years (men 56.9 ± 13.3 years, women 55.0 ± 12.0 years, range 15–88). The prevalence of left ventricular systolic dysfunction (LVSD) was 18.1% in the study population (mild LVSD = 9.6%, moderate LVSD = 3.7% and severe LVSD = 4.8%). In a multivariate analysis, male gender, body mass index and LV mass were the predictors of LVSD.

Conclusion: Significant numbers of hypertensive subjects in this study had varying degrees of left ventricular systolic dysfunction. Early introduction of disease-modifying drugs in these patients, such as angiotensin converting enzyme inhibitors or angiotensin receptor blockers may retard or prevent the progression to overt heart failure.

Keywords: hypertension, echocardiography, systolic dysfunction, Nigeria

Submitted 19/9/09, accepted 16/8/10


DOI: 10.5830/CVJA-2010-063

High blood pressure affects about a billion people worldwide.1-3 It has been predicted that by 2025, more than 1.5 billion adults will have hypertension.4,5 In the year 2001, hypertension was estimated to be responsible for 7.6 million premature deaths worldwide (13.5% of total global mortality) and it was also responsible for 92 million disability-adjusted life years (DALYs).4-6 The condition has been rightly described as the foundation of cardiovascular disease in sub-Saharan Africa.6 The overall prevalence has been put at 10 to 15% but rates as high as 30 to 32% have been reported.7

Hypertension and its complications are responsible for about 25% of urban hospital medical admissions in Nigeria,6 as well as for over 80% of cardiac clinic consultations in the country. It is the most frequently diagnosed medical illness in elderly populations7 and senior executives.8

High blood pressure is also by far the commonest cause of chronic renal failure, stroke, heart failure and sudden unexpected death in Nigeria.6

In Nigeria, the prevalence of asymptomatic left ventricular systolic dysfunction (LVSD) among people with hypertension is unknown. The aim of the study was therefore to determine the prevalence of asymptomatic LVSD in hypertensive subjects in Abeokuta, Nigeria.

Methods

The study was conducted at the Federal Medical Centre (FMC), Idi-Aba and the Sacred Heart Hospital (SHH), Lantoro, both in Abeokuta, the capital city of Ogun State in south-western Nigeria. FMC was established in 1993 by the federal government of Nigeria to cater for the health needs of the people of Ogun State and its environs in south-western Nigeria. The state has a population of about 3.2 million and a surface area of about 16 409.26 km². SHH is one of the oldest hospitals in Nigeria, established in 1897 by the German Catholic Mission.

Cardiological services commenced in the city in September 2005 and since then a registry of patients and services rendered has been kept. A cardiologist (OSO) covers the two cardiac units,
which are about 5 km apart, assisted by senior medical officers and postgraduate resident doctors and well as nurses. Facilities available for cardiac evaluation include chest radiography, 12-lead electrocardiography (ECG), exercise ECG, Holter ECG, ambulatory blood pressure-monitoring devices, spirometry and echocardiography (ECHO).

This was a cross-sectional study, conducted within a three-year period. Hypertensive patients were eligible for the study if they fulfilled the following criteria: (1) no evidence of valvular abnormality. This was based on clinical examination and absence of features of valvular heart disease at echocardiography; (2) absence of congestive heart failure based on previous history of admission for heart failure or symptoms and signs of heart failure in the past or at the time of evaluation, using the Framingham criteria; (3) absence of sickle cell disease based on self-reported haemoglobin electrophoretic pattern of the subject and/or absence of stigmata of the disease; (4) absence of self-reported history of renal failure or serum creatinine ≥ 2 mg/dl; (5) absence of ischaemic heart disease based on history, as well as absence of ischaemic ECG changes at the time of the study (other than left ventricular hypertrophy with strain pattern); (6) other exclusion criteria included morbid obesity, pulmonary heart disease (cor pulmonale), chest abnormality that obscured echo-window and left bundle branch block pattern on the 12-lead ECG.

Using a simple questionnaire, a nurse screened the patients for history or symptoms of these and history of previous hospital admissions relating to the exclusion criteria. All the echocardiography request forms were also assessed for evidence of exclusion criteria. Fig. 1 shows how the patients were selected for final analysis. Both treated and untreated hypertensive subjects were recruited. Hypertension was defined according to international criteria.16

Baseline clinical and demographic characteristics were obtained from the subjects. These included date of birth, age, gender and history of diabetes. Blood pressure measurements were obtained according to standard guidelines,12 with a mercury sphygmomanometer (Accosson London). Systolic and diastolic blood pressures were measured at Korotkoff sounds phases I and V, respectively. Blood pressure was measured three times on the right arm, after a five-minute rest, and averaged. Subjects were weighed without shoes and in light clothing on a standard beam balance. Height was measured to the nearest centimetre using an in-the-shoe and end-systole. Where optimal M-mode imaging could not be obtained, 2-D linear measurements were obtained according to the ASE criteria.12

Left atrial end-systolic diameter was obtained from the trailing edge of the posterior aortic–anterior left atrial complex. Measurements were obtained in up to three cardiac cycles, according to the ASE convention.12

One experienced cardiologist performed all the echocardiography. In our laboratory, the intra-observer concordance coefficient and measurement error have been reported.14

Left ventricular systolic performance (LVSP) was assessed using the fractional shortening of the left ventricle and the ejection fraction. Left ventricular ejection fraction (LVEF) was calculated using the Teichholz formula.15 Fractional shortening was calculated from LV internal dimensions in diastole and systole:

\[
\text{Fractional shortening} = \frac{LVID_d - LVID_s}{LVID_d} \times 100
\]

Left ventricular mass (LVM) was calculated using the formula of Devereux and Reichek.16 This has been shown to yield LVM closely related to autopsy measurements \((r = 0.90)\) and it had good inter-observer reproducibility \((p = 0.93)\) in one study.17 Relative wall thickness (RWT) was derived from \(2 \times \text{posterior wall thickness}/\text{LV internal diameter} \)

Left ventricular hypertrophy (LVH) was defined by LV mass indexed by allometric signal \((\text{height}^{2.7}) > 51 \text{ g/m}^2\).18 This partition value of 51 g/m\(^2\) was used since this was the only criterion that demonstrated as the optimal threshold value for left ventricular hypertrophy in blacks, irrespective of gender, in two previous studies. Left ventricular systolic function was categorised as follows:19 normal LV function, EF ≥ 50%; mild LVSD, EF 40–49%; moderate LVSD, EF 30–39%; and severe LVSD, EF < 30%.

Statistical analysis

SPSS version 11.0 software (SPSS, Chicago, IL, USA) was used in the analysis of the data. Continuous variables were expressed as mean ± SD, while categorical variables were expressed as counts (percentages). Comparison between the two groups was assessed with the Student’s t-test for independent variables, while the \(\chi^2\) analysis was used to compare proportions. Analysis of variance (ANOVA) with Scheffe’s post hoc test was used for the comparison of multiple groups. A two-tailed \(p\)-value of 0.05 was assumed statistically significant.

Results

A total of 832 subjects, 415 men (49.9%) and 417 women (50.1%) were eligible for analysis. Fig. 1 shows the criteria for selection of subjects for analysis.

The overall mean age of the population was 56.0 ± 12.7 years (range 15–88). Fig. 2 is a histogram showing the age distribu-
The majority of the subjects fell within the middle-aged group, with a peak age of 50 years. Forty-six subjects (5.5%) had a self-reported history of diabetes (25 men, 6.0% and 21 women, 5.0%).

Tables 1 and 2 show the clinical and demographic characteristics of the subjects in the men and women, respectively. Patients with L VSD were older. Those with normal left ventricular systolic function (L VSF) were heavier and had a larger body surface area. Diastolic blood pressure as well as mean arterial blood pressure were higher in individuals with severe L VSD.

Normal L VSF, defined as ejection fraction (EF) \( \geq 50\% \) was present in 89.9% of the subjects. The remaining 18.1% had L VSD (mild 9.6%, moderate 3.7% and severe 4.8%). Figs 3 and 4 depict the distribution of the subjects according to L VSF and gender.

Men had a higher prevalence of L VSD than women (24.4 and 12.3%, respectively) and this was statistically significant \( (p < 0.0001) \). Compared with individuals with normal L VSF

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Normal LVSF</th>
<th>Mild LVSF</th>
<th>Moderate LVSF</th>
<th>Severe LVSF</th>
<th>ANOVA p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>56.4 (13.8)</td>
<td>62.7 (9.0)</td>
<td>58.9 (12.5)</td>
<td>61.5 (16.8)</td>
<td>0.039</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>77.9 (15.5)</td>
<td>72.3 (14.8)*</td>
<td>63.0 (14.8)*</td>
<td>68.2 (20.0)*</td>
<td>0.0001</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>169.0 (7.4)</td>
<td>169.8 (5.3)</td>
<td>166.4 (9.1)</td>
<td>167.5 (8.2)</td>
<td>NS</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>27.3 (5.0)</td>
<td>25.0 (4.7)*</td>
<td>22.6 (5.9)*</td>
<td>24.3 (7.0)**</td>
<td>0.0002</td>
</tr>
<tr>
<td>BSA (m²)</td>
<td>1.88 (0.19)</td>
<td>1.83 (0.18)*</td>
<td>1.69 (0.24)**</td>
<td>1.76 (0.23)*</td>
<td>0.0001</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>84.5 (14.9)</td>
<td>81.2 (11.1)</td>
<td>83.4 (12.4)</td>
<td>88.9 (13.8)</td>
<td>NS</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>91.0 (14.9)</td>
<td>84.2 (12.7)*</td>
<td>85.6 (11.5)</td>
<td>99.0 (15.9)**</td>
<td>0.018</td>
</tr>
<tr>
<td>Pulse pressure (mmHg)</td>
<td>57.0 (17.3)</td>
<td>57.8 (17.3)</td>
<td>59.4 (19.5)</td>
<td>53.9 (16.1)</td>
<td>NS</td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>110.0 (15.9)</td>
<td>103.4 (14.7)*</td>
<td>105.4 (11.9)</td>
<td>116.9 (29.0)*</td>
<td>0.024</td>
</tr>
</tbody>
</table>

**BMI** = body mass index, **BSA** = body surface area, **BP** = blood pressure, **MAP** = mean arterial pressure.

**NS** = not significant, \(^* p < 0.05\) versus normal L VSF, \(^{**} p < 0.05\) versus mild L VSD.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Normal LVSF</th>
<th>Mild LVSF</th>
<th>Moderate LVSF</th>
<th>Severe LVSF</th>
<th>ANOVA p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>56.4 (13.3)</td>
<td>60.1 (10.1)</td>
<td>60.1 (13.5)</td>
<td>55.4 (17.0)</td>
<td>NS</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>76.2 (14.9)</td>
<td>74.5 (154.6)</td>
<td>64.2 (16.4)</td>
<td>71.0 (19.9)</td>
<td>NS</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>168.4 (7.5)</td>
<td>169.2 (9.4)</td>
<td>166.3 (9.1)</td>
<td>167.6 (7.7)</td>
<td>NS</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>26.9 (4.9)</td>
<td>26.4 (7.8)*</td>
<td>23.1 (5.4)*</td>
<td>25.2 (6.3)**</td>
<td>0.007</td>
</tr>
<tr>
<td>BSA (m²)</td>
<td>1.86 (0.19)</td>
<td>1.84 (0.17)</td>
<td>1.71 (0.22)</td>
<td>1.79 (0.24)**</td>
<td>0.001</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>147.2 (22.3)</td>
<td>142.0 (21.7)</td>
<td>143.2 (19.1)</td>
<td>148.5 (33.5)</td>
<td>NS</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>90.4 (14.7)</td>
<td>85.1 (12.5)*</td>
<td>85.5 (11.0)</td>
<td>98.5 (24.9)</td>
<td>0.002</td>
</tr>
<tr>
<td>Pulse pressure (mmHg)</td>
<td>57.4 (16.5)</td>
<td>57.6 (17.1)</td>
<td>58.5 (18.7)</td>
<td>52.1 (17.5)</td>
<td>NS</td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>110.2 (16.0)</td>
<td>103.5 (14.5)</td>
<td>105.5 (11.3)</td>
<td>116.3 (28.2)</td>
<td>0.023</td>
</tr>
</tbody>
</table>

**BMI** = body mass index, **BSA** = body surface area, **BP** = blood pressure, **MAP** = mean arterial pressure.

**NS** = not significant, \(^* p < 0.05\) versus normal L VSF, \(^{**} p < 0.05\) versus mild L VSD.
or mild LVSD, those with severe LVSD were older, more likely to be men, had larger left atrial diameter, larger LV dimensions and LV mass, and as expected, lower fractional shortening and ejection fraction. This finding was consistent in both genders and progressed from normal LVSF to severe LVSD (Tables 3, 4).

We developed a linear regression model for the whole population (as the pattern was similar in both genders). LVEF was used as the dependent variable, while independent variables were taken from clinical variables (age, gender, body mass index, body surface area) and echocardiographic variables [left atrial diameter, LV internal dimensions, LV mass, relative wall thickness (RWT)] that were significant in the univariate analysis.

Although LV dimensions were significantly related to LVEF in the univariate analysis, they were not added in the final model since these parameters were used in the determination of LVM. Categorical variables such as gender and presence or absence of diabetes mellitus were entered as indicator variables. None of the blood pressure variables were significant in the univariate analysis.

In the univariate analysis, EF was related to age [B (unstandardised regression coefficients) = −0.84, β (standardised regression coefficient) = −0.72, p = 0.036]; gender (B = −5.42, β = −1.84, p < 0.0001); BMI (B = 0.31, β = 0.13, p = 0.0002); left atrial diameter (B = −5.72, β = −0.25, p < 0.0001); end-diastolic diameter (B = −7.70, β = −0.45, p < 0.0001), end-systolic diameter (B = −11.97, β = −0.76, p = 0.0001); LVM (B = −0.48, β = −0.32, p < 0.0001); and RWT (B = 14.38, β = 0.19, p < 0.0001).

In a multivariate analysis, lower LVEF was independently related to BMI, gender, LV mass, left atrial diameter and relative wall thickness.

### TABLE 3. LV FINDINGS IN MALE SUBJECTS ACCORDING TO FUNCTIONAL STATUS

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Normal LVSF</th>
<th>Mild LVSD</th>
<th>Moderate LVSD</th>
<th>Severe LVSD</th>
<th>ANOVA p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>AO diameter (cm)</td>
<td>3.10 (0.44)</td>
<td>3.25 (0.41)*</td>
<td>3.07 (0.39)</td>
<td>3.15 (0.45)</td>
<td>NS</td>
</tr>
<tr>
<td>LA diameter (cm)</td>
<td>3.78 (0.58)</td>
<td>4.03 (0.58)*</td>
<td>4.34 (0.79)*</td>
<td>4.45 (0.67)*</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>IVSd (cm)</td>
<td>1.20 (0.31)*</td>
<td>1.32 (0.25)</td>
<td>1.13 (0.23)*</td>
<td>1.20 (0.34)</td>
<td>NS</td>
</tr>
<tr>
<td>IVSs (cm)</td>
<td>1.59 (0.39)</td>
<td>1.47 (0.33)</td>
<td>1.30 (0.16)*</td>
<td>1.41 (0.48)*</td>
<td>0.0003</td>
</tr>
<tr>
<td>LVIDd (cm)</td>
<td>4.67 (0.69)</td>
<td>5.24 (0.86)*</td>
<td>6.11 (0.98)**</td>
<td>6.06 (1.11)**</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LVIDs (cm)</td>
<td>3.01 (0.61)</td>
<td>4.15 (0.88)*</td>
<td>5.07 (0.87)**</td>
<td>5.20 (1.13)**</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>PWTd (cm)</td>
<td>1.28 (0.36)</td>
<td>1.27 (0.41)</td>
<td>1.29 (0.31)</td>
<td>1.32 (0.41)</td>
<td>NS</td>
</tr>
<tr>
<td>PWTs (cm)</td>
<td>1.85 (0.38)</td>
<td>1.66 (0.37)*</td>
<td>1.61 (0.39)**</td>
<td>1.66 (0.43)*</td>
<td>0.0003</td>
</tr>
<tr>
<td>FS (%)</td>
<td>35.7 (8.0)</td>
<td>21.1 (7.1)*</td>
<td>17.0 (4.5)**</td>
<td>14.4 (8.3)**</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LVM/BMI (g/m²)</td>
<td>221.0 (91.2)</td>
<td>286 (121.6)*</td>
<td>373.1 (122.1)*</td>
<td>356.4 (169.6)*</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LVM/BSA (g/m²)</td>
<td>119.6 (48.6)</td>
<td>155.3 (62.9)*</td>
<td>201.8 (78.3)*</td>
<td>203.0 (99.9)*</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

AO = aortic root, LA = left atrium, IVSd = interventricular septum in diastole, IVSs = interventricular septum in systole, LVIDd = left ventricular internal diameter in diastole, LVIDs = left ventricular internal diameter in systole, PWTd = posterior wall thickness in diastole, PWTs = posterior wall thickness in systole, FS = fractional shortening, EF = ejection fraction, LVM = left ventricular mass, BSA = body surface area, HT = height. NS = not significant, *p < 0.05 vs normal LVSF, p < 0.05 vs mild LVSD.

### TABLE 4. LV FINDINGS IN FEMALE SUBJECTS ACCORDING TO FUNCTIONAL STATUS

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Normal LVSF</th>
<th>Mild LVSD</th>
<th>Moderate LVSD</th>
<th>Severe LVSD</th>
<th>ANOVA p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>AO diameter (cm)</td>
<td>3.08 (0.44)</td>
<td>3.22 (0.42)</td>
<td>3.07 (0.39)</td>
<td>3.15 (0.45)</td>
<td>NS</td>
</tr>
<tr>
<td>LA diameter (cm)</td>
<td>3.75 (0.58)</td>
<td>4.01 (0.56)*</td>
<td>4.34 (0.79)*</td>
<td>4.45 (0.67)*</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>IVSd (cm)</td>
<td>1.20 (0.31)*</td>
<td>1.33 (0.25)</td>
<td>1.13 (0.23)*</td>
<td>1.20 (0.34)</td>
<td>0.027</td>
</tr>
<tr>
<td>IVSs (cm)</td>
<td>1.57 (0.38)</td>
<td>1.47 (0.32)</td>
<td>1.30 (0.16)*</td>
<td>1.20 (0.34)*</td>
<td>0.0006</td>
</tr>
<tr>
<td>LVIDd (cm)</td>
<td>4.63 (0.71)</td>
<td>5.25 (0.87)*</td>
<td>6.11 (1.00)*</td>
<td>6.06 (1.11)*</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LVIDs (cm)</td>
<td>2.99 (0.62)</td>
<td>4.17 (0.85)*</td>
<td>5.07 (0.87)*</td>
<td>5.20 (1.13)*</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>PWTd (cm)</td>
<td>1.27 (0.52)</td>
<td>1.24 (0.40)</td>
<td>1.29 (0.31)</td>
<td>1.66 (0.43)</td>
<td>NS</td>
</tr>
<tr>
<td>PWTs (cm)</td>
<td>1.84 (0.38)</td>
<td>1.67 (0.36)*</td>
<td>1.61 (0.39)*</td>
<td>1.66 (0.43)</td>
<td>0.0003</td>
</tr>
<tr>
<td>FS (%)</td>
<td>35.6 (7.9)</td>
<td>21.0 (6.6)*</td>
<td>17.0 (4.5)*</td>
<td>14.4 (8.3)*</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LVM/BMI (g/m²)</td>
<td>145.7 (38.3)*</td>
<td>174.3 (73.0)*</td>
<td>198.1 (77.5)</td>
<td>218.3 (48.8)*</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LVM/BSA (g/m²)</td>
<td>113.5 (45.9)</td>
<td>182.3 (48.8)</td>
<td>145.7 (38.3)*</td>
<td>174.3 (73.0)*</td>
<td>0.0001</td>
</tr>
<tr>
<td>LVM/HT².7 (g/m²)</td>
<td>56.5 (22.5)</td>
<td>64.02 (6.7)*</td>
<td>73.4 (18.2)*</td>
<td>81.8 (30.5)*</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

AO = aortic root, LA = left atrium, IVSd = interventricular septum in diastole, IVSs = interventricular septum in systole, LVIDd = left ventricular internal diameter in diastole, LVIDs = left ventricular internal diameter in systole, PWTd = posterior wall thickness in diastole, PWTs = posterior wall thickness in systole, FS = fractional shortening, EF = ejection fraction, LVM = left ventricular mass, BSA = body surface area, HT = height. NS = not significant, *p < 0.05 vs normal LVSF, p < 0.05 vs mild LVSD.
Discussion

Hypertension is the commonest cardiovascular disease in Nigeria and sub-Saharan Africa. It is the commonest risk factor for heart failure, stroke and chronic renal impairment. In Nigeria and most African countries, the majority of patients first present with evidence of target-organ damage such as overt heart failure. Most often, overt heart failure is preceded by asymptomatic left ventricular systolic dysfunction. Information on the prevalence and burden of both symptomatic and asymptomatic LVSD is based on population studies as well as studies done in hypertensive subjects in Europe and America.21-23

The burden of LVSD (symptomatic or asymptomatic) in hypertensive subjects is largely unknown in Nigeria and in most African countries, hence the reason for the present study. Echocardiographic methods have been shown to provide a high yield of quantitative measurement of LV function and can be used to assess the determinants of LV function, both in hypertensive and general populations.

The main findings of the study are: the majority of our hypertensive patients fell within the middle-aged group with a peak age of 50 years, about 18% of our hypertensive subjects had asymptomatic LVSD, the prevalence of LVSD was higher in men than in women, LVSD increased with age, although LVSD was independent of age, and the main predictors of LVSD were male gender, body mass index, left ventricular mass and LV relative wall thickness.

All over sub-Saharan Africa, the peak age of presentation of cardiovascular diseases such as hypertension has been well defined.23-26 As in the present study, most patients are within the age group of 40 to 60 years, often with a peak age of 45 to 50 years, as observed in this study. The implication is that where complications arise, it is usually associated with high DALYs, with a huge impact on the socio-economic growth of the family and nation, as the population affected is in the prime of life. This is contrary to the situation in developed countries where most cardiovascular diseases manifest after the age of 65 years.

In a univariate analysis, age was related to LVEF. However, when other factors such as gender, LV mass, relative wall thickness and BMI were factored in, the association with age became insignificant. The plausible reason for this is that the impact of age on LVSD is probably mediated through other factors. Our finding is similar to the report of other workers.22,23,27,28

The study shows that the prevalence of impaired LVSF is about twice as common in men as in women. In a multivariate analysis, male gender was found to be an independent predictor of impaired LVSF. This is similar to the findings of authors in studies done in hypertensive subjects or in the general population.22-25-28 The reasons for this are not clear but it is well known that cardiovascular diseases generally occur earlier in men than in women. In our setting, women are also more likely to attend follow-up clinics as well as take their medication as prescribed.

Tables 1 and 2 show that diastolic blood pressure and mean arterial blood pressure were higher in the group with severe LVSD compared to other groups. No significant difference was found in the systolic blood pressure and pulse pressure among the groups.

In univariate and multivariate analyses, blood pressure was not found to be related to LVSF. This finding is similar to that of Devereux et al.21 but at variance with studies done in the general population, where the relationship of blood pressure with LVSF persisted in the multivariate analysis.21,25,28 This may be may be due to the fact that most of our patients were on antihypertensive medications.

In this study, BMI was found to decrease from subjects with normal LVSF to those with severe LVSD (although the lowest BMI was in those with moderate LVSD in both men and women). The impact of BMI persisted in the multivariate analysis. This relationship between LVSF and BMI was also reported by Devereux et al.21 Because our population was relatively lean, one plausible reason for the finding may be the known relationship between chronic LVSD and weight loss (cardiac cachexia).

In a univariate analysis, we did not find any relationship between LVSD and the presence of diabetes in this study. This is at variance with the report by some workers.22,24 The reason for the negative finding in our study may be that we relied on self-reported history of diabetes. Many more subjects with diabetes could have been detected if metabolic profiles were run in our study subjects.

The left atrial size was found to be independently related to LVSD. The larger the left atrium, the poorer the LVSF. Similar findings have been reported by other investigators.22,24 Left atrial size is a known strong marker or surrogate of left diastolic function. The latter is known to have a positive relationship with LVSF.25,34

Limitations of the study

We noted the following limitations with this study. It was a hospital-based study and may not reflect the situation in the general population. We did not run metabolic profile functions (blood glucose, lipid, uric acid, insulin levels, etc) in the present study, as was done in studies in industrialised nations, due to lack of funds.

Newer measures of assessment of LVSF such as LV mid-wall shortening, circumferential end-systolic measurements as well as measures of arterial wall stiffening (pulse pressure/stroke index) were not assessed in our study. Absence of ischaemic heart disease was only assessed based on clinical history and 12-lead ECG. This may not exclude sub-clinical ischaemic heart disease.

Conclusions

LVSD, assessed as ejection fraction < 50%, was detected in 18.1% of our hypertensive population, who did not have symptoms of overt heart failure. Male gender, body mass index, LVM and relative wall thickness were found as independent predictors of LVSF in our study.

Significant numbers of hypertensive subjects in this study had varying degrees of left ventricular systolic dysfunction. Early introduction of disease-modifying drugs in these patients, such as angiotensin converting enzyme inhibitors/angiotensin receptor blockers may retard or prevent the progression to overt heart failure.

It must be stated that since echocardiography is expensive, it cannot be placed as the first line of systematic screening of hypertensive patients, however, the predictive factors of LVSD are accessible to primary-care physicians. For instance, the combination of male gender and obesity should draw the attention of clinicians to the possible presence of LVSD, a pathogenic precursor of heart failure.
References


Prevalence of the metabolic syndrome in people of Asian Indian origin: outcomes by definitions
M DAS, S PAL, A GHOSH

Abstract
Background: The prevalence of the metabolic syndrome (MS) is high among south Asian Indians. In order to better comprehend the MS, its definition and modifications require region-specific cut-off values and common minimum criteria for people of Indian origin.
Methods: To define the MS, the criteria as defined in the National Cholesterol Education Program (NCEP): expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III) (ATP III 2001), followed by the modified ATP III of 2005 were used, along with a modified version specific to the people of south Asian origin (ATP III SAS, 2009).
Results: The three definitions showed differences in prevalence of the MS among the adult Asian Indians. According to the criteria of NCEP ATP III 2001, the prevalence was found to be 32.3%. Using the modified ATP III 2005, the prevalence was 48.3%, and for south Asian-specific (SAS) ATP III, it was 31.4%. For all three definitions, females had a considerably higher prevalence of the MS than males. It was also observed that that a large number of individuals were misclassified due to lack of common minimum criteria.
Conclusion: In order to curb the growing threat of the MS, and to aid clinical management among people of Indian origin, a more comprehensive definition of the MS is urgently required.

Keywords: obesity, metabolic syndrome, CVD, diabetes, Asian Indians

People of Indian origin are ethnically a particularly vulnerable group from the standpoint of metabolic abnormalities. Throughout the Asia-Pacific region, there are differences in the prevalence of obesity and metabolic disturbances. South Asians (e.g. Indians) have a more centralised distribution of body fat and a markedly higher mean waist–hip ratio (WHR) for a given level of body mass index (BMI) compared to Europeans. In Asian populations, morbidity and mortality is occurring in people with lower BMI and smaller waist circumference (WC). Therefore they tend to accumulate intra-abdominal fat without developing generalised obesity.1,2

The metabolic syndrome (MS), which can be defined as the constellation of cardiovascular disease (CVD) risk factors, is one of the growing public health burdens in the Asia-Pacific region, although the populations are no more overweight than Europeans and Americans.3 The MS is a phenotype and therefore is used to identify subjects with a high risk, based on easily measurable biological variables. However, it lacks some critical variables, which are population specific, in order to better predict the population’s risk. It therefore needs further validation among Asian Indians.3,4

The present work was an attempt to study the prevalence of the MS using different definitions of the MS in people of Indian origin.

Methods
The cross-sectional study comprised 350 adult Asian Indians (≥ 30 years) (184 males and 166 females) living in and around Calcutta, India. Written consent was obtained from all participants. The institutional ethics committee of the Human Genetic Engineering Research Center (HGERC), Calcutta, India approved the study. Written consent from participants was also obtained prior to actual commencement of the study.

Anthropometric measures, namely height, weight and waist circumference were obtained using standard techniques.5 BMI (kg/m2) was computed accordingly.

Left arm systolic (SBP) and diastolic (DBP) blood pressure measurements were taken twice using a sphygmomanometer and stethoscope and were averaged for the analyses. A third measurement was taken only when the difference between the two measurements was ≥ 5 mmHg. Prior medical records for blood pressure were also taken into consideration.

A fasting blood sample (~7 ml) was collected from each subject for the determination of metabolic profiles. All subjects maintained an overnight fast of approximately 12 hours prior to blood collection. The serum was separated by centrifugation within two hours of collection. Determination of total cholesterol (TC), triglyceride (TG), high-density lipoprotein (HDL) cholesterol and fasting blood glucose (FBG) levels was carried out on the separated serum using a semi-autoanalyser. Low-density lipoprotein (LDL) cholesterol was then calculated using the standard formula:

\[ \text{LDL} = \text{TC} - (\text{HDL} + \text{TG}/5) \]

All biochemical parameters were analysed at the HGERC and were measured in mmol/l.
Definition of the metabolic syndrome

To define the metabolic syndrome, the criteria as set out in the National Cholesterol Education Program (NCEP): expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III) (ATP III, 2001), was followed by the ATP III as modified in 2005, were used, plus the modified version specific to the people of south Asian origin (ATP III SAS 2009). These criteria were as follows:

- waist circumference: male > 90 cm; female > 80 cm
- triglycerides: ≥ 2.25 mmol/l
- HDL: male < 1.03 mmol/l; female < 1.29 mmol/l
- blood pressure: SBP ≥ 130 mmHg and/or DBP ≥ 85 mmHg
- fasting blood glucose: ≥ 5.56 mmol/l.

Statistical analyses

Parameters were expressed as mean and standard deviation (SD), separately for males and females in the study population. The prevalence (%) of the MS and its confounding factors were calculated using standard cut-off values. All statistical analyses were performed using SPSS (PC + version 10.0).

Results

The mean and standard deviation by gender of obesity values, lipid profiles and blood pressure is presented in Table 1. It was observed that males had significantly (p < 0.05) higher mean total cholesterol and fasting blood glucose values (p < 0.01) than females.

The difference in prevalence of the MS according to the three definitions is presented in Table 2. Using the original ATP III (2001) definition, the overall prevalence of the MS in the study was found to be 32.3%. However, according to the ATP III modified criteria (2005), the prevalence was found to be 48.3% among the participants. When the south Asian-specific cut-off values were taken into consideration, the prevalence was found to be 31.4%.

Out of five confounding factors, the three factors playing a crucial role were high abdominal obesity (61.1%), low HDL cholesterol (50.9%) and high blood pressure (63.7%). It was also observed that for all three definitions (NCEP ATP III 2001, ATP III modified 2005, and ATP III SAS 2009), female participants had a considerably higher prevalence of the MS compared to male subjects (Fig. 1).

Discussion

It was observed that the prevalence of the MS was different, depending on the three definitions used. Moreover, the prevalence of elevated triglyceride levels (hypertriglyceridaemia), which is a distinctive feature of people of Indian origin, varied considerably in the study population owing to the use of the south Asian-specific cut-off value for elevated triglycerides. The marked difference in the overall prevalence of the MS from the ATP III (2005) definition to the SAS (2009) definition (48.3 vs 31.4%) was due to the use of the south Asian-specific cut-off values for WC and triglyceride levels. Importantly, whether the modified ATP III (2005) or the revised SAS (2009) definition is used, a large number of individuals are likely to be misclassified due to lack of a common minimum criterion required to better comprehend the problem of the MS among Asian Indians.

Several other studies have shown such discrepancies, not only in the Indian population but also in other Asian countries, such as China and Iran. In a study from India, the World Health Organisation (WHO), ATP III and IDF criteria of the MS identified a differential prevalence of the MS in the study population. The WHO criteria identified a greater number of coronary artery disease (CAD) subjects in males, but not in females.

Studies pertaining to Asian Indians revealed that the ATP III criteria identified a significantly higher proportion of people with the MS compared with the WHO criteria. It was mentioned that lower cut-off values of WC and BMI to define the MS might be critical for the accurate assessment of the MS among Asian Indians. Moreover, inclusion of BMI and making WC a non-obligatory criterion, more cases of the MS were detected. However, for Asian Indians, making WC a mandatory

### Table 1. Descriptive statistics of the study population (n = 350)

<table>
<thead>
<tr>
<th>Variables</th>
<th>Male (n = 184)</th>
<th>Female (n = 166)</th>
<th>Total (n = 350)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
<td>SD</td>
</tr>
<tr>
<td>Age (years)**</td>
<td>54.04</td>
<td>12.40</td>
<td>48.48</td>
</tr>
<tr>
<td>BMI (kg/m2)</td>
<td>22.37</td>
<td>4.09</td>
<td>23.20</td>
</tr>
<tr>
<td>WC (cm)</td>
<td>89.81</td>
<td>10.04</td>
<td>88.90</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>132.97</td>
<td>24.02</td>
<td>137.21</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>82.22</td>
<td>11.41</td>
<td>83.48</td>
</tr>
<tr>
<td>TC (mmol/l)*</td>
<td>2.23</td>
<td>0.31</td>
<td>2.24</td>
</tr>
<tr>
<td>TG (mmol/l)</td>
<td>1.61</td>
<td>0.30</td>
<td>1.57</td>
</tr>
<tr>
<td>HDL (mmol/l)</td>
<td>1.13</td>
<td>0.12</td>
<td>1.13</td>
</tr>
<tr>
<td>LDL (mmol/l)</td>
<td>3.39</td>
<td>0.70</td>
<td>3.25</td>
</tr>
<tr>
<td>VLDL (mmol/l)</td>
<td>0.32</td>
<td>0.006</td>
<td>0.31</td>
</tr>
<tr>
<td>FBG (mmol/l)**</td>
<td>5.17</td>
<td>1.30</td>
<td>4.92</td>
</tr>
</tbody>
</table>

BMI = body mass index; WC = waist circumference; WHR = waist–hip ratio; SBP = systolic blood pressure; DBP = diastolic blood pressure; TC = total cholesterol; TG = triglyceride; HDL = high-density lipoprotein; LDL = low-density lipoprotein; VLDL = very low-density lipoprotein; FBG = fasting blood glucose.

Significant gender difference at *p < 0.05; **p < 0.01.

### Table 2. Prevalence (%) of metabolic syndrome phenotypes by definitions

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Waist circumference (cm)</td>
<td>30.9</td>
<td>61.1</td>
<td>61.1</td>
</tr>
<tr>
<td>Triglycerides (mmol/l)</td>
<td>39.7</td>
<td>39.7</td>
<td>2.3</td>
</tr>
<tr>
<td>High-density lipoprotein (mmol/l)</td>
<td>50.9</td>
<td>50.9</td>
<td>50.9</td>
</tr>
<tr>
<td>Blood pressure (mmHg)</td>
<td>63.7</td>
<td>63.7</td>
<td>63.7</td>
</tr>
<tr>
<td>Fasting blood glucose (mmol/l)</td>
<td>21.7</td>
<td>21.7</td>
<td>21.7</td>
</tr>
<tr>
<td>Metabolic syndrome (%)</td>
<td>32.3</td>
<td>48.3</td>
<td>31.4</td>
</tr>
<tr>
<td>SAS = South Asian specific.</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


Down syndrome and congenital heart disease: why the regional difference as observed in the Libyan experience?

Z ELMAGRPY, A RAYANI, A SHAH, E HABAS, EH ABURAWI

Abstract

Background: Children with Down syndrome (DS) have about a 40 to 50% incidence of congenital heart disease (CHD). The objectives of this study were to evaluate the distribution and frequency of CHD patterns in Libyan children with DS.

Methods: All patients with DS who were referred to the cardiology clinic between January 1995 and December 2008 were reviewed.

Results: Of the 1 193 patients reviewed, 537 (45%) had an associated CHD. Overall there were 349 (65%) patients who had a single cardiac lesion, and 188 (35%) had multiple cardiac lesions. The most common isolated cardiac lesion was atrial septal defect (ASD), found in 125 (23%) patients, followed by atrioventricular septal defect (AVSD) in 103 (19%), and ventricular septal defect (VSD) in 76 (14%).

Conclusion: Atrial septal defect was the most common cardiac lesion. The distribution of CHDs in Libyan children with DS was similar to what has been reported internationally, but the frequency was not compared with international rates.

Keywords: congenital heart disease, Down syndrome, geographical difference, Libya

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doi:10.5830/CVJA-2010-072

Down syndrome (DS) or trisomy 21 is a chromosomal disorder frequently associated with a varied combination of morphological and structural birth defects. These defects are in the form of congenital mental disability, hypotonia, characteristic body features, heart defects, and other systemic congenital malformations. The frequency and severity of these morphological and functional defects vary significantly among affected individuals. The incidence of moderate to severe forms of congenital heart disease (CHD) in Libya is about 5/1 000 live births.1

In 1866, John Langdon Haydon Down first characterised DS as a distinct disease with intellectual impairment.2 In the late fifties, Lejeune and Jacobs independently reported that DS resulted from an extra chromosome 21. Since then the condition has been known as trisomy 21.3,4 This particular trisomy is the most common form of chromosomal abnormality, affecting about one in 700 live births.5 It is characterised by the whole chromosomal aneuploidy in about 95% of cases. The remaining 5% is in the form of translocations and mosaics.6 The risk of pregnancy with DS increases with the mother’s age, and it can occur with a frequency as high as one in 30 in those older than 45 years.7

Approximately 40 to 60% of children with DS have heart defects and among those with CHD, four to 10% are associated with DS.8 The cardiac defects are commonly single, but they can be multiple as well. It is highly recommended that DS patients be referred early for cardiac screening. Chest infection, CHD, blood disorders, leukaemia and lymphoma are not uncommon causes of death.9,10 Nowadays, almost all CHD in DS patients are surgically manageable, with good results. Moreover, the postoperative morbidity and mortality associated with cardiac surgery has fallen dramatically in recent years due to advances in intensive care units, peri-operative care and improved treatment related to respiratory illnesses.11,12

The aim of this study was to determine the mode of presentation, and type and distribution of CHD affecting DS patients in Libya, and to compare this with previously reported studies.

Methods

In a retrospective descriptive study, medical records of clinically diagnosed DS patients were reviewed. There were 1 193 children with DS who had presented to Alfateh University Children’s Hospital, Tripoli, between January 1995 and December 2008. After detailed histories and thorough physical examinations were recorded, two-dimensional echocardiography and Doppler studies were performed using the ALOKA SSD-800 before 2005, and the Philips EnVisor C HD, Philips Medical Systems after 2005.

The data were analysed by descriptive statistics, using Microsoft Excel and Minitab version 16 statistical software packages. Previously reported literature was reviewed to compare our results with the international geographical distribution of cardiac defects in patients with DS.

Results

There were 1 193 patients with DS who attended the cardiac clinic and of these, 537 (45%) had CHD. The male-to-female ratio was 1:1.4. The reasons for presentation are given in Table 1, with the commonest being routine screening (44%). Cardiac
murmur was the reason for referral in 177 (33%) patients, heart failure in 62 (12%), chest infection in 36 (7%), and cyanosis in 19 patients (4%).

Of the overall number of patients with CHD, 349 (65%) had a single cardiac lesion, whereas the remaining 188 (35%) had multiple defects. The most common single defect was atrial septal defect (ASD), which was found in 125 (24%) patients, followed by atroventricular septal defect (AVSD) in 103 (19%), and ventricular septal defect (VSD) in 76 (14%) cases. Patent ductus arteriosus (PDA) occurred in 28 (5%) cases.

Other common defects such as combined ASD plus VSD with other complex lesions was found in 77 (14%) patients, VSD plus PDA was found in 42 (8%), and 40 (7%) had ASD plus PDA. PDA was the most common cardiac defect associated with other cardiac lesions. It was found in association with VSD and ASD in 82 patients (15%) (Table 2).

The median age (range) at diagnosis with ASD was three months (three days – 15 years) and for those with complex and mixed cardiac lesions it was four months (two days – 18 years) (Table 2). The rare associations of complex CHD were those of double-outlet right ventricle and transposition of the great arteries in two patients, pulmonary atresia with VSD in one patient and a combination of complete atroventricular septal defect with tetralogy of Fallot in three patients.

**Discussion**

Approximately 50% of the patients evaluated for DS had an associated CHD. This finding is similar to internationally reported figures. ASD of secondum type was the most common single congenital cardiac defect and was found in 125 of the 537 DS patients (24%). This finding was not consistent with what has previously been reported in Europe, Sudan and the USA, where ASD was reported to occur in only 5% of the DS patients in Europe and Sudan and 8% in the USA patients. ASD of secondum type has been reported in Mexico in 38% and Saudi Arabia in 21% of patients with DS. These high distributions are similar to that in our report.

In most of the European countries, Sudan, Turkey and the USA, A VSD was the most common cardiac defect. In Asia on the other hand, VSD was the most common single cardiac defect, followed by ASD or AVSD. In our series, AVSD with a common atrioventricular valve was the second most common CHD, found in 103 (19%) patients. In Guatemala, PDA (29%) followed by VSD (28%) were the most common cardiac defects.

The isolated cardiac lesions represented about 65% of all CHD in our study, compared with 80% in Guatemala, 74% in Mexico, and 78% in Turkey (Table 3). Furthermore, patients' age at diagnosis with ASD was younger than those with complex and other associated cardiac lesions. This minimised the possible bias that patients with more complex lesions died earlier before diagnosis, compared with those with ASD.

On reviewing the literature (Table 3), it appears that the frequency and distribution of CHD in DS varies in different geographical regions. The reason for this difference in the

**TABLE 1. CARDIAC EVALUATIONS OF THE PATIENTS STUDIED**

<table>
<thead>
<tr>
<th>Reason for cardiac evaluation</th>
<th>Number (n=537)</th>
<th>M:F ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Screening</td>
<td>237 (44%)</td>
<td>1:1.4</td>
</tr>
<tr>
<td>Murmur</td>
<td>177 (33%)</td>
<td>1:1.1</td>
</tr>
<tr>
<td>Heart failure</td>
<td>62 (12%)</td>
<td>1:1.2</td>
</tr>
<tr>
<td>Cyanosis</td>
<td>19 (4%)</td>
<td>1:1.6</td>
</tr>
<tr>
<td>Chest infection</td>
<td>36 (7%)</td>
<td>1:1</td>
</tr>
<tr>
<td>Others</td>
<td>6 (1%)</td>
<td><strong>1:2.</strong></td>
</tr>
</tbody>
</table>

**TABLE 2. THE FREQUENCY AND TYPES OF CONGENITAL HEART DISEASE**

<table>
<thead>
<tr>
<th>Cardiac lesions</th>
<th>Patients, n = 537 (%)</th>
<th>Age*</th>
<th>M:F ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single lesion</td>
<td>349 (65%)</td>
<td>4 months (3 days – 18 years)</td>
<td>1:1.4</td>
</tr>
<tr>
<td>ASD</td>
<td>125 (23%)</td>
<td>3 months (3 days – 15 years)</td>
<td>1:1.1</td>
</tr>
<tr>
<td>AVSD</td>
<td>103 (19%)</td>
<td>3 months (3 days – 12 years)</td>
<td>1:1.6</td>
</tr>
<tr>
<td>VSD</td>
<td>76 (14%)</td>
<td>4 months (4 days – 14 years)</td>
<td>1:1</td>
</tr>
<tr>
<td>PDA</td>
<td>28 (5%)</td>
<td>5 months (1 month – 18 years)</td>
<td>1:2</td>
</tr>
<tr>
<td>TOF</td>
<td>13 (2%)</td>
<td>3 months (3 weeks – 9 months)</td>
<td>1:1</td>
</tr>
<tr>
<td>COA</td>
<td>4 (1%)</td>
<td>5 months (1 week – 6 months)</td>
<td>1:0.3</td>
</tr>
<tr>
<td>Multiple lesions</td>
<td>188 (35%)</td>
<td>4 months (2 days – 18 years)</td>
<td>1:1.4</td>
</tr>
<tr>
<td>ASD with VSD plus others</td>
<td>77 (14%)</td>
<td>1 year (2 days – 18 years)</td>
<td>1:1.5</td>
</tr>
<tr>
<td>VSD with PDA plus others</td>
<td>42 (8%)</td>
<td>1.5 months (1–3 months)</td>
<td>1:0.8</td>
</tr>
<tr>
<td>ASD plus PDA with others</td>
<td>40 (7%)</td>
<td>4 months (1.5 months – 1.5 years)</td>
<td>1:0.8</td>
</tr>
<tr>
<td>ASD with pulmonary stenosis</td>
<td>11 (2%)</td>
<td>30 days (4 days – 3 years)</td>
<td>1:3</td>
</tr>
<tr>
<td>Other rare associations</td>
<td>19 (4%)</td>
<td>2 months (2 days – 2 years)</td>
<td>1:1</td>
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</tbody>
</table>

ASD, atrial septal defect; AVSD, atrioventricular septal defect; VSD, ventricular septal defect; PDA, patent ductus arteriosus; TOF, tetralogy of Fallot; COA, coarctation of aorta.

*Median (range) age at diagnosing congenital heart disease.
distribution of CHD among DS patients is not clear, although some consistency is observed between certain global areas. This variation in geographical distribution may be caused by numerous factors, one of which could be the genetic make up of each nation or global region; or it could be due to specific embryological mechanisms.

Types of CHD can also be determined by cell characteristics in each nation or population. The embryology and anatomy of VSD, ASD and PDA are quite different from that of AVSD. Some publications have suggested that ethnicity and different geographic factors, such as high altitude with lower partial pressures of oxygen may contribute to a higher frequency of PDA.

The most common mode of presentation of CHD in DS was the routine referral to cardiology clinics, but only 44% of the cases were presented in this manner. There were 62 patients (12%) who presented with heart failure; this was probably due to the fact that these patients were missed or not referred at an earlier age for cardiac screening. This stresses the importance of early referral to cardiology clinics.

The mother’s age is an important risk factor for DS, with the risk of giving birth to a child with DS increasing from 1 in 1,250 at age 25, to 1 in 1,000 at age 30, to 1 in 400 at age 35, to 1 in 100 at age 40, to 1 in 30 at age over 45 years. Nevertheless, about 80% of infants with DS are born to mothers who are under 35 years of age. In our series, CHD was more common in children whose mothers were in the age range of 31 to 45 years (71%), which is comparable with international figures. In addition, the single and multiple cardiac lesions were nearly doubled in those of older mothers.

On the other hand, there was no specific association between ASD and mothers’ ages. Interestingly, we found tetralogy of Fallot in 13 children of mothers who were over 30 years of age, and not in younger mothers. Coarctation of the aorta is unusual in patients with DS; however, we found this to occur in 1% of the cases, which is similar to a previous report from the USA.

There are a number of limitations in our study, such as the fact that the figures reported herein are not population based, and any patients with DS who died at home or at other hospitals and had never been diagnosed with CHD were not included. Moreover, cyogenetic studies were not routinely performed on all patients because diagnosis was mainly based on clinical grounds. Due to poor organisation and infrastructure at our cardiac centre in previous years, we were unable to accompany the presented figures with any surgical results. Irrespective of these limitations, we believe that we have made some progress in documenting the distribution of CHD in Libyan children with DS.

**Conclusion**

This is the first study to document the types, distribution and frequency of CHDs in Libyan children with DS. ASD was the most common single cardiac lesion in DS. The distribution of CHDs in Libyan children with DS was similar to what has been reported internationally but the frequency was not compared with international rates. We stress the importance of early referral and screening for CHDs in this group of patients.

**References**

20. Lo NS, Leung PM, Lau KC, Yeung CY. Congenital cardiovascular

International Society of Cardiovascular Disease Epidemiology and Prevention

44th 10-day International Teaching Seminar on Cardiovascular Disease Epidemiology and Prevention

15–27 January 2012
Cape Town, South Africa

The International Society of Cardiovascular Disease Epidemiology and Prevention announces the 44th 10-day international teaching seminar on cardiovascular disease epidemiology and prevention to be held 15–27 January 2012 in Cape Town, South Africa in conjunction with the South African Medical Research Council and the University of Cape Town.

Approximately 36 fellows can be accepted. The Society’s seminar committee will make the final selection. Nominees should ideally be at the postgraduate level with residency training or its equivalent, and be interested in cardiovascular disease epidemiology.

Normally, preference is given to younger candidates, with little or no formal training in epidemiology. Tuition, board and accommodation are provided without cost to fellows. Fellows and their sponsors are responsible for their own travel costs to the seminar. Should any accepted fellow be unable to attend, no substitute not reviewed by the seminar committee may be sent as an alternate by the institution.

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Applications, including (1) a letter of nomination by the chief of department or institution, or other relevant sponsor, (2) a personal letter of application from the nominee, and (3) the applicant's curriculum vitae, should be received before 15 September 2011 by the seminar coordinator, address below. Applications can be sent by e-mail but a signed hard copy should follow in the post.

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Diagnosis and follow up of patients with primary cardiac tumours: a single-centre experience of myxomas

S MANDUZ, N KATRANCIOGLU, O KARAHAHAN, O YUCEL, MB YILMAZ

Abstract

Objective: In this study, 12 patients who were diagnosed as having cardiac tumours and were operated on in the Department of Cardiovascular Surgery following referral from the Department of Cardiology were enrolled between January 1995 and October 2007.

Methods: The symptoms, clinical findings, diagnostic methods, localisation of masses and surgical applications were recorded retrospectively.

Results: There were 10 female (83%) and two (17%) male patients; their ages ranged from 35 to 70 years (mean 68.7 years). Twelve patients were diagnosed with myxomas, nine of which were located within the left atrium and three in the right atrium. The most common symptoms at clinical presentation were those associated with heart failure or embolisation. Diagnosis of the tumours was made by echocardiography in all patients. The masses were completely resected in eight patients and the interatrial septae were partially excised with mass resection in two patients. The defect was reconstructed with a pericardial patch in one of the patients, and primarily reconstructed in the other. We carried out debridement with mass resection in another case. Femoro–popliteal aorto–iliac thrombo-endarterectomy was performed with mass resection in a further case.

Conclusion: Atrial myxomas are the most common primary cardiac tumours. They can cause valvular or inflow–outflow tract obstruction, thrombo-embolism, arrhythmias, or pericardial disorders. Most atrial myxomas are benign but due to non-specific symptoms, early diagnosis may be a challenge and they must be removed by surgical resection. Diagnosis and follow up with the collaboration of cardiology and cardiovascular surgery departments is important for meticulous care of these patients.

Keywords: myxoma, diagnosis, surgery

Primary cardiac tumours are rare. Their prevalence ranges from 0.0017 to 0.28% in various autopsy series, and they are up to 20 times less frequent than are secondary tumours of the heart. The prevalence of primary cardiac tumours other than benign myxomas is even lower. In 1954, Clarence Crafoord removed an intra-atrial myxoma for the first time. Echocardiography has enabled better visualisation of the cardiac structures and accurate diagnosis.

Approximately 75% of sporadic myxomas occur in females. Myxomas have been reported in patients aged three to 83 years. They are rarely seen in children, accounting for only nine to 15% of all cardiac tumours from birth to adolescence.

Early diagnosis and surgical removal of the tumour with decreased mortality and morbidity is related to the symptoms produced, such as tumour embolism, heart failure, mechanical valvular obstruction, and various constitutional symptoms. We retrospectively reviewed our case series with particular attention to myxomas.

Methods

In this study, 12 patients who suffered from myxomas were diagnosed and operated on in the Departments of Cardiology and Cardiovascular Surgery, respectively, between January 1995 and October 2007. Symptoms, clinical findings, diagnostic methods, localisation of the mass and surgical application were evaluated retrospectively.

Echocardiographic examinations were performed by an experienced echocardiographer using available ultrasound equipment (GE-Vivid 4 with a 3.5 MHz transducer, Wisconsin, USA) at baseline, and as required during follow up. Pre-operative coronary angiography was performed in patients with known or suspected coronary artery disease.

Results

There were 10 female (83%) and two (17%) male patients; their ages ranged from 35 to 70 years (mean 68.7 years). All patients were diagnosed as having myxomas on pathological verification. Nine of these myxomas were in the left atrium and three were in the right atrium. All myxomas were sporadic. The most common symptoms at clinical presentation were those associated with cardiac insufficiency or embolisation. There was haemoptysis in one patient with bronchiectasis.

Diagnosis of the tumours was made by echocardiography before surgery in all patients (Fig. 1). Computed tomography and angiography were also used in some of the patients as required. The masses were completely resected in eight patients and the interatrial septae were partially excised with mass resection in two patients (Fig. 2). The defect was reconstructed with a pericardial patch in one patient and primarily reconstructed in the other. We carried out debridement with mass resection in another case. Femoro–popliteal aorto–iliac thrombo-endarterectomy was performed with mass resection in a further case and the embolectomy material was confirmed as a myxoma. Coronary
artery bypass surgery was performed in a patient with coronary artery disease (Table 1).

The minimum follow-up period was 12 months and the maximum was 132 months (median, 60 months). One of the patients with myxoma died in the early postoperative period due to cerebrovascular accident.

In some of the cases, pleural effusion was detected with computed tomography and chest X-ray (Fig. 3). We used abdominal and peripheral Doppler ultrasound in case 12, and found a subacute thrombus which totally obstructed the abdominal aorta, extending 3 cm in the proximal part down to the bifurcation and including 4 cm proximally in the common femoral artery. The details of the cases are presented in Table 1.

Discussion

Cardiac myxomas most commonly occur in the third to fourth decade of life, and approximately 75% of sporadic myxomas occur in females.² They frequently occur in the left atrium in 75% of cases. The right atrium is involved in 15 to 20% of cases. There is no difference in terms of frequency of involvement of the ventricles (6–8%).² There were 10 female (83%) and two (17%) male patients. In addition, left atrial involvement was observed in 67% of the cases in our study, in accordance with the current literature.

Cardiac myxomas originate from primitive, multipotential mesenchymal cells present in the heart wall as embryonic remnants. Histopathologically, a myxoma is composed of an abundant acid mucopolysaccharide matrix in which polygonal cells and immature endothelial cells forming blood vessels are embedded in chronic inflammation.⁵,⁶ Masses from the 12 cases in our study were histopathologically typical of myxomas.

Myxomas cause peripheral embolisms, in which fragments of the tumour break away into the blood stream and cause clots or blockages. Systemic embolism is encountered in 30 to 45% of myxoma cases.⁹⁻¹¹ A massive embolism can cause death. There were two cases with femoral artery embolism in our series, which were confirmed on pathological evaluation. Fortunately, in our series, no patient had a cerebral embolism, which may have been fatal.

On the other hand, aneurysms may also occur in these patients, causing symptoms associated with central nervous system involvement.¹² Therefore a careful examination for any symptom that could possibly be associated with nervous system involvement should be an essential part of the therapeutic approach.

An important aspect of our study was that the tumour was detected in all patients by echocardiography, which was performed due to the non-specific symptoms of the patients. Coronary angiography, however, was performed in older patients who were thought to have coronary artery disease. Echocardiographic follow up was done on a routine basis in the third, sixth and twelfth months and thereafter annually in all patients. We feel that routine echocardiographic follow up may help in earlier diagnosis and timely intervention to avoid neurological sequelae.

Operative resection of the myxomas is the treatment of choice. Some authors believe that resection should be performed immediately after the diagnosis is made.¹³⁻¹⁴ We performed our operations immediately after the diagnosis.

Conclusion

The development of diagnostic techniques and the routine practice of echocardiography have enabled us to define cardiac tumours earlier, important for both the initial diagnosis and for detecting a recurrence. Hence, mortality and morbidity were
quite low in our series. Untreated benign cardiac tumours can be distressing to both patient and physician.

Treatment of myxomas is usually done by surgical removal of the tumour. Complete resection, given the low operative mortality rate that can be accomplished in experienced hands, and then follow up by serial echocardiography over five or six years to monitor for recurrences are crucial for an appropriate therapeutic approach, although late recurrences with neurological symptoms have been noted in the literature.12,13

References


<table>
<thead>
<tr>
<th>Case</th>
<th>Age</th>
<th>Gender</th>
<th>Final diagnosis</th>
<th>Presenting symptoms</th>
<th>BP (mmHg)</th>
<th>Pulse (beats/min)</th>
<th>Rhythm</th>
<th>NYHA</th>
<th>Diagnostic methods</th>
<th>Valve disease</th>
<th>Pericardial effusion</th>
<th>Surgical procedure</th>
<th>Outcome</th>
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<td>F</td>
<td>LA myxoma</td>
<td>Dyspnoea</td>
<td>120/60</td>
<td>82</td>
<td>AF</td>
<td>2</td>
<td>Echo</td>
<td>2º MR</td>
<td>2º TR</td>
<td>Tumour resection</td>
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<td>2</td>
<td>70</td>
<td>M</td>
<td>LA myxoma</td>
<td>Dyspnoea + palpitations</td>
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<td>Sinus rhythm</td>
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<td>116</td>
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<td>2</td>
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<td>3</td>
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<td>Fatigue + emesis</td>
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<td>1º TR</td>
<td>Off-pump LIMA–LAD bypass + tumour resection</td>
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<td>AF</td>
<td>3</td>
<td>Echo + CAG</td>
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<td>3</td>
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<td>2º TR</td>
<td>–</td>
<td>Tumour resection + tricuspid De Vega plasty</td>
<td>Healing</td>
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</table>

RA = right atrial, LA = left atrial, AF = atrial fibrillation, Echo = echocardiography, CAG = coronary angiography, CT = computed tomography, CDUS = colour Doppler ultrasonography, MR = mitral regurgitation, TR = tricuspid regurgitation, AR = aortic regurgitation, MS = mitral stenosis, LIMA–LAD = left internal mammary artery–left anterior descending artery, De Vega plasty = De Vega's tricuspid annuloplasty, MVR = mitral valve repair.
Role of stromal-derived factor-1<alpha>/CXCR4 in neo-intimal repair

J SHENG, W-W CAI, N-Y FANG, S-Q WANG, J-J WU

Abstract

Neo-intimal hyperplasia is one of the major causes of restenosis in which stromal cell-derived factor-1<alpha> (SDF-1<alpha>) and its receptor CXCR4 play an important role. In a rat common carotid artery balloon injury model, the number of CD34+CXCR4+ cells was significantly increased immediately after injury (p < 0.01), followed by a gradual decrease to baseline seven days after the injury. Furthermore, the plasma (SDF-1<alpha>) level was markedly elevated, and peaked 24 hours after injury (p < 0.01), followed by a rapid decrease to baseline level seven days after the injury. In the injured common carotid artery, the mRNA expression of (SDF-1<alpha>) was elevated immediately after injury, followed by a gradual decline, but that of CXCR4 was increased four days after injury.

Immuno-histochemistry displayed CXCR4-positive staining one day after injury, which then gradually increased and continued for at least one month. In addition, administration of AMD3100 (200 ng/kg, i.p.), a CXCR4 antagonist, did not affect the number of CD34+CXCR4+ cells, the elevated level of plasma (SDF-1<alpha>) and expression of (SDF-1<alpha>) mRNA.

The expression of CXCR4 mRNA and protein however was markedly decreased, and detectable CXCR4-positive cells occurred four days after injury, followed by a decreased intensity of staining. We also found that, three months after balloon injury, stenosis of the carotid artery intima in the group that received AMD3100 was significantly less than in the untreated group (p < 0.05). Therefore, (SDF-1<alpha>/CXCR4 played a crucial role in the intimal hyperplasia, and restenosis may have been attenuated after inhibition of CD34+CXCR4+ cells in the intima.

Keywords: percutaneous transluminal coronary angioplasty, percutaneous coronary intervention, restenosis, chemokine, stromal cell-derived factor-1<alpha>, CXCR4

Percutaneous transluminal coronary angioplasty (PTCA) and percutaneous coronary intervention (PCI) are effective techniques in the treatment of cardiovascular diseases, including acute myocardial infarction (AMI). But a relatively high incidence of restenosis after PTCA or PCI is a major problem, causing failure of treatment. Neo-intimal hyperplasia after vascular injury plays an important role in post-treatment restenosis, which is mainly caused by excessive cell deposition in the neo-intima. Therefore, blocking cell deposition may be a promising strategy in the prevention of post-injury restenosis.

Stromal cell-derived factor-1 (SDF-1) is one of the chemokines that belong to the intercrine family and is officially designated as chemokine (C-X-C motif) ligand 12 (CXCL12). The receptor for this chemokine is CXCR4, which was previously called fusin. SDF-1 is a strong chemo-attractant in directing progenitor cell trafficking, cell migration and angiogenesis. It has been confirmed that the expression of SDF-1 was elevated in the peri-infarct area after AMI, which recruited CXCR4+ cells to participate in myocardial repair and angiogenesis.

In humans and rats, both SDF-1 and CXCR4 show a high degree of sequence homology. In rats, the SDF-1 gene encodes three splice variants: α, β and γ. In the present study, a rat carotid artery balloon injury model was used to mimic human coronary neo-intimal repair after PTCA or PCI. By investigating the expression of SDF-1α and CXCR4 after injury and using a CXCR4 antagonist (AMD3100) to block the interaction between SDF-1 and CXCR4, we found that SDF-1α/CXCR4 played a critical role in neo-intimal hyperplasia.

Methods

A total of 156 male Sprague Dawley rats weighing 286 ± 14.3 g were purchased from the SLAC Laboratory Animal Co, Ltd, Shanghai, China, and housed in a temperature-controlled environment (22–24°C) with a 12-h light–dark cycle. The local ethics committee of the School of Medicine, Shanghai Jiao-Tong University (No. 0708253) approved all procedures.

The rats were randomly divided into three groups: a control group (group C; n = 12), a surgical group (group S; n = 72), and the AMD3100 treatment group (group A, n = 72). The rats in groups S and A were further divided into six sub-groups (n = 12 per group).

The rats were sacrificed as follows. Groups S<sub>s</sub> and A<sub>s</sub> were sacrificed 30 min after surgery, groups S<sub>d1</sub> and A<sub>d1</sub> one day after surgery, groups S<sub>d2</sub> and A<sub>d2</sub> four days post surgery, groups S<sub>d3</sub> and A<sub>d3</sub> seven days after surgery, groups S<sub>d4</sub> and A<sub>d4</sub> one month after surgery, and groups S<sub>d5</sub> and A<sub>d5</sub> three months post surgery.

The rat common carotid artery balloon injury model was carried out in groups S and A as previously described, and rats in the control group underwent a sham operation. Briefly, the rats were intraperitoneally anaesthetised with 2.5% pentobarbital sodium (40 mg/kg) and fixed in the supine position. A midline incision was made in the neck, and then the left common carotid...
Flow cytometric analysis

The peripheral blood (300 µl) was incubated with FITC-conjugated anti-mouse CD34 (eBioscience, USA) and phycoerythrin-conjugated anti-human CXCR4 (eBioscience, USA) monoclonal antibodies for 30 min at 4°C (n = 12 per group). The cells were double-labelled with CD34 and CXCR4. The red blood cells and platelets were subsequently lysed in erythrocyte lysis buffer for 15 min, followed by centrifugation and washing. The cells were then re-suspended in phosphate-buffered saline (PBS) and analysed on a FACS Caliber flow cytometer (BD FACSCalibur, America). Isotype-matched FITC-conjugated and phycoerythrin-conjugated antibodies (eBioscience, USA) were used as controls. The number of CD34+CXCR4+ cells was presented as the absolute number in a total of 50 000 leukocytes.

Enzyme-linked immunosorbent assay of plasma SDF-1α

The plasma level of SDF-1α was determined by the enzyme-linked immunosorbent assay (ELISA) using an ELISA kit (R&D system, USA) according to manufacturer’s instructions.

Real-time polymerase chain reaction analysis of SDF-1α and CXCR4

Total RNA was extracted from the injured arteries. For synthesis of cDNA, 1 µg of total RNA was reverse-transcribed with Promega RT system. Then the transcribed cDNA was amplified by polymerase chain reaction (PCR) (T3000 PCR instrument, Biometra, Germany) with specific primers as follows: SDF-1α forward: 5′- CCAATCGAGAAATGGGACAAGA-3′, reverse: 5′- GATGAGGTCTATACGGAGCA-3′ (381 bp); CXCR4 forward: 5′- GTGGGCAATGGGATGGTAAT -3′, reverse: 5′- GTGGGCGTGAGAAATGGGCAAGGTAG-3′ (267 bp). The primers were synthesised by Shanghai Sangon Biological Engineering Technology & Services Co, Ltd (Shanghai, China). Reactions involved 10 min at 95°C, 40 cycles at 95°C for 15 sec, and then 60°C for one min. The products of PCR were detected with 1.8% agarose electrophoresis and visualised under a gel imaging and analysis system (Alpha FluorchemTM8900, USA).

Western blot analysis

The artery tissues were lysed in radio-immunoprecipitation assay (RIPA) buffer (n = 6 per group). The protein concentration in the supernatant was measured spectrophotometrically at 595 nm. Forty µg of protein was loaded onto SDS polyacrylamide gel for electrophoresis (Invitrogen, China) and transferred to PVDF membranes (Millipore, USA). The membrane was incubated with anti-CXCR4 antibody (1:500; rabbit anti-mouse; eBioscience, USA) and anti-ß-actin antibody (1:1000; goat anti-mouse, Santa Cruz, USA) overnight at 4°C. The membrane was then incubated with secondary antibodies (donkey anti-rabbit antibody, 800DX 1:5000, eBioscience, USA; donkey anti-goat antibody, 700DX 1:2000 Sigma, USA) for one hour, followed by detection with an infrared fluorescence imaging and analysing system (Odyssey v1.2) (FIAS, Odyssey LI-COR USA).

Immuno-histochemistry

Sections were then treated with 1.5% peroxide to inactivate peroxidase activity, followed by blocking with 3% bovine serum albumin. These sections were subsequently incubated with anti-CXCR4 antibody (1:250, eBioscience, USA) overnight at 4°C. The sections were then incubated with biotin-conjugated secondary antibody (1:500; Sigma, USA) or immunoglobulin G (1:500; Santa Cruz, USA). The sections were stained with haematoxylin/eosin (H&E), dehydrated and mounted. H&E staining was performed on other sections from each group (n = 6) to observe the intimal change after balloon injury. The thickness of the intima was determined using the Image 45 pro analysis program.

Statistical analysis

Experiments were performed at least three times and data were presented as the mean ± standard deviation (SD). Statistical analysis was performed with SPSS version 11.0 (SPSS Inc, Chicago, IL, USA). The unpaired t-test was used for comparisons between two groups and one-way ANOVA between multiple groups. A value of p < 0.05 was considered statistically significant.

Results

As shown in Table 1, compared with group C, the number of peripheral CD34+CXCR4+ cells in groups S and A was significantly increased immediately after intimal injury (S/A) (p < 0.01), followed by a gradual decline to baseline seven days after injury. In group A, the number of CD34+CXCR4+ cells was increased within 24 hours after intraperitoneal administration of AMD3100, followed by a rapid decline (p < 0.05), which may have been related to stimulation of the bone marrow by AMD3100. As shown in Table 2, the plasma level of SDF-1α after intimal injury was markedly increased and reached a maximum one day after injury (p < 0.01), followed by a rapid decrease to baseline on day seven. The administration of AMD3100 did not affect the plasma level of SDF-1α.

Total RNA was extracted from the injured common carotid...
arteries for detection of SDF-1α and CXCR4 mRNA with RT-PCR. Results showed the expression of SDF-1α mRNA in groups S and A was detectable immediately after injury, followed by a gradual decrease, but it was undetectable one month later. Administration of a CXCR4 antagonist seemed to have no effect on expression of SDF-1α mRNA (Fig. 1).

However, the expression of CXCR4 mRNA was detected four days after injury and continued for one month (Fig. 1). AMD3100 is an antagonist of CXCR4, which inhibits the interaction between SDF-1α and CXCR4, so the expression of CXCR4 mRNA was decreased in group A compared with that in group S (Fig. 2).

Western blot assay was performed to evaluate the expression of CXCR4 protein in the arteries. As shown in Fig. 3, the expression of CXCR4 protein was reduced immediately after injury, followed by a gradual decrease, but it was undetectable one month later. The expression of CXCR4 protein was reduced immediately after injury, followed by a gradual decrease, but it was undetectable one month later. The degree of intimal hyperplasia in group A was lower than in group S after one month (p < 0.05), and the difference between the two groups remained after three months (p < 0.05) (Table 3, Fig. 5).

Discussion
Coronary heart disease is one of the commonest causes of death. Since the use of PTCA in the treatment of coronary atherosclerosis, numerous patients with coronary heart disease have benefited from PCI, but the relatively high incidence of restenosis after PCI has been a major problem, despite the short-term success of this technique. So far, no effective treatment strategies have been successful in preventing restenosis after PCI. Studies have demonstrated that excessive proliferation of the neo-intima plays a critical role in restenosis. Therefore, appropriate inhibition of neo-intimal proliferation may be a promising strategy in the prevention of restenosis.

Proliferation of stem/progenitor cells occurs following tissue ischaemia or damage such as acute myocardial infarction. Many cells may migrate into the ischaemic region to participate in tissue repair and angiogenesis. So far, the mechanisms underlying the progenitor cell migration to the injured site are poorly understood. Recently, stem or progenitor cell therapy has been a treatment choice for the improvement of neovascularisation and left ventricular function following acute myocardial infarction. Various types of stem cells and progenitor cells have been successfully used in the experimental acute myocardial infarc-
We speculated that, besides stem/progenitor cells being involved in intimal repair, their abnormal implantation in the neo-intima may be the main cause of vascular restenosis, in which SDF-1, an important chemokine, plays a crucial role.

SDF-1, a small (~8–14 kDa) pro-inflammatory chemokine, is the main regulator of cell trafficking and adhesion. It binds and activates a subset of G protein-coupled receptors with seven transmembrane domains called CXCR4, which are expressed on the surface of target cells. Although CXCR7 is also the receptor of SDF-1, CXCR4 is the only receptor known to have a definite physical role in cell trafficking, and SDF-1 is the only physical ligand for CXCR4.

The rat SDF-1 gene encodes three splice variants: α, β and γ. SDF-1α is mainly observed in the liver, spleen, kidney, heart, brain and lung and SDF-1β in the liver, kidney, spleen and thymus. SDF-1γ is predominately noted in the heart, lung, brain and peripheral nerve system. Although the levels of SDF-1γ in the heart are high, significant changes in the expression of

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**Fig. 4.** A: In group S, the positive staining for CXCR4 was detectable one day after injury and lasted for at least one month. Discontinuous brown spots were shown at the injured area. With time, the spots gradually fused to form a brown line with a slowly enhancing intensity. B: In group A, the positive staining was observed four days after injury and was sustained for one month, with a weak intensity when compared with that in group S.
SDF-1α were found after cardiac injury.

The interaction between SDF-1α and CXCR4 plays a crucial role in immune defense and SDF-1α is up-regulated by numerous stimuli including antigens, polyclonal stimulants, cell irritants and cytokines.14,15 In the present study, results show plasma levels of SDF-1α were significantly increased after injury, followed by a decrease to baseline four days after injury.

The number of CD34+CXCR4+ cells was markedly increased immediately after injury, followed by a gradual decline. The administration with AMD3100 increased the number of CD34+CXCR4+ cells, but no statistical significance was observed in the number of CD34+CXCR4+ cells and plasma levels of SDF-1α.

Therefore, the increased plasma levels of SDF-1α and the elevated numbers of CD34+CXCR4+ cells after arterial injury may have been related to neo-intimal repair.

Numerous studies have found that SDF-1α not only stimulated haematopoietic stem cell engraftment but also recruited progenitor cells to the ischaemic region by interacting with CXCR4.16 After heart surgery or acute myocardial infarction, the expression of SDF-1α in the peri-injury zone was up-regulated, with profoundly increased numbers of stem/progenitor cells in the injured region.17,18

Inhibition of the SDF-1α/CXCR4 axis could partially block the recruiting of progenitor/stem cells to the injured tissues or peri-infarct myocardium.19 Likewise, inhibition of CXCR4 with the anti-CXCR4-antibody could also significantly reduce SDF-1α-induced adhesion of EPC to mature endothelial cells, the in vitro migration of EPC,17 and the in vivo recruitment of myeloid EPC to the ischaemic limb in a hind limb ischaemia model.20 Moreover, over-expression of SDF-1α enhanced the homing and incorporation of stem cells into ischaemic tissues.21,22 These findings support the notion that SDF-1α played a crucial role in the recruitment of circulating or intravenously infused cells.

In this study, our results showed the expression of SDF-1α mRNA was elevated immediately after injury and reached a maximum four days later, followed by a decrease to baseline seven days after injury. However, the expression of CXCR4 mRNA was increased four days after injury and reached a maximum seven days after injury, followed by a gradual decrease to baseline.

Immuno-histochemistry indicated CXCR4-positive staining was found in the neo-intima (Fig. 4A, B) of the common carotid...
artery after injury, followed by a gradual increase in staining intensity. After the administration of AMD3100, an antagonist against the interaction between CXCR4 and SDF-1α, the expression of CXCR4 mRNA and protein was significantly decreased. The intensity of CXCR4-positive staining was also less and the time to when CXCR4-positive staining occurred was delayed. After three months, the two groups were no longer showing CXCR4-positive staining, which may have been because the interaction between SDF-1α and CXCR4 occurred only in the early injury period.

Carotid artery hyperplasia was observed with H&E staining after balloon injury. We found that compared with the control group after one and three months, hyperplasia of the neo-intima had occurred in groups S and A (p < 0.05 and 0.01). The degree of intimal hyperplasia in group A was lower than in group S after one month (p < 0.05), and the difference between the two groups remained after three months (p < 0.05).

We therefore postulated that the expression of SDF-1α mRNA in the left common carotid artery was increased after injury, leading to an elevated plasma level of SDF-1α, which exerted chemotactic effects on the migration of CD34+CXCR4+ cells into the injured tissues as a result of the concentration gradient of SDF-1α. The deposited cells then took part in the neo-intimal repair or even caused restenosis.

The results demonstrated that intimal repair was closely associated with the interaction between SDF-1α and its receptor CXCR4. The elevated plasma levels of SDF-1α after injury recruited peripheral CD34+CXCR4+ cells into the damaged endothelium, thus leading to formation of the neo-intima. In the injured artery, the expression of CXCR4 mRNA and protein, as well as the CXCR4-positive staining in the neo-intima was observed to be increased.

With an antagonist (AMD3100) against the interaction between SDF-1α and CXCR4, the expression of CXCR4 mRNA and protein, as well as the CXCR4-positive staining was decreased. H&E staining also showed that after the intervention of AMD3100, the rat carotid artery neo-intimal thickness was still more than the normal control group, but thinner than in the non-intervention group. Therefore, we speculated that the SDF-1α/CXCR4 axis played an important role in neo-intimal proliferation.

Conclusion
In this study, we investigated short- and long-term changes in the SDF-1α/CXCR4 axis in the rat common carotid artery neo-intima after injury. More studies are required to explore the long-term changes in neo-intimal proliferation after administration of AMD3100, and the specific signalling pathway involved in the SDF-1α/CXCR4 axis. This may provide useful information for prevention of restenosis after PTCA or PCI.

References
The effect of mebudipine on cardiac function and activity of the myocardial nitric oxide system in ischaemia–reperfusion injury in rats

R GHYASI, M MOHAMMADI, R BADALZADEH, B RASHIDI, G SEPEHRI

Abstract

Objectives: Previous studies have suggested that failure of the synthesis of nitric oxide is involved in the pathophysiology of myocardial ischaemia–reperfusion injury. In this study, we investigated the effect of mebudipine, a new dihydropyridine calcium channel blocker, on cardiac function and activity of the myocardial nitric oxide system in ischaemia–reperfusion injury in isolated rat hearts.

Methods: Forty male Wistar rats (250–300 g) were divided into four groups (n = 10): sham, control, vehicle and drug groups. The animals were anesthetised with sodium pentobarbital (6 mg/kg intraperitoneal). The hearts were quickly removed, mounted on a Longendorff apparatus and perfused with Krebs-Henseleit solution under constant pressure at 37°C. After 20 min stabilisation period, the ischaemic groups received 30 min global ischaemia and 120 min reperfusion. For the drug and vehicle groups, before ischaemia the hearts were perfused with mebudipine (10⁻³ µM) or ethanol-enriched solution (0.01%) for 25 min, respectively. Myocardial function, and creatine kinase, lactate dehydrogenase and total nitric oxide metabolite (nitrite and nitrate) levels were analysed.

Results: Cardiac functions had recovered significantly in the mebudipine group (p < 0.01). Furthermore, mebudipine remarkably reduced the levels of lactate dehydrogenase and creatine kinase in the coronary effluent and increased myocardial nitric oxide metabolite levels compared with the control group.

Conclusion: Our results indicate that mebudipine reduced the intensity of myocardial ischaemia–reperfusion injury, and that activation of the myocardial nitric oxide system played an important role in this regard.

Keywords: ischaemia, nitric oxide, reperfusion, mebudipine, isolated heart

Early reperfusion is an absolute prerequisite for the survival of ischaemic myocardium. However, reperfusion has been considered a double-edged sword because reperfusion itself may lead to additional accelerated myocardial injury beyond that generated by ischaemia alone. This results in a spectrum of reperfusion-associated pathologies, collectively called reperfusion injury.1 The underlying pathophysiological mechanisms of ischaemia–reperfusion have not been fully elucidated. It has been suggested that an overproduction of oxygen-derived free radicals2 and intracellular calcium overload during the first minutes of reflow might be involved.3 However, oxygen-derived free radicals and hypercontracture due to calcium overload are not the only candidates responsible for reperfusion injury. Other factors of importance in the pathogenesis of reperfusion injury include platelet- and neutrophil-mediated injury, the renin–angiotensin system and the complement activation.2

It is known that nitric oxide (NO) is involved in the regulation of myocardial contractility and contributes to myocardial protection in ischaemic pre- and postconditioning.4 NO plays multiple roles in the cardiovascular system, mediating a number of physiological and pathophysiological processes. In smooth muscle cells, NO activates guanylate cyclase by a hem-dependent mechanism, resulting in an increased concentration of guanosine 3',5'-cyclic monophosphate (cGMP), which leads to a decreased intracellular concentration of Ca²⁺ and subsequent relaxation of the vessels.4

Reduced basal availability of NO and impairment of endothelial NO-dependent mechanisms due to dysfunction of the normally protective endothelium may be involved in the pathogenesis of several cardiovascular diseases, including atherosclerosis, hypertension, heart failure, coronary heart disease, arterial thrombotic disorders and stroke.5 In cardiomyocytes, the NO/cGMP pathway is involved in the inhibition of Ca²⁺ influx by cGMP-dependent phosphorylation of L-type Ca²⁺ channels,5 antagonism of the effects of β-adrenergic stimulation, and decrease in myocardial contractility and heart rate, as well as in reduction in myocardial oxygen consumption and opening of the sarcolemmal K⁺ channels. Reduced Ca²⁺ current may alleviate Ca²⁺ overload associated with acute myocardial ischaemia as one of the major mechanisms of ischaemic injury.1

Ca²⁺ channel antagonists are used for a variety of diseases, including heart and coronary disease and have become one of the standard first choices of drugs for essential hypertension. They
have also become established as therapeutic drugs for angina pectoris, together with β-adrenoceptor antagonists and nitrates.\(^1\) Ca\(^{2+}\) channel antagonists have several features that may relate to myocardial protection during ischaemia and reperfusion. The main effect is reduction in oxygen demand due to a decrease in heart rate and myocardial contractility.\(^1\) Interference with neutrophil mobilisation and activation may protect against the production of free radicals and the release of proteolytic enzymes.\(^1\) A direct protective effect may also be produced by interference with ischaemia-induced intracellular Ca\(^{2+}\) overload.\(^10,11\)

Dihydropyridine Ca\(^{2+}\) channel blockers were reported to protect the endothelial function of renal resistance arteries in hypertensive rats\(^2\) and the mesenteric arteries of rats in circulatory shock.\(^13\) Endothelial function is important for the preservation of the organ function against ischaemic or hypertensive stress.\(^14,15\) Many studies have reported that Ca\(^{2+}\) channel blockers such as amlodipine, nifedipine and benidipine increase NO production.\(^16,17\)

Mebudipine is a new calcium channel blocker with a dihydropyridine structure that has a comparable pharmacological effect while offering some advantages, such as a longer biological half-life to reach peak effect and vasoselectivity.\(^18,19\) There are no reports on the cardioprotective activity of mebudipine and it seems that it may attenuate endothelial dysfunction and increase the production of NO in ischaemic hearts. Therefore, this study was designed to examine the effect of mebudipine on cardiac function and the activity of the myocardial nitric oxide system following ischaemia–reperfusion injury in isolated rat hearts.

**Methods**

Forty male Wistar rats (250–300 g) were obtained from the laboratory animal house at Tabriz University of Medical Sciences. They were housed in an animal room at 22–24ºC and given free access to commercial rat chow and tap water. All the experimental procedures used, as well as rat care and handling were in accordance with guidelines provided by the Experimental Animal Laboratory and approved by the Animal Care and Ethics Committee of the Tabriz University of Medical Sciences. The animals were randomly divided into four groups (n = 10): a sham group (without ischaemia), control group (ischaemia without drug), drug group (ischaemia with drug) and vehicle group (ischaemia with ethanol: 0.01%).

**Longendorff protocol**

All animals were anaesthetised intraperitoneally with sodium pentobarbital (60 mg/kg) and heparinised with sodium heparin (300 IU intraperitoneally). After opening the chest cavity, the hearts were quickly excised and immersed in ice-cold Krebs-Henseliet (K-H) solution. Then the aortae were cannulated and filled with normal saline to produce a left ventricular end-diastolic pressure (LVEDP) of 5–10 mmHg at baseline, and the balloon volume was maintained constant throughout the experiment. The LVEDP, LV peak systolic pressure (LVSP) and the peak rates of positive and negative changes in LV pressure (±dp/dt) were measured with a Power Lab System (ADInstruments, Australia). The LV developed pressure (LVEDP) was calculated as follows:

\[
\text{LVEDP} = \text{LVSP} – \text{LVEDP} \text{ (mmHg)}.
\]

The haemodynamic data were recorded continuously on a computer using a Powerlab system. The heart rate (HR) was calculated using a bioelectric amplifier (ADInstruments, Australia) from the electrocardiogram that recorded via two electrodes attached to the apex and the right ventricle of the heart and one reference electrode.

**Ischaemia–reperfusion protocols**

The hearts were allowed to equilibrate for 20 min prior to each study. For the ischaemic control group, the hearts were perfused with the K-H solution for 20 min, and then global ischaemia was conducted by interrupting the aortic flow for 30 min, followed by reperfusion with K-H solution for up to 120 min. In the drug and vehicle groups, before ischaemia, the hearts were perfused with mebudipine (0.1 nm) or an ethanol-enriched solution (0.01%) for 25 min, respectively.

Several experimental studies have proven Ca antagonists to be cardioprotective when applied in a concentration that does not produce a negative inotropic or chronotropic effect.\(^20-22\) Mebudipine was therefore applied throughout the study at a concentration of 0.1 nm, which did not cause a negative inotropic or chronotropic effect.

**Biochemical measurements**

During the first 10 min of the reperfusion period, the coronary effluent was sampled for lactate dehydrogenase (LDH) and myocardial creatin kinase (CK-MB) measurement. The concentration of LDH and CK in the coronary effluent was measured using related kits (Parsazmoon, Iran) and expressed as units per litre. NO production (nmol/g protein) in the heart homogenates was determined by measuring the total nitrite and nitrate concentration (NO metabolites), using the Griess method.\(^23\)

Deproteinised heart homogenates were used for determination of NO metabolite concentrations (NO\(_x\)). Briefly, 100 μl of supernatant was applied to a microtitre plate well; 100 μl vanadium (III) chloride (8 mg/ml) was added to each well (for reduction of nitrate to nitrite) and this was followed by the addition of the Griess reagents, 50 μl sulfanilamide (2%) and 50 μl N-(1-naphthyl) ethylenediamine dihydrochloride (0.1%). After 30 min incubation at 37ºC, the absorbance was read at 540 nm using an ELISA reader (Lab System, Fanland). The concentration of NO\(_x\) in the heart homogenates was determined from standard linear curves established from 0–150 μmol/l sodium nitrite.

**Statistical analyses**

All numerical data are expressed as mean ± SEM. Data on cardiac function were subjected to a two-way analysis of vari-
Fig. 1. Effect of ischaemia–reperfusion on LDH and CK-MB levels in three groups of rats. **p < 0.01 compared with control group.

Fig. 2. Effect of ischaemia–reperfusion on NO levels in three groups of rats. *p < 0.05 compared with control group.

during reperfusion.

Previous studies indicated that mebudipine improved characteristics such as tissue selectivity and significant negative chronotropic effects, and had no noticeable negative effect on the contractility of the heart, but there have been no studies on the cardioprotective effects of mebudipine against ischaemia–reperfusion injury. This is the first report that a dihydropyridine calcium channel blocker, mebudipine, has the capability of increasing cardiac NO levels in ischaemic hearts, which attenuates the severity of the myocardial ischaemia–reperfusion injury.

It was reported that the other members of this group of drugs, amiodipine, nifedipine and bendipine have cardioprotective effects against myocardial ischaemia–reperfusion injury via

Fig. 3. Effect of reperfusion on LV function in three groups of rats. *p < 0.05 compared with control group.

Results

There were no significant differences in baseline values between all groups (Table 1). In the isolated hearts, when experimental ischaemia was produced by the cessation of coronary perfusion, LVDP and HR rapidly decreased and stopped. A progressive increase in LVEDP was noted in all groups. During the reperfusion periods (10, 30 and 60 min), mebudipine attenuated the increase in LVEDP in the drug-treated group compared with the control group (p < 0.01). The administration of mebudipine before ischaemia caused cardiac function to return during the reperfusion period. Mebudipine significantly increased the LVDP and + dp/dt (time = 10, 30 min) (p < 0.05), and increased the coronary flow and – dp/dt notably (Table 1).

LDH and CK release in the coronary effluent, as an indicator of cell damage and tissue injury, decreased in the drug-treated group compared with the control group (p < 0.01) (Fig. 2).

Discussion

We examined the influence of mebudipine on myocardial injury resulting from global ischaemia and reperfusion in isolated rat hearts, determined mechanically and biochemically. The findings of this study were that exposure to mebudipine 25 minutes before global ischaemia facilitated the recovery of contractility, decreased LDH and CK levels (indicators of cardiac cellular injury during reperfusion), and attenuated the increase in LVEDP

Table 1. Levels of HR, LVEDP, LVDP, + dp/dt and CF in Three Groups of Rats

<table>
<thead>
<tr>
<th>Parameter/group</th>
<th>Stabilisation</th>
<th>Reperfusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR (pulse/min)</td>
<td>10 min</td>
<td>30 min</td>
</tr>
<tr>
<td>Control</td>
<td>284 ± 6.7</td>
<td>204 ± 220</td>
</tr>
<tr>
<td>Vehicle</td>
<td>275 ± 8.2</td>
<td>191 ± 216</td>
</tr>
<tr>
<td>Drug</td>
<td>261 ± 13.4</td>
<td>173 ± 205</td>
</tr>
<tr>
<td>LVEDP (mmHg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>7.4 ± 0.3</td>
<td>2.5 ± 29.3</td>
</tr>
<tr>
<td>Vehicle</td>
<td>7 ± 0.3</td>
<td>3.1 ± 33.3</td>
</tr>
<tr>
<td>Drug</td>
<td>6.7 ± 0.4</td>
<td>1.2** ± 15.5</td>
</tr>
<tr>
<td>LVDP (mmHg/s)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>9.8 ± 5.6</td>
<td>42 ± 3.8</td>
</tr>
<tr>
<td>Vehicle</td>
<td>93 ± 7.1</td>
<td>46 ± 5.1</td>
</tr>
<tr>
<td>Drug</td>
<td>81.6 ± 5.6</td>
<td>69 ± 8**</td>
</tr>
<tr>
<td>+ dp/dt (mmHg/s)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>3388 ± 310</td>
<td>1494 ± 468</td>
</tr>
<tr>
<td>Vehicle</td>
<td>3229 ± 270</td>
<td>1522 ± 259</td>
</tr>
<tr>
<td>Drug</td>
<td>3066 ± 336</td>
<td>439** ± 2755</td>
</tr>
<tr>
<td>– dp/dt (mmHg/s)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>1999 ± 217</td>
<td>127 ± 974</td>
</tr>
<tr>
<td>Vehicle</td>
<td>1909 ± 264</td>
<td>248 ± 1050</td>
</tr>
<tr>
<td>Drug</td>
<td>1863 ± 259</td>
<td>1563 ± 196</td>
</tr>
<tr>
<td>CF (ml/min)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>9.8 ± 0.54</td>
<td>7.5 ± 0.18</td>
</tr>
<tr>
<td>Vehicle</td>
<td>9.5 ± 0.27</td>
<td>6.2 ± 0.44</td>
</tr>
<tr>
<td>Drug</td>
<td>10.1 ± 0.35</td>
<td>8.2 ± 0.88</td>
</tr>
</tbody>
</table>

Results are expressed as mean ± SEM. for each group (n = 10). *p < 0.05 compared with control group and "p < 0.01 compared with control group.
NO-dependent mechanisms. Therefore the enhancing effects of NO may not be attributable to the mebupidine, although its capability to increase NO levels due to calcium channel antagonists may be different.

NO is not only produced by endothelial cells, but also by cardiomyocytes, erythrocytes, platelets, leukocytes and fibroblasts in the heart. Several stimuli facilitate NO production. Acetylcholine, bradykinin, purine and norepinephrine stimulate NO synthase. NO is believed to attenuate the severity of myocardial ischemia via several mechanisms. NO increases coronary flow, and reduces leukocyte and platelet aggregation.

In our study, the enhancement of coronary flow was notable but not significant, possibly due to the concentration of mebupidine that we used. Furthermore, other known physiological effects of NO, such as reduction of ventricular pressure and augmentation of collateral coronary flow may have contributed to the protective effect of mebupidine against ischemia–reperfusion injury.

In addition, NO may have regulated oxidant-induced alterations in the intracellular Ca2+ concentration that caused cytoskeleton derangement, changes in cell shape and ultimately cell necrosis. In the first minutes of reperfusion, the myocardium may be damaged by the development of contracture (a sustained shortening and stiffening of the myocardium), causing mechanical stiffness, tissue necrosis and the stone-heart phenomenon. Reperfusion-induced contracture can have two different causes, Ca2+ overload and depletion of ATP. Because the volume of the balloon was kept constant during ischemia and reperfusion in this preparation, an increase in LVEDP reflected an increase in left ventricular wall stiffness or contracture.

Mebupidine significantly attenuated the increase in LVEDP during reperfusion, therefore this drug could decrease cell damage and tissue necrosis. Since this study revealed that mebupidine increased NO levels and reduced LDH and CK release, mebupidine may be effective as a calcium channel antagonist in ischaemic hearts.

Conclusion

The results of this study confirmed the protective effect of mebupidine against ischemia–reperfusion injury due to prevention of increased LVEDP, enhanced LVDP and the metabolites of NO, and decreased levels of LDH and CK. Therefore, it may be beneficial for reducing ischemia–reperfusion injuries.

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References


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Analysis of omega-3 fatty acid content of South African fish oil supplements

MARETHA OPPERMANN, DE WET MARAIS, AJ SPINNLER BENADE

Abstract

Introduction: Substantial evidence describes the protective effects of marine-derived omega-3 (n-3) polyunsaturated fatty acids (PUFA) on cardiovascular diseases as well as many other conditions. Numerous fatty acid preparations are marketed for supplementing the Western diet, which is low in n-3 fats. Since these preparations may vary in their n-3 PUFA content, we tested 45 commercially available products on the South African market for their fatty acid composition.

Method: Forty-five commercially available n-3 fatty acid supplements were analysed using gas–liquid chromatography to determine their fatty acid content.

Results: More than half of the n-3 supplements available on the South African market contained ≤ 89% of the claimed content of EPA and/or DHA as stated on the product labels. To meet ISSFAL’s recommendation of 500 mg EPA + DHA/day can cost consumers between R2 and R5 per person per day (R60 to R150 p/p/month). Regarding rancidity, the majority of capsules contained conjugated diene (CD) levels higher than that of vegetable oil obtained from opened containers (three months) used for domestic cooking purposes, despite the addition of vitamin E as antioxidant.

Conclusion: Since no formal regulatory structure for dietary supplements currently exists in South Africa, consumers depend on self-regulation within the nutraceutical industry for assurance of product quality, consistency, potency and purity. Our results indicate that more than half of the n-3 fatty acid supplements available on the South African market do not contain the claimed EPA and/or DHA contents as stated on product labels, and they contained CD levels higher than that in unused vegetable oils obtained from opened containers used for domestic cooking purposes.

Keywords: supplements, eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA), conjugated dienes (CD), fish oil

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During the past few years, evidence-based nutritional research has confirmed the importance of omega-3 (n-3) fatty acids in reducing the risk for cardiovascular disease (CVD). Recently, there has been increasing understanding of the essentiality of n-3 fatty acids in reducing cardiovascular disease (CVD). N-3 fatty acids possess a wide range of biological effects, including reducing inflammatory responses, lowering triglyceride levels, reducing risk of arrhythmias, a small dose-dependent hypotensive effect, anti-atherogenic effects and a reduction in platelet aggregation, all of which contribute to protection against CVD.

The n-3 fatty acids of particular concern for the prevention of CVD are eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). EPA and DHA are very-long-chain n-3 fatty acids. The ability of the body to manufacture them from the precursors is limited and to ensure adequate supply of these fatty acids, their dietary source is of vital importance. These fatty acids are predominantly found in fish and fish oils. Fatty fish such as herring, mackerel, tuna, salmon and trout are rich dietary sources of EPA and DHA.

Since solid and voluminous scientific backing for the health benefits of n-3 fatty acids exists, a high level of public awareness and acceptance of n-3 fatty acids is becoming more apparent. Considering the fact that it is not always possible to consume adequate amounts of n-3 fatty acids through the diet, the interest in n-3 fatty acid supplements has soared. The position of the American Dietetic Association on nutritional supplements is that supplements can help some individuals meet their nutrient needs when their diet is inadequate due to different circumstances, including being in an ‘at-risk’ life-stage group for a nutrient deficiency. Examples of such risk groups include the geriatric population, pregnant women, individuals with compromised nutritional status and those with a limited variety in food selection, which prevents achieving nutrient adequacy.

However, although research has shown beneficial effects with increased intakes in n-3 fatty acids, excess intakes can be just as harmful as a deficiency and therefore n-3 fatty acids should be supplemented with caution. Detrimental effects of excess intake of n-3 fatty acids in healthy populations include depression of the immune function, bleeding and increased risk of haemorrhagic stroke, as well as increased lipid peroxidation resulting in oxidative damage to various tissues. At this point in time there is not sufficient supporting data to establish an upper limit (UL) or safe intake of n-3 fatty acids, however, the FDA has ruled that intakes of up to 3 g/d of marine n-3 fatty acids are generally recognised as safe (GRAS) for inclusion in the diet.

Undesirable effects from consuming n-3 fatty acids have also been identified in a few selected populations. It has been suggested that diabetics or individuals with impaired glucose tolerance must use n-3 fatty acid supplements with caution since it might have detrimental effects on glucose homeostasis. Increased incidences of nosebleeds have also been reported in individuals with hypercholesterolaemia with n-3 fatty acid supplementation. Furthermore, simultaneous intake of n-3 fatty acids with medication such as aspirin and warfarin will excessively prolong bleeding times in individuals using anti-coagulants.
Recommendations regarding the daily intake of n-3 fatty acids vary between 400 and 1 000 mg EPA + DHA in the form of food or supplements. Nevertheless, it is still not known what the optimal daily intake of EPA and/or DHA should be and how these fatty acids affect the metabolism of 18-carbon fatty acids and longer n-6 and n-3 fatty acids, and whether this might result in any adverse health outcomes. Based on the available evidence, n-3 fatty acid supplements provided in the appropriate dose would be expected to confer health benefits, especially in individuals who do not eat fish.

To obtain these suggested daily intakes might be challenging for the consumer if only fatty fish is eaten, since ample amounts of about 220 to 240 g fatty fish (e.g. salmon) must be consumed weekly to reach a daily intake of 500 mg EPA + DHA. Therefore, fish oil preparations may be helpful to reach amounts of about 220 to 240 g fatty fish (e.g. salmon) must be consumed weekly to reach a daily intake of 500 mg EPA + DHA. Moreover, fish oil preparations rely on fish oil as a source of EPA and DHA, which and more controllable way of consuming n-3 fatty acids, all effective in most studies.18

In a recent study2 in Belgium, 15 food supplements formulated as soft capsules containing n-3 fatty acids were evaluated by desegregation, determination of peroxide values and assay of the n-3 fatty acid content. All the products contained purified fish oil rich in n-3 fatty acids, mainly EPA and DHA, and were available as triglycerides, ethyl esters or free fatty acids. Seven of the 15 food supplements deviated from one or more of the criteria with regard to the recommended peroxide value and the content of one or more of the fatty acids.

In an analysis of n-3 fatty acids in fish oil supplements conducted in Austria, nine supplements were analysed using capillary gas chromatography to determine the n-3 fatty acid content. In comparison with the manufacturer's information, four supplements did not differ significantly from the concentrations given, whereas four supplements contained substantially more EPA and DHA than stated on the label. One of the manufacturers did not declare the amount of n-3 fatty acids in the product. Regarding manufacturer's recommendations for daily intake, one of the supplements exceeded the amount recommended by healthcare organisations. Five of the nine supplements lacked more than 30% EPA and DHA to meet the American Heart Association’s recommendations. Additionally, two supplements failed to achieve the range of 0.5 to 1.8 g n-3 fish oil found to be effective in most studies.19

Currently, no similar existing data are available for n-3 fatty acid supplements offered on the South African market. Although n-3 fatty acids in the form of supplements appear to be the safer and more controllable way of consuming n-3 fatty acids, all preparations rely on fish oil as a source of EPA and DHA, which may show the same variability as the natural product these preparations are derived from. Additionally, South African consumers have little reason to doubt the package label claims on conventional medicinal products. What the optimal daily intake of EPA and/or DHA should be and how these fatty acids affect the metabolism of 18-carbon fatty acids and longer n-6 and n-3 fatty acids, and whether this might result in any adverse health outcomes. Based on the available evidence, n-3 fatty acid supplements provided in the appropriate dose would be expected to confer health benefits, especially in individuals who do not eat fish.

To obtain these suggested daily intakes might be challenging for the consumer if only fatty fish is eaten, since ample amounts of about 220 to 240 g fatty fish (e.g. salmon) must be consumed weekly to reach a daily intake of 500 mg EPA + DHA. Moreover, fish oil preparations rely on fish oil as a source of EPA and DHA, which and more controllable way of consuming n-3 fatty acids, all effective in most studies.18

The conjugated diene (CD) content of oils represents an early stage of oxidation (rancidity). The content of conjugated dienes in the 45 n-3 capsules were determined spectrophotometrically as described by Recknagel and Glende. Since no CD reference values were available for oils, the CD content of fresh, unopened sunflower, olive palm and canola oil were used against which to compare the supplements’ CD contents. The CD contents of sunflower, olive and canola oil were 4.28, 6.68 and 8.28 μM, respectively. The CD contents of sunflower, olive and canola oil of which half of the contents had already been used were 16.8, 18.2 and 18.7 μM, respectively.

The content of mercury in the 45 n-3 capsules was determined by atomic absorption spectroscopy according to the method of Aduna de Paz et al. Samples were digested with nitric acid (HNO₃) and hydrogen peroxide (H₂O₂) in a microwave oven (Milestone MLS-1200 MEGA, Milestone GmbH) equipped with a high-pressure rotor for six teflon vessels. Total mercury (Hg) was determined by cold vapour generation on a Thermom atomic absorption spectrophotometer (SOLAR M Series) coupled to a vapour generator (Thermo model VP100, Thermo Scientific), using SnCl₂ as the reductant. Standard quality-control procedures were adopted throughout. Spiked samples gave an average recovery of 94.1%.

A Varian model 3300 chromatograph was used and fitted with a BPX-70 fused silica capillary column (30 m × 0.32 mm i.d., 0.25-mm film thickness). The injector and flame ionisation detector was at 240 and 280°C, respectively. The column temperature was programmed from 160 to 220°C at a rate of 3°C per minute. A hydrogen column flow rate of 30 cm sec⁻¹ was used. The method of fatty acid extraction and methylation as...
described by Christie was slightly modified to suit our analytical requirements: 100 mg of sample was dissolved in 20 ml chloroform/methanol (2:1); 200 μl of this solution was then dried under a stream of nitrogen and 2 ml of a fresh solution of 5% sulphuric acid in methanol was added in glass-stoppered tubes and incubated in a water bath at 70°C for two hours. After cooling, 1 ml of distilled water and 2 ml of hexane were added to the sample and vortexed for one minute. The hexane phase was allowed to separate and was then transferred to a glass tube to be evaporated under a stream of nitrogen at 40°C.

The residue was then re-dissolved in 50 μl carbon disulphide (CS₂) and 1 μl was injected into the gas chromatograph. Heptadecanoic acid was used as an internal standard. Butylated hydroxy toluene was added as an antioxidant to all samples. The EPA and DHA content of the samples were quantified and expressed as a percentage of EPA and DHA of total fatty acid content.

One of the objectives of this research was to compare the EPA and DHA contents, as claimed by manufacturers on the supplement label, with the actual measured contents. An acceptable range between 90 and 110% of the manufacturers’ claimed content for EPA and DHA was proposed. Therefore, supplements containing ≤ 89% of the claimed EPA and/or DHA content were perceived as substandard supplements, while those containing more than 110% were considered to be excessive. The coefficient of variance (CV) for the analysis of EPA and DHA was 2%.

Results
Comparison with the manufacturers’ labelling information (Fig 1) showed that 56% (n = 25) and 51% (n = 23) of the supplements failed to meet the lowest range of 89% for EPA and DHA concentrations, respectively. Only 31% (n = 14) of the EPA and 36% (n = 16) of the DHA contents of supplements were within the acceptable range of 90 to 110%. Thirteen per cent (n = 6) of the preparations held EPA more than stated, while a similar number (13%; n = 6) of supplements had a higher DHA content than indicated.

Number of capsules and price to reach recommendations
Currently there are no South African daily dietary intake recommendations for n-3 fatty acids. However, manufacturers of n-3 fatty acid supplements suggest a daily dosage of capsules on their labels, with no indication of the basis on which these recommendations were made. For the purpose of this publication, the International Society for the Study of Fatty Acids and Lipids (ISSFAL) recommendation of 500 mg EPA + DHA per day for the prevention of cardiovascular disease was applied as guideline. Fig. 2 provides a summary of the number of capsules needed to reach ISSFAL’s recommendations while Fig. 3 highlights the cost (ZAR) to achieve a daily intake of 500 mg EPA + DHA/day.

Forty-two per cent (n = 19) of supplements were able to supply 500 mg EPA + DHA/day with the administration of two capsules per day, while only 7% (n = 3) of supplements could provide the recommended intake by consumption of one capsule per day. In 20% (n = 9) of the supplements, more than five capsules per day had to be ingested daily to meet the ISSFAL recommendation.

The majority (38%; n = 17) of the supplements varied between R2.01 and R5.00 per day to meet the ISSFAL recommendation of 500 mg EPA + DHA/day. This represents an amount of R60.30 to R150.00 per month. Less than a third (31%; n = 14) of the supplements were priced between R1.01 and R2.00 per day (R30.30 to R60.00 per month). Some supplements (4%; n = 1) even cost up to R30.00 to R40.00 per day to supply a 500-mg EPA + DHA dosage.
EPA to DHA ratio

Fish oils from different sources contain variable mixtures of EPA and DHA. Most commercially available fish oils contain a proportion of 2:1 EPA to DHA.22 Regarding the EPA to DHA ratio in South African n-3 fatty acid supplements, most of the studied supplements (40%; n = 18) had an EPA:DHA ratio of 1.51–2:0:1, while 36% (n = 16) of supplements had a 2.1–2.5:1 EPA:DHA ratio. Only a few (13%; n = 6) supplements had a higher DHA:EPA ratio (EPA:DHA ratio < 0.5) (see Table 1).

Conjugated dienes

The majority (73%; n = 33) of commercially available n-3 fatty acid supplements had a CD content higher than 21 μM. Only 27% (n = 12) of the n-3 fatty acid preparations contained a CD content of less than 20 μM, while barely any supplements (n = 4; 9%) contained a CD content comparable to fresh, unopened oils (see Fig. 4). These values were measured notwithstanding the presence of added vitamin E as an antioxidant.

Mercury contamination

Mercury was virtually absent from the oils in the supplements and was therefore not of any health concern in these samples.

Discussion

An extensive variety of n-3 fatty acid supplements are available to the South African consumer, however, our results have shown that supplements vary to a large extent in terms of claimed and measured EPA and/or DHA content, levels of fatty acid oxidation, EPA to DHA ratio, as well as numbers of capsules and price to meet international dietary recommendations. When comparing claimed to measured contents of EPA and DHA in South African n-3 fatty acid supplements, it is of concern that information appearing on almost two-thirds of these supplements’ labels was not a true reflection of the actual contents of the supplements. It was decided to compare supplements against an arbitrary 90 to 110% standard. In other words, supplements’ label information was considered as a truthful reflection of the measured content if the measured contents of EPA and/or DHA content analyses were between 10% less or 10% more, compared to the claimed content.

More than half of commercially available South African n-3 fatty acid supplements failed to attain 90% of the claimed contents of EPA or DHA or both, while approximately 15% of supplements contained more than 110% of the claimed contents of EPA or DHA or both. Since the typical Western diet is characterised by a low n-3 and very high n-6 fatty acid intake, many consumers rely on supplements to increase their daily n-3 intakes. Unfortunately, if unreliable information is published on labels, consumers are supplied with misleading information, leading to erroneous dosages, with subsequent consequences.

If a supplement contains less n-3 fatty acids than claimed, consumers waste their money without optimal improvement of their n-3 fatty acid status. In contrast, excess n-3 fatty acid intakes can be just as detrimental as a deficiency. Adverse effects of excess intake of n-3 fatty acids in healthy populations include suppression of the immune function, bleeding and increased risk of haemorrhagic stroke, as well as increased lipid peroxidation, resulting in oxidative damage to various tissues. Furthermore, simultaneous intake of n-3 fatty acids with medication such as aspirin and warfarin will excessively prolong bleeding times in individuals using anti-coagulants.7 The FDA has ruled that intakes of up to 3 g/d of marine n-3 fatty acids are generally recognised as safe (GRAS) for inclusion in the diet.7

Regarding the number of capsules needed to meet optimal n-3 fatty acid intakes, our results indicate that only a few supplements were able to provide the daily need in one capsule. Some supplements even required a dosage of more than five capsules to meet international recommendations. In addition to this, our analyses have shown that the majority of n-3 supplements on the South African market were priced between R2.01 and R5.00 per day to meet the ISSFAL recommendation of 500 mg EPA + DHA per day. This represents an amount of R60.30 to R150.00 per individual per month. To provide a family of four with the daily recommended intake of 500 mg EPA + DHA adds up to between R242.40 and R600.00 per family per month.

Since malnutrition, especially in poverty-stricken areas, is a major health problem in South Africa, it can be accepted that many people have either a marginal or deficient n-3 fatty acid status. Considering the current financial situation in South Africa, in combination with a large part of the South African population living in poverty, this amount is substantial in terms of monthly expenses for the average South African family. Hence, it is impossible for the average South African to consume an n-3 fatty acid supplement on a regular basis. Some supplements are even more expensive and can cost up to R1 060 per person per month to meet the recommended intake of 500 mg EPA + DHA per day.

The ratio of EPA to DHA in n-3 supplements has become an important point of discussion. Gorjão et al.22 reported that most commercially available fish oils present with a 2:1 ratio of EPA to DHA, while numerous cold-water oily fish sources

### Table 1. EPA to DHA Ratio in South African n-3 Fatty Acid Supplements

<table>
<thead>
<tr>
<th>Ranges</th>
<th>EPA:DHA ratio (n)</th>
<th>EPA:DHA ratio (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 0.5:1</td>
<td>6</td>
<td>13</td>
</tr>
<tr>
<td>1.5:1</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>1.51–2.0:1</td>
<td>18</td>
<td>40</td>
</tr>
<tr>
<td>2.1–2.5:1</td>
<td>16</td>
<td>36</td>
</tr>
<tr>
<td>2.51–3.0:1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>3.0–3.5:1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>&gt; 5:1</td>
<td>2</td>
<td>4</td>
</tr>
</tbody>
</table>
have higher DHA to EPA ratios. According to Kris-Etherton et al., the majority of commercially available n-3 fatty acid supplements in the United States provide 180 mg EPA and 120 mg DHA per capsule, representing a ratio of 1.5:1 EPA to DHA. EPA and DHA have different effects on various health aspects and under certain conditions it seems that a higher DHA to EPA ratio is preferable.

In the brain, DHA is the main n-3 polyunsaturated fatty acid, and the importance of DHA in neural and visual development and function, especially during pregnancy, lactation and infancy, is well documented. Additionally, deficits in DHA appear to contribute to inflammatory signalling, apoptosis and neuronal dysfunction in the progression of Alzheimer’s disease (AD), a common and progressive age-related neurological disorder unique to structures and processes of the human brain.

With regard to cell function, Gorjão et al. reported that some studies have shown that EPA and DHA have diverse effects on cell functions such as leukocyte functions. EPA and DHA also modulate the expression of genes in lymphocytes differently, and affect the activation of intracellular signalling pathways involved with lymphocyte proliferation in a different way, therefore necessitating different EPA to DHA ratios to ensure optimal function.

Mori and Woodman compiled a review on the independent effects of EPA and DHA on risk factors for cardiovascular disease in humans. From their report, it seems that EPA and DHA have diverse haemodynamic and anti-atherogenic effects. According to Mori and Woodman, both EPA and DHA are effective in reducing serum triglyceride levels but only DHA has the ability to increase high-density lipoprotein cholesterol (HDL-C). DHA also increases low-density lipoprotein (LDL) particle size, a potential anti-atherogenic effect. Neither EPA nor DHA show any effects on total cholesterol, while it appears that DHA is more effective in reducing blood pressure and heart rate when compared to EPA.

However, most clinical data available on the cardiovascular effects of n-3 fatty acids used a combination of EPA + DHA supplementation. Future research studies should therefore assess the individual effects of EPA and DHA in a variety of clinical settings and target populations, before decisions can be made on specific ratios of EPA to DHA in supplements and food fortified with either EPA or DHA.

Conjugated dienes (CDs) contain two or more double bonds and are formed during the oxidation process of unsaturated fatty acids to ensure a more stable radical. CDs are used to determine primary oxidation products and therefore provide an early indication of the levels of lipid oxidation. Although primary oxidation products such as CDs have no colour or flavour of their own, they can readily be decomposed to secondary products such as aldehydes, ketones and alcohols. These secondary oxidation products have distinctive flavours and contribute to the offensive taste of decomposed seafood and marine oils.

Considering the CD content of commercially available South African n-3 fatty acid supplements, it seems that the majority contain high amounts of primary oxidation products. No clear relationship could be established between the expiry dates and the CD content of the n-3 supplements. These results therefore suggest that a considerable variation exists in the quality of the fish oil present in n-3 capsules in South Africa. This indicates that the oils present in many of the supplements are in the first stages of rancidity and hence negatively influence the quality of the product that consumers buy.

An additional health concern related to fish and fish oil supplements is that some species of fish may contain considerable levels of heavy metals such as methyl mercury. Methyl mercury may be present at low levels in fresh waters and oceans but tends to concentrate in the aquatic food chain such that levels are generally highest in older, larger, predatory fish and marine mammals. Fish and seafood are a major source of human exposure to methyl mercury.

Methyl mercury has a relatively long half-life in human tissue and can accumulate in individuals who consume contaminated fish and fish oils on a regular basis. Skinning and trimming is usually recommended to reduce exposure to contaminants but because methyl mercury is distributed throughout the muscle, skinning and trimming does not significantly reduce mercury concentrations in fillets. Pregnant and lactating women as well as children are generally advised against the consumption of shark, swordfish, king mackerel and tilefish, since these species may contain higher levels of mercury. Our analysis has shown that mercury was virtually absent in the oils present in the South African samples and it is therefore not of any health concern.

It is undoubtedly the responsibility of manufacturers to provide accurate information on supplement labels to protect the consumer against misleading health and nutrient claims, to ensure the safety of the consumer and to guarantee a high-quality, consistent product. However, in South Africa this does not seem to be the case.

Possible reasons for substandard supplements on the South African market may include: poor quality of imported fish oil, seasonal differences in EPA and/or DHA concentrations of imported fish oils, lack of proper labelling legislation of food supplements, inappropriate handling of fish oil when harvested, improper storage conditions of both fish oil and supplements, oxidation of fatty acids, ineffective quality assurance by supplement manufacturers, and infrequent or poor batch-control analyses. If these issues are not addressed and legislation on food supplements is not enforced, South African consumers will have to deal with substandard dietary supplements.

Conclusion

More than half of the n-3 supplements available on the South African market contained less than the amount of EPA and/or DHA content as claimed on the labels of the products, which has considerable cost implications for the consumer. Early indicators of rancidity in the majority of capsules suggest a wide variation in the quality of the marine oils present in the n-3 capsules available on the South African market. This is despite the addition of vitamin E as antioxidant. South African n-3 fatty acid supplements appear to be virtually free of methyl mercury.

We thank Mr Francois Wewers from the Department of Chemistry, CPUT for the determination of the mercury content of the fish oil capsules.

References

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Potentially increasing rates of hypertension in women of childbearing age and during pregnancy – be prepared!

J MOODLEY

Abstract
The incidence of hypertension in young women is likely to increase in the near future because of the rising rates of the metabolic syndrome, obesity and dyslipidaemia worldwide. Consequently, more women will be on antihypertensive agents, which have the potential for teratogenicity. It is also likely that the increasing number of young women with essential hypertension who become pregnant will develop pregnancy-specific disorders such as pre-eclampsia. Health professionals should be aware of the effects of hypertension in women during the childbearing years, as well as the impact of pre-eclampsia on cardiovascular disease in later life. Pre-conception counselling skills, and knowledge on the use of antihypertensives and the changes that occur during pregnancy should be added to the clinical armamentarium of all health professionals.

Keywords: pregnancy hypertension, childbearing years, antihypertensive medication

Hypertensive disorders are the commonest medical complications occurring in pregnancy. They occur in approximately 6–8% of all pregnancies in the USA and cover a spectrum of disorders, such as chronic hypertension, gestational hypertension and pre-eclampsia/eclampsia syndrome. In South Africa, rates of hypertensive disorders in pregnancy are higher. A community-based study found a 12% incidence of hypertensive disorders in pregnancy in KwaZulu-Natal, while a tertiary facility-based study reported a rate of prevalence of 18%.

Of recent concern is the increasing prevalence worldwide of obesity and the metabolic syndrome. Pregnant women who develop pre-eclampsia de novo share many of the risk features of the metabolic syndrome, namely, dyslipidaemia, obesity and insulin insensitivity. Therefore, increasing numbers of women could develop hypertension in their childbearing years and during pregnancy.

An increase in the numbers of young women presenting with hypertension would create challenges for general medical practitioners, obstetricians and specialist physicians. Firstly, significant hypertension requires investigation for an underlying cause. Secondly, the selection of antihypertensive agents for the treatment of essential hypertension in women of childbearing age poses challenges, as most antihypertensive medications are potentially teratogenic. Thirdly, several well-defined clinical hypertensive conditions, such as pre-eclampsia, are associated with high rates of maternal and neonatal morbidity and mortality. Lastly, hypertensive pregnancy disorders were traditionally not considered to have any long-term deleterious effects on cardiovascular health. However, recent studies have shown that pregnancy-specific hypertension is a risk factor for cardiovascular health later in life.

Intensive counselling on the long-term impact of hypertensive disorders in pregnancy, the potential teratogenic effects of antihypertensive agents, appropriate diagnosis of pregnancy-specific hypertensive conditions and timely interventions therefore require an interdisciplinary approach if complications arising from these conditions are to be minimised.

Treatment of essential hypertension in women of childbearing age
Although the Joint National Committee (JNC7) definition of hypertension and the treatment goals do not vary according to age and gender, the use of antihypertensive drugs in women of childbearing age and during pregnancy should be carefully considered in respect of their teratogenic potential. It is well established that angiotensin converting enzymes and receptor blockers have similar foetal effects in that they are associated with foetal renal agenesis, especially if used in the first trimester. However, several other antihypertensive agents seem to carry minimal teratogenic risks to the foetus (Table 1).

Women of childbearing age with class I hypertension usually do not require antihypertensive medications. Successful lifestyle modifications and exercise in this group have been reported to demonstrate better blood pressure control. Furthermore, essential hypertension is independently associated with pre-eclampsia, and antihypertensive therapy in this group does not prevent the development of pre-eclampsia/eclampsia.

Normal haemodynamic changes in pregnancy
Physiological changes in pregnancy may mimic signs of early congestive cardiac failure, and all health professionals should be aware of this. Briefly, changes in the cardiovascular system begin early in pregnancy, reaching a maximum at 28 weeks’ gestation. Within the first 12 weeks of pregnancy, the total intravascular
plasma volume increases by 30–40%. Red blood cell mass increases by approximately 20%, but with the increased volume there is a relative decrease in the haematocrit.

The cardiac output increases on average by approximately 35%, commencing early in the first trimester, reaching a peak at 14 to 16 weeks and remaining at a plateau until labour. In labour, cardiac output increases moderately with each contraction and more appreciably with each expulsive effort in the second stage of labour. Most of the increase in cardiac output falls dramatically very soon after delivery (Fig. 1).

The increase in cardiac output in pregnancy is the result of an increase in pulse rate and stroke volume. The heart rate increases on average by 15 to 20 beats per minute and the stroke volume by 5–10 ml. Cardiac output is also influenced by maternal position. In the supine position (the patient lying on her back), venous return is reduced owing to pressure exerted by the pregnant uterus on the inferior vena cava. This reduced return leads to reduced output and hypotension (supine hypotension syndrome). This phenomenon is most often seen in late pregnancy.

Arterial blood pressure (Fig. 2)
In the lateral recumbent position, the blood pressure is higher in the upper arm than the lower (10–12 mmHg). While sitting, the blood pressure is slightly higher than in the supine position. Peripheral vascular resistance decreases during pregnancy due to the relaxing effect of progesterone on the smooth muscles. The subsequent decrease in blood pressure reaches a nadir in the second trimester compared with the early third trimester – the well-known drop in blood pressure.

The average decrease in systolic blood pressure is 5–10 mmHg and the decrease in diastolic is 10–15 mmHg. If this decrease fails to occur, it is reported that such women are more likely to develop hypertension in the third trimester of pregnancy.

**Definition of hypertension in pregnancy**
Hypertension in pregnancy is defined as systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg (Korotkoff 5). It should be noted that because elevations of both systolic and diastolic blood pressure have been associated with adverse maternal and foetal outcomes, both are important. Also, detecting a rise in blood pressure from ‘booking’ or pre-concep-

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**TABLE 1. ANTIHYPERTENSIVE DRUGS FOR USE DURING PREGNANCY**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Route</th>
<th>Dose</th>
<th>Time</th>
<th>Action</th>
<th>Side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methyldopa</td>
<td>po</td>
<td>0.25–1.5 g twice/day</td>
<td>3–5 days</td>
<td>False neurotransmitter</td>
<td>Orthostasis, sleepiness, depression</td>
</tr>
<tr>
<td>Labetalol</td>
<td>po</td>
<td>200–1200 mg/d two or three times/day in divided doses</td>
<td>2–4 h acte within 5 min</td>
<td>Non-selective β-blockade</td>
<td>Tremulousness, headache</td>
</tr>
<tr>
<td>Nifedipine</td>
<td>po</td>
<td>30–120 mg/day</td>
<td>30 min</td>
<td>Calcium channel blocker</td>
<td>Oedema, orthostasis, dizziness</td>
</tr>
<tr>
<td>Monohydradrazine</td>
<td>po</td>
<td>50–300 mg/d two or three times/day</td>
<td>1–2 h/20–30 min</td>
<td>Direct vasodilator</td>
<td>Lupus-like syndrome with chronic use</td>
</tr>
<tr>
<td>Dihydradazine</td>
<td>iv</td>
<td>10 mg every 2 h as needed</td>
<td>5 min</td>
<td>Direct vasodilator</td>
<td>Lupus-like syndrome with chronic use</td>
</tr>
<tr>
<td></td>
<td>po</td>
<td>12.5–25 mg daily</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hydrochlorothiazide</td>
<td>po</td>
<td>12.5–25 mg daily</td>
<td>3–5 d</td>
<td>Diuretic</td>
<td></td>
</tr>
<tr>
<td>Emergency medications</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Labetalol as noted</td>
<td>iv</td>
<td>200–1200 mg/d two or three times/day</td>
<td>2–4 h acte within 5 min</td>
<td>Direct vasodilator</td>
<td>Hypotension, hypoglycaemia</td>
</tr>
<tr>
<td>Hydralazine as noted</td>
<td>iv</td>
<td>10 mg every 2 h as needed</td>
<td>5 min</td>
<td>Direct vasodilator</td>
<td>Hypotension, hypoglycaemia</td>
</tr>
<tr>
<td>Nifedipine as noted</td>
<td>po</td>
<td>30–50 mg/day</td>
<td>30 min</td>
<td>Calcium channel blocker</td>
<td>Oedema, orthostasis, dizziness</td>
</tr>
<tr>
<td>Diazoxide</td>
<td>iv</td>
<td>0.25 μg/kg/min</td>
<td>1–2 min</td>
<td>Direct vasodilator</td>
<td>Hypotension, hypoglycaemia</td>
</tr>
<tr>
<td>Nitroprusside</td>
<td>iv</td>
<td>30–50 mg/day</td>
<td>2–4 min</td>
<td>Direct vasodilator</td>
<td>Hypotension, cyanide toxicity if used &gt;4 h</td>
</tr>
</tbody>
</table>

po = per os; iv = intravenous
tension blood pressure (> 30/15 mmHg) should lead to closer monitoring, but it is not diagnostic of hypertension in pregnancy.12

**Chronic hypertension**

Chronic hypertension presents prior to pregnancy or before the twentieth week of gestation. It is reported to complicate 3% of all pregnancies and is more common in women who are obese or those over the age of 35 years. It is important to note that 20–30% of women with chronic hypertension go on to develop superimposed pre-eclampsia.13

**Pre-eclampsia/eclampsia syndrome**

Pre-eclampsia is a syndrome of new-onset hypertension (> 140/90 mmHg) occurring after the twentieth week of gestation, with proteinuria (2+ on dipstick on two occasions six hours apart or > 3 g/24-hour urine collection).15

The aetiology remains elusive but current views suggest that it is a two-stage disorder.14 Put simply, the first stage is one of placental hypoperfusion, resulting in the release of a variety of substances (apoptotic cells, trophoblastic debris and anti-angiogenic factors) which cause multisystemic endothelial damage. The second stage presents as the clinical syndrome of hypertension, proteinuria, hepatic and central nervous system dysfunction. It is difficult to predict which organ system will be predominantly affected, but in general terms, the clinical signs of hypertension and proteinuria are the commonest. Pre-eclampsia therefore represents a spectrum of endothelial damage leading to downstream health effects.

Pre-eclampsia is divided into mild and severe categories. Severe disease is characterised by hypertension, namely, blood pressure values above 160/100 mmHg, proteinuria above 5 g per 24 hours, neurological symptoms (headache, visual disturbances), renal compromise (elevated serum creatinine and urea), hepatic dysfunction and haemolysis, and intra-uterine growth restriction. The presence of these symptoms and signs constitutes a medical/obstetric emergency, requiring admission to hospital and a multi-disciplinary approach to management.12

Although the exact aetiological mechanism is not known, epidemiological evidence suggests that pre-eclampsia affects the future health of the woman and her baby. Women with a history of pre-eclampsia are twice as likely to develop hypertension and proteinuria, hepatic and central nervous system damage. The second stage presents as the clinical syndrome of hypertension, proteinuria, hepatic and central nervous system dysfunction. It is difficult to predict which organ system will be predominantly affected, but in general terms, the clinical signs of hypertension and proteinuria are the commonest. Pre-eclampsia therefore represents a spectrum of endothelial damage leading to downstream health effects.

The ultimate therapy for pre-eclampsia is delivery of the baby, because the exact cause of the disease is not known. Clinical management is therefore individualised. In women with early-onset superimposed pre-eclampsia, blood pressure levels may increase quickly, be labile and require therapy as for a hypertensive emergency. In such circumstances, rapid lowering of high blood pressure and delivery of the baby, even if premature, may be required to prevent maternal complications. Treatment of high blood pressure alone will not prevent obstetric complications in such settings, and delivery of the foetus may be necessary to prevent adverse events in pregnancy, labour and the puerperium.

There is no doubt in the literature that women with sustained blood pressure values above 160 mmHg systolic and/or 110 mmHg diastolic should be treated with antihypertensive agents. On the other hand, there is little evidence to support antihypertensive therapy in pregnant women with blood pressure values below 160/100 mmHg. Nevertheless, in the clinical situation, there is a tendency to use antihypertensive medications in such circumstances, together with lifestyle modifications (diet and exercise).

Lifestyle modifications should ideally be initiated prior to conception in women with chronic hypertension, and continued in pregnancy. Exercise has been associated with reductions in gestational hypertension and a lower risk of eclampsia/pre-eclampsia. Due consideration however, needs to be given when making recommendations to maintain calorie intake and preventing injury.14–15

**Antihypertensive drugs in pregnancy**

Table 1 lists the commonly used antihypertensive drugs. First-line agents include methyldopa, nifedipine and labetalol. Methyldopa is the most commonly used antihypertensive medication and the most studied. It has a long history of safety, is well tolerated and efficacious, and is often the first medication attempted in pregnant women. Methyldopa can be used three times daily, particularly if high doses are required. This dose makes it a cost-effective method of treatment. Labetalol has also been studied extensively and found to be effective, although some studies have associated it with foetal growth restriction.

Angiotensin converting enzymes/angiotensin receptor blockers should be avoided in pregnancy and in women intending to become pregnant. These agents are associated with renal agensis and foetal death.15 If a woman becomes pregnant while on angiotensin converting enzymes/angiotensin receptor blockers, these agents should be stopped immediately and alternate agents that have been found to be safe in pregnancy should be used. It is also important to note that if these agents are to be considered for use in young women of childbearing age, careful counselling and contraceptive advice must be offered.12,20

There are theoretical concerns regarding the use of diuretics during pregnancy. These include decreased placental perfusion and neonatal thrombocytopenia; therefore diuretics are not first-line agents. Calcium channel blockers are used in pregnancy. Most of the literature is on the use of nifedipine and it is regarded as safe for use in pregnancy.11 Other calcium channel blockers are probably safe although the manufacturers do not recommend their use. Selective β-blockers are considered safe during pregnancy but high doses are associated with neonatal hypoglycaemia and low birth-weight babies.15

Antihypertensive medication needs to be continued after delivery because blood pressure remains elevated for at least three to five days following delivery. Observational studies suggest that up to 25% of women with severe pre-eclampsia have ongoing postnatal hypertension. Consequently, a step-down approach to reducing the use of antihypertensive agents should be taken rather than stopping abruptly. Most antihypertensive agents are expressed in breast milk in minimal quantities.

**Hypertension in young women: pregnancy and the general practitioner**

In South Africa, the general practitioner is often faced with
women requesting a diagnostic test for pregnancy. It is incumbent on these professionals to ensure that blood pressure measurements are taken, so that careful counselling is given about the options of antihypertensive agents in respect of their safety in pregnancy. General practitioners also need to be aware of the supine hypotensive syndrome associated with pregnancy and the fact that Korotkoff 5 is used for measurement of diastolic blood pressure in pregnancy.23

Furthermore, general practitioners may be faced with a pregnant women presenting with severe hypertension during pregnancy, with or without symptoms and signs of a hypertensive emergency. These situations must be recognised and antihypertensive therapy initiated prior to referral to an appropriate health facility or specialist. Figs 3 and 4 summarise clinical management and may be useful for general practitioners, obstetricians and physicians. Ideally, such patients should be managed in referral centres, staffed by experts in hypertensive disorders of pregnancy.

**Conclusions**

Hypertension in pregnancy is associated with significant maternal and perinatal morbidity and mortality. Regular blood pressure monitoring, detection of signs of pregnancy-associated hypertensive disorders in pregnancy, and may have a positive impact on women’s cardiovascular events and outcomes years after the affected pregnancies.

**Fig. 3. Management of mild gestational hypertension or pre-eclampsia.**

**Fig. 4. Management of severe pre-eclampsia.**

hypertensive conditions and management by health professionals experienced in this field will minimise sequelae associated with hypertensive disorders in pregnancy, and may have a positive impact on women’s cardiovascular events and outcomes years after the affected pregnancies.

**References**


**Cardiovascular Journal of Africa 2010 winner of best scientific article**

The first Andries Brink Kaye award for the most outstanding article published in 2010 in the *Cardiovascular Journal of Africa* was awarded during the South African Heart Congress in East London.

Prof Andries Brink, left, with award winner Andrea de Kock, for her article titled “Coping and metabolic syndrome indicators in urban black South African men: the SABPA study”.

Photograph kindly supplied by SA Cardiology & Stroke Journal
A rare complication after coronary artery bypass graft surgery: Ogilvie’s syndrome

A GULER, MA SAHIN, K ATILGAN, M KURKLUOGLU, U DEMIRKILIC

Abstract
Gastrointestinal (GI) complications occur in less than 2% of patients undergoing open-heart surgery. Acute colonic pseudo-obstruction, known as Ogilvie’s syndrome, is also a rare complication encountered in 0.046% of patients undergoing coronary artery bypass graft surgery. It is characterised by massive colonic dilatation without mechanical obstruction in patients with underlying medical or surgical conditions. In this report we describe a patient who suffered from acute renal failure requiring haemodialysis, and subsequently Ogilvie’s syndrome, which was treated with high-dose neostigmine.

Keywords: Ogilvie’s syndrome, neostigmine, coronary bypass surgery

Case report
The patient was a 55-year-old male with a 15-year history of non-insulin-dependent diabetes mellitus, and hypertension for the past three years. He had been referred the previous year to the cardiology department for chest pain on exertion. A coronary angiogram showed serious coronary artery disease, which suggested he needed CABG surgery. His pre-operative medications included oral antidiabetics, beta-blockers and angiotensin receptor blockers. His pre-operative blood analyses were within normal limits, except that he was anaemic with a haemoglobin/haematocrit of 10.1 g/dl (27.3%) and serum urea/creatinine of 102/2.0 mg/dl.

After undergoing six-vessel CABG surgery, the patient developed oliguria and required continuous venovenous haemofiltration at the bedside in the intensive care unit. He also required two additional re-explorations for bleeding, the first six hours, and the second four days after the initial surgery. During the re-explorative surgery, eight fresh, frozen plasmas and six erythrocyte suspensions were transfused to the patient. At the end of the 14th postoperative day, the patient was haemodynamically stable and his general condition had improved, but he began to complain of abdominal distention without stool or flatus passage.

On physical examination, the bowel sounds were diminished and the abdomen was markedly distended and painful, but there was no sign of peritoneal inflammation. Therefore, supportive measures including nil per os with total parenteral nutrition, fluid and potassium supplements, and placement of a rectal tube were undertaken to decompress the dilated colonic segments.

As the patient’s renal failure failed to resolve, he began to receive intermittent dialysis with fluid restriction, which made it harder to regulate is caloric intake and potassium supplementation. He had already been weakened by surgery. Bedside abdominal ultrasound showed dilated and unmovable bowel segments, with generalised fluid accumulation between them. An abdominal antero-posterior radiography (Fig. 1) and a computerised tomography (CT) scan of the patient (Fig. 2) showed dilated colonic segments full of flatus and faeces, and caecal distension of 11 cm, with normal-appearing small bowel segments.

Despite supportive measures, no passage of flatus or stool was observed and the abdominal distention failed to resolve. One week after the onset of the abdominal symptoms, we decided to administer intravenous neostigmine, since we had not been able to find any evidence supporting obstruction, even on CT or ultrasound. Half an hour after intravenous administration of 2 mg neostigmine, ordered for three days, we observed the passage of 11 cm, with normal-appearing small bowel segments.

Discussion
Acute colonic pseudo-obstruction is a rare complication, encountered in 0.046% of patients undergoing CAGB surgery. Its first description is attributed to William Heneage Ogilvie, who...
described this syndrome in two patients with sudden onset of abdominal pain, constipation and large bowel dilatation without an organic cause of obstruction. The syndrome is therefore known as Ogilvie’s syndrome. Even though the pathophysiology of ACPO is not fully demonstrated, it is deemed to be the result of large bowel parasympathetic dysfunction. Agents that increase parasympathetic tone have been shown to be successful in resolving pseudo-obstruction without colonic decompression or surgical manipulation. Various studies have shown initial success rates between 73 and 88% and long-term response rates between 88 and 100% with the use of neostigmine methyl sulfate in patients with this condition.

Appropriate assessment of the markedly dilated colon involves urgent gastroenterological evaluation to rule out any cause of obstruction because this condition may lead to subsequent ischaemia and perforation of the colon. ACPO is characterised by abdominal distension, nausea and/or vomiting, with failure to pass flatus and stools, and occurs in up to 60% of patients. In 3 to 15% of patients, massive colonic dilatation may cause ischaemia and perforation, with subsequent clinical findings of peritonitis. There is no common size of caecal distension mandating intervention. According to various authors, surgical treatment is indicated if the caecal size is greater than 8 to 12 cm. However, the symptoms, the patient’s condition, and progression of the disease are considered when deciding on surgical intervention.

ACPO occurs in about 1% of hospitalised patients and 0.046% of patients undergoing CABG surgery. The prevalence is higher in late middle age (around 60 years) and it is slightly more common (60%) in men. Because of delayed diagnosis and inappropriate treatment, ACPO is responsible for considerable morbidity, with an overall mortality rate of 25 to 31%, and 40 to 50% of patients developing ischaemia or perforation.

Diagnosis relies on accurate clinical observation and simple abdominal radiography, showing variable degrees of colonic dilatation, mainly involving the proximal colon. A water-soluble contrast enema (a sensitivity of 96% and specificity of 98%) or computed tomography (a sensitivity and specificity of 91%) should be performed to differentiate mechanical obstruction from pseudo-obstruction.

Based on the concept of parasympathetic dysfunction, intravenous neostigmine has been tested in controlled trials and remains the mainstay of treatment. In various studies, the success rate of neostigmine treatment has been shown to be 73 to 94% after the first dose, and up to 100% after the second. Conservative treatment consisting of a nasogastric tube, fluid resuscitation and enemas may be helpful in almost half the patients (53%). Colonoscopic decompression is successful in 77% of patients, but there is a high rate of recurrence and complications associated with the procedure. Therefore colonoscopic or surgical decompression is reserved for situations when conservative treatment fails, or if the caecum is on the verge of perforation.

In our case, haemodialysis, fluid restriction due to low urine output, lack of early mobilisation because of surgical complications and multiple blood transfusions may have contributed to the occurrence of ACPO. Additionally, calorie, fluid and electrolyte administration was not optimal in our case because of generalised oedema and the patient’s dependence on dialysis. This is an unfavorable situation in a postoperative patient.

**Conclusion**

Although ACPO is an unexpected and rare complication after CABG surgery, rapid and effective treatment is generally possible with neostigmine. Therefore, early recognition of this syndrome is important to prevent fatal complications.

**References**


Anaesthesia for emergency Caesarean section in a patient with peripartum cardiomyopathy

BABATUNDE OSINAIKE, JOHNSON OGAH

Abstract
Peripartum cardiomyopathy (PPCM) is defined as the onset of acute heart failure without demonstrable cause in the last trimester of pregnancy or within the first six months after delivery. We report a case of PPCM (LVEF < 39%) in a 30-year-old housekeeper requiring emergency Caesarean section, who was successfully managed with combined spinal–epidural anesthesia, using low-dose fentanyl for the spinal anesthesia.

Keywords: peripartum cardiomyopathy, combined spinal–epidural anesthesia, Caesarean section

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Peripartum cardiomyopathy (PPCM) is a relatively rare form of acute heart failure associated with pregnancy, and defined as the onset of acute heart failure in the last trimester or early postpartum period, in the absence of infectious, metabolic, toxic, ischaemic and valvular causes of myocardial dysfunction. Many terms are used to describe this disorder, including toxic post-partal heart failure, postpartum heart disease, postpartum myocardosis, Meadows’ syndrome, idiopathic myocardial degeneration associated with pregnancy, Zaria syndrome, and postpartum cardiomyopathy.4,4

The diagnosis of this disorder is said to depend on the following criteria: (1) development of congestive heart failure (CHF) secondary to decreased left ventricular systolic function in the last month of pregnancy or within five months after delivery; (2) absence of pre-existing cardiac dysfunction; (3) absence of determinable cause of cardiomyopathy; and more recently, (4) left ventricular systolic dysfunction demonstrated by classic echocardiographic criteria: left ventricular ejection fraction less than 45%, or M-mode fractional shortening less than 30%, or both, and end-diastolic dimension more than 2.7 cm/m².5-6

The Hausa tribe of northern Nigeria has the highest known incidence in the world; about 13% of all female admissions having this condition, and the incidence has been reported to be as high as 1:100. This is probably related to a local Hausa custom of ingesting a form of lake salt in the immediate postpartum period, a practice that can produce significant volume overload. The disease is less common among other ethnic groups in Nigeria.

The anaesthetic management of labour and delivery in pregnant patients with peripartum cardiomyopathy is not well defined and we are unaware of any case report on the anaesthetic management of this subset of patients presenting for Caesarean section (CS) in West Africa. We therefore present a patient with peripartum cardiomyopathy requiring CS who was managed with combined spinal–epidural (CSE) anaesthesia.

Case report
A 30-year-old housekeeper with body mass index of 22.2 kg/m², G4P0+3, was transferred from a peripheral hospital where she had presented at 34 weeks of gestation with pregnancy-induced hypertension and symptoms of cardiac failure. On admission, she gave a history of a week of breathlessness, with cough productive of scanty, whitish, frothy sputum, and associated orthopnoea. She had a previous history of pedal oedema of one month’s duration before presentation. She was not a known hypertensive, diabetic or asthmatic and had no history of drug allergy. There was no previous hospital admission except for a voluntary termination of pregnancy six years earlier.

At the time of admission, she was dyspnoeic lying down, her heart rate was 120 beats per minute and blood pressure (BP) was 160/120 mmHg. On auscultation of the chest, there were bilateral coarse crackles along with a triple rhythm. The chest radiograph showed cardiomegaly with bilateral pleural effusion. The electrocardiogram (ECG) showed sinus tachycardia with widespread ST–T changes in the anterolateral leads and left atrial enlargement. The echocardiogram showed a dilated left atrium, poor left ventricular systolic function, restrictive diastolic dysfunction and mild pericardial effusion about 1 cm over the left ventricle with left ventricular ejection fraction of 39%. More
investigations and results are listed in Table 1.

Treatment included intravenous (iv) furosemide 20-mg bolus, then 20 mg 12 hourly, iv magnesium sulphate (MgSO₄) 4-g bolus then 5 g in 500 ml 0.9% saline to run over five hours for five doses. Also, iv hydralazine 5-mg bolus over 15 minutes, to repeat if systolic and diastolic blood pressure are ≥160 and 110 mmHg, respectively, intra-nasal oxygen at 6 l/min and nursed in the cardiac position.

Some improvements in clinical condition were observed about eight hours after commencement of therapy. The respiratory rate reduced to 36/min, the diastolic blood pressure reduced to less that 100 mmHg and the chest became clearer, however some episodes of foetal tachycardia were observed. Following the improvement in cardiac symptoms, the decision was taken to urgently deliver the baby by Caesarian section. The anesthetist was informed, and in view of the urgency involved, no invasive monitoring could be provided.

On arrival in the operating room, her blood pressure was 119/86 mmHg, pulse rate was 102 bpm, and oxygen saturation was 98%. On auscultation, she still had a few crepitations in both lung bases bilaterally. Peripheral venous cannulation was done with an 18-guage iv cannula and a 0.9% saline infusion was started. ECG leads, a pulse oximetry probe and non-invasive blood pressure cuff were attached for continuous monitoring.

In view of the cardiac condition and the desire of the obstetrician to urgently deliver the baby, combined spinal–epidural (CSE) was chosen. After preloading with 250 ml of 0.9% saline over 30 minutes, CSE was performed at the L4–L5 interspace in the sitting position; 25 μg of fentanyl was injected through a 27-gauge 120-mm Sprotte needle into the cerebrospinal fluid, which was introduced through a 16-guage Tuohy needle.

An epidural catheter was inserted through which two doses of 5 ml of 0.5% plain bupivacaine was administered. The patient was placed in the supine position and a wedge was placed under the right hip to minimise aorto-caval compression. Oxygen was administered with a facemask at a flow rate of 5 l/min. The upper levels of sensory block obtained were T8 at three minutes and T6 at five minutes; 250 ml of 0.9% saline and 500 ml of pentastarch were administered intra-operatively to treat hypotension. A vasopressor was not administered.

The operation proceeded uneventfully and a healthy female baby of 1.45 kg was delivered eight minutes later (Apgar score 9/10). Intravenous oxytocin 10 mg was administered slowly at the delivery of the placenta and 30 mg was put into 500 ml of 0.9% saline to run as an infusion for five hours. The patient was haemodynamically stable throughout the procedure. The surgery lasted 30 minutes and estimated blood loss was 500 ml.

The patient’s husband declined admission to the intensive care unit because of financial constraints; hence the patient remained under high-dependency care in the labour ward. Epidural analgesia was employed for the first 14 hours post-operatively.

**Discussion**

Although the aetiology of peripartum cardiomyopathy is uncertain, viral, autoimmune and idiopathic causes have been considered. Some cases of PPCM are being postulated to be part of the spectrum of familial dilated cardiomyopathy (DCM) presenting in the peripartum period. It is usually a diagnosis of exclusion, however there is an increased incidence of PPCM with multiple gestation, pre-eclampsia, obesity, advanced maternal age, African descent and prolonged tocolysis. Worldwide, the frequency of peripartum cardiomyopathy is highest where a large proportion of the women are of African descent, such as Nigerian, Haitian and South African. The lowest frequency of peripartum cardiomyopathy has been reported in studies where women of African descent were less common. The highest reported incidence is in Nigeria, at 980 out of 100 000 deliveries. This very high incidence may be related to a local custom of ingesting salt in the postpartum period, which increased the detection of peripartum cardiomyopathy by increasing heart failure symptoms. Desai et al. found a case incidence of 100 out of 100 000 deliveries in South Africa. Fett et al. reported an incidence in a predominately rural population in Haiti of 334 out of 100 000 deliveries. The high incidence of PPCM in our region requires that peri-operative management of this subset of patients be well reported.

The presence of PPCM in a parturient requires expert anaesthetic management for labour or for Caesarean section. Aggressive pain management for labour is indicated to keep the heart rate and systemic vascular resistance under control and to attenuate the volume overloading effect of each uterine contraction. The literature regarding the anaesthetic management of peripartum cardiomyopathy is sparse, although several anaesthetic options for CS have been reported. These include general anaesthesia (GA) with inhalational agents, general anaesthesia with remifentanil, epidural anaesthesia, spinal anaesthesia, and combined spinal–epidural anaesthesia (CSE).

Considerations for regional anaesthesia in patients with PPCM are similar to those with other causes of heart failure. With regard to anaesthesia for Caesarean section, general anaesthetic techniques involve drugs, which cause myocardial depression and reduced systemic vascular resistance (SVR); and positive-pressure ventilation, which decreases the venous return to the heart. Also, the effects of stimulation of the sympathetic nervous system following laryngoscopy and endotracheal intubation may be inimical for a failing heart. General anaesthesia may be necessary for urgent CS. However, performing a rapid-sequence induction on a patient with compromised cardiac function can be very challenging. When time permits, a carefully administered regional anaesthetic seems to be advantageous.

In addition to avoiding the stress of GA, the vasodilatation produced by regional anaesthesia is beneficial with isolated left ventricular dysfunction. The goals during the management of anaesthesia in patients with cardiomyopathy include avoidance of drug-induced myocardial depression, maintenance of normo-

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**TABLE 1. HAEMATOLOGICAL AND BIOCHEMICAL INVESTIGATIONS**

<table>
<thead>
<tr>
<th>Investigation/test</th>
<th>Before surgery</th>
<th>After surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Packed cell volume (PCV)</td>
<td>47%</td>
<td>34%</td>
</tr>
<tr>
<td>White cell count (WBC)</td>
<td>15 400/cm³</td>
<td>136 000/μl</td>
</tr>
<tr>
<td>Platelet count</td>
<td>136 000/μl</td>
<td></td>
</tr>
<tr>
<td>International normalised ratio (INR)</td>
<td>1.1</td>
<td></td>
</tr>
<tr>
<td>Serum electrolytes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>potassium</td>
<td>5.2 meq/l</td>
<td>3.3 meq/l</td>
</tr>
<tr>
<td>sodium</td>
<td>134 meq/l</td>
<td>135 meq/l</td>
</tr>
<tr>
<td>bicarbonate</td>
<td>17 meq/l</td>
<td>18 meq/l</td>
</tr>
<tr>
<td>urea</td>
<td>31 mg/dl</td>
<td>51 mg/l</td>
</tr>
<tr>
<td>creatinine</td>
<td>1.0 mmol/dl</td>
<td>0.9 mmol/l</td>
</tr>
</tbody>
</table>
volaemia and prevention of increased ventricular afterload.24 These factors that guided our choice of regional anaesthesia in this patient. Epidural anaesthesia produces changes in preload and afterload that mimic pharmacological goals in the treatment of patients with cardiomyopathy.

With this in mind and the need to urgently deliver the baby, we opted for a CSE and, considering the fact that spinal anaesthesia may lead to a sudden and rapid reduction in systemic vascular resistance and thereby preload, which might be disastrous in a low-cardiac output condition, we used a low dose of fentanyl as the spinal anesthetic. With this technique, the patient was ready for surgery in five minutes and we had stable cardiovascular haemodynamics. Usually volume preloading with 500 ml to one litre of crystalloid or colloid is employed to minimise the hypotension that follows sympathetic blockade. However, preloading in this patient was restricted to 250 ml of 0.9% saline to prevent worsening of the cardiac symptoms.

Indira et al.,25 in a similar case report, employed CSE in a patient with ejection fraction less than 25%. They injected 5 mg of 0.5% hyperbaric bupivacaine with 20 μg fentanyl intrathecally and fractionated doses of 5 ml of 2% lidocaine into the epidural space. They reported no hypotension intra-operatively. Similarly, Shnaider et al.26 reported a case of peripartum dilated cardiomyopathy presenting for CS who was successfully managed with CSE. They injected 6 mg of hyperbaric bupivacaine (0.8 ml of 0.75%) together with 15 μg of fentanyl in the subarachnoid space. Supplementation of the subarachnoid block was done with epidural bupivacaine 5 ml of 0.5 and 0.25% at 60 and 105 minutes, respectively. Their patient had stable haemodynamics throughout the procedure. Epidural lidocaine, titrated in small aliquots together with fentanyl, has been successfully employed in a patient with pulmonary hypertension and cardiomyopathy.27

Oxytocin has been known to decrease mean arterial pressure by 30% and systemic vascular resistance by 50%, and increase cardiac output by 50% and heart rate and stroke volume by 20 to 30%.28 These effects may worsen the condition of a patient with cardiac failure. However, this creates a dilemma since withholding oxytocin may lead to haemorrhage, which may also be dangerous in these patients. We slowly administered the oxytocin following the delivery of the placenta to reduce these effects, and subsequently commenced an infusion using a reduced dose. Dob and Yentis29 recommended giving 5 units of oxytocin in 20 ml saline over five to 10 minutes, followed by 40 units in 500 ml saline to run for four to five hours.

Several authors30–33 have used invasive monitoring to manage more symptomatic cases, while others34–36 have used a non-invasive monitoring technique for asymptomatic and haemodynamically stable patients. Elective use of invasive monitoring (arterial and central venous) is justified in a symptomatic patient with an elevated jugular venous pressure, third and fourth heart sounds, orthopnoea, paroxysmal nocturnal dyspnoea or shortness of breath at rest, with clinical evidence of a low cardiac output or echocardiographic evidence of significant myocardial depression (poor contractility, left ventricular wall motion abnormalities).37

Although our patient had some significant symptoms, she did not have any form of invasive monitoring before presenting for anaesthesia and we were unable to provide one because of the urgency required to deliver the baby. Colloid was employed to restrict intra-operative fluid therapy, and supplemental oxygen was administered to ensure that oxygen saturation remained between 98 and 100%. Non-invasive cardiac monitors such as Doppler ultrasound and impedance cardiography have been used with good results in patients with PPCM, although limitations include cost and technical difficulties, especially in low-resource countries.

**Conclusion**

Our opinion is that combined spinal– epidural, employing low-dose fentanyl for the spinal anaesthesia is a suitable option for patients with PPCM scheduled for emergency Caesarean section.

**References**

Diagnostic assessment of prosthetic mitral valve thrombosis by real-time three-dimensional transoesophageal echocardiography and successful thrombolytic treatment

HUMBERTO MORAIS, TELMO MARTINS, JOSÉ ROBERTO, FIDEL CÁCERES-LÓRIGA

Abstract

Prosthetic valve thrombosis (PVT) is a rare but serious complication of valve replacement, most often encountered with mechanical prostheses. The different therapeutic modalities for PVT (fibrinolysis with heparin treatment or surgery) will largely be influenced by the presence of valvular obstruction, the valve location (left or right sided), the patient’s clinical status, the existence of and expertise in therapeutic modalities at the institution, and the patient’s decision. This report describes a patient with thrombosis of a prosthetic mitral valve, which was successfully treated with recombinant streptokinase in a hospital without cardiac surgery. In this context, the authors present a review of the literature.

Keywords: prosthetic valve thrombosis, fibrinolysis, real-time three-dimensional transoesophageal echocardiography, transcatheter echocardiography, Angola

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was in NYHA class I. The mitral valve area and the mean gradient were 1.76 cm² and 6 mmHg, respectively.

**Discussion**

PVT is a serious complication of valve replacement, associated with high mortality rates. The main pathogenic factors of PVT have been identified, including mitral position of the prosthesis, type of prosthesis, atrial fibrillation, atrial enlargement, ventricular dysfunction, multivalve replacements, and pregnancy. However, the most common cause is a sub-therapeutic level of anticoagulation, which had been the case with our patient (the patient had stopped taking warfarin two months earlier). This shows the importance of adherence by these patients to their antithrombotic treatment, and the necessity of INR control.

When PVT is first suspected, a careful physical examination should be performed, with particular attention being paid to muffling or disappearance of prosthetic sounds and the appearance of a new regurgitant or obstructive murmur. The initial diagnostic work up includes transthoracic echocardiography and cinefluoroscopy for mechanical valves. Transthoracic Doppler echocardiography is the imaging technique more frequently used.

PVT may be suspected with increased transvalvular gradients. However, this measurement is non-specific as the gradient may be increased by other conditions. On the other hand, normal gradients do not rule out obstruction in the presence of left ventricular dysfunction or hypovolaemia.

Cinefluoroscopy is an important part of the diagnostic evaluation of a suspected PVT, however this technique is not helpful in identifying non-obstructive PVT or differentiating pannus from thrombus. Transoesophageal echocardiography is the diagnostic tool with a higher sensitivity for identifying an abnormal cardiac mass. Moreover, TTE provides important additional information to guide therapy and is often performed to complete the investigation.

Recent reports show that diagnostic use of three-dimensional real-time TEE offered a useful and comprehensive evaluation of prosthetic thromboses (number, size and precise location). In spite of its unique features, it is not clear if this new technique is cost effective in the management of PVT. Certainly, more information is needed.

In our case, we used three echocardiographic modalities (TTE Doppler, TEE, real-time 3D TEE) to complement each other in the diagnosis of the PVT and for guidance in the thrombotic therapy.

Emergency surgical treatment (thrombectomy or valve replacement) has been considered the traditional management for PVT. However, recent surgical series report high mortality, particularly in severe NYHA functional classes. Durrleman et al. presented a series of 39 patients with PVT over a 20-year period, who underwent thrombectomy or valve replacement, with an associated mortality of 25 and 41%, respectively. Oskokeli et al., in 30 patients with left-side PVT, reported a post-operative early hospital mortality of 7.1% (NYHA classes II–III) and 31.3% (NYHA class IV), and Toker et al., in 63 cases, a total mortality of 20.6%.

The current guidelines for the management of PVT remain controversial. Recent guidelines still recommend surgery as first-line therapy in critically ill patients (NYHA class III–IV).
and in those with large clots. Thrombolysis remains an alternative therapy for patients with a high surgical risk or contraindication to surgery, or if surgery is not available.3,5

The individual experience of several authors has led to the decision to recommend thrombolysis as first-line therapy in PVT.1,6-10 Accordingly, in the recent PVT guidelines of the Society of Heart Valve Disease, thrombolysis was recommended as first-line therapy in all patients with PVT and a thrombus diameter ≥ 5 mm, regardless of the obstruction and NYHA functional class. Surgery is reserved only for cases with failed thrombolytic therapy or where there was a contraindication to thrombolysis (evidence B).1,4

Nagy et al.19 in a study with the objective of analysing the predictors of the outcome of thrombolytic therapy in 62 events of prosthetic mitral valve thrombosis, showed that, based on previous data and the present findings, thrombolysis may be considered a first-line treatment in all patients with PVT, since the complication and success rates of thrombolysis are independent of valve type, NYHA functional class, and thrombus size.

In a recent systematic review on the role of thrombolysis in the treatment in left-sided PVT, Reyes et al.20 reported on 904 patients treated between January 1970 and January 2007. Clinical improvement was observed in 86% of the patients and failure in 14%. The peripheral and cerebral embolism rate was 5% and 4%, respectively. Major bleeding was 4% and intracranial haemorrhage was 1%.

Shapira et al.,21 in a current review, affirms that thrombus size is probably the most important determinant of complications. If small, thrombolysis is probably advised across all degrees of functional class, as suggested by the American College of Chest Physicians.

Taljaard and Doubell22 report the results of a case series of a total of 32 patients presented on 34 occasions with prosthetic valve obstruction at Tygerberg Hospital between January 1991 and February 2001. Valve replacement was performed on 20 patients, six received thrombolysis and the remaining eight patients did not receive any treatment. The conclusion of this study was that, given the extremely high mortality rate with surgical treatment, six received thrombolysis and the remaining eight patients did not receive any treatment. The conclusion of this study was that, given the extremely high mortality rate with surgical treatment, we chose thrombolysis as first-line therapy in our patient.

We chose thrombolysis as first-line therapy in our patient. This is another case where the benefits and safety of thrombolysis in the treatment of PVT are evident.

Conclusion

In the absence of randomised, controlled trial data, thrombolysis appears to be an effective treatment. It should be considered in all patients, even when a surgical strategy is readily available. In the absence of on-site cardiothoracic surgical support, it is reasonable to consider this first-line treatment in appropriate patients.

References

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Drug Trends in Cardiology

Dramatic reductions in plaque volumes on maximum statin therapy

Largest IVUS trial shows equal plaque regression with atorvastatin and rosuvastatin

The SATURN trial, which evaluated the extent of plaque regression in patients with symptomatic coronary artery disease (CAD) over a two-year period using maximum doses of atorvastatin and rosuvastatin, showed no difference between these two statins with regard to the primary endpoint of percentage reduction of atheroma volume.1

‘The extent of regression with both statins at maximum dose was unprecedented in our experience and relates well to the very low event rate seen in this clinical trial’, Dr Stephen Nicholls from the Cleveland Clinic, USA and principal investigator of this Astrazeneca-sponsored study noted (Fig. 1).

The SATURN study (Study of Coronary Atheroma by InTravascular Ultrasound: Effect of Rosuvastatin versus Atorvastatin), a prospective randomised, multicentre, double-blind study, is the largest imaging study in cardiovascular medicine to date and adds to the collective experience of using intravascular ultrasound (IVUS) to detect changes in coronary atheroma volume (Fig. 2).

The primary-efficacy parameter of the SATURN trial was set as the change in percentage atheroma volume in matched coronary artery segments performed at baseline and at the end of the 104-week treatment period.2 The secondary endpoints included the change in total atheroma volume on therapy, change in lipid and lipoprotein values, and a safety evaluation, including analysis of adverse events and laboratory data. The incidence of major adverse cardiovascular events was explored in the total patient cohort as a function of changes in IVUS variables, but did not have the power to directly compare the treatment groups with regard to clinical events.

A total of 1 385 subjects aged 18 years and older with at least 20% or more lumen stenosis in a native epicardial

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Cohort (n = 1 385) n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>57.6 ± 8.6</td>
</tr>
<tr>
<td>Males</td>
<td>998 (72)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>29.3 ± 5.3</td>
</tr>
<tr>
<td>Overweight (BMI ≤ 25 to &lt; 30 kg/m²)</td>
<td>617 (45)</td>
</tr>
<tr>
<td>Obese (BMI ≥ 30 kg/m²)</td>
<td>522 (38)</td>
</tr>
<tr>
<td>Previous MI</td>
<td>329 (24)</td>
</tr>
<tr>
<td>Previous PCI</td>
<td>303 (22)</td>
</tr>
<tr>
<td>Previous CVA/TIA</td>
<td>34 (2)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>945 (69)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>207 (15)</td>
</tr>
<tr>
<td>Current smoking</td>
<td>442 (32)</td>
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<tr>
<td>Peripheral artery disease</td>
<td>85 (8)</td>
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<tr>
<td>Baseline aspirin use</td>
<td>1114 (80)</td>
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<td>Baseline statin use</td>
<td>823 (59)</td>
</tr>
<tr>
<td>Baseline beta-blocker use</td>
<td>923 (67)</td>
</tr>
<tr>
<td>Baseline ACE inhibitor use</td>
<td>582 (42)</td>
</tr>
<tr>
<td>Baseline ARB use</td>
<td>180 (13)</td>
</tr>
</tbody>
</table>

Continuous data presented as mean (± 80) and categorical data as n (%). Baseline medications included selected medication that was taken within 90 days of consent.

ACE, angiotensin converting enzymes; ARB, angiotensin receptor blocker; BMI, body mass index; CVA, cerebrovascular accident; MI, myocardial infarction; PCI, percutaneous coronary intervention; TIA, transient ischaemic attack.

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Fig. 1. Primary IVUS efficacy parameter.  
Fig. 2. LCL-C and disease progression.
coronary artery (on visual estimation of a clinically indicated coronary angiogram) and a target vessel for imaging with less than 50% obstruction were randomised in the trial. The clinical characteristics of patients enrolled in SATURN are summarised in Table 1.

Screening process
Patients who were not on a statin had to have an LDL cholesterol greater than 2.6 mmol/l, while those on treatment were required to have a level higher than 2.1 mmol/l. Patients with uncontrolled hypertension, heart failure, renal dysfunction or liver disease were excluded from the trial.

In the screening period, patients were randomly assigned to either atorvastatin 40 mg or rosuvastatin 20 mg daily for two weeks to ascertain side effects and compliance. Patients with an LDL cholesterol less than 3 mmol/l and a triglyceride level of less than 5.6 mmol/l underwent randomisation, this time to a full dose of atorvastatin (80 mg daily) or rosuvastatin (40 mg daily) for the two-year study period, at the end of which a second IVUS assessment of the originally imaged target vessel was performed.

Clinical events were adjudicated by members unaware of the treatment assignments. Lipids were measured at six, 12, 18 and 24 months, while C-reactive protein was measured annually.

After 104 weeks of treatment, 1 039 patients remained in the study (75%). Of these, 519 were in the atorvastatin and 520 in the rosuvastatin groups, with no significant differences between the two treatment groups. During treatment, levels of LDL cholesterol were lower in the rosuvastatin group (1.6 vs 1.8 mmol/l) and HDL cholesterol levels were different (1.25 mmol/l in the atorvastatin vs 1.3 mmol/l in the rosuvastatin group). There was also a difference in the LDL:HDL cholesterol ratio, with those in the rosuvastatin group having lower values than those in the atorvastatin group. Median C-reactive protein levels were similar.

Results
The results showed that the primary-efficacy endpoint of percentage atheroma volume was not significantly different between the two treatment groups and cardiovascular events were also similar with regard to total atheroma volume. With regard to the secondary-efficacy evaluation, rosuvastatin treatment led to a greater reduction in total atheroma volume than in the atorvastatin-treated group. The rate of abnormal laboratory levels was low and glycated haemoglobin levels did not change significantly in either group during the two-year period.

With the added recognised use of rivaroxaban as an Xa inhibitor locally.

The ATLAS ACS 2-TIMI 51 trial results were widely welcomed at the AHA, with the lead investigator, Dr Michael Gibson of Harvard Medical School noting that rivaroxaban treatment for about two years in ACS patients resulted in a very robust reduction in the primary endpoint of cardiovascular death, myocardial infarction and stroke (RRR of 16%). The risk of all-cause death was reduced by 30% with the addition of rivaroxaban to the standard treatment of ACS.

‘Importantly, this benefit in reduced deaths was also seen as a reduction in sudden unwitnessed deaths, which we know from autopsy studies is primarily due to thrombotic events. Also rivaroxaban reduced stent thrombosis by 31%. These two aspects together give me confidence that the benefits we are seeing are due to the inhibition of thrombin generation. We now know we have a new target of blocking thrombin production as an important way of improving outcomes in ACS’, Dr Gibson noted.

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The beneficial results of rivaroxaban treatment are very important to patient care, as there is a large unmet need in ACS management. This is seen in the fact that despite the widespread use of dual antiplatelet therapy, patients who have had a recent ACS event continue to be at increased risk of major cardiovascular events, at an annual rate of 10%.

Dr Paul W Armstrong, Edmonton, Canada was the discussant at the clinical trial session and he noted that this study is a welcome and transforming advance in the management of ACS. In evaluating the ATLAS ACS 2-TIMI 51 trial, it is important to note which patients benefitted in this large multi-centre trial conducted in 766 sites in 44 countries. The more than 15 000 adult patients included in the study had symptoms of ACS and were diagnosed with ST-segment elevation myocardial infarction (STEMI), non-


Raft of rivaroxaban good news from the USA, implications for South African clinical practice

Rivaroxaban has been approved by the US Food and Drug Administration (FDA) for the prevention of stroke and systemic embolism in non-valvular atrial fibrillation. From the American Heart Association (AHA) 2011 congress earlier this week, the results of the ATLAS ACS 2-TIMI 51 trial have shown rivaroxaban improves cardiovascular outcomes and reduces cardiovascular and all-cause mortality in acute coronary syndromes (ACS).12

With the added recognised use of rivaroxaban in knee and hip arthroplasty and in the prevention and treatment of venous thromboembolism, deep-vein thrombosis and pulmonary embolism,13 South African medicine regulators will need to widen their assessment of the value of this factor Xa inhibitor locally.

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STEMI or unstable angina.

Key exclusion criteria were patients with a history of stroke (ischaemic stroke or transient ischaemic attack), previous gastrointestinal or intracranial bleeding, or evidence of bleeding sequelae such as a platelet count of less than 90 000 per mm³, a haemoglobin level lower than 10 g/dl and a low creatinine clearance rate of less than 30 ml/min on screening for possible study entry.

'The reason for excluding patients who had a stroke derives from our knowledge that if you have had a stroke, even dual anti-platelet therapy may not be optimal. To support this approach, a few stroke patients did slip into the ATLAS study and their outcome was poor', Dr Gibson noted during the post-clinical trial interviews.

'However, in patients who did experience a stroke during this TIMI trial, those on rivaroxaban had a better neurological recovery. This may well be due to the fact that thrombin is known to increase apoptosis in the neural system and inhibition of thrombin generation can reduce neural apoptosis, offering a useful hypothesis for some of the benefits on stroke severity seen in this trial', Dr Gibson explained.

The ATLAS-ACS 2-TIMI 51 trial was a phase-three trial initiated with an oral dosage of either 2.5 or 5 mg rivaroxaban twice daily (bid). This dosage was based on a previous phase-two dose-finding trial. Patients received aspirin, a thienopyridine and placebo, or one of the two rivaroxaban doses on an average of 4.7 days after revascularisation procedures had been done and the patient was stable. Importantly patients did as well on the lower dose, with less bleeding than on the higher dose. There was an increase in major bleeding rates not related to coronary bypass grafting and intracranial bleeding without a significant increase in fatal bleeding or adverse events in patients receiving rivaroxaban compared to standard therapy.

**Expert opinion**

Prof Sylvia Haas, Technical University, Munich, Germany, a well-known expert from Munich and frequent visitor to South Africa commented on the importance of this study for clinical practice.

The results of ATLAS ACS 2-TIMI 51 have the potential to lead into a new era in secondary prevention of thromboembolic complications after ACS. This landmark study aimed to lower cardiovascular events in patients with recent ACS compared to standard care and this has been successfully achieved for both doses of the oral factor Xa inhibitor rivaroxaban tested, and for each dose alone.

A cumulative incidence of 10.7% for the combined endpoint, consisting of cardiovascular death, myocardial infarction (MI) and stroke, was seen in patients randomised to placebo and this was reduced to 8.9% for both rivaroxaban groups combined. In patients treated with the higher dose of rivaroxaban of 5 mg bid, this endpoint was significantly reduced to 8.8%, and for patients treated with 2.5 mg bid to 9.1%, which was also statistically significant. There were also reductions in rates of death from both cardiovascular causes and any cause for the 2.5-mg dose but not for the 5-mg dose.

As expected, the bleeding rates were higher for the patients receiving the combination of anticoagulation and anti-platelet therapy. This effect was dose related, i.e. bleeding rates were lower in the 2.5- than in the 5.0-mg group. Although the rate of intracranial bleeding was higher than with placebo, there was no increase in fatal bleeding events.

In conclusion, rivaroxaban is the first new oral anticoagulant to demonstrate a clinically relevant benefit in ACS.

1. FDA Announcement, 11 November 2011.
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Global PANORAMA study collects largest database on 10 000 patients from the Middle East and Africa

Medtronic in the Middle East and Africa area has recently announced that the PANORAMA study has successfully enrolled its ten thousandth patient. This study is the first in the world to include more than 31% of its patient population from the Middle East and African region (MEA), and more specifically from 20 different enrolling centres in South Africa, Saudi Arabia, Kuwait and Turkey.

This is expected to allow healthcare practitioners in the field to better assess and understand patient characteristics specific to our region and help evaluate whether treatment required for patients in the MEA should be different from that in other countries, especially Europe and the USA. To date, there is very little evidence available to shed light on regional differences in practice patterns, but PANORAMA is expected to provide the missing data.

‘The PANORAMA study is an important international registry; yet, it will be our local data that will be unique’, commented Prof A Okreglicki, director of the Interventional Cardiac Electrophysiology Laboratory at the Groote Schuur Hospital in Cape Town. Some of the first results from this study were presented at the recent SA Heart meeting held in East London.

Unitas Hospital, Gauteng sheds light on South African responder patterns in patients undergoing cardiac resynchronisation therapy

This study of mainly male patients (22 in total), average age 65 years, has shown an overall significant improvement in ejection fraction (EF) in patients who received cardiac resynchronisation therapy (CRT). The majority were normal responders (improvement in left ventricular EF in the range of 3–5%) but the percentage of hyper-responders (13.6%) and super-responders (18%) was higher than in other previously described studies. The authors noted this might be due to the highly selected population and the initial broad QRS duration, a mean of 141.4 ms, which improved on average by 19 ms.

Pacemaker implantation in South Africa: patient demographics and implant data

In this first overview of 904 patients from 13 hospitals in South Africa, of which 12 were in the private sector, differences in approach between a well-resourced public hospital (Groote Schuur Hospital) and the private sector were noted. In common were baseline characteristics where the patients were mainly Caucasian (85%), 57% male and aged 68 ± 16 years; 20% were in atrial fibrillation and 23% had heart failure.

The primary indication at enrollment varied, with atrio-ventricular block being more common in the public sector (70 vs 19%), and sinus node disease being more common in the private sector (67 vs 20%).

Use of devices also differed, with one-chamber devices being more commonly used in the public sector and two- and three-chamber devices being used in the private sector.

Focus on baseline characteristics and demographic differences in ICD patients in the Gulf region (Saudi Arabia and Kuwait)

Between May 2005 and November 2010, 610 patients (age 58.7 ± 14.6 years, 79.7% male) were implanted with an ICD in one centre in Kuwait and six centres in Saudi Arabia. The data were compared with 1 205 patients in the rest of the world (age 59.1 ± 15.0 years, 82.3% male).

PANORAMA shows that the population from the Gulf region has some specific characteristics and that patient treatment is different from that in the rest of the world. More often patients suffer from diabetes mellitus, hypertension and hypercholesterolaemia, less often they have myocardial infarction and atrial fibrillation, are treated for primary prevention, receive a dual-chamber device and the RV defibrillation lead is more often placed in the septal areas to mimic more physiologic ventricular activation.

A giant pericardial cyst

İSLAM KAKLIKKAYA

Abstract
Pericardial cysts are rare, benign, congenital anomalies. Most are asymptomatic and are found incidentally on chest radiographs. Some may cause symptoms and complications. Giant pericardial cysts are even more rare, and few reports on their natural history, presentation and management are available.

This report describes a giant pericardial cyst that exerted pressure on the heart and lungs and was excised surgically. Subsequently, the patient has been asymptomatic for nine years and appears to be in complete remission.

Keywords: pericardial cyst, surgical treatment

Submitted 7/1/10, accepted 31/8/10
Cardiovasc J Afr 2011; 22 (6): online publication www.cvja.co.za
DOI: 10.5830/CVJA-2010-076

Pericardial cysts are caused by the incomplete coalescence of foetal lacunae during the development of the pericardium. They are usually unilocular, well-margined, spherical or teardrop-shaped cysts that may be attached to the pericardium directly or by a pedicle. Pericardial cysts are lined by endothelium or mesothelium and contain clear serous fluid (‘spring water’). These cysts do not connect with the pericardial space.

They are asymptomatic in more than 50% of cases and are detected incidentally on chest X-ray. They are generally more likely to be found in middle-aged adults, most frequently in the third or fourth decade of life, and equally in men and women. Some pericardial cysts may cause symptoms and complications such as right ventricle outflow obstruction, pulmonary stenosis, pericardial tamponade and partial erosion of the superior vena cava.

Case report
The patient was a 39-year-old man who had reported several episodes of left pleuritic chest pain and who had been diagnosed elsewhere with a Morgagni diaphragmatic hernia. His medical history included severe hypertension (220/120 mmHg). The patient was generally active and was otherwise in good health. He had smoked one packet of cigarettes daily for 25 years, and had a dry cough. He had had palpitations, non-specific gastrointestinal system complaints, nausea, vomiting and dyspepsia for five years. He had seen many doctors, including psychiatrists, for these complaints. He was transferred from a state hospital to our clinic with the working diagnosis of diaphragmatic hernia for surgical treatment.

On examination, he was in no distress. His blood pressure was 180/90 mmHg, the heart rate was 90 beats/min, and he had a regular heartbeat with normal heart sounds and no murmurs. An electrocardiogram revealed a sinus tachycardia and non-specific ST-T changes in V5–6.

The breath sounds were absent on auscultation of the lower two-thirds of the left hemithorax. On percussion, there was dullness in the fifth left intercostal area, which indicated Traube’s space was obliterated.

He was afebrile, acyanotic, normal coloured and anicteric. No jugular venous distention was seen. The postero-anterior chest X-ray showed atelectasis of the inferior lobe of the left lung, caused by a mass in the left hemithorax, massive pleural effusion in the left lower hemithorax, and mild cardiomegaly (Fig. 1).

Routine laboratory tests were unremarkable. The purified protein derivative of tuberculin test was equivocal.

The transthoracic echocardiogram suggested that the mass was a thin-walled, cyst-like structure adherent to the left ventricle. No intracardiac masses or other echocardiographic abnormalities such as a prominent fad pad, solid tumour, aortic aneurysm, left ventricle aneurysm and prominent left atrial appendage were found.

Subsequent contrast-enhanced computed tomography (CT) revealed a cystic mass in the left mediastinum above the diaphragm, surrounding the left cardiac border (Fig. 2). The mass measured 22 × 15 × 17 cm (transverse × anteroposterior × vertical).
cranio-caudal). In addition, a subpleural bulla approximately 2 cm in diameter was observed in the anterior apex of the left upper lobe, and marked compressive atelectasis of the left lower lung was noted. No additional mediastinal, hilar, airway or lung parenchyma abnormalities were identified.

As the mass was symptomatic and the diagnosis remained in question, the patient was scheduled for operative exploration. The mass, thought to be a pericardial cyst, was removed via an open thoracotomy.

After a left-sided thoracotomy, 2 000 ml of serosanguinous fluid were aspirated from the pericardial cyst sac, with complete excision of the mediastinal mass, measuring $22 \times 15 \times 17$ cm (Fig. 3). The cyst was full of golden-yellow liquid and was adherent to the lung and phrenic and anterior vagus nerves laterally. The pericardial cyst was connected to the inferior pericardial surface by a thin, mobile, vascular pedicle, which was ligated when the mass was resected.

The mass was bright and soft. It was on the left side of the diaphragm, and exerted pressure on the left side of the heart and pericardium and on the lower lobe of the left lung, causing compressive atelectasis. The atelectic lung was expanded manually. The $2 \times 2$-cm bulla in the left upper lobe of the lung was sutured. The procedure was finished successfully in the usual manner after closed drainage (water-sealed drainage) of the thoracic cavity.

Histological examination confirmed the diagnosis of a pericardial cyst (fibrovascular cyst wall) with no evidence of malignancy or tissue other than pericardium. Cultures of both the cystic and pericardial liquids were negative. Notably, no giant cells, granulomata, acid-fast bacilli or fungi were identified.

No postoperative complications were noted. The patient had an unremarkable recovery and was discharged on postoperative day six.

**Discussion**

Pericardial cysts are benign intrathoracic lesions that occur in one in every 100 000 persons and constitute 7% of all mediastinal tumours.7 Pericardial cysts can be suspected if the patient complains of non-specific chest pain, dyspnoea, cough or epigastric fullness. Although complications are uncommon, unexpected life-threatening events have been reported, such as acute cardiac tamponade,6 and sudden death.7 No cases of malignant degeneration have been reported. Spontaneous resolution of pericardial cysts is unusual, although two cases of presumed spontaneous resolution have been reported.8

The cysts range in size from 2–3 cm, up to a maximum of 28 cm reported by Braude et al.9 In our case, the pericardial cyst measured $22 \times 15 \times 17$ cm. As the patient had seen many different doctors, including a psychiatrist, with various complaints, the diagnosis was rather belated.

Of all pericardial cysts, 70–75% are located at the right cardiophrenic angle, 22% at the left, and the rest are in the posterior or anterior superior mediastinum.3 In our case, the pericardial cyst occurred in the left cardiophrenic area, to which it was attached by a pedicle over the fat tissue on the left side of the pericardium.

Solid tumours should be considered in the differential diagnosis, including angiomas, lipomas, neurogenic tumours, sarcomas, lymphomas, bronchogenic carcinomas, metastases, granulomatous lesions, and abscesses, along with interstitial bronchogenic cysts, lymphangiomas, diaphragmatic hernias, aneurysms of the heart or great vessels, and other diseases.10

Once a pericardial cyst is suspected on the chest X-ray, thoracic CT with intravenous contrast is commonly used to confirm the diagnosis. However, the diagnosis of a pericardial cyst using CT can be challenging, and the exact location cannot always be ascertained.11 In our case, although CT was conducted in another hospital, a diaphragmatic hernia was diagnosed, and the patient was transferred to our clinic for surgery.
Hynes et al. first used two-dimensional echocardiography to diagnose a pericardial cyst. Transoesophageal echocardiography can be useful if transthoracic echocardiography is inadequate for making the diagnosis. However, no studies have been done to ascertain the superiority of contrast CT over MRI and echocardiography for diagnosis or follow up.

The treatment options for pericardial cysts include simple observation, excision by thoracotomy, thoracoscopic surgical removal, and percutaneous aspiration with the injection of a sclerosing agent such as ethanol to decrease the likelihood of cyst recurrence. The indications for resection of pericardial cysts include large size, symptoms, patient concern, uncertain malignant potential, and the prevention of complications. Histologically, these cysts contain a single layer of mesothelial cells, with the remainder of the wall composed of connective tissue with collagen and elastic fibres.

Pericardial cysts can cause complications via the erosion of adjacent structures, such as the right ventricle wall or superior vena cava. Other complications include cyst rupture, cardiac tamponade, mitral valve prolapse, obstruction of the right main-stem bronchus, and even sudden death.

Treatment is usually required in symptomatic patients or in those with an unclear diagnosis. In other patients, close follow up is sufficient.

Conclusion

Pericardial cysts are rare, benign, mediastinal lesions. They occur most frequently in the third or fourth decade of life and equally among men and women. In order to prevent complications, pericardial cysts can be resected if the cyst is large, symptomatic, or of uncertain malignant potential.

References

Case Report

Right common iliac artery stenosis and stent insertion in Behçet’s disease

Z ULUSAN, AS KARADAG, A HARMAN, F BOYVAT, S BILGIC

Abstract
Behçet’s disease is a multisystem inflammatory disorder that is classified among the vasculitides and can affect all types and sizes of blood vessels. Vascular manifestations of Behçet’s disease are venous and arterial occlusion, and arterial aneurysms. As vasculitis of the vasa vasorum is the main pathological hallmark of Behçet’s disease, it is generally seen as superficial thrombo-phlebitis or occlusion of the major veins; however arterial obstruction and aneurysms may also be seen to a lesser extent. Iliac artery stenosis is highly uncommon.

Here, a case of common iliac stenosis in a 48-year-old patient with Behçet’s disease is reported. As the risk of aneurysm during an operation was high in this patient, he was treated with vascular stent implantation. Due to stent occlusion two months after the operation, percutaneous transluminal angioplasty was performed with an 8-mm balloon. During the three-year follow up, no obstruction was observed.

Keywords: artery stenosis, stent, Behçet’s disease

Behçet’s disease is a recurrent, inflammatory disorder involving multisystems of the body. It was originally described as a triad including oral aphthous ulcers, genital ulcers and uveitis. After the triad was described, systemic involvement of the central nervous system, pulmonary, gastrointestinal, vascular and musculoskeletal systems were also defined related to BD.

The disease is called vasculo-BD when the vascular system is involved. There is a 2–7% arterial involvement in 20- to 40-year-old male BD cases. Arterial involvement is more prevalent in this group of patients when the eyes are also involved. Pseudoaneurysm is the most frequent form of arterial involvement and occlusion is less common. It is almost impossible to estimate the incidence of iliac artery stenosis since it is very uncommon and there were no data for its incidence in the literature. Here, a case of common iliac artery stenosis in a 48-year-old patient with Behçet’s disease is reported, together with its management.

Case report
A 48-year-old man was admitted to our hospital with an acute, severe, cramp-like pain reflecting on his right thigh and leg. The patient had been suffering from recurrent oral ulcers and attacks of genital ulcers and uveitis since the age of 22 years. He later developed erythema nodosum. A skin pathology test was positive at 48 hours. He had previously been diagnosed with BD 24 years earlier, and he was on colchicine treatment. There were no other features in his history, and he was a non-smoker.

The patient’s pain started during a 1 000-m walk, and it

Fig. 1. Right common iliac artery stenosis.
gradually got worse. Over the next two months he could walk only about 200 m without pain, which was acute, cramp-like and recurrent, and mostly resolved spontaneously. On physical examination, his pulses on the right femoral, popliteal, tibial and dorsalis pedis arteries were palpated weakly. There were aphthous ulcers in the oral cavity. The skin pathology test was positive. Blood pressure measured on the right arm was 110/70 mmHg and his heart rate was 80 beats per minute.

On laboratory examination, his erythrocyte sedimentation rate was 45 mm/h, white blood cell count was 12 000/mm³, haematocrit was 43%, haemoglobin was 14.4 g/dl, triglycerides were 100 mg/dl, total cholesterol was 180 mg/dl, high-density lipoprotein cholesterol was 43 mg/dl, low-density lipoprotein cholesterol was 118 mg/dl, and very low-density lipoprotein cholesterol was 20 mg/dl. Serum complements were normal, there were no anti-nuclear antibodies, and the rheumatoid factor was negative. His body mass index was 24 kg/m².

Doppler ultrasonography (US) showed 80% stenosis in the right iliac artery. Since the patient was symptomatic, digital subtraction angiography was performed. Ninety per cent stenosis was detected at the right common iliac artery (Fig. 1), with a pressure gradient of 32 mmHg, and the patient underwent an 8-mm-diameter stent implantation (express, Boston Scientific, Natick, MA, USA) into the iliac artery (Fig. 2).

One month later, the symptoms recurred. On Doppler US, intrastent obstruction was observed. Digital subtraction angiography was performed and 90% stenosis of the right iliac artery stent was confirmed (Fig. 3). The gradient was measured across the stenosis and it was found to be 28 mmHg. Percutaneous transluminal angioplasty (PTA) was then performed with an 8-mm balloon (Fig. 4). After removal of the 6F vascular sheath, the artery was manually compressed to assure haemostasis at the puncture site. The gradient across the stenosis was lowered to 4 mmHg after PTA.

The patient was discharged on day two without any complications. During the three-year follow up, the patient had no pain and he could walk regular distances. He had a normal ultrasound examination and on intermittent Doppler US controls, no obstruction was observed in the stent. No femoral aneurysm appeared.

Discussion
Behçet’s disease has largely been recognised as an unclassified vasculitis affecting blood vessels of all types and sizes. One kind of vasculitis is large-artery involvement. Large and small vascul-
lar involvement can be single or concurrent. Disconnection, disintegration and perivascular inflammatory cell infiltration of the medial elastic fibres and degeneration in the vasa vasoorum have been observed on microscopic examination. In one study, pseudo-aneurysms were common in large or medium-sized arteries, whereas obstructions and stenoses were common in the distal run-off arteries of the lower extremities. Different luminal diameters of the involved arteries accounted for the frequent involvement of the distal run-off arteries.

The stage of active vasculitis of BD is pathologically characterised by massive infiltration of acute inflammatory cells, particularly involving layers of the media and adventitia. At this stage, the intima is swollen and the lumen is commonly thrombosed. Obstructions and stenoses therefore usually occur in the smaller arteries. If there is no thrombosis in the vessel and there is advanced vasculitis, severe inflammation makes the arterial wall weak and sets the stage for the formation of pseudoaneurysm.

Vascular involvement can be observed in up to 40% of patients, and venous disease is more frequent than arterial disease. Venous occlusions, superficial venous thrombosis, deep-vein thrombosis, vena cava thrombosis, cerebral venous thrombosis, Budd-Chiari syndrome, portal vein thrombosis and varices can be seen related to the venous system.

Arterial involvement occurs in only one to 7% of patients with Behcet’s syndrome. Aneurysms, stenoses and obstructions comprise the arterial complications. The most frequently affected artery is the aorta, followed by the pulmonary, femoral, subclavian, popliteal, brachial, iliac and common carotid arteries, with decreasing frequency. Iliac artery aneurysm is seen at a rate of only 0.6%.

It is very important to identify patients with vasculo-Behçet, because they are at risk of developing recurrent vascular lesions after the first episode of vascular injury, and are predisposed to progressive multifocal vessel-related complications. Therefore, their prognosis is worse and they may need more aggressive treatment. Men and patients whose disease started at a younger age are at a higher risk for vascular involvement. Male patients are much more likely to be affected with arterial disease, compared to females. Smoking may be a risk factor for arterial disease in patients with BD. Due to weakness and fragility of the vessel wall and arteritis, open surgical intervention may result in complications, such as the development of pseudo-aneurysms and thrombosis at the sites of anastomosis.

Surgical intervention frequently results in complications, such as recurrent pseudo-aneurysms, graft occlusions, or the development of new aneurysms at the anastomotic or other sites, because of further damage to the vulnerable vessel wall. Development of aneurysm ranges from one to 12 months postoperatively. Pseudo-aneurysm is the development of a pulsatile haematoma as a result of rupture of the whole vessel wall. Aneurysms have the risk of rupture and infection. Aneurysm formation is observed in these patients, even at the insertion sites of venous lines placed for imaging methods.

Surgery is generally indicated for the treatment of systemic arterial aneurysms, as there is a risk of rupture. On the other hand, due to the weakness and fragility of the vessel wall and arteritis, open surgery has complications, such as the development of pseudo-aneurysms and thrombosis at the anastomotic sites. We therefore did not consider a surgical approach for the present patient, and there was a risk of aneurysm during percutaneous implantation of a stent into the iliac artery. During the three-year follow up of the patient, however, no aneurysm or stent occlusion was observed.

When there are no symptoms, non-operative treatment is elected for obstructive or stenotic lesions. However, corticosteroids, immunosuppressives or surgical intervention may be appropriate.

Initial success rates of selective stent placement for iliac artery stenosis are 97 to 99%, and the three-year patency rates range from 74 to 86%. Stents have improved the initial rate of endovascular treatment of iliac artery occlusions. The rate of early stent occlusion was reported to be 1% in patients who had stents for iliac artery stenosis. The patency rates for three and 10 years after balloon dilatation for intrastent stenosis were 64–85% and 46%, respectively. Balloon dilatation is also thought to enhance long-term treatment outcomes.

Oclusion of arteries is less common in BD and stent implantation is a good choice of treatment in these patients as the risk of aneurysm is high after surgical intervention.

References
Case Report

Percutaneous closure of a tricuspid paravalvular leak with an Amplatzer duct occluder II via antegrade approach

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Abstract

Paravalvular leaks are seen after valve-replacement surgery and most patients with these leaks are asymptomatic, probably due to the small size of the leak. Nevertheless, a paravalvular leak after tricuspid valve replacement is a rare complication and may cause severe haemolysis and hepatic dysfunction. It is usually treated surgically. There are no data on percutaneous transcatheter closure of paravalvular leaks. In this report, we present a successful percutaneous closure of a paravalvular leak using an Amplatzer duct occluder II device after a tricuspid valve replacement in a patient with high operative risk who had also had mitral and aortic valve replacements.

Keywords: tricuspid valve replacement, paravalvular leak, percutaneous transcatheter closure

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Almost 210 000 valve-replacement surgeries are performed worldwide annually.1 A paravalvular leak (PVL) is a potential complication of cardiac valve-replacement surgery and may cause severe haemolysis or haemodynamic instability.2 In such cases, haemolysis rarely resolves spontaneously and usually requires a further operation. Re-operation is associated with higher rates of morbidity and mortality. Also, the risk of recurrent paravalvular insufficiency is high after re-operation. Although, there is no specifically designed transcatheter device available for repair of paravalvular leaks, percutaneous transcatheter closure of a PVL may be a promising alternative to surgery.

In this report, we present a case of successful percutaneous closure of a tricuspid PVL using an Amplatzer duct occluder (ADO) II device under the guidance of three-dimensional (3D) transoesophageal echocardiography (TEE) in a patient in whom severe haemolysis and hepatic dysfunction had developed due to a PVL after tricuspid valve replacement.

Case report

A 57-year-old man with aortic and mitral valve replacements five years earlier, and a tricuspid valve replacement with a 31-mm St Jude Medical valve prosthesis three years earlier, was admitted to our hospital for congestive heart failure (NYHA, class III). Laboratory examination revealed severe haemolysis (serum haemoglobin 9.8 g/dl, reticulocyte count 3.8%, lactic dehydrogenase (LDH) 1 080 U/l). The left ventricular ejection fraction measured 40% and a localised moderate PVL was shown on transoesophageal echocardiography (TEE) (Fig. 1).

The patient was symptomatic and the operation was very high risk because of the two previous valve operations. The standard Euroscore of the patient was calculated at 6 points (estimated mortality 10.9–11.5%). Percutaneous closure of this PVL was decided on and informed patient consent was obtained.

The procedure was performed under general anaesthesia with the guidance of 3D TEE. After heparinisation, a 6F multipurpose diagnostic catheter was placed into the right atrium. A 0.035-inch straight-tipped glide wire (Terumo Inc, Japan) was advanced into the right ventricle passing through the PVL site, and confirmed with 2D and 3D TEE. Subsequently, a 6F multipurpose diagnostic catheter was advanced through the defect. The glide wire was then changed with a 0.035-inch super-stiff Amplatzer guidewire (260 cm).

The delivery system was placed into the right ventricle over this extra-stiff wire. The ADO II device (waist diameter 6 mm, disc diameter 12 mm) was screwed to the delivery cable, loaded...
into the sheath, and passed across the PVL. The distal disc was opened and then placed into the orifice of the PVL. Subsequently, the proximal disc was opened in the right atrium. The device was released after establishing that the position of the device was correct (Fig. 2). Closure of the defect was demonstrated with 3D TEE and complete disappearance of the leak was confirmed with 2D TEE (Fig. 3). The total procedural time was 32 minutes and fluoroscopy time was 11 minutes. The post-procedure course was uneventful with normal prosthetic valve function.

Discussion
Paravalvular regurgitation is a complication of prosthetic cardiac valve placement. This may occur soon after or many years post surgery. Small PVLs can be detected in up to half of the patients, using echocardiographic imaging. Larger defects are detected in 3 to 7.5% of patients with valve replacements and the detection rate has increased if TEE is used.3

PVLs are most often found in association with mitral valve prostheses, less often with aortic, and only rarely with pulmonary or tricuspid valve prostheses.4 PVLs may develop more commonly in patients with heavy annular calcification and localised infection.6 Technical mistakes, including incomplete apposition of the sewing ring to the native tissue or breaks in one of the sutures may lead to dehiscence and PVLs.6

Most cases of PVLs are small. They have little clinical significance and tend to improve or disappear over time. However, severe perivalvular regurgitation may lead to some symptoms. These leaks can cause haemolytic anaemia as a result of red cell fragmentation in the high shear-stress regurgitant jet, decreased exercise tolerance or dyspnoea as a result of congestive heart failure, pulmonary hypertension and infective endocarditis.1,7

Spontaneous closure has rarely been encountered. Medical therapy is usually palliative and directed at the congestive heart failure or haemolysis. Re-operation is the gold-standard therapy for symptomatic patients with PVLs, but it is associated with a higher mortality and morbidity rate than that of the initial operation.7 Also, re-operations are associated with increased risk of PVLs.9 Percutaneous repair of perivalvular regurgitation has been proposed as an alternative therapy to avoid the risk of surgery.

Hourihan et al.10 in 1992 reported the first successful percutaneous closure of a PVL, using a Rashkind umbrella device in a patient with an aortic paravalvular leak. Over the years, many devices have been used for percutaneous closure of PVLs, which are often irregular, tortuous and frequently crescent-shaped. The success rate of this procedure depends on the type of PVL and the shape of the closure device. Regurgitation may persist due to incomplete closure of the PVL because of an unsuitable shape of device for the leak.

There is no specifically designed transcatheter device approved for percutaneous closure of PVLs. ADO II, which is designed for closing a patent ductus arteriosus, has a circular shape with two discs and a smaller waist size. Therefore, an ADO II device can provide effective closure for PVLs and improvement of symptoms. For these reasons, an ADO II device was used in our case. Using periprocedural transoesophageal echocardiography provided important anatomical details and helped in optimal device selection and delivery.

Despite this technically feasible and safe treatment modality, there are few reported cases of percutaneous closure of PVLs. Most have been involved with the mitral valve, and a successful percutaneous closure of an aortic PVL was reported. There is no reported case in the literature of a transcatheter closure of a PVL after tricuspid valve replacement. This is probably a result of the few patients receiving tricuspid valve replacements, not because of technical difficulties. To the best of our knowledge, this is the
first case report showing percutaneous transcatheter closure of a tricuspid PVL using an ADO II device.

Conclusion
Haemodynamically important PVLs after any valve replacement may be closed percutaneously using an ADO II. Percutaneous transcatheter closure of PVLs is technically feasible and a safe treatment modality, which could be regarded as a promising alternative to surgery in patients with high surgical risk.

References
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