Hypertensive Heart Failure

S Ramakrishnan, SS Kothari, VK Bahl
Department of Cardiology, All India Institute of Medical Sciences, New Delhi

Heart failure is increasingly recognized worldwide. Hypertension and ischemic heart disease are the two cardinal causes of heart failure. Over the years, a voluminous amount of literature has accumulated regarding various facets of hypertensive heart failure. Despite this, the risk and mechanisms of heart failure in patients with hypertension is not completely understood. Further, due to the common coexistence of coronary artery disease (CAD) and hypertension in the population, the relative contributions of CAD and hypertension to heart failure have been difficult to disentangle. This article provides an overview of the salient aspects of hypertensive heart failure (HHF) from a clinical standpoint.

Epidemiology

The data on the prevalence of hypertension in patients with heart failure are rather discordant. In the Framingham Heart Study cohort, hypertension antedated the development of congestive heart failure (CHF) in 91% of cases and was associated with a two- to three-fold risk of development of CHF after adjusting for age and other risk factors. Hypertension also had a high population-attributable risk (the percentage of heart failure cases that can be attributed to hypertension) for CHF, viz. 39% in men and 59% in women in the Framingham study. In contrast, hypertension was found to be the primary factor in only 17% of hospitalized heart failure patients. Moreover, hypertension was reported to be the primary etiological factor in only 4% of heart failure patients in an overview of 31 studies.

Recent data from two population-based studies indicate that hypertension is responsible for CHF in 4%–20% of patients. In a Swedish study of 7500 patients followed up for 27 years, the identified etiological factors for CHF were hypertension in 20.3%, and CAD either alone or in combination with hypertension in 58.8%. Fox et al. have reported hypertension to be the primary attributable factor for CHF in only 4.4% of incident cases of CHF examined prospectively. This study emphasized the fact that associated CAD might be clinically underestimated if coronary angiography is not routinely performed. However, the contribution of hypertension to heart failure in patients with significant CAD was not analyzed in the study. Myocardial infarction (MI) is associated with a five- to six-fold increase in the risk of heart failure in hypertensive patients. Antecedent hypertension interacts with neurohumoral activation, and thereby adversely modifies early ventricular remodeling to increase the risk of heart failure after MI. Taken together, these data suggest that while hypertension clearly causes or contributes to heart failure, the absolute risk of heart failure in an individual remains low in the absence of other factors.

Individual Risk Assessment

In addition to CAD, several other patient-related risk factors influence the risk of heart failure. These include age, gender, race, diabetes, valvular heart disease, obesity, severity of hypertension, left ventricular hypertrophy (LVH), and alcoholism. An Italian study suggests that in a 60-year-old asymptomatic man with a systolic blood pressure (BP) of 160 mmHg, the risk of developing heart failure is 0.37% per year in the absence of LVH, which increases to 0.9% per year in the presence of hypertrophy. If ischemic heart disease, valvular heart disease, and diabetes coexist in the same subject, then the risk of heart failure rises to 5.1% and 9.5% in the absence and presence of LVH, respectively.

In humans, what degree and duration of hypertension would cause LVH or heart failure has not been determined. No threshold of BP has been observed for a substantive change in risk for heart failure, yet 70%–80% of patients with heart failure and hypertension have a BP >160/100 mmHg. The incidence of CHF is clearly greater at increasing levels of blood pressure and lower with lesser systolic BP. The etiology of hypertension could also influence the risk of CHF. Renovascular hypertension is associated with more target organ damage and possibly more CHF.

The incidence of heart failure increases as a function of age. In the young and middle-aged, the incidence of heart failure correlates with diastolic and mean pressures. However, in the elderly, both these measures correlate
poorly with heart failure. Instead, pulse pressure, a measure of pulsatile load, is a powerful and independent predictor of heart failure.\textsuperscript{13} A wide pulse pressure is either an indicator or a consequence of aortic stiffness, which increases the systolic BP and lowers the diastolic BP by a variety of mechanisms. An increase in the systolic BP increases the load, and lower diastolic BP reduces the coronary perfusion pressure, thereby increasing the vulnerability of the heart to failure.\textsuperscript{13} Both hypertension and LVH are stronger risk factors for CHF in women as compared to men. However, women have a lower prevalence of LVH than men for any given level of blood pressure.\textsuperscript{14} In obese hypertensive patients, varying combinations of pressure and volume overload are seen, resulting in a mixed eccentric-concentric form of LVH.\textsuperscript{15} Moreover, obesity is an important independent predictor of left ventricular (LV) mass, and the effects of hypertension and obesity are additive.\textsuperscript{16}

Diabetes is emerging as an important precursor of heart failure.\textsuperscript{7} In the United Kingdom Prospective Diabetic Study (UKPDS),\textsuperscript{10} the incidence of heart failure in 4801 white men with type 2 diabetes was 2.4 per 1000 person-years’ follow-up in patients with a systolic BP in the range of 120–129 mmHg, and rose to 7.0 in patients with a systolic BP >160 mmHg. However, no threshold of BP was seen for the occurrence of heart failure.

Left Ventricular Hypertrophy

Left ventricular hypertrophy represents the major biological adaptation to increased pressure load and its limitations. Thus, understanding ventricular remodeling influences the entire issue of heart failure in hypertension and its therapy. Although cardiac failure would possibly occur earlier in the absence of LVH, LVH is clearly a double-edged sword. Hypertensive LVH has repeatedly been shown to be an independent marker of cardiac failure, accelerated atherosclerosis of the coronary arteries, lethal cardiac arrhythmias, and sudden death.\textsuperscript{17} The increased risk of sudden death can be explained at least in part by the repolarization abnormalities described in patients with hypertensive LVH. Graded prolongation of the QT interval occurs with increasing LV mass index, and measures of QT dispersion are also related to the LV mass.\textsuperscript{18} Abnormalities of the QT interval occur irrespective of the geometry of LVH.\textsuperscript{14} Each 50 g/m\textsuperscript{2} increase in LV mass is associated with a 1.49 increase in the relative risk of cardiovascular disease for men and a 1.57 increase for women.\textsuperscript{19} However, individuals differ in their response of LVH to a given pressure load. Only 15%–20% of hypertensive patients show echocardiographic evidence of LVH\textsuperscript{18} and, in hypertensive patients, it is estimated that approximately 40% of the variance in LV mass is accounted for by the total LV load.\textsuperscript{19} Further, LVH occurs in the absence of hypertension and, in some cases, precedes its development (cardiogenic hypertension).\textsuperscript{20} Old age, male sex, obesity, diabetes in women, black race, and certain genetic influences such as angiotensin-converting enzyme (ACE) polymorphisms lead to a greater LVH for a given BP.\textsuperscript{21} The geometric pattern of LVH in hypertension also influences the risk. The 10-year incidence of cardiovascular events is reported to be 30% in those with concentric LVH, 25% in those with eccentric LVH, 15% in those with concentric remodeling (increased relative wall thickness with a normal LV mass), and 9% in those with a normal LV mass.\textsuperscript{22}

### Cellular Mechanisms of Left Ventricular Hypertrophy and Heart Failure

Mechanical forces are thought to be the principal determinants of cardiac hypertrophy. The principal mechanical contributor that promotes LVH in early hypertension is sustained increase in systemic vascular resistance.\textsuperscript{19} The molecular mechanisms that translate increased wall stress to cellular hypertrophy are beginning to be elucidated.\textsuperscript{22} Increased wall stress activates a stretch receptor that releases intracellular calcium and activates calcineurin, which, acting through a series of subcellular events, activates fetal cardiac and growth genes, such as c-myc and c-jun, to upregulate protein synthesis.\textsuperscript{24} The mechanical forces work in tandem with potent neurohumoral mediators such as angiotensin II, norepinephrine, and insulin.\textsuperscript{23}

The hypertrophy that occurs in hypertensive heart disease (HHD) is not homogeneous. In contrast to the hypertrophy seen in athletes, in HHD it is disproportionate, and predominantly involves noncardiomyocytes. Thus, it is not the quantity but the quality of the myocardium that distinguishes HHD from the adaptive hypertrophy of the athlete.\textsuperscript{25} In certain disease states such as chronic anemia, small arteriovenous fistula, atrial septal defect, or hyperthyroidism, cardiac hypertrophy occurs with preserved homogeneity. These conditions are not associated with activation of the circulating renin-angiotensin system.\textsuperscript{26} Several attempts have been made to differentiate physiologic and pathologic hypertrophy by noninvasive means. It has been shown that the long-axis mean annular velocities measured by tissue Doppler are significantly decreased in HHD as compared to athletes.\textsuperscript{27}

Fibrosis, an integral feature of the adverse structural
remodeling of the heart seen in HHD, appears in two morphologically distinct forms: a reactive form expressed as a perivascular/interstitial fibrosis, and a reparative fibrosis represented by microscopio scars that replace necrotic myocytes. A diver accumulation of extracellular matrix initially increases myocardial stiffness, and its continued accumulation impairs contractile behavior. Early evidence suggests that the measurement of serum concentrations of procollagen type I C-terminal propeptide (a peptide that is cleaved from procollagen type I during the synthesis of fibril-forming collagen type I) may provide indirect information on the extent of myocardial fibrosis. Gadolinium-DTPA delayed-enhancement magnetic resonance imaging (de-MRI) is accurate in assessing regional fibrosis noninvasively.

Imaging studies using 111In-labeled monoclonal antimyosin antibodies have shown that cell damage occurs early in HHD, and abnormally stimulated apoptosis of cardiomyocytes and noncardiomyocytes could be responsible for such cell damage. Local factors that may trigger apoptosis include mechanical forces, oxidative stress, hypoxia, and an unbalanced presence of growth factors and cytokines (e.g. angiotensin II) or neurotransmitters (e.g. norepinephrine). Since signals that potentially mediate hypertrophy are largely the ones proposed to mediate apoptosis also, it has been proposed that when growth signals persist chronically in terminally differentiated cells, they produce a contradictory genetic demand and trigger the apoptosis. The absence of a clear association between cardiomyocyte apoptosis and absolute BP values indicate that nonhemodynamic factors, especially angiotensin, may be more important.

Clinical Transition to Heart Failure

In humans, HHD leads to three recognizable stages in evolution of heart failure: LVH, diastolic dysfunction, and systolic dysfunction, not necessarily in the same order.

Abnormalities of LV diastolic filling are observed in various forms of hypertension in adults as well as children, and the prevalence may be as high as 22% in asymptomatic hypertensive patients with a BP of >140/90 mmHg. Diastolic filling abnormalities have been shown to generally correlate with LV mass, and BP. However, diastolic dysfunction could precede the onset of hypertension in the young male offspring of hypertensive parents.

In hypertensive patients, diastolic heart failure is increasingly being recognized as a cause of CHF. However, the incidence is not clear, as establishing a definite diagnosis is difficult. In previous published studies on unselected heart failure populations, the reported prevalence of patients having preserved systolic function varied widely, from 13% to 74%. Each 1 mmHg increase in pulmonary capillary wedge pressure, a measure of diastolic dysfunction, is shown to be associated with a 23% increase in the risk of all-cause mortality, and a 13% increase in the risk of cardiovascular events in the 174 patients of uncomplicated hypertension followed up for 10 years.

In the absence of MI, hypertensive patients with LVH commonly have supernormal ejection phase indices on echocardiography, and a significant decrease in LV ejection fraction occurs very late in the course of HHD. Yet, normalcy of these ejection indices may not imply normal systolic function in hypertension. When indices such as mid-wall fractional shortening are used, up to 16% of hypertensive patients were found to have depressed LV systolic function. Hypertensive patients also have a depressed end-systolic stress relationship. Furthermore, hypertension may lead to exercise-induced systolic LV dysfunction even though the resting LV function may be normal. A acute heart failure (pulmonary edema) in a hypertensive patient could be due to transient systolic dysfunction, diastolic dysfunction, ischemia, or mitral regurgitation. However, nearly 40% of hypertensive patients have a normal LV ejection fraction indicating diastolic dysfunction as the cause. Normally, the left ventricle compensates for an increase in systolic load by increasing end-diastolic volume (i.e., using preload reserve). In a patient with diastolic dysfunction, this small increase in left ventricular end-diastolic volume may be associated with a marked elevation in diastolic pressure, because of the reduced distensibility of the left ventricle, thereby precipitating pulmonary edema. Common precipitants of overt heart failure in patients with diastolic dysfunction include old age, tachycardia, sudden severe increase in overload such as a hypertensive crisis, and loss of atrial kick. The relative contribution of significant ischemia due to epicardial obstructive CAD in the causation of pulmonary edema is difficult to quantify. More than 60% of hypertensive patients presenting with flash pulmonary edema had epicardial obstructive CAD in one study. Interestingly, however, the flash pulmonary edema recurred in half the patients even after revascularization. The diagnosis of CAD in patients suspected of having HHF is difficult. The sensitivity and specificity of noninvasive stress tests are altered by both heart failure and hypertension. In heart failure patients, noninvasive stress tests can be less sensitive due to the low level of stress.
obtainable, and less specific due to doubtful echocardiographic pictures and perfusion images of dilated, hypokinetic ventricles. The baseline electrocardiogram also often shows intraventricular conduction delays and altered repolarization at rest. Hence, it has been suggested that in heart failure patients the coronary angiogram may be the sole determining test for excluding obstructive epicardial CAD. However, to assign ischemia as the etiology of heart failure in the presence of hypertension, the anatomic disease should be associated with regional wall motion abnormalities, perfusion abnormalities, or ischemic valvular dysfunction. It has been suggested that in HHF patients with a preserved LV ejection fraction, two groups could be identified based on LV mass. If there was a high degree of reactive hypertrophy, the patients had a lower chance of a positive stress test, whereas patients with only moderate hypertrophy have a high rate of epicardial obstructive CAD.

Recently, tissue Doppler measurement of the cyclic variation index of the backscatter signal at the septum level has shown significant alterations in hypertensive patients, and it correlates with the LV mass and geometry of LVH. The alterations could be reversed with antihypertensive treatment. Hence, ultrasonic tissue characterization has the potential to identify early those hypertensive patients at risk of adverse remodeling.

**Impact of Treatment**

The reported median survival following the diagnosis of heart failure in hypertensive subjects is 1.37 years in men and 2.48 years in women. The 5-year survival rates are reported to be 24% in men and 31% in women. The prognosis may be better for patients with diastolic dysfunction. For example, in heart failure patients with preserved systolic function, the annual mortality was reported to be 8.7% vs. 3.0% for matched controls, and in patients with LV systolic dysfunction, the annual mortality was 18.9% vs. 4.1% for matched controls in the Framingham cohort. Hence, treatment is required before the onset of clinical heart failure.

The efficacy of antihypertensive medications in reducing the incidence of heart failure in diastolic as well as isolated systolic hypertension has been well documented. Meta-analysis of long-term hypertension has also shown that sustained lowering of blood pressure is effective in preventing LVH and CHF, regardless of the agent used, a finding not corroborated by a recent meta-analysis. Currently, there is no clear evidence that one class of antihypertensive agent is more effective than the other in retarding the progression of HHD; however, there is some evidence that calcium-channel blockers may be less effective. In the recently reported ALLHAT study, the amlodipine group had a 38% higher risk of heart failure, and a 35% higher risk of hospitalized/fatal heart failure as compared to chlorthalidone. The recent meta-analysis has also shown that the risk of heart failure was 15% higher with calcium-channel blockers as compared to beta-blockers, and 18% higher as compared to ACE inhibitors. The relative superiority of ACE inhibitors and diuretics is not clear, as two recent large trials have yielded conflicting results. In the ALLHAT study, the lisinopril group had a 19% increased risk of heart failure as compared to patients treated with chlorthalidone, whereas in the second Australian national blood pressure study, the incidence of heart failure was not significantly different between ACE inhibitor- and diuretic-treated patients.

Management of hypertension should not focus merely on a reduction in BP, but must also target the adverse structural remodeling that begets HHD. Such approaches target diastolic dysfunction, adverse remodeling, apoptosis, fibrosis, and neurohumoral mediators. Drugs that are shown to be reparative include ACE inhibitors, angiotensin-1 receptor antagonists, endothelin antagonists, and aldosterone receptor antagonists. Two approaches that influence apoptosis include inhibition of apoptotic signals that trigger the process, and direct blockade of the intracellular apoptotic mechanisms. Drugs shown to be effective are antiapoptotics include ACE inhibitors, losartan, alfa-blockers, and calcium-channel blockers. Hydralazine and diuretics have been shown to have no effect on apoptosis.

Gene therapy, targeting abnormalities of ion handling, cellular signaling, neurohumoral control, and apoptosis, hold promise in retarding the progression to heart failure. ACE inhibitors have been shown to cause regression in fibrosis, leading to improvement in diastolic dysfunction as compared to diuretics. Further progress on specific therapy is awaited.

**Conclusions**

The data on the prevalence of hypertension in heart failure are rather discordant. The duration and severity of hypertension critical to cause heart failure is not known. For the same degree of hypertension, several patient-related factors modify the occurrence of heart failure. In patients with HHF, CAD needs to be carefully evaluated. Mechanisms of hypertrophy and remodeling that contribute to systolic and diastolic dysfunction are beginning to be understood. Antihypertensive treatment
reduces the risk of HHF (possibly with some differences among various antihypertensive drugs). Specific therapies targeting adverse cardiac remodeling are under development.

References

22. Koren MJ, Devereux RB, Casale PN, Savage DD, Laragh JH. Relation of left ventricular mass and geometry to morbidity and mortality in uncomplicated essential hypertension. Ann Intern Med 1991; 114: 345–352
40. Gandhi SK, Powers JC, Nomer AM, Fowle K, Kitzman DW, Rankin...
Ramakrishnan et al. Hypertensive Heart Failure

Indian Heart J 2003; 55: 21–26

48. Veterans Administration Cooperative Study Group on Antihypertensive Agents. Effects of treatment on morbidity in hypertension. Results in patients with diastolic blood pressure averaging 90 through 115 mm Hg. JAMA 1970; 213: 1143–1152
52. The ALLHAT officers and coordinators for the ALLHAT collaborative research group. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). JAMA 2002; 288: 2981–2997
Role of Infections in Atherogenesis

Sandeep T Laroia, Apar Kishor Ganti, Anil Potti
Department of Medicine, University of North Dakota School of Medicine and Health Sciences, USA

In 1921, Ophuls proposed that infections could lead to atherosclerosis. This hypothesis was based on pathologic specimens of blood vessels, which showed macrophage infiltrates and foam cells. Five decades later, in 1978, Fabricant et al. once again showed arterial lesions similar to atherosclerosis in chicken infected with the avian herpesvirus. Recent advances in diagnostic techniques have facilitated the re-emergence of this hypothesis. It is now well accepted that atherosclerosis is an inflammatory process, and a natural corollary of this concept is that microorganisms could be the prime initiators of this process. Data from several studies indicate an increased prevalence of chronic infections in atherogenesis. The agents that have been implicated in this process are Chlamydia pneumoniae, Helicobacter pylori, herpes simplex virus, and cytomegalovirus (CMV). In this article, we evaluate the evidence available both for and against the different etiological agents, and their current status in the pathogenesis of atherosclerosis.

Basic Scheme of Atherogenesis

Simplified, atherogenesis is the passage of low-density lipoprotein (LDL)-cholesterol through dysfunctional endothelium at points of low shear stress. In addition, mechanical stress can lead to the aggravation of this phenomenon. LDL-cholesterol penetrates the dysfunctional endothelium and undergoes oxidation. The oxidized LDL causes further endothelial dysfunction. Monocytes penetrate the endothelium, differentiate into macrophages, attract more macrophages and the resultant foam cells, which are lipid-laden macrophages, accumulate in the region. These cells may ultimately rupture, causing the release of toxic inflammatory mediators that trigger a fibroproliferative response from smooth muscles.

Potential Role of Infections in Atherogenesis

Endothelial dysfunction, the trigger for atherogenesis, can be induced by systemic or local infection. Multiple mechanisms have been proposed which include the following:

1. Bacterial endotoxins and tumor necrosis factor (TNF-alpha) can inhibit vasodilator nitric oxide generated by endothelial-dependent processes;
2. Endothelial stunning, a mechanism which hypothesizes that periods of endothelial inactivity can be induced by a brief exposure to endotoxin;
3. Direct infection of the endothelium by infectious agents, especially the herpesviruses including CMV;
4. Altered expression of growth-controlling proteins by vascular smooth muscles after infection with certain viruses, which leads to these cells obtaining a growth advantage and thus may contribute to atherosclerosis and restenosis.

Furthermore, C-reactive protein (CRP) and fibrinogen (acute phase reactants), which are strong independent predictors of subsequent cardiovascular events, are found to be elevated in infectious states as well, and elevated levels of cytokines are found in both infections and acute coronary syndromes. These circulating cytokines may cause abnormal endothelial function, increased thrombosis, and toxic free radical generation, leading to accelerated atherogenesis.

Evidence for the Role of Infections in Atherosclerosis

Herpesviridae, especially CMV, H. pylori, and C. pneumoniae, have been extensively studied for their effect on atherosclerosis. Tables 1, 2, and 3 list the various studies that showed a positive correlation between atherogenesis and infection by herpesviruses, H. pylori, and C. pneumoniae, respectively. These studies included both human and experimental research. The experimental works listed include those involving both experimental animals and tissue studies.

Evidence Against the Role of Infections in Atherosclerosis

Though there are a number of reports favoring the role of infections in atherosclerosis, there are also studies that do not support this hypothesis. These studies have used different methodologies and have produced conflicting results. It is important to note that the role of infections in atherosclerosis is still a topic of ongoing research and further studies are needed to clarify the extent to which infections contribute to this disease.
Evidence favoring the role of CMV and other herpesviridae in atherogenesis

<table>
<thead>
<tr>
<th>Reference</th>
<th>Year</th>
<th>Number of subjects (n)</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grattan et al.16</td>
<td>1989</td>
<td>301</td>
<td>Increased risk of developing vascular lesions in post-transplant patients with clinical CMV infection</td>
</tr>
<tr>
<td>Zhu et al.17</td>
<td>2000</td>
<td>238</td>
<td>CMV seropositivity associated with increased CRP levels, a significant determinant of CAD</td>
</tr>
<tr>
<td>Muhlestein et al.18</td>
<td>2000</td>
<td>985</td>
<td>CMV seropositivity and elevated CRP, in combination, are independent predictors of mortality in patients with CAD</td>
</tr>
<tr>
<td>Siscovick et al.19</td>
<td>2000</td>
<td>213</td>
<td>Presence of IgG antibodies to HSV-1 is associated with a 2-fold increase in the risk of incident MI and CAD-related death</td>
</tr>
<tr>
<td>Horvath et al.20</td>
<td>2000</td>
<td>244</td>
<td>Genomic DNA of CMV is found in arterial walls at a significantly higher rate in IHD patients than the nonischemic control group</td>
</tr>
<tr>
<td>Sorlie et al.21</td>
<td>2000</td>
<td>515</td>
<td>Population with the highest antibody levels of CMV (approximately the upper 20%) showed an increased relative risk of CHD</td>
</tr>
<tr>
<td>Kaftan et al.22</td>
<td>1999</td>
<td>310</td>
<td>Titer of anti-CMV antibody and the levels of CRP can predict patients with a high risk of CAD</td>
</tr>
<tr>
<td>Neumann et al.23</td>
<td>2000</td>
<td>551</td>
<td>Previous CMV infection increased the risk of coronary thrombotic events after stent placement</td>
</tr>
<tr>
<td>Biocina et al.24</td>
<td>1999</td>
<td>284</td>
<td>Patients undergoing orthotopic heart transplantation who experienced CMV disease had significantly worse long-term survival compared to those with the infection only or without the infection</td>
</tr>
<tr>
<td>Blum et al.25</td>
<td>1998</td>
<td>65</td>
<td>Patients with high anti-CMV titer had a higher prevalence of CAD and a higher restenosis rate than those with a lower antibody titer</td>
</tr>
<tr>
<td>Zhou et al.26</td>
<td>1996</td>
<td>75</td>
<td>Patients who were seropositive for CMV had a greater than 5-fold increased risk of restenosis following coronary atherotomy</td>
</tr>
<tr>
<td>Alber et al.27</td>
<td>2000</td>
<td>NA</td>
<td>Atheroma formation was accelerated in apo E/−/− mice infected with murine gamma-herpesvirus-68 compared with control uninfected apo E/−/− mice</td>
</tr>
<tr>
<td>Lemstrom et al.28</td>
<td>1997</td>
<td>NA</td>
<td>Treatment with ganciclovir significantly reduced intimal thickening in the presence of CMV infection</td>
</tr>
<tr>
<td>Zhou et al.29</td>
<td>1999</td>
<td>60</td>
<td>CMV infection of immunocompetent adult rats increased the neointimal response to vascular injury</td>
</tr>
<tr>
<td>Lin et al.30</td>
<td>2000</td>
<td>40</td>
<td>Bovine herpesvirus-4 can accelerate the atherosclerotic process in rabbits</td>
</tr>
</tbody>
</table>

CMV: cytomegalovirus; HSV: herpes simplex virus; CRP: C-reactive protein; CAD: coronary artery disease; CHD: coronary heart disease; apo E: apolipoprotein E; IHD: ischemic heart disease

Infections in atherosclerosis, the number of reports arguing against such a role is equally impressive. In the discussion that follows, a few reports which showed no effect of infection in the pathogenesis of atherogenesis have been listed.

Evidence against herpesviridae: Siscovick et al.19 did not find any correlation between the presence of IgG antibodies to CMV and the risk of acute myocardial infarction (AMI) or coronary artery disease (CAD) in elderly patients. Choussat et al.60 studied systemic markers of inflammation in patients with unstable angina or non-Q wave MI, and the relationship between these markers, seropositivity to chronic infections (CMV, H. pylori, and C. pneumoniae), and prognosis. They found no association between the levels of each inflammatory marker and the serologic status. Furthermore, levels of inflammatory proteins in patients seronegative to all 3 agents were comparable to those of patients seropositive to 2 or 3 infectious agents. The composite end-points of death, MI, recurrent angina, or revascularization at 1-year follow-up did not differ according to the serologic status.63 To determine if CMV infection is a risk factor for primary CAD and the association between CMV infection and CAD (>50% blockage in any coronary artery), Adler et al.64 investigated nearly 900 successive nontransplant patients undergoing coronary angiography. By the use of logistic regression, they found that CMV seropositivity (p=0.462), the level of IgG antibodies to CMV whole-cell antigen (p=0.98), or the levels of IgG antibodies to CMV glycoprotein B (p=0.67) were not significantly associated with CAD. These data suggest that CMV infection is not a major risk factor for the development of primary CAD in adults.64
Evidence against Helicobacter pylori: A Finnish group failed to show a statistically significant relationship between patients infected with H. pylori and CAD; interestingly, this study showed higher levels of serum triglycerides in patients seropositive for H. pylori. In their study, Tsai and Huang showed that H. pylori seropositivity was not associated with several coronary risk factors in either cases or controls. The proportion of H. pylori-positive patients was higher among cases with triple-vessel disease (77.5%) than in those with double-vessel (67.3%) and single-vessel (65.7%) disease; however, the differences were not statistically significant. In this study, no increase was found in H. pylori seropositivity in subjects with CAD. In a recent review, Menge et al. found that the present data were inconclusive regarding the association between H. pylori infection and CAD. They concluded that proposed links between H. pylori infection and coronary heart disease (CHD), such as hyperhomocysteinemia or autoimmune mechanisms due to cross-reacting antibodies to H. pylori heat-shock protein with human endothelium-derived heat-shock protein, need further confirmation. Quinn et al. studied the relationship between angiographically defined CAD and serologic evidence of H. pylori infection in 488 patients undergoing elective coronary angiography. There was no association between H. pylori infection and CAD. Basilio et al. retrospectively analyzed 149 subjects who underwent an esophagogastroduodenoscopy, in whom the search for H. pylori was histologically performed, and found that the prevalence of CAD was not significantly different from that observed in H. pylori-free patients (26% vs. 21%; p=0.527). Lastly, a meta-analysis of 18 epidemiological studies involving over 10,000 patients failed to demonstrate any significant association between H. pylori infection and CAD. Khurshid et al. prospectively studied 179 patients undergoing coronary angiography for suspected CAD and found that H. pylori infection rates were similar in patients with normal and abnormal coronary arteries, and infection with H. pylori was not an independent risk factor for CAD. In patients with CAD, H. pylori infection was not a risk factor for more severe disease.

Evidence against Chlamydia pneumoniae

Patient data: The Physicians Health Study prospectively measured IgG antibodies against C. pneumoniae in 343 participants with first MI. A similar number of age- and smoking-matched controls were also followed up for a period of 12 years. The prevalence of seropositivity was the same in both the groups. Markus et al. obtained ultrasonic images of the carotid artery to determine the intima-media thickness (IMT) and the thickness of any atheroma plaques, and found no evidence that serological evidence of C. pneumoniae infection is associated with early atherosclerosis. They also found no evidence that C. pneumoniae results in a chronic systemic inflammatory state. Hoffmeister et al. investigated the association between seropositivity to chlamydial lipopolysaccharide

Table 2. Evidence favoring the role of Helicobacter pylori in atherogenesis

<table>
<thead>
<tr>
<th>Reference</th>
<th>Year</th>
<th>Number of subjects (n)</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mendall et al.</td>
<td>1994</td>
<td>200</td>
<td>Seropositivity for H. pylori confers a 2-fold risk of CAD</td>
</tr>
<tr>
<td>Patel et al.</td>
<td>1995</td>
<td>388</td>
<td>76.6% of men with ischemia or infarction were seropositive compared with 45.5% of men with normal electrocardiograms</td>
</tr>
<tr>
<td>Gunn et al.</td>
<td>2000</td>
<td>556</td>
<td>1.80-fold increase in AMI risk, which increased further to 2.25-fold in subjects &lt;55 years of age</td>
</tr>
<tr>
<td>Kahan et al.</td>
<td>2000</td>
<td>200</td>
<td>Seropositivity for H. pylori is associated with previous AMI</td>
</tr>
<tr>
<td>Farsak et al.</td>
<td>2000</td>
<td>85</td>
<td>H. pylori DNA was found in 17 of 46 (37%) endarterectomy specimens with atherosclerotic plaques and in none of the controls</td>
</tr>
<tr>
<td>Hoffmeister et al.</td>
<td>2001</td>
<td>405</td>
<td>Significant association is observed between H. pylori infection and decreased HDL-cholesterol levels</td>
</tr>
<tr>
<td>Pieniazek et al.</td>
<td>1999</td>
<td>157</td>
<td>Infection significantly increases the risk of CAD</td>
</tr>
<tr>
<td>Ameriso et al.</td>
<td>2001</td>
<td>38</td>
<td>H. pylori is present in a substantial number of carotid atherosclerotic lesions</td>
</tr>
<tr>
<td>Laurila et al.</td>
<td>1999</td>
<td>880</td>
<td>The serum triglyceride and total cholesterol concentrations were significantly higher in males with positive antibody titers than in those with no infection (p&lt;0.001)</td>
</tr>
<tr>
<td>Markus et al.</td>
<td>1998</td>
<td>357</td>
<td>H. pylori seropositivity was associated with large-vessel disease and lacunar stroke</td>
</tr>
<tr>
<td>Birnie et al.</td>
<td>1998</td>
<td>136</td>
<td>Anti-heat shock protein 65 titers correlated with both the severity and extent of coronary atherosclerosis</td>
</tr>
</tbody>
</table>

H. pylori: Helicobacter pylori; CAD: coronary artery disease; AMI: acute myocardial infarction; HDL: high-density lipoprotein
Table 3. Evidence favoring the role of *Chlamydia pneumoniae* in atherogenesis

<table>
<thead>
<tr>
<th>Reference</th>
<th>Year</th>
<th>Number of subjects (n)</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hu et al.42</td>
<td>1999</td>
<td>40</td>
<td>Infection exacerbated the development of atherosclerosis in mice</td>
</tr>
<tr>
<td>Muhlestein et al.43</td>
<td>1998</td>
<td>30</td>
<td>Intranasal infection accelerated intimal thickening in rabbits given a cholesterol-enhanced diet. Also, treatment with azithromycin after exposure prevents accelerated intimal thickening</td>
</tr>
<tr>
<td>Liu et al.44</td>
<td>2000</td>
<td>NA</td>
<td>Infection for 6 months produced a significantly greater exacerbation of aortic atherosclerosis in LDLR⁻/⁻ mice in the presence of a high-cholesterol diet</td>
</tr>
<tr>
<td>Kuo et al.45</td>
<td>1993</td>
<td>36</td>
<td><em>C. pneumoniae</em> was detected in coronary artery atheromas by immunocytochemistry and PCR in 20 of 36 autopsy cases with coronary artery atheromas</td>
</tr>
<tr>
<td>Muhlestein et al.46</td>
<td>1996</td>
<td>114</td>
<td>Atherectomy specimens of patients with symptomatic CAD showed positive chlamydial antigen by direct immunofluorescence in 73% of patients</td>
</tr>
<tr>
<td>Ericson et al.47</td>
<td>2000</td>
<td>60</td>
<td>Direct immunofluorescence for chlamydial antigen was reactive in 86% of cases with severe atherosclerosis but in only 6% of cases with mild atherosclerosis (p&lt;0.01)</td>
</tr>
<tr>
<td>Maass et al.48</td>
<td>1998</td>
<td>70</td>
<td>Coronary artery endarterectomy specimens showed viable chlamydial organisms in 16% and chlamydial DNA in 30%</td>
</tr>
<tr>
<td>Bartels et al.49</td>
<td>1999</td>
<td>58</td>
<td>Viable <em>C. pneumoniae</em> was recovered from 16% of occluded vein grafts while except for 1 native saphenous vein, all control vessels were negative for <em>C. pneumoniae</em></td>
</tr>
<tr>
<td>Farsak et al.35</td>
<td>2000</td>
<td>85</td>
<td><em>C. pneumoniae</em> DNA was found in 26% of 46 endarterectomy specimens and none of the healthy vascular wall specimens (p&lt;0.001)</td>
</tr>
<tr>
<td>Ouchi et al.50</td>
<td>2000</td>
<td>177</td>
<td>62% of atherosclerotic plaques from symptomatic patients were infected with <em>C. pneumoniae</em> compared with just 2% of nonatherosclerotic tissues</td>
</tr>
<tr>
<td>Saikku et al.51</td>
<td>1998</td>
<td>213</td>
<td>In a series of 213 patients with AMI, 38% showed strong seropositivity, 35% showed intermediate seropositivity, and 28% showed no detectable antibodies</td>
</tr>
<tr>
<td>Gabriel et al.52</td>
<td>1998</td>
<td>282</td>
<td>Patients with CAD had a higher prevalence of <em>C. pneumoniae</em> PCR from pharyngeal specimens (36% v. 22%)</td>
</tr>
<tr>
<td>Toss et al.53</td>
<td>1998</td>
<td>256</td>
<td>Among 256 patients with unstable angina, increased antibody titers to <em>C. pneumoniae</em> were more common than in controls (36% v. 19%). Even asymptomatic atherosclerosis specimens showed increased antibody titers</td>
</tr>
<tr>
<td>Melnick et al.54</td>
<td>1993</td>
<td>300</td>
<td>In 300 patients, cardiac wall thickening seen on ultrasound (a marker for asymptomatic atherosclerosis) was correlated with positive antibody titers (73% v. 63%)</td>
</tr>
<tr>
<td>Burian et al.55</td>
<td>2001</td>
<td>405</td>
<td>Presence of high-level antibodies to <em>C. pneumoniae</em> is an independent risk factor for the development of coronary atherosclerosis</td>
</tr>
<tr>
<td>Leowattana et al.56</td>
<td>2000</td>
<td>243</td>
<td>A significantly higher percentage of patients with CAD had positive IgG and IgA antibodies to <em>C. pneumoniae</em> as compared to healthy controls</td>
</tr>
<tr>
<td>Maass et al.57</td>
<td>2000</td>
<td>188</td>
<td><em>C. pneumoniae</em> was detected in 52 (28%) of 188 persons with unstable angina and in 13 (26%) of 50 persons with MI</td>
</tr>
<tr>
<td>Kaftan et al.58</td>
<td>2000</td>
<td>160</td>
<td>Levels of triglyceride, LDL-cholesterol, CRP, fibrinogen, and total cholesterol/HDL-cholesterol ratio had a direct relationship, but the level of HDL-cholesterol had a negative relationship with seropositivity</td>
</tr>
<tr>
<td>Sessa et al.59</td>
<td>1999</td>
<td>228</td>
<td>Significant correlation exists between chronic <em>C. pneumoniae</em> infection and dyslipidemias in the AMI and CAD groups</td>
</tr>
<tr>
<td>Wong et al.60</td>
<td>1999</td>
<td>804</td>
<td>Circulating <em>C. pneumoniae</em> DNA is a predictor of CAD in men</td>
</tr>
<tr>
<td>Dechend et al.61</td>
<td>1999</td>
<td>NA</td>
<td>Tissue factor, PAI-1, and interleukin-6 expression was increased in infected cells, and NF-κB was activated in human vascular endothelial and smooth muscle cells</td>
</tr>
<tr>
<td>Fong62</td>
<td>2000</td>
<td>NA</td>
<td>Early institution of antimicrobials with antichlamydial activity within 5 days of infection largely prevented aortic lesions in New Zealand white rabbits</td>
</tr>
</tbody>
</table>

*C. pneumoniae*: *Chlamydia pneumoniae*; CAD: coronary artery disease; AMI: acute myocardial infarction; LDL: low-density lipoprotein; CRP: C-reactive protein; HDL: high-density lipoprotein; PCR: polymerase chain reaction; PAI: plasminogen activator inhibitor
Recent review, Haberbosch and Jantos concluded from the demonstration of seropositivity against C. pneumoniae that only a small percentage of patients with CAD—stable CAD, unstable CAD, and controls—showed a difference in IgG and IgA seropositivity among patients with C. pneumoniae infection. They did not find any strong association between C. pneumoniae IgG titers and incident CAD. Romeo et al. tried to correlate the severity of CAD with seropositivity to C. pneumoniae prospectively. They found no significant difference in IgG and IgA seropositivity among patients with stable CAD, unstable CAD, and controls. They concluded that only a small percentage of patients with CAD demonstrated seropositivity against C. pneumoniae. A recent case-control study investigated the relationship between the presence of C. pneumoniae IgG and IgA and angiographically diagnosed CAD. When cases were compared with controls whose angiographic results were normal, after adjusting for established risk factors (cholesterol, smoking, hypertension, diabetes, age, gender, and family history), the estimated risk of CAD was 0.79 for the presence of IgG and 0.94 for IgA. These results do not support an association between C. pneumoniae infection and CAD. In a recent review, Wong et al. concluded that more evidence is required before C. pneumoniae can be accepted as playing a role in atherosclerosis.

Animal data: Aalto-Setala et al. infected apolipoprotein E (apo E)-deficient mice with C. pneumoniae and placed them on either a high- or low-fat diet. They found that C. pneumoniae infection did not influence the lesion size in either mouse strain. They also could not demonstrate C. pneumoniae by polymerase chain reaction in any of the atherosclerotic lesions of the infected animals. They did not find any inflammatory signs in the myocardium of C. pneumoniae-infected mice. They concluded that C. pneumoniae infection did not accelerate atherogenic changes in the aortic root of apo E-deficient mice. Blessing et al. inoculated C57BL/6J mice with C. pneumoniae. They observed inflammatory changes in the heart or aorta in a small number of chronically infected mice but no evidence of atherosclerotic lesions in any of them. Their findings suggested that chronic C. pneumoniae infection could induce inflammatory changes in the heart and aorta of C57BL/6J mice but did not initiate definitive atherosclerosis. In a recent review, Haberbosch and Jantos concluded from the present data that chronic infection with the pathogen is not an independent risk factor for atherosclerosis.

**Intervention Studies**

The ACADEMIC trial reported 302 patients with seropositivity to C. pneumoniae. Subjects received azithromycin and placebo for 3 months. At 6 months, the azithromycin-treated group showed a reduced global index of inflammation, which comprised CRP, TNF-alpha; and interleukins 1 and 6 compared with a placebo. However, cardiovascular events were similar in the two groups at 6 months. At 2-year follow-up, there was a 20%–30% risk reduction. Parchure et al. carried out a randomized, prospective, double-blind, placebo-controlled trial in 40 male patients with documented CAD and positive C. pneumoniae IgG antibody titers. They showed that patients who received azithromycin had a significant improvement in flow-mediated dilatation of the brachial artery. They then concluded that treatment with azithromycin had a favorable effect on endothelial function in patients with documented CAD and evidence of C. pneumoniae infection, irrespective of antibody titer levels.

A pilot study of 60 survivors of AMI with persistent elevated anti-chlamydial antibody titers was designed so that subjects were randomized to receive placebo or azithromycin. Azithromycin-treated patients showed an apparent reduction in cardiovascular events from 28% to 8%. There was no significant difference between a single- and double-dose course of azithromycin. The ROXIS trial randomized 202 patients with unstable angina or non-Q wave MI to roxithromycin or a placebo. At the end of the treatment period, the rates of recurrent ischemia were 1% v. 5.4%, MI 0% v. 2.2%, and ischemic events 0% v. 2.2% in the roxithromycin v. placebo group, respectively. At 6 months, the individual and composite event rates remained lower in the roxithromycin group, but the difference was not statistically significant. In the AZACS trial, patients with acute coronary syndromes (unstable angina or MI) were randomized in a double-blind, placebo-controlled fashion to either azithromycin 500 mg/day followed by 250 mg/day for 4 days or a matching placebo. They found that in patients with AMI or unstable angina, short-term treatment with azithromycin did not have an effect on the recurrence of ischemic events during a 6-month follow-up period. There was no difference between patients who tested positive for the presence of C. pneumoniae antibodies and those who did not. Similarly, in the WIZARD trials, which sought to assess the use of...
antibiotics to prevent recurrent CHD, the antibiotic regimen comprising weekly azithromycin in adult patients >6 weeks post-MI with elevated C. pneumoniae IgG titers, achieved a 7% nonsignificant reduction in the incidence of recurrent cardiovascular disease at 11 weeks. The baseline titer of IgG antibodies against C. pneumoniae had no effect on the outcome.  

Conclusions

Atherosclerosis is an inflammatory process. Hence, microorganisms could be the prime initiators of this process. Endothelial dysfunction, the trigger for atherogenesis, can be induced by systemic or local infection. Circulating cytokines, released by any stimulus, may cause abnormal endothelial function, increased thrombosis and toxic free-radical generation, leading to accelerated atherosclerosis. As in leprosy, Whipple’s disease, syphilis and ehrlichiosis, Koch’s postulates cannot be used to determine the role of infection in atherosclerotic disease. Regarding the role of infection in CAD, important indirect evidence comes from prevention of the disease by means of specific interventions.

The data for and against the role of infection in atherosclerotic vascular disease are equally impressive. However, the few prospective clinical trials evaluating the role of antibiotics in the secondary prevention of CAD have not shown a significant decrease in clinically major cardiovascular events. Larger studies with a longer duration of follow-up may be more useful in assessing the exact pathogenetic mechanism of infection in atherosclerotic heart disease, and also the role of antibiotic therapy in the treatment of CAD.

Based on the current data, however, it is not possible to be certain one way or the other about the role of infection in the pathogenesis of atherogenesis, and the subsequent complications of atherosclerosis. Further studies are required to solve this complex problem.

References

16. Grattan MT, Moreno-Cabral CE, Starnes VA, Oyer PE, Stinson EB, Shumway NE. Cytomegalovirus infection is associated with cardiac allograft rejection and arteriosclerosis. JAMA 1989; 261: 3561–3566
with coronary artery disease and may predict post-coronary balloon angioplasty restenosis. Am J Cardiol 1998; 81: 866–868


35. 40. Markus HS, Mendall MA.

36. 33. Gunn M, Stephens JC, Thompson JR, Rathbone BJ, Samani NJ.


Infections in Atherogenesis

34 Larøia et al. Infections in Atherogenesis

Indian Heart J 2003; 55: 27-34


Utility of N-Terminal Pro-Brain Natriuretic Peptide for the Diagnosis of Heart Failure

Jacob V Jose, Satya N Gupta, Dhayakani Selvakumar
Christian Medical College and Hospital, Vellore

Background: The goal of this study was to evaluate the utility of plasma N-terminal pro-brain natriuretic peptide for the diagnosis of heart failure in patients presenting with shortness of breath.

Methods and Results: We measured plasma levels of N-terminal pro-brain natriuretic peptide in 119 patients presenting with shortness of breath. The patients were divided into two groups based on the Framingham criteria and echocardiographic results—those with heart failure and those not in heart failure. Plasma levels of N-terminal pro-brain natriuretic peptide were compared in the two groups. The mean N-terminal pro-brain natriuretic peptide concentration in patients with heart failure (n=73) was higher than that in those not in heart failure (389±148 fmol/ml v. 142±54 fmol/ml, p<0.001). N-terminal pro-brain natriuretic peptide values increased significantly as the functional severity of heart failure increased (p<0.001). The mean N-terminal pro-brain natriuretic peptide levels were 261±34 fmol/ml for patients in New York Heart Association functional class I, 300±161 fmol/ml for patients in New York Heart Association functional class II, 427±103 fmol/ml for patients in New York Heart Association functional class III and 528±170 fmol/ml for patients in New York Heart Association functional class IV. Using a cut-off value of 200 fmol/ml, the sensitivity of N-terminal pro-brain natriuretic peptide was 97%, specificity was 89% and accuracy for differentiating heart failure from other causes of shortness of breath was 93%.

Conclusions: Our results suggest that N-terminal pro-brain natriuretic peptide can be reliably used for the diagnosis of heart failure in an outpatient setting, and this will improve the ability of clinicians to differentiate patients with shortness of breath due to heart failure from those with other causes of shortness of breath.

Key Words: Heart failure, Natriuretic peptide, Echocardiography
those with cardiac impairment, the proportional and absolute increment of NT-proBNP above the normal level exceeds that of BNP, which suggests that it may be a more discerning marker.13,14 Though there are a number of studies regarding the role of BNP in HF, NT-proBNP has not been studied extensively. Thus, this study was undertaken to evaluate the utility of NT-proBNP for the diagnosis of HF.

Methods

Patient characteristics: One hundred nineteen patients presenting with shortness of breath (either acute or chronic) over a 6-month period to our emergency and outpatient departments were enrolled in the study. Associated symptoms were edema, weight gain, cough, or wheezing. Patients with acute coronary syndromes were excluded. All the subjects underwent physical examination, chest X-ray, supine 12-lead electrocardiogram (ECG) and blood pressure (BP) measurement. Other data recorded included history, risk factors, and drug treatment. Echocardiography was performed in all the patients using a Sonos 5500 machine. Left ventricular end-systolic and diastolic volumes were measured, and ejection fraction determined based on the American Society of Echocardiography recommendations.15

NT-proBNP measurement: Two ml of blood was collected in a chilled clotted tube and centrifuged immediately. The plasma was stored at –80 °C until the NT-proBNP assay was carried out. Plasma NT-proBNP concentration was measured using a Biomedica kit. This kit was a competitive enzyme immunoassay (EIA) designed to measure the immunoreactive NT-proBNP in diluted human serum, plasma or urine samples. To achieve high specificity, the kit incorporates an immunoaffinity purified sheep antibody specific for NT-proBNP (8-29) immobilized to the surface of a microtiter plate well.

The assay is based on competitive reaction of the unlabeled peptide in the standards or samples, and horseradish peroxidase-labeled peptide (tracer) for the limiting binding sites of the NT-proBNP (8-29) specific antibody. The assay had a detection limit (±2 SD) of 5 fmol/ml. The intra-assay and interassay coefficients of variation were 6.5% and 4.4%, respectively. The assay was performed within 3 months of sampling. The author, who was involved in NT-proBNP measurement, was blinded to clinical information regarding HF.

Diagnosis of heart failure: We divided our patients into two groups: patients with shortness of breath due to HF and patients with shortness of breath not due to HF. The diagnosis of HF was based on the Framingham criteria and echocardiography.16 For patients with a diagnosis other than HF, confirmation was attempted using the following variables: normal chest X-ray and normal left ventricular function by echocardiogram. In the group of patients with HF, there were patients with systolic and diastolic dysfunction: of the 73 patients with HF, 14 had diastolic dysfunction.

Statistical analysis: To evaluate the utility of NT-proBNP measurement for the diagnosis of HF, we computed sensitivity, specificity, and accuracy. All the values are expressed as mean±2 SD. Comparison among values obtained for the HF group and for those not in HF was made by multivariate analysis. A value of p<0.05 was considered statistically significant. The plasma level of NT-proBNP was also compared in each stage of NYHA functional class in patients with HF. A receiver–operating characteristics curve was obtained to determine various cut-off values of NT-proBNP peptide for the diagnosis of HF.

Baseline characteristics: The baseline characteristics of the overall study group of 119 patients are shown in Table 1. The mean age of the study population was

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Heart failure n=73 (61.3%)</th>
<th>No heart failure n=46 (38.7%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>53.35±11.62</td>
<td>54.26±13.37</td>
</tr>
<tr>
<td>Male sex</td>
<td>51 (69.8)</td>
<td>27 (58.6)</td>
</tr>
<tr>
<td>History</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>33 (45.2)</td>
<td>16 (34.7)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>27 (36.9)</td>
<td>14 (30.7)</td>
</tr>
<tr>
<td>History of MI</td>
<td>28 (38.3)</td>
<td>6 (13.0)</td>
</tr>
<tr>
<td>Smoking</td>
<td>31 (42.4)</td>
<td>26 (56.5)</td>
</tr>
<tr>
<td>Symptoms</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyspnea</td>
<td>73 (100)</td>
<td>46 (100)</td>
</tr>
<tr>
<td>Orthopnea</td>
<td>42 (57.5)</td>
<td>3 (6.5)</td>
</tr>
<tr>
<td>Nocturnal cough</td>
<td>16 (21.9)</td>
<td>11 (23.9)</td>
</tr>
<tr>
<td>Signs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rales</td>
<td>49 (67.1)</td>
<td>17 (36.9)</td>
</tr>
<tr>
<td>Increased JVP</td>
<td>50 (68.4)</td>
<td>11 (23.9)</td>
</tr>
<tr>
<td>Ankle edema</td>
<td>52 (71.2)</td>
<td>5 (10.8)</td>
</tr>
<tr>
<td>S3 gallop</td>
<td>36 (49.3)</td>
<td>2 (4.3)</td>
</tr>
<tr>
<td>Resting tachycardia</td>
<td>26 (35.6)</td>
<td>15 (32.6)</td>
</tr>
<tr>
<td>Cardiomegaly on CXR</td>
<td>44 (60.2)</td>
<td>9 (19.5)</td>
</tr>
</tbody>
</table>

MI: myocardial infarction; JVP: jugular venous pressure; CXR: chest X-ray
53.7±12.4 years. There were 78 men (65.5%) and 41 women (34.5%). Patients were grouped according to whether they had HF or not, based on the Framingham criteria. The final assessment revealed that 73 patients (61.3%) had HF as a cause of their shortness of breath, while 46 (38.7%) had a cause other than HF; these included bronchial asthma, chronic obstructive pulmonary disease, pneumonia, carcinoma lung, psychogenic dyspnea. There was no significant difference in the age and sex ratio in both the groups of patients. Patients with HF were more likely to have had a previous history of myocardial infarction and clinical signs of HF.

Results

NT-proBNP and final diagnosis: Patients with a final diagnosis of HF had a mean (±SD) NT-proBNP level of 389±148 fmol/ml compared with 142±54 fmol/ml in patients not in HF. The difference between the groups was statistically significant (p<0.001). Figure 1 is a box plot of NT-proBNP values for patients with HF and those not in HF.

NT-proBNP and clinical severity of heart failure: The mean NT-proBNP level was 261±34 fmol/ml for NYHA functional class I, 300±161 fmol/ml for NYHA functional class II, 427±103 fmol/ml for NYHA functional class III and 528±170 fmol/ml for NYHA functional class IV patients. NT-proBNP values increase significantly as the functional severity of HF increases (p<0.001). Figure 2 shows NT-proBNP values in relation to the NYHA functional class.

NT-proBNP and left ventricular ejection fraction: There was a significant negative linear correlation between plasma NT-proBNP and the left ventricular ejection fraction (r=−0.69; p<0.001) (Fig. 3). The level of NT-proBNP in patients with a left ventricular ejection fraction less than 40% was significantly higher in comparison to its level in patients with left ventricular ejection fraction more than 40% (406±152 fmol/ml v. 171±83 fmol/ml).

Receiver–operating characteristics curve: The capacity of NT-proBNP to differentiate between shortness of breath due to HF and that due to other causes was assessed with a receiver–operating characteristics curve analysis (Fig. 4). The area under the receiver–operating characteristics curve when NT-proBNP was used to differentiate HF from other causes of shortness of breath was 0.94 (95% confidence interval: 0.90–0.98; p<0.001). An NT-proBNP cut-off value of 200 fmol/ml had a sensitivity of 97%, a specificity of 89% and an accuracy of 93% for differentiating between HF and other causes of shortness of breath.

Multivariate analysis: In multiple logistic regression analysis, we found that NT-proBNP was a strong independent predictor for HF with an odds ratio of 8.94.
The other variable, which was better than NT-proBNP, was the presence of S₃ gallop (Table 2).

Our results suggest that the levels of NT-proBNP increase with increasing severity of HF. NT-proBNP levels were higher in patients in a higher NYHA class. Our results are in accordance with the study by Hunt et al. Patients with left ventricular ejection fraction <40% had NT-proBNP levels of 406±152 fmol/ml, whereas patients with left ventricular ejection fraction >40% had values of 171±83 fmol/ml. In the study by Campbell et al., NT-proBNP had a sensitivity of 100% for differentiating patients with left ventricular ejection fraction <45%.

In our study, NT-proBNP levels showed a negative correlation with the left ventricular ejection fraction (Fig. 3). When we used a cut-off value of 200 fmol/ml for NT-proBNP, the sensitivity was 97% for the diagnosis of HF. Our findings suggest that NT-proBNP could be a reliable marker for the diagnosis of HF.

Discussion

Our study was designed to assess the diagnostic value of the plasma level of circulating NT-proBNP as a noninvasive indicator of HF. Our results suggest that NT-proBNP can be used as a reliable marker for identification of left ventricular dysfunction in a group of patients presenting with shortness of breath. We found that a cut-off value of 200 fmol/ml had an accuracy of 93%.

Echocardiography, although currently the gold standard for the diagnosis of left ventricular dysfunction, is costly and has limited availability in an urgent care setting. Dyspneic patients may be unable to hold their breath long enough during an echocardiographic study for a good image to be obtained. In addition, technical difficulty due to obesity and lung disease may also interfere in getting a good echocardiographic image. Therefore, even if echocardiography is available in the emergency department, an accurate, sensitive, and specific blood test for HF would be a useful addition to the clinical armamentarium. Brain natriuretic peptide measurement is a useful tool for evaluating possible left ventricular dysfunction and ventricular failure. Insufficient data are available on NT-proBNP, but BNP and NT-proBNP appear to be equivalent markers. In our study, the NT-proBNP level was significantly higher in patients with HF in comparison with those not in HF. Our results concur with those reported previously from the West.

Our results suggest that the levels of NT-proBNP increase with increasing severity of HF. NT-proBNP levels were higher in patients in a higher NYHA class. Our results are in accordance with the study by Hunt et al. Patients with left ventricular ejection fraction <40% had NT-proBNP levels of 406±152 fmol/ml, whereas patients with left ventricular ejection fraction >40% had values of 171±83 fmol/ml. In the study by Campbell et al., NT-proBNP had a sensitivity of 100% for differentiating patients with left ventricular ejection fraction <45%. In our study, NT-proBNP levels showed a negative correlation with the left ventricular ejection fraction (Fig. 3). When we used a cut-off value of 200 fmol/ml for NT-proBNP, the sensitivity was 97% for the diagnosis of HF. Our findings suggest that NT-proBNP could be a reliable marker for the diagnosis of HF.

Our results suggest that the determination of cardiac ventricular peptides substantially improves the diagnostic accuracy of the assessment of left ventricular dysfunction in a patient population with suspected HF. The results demonstrate that measurement of NT-proBNP levels in the blood improves the ability of the clinician to differentiate between patients with shortness of breath due to HF and shortness of breath due to other causes in an acute care setting. This should be especially true among patients in whom the diagnosis of HF is not clinically obvious. The BNP/NT-proBNP test is now available in a rapid form, thus making diagnostic information immediately available to the acute care physician. Use of this test in conjunction with other clinical information should lead to a more accurate initial diagnosis of HF.

Limitations of the study: As this study was conducted in a tertiary care center, it needs to be confirmed whether these results can be generalized to the primary care level. A larger study, including the patient’s clinical findings,
chance that an individual had HF by routine clinical methods. We did not look at the group of patients who could not be diagnosed to have HF by routine clinical methods. Such a study would give the incremental value of NT-proBNP over routine clinical methods.

Conclusions: Plasma NT-proBNP is a sensitive indicator of cardiac dysfunction. Our results suggest that NT-proBNP can be used reliably for the diagnosis of HF in an outpatient setting. The results demonstrate that measurement of NT-proBNP levels will improve the ability of clinicians to differentiate between patients with shortness of breath due to HF and that due to other causes.

Acknowledgment
We would like to express our thanks to Mr Pramod, statistician, for helping us with the statistical work.

References
Usefulness of Intravenous Metoprolol During Positive Isoproterenol Tilt-Table Test in the Choice of Treatment for Neurocardiogenic Syncope

İbrahim Baran, Kani Gemici, Bülent Özdemir, Murat Saraç, Sümeyye Güllülü, Ali Aydinlar, Jale Cordan
Department of Cardiology, Uludag University, School of Medicine, Bursa, Turkey

Background: Isoproterenol tilt-table testing provides a diagnosis of neurocardiogenic syncope in patients with syncope or near-syncope. Although acute beta-blockade may prevent the development of syncope during isoproterenol tilt-table testing, the use of beta-blockers for chronic prophylaxis may not be effective for some patients who show a positive response to isoproterenol tilt-table testing. We evaluated whether the efficacy of intravenous metoprolol in preventing symptoms during repeated tests would be helpful in selecting patients suitable for long-term therapy.

Methods and Results: We studied 55 patients (35 females, 20 males; mean age 36±11 years) who had been chosen from a group referred to our institute with a history of unexplained syncope (≥2 syncopal episodes) and a positive response to isoproterenol tilt-table testing. After a positive response to isoproterenol tilt-table testing, 5 mg metoprolol was infused intravenously as a bolus and the test repeated. Thirty-five patients (group I) showed a positive response again and 20 (group II) showed a negative response. We started 50 mg metoprolol once a day for patients in group I while group II was divided into 2 subgroups: the first subgroup (group 2a, 12 patients) was started on 50 mg sertraline or 20 mg paroxetine once a day and the second subgroup (group 2b, 8 patients) was started on 5 mg midodrine orally once a day. Two months later, isoproterenol tilt-table testing was repeated. In group I, 13 of 35 patients (37%) were positive on isoproterenol tilt-table testing while in group II, 8 of 20 patients (40%) were positive on isoproterenol tilt-table testing (p not statistically significant). The therapies of the two groups were then interchanged. Two months later (4 months from the beginning of the study), the isoproterenol tilt-table test was repeated. Eleven patients in group I (31%) and 6 in group II (30%, p not statistically significant) showed a positive response again.

Conclusions: We conclude that acute beta-blockade response to positive isoproterenol tilt-table testing is not a useful predictor for the assessment of chronic prophylaxis for neurocardiogenic syncope. (Indian Heart J 2003; 55: 40–43)

Key Words: Neurocardiogenic syncope, Tilt-table test, Beta-blockers
Methods

Patients: We studied 89 patients (53 females and 36 males; mean age 38±16 years) who had been referred to our institute with a history of unexplained syncope (>2 syncopal episodes). Cardiac and neurologic examination, electrocardiogram, chest X-ray and echocardiogram were normal in all the patients. Fifty-five patients (35 females, 20 males; mean age 36±11 years) with a positive response to ITTT (Table 1) formed the study group.

Around 1 week later, the ITTTs were repeated with standard protocol and completed after an infusion of 5 mg metoprolol (Table 2). Thirty-five patients (group 1) again showed a positive response while 20 (group 2) showed a negative response. We started patients in group 1 on 50 mg metoprolol once a day. Group 2 was divided into two subgroups; the first subgroup: group 2a (12 patients) was started on 50 mg sertraline or 20 mg paroxetine once a day and the second subgroup: group 2b (8 patients) on 5 mg midodrine orally once a day. Two months later, the ITTTs were repeated. During the ITTT, 3 patterns of positive response were observed. A vasodepressor response was associated with a marked decrease in systolic blood pressure (a decrease of at least 20 mmHg in the systolic blood pressure). A cardioinhibitory response was characterized by a marked decrease in heart rate (≥20%) or asystole ≥5 s at the onset of symptoms. A mixed pattern of response was characterized by a decrease in both blood pressure and heart rate, frequently associated with the development of junctional rhythm.

Table 1. Clinical characteristics of the study groups

<table>
<thead>
<tr>
<th></th>
<th>Group 1</th>
<th>Group 2a</th>
<th>Group 2b</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>35</td>
<td>12</td>
<td>8</td>
</tr>
<tr>
<td>Mean age (years)</td>
<td>37±12</td>
<td>34±10</td>
<td>35±11</td>
</tr>
<tr>
<td>Women/men ratio</td>
<td>22/13</td>
<td>7/5</td>
<td>5/3</td>
</tr>
<tr>
<td>Syncopal episodes/year</td>
<td>5</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>Time to positive ITTT (seconds)</td>
<td>39</td>
<td>47</td>
<td>44</td>
</tr>
<tr>
<td>Baseline heart rate (bpm)</td>
<td>110</td>
<td>106</td>
<td>103</td>
</tr>
<tr>
<td>Baseline systolic BP (mmHg)</td>
<td>118</td>
<td>121</td>
<td>114</td>
</tr>
</tbody>
</table>

ITTT: isoproterenol tilt-table test; BP: blood pressure; bpm: beats per minute; p value not statistically significant

Table 2. The ITTT protocol form prepared for our clinic

<table>
<thead>
<tr>
<th>Stages</th>
<th>Minutes</th>
<th>Tilt</th>
<th>Systolic BP</th>
<th>Heart rate</th>
<th>ECG</th>
<th>Symptoms</th>
<th>Isoproterenol</th>
<th>Metoprolol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Step I</td>
<td>0, 3, 5, 10 and 15</td>
<td>0°</td>
<td>Systolic BP</td>
<td>Heart rate</td>
<td>ECG</td>
<td>Symptoms</td>
<td>Isoproterenol</td>
<td>Metoprolol</td>
</tr>
<tr>
<td>Step II</td>
<td>20, 25, 30, 35, 40 and 45</td>
<td>80°</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Step III</td>
<td>47 and 50</td>
<td>0°</td>
<td>3 mcg/min</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Step III</td>
<td>53</td>
<td>80°</td>
<td>3 mcg/min</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Step III</td>
<td>55,57 and 60</td>
<td>80°</td>
<td>5 mcg/min</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Step IV</td>
<td>61 and 62</td>
<td>0°</td>
<td>5 mcg/min</td>
<td>5 mg i.v.</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Step IV</td>
<td>64, 66, 68 and 70</td>
<td>80°</td>
<td>5 mcg/min</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

ITTT: isoproterenol tilt-table test; BP: blood pressure; ECG: electrocardiogram
position. Presyncope was defined as a state of lightheadedness associated with symptoms of decreased vision, nausea, vomiting, partial loss of postural tone or slow response times to verbal stimuli, which substantially reproduced the clinical presyncope of the patients.

**Follow-up:** All the patients were followed up to detect recurrent syncopal or presyncopal attacks, and also complaints related to adverse effects of the drugs. Two months later, the ITTTs were repeated, and the previous treatment changed to an alternative one.

**Statistical analysis:** Data are expressed as mean±SEM. The paired and unpaired Student’s t test was used to compare all numerical variables among the groups. A p value <0.05 was considered statistically significant.

**Results**

The study population consisted of 35 females and 20 males with a positive response to the ITTT. They had had a median of 4.8 syncopal attacks per year. During the second test after a positive response to the ITTT, 5 mg metoprolol was infused as a bolus in the resting supine position and the patient was tilted again to 80°. Thirty-five patients (group 1) showed a positive response again while 20 (group 2) showed a negative response with metoprolol. Group 1 was started on 50 mg metoprolol orally once a day and group 2 subdivided into two subgroups—the group given SSRIs and that given midodrine. The SSRIs group (group 2a) was started on 50 mg sertraline or 20 mg paroxetine once a day and the midodrine group (group 2b) was started on 5 mg midodrine once a day orally. No patient suffered from side-effects necessitating cessation of therapy. Two months later, the ITTTs were repeated. In group 1, 13 of 35 ITTTs (37%) were positive while 8 of 20 ITTTs (40%) were positive in group 2 (p not statistically significant). The therapies of the two groups were interchanged. The patients in group 1 were given sertraline/paroxetine or midodrine randomly. Two months later (4 months from the beginning of the study), the ITTTs were repeated. Eleven patients in group 1 (31%) and 6 patients in group 2 (30%, p not statistically significant) again showed a positive response to the ITTTs.

**Discussion**

The treatment of patients with neurocardiogenic syncope is controversial. Neither the underlying mechanisms nor the best modality of treatment have been clarified. Many drugs, including disopyramide, beta-blockers, scopolamine, fludrocortisone, midodrine, SSRIs, and etilefrine have been used for treatment._router:1

The tilt-table test is an important diagnostic tool for the evaluation of patients with unexplained syncopae. The tilt-table test provides a diagnosis of neurocardiogenic syncope in many patients who faint.12,13

Beta-blockers have been widely used in the treatment of patients with neurocardiogenic syncope and are frequently chosen as first-line drug therapy. Metoprolol and atenolol have been the most frequently studied beta-blockers in neurocardiogenic syncope. Following a positive tilt-table test, treatment with beta-blockers may not have a substantial effect in preventing recurrence of syncope.14 Mahanonda et al. performed the only randomized, double-blind, placebo-controlled trial to evaluate the efficacy of oral beta-blockers in the treatment of neurocardiogenic syncope. They compared the efficacy of a beta-blocker with a placebo in patients who had had at least 1 episode of syncope or 2 episodes of presyncope within one month before presentation. The response rate after one month of treatment was 62% versus 5% in the atenolol and control groups, respectively. However, the efficacy of beta-blockers was also examined in other studies, yielding controversial results. Sheldon et al. for example, concluded that treatment with beta-blockers had no major effect on recurrence of syncope. Cox et al. prospectively evaluated the efficacy of propranolol in preventing neurocardiogenic syncope. Oral beta-blockers were found to be effective by the tilt-test criteria in the majority (94%) of patients. While taking beta-blockers, 10% of patients had recurrent clinical symptoms. In conclusion, they stated that intravenous propranolol was very effective in blocking the neurocardiogenic reflex during tilt-table testing, and that it could predict a good response to oral beta-blockers.

In our study, we evaluated the efficacy of beta-blockers compared with midodrine and SSRIs in preventing recurrences in patients with clinically diagnosed neurocardiogenic syncope. We followed up the patients for at least 4 months. Due to the acute efficacy of an intravenous beta-blocker during a positive ITTT, we hoped that it would also be useful for long-term therapy. However, in the long term, beta-blockers did not show as good an efficacy as expected. Also, the positive response to intravenous metoprolol did not reliably predict a good response to long-term oral administration.

**Conclusions:** The study is ongoing. We conclude that acute beta-blockade response to a positive ITTT is not a useful predictor of the success of beta-blockers in long-term prophylaxis of neurocardiogenic syncope.
References

Noninvasive Assessment of Endothelial Dysfunction by Brachial Artery Flow-Mediated Dilatation in Prediction of Coronary Artery Disease in Indian Subjects

Uday M Jadhav, Anand Sivaramakrishnan, NN Kadam
Department of Non-Invasive Cardiology, MGM New Bombay Hospital, Mumbai

Background: A noninvasive technique for testing endothelial function by ultrasound measurement of flow-mediated dilatation has recently generated considerable interest as a marker of atherosclerosis, and in the prediction of clinical coronary events and coronary artery disease.

Methods and Results: We measured the flow-mediated dilatation of the brachial artery (endothelium-dependent vasodilatation) in 136 subjects, with or without evidence of coronary artery disease. Endothelial dysfunction was diagnosed if flow-mediated dilatation was less than 4.5%. Of the 136 subjects (age group 40–70 years) recruited for the study, 94 were males and 42 females. Sixty-eight subjects had evidence of coronary artery disease as diagnosed by documented hospitalization due to myocardial infarction or acute coronary syndrome, proved by coronary angiography when feasible or noninvasive cardiac evaluation. Endothelial dysfunction was detected in 90 subjects (66.2%). Prevalence of coronary artery disease was higher among subjects with endothelial dysfunction compared to those without (57.5% v. 34.7%, p=0.013). Prevalence of endothelial dysfunction was significantly higher among subjects with coronary artery disease as compared to those without coronary artery disease (76.4% v. 55.8%, p=0.012). The present study showed a sensitivity of 76%, specificity of 44%, positive predictive value of 58% and negative predictive value of 65% for endothelial dysfunction in the prediction of coronary artery disease. Multiple regression analysis using coronary artery disease as a dependent variable revealed a statistically significant association with endothelial dysfunction (p=0.033) even after the inclusion of traditional risk factors into the model.

Conclusions: We conclude that endothelial dysfunction shows a strong association with coronary artery disease and can be a useful noninvasive tool for the evaluation of coronary artery disease (Indian Heart J 2003; 55: 44-48)

Key Words: Coronary artery disease, Endothelial dysfunction, Doppler ultrasound
endothelium-dependent dilatation. Endothelium-independent dilatation can be assessed by measuring the arterial diameter after administration of sublingual nitroglycerin.

We undertook this study to assess the role of a simple technique of flow-mediated dilatation (FMD) measurement in predicting coronary artery disease (CAD). This study assesses the endothelium-dependent dilatation of conduit vessels, and there are other methods for resistance vessels. Differences may exist with regard to endothelium-dependent dilatation of the conduit versus resistance arteries, and these differences have potential implications.

**Methods**

A total of 136 patients, both hospitalized as well as outpatient, were included in the study. Informed consent was obtained from the study subjects who were divided into two groups: with CAD (68 subjects) and without CAD (68 subjects). Coronary artery disease was diagnosed along with clinical presentation by electrocardiography (ECG), symptom-limited exercise stress test, Doppler echocardiography, and coronary angiography, when feasible. Of the 68 subjects with CAD, 42 had evidence of myocardial infarction or acute coronary syndrome, 13 had evidence on coronary angiography, and 13 had ECG, stress test, and echocardiographic manifestations suggestive of CAD. Of the 136 subjects, 20 had type 2 diabetes mellitus, 51 had hypertension, 37 had diabetes with concomitant hypertension, and 28 had no diabetes or hypertension. The mean age was 52 years with a range of 40–74 years. The subjects included 94 males and 42 females.

The ultrasound method for measuring endothelium-dependent and endothelium-independent arterial dilatation has been described previously. The brachial artery diameter was measured on B-mode ultrasound images, with the use of a 7.0 MHz linear-array transducer with Imagepoint Hx ultrasound equipment (Agilent Technology, India). The right brachial artery was studied in all the subjects. Brachial artery endothelial function was studied after the subject had abstained from alcohol, caffeine, and smoking for 8 h. Scans were obtained with the subject at rest, during reactive hyperemia and again with the subject at rest. The subjects were asked to lie quietly for at least 10 min before the first scan. The brachial artery was scanned in longitudinal section 2–15 cm above the elbow, and the center of the artery was identified when the clearest picture of the anterior and posterior intimal layers was obtained. The transmit (focus) zone was set to the depth of the near wall, because of the greater difficulty in evaluating the “m” line (the interface between the media and adventitia) of the near wall as compared with that of the far wall. Depth and gain settings were set to optimize images of the interface between the lumen and the arterial wall, and the images were magnified. Settings for operating the machine were not changed during the study.

When a satisfactory transducer position was found, the skin was marked and the arm was kept in the same position throughout the study. A resting scan was obtained, and the velocity of arterial flow measured with a pulsed Doppler signal at a 70° angle to the vessel, with the range gate (1.5 mm) in the center of the artery. Increased flow was then induced by the inflation of a sphygmomanometer cuff placed around the forearm (distal to the scanned part of the artery) to a pressure of 200 mmHg for 4.5 min, followed by release. A second scan was performed continuously for 30 s before and 90 s after deflation of the cuff, including a repeated recording of flow velocity for the first 15 s after the cuff was released.

Flow-mediated dilatation was calculated, and the average results of the two observations recorded. The system software was designed for online recording, which was assessed visually to ensure that the best possible recording was obtained and artefacts minimized. Automatic tracking was not performed. ECG was monitored throughout the scans and the artery diameter measured at end-diastole. Interobserver and intraobserver variability was studied in 20 healthy subjects with a mean age of 42.4 years. Interobserver variability was 1.6% and intraobserver variability was 2.2%. This method is accurate and reproducible for measuring small changes in arterial diameter with low rates of interobserver error in measuring FMD. Flow-mediated dilatation was presented as the percent change from baseline to hyperemia. Endothelial dysfunction was defined as FMD <4.5%, as has been previously described.

Clinical examination included blood pressure measurement, cardiovascular examination, anthropometrical measurements, and body-mass index (BMI). Biochemical assessment included fasting blood sugar (FBS) and post-prandial blood sugar levels, glycated hemoglobin, urine for microalbumin, and comprehensive lipid profile. Plasma glucose and lipid estimation were done after an overnight fast of 12 h. Biochemical analysis was done on Technicon RA-1000 Auto Analyser. Plasma glucose, serum cholesterol, serum triglycerides, and high-density lipoprotein (HDL)-cholesterol (HDL-c) were estimated with kits supplied by AUTOA K-Bayer Diagnostics, India. Plasma glucose estimation was done by the GOD/POD method.
serum cholesterol by the enzymatic method and triglycerides by the enzymatic calorimetric method. HDL-c was estimated after precipitating low-density lipoprotein (LDL) and chylomicron fractions by the addition of phosphotungstic acid in the presence of magnesium ions and very low-density lipoprotein (VLDL). LDL-cholesterol (LDL-c) was calculated using the Friedewald formula, namely,

$$\text{LDL-c} = \text{Total cholesterol} - \left( \frac{\text{Triglycerides}}{5} + \text{HDL} \right)$$

The baseline characteristics of the study group and the relevant brief results of the lipid profile are shown in Tables 1 and 2.

**Statistical analysis:** Data collected were managed on an Excel spreadsheet. One-way ANOVA or Student's t test was used as appropriate to compare the mean of the continuous variables. Chi-square test was used to compare proportion. Pearson's correlation coefficient was used to determine if an association existed among the risk factors. All the groups were combined for Pearson's correlation analysis. Multiple regression analysis was carried out using CAD as the dependent variable and factors such as BMI, smoking, hypertension, FBS, serum cholesterol, triglycerides, HDL-c, LDL-c as independent variables. The subjects were compared for the age groups less than and greater than 50 years, smokers and non-smokers, BMI <23 kg/m² and >23 kg/m², LDL-c <130 mg/dl and >130 mg/dl, HDL-c <40 mg/dl and >40 mg/dl, total cholesterol to HDL-c ratio <5.5 and >5.5, triglycerides <200 mg/dl and >200 mg/dl, and the subgroup of hypertension±diabetes mellitus. All analyses were performed with the SPSS version 10 and p values less than 0.05 were considered significant.

### Results

The percentage distribution of FMD in subjects with various risk factors is shown in Table 3. There was a 66.2% prevalence of ED in the present study population. In subjects with evidence of CAD, 76.4% had endothelial dysfunction as indicated by FMD <4.5% as compared to 55.8% in those without obvious evidence of CAD (Table 4). This was highly significant with p<0.001. The correlation of FMD with CAD is illustrated in Fig.1. The odds ratio for FMD <4.5% was 3.90 in those with CAD as against those without obvious CAD, making it an important marker for preclinical and clinical CAD.

The prevalence of CAD among subjects with FMD <4.5% was calculated by the following method:

$$\text{Prevalence} = \frac{\text{Number of subjects with CAD and FMD <4.5%}}{\text{Number of subjects with FMD <4.5%}} \times 100$$

The prevalence of CAD among subjects with FMD >4.5% and prevalence of FMD <4.5% in subjects with and without CAD were calculated in the same way. The prevalence of CAD was significantly higher among subjects with FMD <4.5% compared to those with FMD >4.5% (57.5% v. 34.7%, p=0.013). Prevalence of FMD <4.5% was significantly higher among subjects with CAD compared to those without CAD (76.4% v. 55.8%, p=0.012). Multiple regression analysis using CAD as a dependent variable revealed a statistically significant association with endothelial dysfunction (p=0.033) even after the inclusion of traditional risk factors into the model, as shown in Table 5.

### Table 1. Clinical characteristics of the study group

<table>
<thead>
<tr>
<th>Parameters</th>
<th>CAD (n=68)</th>
<th>Non-CAD (n=68)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>56.53±11.47</td>
<td>48.74±11.0</td>
<td>0.0001</td>
</tr>
<tr>
<td>Male (%)</td>
<td>50 (53.1)</td>
<td>44 (66.8)</td>
<td>0.265</td>
</tr>
<tr>
<td>Smoking (%)</td>
<td>51 (75)</td>
<td>17 (25)</td>
<td>0.012</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>21 (30.9)</td>
<td>30 (44.1)</td>
<td>0.374</td>
</tr>
<tr>
<td>Diabetes mellitus (%)</td>
<td>10 (14.7)</td>
<td>10 (14.7)</td>
<td>0.374</td>
</tr>
<tr>
<td>Body-mass index (kg/m²)</td>
<td>25.68±4.14</td>
<td>26.03±3.66</td>
<td>0.602</td>
</tr>
<tr>
<td>Fasting plasma glucose (mg/dl)</td>
<td>114.61±41.92</td>
<td>114.11±50.39</td>
<td>0.951</td>
</tr>
<tr>
<td>Total cholesterol (mg/dl)</td>
<td>194.93±43.71</td>
<td>184.73±38.66</td>
<td>0.270</td>
</tr>
<tr>
<td>LDL-cholesterol (mg/dl)</td>
<td>122.26±43.71</td>
<td>111.18±33.89</td>
<td>0.110</td>
</tr>
<tr>
<td>HDL-cholesterol (mg/dl)</td>
<td>40.93±5.80</td>
<td>41.73±6.10</td>
<td>0.457</td>
</tr>
<tr>
<td>Triglycerides (mg/dl)</td>
<td>155.02±66.96</td>
<td>160.44±107.70</td>
<td>0.754</td>
</tr>
<tr>
<td>Cholesterol–HDL ratio</td>
<td>4.79±1.11</td>
<td>4.52±0.92</td>
<td>0.157</td>
</tr>
</tbody>
</table>

Values in parentheses are percentages

LDL: low-density lipoprotein; HDL: high-density lipoprotein

### Table 2. Clinical characteristics of the study group in the context of endothelial dysfunction

<table>
<thead>
<tr>
<th>Parameters</th>
<th>FMD &lt;4.5%</th>
<th>FMD &gt;4.5%</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>53.73±11.67</td>
<td>50.48±12.06</td>
<td>0.130</td>
</tr>
<tr>
<td>Male (%)</td>
<td>67 (74.4)</td>
<td>27 (58.7)</td>
<td>0.060</td>
</tr>
<tr>
<td>Smoking (%)</td>
<td>71 (78.9)</td>
<td>42 (91.3)</td>
<td>0.068</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>29 (32.2)</td>
<td>22 (47.8)</td>
<td>0.048</td>
</tr>
<tr>
<td>Diabetes mellitus (%)</td>
<td>15 (16.7)</td>
<td>5 (10.9)</td>
<td>0.072</td>
</tr>
<tr>
<td>Body-mass index (kg/m²)</td>
<td>25.48±3.89</td>
<td>26.61±3.85</td>
<td>0.109</td>
</tr>
<tr>
<td>Fasting plasma glucose (mg/dl)</td>
<td>118.7±49.1</td>
<td>106.0±39.1</td>
<td>0.140</td>
</tr>
<tr>
<td>Total cholesterol (mg/dl)</td>
<td>192.7±77.9</td>
<td>141.7±66.8</td>
<td>0.270</td>
</tr>
<tr>
<td>LDL-cholesterol (mg/dl)</td>
<td>120.0±39.7</td>
<td>110.9±34.5</td>
<td>0.206</td>
</tr>
<tr>
<td>HDL-cholesterol (mg/dl)</td>
<td>41.1±6.3</td>
<td>41.7±5.4</td>
<td>0.634</td>
</tr>
<tr>
<td>Triglycerides (mg/dl)</td>
<td>161.9±96.7</td>
<td>150.0±74.8</td>
<td>0.511</td>
</tr>
<tr>
<td>Cholesterol–HDL ratio</td>
<td>4.8±1.1</td>
<td>4.4±0.8</td>
<td>0.096</td>
</tr>
</tbody>
</table>

Values in parentheses are percentages

LDL: low-density lipoprotein; HDL: high-density lipoprotein
The present study showed ED to have a sensitivity of 76%, specificity of 44%, positive predictive value of 58% and negative predictive value of 65% in the prediction of CAD. Changes in the flow velocity during the hyperemic phase were inconsistent and not statistically significant in subjects with and without CAD (group without CAD –34.25% to 83.10%, mean 11.03%, SD 28.64; versus group with CAD –22.06% to 51.91%, mean 14.29%, SD 21.47, p>0.05).

Table 3. Percentage distribution of flow-mediated dilatation in subjects with risk factors

<table>
<thead>
<tr>
<th>Normal</th>
<th>Type 2 diabetes</th>
<th>Hypertension</th>
<th>Diabetes with hypertension</th>
</tr>
</thead>
<tbody>
<tr>
<td>FMD &lt;4.5%</td>
<td>17 (55.9)</td>
<td>15 (16.7)</td>
<td>29 (32.2)</td>
</tr>
<tr>
<td>within subgroup</td>
<td>16 (92.4)</td>
<td>14 (87.5)</td>
<td>31 (100)</td>
</tr>
<tr>
<td>FMD &gt;4.5%</td>
<td>11 (55.9)</td>
<td>5 (31.3)</td>
<td>22 (100)</td>
</tr>
<tr>
<td>within subgroup</td>
<td>10 (90.9)</td>
<td>4 (80)</td>
<td>20 (100)</td>
</tr>
<tr>
<td>Total</td>
<td>28 (41.2)</td>
<td>20 (30.3)</td>
<td>51 (74.2)</td>
</tr>
<tr>
<td>within subgroup</td>
<td>26 (92.9)</td>
<td>18 (90)</td>
<td>44 (100)</td>
</tr>
</tbody>
</table>

Values in parentheses indicate percentages
FMD: flow-mediated dilatation
Pearson Chi-square= 5.406, p=0.138

Table 4. Correlation of flow-mediated dilatation of the brachial artery with CAD on univariate analysis

<table>
<thead>
<tr>
<th>Without CAD</th>
<th>With CAD</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>FMD &lt;4.5%</td>
<td>38 (55.9)</td>
<td>52 (76.5)</td>
</tr>
<tr>
<td>FMD &gt;4.5%</td>
<td>30 (44.1)</td>
<td>16 (23.5)</td>
</tr>
<tr>
<td>Total</td>
<td>68</td>
<td>68</td>
</tr>
</tbody>
</table>

Values in parentheses indicate percentages
FMD: % change in flow-mediated dilatation; CAD: coronary artery disease
Pearson Chi-Square=6.439, p=0.011
Odds ratio: FMD <4.5%/FMD <4.5% for CAD=3.90
(95% CI lower: 0.187, CI upper: 0.814)

Table 5. Multiple regression analysis using CAD as a dependent variable

| Sex       | 0.954 | 1.047 |
| Age       | 0.019 | 1.053 |
| Smoking   | 0.198 | 2.411 |
| BMI >23 kg/m² | 1.000 | 1.000 |
| Cholesterol >180 mg/dl | 0.555 | 1.473 |
| LDL-c >130 mg/dl | 0.624 | 1.395 |
| HDL-c <40 mg/dl | 0.539 | 0.717 |
| Triglycerides >200 mg/dl | 0.560 | 1.390 |
| FMD (%) <4.5 | 0.033 | 0.321 |
| Risk groups | 0.173 | 0.723 |

BMI: body-mass index; LDL-c: low-density lipoprotein cholesterol; HDL-c: high-density lipoprotein cholesterol; FMD: flow-mediated dilatation

Fig. 1. Percentage distribution of subjects with endothelial dysfunction in relation to CAD.

Discussion

Ultrasonography is a reliable and accurate technique to determine FMD in the superficial arteries. Reproducibility of FMD determination is best in the brachial artery in healthy subjects and in patients with atherosclerosis.3,6 B-mode ultrasound scan including brachial artery FMD may be of clinical value in the screening of patients with CAD.6

In a study by Schroeder et al.,7 patients with CAD had a significantly lower FMD% than patients without CAD. They reported a sensitivity of 71%, a specificity of 81% with a positive predictive value of 0.95 and a negative predictive value of 0.41 for FMD in the prediction of CAD. They found a better specificity and higher sensitivity for FMD as compared to angina pectoris (sensitivity 95%, specificity 47.6%), exercise ECG (sensitivity 82.4%, specificity 57.1%), and myocardial perfusion imaging (sensitivity 100%). The present study showed a sensitivity of 76%, specificity of 44%, positive predictive value of 58%, and negative predictive value of 65% for ED in the prediction of CAD. The specificity and positive predictive value can be improved by the selection of a healthy control group in the true sense, inclusion of only coronary angiography-documented cases, and utilizing automated tracking for the measurement of arterial diameter.

In a study by Neunteufl et al.,8 impaired FMD in CAD patients was related to the extent of CAD, to the maximum percent diameter stenosis in one of the major coronary vessels, brachial artery diameter, and plasma cholesterol level on univariate analysis. On multiple regression analysis, the extent of CAD (1-, 2- or 3-vessel disease) and the baseline brachial artery diameter were independently associated with FMD in CAD patients.8
Endothelial-dependent and -independent functions are impaired in patients with CAD, and the extent of FMD has been shown to significantly correlate with serum HDL-c levels on univariate and multivariate analysis. Patients with unstable angina have also been shown to have ED compared to normal individuals. Long-term follow-up of 28 months in subjects with severe ED in the absence of obstructive CAD was shown to be associated with increased cardiac events. Coronary ED may play a role in the progression of coronary atherosclerosis.

The obvious limitation of the present study is the lack of angiographic documentation in both the groups, except for undisputed evidence of CAD in 41 subjects in the CAD group. This was not performed for ethical, logistic, and socioeconomic reasons. It was not known whether participants in the group without CAD with FMD >4.5% already had significant subclinical atherosclerosis at the time of enrollment to the study, which can negate the argument for the above limitation. The present study is not a prospective cohort study, and a long-term follow-up of the subjects without CAD is required.

Conclusions: In conclusion, the present study shows that ED is associated with and is also an independent risk factor for CAD. Assessment of ED should be included along with other conventional risk variables such as lipoproteins to identify individuals at increased risk for CAD at an early stage, given the paucity of facilities for invasive evaluation in India. Longitudinal studies are required to demonstrate the utility of ED as a predictor of CAD in the Indian population.

Acknowledgment

We would like to thank Dr DP Singh for his assistance with the statistical analysis.

References

Supravalvar Aortic Stenosis: Clinical and Hemodynamic Profile, and Surgical Outcome

S Harikrishnan, SR Krishna Manohar, Krishna Kumar Nair, Jaganmohan Tharakan, Thomas Titus, VK Ajith Kumar, Anil Bhat, S Sivasankaran, Francis Bimal, KM Krishna Moorthy, R Padma Kumar
Departments of Cardiology and Cardiac Surgery, Sree Chitra Tirunal Institute for Medical Sciences and Technology, Thiruvananthapuram

Background: Supravalvar aortic stenosis is the rarest of left ventricular outflow obstructions. Data on this rare entity from India are scarce.

Methods and Results: We retrospectively analyzed the data of 15 patients (13 males, mean age 15.5±10.18 years) with a diagnosis of supravalvar aortic stenosis confirmed by cardiac catheterization. Five patients had morphological features of Williams’ syndrome. One patient had diffuse while the rest had discrete type of supravalvar aortic stenosis. Five patients did not have any associated lesions. A 9-year-old male had an ascending aortic aneurysm, and 3 patients had associated peripheral pulmonary artery stenosis. One child had a subaortic ventricular septal defect, and another had severe mitral regurgitation. Twelve patients had electrocardiographic evidence of left ventricular hypertrophy. Three patients had mild aortic valvar stenosis while 2 had aortic regurgitation. Six patients had dilated coronary arteries. Two patients with supravalvar aortic gradients of 20 and 40 mmHg were kept on close follow-up. One patient was not willing to undergo surgery while the other is awaiting surgery. Eleven patients underwent surgical correction. Dacron or pericardial patch aortoplasty was done in all the patients. In addition, one patient each underwent pulmonary artery plasty, ventricular septal defect closure, repair of ascending aortic aneurysm, and mitral valve replacement. The patient with diffuse type of supravalvar aortic stenosis underwent augmentation aortoplasty. Two patients died perioperatively. One was lost to follow-up. Two had moderate residual gradients. The rest of the patients were in New York Heart Association functional class I on follow-up of 6.3±4.7 years.

Conclusions: Repair of supravalvar aortic stenosis by single sinus aortoplasty is safe and produces good results. (Indian Heart J 2003; 55: 49–54)

Key Words: Supravalvar aortic stenosis, Williams’ syndrome, Aortoplasty
complications were also collected. Follow-up data were collected and those patients who did not have recent follow-up data were called for a review and their data collected.

Results

Among the 12,400 patients who underwent cardiac catheterization for evaluation of congenital heart disease, there were 15 patients (0.12%, 13 males) who had the diagnosis of SVAS confirmed by catheterization and angiography. The average age was 15.5±10.18 years. The youngest was a 15-month-old male child and the oldest was a 34-year-old male. Five patients had morphological features of Williams' syndrome; of them, only 1 had hypercalcemia (Tables 1 and 2).

All the patients had discrete type of SVAS (Figs 1 and 2), except 1 (6.6%) who had the diffuse variety (Fig. 3). The mean peak gradient across the supra-aortic region was 101.63±59.69 mmHg.

The mode of presentation was congestive heart failure (CHF) in 3 patients. One patient, a 14-year-old male, presented with severe anemia and CHF (hemoglobin 4 g%), the other 2 patients presented with CHF in infancy. A 27-year-old male patient presented with recurrent presyncope. He had a very high LVOT gradient of 215 mmHg. Three patients were in the New York Heart Association (NYHA) functional class I at presentation. The rest of the patients were in NYHA class II.

Two patients underwent repeat cardiac catheterization on follow-up. One 10-year-old boy with class II symptoms, who had an initial gradient of 24 mmHg, which increased to 80 mmHg after 6 years, was advised surgery. Another 10-year-old boy whose initial gradient of 31 mmHg increased to 76 mmHg after 5 years also underwent surgery. One patient with a gradient of 40 mmHg had the same echocardiographic gradient 9 years post-catheterization and has been kept on follow-up.

Associated lesions: Five patients did not have any associated lesions. One patient, a 9-year-old male, had an ascending aortic aneurysm necessitating repair. Three patients had associated peripheral pulmonary artery stenosis. Of them, 2 patients had features of Williams' syndrome. One patient had moderate aortic regurgitation (AR) while another had a small perforation in the noncoronary aortic cusp with mild AR, requiring repair. A 10-year-old child had a subaortic ventricular septal defect (VSD), and mild valvar AS (AS gradient of 20 mmHg). A 15-month-old child had mitral valve prolapse (MVP), and moderate-to-severe mitral regurgitation (MR), requiring mitral valve repair.

Electrocardiograms: Two patients with supravalvar gradients of 20 and 40 mmHg had normal ECGs. A 6-year-

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Age (years)</th>
<th>Sex</th>
<th>Dysmorphism</th>
<th>Aortic valve</th>
<th>Associated cardiac lesions</th>
<th>Coronaries</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>14</td>
<td>M</td>
<td>Nil</td>
<td>Normal</td>
<td>Nil</td>
<td>Normal</td>
</tr>
<tr>
<td>2</td>
<td>27</td>
<td>F</td>
<td>Nil</td>
<td>Thickened, stenotic</td>
<td>Valvular AS</td>
<td>Normal</td>
</tr>
<tr>
<td>3</td>
<td>1.25</td>
<td>M</td>
<td>Nil</td>
<td>Normal</td>
<td>MVP MR</td>
<td>NA</td>
</tr>
<tr>
<td>4</td>
<td>6</td>
<td>M</td>
<td>Nil</td>
<td>Valve commissures fused to ridge, NCC perforation</td>
<td>Mild AR</td>
<td>Dilated</td>
</tr>
<tr>
<td>5</td>
<td>16</td>
<td>M</td>
<td>WS</td>
<td>Normal</td>
<td>Nil</td>
<td>Normal</td>
</tr>
<tr>
<td>6</td>
<td>18</td>
<td>M</td>
<td>WS</td>
<td>Thickened, stenotic</td>
<td>VSD+valvular AS</td>
<td>Normal</td>
</tr>
<tr>
<td>7</td>
<td>10</td>
<td>M</td>
<td>WS</td>
<td>Normal</td>
<td>RPA stenosis</td>
<td>Normal</td>
</tr>
<tr>
<td>8</td>
<td>27</td>
<td>M</td>
<td>Nil</td>
<td>Normal</td>
<td>Innominate artery narrowing</td>
<td>Dilated</td>
</tr>
<tr>
<td>9</td>
<td>4.5</td>
<td>M</td>
<td>WS</td>
<td>Adherent LCC</td>
<td>Nil</td>
<td>Dilated, tortuous</td>
</tr>
<tr>
<td>10</td>
<td>10</td>
<td>M</td>
<td>Nil</td>
<td>Normal</td>
<td>Nil</td>
<td>Normal</td>
</tr>
<tr>
<td>11</td>
<td>9</td>
<td>M</td>
<td>Nil</td>
<td>Normal</td>
<td>Ascending aortic aneurysm</td>
<td>Dilated</td>
</tr>
<tr>
<td>12</td>
<td>15</td>
<td>F</td>
<td>Nil</td>
<td>Normal</td>
<td>LPA stenosis</td>
<td>Normal</td>
</tr>
<tr>
<td>13</td>
<td>26</td>
<td>M</td>
<td>Nil</td>
<td>Adherent LCC</td>
<td>Nil</td>
<td>Dilated</td>
</tr>
<tr>
<td>14</td>
<td>10</td>
<td>M</td>
<td>WS</td>
<td>Normal</td>
<td>LPA, RPA stenosis</td>
<td>Dilated, tortuous</td>
</tr>
<tr>
<td>15</td>
<td>34</td>
<td>M</td>
<td>Nil</td>
<td>Adherent cusps, AR</td>
<td>Nil</td>
<td>Normal</td>
</tr>
</tbody>
</table>

WS: Williams' syndrome; LCC: left coronary cusp; NCC: noncoronary cusp; AS: aortic stenosis; VSD: ventricular septal defect; AR: aortic regurgitation; MVP: mitral valve prolapse; MR: mitral regurgitation; LPA: left pulmonary artery; RPA: right pulmonary artery; NA: data not available
old patient with a gradient of 70 mmHg also did not have left ventricular hypertrophy (LVH). All the other patients had ECG evidence of LVH. The presence of LV strain did not correlate with the severity of stenosis.

Aortic valve morphology: Three patients had gradients across the aortic valve in addition to the gradients at the supravalvar region. These gradients were minimal (10, 20, and 14 mmHg) against supravalvar gradients of 120, 170 and 202 mmHg, respectively. All the patients who underwent surgery had their valves examined peroperatively and the findings were noted. Nine patients had normal valves. Details of valve abnormalities are given in Table 1. No patient needed any intervention for valvular anomalies except one who had a small noncoronary cusp perforation which had to be repaired during patch aortoplasty. One patient with moderate AR is awaiting surgery.

Coronary morphology: Coronary anatomy was available for analysis in 13 of the 15 patients. Seven of the 13 patients had dilated coronary arteries, especially the proximal coronary arteries (Figs 2 and 3). Two patients had tortuous, dilated coronary arteries.

Two patients with supravalvar aortic gradients of 20 and 40 mmHg were kept on close follow-up. The relatives of one 10-year-old male patient were not willing for surgery. One patient is awaiting surgery. The remaining patients (n=11) underwent surgical correction.

Surgical technique: All the patients were operated (n=11) under standard cardiopulmonary bypass (CPB) with moderate hypothermic and cold cardioplegic myocardial protection. Ten patients, who had a classical hourglass type of narrowing, underwent repair by the technique of single sinus aortoplasty, using a diamond-shaped dacron patch in 6 patients and gluteraldehyde-tanned autologous pericardial patch in 4. The child with diffuse narrowing of the ascending aorta underwent widening of the ascending aorta with a tanned pericardial patch from the noncoronary sinus to the origin of the innominate artery. Associated procedures in our patients included mitral valve repair, closure of VSD, repair of saccular aneurysm of the ascending aorta, and pericardial patch widening of the origin of the right pulmonary artery (one case each).

Surgical results and follow-up data: Therewere 2 deaths, both due to uncontrollable bleeding from the aortic suture line, which occurred in the immediate postoperative period. One patient was lost to follow-up. Follow-up was for 6.33±4.71 years. The patient with diffuse type of SVAS showed a gradient of 66 mmHg on follow-up echocardiogram. All the other patients were in NYHA functional class I on follow-up and echocardiographic assessment showed good results, except in 2 patients who showed mild valvar gradient with mild valvar regurgitation.

Discussion

Supravalvar aortic stenosis is relatively rare and the least common of the congenital LVOT obstructions. The patients can be classified into three groups according to the mode of presentation.
Morphologically, SVAS can be categorized into three types.

1. **Hourglass type**: the most common type, characterized by a constricting annular ridge at the superior margin of the sinus of Valsalva.


3. **Hypoplastic type**: with uniform hypoplasia of the ascending aorta which may extend into the arch vessels.

Supravalvar aortic stenosis is unique among LVOT obstructions because, among systemic vessels, the coronary arteries alone are exposed to high systolic pressures, which lead to dilatation, tortuosity and premature atherosclerosis of these arteries, thus making the patient susceptible to sudden cardiac death before and after repair. The coronary ostia may be obstructed by the overhanging thick sinus rims as well as bound-down aortic cusps. This more commonly occurs in the left sinus, but can also occur in the right. Also, the free edges of the aortic cusps (which are thickened in one-third of patients) may be adherent to the intraluminal supravalvar aortic ridge. This contributes to LVOT obstruction, interferes with coronary blood flow, and is also responsible for the associated aortic regurgitation.

Five of our 15 patients had associated aortic valve...
anomalies. In the series by Sharma et al., 25% of the patients had a bicuspid aortic valve, 12% had aortic regurgitation, 11% had valvar aortic stenosis, and 10% had subvalvar stenosis. In the series of 13 patients by Braunstein et al., one patient had subaortic obstruction.

Williams–Beuren’s syndrome is associated with a microdeletion in the chromosomal region 7q11.23 encompassing, among others, the elastin gene. The syndrome is routinely confirmed by detecting elastin hemizigosity by fluorescence in situ hybridization (FISH). Previous reports suggest that hemizigosity of the elastin gene is responsible for the typical vasculopathy of this syndrome, namely, SVAS and pulmonary arterial stenosis.

Williams–Beuren’s syndrome is associated with the nonfamilial form of SVAS, in which there is a peculiar facies (small chin, large mouth, patulous lips, blunt and upturned nose, widely set eyes with internal strabismus, epicanthic folds, broad forehead, baggy cheeks, lacy iris pattern, and malformed teeth with malocclusion), short stature, and mental retardation. Adult patients are short-statured, may have kyphoscoliosis, and may develop progressive joint limitation and hypertension. These patients may have idiopathic infantile hypercalcemia, pulmonary artery stenosis (especially peripheral pulmonary stenosis), renal artery anomalies, tortuous retinal arteries, systemic hypertension, and gastrointestinal and urinary tract anomalies.

In Williams’ syndrome, SVAS seems to progress rapidly while peripheral pulmonary stenosis improves with time. Associated cardiac lesions described are pulmonic stenosis (both valvar and peripheral), mitral valve anomalies with MR, and aneurysm of the ascending aorta and subaortic obstruction. Etiologic factors proposed are idiopathic hypercalcemia, disturbance of vitamin D metabolism and calcium homeostasis, and rubella.

In our series, there were no familial cases of SVAS, but there were 5 cases of Williams’ syndrome. Of them, 2 had peripheral pulmonary artery stenosis and one had aortic valvar stenosis. Only one of these patients had hypercalcemia; however, vitamin D challenge or calcium loading tests were not done in these patients to unmask calcium homeostatic defects. Seven of the 13 patients in the series by Braunstein et al. 17 and 14 of the 101 patients in the series by Brown et al. 18 had Williams’ syndrome.

The treatment of SVAS is surgical if the patient has significant gradients. SVAS is less amenable to operative treatment than either valvar or discrete subvalvar stenosis. Successful surgery for SVAS using patch graft enlargement of the noncoronary sinus of Valsalva was first reported from the Mayo clinic. 11 After that, many series on surgical results in patients with SVAS have been reported. 6,10–18

The discrete type of SVAS is more amenable to surgery than the diffuse type. In the discrete type, aortotomy is done above the valve, and the incision carried into the right or noncoronary sinus of Valsalva. The intimal shelf is then resected and a diamond-shaped pericardial/dacron patch incorporated into the incision to enlarge the aortic diameter to normal.

In the single-center experience of SVAS from the Texas Heart Institute, 32% of the patients had discrete type of SVAS, and were treated with simple patch aortoplasty (placing a diamond-shaped patch across the sinus rim in the noncoronary sinus of Valsalva) with good results and only 4% mortality. Though this operation was effective in relieving the pressure gradients, it did nothing to rebuild/remodel the diseased aortic root. Doty et al. 19 have proposed the use of extender aortic conduits for the intercoronary space into both the noncoronary sinus and right coronary sinus for a wider and anatomically more symmetrical repair, even in cases with discrete stenosis.

Surgical treatment options for the diffuse form of SVAS are less well defined. It may become necessary to replace or widen the entire hypoplastic aorta with an appropriate prosthesis. 16,17 Extended patch aortoplasty and apicoaortic conduits are the procedures that have been tried. Sharma et al. 6 have treated two patients with the diffuse variety of SVAS with another technique: extensive endarterectomy of the ascending aorta and arch, with patch aortoplasty extended into the aortic arch. Since the morphologic defect in SVAS involves the media and intima, it seems logical to remove these by endarterectomy. 9

Only 1 of our patients had the diffuse variety of SVAS (6.6%), compared with 15% of patients in the series by Sharma et al. 6 In the series by Brown et al., 10 28/101 patients had the diffuse variety of SVAS, and they were treated with either an apical aortic conduit or extensive endarterectomy with patch aortoplasty, with encouraging results. In the series by Braunstein et al., 2/13 patients with the diffuse variety of SVAS had excellent results with bisinus patching and extending the patch to the descending aorta.

Thirty-three patients in the surgical series by Sharma et al. 6 had other associated obstructive lesions of the LVOT requiring surgical correction. Though 2 patients in our series had associated valvar stenosis, this did not warrant surgical correction. Of patients with SVAS, 30% are reported to have thickened aortic valve cusps. Two patients (18%) developed minor AR postoperatively in our series. The exact incidence of AR in the series by Sharma et al. 6 is not clear. However, the incidence of 44% of new AR in the series by Braunstein et al. 7 is much higher.

Four patients in our series had associated cardiac lesions, which required surgical correction. PA plasty was done in 1 of our patients. There were no cases which required PA
plasty in the Braunstein series,7 while 1 patient required PA plasty in the series by Sharma et al.6 One patient in the series by Sharma et al.6 had pseudoaneurysm of the ascending aorta, while 1 of our patients had an aneurysm of the ascending aorta requiring aneurysmorraphy.

We had 2 early deaths due to bleeding (18.18%) but no late deaths at a mean follow-up of more than 6 years.

None of our 11 patients required reoperation at a mean follow-up of more than 6 years. In the series by Sharma et al.,6 22% of the patients required reoperation at some time during the follow-up period, and there were 5 late deaths in those with complex forms of the disease. We had only 1 patient with the diffuse form of the disease who underwent extended patch aortoplasty but had moderate residual gradient on follow-up. In a large experience of 101 patients with SVAS,10 the overall survival including operative mortality was 98% at 10 years, and 97% at 20 and 30 years.

This study has several weaknesses. It was a retrospective study, and the numbers were too small to draw conclusions. The patients did not undergo hemodynamic or angiographic study postoperatively.

We conclude that repair of SVAS by single sinus aortoplasty is safe, and produces good results.

References

The Efficacy and Tolerability of Sildenafil in Patients With Moderate-to-Severe Pulmonary Hypertension

Anil Bharani, Vivek Mathew, Ashutosh Sahu, Basant Lunia
Division of Cardiology, Department of Medicine, M.G.M. Medical College and M.Y. Hospital, Indore

**Background:** Pulmonary arterial hypertension is a life-threatening disease for which continuous intravenous infusion of prostacyclin has proved effective. However, it carries the risk of serious complications arising from the complex delivery system. Prostacyclin analogs, endothelin antagonists, and the phosphodiesterase-5 inhibitor sildenafil are emerging promising therapies. This study was aimed at evaluating the utility of oral sildenafil in patients with pulmonary hypertension of varied etiology, poorly controlled on conventional treatment.

**Methods and Results:** Ten consecutive patients with pulmonary hypertension, either primary or related to previous left-to-right shunts, thromboembolism, or interstitial lung disease, poorly controlled on conventional therapy such as warfarin, calcium antagonists, digitalis, and diuretics, were included. A thorough clinical, laboratory, and comprehensive echo Doppler evaluation was performed before enrollment in the trial to establish the diagnosis and obtain baseline data. Subjects received sildenafil 25 mg 8 hourly, or a matching placebo for two weeks each, in a randomized, double-blind, crossover design. A run-in period of two weeks was permitted between the two therapies during which patients continued to receive the conventional therapy without any vasodilator. At the end of each therapy period, the patients were evaluated for symptoms, New York Heart Association class, distance covered during the 6 min walk test, rating of modified Borg dyspnea score, and systolic pulmonary artery pressure using echo Doppler. The differences in the above variables at the end of sildenafil and placebo therapies were compared. Nine patients completed the study protocol. Sildenafil, compared to placebo, was associated with improved exercise tolerance as determined by the 6 min walk test (266.67±131.45 m v. 170±105 m; p<0.005), decrease in modified Borg dyspnea score (3.56±1.01 v. 5.11±1.45; p<0.01), decrease in Doppler-estimated pulmonary artery systolic pressures (55.33±16.52 mmHg v. 75.33±19.75 mmHg; p<0.005), improvement in New York Heart Association class (2 patients), and improvement in symptoms. Sildenafil was well tolerated with no untoward effects; further, no significant changes in heart rate or blood pressure occurred during the study period.

**Conclusions:** Sildenafil improves exercise capacity and symptoms, and decreases pulmonary artery pressures in patients with primary or secondary pulmonary hypertension of varied etiology. (Indian Heart J 2003; 55: 55–59)

**Key Words:** Pulmonary hypertension, Sildenafil, Echocardiography

---

Pulmonary arterial hypertension (PAH) is characterized by a progressive increase of pulmonary vascular resistance leading to right ventricular failure and death (WHO 1998). Pulmonary arterial hypertension includes primary pulmonary hypertension (PPH) with no apparent cause, PAH secondary to congenital shunt lesions, connective tissue disorders, and portal hypertension, drug-induced PAH, and HIV-related PAH. The current therapeutic options available for PAH include anticoagulants, calcium-channel blockers, epoprostenol (prostacyclin), iloprost, beraprost, the endothelin receptor antagonist bosentan, and phosphodiesterase type-5 (PDE5) inhibitor sildenafil. However, in many parts of the world, therapeutic options for patients with PAH are limited in the absence of availability of prostacyclins and thus sildenafil could be a useful alternative.

Sildenafil-induced inhibition of PDE5 increases the cellular levels of cGMP, potentiating vascular smooth muscle relaxation, particularly in the lungs where PDE5 is found in high concentrations. Sildenafil has been reported to inhibit hypoxia-induced pulmonary
hypertension, cause sustained reduction in pulmonary artery pressures and pulmonary vascular resistance in PPH, blunt the rebound pulmonary hypertension seen following withdrawal of inhaled nitric oxide, lead to impressive clinical benefits in childhood PPH, and cause selective pulmonary vasodilatation in a lamb model of PAH.

We report the results of a randomized, double-blind, placebo-controlled, crossover study designed to determine the efficacy of short-term oral administration of sildenafil on exercise capacity, symptoms, and Doppler-determined pulmonary artery pressures in NYHA class II–IV patients with PAH.

Methods

Selection of patients: Ten consecutive, symptomatic (NYHA class ≥II) patients with Doppler-estimated pulmonary systolic pressure ≥35 mmHg with normal left ventricular function and no reversible cause for PAH were taken up for the study. They gave well-informed written consent for participation in the study and all except one completed the study protocol. The institutional ethics committee approved the protocol. Patients were excluded if they had any contraindications to sildenafil therapy or if they had any reversible cause for pulmonary hypertension such as valvular heart disease.

Study design: The study was carried out at a large referral center of central India as a prospective, randomized, double-blind, crossover trial. To establish the diagnosis, patients were subjected to a thorough physical examination, routine laboratory evaluation, chest X-ray, electrocardiogram (ECG), and comprehensive echocardiographic evaluation at baseline. Before randomization, they were allowed a run-in period of one week after stoppage of their previous vasodilator therapy; they then received either sildenafil 25 mg 8 hourly or matching placebo for two weeks in a crossover design with a washout period of at least two weeks between the two therapies.

Outcome measures: The patients were evaluated for exercise capacity as indicated by the 6 min walking distance. The secondary measures of efficacy were change in symptoms and NYHA functional class, change in modified Borg dyspnea index (a measure of perceived breathlessness on a scale of 0 to 10, with higher values indicating more severe dyspnea), and change in resting pulmonary artery systolic pressures as estimated from Doppler tricuspid regurgitant jet velocities or from the gradient across the ventricular septal defect or patent ductus, wherever applicable. Echo-Doppler studies (GE Logic 500, MD, USA) were done by a single experienced observer who was blind to the therapy patients were receiving.

Statistical analysis: Changes in variables during treatment with sildenafil and placebo were analyzed with the paired Student’s t test. The null hypothesis was that there should be no significant difference in the exercise capacities and the pulmonary systolic pressures before and after 2 weeks of sildenafil therapy. A probability value of p<0.05 was considered significant.

Results

Baseline study group characteristics: There were 5 females and 4 males, 19 to 60 years of age, in NYHA functional classes II–IV, having pulmonary hypertension of varied etiologies. They were receiving conventional therapy including warfarin and nifedipine, and two patients were on diuretics and digoxin for treatment of heart failure (Table 1).

Table 1. Study group characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patients (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>18–60 years</td>
</tr>
<tr>
<td></td>
<td>Mean 32.11 years, SD 15.06 years</td>
</tr>
<tr>
<td>Sex</td>
<td>Male 4</td>
</tr>
<tr>
<td></td>
<td>Female 5</td>
</tr>
<tr>
<td>NYHA class</td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>II 3</td>
</tr>
<tr>
<td></td>
<td>III 5</td>
</tr>
<tr>
<td></td>
<td>IV 1</td>
</tr>
<tr>
<td>Post-sildenafil therapy</td>
<td></td>
</tr>
<tr>
<td></td>
<td>II 4</td>
</tr>
<tr>
<td></td>
<td>III 5</td>
</tr>
<tr>
<td></td>
<td>IV 0</td>
</tr>
<tr>
<td>Diagnosis</td>
<td></td>
</tr>
<tr>
<td>Primary pulmonary hypertension</td>
<td>3</td>
</tr>
<tr>
<td>Pulmonary hypertension associated with:</td>
<td></td>
</tr>
<tr>
<td>Interstitial lung disease</td>
<td>2</td>
</tr>
<tr>
<td>Thromboembolism</td>
<td>1</td>
</tr>
<tr>
<td>Eisenmenger syndrome</td>
<td></td>
</tr>
<tr>
<td>Ventricular septal defect</td>
<td>2</td>
</tr>
<tr>
<td>Patent ductus arteriosus</td>
<td>1</td>
</tr>
<tr>
<td>Treatment at inclusion</td>
<td></td>
</tr>
<tr>
<td>Warfarin</td>
<td>9</td>
</tr>
<tr>
<td>Nifedipine</td>
<td>4</td>
</tr>
<tr>
<td>Frusemide</td>
<td>2</td>
</tr>
<tr>
<td>Spironolactone</td>
<td>2</td>
</tr>
<tr>
<td>Digoxin</td>
<td>2</td>
</tr>
</tbody>
</table>
lead to improved symptoms, hemodynamics, and reduced mortality. The prostacyclin analogs iloprost and beraprost produce marked clinical benefits in patients with PAH. The orally administered endothelin receptor antagonist bosentan is reported to be effective and well tolerated in patients with PAH. While mortality benefits with these newer agents are yet to be ascertained, each therapy has certain limitations. Epoprostenol, the current gold standard of therapy for PPH, is associated with serious complications arising from the complex delivery system. Sildenafil, which is currently approved for the treatment of erectile dysfunction, is emerging as a new promising therapeutic agent for the treatment of secondary PAH and PPH.

Table 2. Change in 6 min walking distance, modified Borg dyspnea score and Doppler pulmonary artery pressure

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Baseline</th>
<th>Placebo</th>
<th>Sildenafil</th>
<th>t</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 min walking distance (m)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>163.89</td>
<td>170</td>
<td>266.67</td>
<td>5.98</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>SD</td>
<td>110.73</td>
<td>105</td>
<td>131.45</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Borg dyspnea score</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>5.22</td>
<td>5.11</td>
<td>3.56</td>
<td>3.56</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>SD</td>
<td>1.64</td>
<td>1.45</td>
<td>1.01</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulmonary artery pressure (mmHg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>80.78</td>
<td>75.33</td>
<td>55.33</td>
<td>4.33</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>SD</td>
<td>21.30</td>
<td>19.75</td>
<td>16.52</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Exercise capacity:** The distance walked in 6 min at baseline and at the end of sildenafil or placebo therapies is given in Table 2. The patients showed a significant improvement in exercise capacity while on sildenafil therapy compared to placebo (p<0.005, Fig. 1A).

**Symptoms and Borg dyspnea index:** All the patients showed improvement in symptoms after 2 weeks of sildenafil therapy compared to placebo. The Borg dyspnea index of perceived exertion after the 6 min walk showed statistically significant improvement at the end of sildenafil therapy (p<0.01, Table 2, Fig. 1B). There was improvement in the NYHA class in only two patients. There was no mortality.

**Pulmonary artery pressures:** Table 2 gives the pulmonary artery systolic pressures as estimated from the Doppler studies. Sildenafil therapy was associated with significant reduction in the pulmonary artery pressures compared to placebo (p<0.005, Fig. 1C).

**Side-effects and tolerance:** Sildenafil therapy was tolerated well with no adverse effects reported during this short-term study. No substantial changes in heart rate or systemic arterial pressure were observed during sildenafil treatment. Two sexually active males included in the study experienced no change in overall sexual performance or libido during sildenafil therapy.

**Discussion**

Primary pulmonary hypertension is a rapidly progressive disease which is uniformly fatal if untreated. Until 1981, when heart-lung transplantation was introduced, no treatment was available. Challenged by the limited number of suitable donors and the complications associated with organ transplantation, the search for effective medical therapies is ongoing. Continuous epoprostenol infusions...
The salutary effects of sildenafil on symptoms and exercise performance in patients with PAH have been reported in small studies and in anecdotal case reports, which are comparable to those of the prostanoids. However, large controlled trials with sildenafil to address the issue of improving survival in patients with PPH and PAH are not yet available. This short-term, double-blind, placebo-controlled, crossover study has demonstrated that oral sildenafil in a dosage of 25 mg 8 hourly improves exercise capacity, symptoms, and causes significant decrease in Doppler-estimated pulmonary artery pressures.

As in other trials performed on patients with PAH, the primary end-point of this study was the 6 min walking distance that has been shown to be an independent predictor of mortality. Following treatment, the distance observed in our patients was 96.67 m, which matches the effect observed with intravenous epoprostenol in NYHA class III–IV patients, and with beraprost in NYHA class II–III patients with PPH. Improvement in the 6 min walking distance was observed in all patients (NYHA class II–IV) in our study. However, improvement in the 6 min walk test was seen only in patients with PPH receiving beraprost but not in those with secondary PAH.

Sildenafil alone or in combination with inhaled iloprost has been shown to improve exercise performance in patients with PPH and secondary PAH. The improvement in the 6 min walking distance was associated with a concomitant significant improvement in the perception of dyspnea, as assessed by a reduction of the Borg dyspnea score. Perceptual estimates, obtained by psychophysical ratio-scaling method such as the Borg dyspnea scale, are very useful in judging the perceptual variation and are complementary to physiological measurement of work capacity and physical performance. Despite improvement in symptoms and exercise capacity in all the patients, improvement in NYHA class was seen only in two patients. This was perhaps related to the shorter duration of our study. Similar observations were reported in patients with PAH who were treated with beraprost for 12 weeks.

Sildenafil therapy was associated with a significant decrease in Doppler-estimated tricuspid regurgitation velocities and pulmonary systolic pressures in our study. The available studies on sildenafil are few. In a young male with severe PAH, sildenafil 100 mg five times per day for 3 months led to a decrease in the Doppler-estimated pulmonary artery pressure from 120 mmHg to 90 mmHg with improvement in the myocardial oxygen consumption during exercise, and dramatic improvement in symptoms and aerobic capacity. Similarly, in the case of a 4-year-old girl with severe PPH with poor response to prostacyclin, oral sildenafil (2 mg/kg 4 hourly) led to a significant decrease in pulmonary artery pressures, rise in oxygen saturation, improved exercise capacity, and impressive clinical recovery, permitting discontinuation of prostacyclin and oxygen therapy.

A recent study reported long-lasting reduction in the mean pulmonary artery pressure and pulmonary vascular resistance with sildenafil and additional improvement after iloprost inhalation in patients with PPH. No significant changes in heart rate or blood pressure were observed during the treatment. A other study reported impressive clinical benefits associated with combination therapy using oral sildenafil and inhaled iloprost in patients with severe PAH.

In a randomized, double-blind, placebo-controlled study, sildenafil 100 mg given orally to ten healthy volunteers inhibited hypoxia-induced pulmonary hypertension, a response mediated through the eNOS-NO-cGMP pathway. Sildenafil has been reported to blunt the rebound pulmonary hypertension seen following withdrawal of inhaled nitric oxide. In lambs with acute pulmonary hypertension, sildenafil decreased the pulmonary artery pressure and pulmonary vascular resistance resulting from selective pulmonary vasodilatation. In a recent study, a single oral dose of sildenafil (75 mg) was found to be as effective as and selective a pulmonary vasodilator as inhaled nitric oxide in patients with severe PAH referred for heart-lung transplantation. Sildenafil was superior to nitric oxide in that it led to a greater increase in cardiac output and did not increase wedge pressure. Sildenafil was assessed for childhood and neonatal pulmonary hypertension (16 patients), given either acutely (0.25–0.5 mg/kg) prior to hemodynamic measurements in the cath lab, or chronically after gradual withdrawal of nitric oxide in refractory suprasystemic PAH, or for chronic treatment of PPH or PAH. During cardiac catheterization, the mean pulmonary artery pressure decreased (50±8 mmHg to 38±12 mmHg, p<0.05), and pulmonary vascular resistance decreased with no change in the mean systemic pressure or systemic vascular resistance. During chronic use, sildenafil attenuated the rise in pulmonary artery pressure, permitted discontinuation of nitric oxide and led to 200% improvement in the 6 min walk distance in the remaining patients.

Sildenafil has been well tolerated without major side effects. We did not come across hypotension, syncope, or any other untoward effect attributable to sildenafil in our study. Our results concur with those of other studies to support the safety and impressive clinical benefits.
associated with sildenafil therapy in patients suffering from PPH or secondary PAH. Sildenafil therapy was not found to have any important hemodynamic effect in patients with stable coronary artery disease but caution must be exercised in patients receiving diuretics and/or nitrates.

To conclude, our study results show the beneficial effects of sildenafil in patients with PPH and secondary PAH in adults. These include significant improvement in exercise capacity as indicated by improvement in the 6 min walk distance, decrease in modified Borg dyspnea index of perceived exertion, and decrease in pulmonary artery systolic pressures. The drug is well tolerated with no substantial change in heart rate or blood pressure. The small sample size and short duration of the study are acceptable limitations. Large, long-term, randomized, multicenter trials are needed to answer questions regarding the long-term utility and survival benefits with the PDE5 inhibitor sildenafil in patients with PPH and secondary PAH.

Acknowledgments

We acknowledge the help received from Professor LK Mathur, Department of Biostatistics, M.G.M. Medical College, Indore, for statistical analysis and Mrs Prasanna Nair for secretarial assistance.

References

8. Abrams D, Schulze-Neuck I, Magee AG. Sildenafil as a selective pulmonary vasodilator in childhood primary pulmonary hypertension. Heart 2000; 84: E4
25. Arruda- Olson AM, Mahoney DW, Nehra A, Leckel M, Pelikka PA. Cardiovascular effects of sildenafil during exercise in men with known or probable coronary artery disease: a randomized crossover trial. JAMA 2002; 287: 719–725
Polymorphisms in the Apoprotein B-100 Gene: Association With Plasma Lipid Concentration and Coronary Artery Disease

Ratna Dua Puri, Satyendra Tewari, Nakul Sinha, V Ramesh, Faisal Khan, Vivek P Singh, Suraksha Agrawal
Departments of Medical Genetics, Cardiology and Pathology, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow

Background: The aim of this study was to investigate the association of apolipoprotein B gene polymorphisms with coronary artery disease and lipid levels in Indians.

Methods and Results: One hundred patients of angiographically proven atherosclerotic coronary artery disease and one hundred age- and sex-matched control subjects (treadmill negative) were included in the study. Serum lipids including cholesterol, triglycerides, high-density lipoprotein, low-density lipoprotein, very low-density lipoprotein, and apolipoprotein B were analyzed. Genomic DNA was extracted and the apolipoprotein B 3' hypervariable region amplified by polymerase chain reaction. Regions carrying Xba1, EcoR1, and Msp1 restriction sites present in the apolipoprotein B gene were amplified and digested separately by the respective enzymes. Restriction fragment length polymorphism analysis showed that EcoR1 with the R+/R+ genotype was significantly more common in patients with coronary artery disease. Overall, the genotypes EcoR1+/+, Msp1+/+, Xba1+/+ and Eco R1+/+ Msp1+/–, Xba1–/– were significantly more common in patients as compared to controls (p<0.05). When gene polymorphisms were compared with lipid abnormalities, the genotypes EcoR1+/+, Xba1–/–, and Msp1+/+ were more frequent in patients with elevated apolipoprotein B and very low-density lipoprotein levels. On the other hand, these genotypes were less common in patients with increased total cholesterol and low-density lipoprotein levels. When we studied the individual alleles of the variable number of tandem repeats region, we observed that allele 34 was significantly increased in patients with coronary artery disease as compared to controls. Allele 36 was present with a frequency of 1% in controls while it was totally absent in patients.

Conclusions: This study identifies the apolipoprotein B gene polymorphism associated with coronary artery disease. An association between apolipoprotein B gene polymorphisms and elevated apolipoprotein B and very low-density lipoprotein levels was observed. However, there was no positive association with other elevated lipid levels in North Indians from Uttar Pradesh. (Indian Heart J 2003; 55: 60–64)

Key Words: Apolipoprotein B, Polymorphism, Coronary artery disease

Elevated serum low-density lipoprotein (LDL) concentration is an important risk factor for developing atherosclerotic coronary artery disease (CAD) in humans. Apolipoprotein (apo) B-100 is the principal protein component of LDL. The interaction of apo B-100 with LDL receptors mediates the uptake of LDL from the liver and peripheral cells; hence, apo B-100 plays an important role in cholesterol homeostasis. The apo B gene is localized on chromosome 2, and the complete structure of the human apo B-100 gene has been elucidated. Cloning and sequencing of the apo B gene has made it possible to study the variation in the apo B gene at the DNA level. A 15 bp AT-rich hypervariable region (HVR) is located adjacent to the 3' end of the apo B gene. It consists of a variable number of tandem repeat sequences (VNTR). Previous studies have reported that some of the "3'VNTR" alleles and restriction fragment length polymorphisms (RFLP) of apo B-100 are directly associated with CAD.
or with variations in plasma lipids. Interestingly, the association of apo B-100 VNTR and RFLPs with plasma lipid concentration or CAD varies in different ethnic groups and has not always been found to be associated with CAD or hyperlipidemia. The incidence of CAD is increasing in India, especially in the younger population. Hence, it is important to delineate risk factors for CAD in Indians. There are very few studies from India which report the effect of apo B polymorphisms on CAD or lipid levels. The present study is an attempt to analyze the allele frequency of apo B-100 3' VNTR and apo B-100 RFLPs in the Indian population and to determine their association with plasma lipid concentration and CAD.

**Methods**

**Subjects:** One hundred patients of angiographically proven CAD evaluated at the Cardiology Department of the Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, Uttar Pradesh, India were included in the study. Patients less than 6 weeks post-myocardial infarction (MI) were excluded from the study. One hundred age- and sex-matched controls were also selected for the study. The controls were subjected to a treadmill test to ensure that they were not suffering from any CAD. Further, all controls with hypertension, diabetes, and endocrine or metabolic disorders were excluded. Informed consent was taken from both the patients and controls.

**Lipid analysis:** Blood samples were taken after a fasting period of 12 hours from all the patients and controls. Serum lipids including cholesterol, triglycerides, high-density lipoprotein (HDL), LDL, and very low-density lipoprotein (VLDL) were analyzed according to methods previously described. Apolipoprotein B levels were assessed by the immunoturbidimetric immunoassay using a commercial kit (Randox Laboratories Ltd, UK).

**DNA preparation:** Genomic DNA was extracted by the high salting-out procedure followed by phenol chloroform extraction and ethanol precipitation.

**Analysis of VNTR:** Apolipoprotein B 3'HVR amplification was carried out by PCR using a forward and reverse oligonucleotide primer encompassing the entire apo B 3' VNTR sequence. The sequence of the primer used was 5' ATGCA AAGGGA AATTATG 3' and 5' CCTTCTCAGTTCCAATAC 3'. The polymerase chain reaction (PCR) was performed in an M.J. Research Inc. Thermocycler, with 26 cycles of denaturation at 94 °C for 1 min, and annealing and extension at 58 °C for 6 min. The amplified product was electrophoresed in 5% polyacrylamide gel, and allele sizing was done using the apo B 3' VNTR allelic ladder and a commercial ladder 50 bp in size (Fig. 1).

**Analysis of RFLP:** Regions of the apo B gene carrying EcoR1, Msp1, and Xba1 restriction sites were amplified separately using their respective primers: 5' CTG, GCT, TGC, TAA CCT, CTC, TG and 3' AAG, CTG, CAA, GAA, ACT, ATT, G and 3' CTA, AAG, TAC, GGA, ACT, CTA, CAA, TGG, CAA, GGT for EcoR1, 5' TCT, CGG, GAA, TAT, TCA, GGA, ACT, ATT, G and 3' CTA, AAG, TAC, GGA, ACT, CTA, CAA, TGG, CAA, GGT for Msp1 and 5' GGA, GAC, TAT, TCA, GAA, ACT, ATT, G and 3' CTA, AAG, TAC, GGA, ACT, CTA, CAA, TGG, CAA, GGT for Xba1. The amplified product was separately digested with the respective enzymes as previously described. Alleles of each polymorphic site were classified as (+) or (−) according to

![Fig. 1. Apo B-gene polymorphism. A: Apo B 3' VNTR analysis; B: Msp1 RFLP analysis; C: Xba1 RFLP analysis; D: EcoR1 RFLP analysis](image-url)
the presence or absence at the cutting site of each restriction enzyme, respectively.

**Statistical analysis:** Allele and genotypic frequency analysis for apo B 3’ VNTR and RFLP was done using the POPGENE-16 version. The Student’s t test was used for comparisons using the SPSS software.

**Results**

One hundred patients with angiographically proven CAD (90 males, 10 females) and 100 normal controls (90 males and 10 females) were evaluated. The mean age of the patients was 50.74±9.7 years, while that of the controls was 50.41±12.23 years.

**Lipid levels:** The mean lipid levels of patients with CAD and controls were not significantly different. However, lipid levels were higher in patients as compared to controls.

**Allele frequency and genotyping for EcoR1, Xba1, and Msp1:** The comparison of the genotypic and allele frequencies of the EcoR1, Xba1, and Msp1 RFLPs of the apo B gene in patients with CAD and controls is shown in Table 1. The only significant RFLP pattern was with EcoR1, with the R+/R+ genotype expressed more frequently in patients with CAD (p=0.001), while the R+/R– genotype was more common in controls (p=0.001). The genotypes E+E+ M+ M+ X+ X+ and E+ E+ M+ M– X– X– were significantly more prevalent in patients with CAD (p<0.05). The genotype E+ E– M+ M– X– X–, on the other hand, was more common in controls (p<0.05).

**VNTR analysis:** Relative frequencies of VNTR in patients with CAD and controls are shown in Fig. 2. The VNTR allele 34 was significantly increased in patients with CAD compared to that in controls, while allele 36 was significantly increased in controls. Interestingly, VNTR allele 36 was totally absent in patients.

**Correlation of VNTR, RFLP, and lipid parameters with the age of the patients with CAD:** When young patients with CAD (age <45 years, n=46) were analyzed, there was no significant increase in any allelic and genotypic frequencies of different apo B polymorphisms as compared to older patients (age ≥45 years, n=54). However, when patients with CAD were compared to controls, the older patients with CAD had a higher frequency of EcoR1 (+) allele, while the EcoR1 (–) allele was less common in both the age subgroups.

**Correlation of RFLP and HVR allele with lipid parameters:** In patients with CAD, the genotypes R+/R+, X/X and M+/M+ were frequent in those with elevated apo B and VLDL levels. On the other hand, these genotypes were less frequent in patients with increased total cholesterol and LDL levels. The allele Msp1 (–) was significantly less common in patients with elevated LDL levels.

Among controls, the trend of association was the same as in the patient group but the results were not significant in the controls, even in those with elevated apo B and VLDL levels.

---

**Table 1. Allele and genotype frequencies of apo B gene RFLPs in patients with CAD and controls**

<table>
<thead>
<tr>
<th>Allele frequency</th>
<th>CAD (n=100)</th>
<th>Controls (n=100)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EcoR1 (+)</td>
<td>0.950</td>
<td>0.820</td>
</tr>
<tr>
<td>EcoR1 (–)</td>
<td>0.050</td>
<td>0.180</td>
</tr>
<tr>
<td>Xba1 (+)</td>
<td>0.285</td>
<td>0.225</td>
</tr>
<tr>
<td>Xba1 (–)</td>
<td>0.715</td>
<td>0.775</td>
</tr>
<tr>
<td>Msp1 (+)</td>
<td>0.825</td>
<td>0.850</td>
</tr>
<tr>
<td>Msp1 (–)</td>
<td>0.175</td>
<td>0.150</td>
</tr>
</tbody>
</table>

**Genotypic frequency (%)*

<table>
<thead>
<tr>
<th></th>
<th>EcoR1/</th>
<th>Xba1/</th>
<th>Msp1/</th>
</tr>
</thead>
<tbody>
<tr>
<td>R+R+</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>R+R–</td>
<td>8</td>
<td>34*</td>
<td>65*</td>
</tr>
</tbody>
</table>

**Genotypes *:

- +, – refers to the presence or absence of a cutting site for restriction endonuclease
- *only significant genotype frequencies have been shown (p<0.005);
- **only significant genotype frequencies have been shown (p<0.001)

APO B: apolipoprotein B; RFLP: restriction fragment length polymorphism; CAD: coronary artery disease; R: EcoR1; M: Msp1; X: Xba1

---

**Fig. 2.** Apo B 3’ VNTR allele frequency distribution among patients with CAD and controls.
Discussion

On the basis of evidence obtained over many years from epidemiological and trial data, LDL- and HDL-cholesterol levels have been the recommended lipid variables in international guidelines for treatment. However, new information shows the importance of apo B and apo A-I as risk predictors for CAD. A reason why apo B may be a stronger predictor of risk than LDL-cholesterol is that apo B is present not only in LDL but also in VLDL, intermediate density lipoprotein, and lipoprotein (a). Therefore, the sum of apo B concentrations in all atherogenic particles might be a better risk marker than total cholesterol and LDL-cholesterol levels only. In our study, the entire lipid levels, including those of apo B, were higher in patients as compared to controls; however, these did not reach statistical significance. One possible explanation for this could be that lipid-lowering drugs were not withheld prior to lipid testing for this study as this would not have been ethically justifiable in patients who had angiographically proven CAD with dyslipidemia and were already on lipid-lowering drugs.

It has been suggested that in addition to quantitative variation in apo B levels in the plasma, genetic variation at the apo B locus may be a new and independent risk factor for CAD.

It has been reported that different VNTR alleles may be associated with CAD and hyperlipidemia. We found an association of VNTR 34 in patients with CAD similar to that reported by Moreel et al. The allelic variation of apo B gene polymorphisms may have some association with various ethnic groups. Deka et al. in a study of allelic frequency distribution at the hypervariable locus 3' to the apo B gene in 5 human populations found 12 segregating alleles in 319 individuals. They found that the two most frequent alleles, 37 and 39, were present in all the populations. When we studied VNTR we found that allele 34 was significantly increased in patients as compared to controls, while allele 36 was completely absent in patients but present in controls. This clearly demonstrates the presence of allelic frequency variation in different populations. These association studies may be of some use when genetic factors are considered as one of the predisposing causes.

There are few studies on Indians that show the association of the apo B gene 3'HVR alleles with CAD and plasma lipid levels. Renges et al. found an association between Xba1 and ins/del polymorphisms of the apo B gene with total cholesterol and HDL-cholesterol levels in South Asians in the UK. Saha et al. reported that DNA polymorphisms of the apo B gene were associated with obesity and serum lipids in healthy Indians in Singapore. Misra et al., on the other hand, have reported that apo B (Xba1 and EcoR1) polymorphisms did not appear to influence serum lipid levels. In our study, we found that the genotypes R'/R', X/X' and M'/M' were frequent in patients with elevated apo B and VLDL levels. However, these genotypes were decreased in patients with elevated cholesterol and LDL levels. Pan et al. found that apo B 3' VNTR genotypic variation had little impact on the risk of dyslipidemia in a Taiwanese population but despite this, the long apo B 3' VNTR alleles occurred more frequently in patients with CAD. Hegele et al. also found a significant correlation between apo B gene polymorphisms and CAD, without any significant association with either LDL or VLDL. Similar results were reported in a porcine model of atherosclerosis in which an apo B variant was associated with atherosclerosis, despite normal lipid levels. Our results show that the apo B gene variations possibly do not affect the apo B–LDL-receptor binding region, and thus do not affect the lipid levels. Other studies have also shown similar trends. We speculated that a mutation in the protein coding region of apo B could affect the interaction of LDL with monocyte macrophages, endothelial cells, ground substance, clotting factors, or the immune system in a manner that would promote atherogenesis.

The clinical relevance of apo B polymorphisms still remains unclear. All studies in the past reflect the genetic heterogeneity of the apo B gene. As CAD is a multifactorial disease, the apo B gene alone may not have a direct effect on the lipid profile or severity and prematurity of CAD. However, it does emphasize the importance of such studies, which may help in future to delineate the high-risk group for CAD, and may be of use in the genetic screening of patients with CAD belonging to different populations.

References

Isolation of the Left Subclavian Artery

Ambuj Roy, Shyam S Kothari, Harminder Singh, Sanjiv Sharma
Cardiothoracic Centre, All India Institute of Medical Sciences, New Delhi

Two cases of isolation of the left subclavian artery from the aortic arch are reported for the rarity of this lesion. One patient was diagnosed clinically, the other after angiography. The isolated left subclavian artery was reimplanted in one patient. This rare anomaly has clinical and surgical relevance and should be diagnosed by diligent clinical and angiographic evaluation. (Indian Heart J 2003; 55: 65–67)

Key Words: Isolated left subclavian artery, Subclavian steal, Arch anomalies

Isolation of the left subclavian artery (LSA) from the right aortic arch is a rare vascular anomaly, in which the left subclavian artery does not communicate with the aortic arch but instead is connected to the left pulmonary artery by the ductus arteriosus. We report two cases of isolated LSA, one of which was diagnosed clinically.

Case Report

Case 1: A two-year-old child presented to us with a history of mild cyanosis since 6 months of age and a history of one episode of a cyanotic spell one month ago. On examination he had mild cyanosis and clubbing. The left arm pulse was weaker compared to the right arm. The blood pressure was 70/40 mmHg in the left arm and 104/60 mmHg in the right arm. Cardiovascular examination revealed a quiet precordium, single second heart sound, and a grade III/VI ejection systolic murmur in the left parasternal area. Chest X-ray showed a right aortic arch, no cardiomegaly and oligemic lung fields. An electrocardiogram (ECG) showed right axis deviation with right ventricular hypertrophy. Typical anatomy of the tetralogy of Fallot (TOF) was seen on echocardiogram. In view of TOF, right aortic arch and weak left arm pulse, isolation of the LSA was suspected. Subsequent catheterization confirmed the presence of TOF with confluent and good-sized pulmonary arteries. Aortogram revealed a right aortic arch. The innominate, right and left common carotid arteries were normal. On aortography, the LSA did not show any opacification (Fig. 1). Late frames showed faint opacification of the LSA by retrograde filling from the left vertebral artery, suggesting the presence of isolation of the LSA (Fig. 2). The child underwent corrective surgery for TOF and reimplantation of the LSA to the left common carotid artery. He is doing well at follow-up after 6 months.

Case 2: A 3.5-month-old male child was brought with a history of cyanosis and failure to thrive, and recurrent episodes of lower respiratory tract infection. There was no history of stridor, wheezing or loss of consciousness. He was born at term and the antenatal history was unremarkable. His present weight was 2.8 kg and the birth weight was 2.5 kg. His pulse rate was 110/min, regular, and all peripheral pulses were palpable and equal. He had mild cyanosis on room air. His blood pressure was 80/56

**Correspondence:** Dr Shyam S Kothari, Department of Cardiology, Cardiothoracic Centre, All India Institute of Medical Sciences, New Delhi 110029. e-mail: kotharis@del2.vsnl.net.in
mmHg in the right arm and 82/60 mmHg in the left arm. The arterial saturation by oximetry was 85% in room air in all four limbs. Cardiovascular examination revealed cardiomegaly, single second heart sound, left ventricular third heart sound, and a pansystolic murmur at the apex. ECG showed left axis deviation with a counterclockwise loop and right ventricular hypertrophy. Chest X-ray revealed cardiomegaly, a right aortic arch, and increased pulmonary blood flow. Echocardiography showed atrioventricular septal defect (AVSD) and a double outlet right ventricle (DORV) with dilated left ventricle and atrium. The great vessels were malposed with an anterior aorta. There was no pulmonic stenosis. Cardiac catheterization and aortography were performed. The aortogram revealed a right aortic arch with absence of filling of the LSA from the aorta (Fig. 3) and delayed retrograde filling from the left vertebral artery. A selective left common carotid angiogram showed retrograde filling of the LSA through the vertebral artery (Fig. 4). Right ventricular angiogram confirmed the presence of a DORV. Hence, a diagnosis of cyanotic congenital heart disease with DORV, AVSD, and isolated LSA was made. The child subsequently developed lower respiratory tract infection and succumbed to it.

**Discussion**

Isolation of the LSA is defined as a loss of continuity between the LSA and the aorta with a persistent connection to the homolateral pulmonary artery through the ductus arteriosus, which may be patent or closed. There is retrograde filling of the LSA through the left vertebral artery, which is fed via the circle of Willis. This leads to the congenital subclavian steal phenomenon. However, if the ductus arteriosus is patent, a shunt between the pulmonary and the systemic circulation is established. Therefore, the inverted left vertebral blood flow supplies only the proximal part of the LSA, before entering the pulmonary artery, leading to pulmonary artery steal. The distal LSA in these cases is usually supplied by anastomoses between the left external carotid artery and the LSA.
Isolated LSA has been diagnosed from infancy to as late as 52 years of age. The condition is diagnosed usually due to the presence of associated cardiac anomalies. However, symptoms of subclavian steal and limb ischemia are present in some patients. Luetmer et al. in their review of the literature reported the presence of symptoms of vertebrobasilar insufficiency in 5 of 30 patients (17%) and limb ischemia in 5 patients. These symptomatic patients are usually older and develop symptoms in the second and third decades of life.

Isolation of the LSA should be suspected if the left arm pulse or blood pressure is found to be lower than that of the right arm in a patient with a right aortic arch, as in the first case reported here. These features may be absent due to the associated lesions, which result in equalization of pressure in the aorta and pulmonary arteries. Bedside diagnosis of an isolated LSA is difficult under such circumstances, as in the second case. The diagnosis of an isolated LSA can be reliably established by aortography, wherein delayed films show late opacification of the LSA from the left vertebral artery.

An isolated LSA is a rare congenital anomaly. It is almost always associated with a right aortic arch. However, only 0.8% of patients with a right aortic arch have an isolated LSA. A solitary case of a left arch with an isolated LSA has been reported in the literature. Nearly 60% of the patients have associated intracardiac anomalies of which TOF is the most common. Other associations include atrial and ventricular septal defects, bilateral patent ductus arteriosus, truncus arteriosus, transposition of the great arteries, hypoplastic left heart syndrome, and DORV. The diagnosis of a right aortic arch with an isolated LSA is imperative for the future management of patients with intracardiac lesions such as TOF, as a Blalock-Taussig shunt in these patients is done on the side opposite the arch. However, because of decreased pressure and flow in an isolated LSA, it cannot be used for a left Blalock-Taussig shunt in these patients.

The embryogenesis of this entity can be explained by using the hypothetical double arch system proposed by Stewart et al. and Edwards. There is interruption of the left aortic arch at two levels, one between the left common carotid artery and the LSA, and the second between the left ductus arteriosus and left dorsal aortic root. This results in a right aortic arch with typical branching of this entity. The branches of the right aortic arch in this entity, in order, are the left common carotid, the right common carotid, and the right subclavian arteries. The LSA becomes detached from the aorta and is connected to the pulmonary artery by the ductus arteriosus. Similarly, interruption of the left arch at corresponding points leads to a left aortic arch with isolation of the right subclavian artery.

Surgical treatment of this condition is required if symptoms of subclavian steal occur or if surgery is done for concomitant heart disease. Corrective surgery involves anastomosis of the LSA with the arch or the left common carotid artery. Recent catheter-based abolition of pulmonary steal has been described by closure of the patent ductus arteriosus.

References
Temporary Endoepicardial Atrioventricular Sequential Pacing for Complete Heart Block Following Complex Surgery for Congenital Heart Disease

Ulhas M Pandurangi, PJ Ruth, Satish C Toal, Snehal Kulkarni, KS Murthy, KM Cherian
Department of Cardiology, Madras Medical Mission, Institute of Cardiovascular Diseases, Chennai

Complete heart block following intracardiac surgical repair for complex congenital heart disease is not uncommon. In the presence of ventricular dysfunction, ventricular pacing alone may not improve the cardiac output. We report the feasibility and efficacy of endoepicardial atrioventricular sequential pacing in a case of postoperative complete heart block. (Indian Heart J 2003; 55: 68-70)

Key Words: Complete heart block, Atrioventricular sequential pacing, Cardiac surgery

Case Report

A 12-year-old girl had undergone surgical closure for atrial and ventricular septal defects, with subpulmonic resection at 6 years of age for situs inversus, dextrocardia, atrial and ventricular septal defects, corrected transposition of the great arteries (c-TGA), subpulmonic stenosis and interrupted inferior vena cava. The patient underwent a redo surgery for new-onset progressive mitral valve regurgitation. An Omnicarbon prosthetic valve (29 mm) was placed at the mitral annulus. A bipolar epicardial ventricular pacing lead was placed as there was CHB following the surgery (Fig. 1). The patient was paced in the VVI mode (Fig. 2) using a temporary pacemaker (Medtronic 5346 DDD temporary pulse generator, Minneapolis, MN, USA). The patient came out of bypass easily. However, despite good surgical results, the patient could not be weaned away from the ventilator even 48 hours post-procedure, as there were signs of reduced cardiac output.

Fig. 1. Complete heart block following surgery.

Fig. 2. Pacing in the VVI mode.
and systemic venous congestion. Despite inotropic support, the systolic blood pressure remained less than 90 mmHg and central venous pressure between 16 and 18 mmHg. The arterial blood gas analyses were suggestive of metabolic acidosis. The loss of atrial kick was considered a contributory factor for the reduced cardiac output and AV sequential pacing was considered to improve the hemodynamics. A temporary bipolar 5F pacing lead was placed in the left-sided right atrium through the left internal jugular vein. The tip of this lead was positioned under the fluoroscope to achieve stable and satisfactory pacing and sensing parameters (Fig. 3). This endocardial lead and the epicardial lead were connected to the AV sequential pacemaker (Medtronic 5388 Inc., Minneapolis, MN, USA). The AV delay was adjusted to 100 ms with the aid of venous pressure monitoring and bedside Doppler study of the mitral inflow and mitral regurgitation (Figs 4 and 5). There was marked improvement in the hemodynamics soon after AV sequential pacing was initiated. The systolic blood pressure could be maintained between 120 and 130 mmHg without inotropic support, and there was prompt normalization of the central venous pressure and arterial blood gas parameters. The patient could be successfully weaned away from the ventilator over 24 hours and underwent dual-chamber permanent pacemaker implantation before discharge from the hospital.

**Discussion**

Complete heart block following cardiac surgery for complex congenital heart disease, like the one our patient had, is not uncommon. Surgical repair for defects associated with c-TGA results in CHB in up to 36% of cases. Postoperative CHB may be managed satisfactorily in most cases by ventricular pacing in the VVI mode alone through epicardial leads. However, in certain situations in which the atrial contribution to ventricular output is critical, as in our case where there was moderate biventricular dysfunction, it has been shown that AV sequential pacing results in better hemodynamics as compared to ventricular pacing alone. It has been common practice in some surgical centers to place atrial and ventricular epicardial pacing leads for post-surgical CHB to achieve AV sequential pacing. However, if only one epicardial lead is available for ventricular pacing, AV sequential pacing can be obtained by an esophageal lead, which can sense atrial potentials. The disadvantages of using esophageal leads are unstable lead position and intermittent sensing failure. In addition, an esophageal lead is not practical in a conscious patient. Placement of another epicardial lead for sequential pacing would add to the perioperative morbidity. Using epicardial leads for ventricular pacing and a Swan-Ganz flow-directed pacing catheter for atrial pacing/sensing to obtain AV sequential pacing has met with variable results. Endocardial atrial lead placement is another option for obtaining AV sequential pacing. Since our patient had interruption of the inferior vena cava, the jugular vein was used for right atrial access. The left jugular vein was
chosen as the patient had situs inversus. This case report highlights the occasional need for AV sequential pacing in a case of postoperative CHB and the feasibility of achieving sequential pacing by endoepicardial leads.

References
9. Waldo AL, MacLean WAH. Diagnosis and treatment of cardiac arrhythmias following open heart surgery. 2nd ed. Mt Kisco, New York: Futura; 1980. p. 64
Concurrent Coronary, Bilateral Iliac and Left Renal Artery Direct Stenting

DK Baruah, NK Panigrahi, AN Srinivas
Department of Cardiology, Apollo Hospitals, Vishakhapatnam

We describe a patient who underwent percutaneous coronary intervention combined with bilateral iliac and left renal artery angioplasty during the same sitting. Stenting of the coronary and peripheral arteries was performed employing the "direct stenting" technique. No complications occurred. The patient was discharged 2 days after the intervention and remains asymptomatic, leading a fully active life during 1 year of follow-up. To our knowledge, unstaged coronary stenting combined with direct stenting of the renal and both common iliac arteries has not been reported previously in India. (Indian Heart J 2003; 55: 71–74)

Key Words: Coronary artery disease, Peripheral vascular disease, Stenting

Atherosclerotic vascular disease can involve both the coronary and peripheral arterial systems. Patients with peripheral vascular disease can present as acute coronary syndrome due to coexisting coronary artery disease and require proper therapeutic attention. Percutaneous intervention to treat both coronary and peripheral vascular disease may offer an alternative to surgery in such situations. Rapid progress in the design of coronary devices and, to a degree, advances in the equipment for peripheral vascular interventions makes it increasingly possible to combine this technique in clinically and anatomically challenging patients. This combined strategy reduces the need for multiple interventions, repeated hospitalizations, and is also cost-effective. We report the case of an elderly woman who presented with acute anterior wall myocardial infarction and recurrent postinfarct angina with a background history of severe claudication of the lower limbs. She had been on drug therapy for peripheral vascular disease till date. She also gave a history of accelerated hypertension with an episode of pulmonary edema and was also diagnosed to have an early stage of nephropathy. Physical examination showed very feeble right lower limb pulses and feeble left lower limb pulses with a supine blood pressure in the right upper limb of 200/110 mmHg. Electrocardiography revealed Q waves in leads V1–V3 with T wave inversion in leads V4–V6. Echocardiogram showed regional wall motion abnormality in the left anterior descending coronary artery territory with a left ventricular ejection fraction of 45%. After informed consent, angiographic study was performed which revealed 90% complex stenosis of the left anterior descending coronary artery (Fig. 1a) with minimal disease of the other coronary arteries and mild LV systolic dysfunction. A peripheral angiographic study revealed 90% stenosis of the right common iliac artery (Fig. 2a), 70% eccentric stenosis of the left common iliac artery (Fig. 2a) and 80% eccentric stenosis of the left renal artery (Fig. 3a).

The patient was pretreated with aspirin 325 mg daily and clopidogrel 75 mg twice a day 48 hours prior to the procedure and, in anticipation of a large contrast load (in the presence of borderline nephropathy), the patient was hydrated with normal saline, 75 ml/hour for 12 hours. To minimize the amount of radiation, it was decided to use the direct stenting technique and all attempts were made to reduce exposure time.

Coronary artery stenting: A 7 F arterial sheath was placed percutaneously in the left femoral artery and the
left coronary artery was engaged using a 6 F Vista Brite Tip® left Judkin's catheter (Cordis). The lesion in the left anterior descending coronary artery was crossed with a 0.014" balance middle weight™ guidewire (Guidant). After quantitative coronary analysis, a Bx velocity stent (Cordis) 2.5 mm in diameter and 23 mm in length was deployed at 14 atm pressure. The final angiogram (Fig. 1b) showed good angiographic result with TIMI III flow distally. A total of 10 000 units of heparin was administered intravenously during the procedure.

**Right common iliac artery stenting:** We used the ipsilateral approach for iliac angioplasty in view of the ostial location of the lesion and the acute angle of the aortic bifurcation. After cannulating the right femoral vein with a 0.38" guidewire, the right femoral artery was punctured under fluoroscopic guidance. This was done because the right femoral artery pulsation was very feeble and difficult to localize. A 7 F sheath was inserted into the right femoral artery and a retrograde angiogram through the sheath delineated the tight stenosis of the right common iliac artery. A peak pressure gradient of 80 mmHg on pull-back was recorded across the lesion. The lesion was crossed with a 0.014" balance middle weight coronary guidewire and exchanged for a 0.035" Amplatz super stiff™ (Boston Scientific) guidewire. A Corinthian™ stent (Cordis) 17 mm
in length and 6 mm in diameter was positioned according to the bony landmarks with the help of retrograde injection through the sheath and deployed at 13 atm pressure. A post-stenting angiogram showed a good result (Fig. 2b). There was no significant gradient across the stented segment on pull-back. The activated clotting time at this point of time was 250 s and 5000 units of heparin were administered.

**Left common iliac artery stenting:** Selective left iliac angiogram was performed through the left femoral sheath to delineate the lesion in the left common iliac artery. Simultaneous pressure recording revealed a 47 mmHg peak pressure gradient across the stenosis. A 0.035" Radifocus® guidewire (Terumo Corporation) was used to cross the lesion and exchanged to a 0.035" Amplatz super stiff guidewire. A Corinthian™ stent (Cordis) 17 mm in length and 6 mm in diameter was deployed to cover the entire lesion at 13 atm pressure. In view of the bilateral ostial disease of the iliac arteries, final dilatation of both stents was carried out by the "kissing balloon" technique. This technique helps in avoiding plaque shift and in proper deployment of both stents. The final injection showed good angiographic result (Fig. 2b) and no significant pressure gradient was recorded across the stented segments.

**Renal artery stenting:** The left renal artery was engaged using a 6 F right coronary guiding catheter (JR 3.5 Vista Brite Tip, Cordis) and the lesion was crossed with 0.014" balance middle weight guidewire. After selective injection and QCA analysis, a GFX stent (AVE, Medtronic) 3.5 mm in diameter and 18 mm in length was positioned carefully and deployed at 14 atm pressure. The post-procedure angiogram (Fig. 3b) revealed a good result with rapid distal flow. Usually, a 3.5 mm diameter stent is undersized for a normal renal artery. In this case, QCA analysis revealed the size of the left renal artery to be 3.6 mm and the left kidney to be smaller than the right. Thus, we decided to use a coronary stent.

The patient was kept under observation for 48 hours and discharged without complications. At 1-year follow-up, she is asymptomatic with good effort tolerance and good lower limb pulses. Her blood pressure is well under control with only one antihypertensive drug.

**Discussion**

Patients with coexistent coronary and peripheral vascular disease constitute a challenging group in clinical practice, one that requires special therapeutic attention. Coronary artery bypass surgery in the presence of acute myocardial infarction and peripheral vascular disease carries a substantial risk of morbidity and mortality. On the other hand, it is well established that in patients who undergo vascular surgery, there is a decrease in survival rate if coronary artery disease is present. In such a clinical situation, percutaneous treatment offers a promising alternative to surgery. There has been rapid growth in interventional cardiology in the past few decades and the introduction of stents has improved the long-term outcome of angioplasty. With constantly improving stent designs, delivery systems and techniques, multivessel stenting has become routine in clinical practice. Introduction of direct stenting has made this procedure more rapid and cost-effective with less exposure to radiation and contrast load. Various studies have been carried out to assess the efficacy
of direct stenting and it has been found to be equivalent in terms of immediate and long-term results to that of stenting with predilatation.11–13

There are few reports on combined multivessel direct stenting involving both the coronary and peripheral vessels.14,15

Our patient was an elderly woman with multiple coronary risk factors and borderline nephropathy; this condition not only carries a higher surgical risk but also a higher risk of complications during percutaneous intervention. We used the direct stenting technique in this patient to reduce the contrast load as well as exposure time. The patient tolerated the procedure well without any major complications with a satisfactory 1-year follow-up record.

Direct stenting is an evolving technique in interventional cardiology which, at present, is applied in selected cases during percutaneous angioplasty. This technique can also be useful when multivessel angioplasty is contemplated.

References


Catheter Ablation of Atrial Tachycardia Using a Real-Time Position Management Mapping System

Anoop K Gupta, Alok Maheshwari, Ranjan K Thakur, Yash Y Lokhandwala
Thoracic and Cardiovascular Institute, Sparrow Health System, Michigan State University, Lansing, MI, USA

Catheter ablation for atrial tachycardia is limited by its low success rate and prolonged procedure time because of difficulties in mapping the site of the tachycardia. A new three-dimensional mapping system, the Cardiac Pathways mapping system, using an ultrasound transducer, has recently become available. We report a case of focal atrial tachycardia ablation with this system. (Indian Heart J 2003; 55: 75-77)

Key Words: Ablation, Tachyarrhythmia, Cardiac mapping

Focal atrial tachycardias are not randomly distributed but rather tend to cluster in certain anatomic zones, the commoner site being along the crista terminalis in the right atrium and from within a pulmonary vein. There are a variety of approaches to mapping and ablation of focal atrial tachycardias.

The Carto system has been used to develop an electroanatomic map of the earliest activation; however, this system requires that the map be developed point by point. Multielectrode basket catheters have also been developed, as have noncontact mapping arrays. Another system, Cardiac Pathways, enabling three-dimensional (3-D) real-time mapping, includes real-time position management in guiding radiofrequency (RF) catheter ablation. We present our initial experience with the Cardiac Pathways mapping system for ablation of focal atrial tachycardia.

Case Report

A 53-year-old woman presented to the arrhythmia clinic with palpitation. Twenty-four-hour Holter monitoring showed a narrow QRS complex tachycardia with a rate of 128 beats/min with warm-up phenomenon. P-wave morphology during tachycardia was similar to the sinus rhythm, suggestive of a focus in the high right atrium (Fig. 1). Clinical examination, chest X-ray and echocardiography showed no abnormality.

The patient was taken up for electrophysiologic study (EPS) after withdrawing all antiarrhythmic drugs for at least five half-lives. EPS was performed using the Cardiac Pathways system. 3-D positional mapping was done with the ablation catheter using both point and isochronal maps. Identification of major structures and the deformation map were performed before mapping the atrium.

Atrial tachycardia was easily inducible with atrial extrastimuli and continuous pacing. Right atrial mapping was performed; the earliest activation of 36 ms from the surface P wave was obtained high in the interatrial septum. A trans-septal puncture was performed using the standard technique to map the left atrium. The earliest activation of 42 ms from the surface P wave was obtained in the roof of the left atrium between the right and left superior pulmonary veins. Isochronal and point mapping of the left atrium also suggested earliest activation in the roof of the left atrium (Figs 2a and b).

Successful RF ablation was performed using a 7 F, 4 mm tip bidirectional steerable cooled ablation catheter (Cardiac Pathways, Sunnyvale, CA, USA), keeping the reference

Correspondence: Dr Anoop K Gupta, Consultant Cardiologist and Electrophysiologist, Krishna Heart Institute, Ghuma, Ahmedabad 380058. e-mail: anoopgupta@msn.com

Fig. 1. Panel A: 12-lead ECG showing atrial tachycardia (128 beats/min). The P wave morphology in the inferior leads is similar to sinus rhythm ECG. Panel B: 12-lead ECG showing baseline sinus rhythm.
ghost catheter at the earliest site of activation during the ablation. No tachycardia could be induced despite a vigorous atrial stimulation protocol with and without isoproterenol after radiofrequency ablation (RFA). The procedure time was 135 min and fluoroscopic time was 18 min. There was no complication during the procedure. Heparin was given at the rate of 100 unit/kg intravenously after the trans-septal puncture.

Cardiac Pathways mapping system

Reference and ablation catheters: Two reference catheters and one mapping/ablation catheter were introduced percutaneously using the subclavian and/or femoral approach. One reference catheter was positioned in the coronary sinus (CS) and the other in the right ventricular (RV) apex. For ablation purposes, a 7 F, 4 mm tip bidirectional steerable cooled ablation catheter (Cardiac Pathways, Sunnyvale, CA, USA) was used. The reference catheters (Cardiac Pathways) have a 6 F fixed curve distal shaft. The shaft of the CS reference catheter contains nine 1 mm ring electrodes and one 2 mm tip electrode (interelectrode distance 1 mm), whereas the RV reference and ablation catheters contain three 1 mm ring electrodes and one 4 mm tip electrode (interelectrode distance 1 mm). The reference catheters are equipped with four ultrasound transducers; the ablation catheter contains three ultrasound transducers. The ultrasound transmitter and receiver device sends a continuous cycle of ultrasound pulses (558.5 kHz) to the transducers of the reference and ablation catheters. By measuring the time delay from the departure of a transmitted ultrasound pulse and the reception of this pulse at the other transducers, assuming a speed of sound in blood of 1550 m/s, the distance between the individual transducers can be calculated. These data are subsequently transferred to the computer and used to define the location of the catheter(s) within the reference frame. Once the 3-D reference frame is established, triangulation can be used to track the position of additional transducers.

Because dimensional and structural characteristics of the catheter are known, it is possible to construct a real-time 3-D graphic representation of the catheters, including the position of the electrodes and the transducer. As one of the transducers is positioned distal to the deflection point of the shaft of the catheter, it is possible to display the curve of the catheter as well. Furthermore, the real-time position management system graphically displays the beat-to-beat movement of the tip of the catheters.

Real-time position management system: The 3-D real-time position management and mapping system (Cardiac Pathways) uses ultrasound-ranging techniques to determine the position of a mapping/ablation catheter relative to two reference catheters. The mapping system consists of an acquisition module and an ultrasound transmitter and receiver unit, both connected to a SPARC 20 computer (Sun Microsystems, Palo Alto, CA, USA). The system is capable of simultaneously processing: (i) seven position management catheters; (ii) 24 bipolar/48 unipolar electrogram signals; (iii) 12-lead ECG; and (iv) two pressure signals. Signals are sampled at 3 kHz per channel with a resolution of 14 bits. The high-pass filters are set at 30 Hz and low-pass filters at 500 Hz. Electrograms and catheter
positions are stored on an optical disk. The original position of the reference catheters can be displayed on the real-time window, thereby allowing repositioning of the catheters after displacement. The frame rate of this real-time imaging is: (i) Catheter cartoon: once per cardiac cycle (ii) Luttle ball of ablation catheter tip: 15 frames/second.

Discussion
Targeting the site of earliest activation preceding the P wave during tachycardia best ablates focal atrial tachycardia, regardless of whether it is due to abnormal automaticity, triggering, or micro re-entry. Pace mapping to match the surface P wave during tachycardia can be used adjunctively, but because of the difficulty in clearly discerning surface P wave morphology, activation mapping is more accurate.

A mapping system provides additional help in mapping atrial tachycardia, especially defining the crista terminalis, which is the commonest site of atrial tachycardia. In addition, it helps in understanding the breakthrough left atrial tachycardia by providing the 3-D anatomy of the atrium. Isochrone mapping usually draws the sequence of activation within the atrium with the red color showing the earliest and violet the late activation.

In our case, although the morphology of tachycardia was suggestive of right atrial origin, successful ablation was performed in the left atrium. Left atrial tachycardias usually arise from near the pulmonary veins but, for several reasons, initial localization can at times be confusing. First, activation times during tachycardia in the CS are usually relatively late with respect to many sites in the right atrium because the CS is inferior and anterior to the pulmonary veins, which are inserted in the posterior aspect of the left atrium. Secondly, rapid conduction from left to right over the Bachmann’s bundle may cause a wrong diagnosis of right atrial origin. Finally, the right superior pulmonary vein enters the left atrium just behind the superior posterior right atrium.

Ultimately, one must identify a site of earliest activation which precedes P wave onset by more than 30 ms for successful ablation. In our case, the earliest activation was 42 ms from the surface P wave. It is mandatory to map the other atrium if the earliest activation is less than 30 ms. However, in our case, we did left atrial mapping despite a good signal in the right atrium to rule out any possibility of breakthrough left atrial tachycardia.

Although the isochrones and point map depend upon the earliest activation signal from the surface ECG, making the activation sequence map does help in localizing the discrete point. The advantage of the Cardiac Pathways system over the Carto and other 3-D mapping systems is that it also indicates the catheter position during mapping; therefore, it guides catheter manipulation during mapping and, secondly, availability of the ghost catheter during ablation, which makes a very appropriate site for focal ablation and reduces the chances of edema formation around the site of origin by avoiding burns in the surrounding area. In addition, the catheters can be re-used to save the cost of the procedure in developing countries such as India. It also significantly reduces the fluoroscopic time as with other electroanatomic mapping systems.

Conclusions: The Cardiac Pathways mapping system helps in the precise location of ablation of atrial tachycardia. Our initial experience with this new mapping system is good. However, its efficacy needs to be evaluated in more patients.

References
An Infant with “Dying Spells”

Shyam S Kothari, Ambuj Roy, Sanjiv Sharma, Anil Bhan
Cardiothoracic Centre, All India Institute of Medical Sciences, New Delhi

A 45-day-old infant presented with the unusual and intriguing symptom of episodic crying and loss of consciousness. The infant was discovered to have a vascular compression of the trachea by the innominate artery, almost serendipitously. He was cured of his symptoms by anterior suspension of the innominate artery.

(Indian Heart J 2003; 55: 78–80)

Key Words: Vascular ring, Apnea, Aortopexy

Vascular rings and slings in infants usually present as stridor, feeding difficulties, and recurrent aspiration. Vascular compression of the trachea by the innominate artery is rare. It may present with one of these symptoms or, more dramatically, as reflex apnea. We report such a case to highlight a rare but curable cause for recurrent apneic spells.

Case Report

A 45-day-old infant was brought with a history of recurrent episodes of unconsciousness and apnea triggered usually (but not exclusively) by crying. He was born at full term, after an unremarkable pregnancy in a primigravida, and had an Apgar score of 8/10 at birth. There was no history of fever, jitteriness, feeding difficulties, seizures, cyanosis, or stridor, and the baby was otherwise healthy. The infant had had several episodes of unconsciousness and apnea since he was 15 days old and was feared dead during these spells, but would recover spontaneously within 1–2 minutes.

On examination, his weight was 4.5 kg, and heart rate 120 per minute, regular. His mental and motor milestones were normal. There were no dysmorphic features. He had situs inversus, and a pansystolic murmur. The chest X-ray showed mild cardiac enlargement, situs inversus, and normal lung fields. Detailed echocardiographic assessment revealed situs inversus, corrected transposition of the great vessels (i.e. atrioventricular and ventriculoarterial discordance), a small ventricular septal defect, and mild pulmonic stenosis. The electrocardiogram (ECG) demonstrated situs inversus but was otherwise unremarkable. The electroencephalogram (EEG) and CT scan of the head were normal.

A seizure disorder, complete heart block, or cyanotic spells were suspected in view of the history and cardiac disorder. Breath-holding spells were also considered. Routine blood chemistry was within normal limits. In the hospital, the infant was observed to have episodes of crying and distress followed by apnea and progressive bradycardia, and even asystole. Two of the episodes required brief assisted ventilation and cardiac massage. Cardiac catheterization confirmed the cardiac lesions but could not explain the symptoms. An aortic angiogram revealed an L-posed aorta with a slightly medial origin of the innominate artery (Fig. 1). In the course of illness, a repeat chest X-ray demonstrated hyperinflated lung fields. In view of this finding, a chest CT scan was done which revealed a right aortic arch with anterolateral tracheal compression by the left-sided innominate artery 1 cm above the carina (Fig. 2). Cinefluoroscopy confirmed compression of the trachea at the level of the innominate artery. The infant underwent aortopexy and left innominate pexy for the relief of tracheal compression. The left innominate artery and the aortic arch were plicated to the second costal cartilage. Subsequently, he has had no recurrence of symptoms and was doing well at six months’ follow-up.

Discussion

The absence of stridor in our patient delayed the correct interpretation of reflex apnea due to tracheal compression by the innominate artery. Innominate artery compression is a rare cause of airway obstruction in infants. The anomalous innominate artery compression syndrome was first described by Gross and Neuhauser in 1948 as...
consisting of cough, stridor, and occasionally apnea. Other authors have subsequently reported abnormal origin and course of the innominate artery as a cause of airway compression, with relief of symptoms following decompressive surgery. However, some authors have disputed the role of the innominate artery in causing symptoms in these children, and believe that intrinsic abnormality of the trachea rather than compression by the innominate artery is responsible for the symptoms. Strife et al. reported that the innominate artery crosses anterior to the trachea, and produces mild to moderate anterior indentation of trachea in 30% of normal children without causing symptoms. Mustard et al. found that only 39 out of 285 children with innominate artery compression had symptoms marked enough to warrant surgery. Thus, the innominate artery probably crosses the trachea in almost all infants, but few children actually have tracheal compression, and even fewer have symptoms requiring intervention. Why only some children have symptoms of compression is not known. A tight or crowded mediastinum and esophageal dilatation due to any cause are some of the reasons postulated. The syndrome has been associated with the presence of congenital heart disease as well as esophageal atresia. The usual symptoms reported due to innominate artery compression are stridor, respiratory distress, recurrent lower respiratory tract infections, and reflex apnea. Apnea is thought to be due to reflex respiratory arrest initiated by compression of the trachea. This may occur as a result of a large bolus of food passing through the esophagus or from accumulation of secretions in the tracheobronchial tree. The symptoms are maximal during infancy with gradual improvement by 2 years of age. The improvement is probably due to strengthening of the airways by increased cartilaginous support and cephalad displacement of the aorta.

The diagnostic modalities are a lateral X-ray that may show an anterior indentation of the tracheal air column. In suspected cases MRI imaging confirms the diagnosis, and is the imaging modality of choice, though a CT scan also provides adequate information, as in our case. Recently, cine MRI has been reported to be useful for dynamic imaging of tracheal compression by the innominate artery. Barium swallow is not helpful because the compression is located anteriorly. The diagnosis can be further confirmed by bronchoscopy, which shows anterior tracheal compression 1–2 cm proximal to the carina. The area of compression is pulsatile and, when levered anteriorly by the tip of the endoscope, leads to diminution of the corresponding radial pulse.

Surgical correction of compression is usually by suspension of the innominate artery to the undersurface of the sternum by a row of braided Dacron sutures (innominate pexy), though some surgeons prefer its reimplantation lower down the aortic arch. Surgical outcomes have been excellent in judiciously selected cases of innominate artery compression.

References
4. Schuster T, Hecker WC, Ring-Mrozik E, Mantel K, Vogl T. Tracheal

Fig. 1. Aortic angiogram shows L-posed aorta but is otherwise unremarkable. In retrospect, the innominate artery is seen to arise more medially.

Fig. 2. Contrast-enhanced CT scan of the chest 1 cm above the carina showing tracheal compression by the innominate artery. Note the flattened, trifoliate appearance of the trachea (arrow).
Low-Molecular-Weight Heparins in Percutaneous Coronary Interventions

AK Kar, I Dutta
Department of Cardiology, Institute of Postgraduate Medical Education and Research, Kolkata

Low-molecular-weight heparins (LMWHs) represent a major advancement in the management of patients with acute coronary syndrome (ACS) or as part of the strategy in candidates undergoing coronary interventions. LMWH are derived from unfractionated heparins (UFH) by chemical or enzymatic depolymerization. They have a mean molecular weight of 4000–5000, as compared to UFH which have a mean molecular weight of 15 000 (5000–30 000). UFH inhibit Factors Xa and IIa in a ratio of 1:1, whereas LMWH inhibit Factors Xa and IIa in ratios between 4:1 and 2:1, depending on their molecular weight. LMWH potentiate antithrombin (AT) III activity, but are relatively less efficient in binding thrombin, and thus lead to a higher ratio of anti-Factor Xa activity to anti-Factor IIa (antithrombin) activity. The anti-Factor Xa activity is particularly important, as it can prevent thrombin generation and interrupt feedback amplification of thrombin production. The thrombin-binding activity of heparin lies primarily in the higher weight glycosaminoglycan chains; therefore, the anti-Factor Xa/anti-Factor IIa ratio of various LMWH varies according to the molecular size of the subfractions they contain. The lesser antithrombin effects of LMWH lead to less prolongation of the activated partial thromboplastin time (aPTT) than UFH; thus, there is no need for aPTT monitoring during therapeutic use of LMWH. LMWH are more resistant to Factor IV-mediated inhibition of heparin activity and do not produce the same degree of platelet activation as UFH.

The important pharmacologic characteristics that distinguish LMWH from UFH include: greater bioavailability; minimal plasma protein and vessel wall binding; more predictable and durable anticoagulant response (T½ 2–4 times that of UFH); ease of subcutaneous or intravenous administration; and inhibition of acute-phase release of von Willebrand factor in ACS.

LMWH have earned their place and established their superiority over UFH in the management of post-surgical deep vein thrombosis and ACS, including unstable angina (UA) and non-Q wave myocardial infarction (NQMI). The Efficacy and Safety of Subcutaneous Enoxaparin in Non-q-wave Coronary Events (ESSENCE) study showed enoxaparin plus aspirin to be superior to UFH plus aspirin in patients with ACS. The need for urgent revascularization was significantly lower in the enoxaparin group. The Heparin and Aspirin Reperfusion Therapy (HART II) study showed that enoxaparin was as effective as UFH as an adjunct to thrombolysis with tissue plasminogen activator (TPA), with a trend towards higher recanalization rates and less reocclusion at 5 or 7 days. Thus, several trials have shown that the LMWH enoxaparin offers the practical and potential pharmacologic advantages over UFH in multiple applications, and logically should also provide a similar benefit during percutaneous coronary intervention (PCI).

However, during coronary and noncoronary interventions, UFH is conventionally used more frequently than LMWH. This is largely due to the fact that interventional cardiologists are sceptical about the efficacy of acute anticoagulation with LMWH. Furthermore, reversibility of the action of heparin is far more prompt and accurate with protamine in case of UFH than with LMWH. Clinicians are also concerned about the safety of a combination of LMWH with glycoprotein (Gp) IIb/IIIa inhibitors, and the safety of transition to the catheterization laboratory in patients who have already received LMWH on the floor.

From 1994 to 1998, four clinical trials using LMWH during or after PTCA were published (their results are summarized in Table 1), the most recent being the National Investigators Collaborating on Enoxaparin (NICE) trials 1,3 and 4 (Table 2). The use of LMWH eliminates the need for continuous IV infusion, anticoagulation monitoring, and dose adjustment associated with UFH.

Data from randomized, controlled clinical trials support the administration of LMWH and/or platelet Gp IIb/IIIa blockade in patients who present with non-ST-elevation ACS. Despite evidence-based support for administering LMWH and/or Gp IIb/IIIa receptor blockers to patients undergoing PCI and those presenting with ACS, algorithms for integrating these agents into clinical practice have not been determined. The NICE trials have evaluated this issue in detail, and the results of these trials are likely to have a major impact on the choice of adjunctive therapy during PCI.
The NICE Story

In the NICE pilot study, 60 patients undergoing PCI were randomly assigned to receive either UFH 10 000 U as an IV bolus with supplemental doses to achieve a target activated clotting time (ACT) greater than 300 s or enoxaparin 1 mg/kg IV bolus immediately before PCI. There were no differences in procedural outcomes or bleeding events observed between the treatment groups in this small randomized trial. Levels of Factor IIa activity were significantly higher in the UFH group, though Factor Xa activity was similar in the two treatment groups.

The pilot trial experience was expanded in the NICE 1 study in which 828 patients undergoing PCI without planned use of abciximab were administered enoxaparin 1 mg/kg within 15 min of arterial sheath insertion. All the patients received aspirin in addition, as an antiplatelet agent. The incidence of major noncoronary artery bypass grafting (CABG) related bleeding was 10.5%, and the composite clinical end-point [death, myocardial infarction (MI), need for urgent revascularization] at 30 days was 7.9% (Figs 1 and 2).

This large, multicenter experience suggests that intravenous enoxaparin in a dose of 1 mg/kg provides adequate, safe, and effective anticoagulation during PCI, the antithrombin efficacy (anti-Factor Xa activity) being similar to UFH administered as an IV bolus of 10 000 U.

Table 1. Clinical trials of LMWH after PTCA

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Drug</th>
<th>No. of patients</th>
<th>Protocol</th>
<th>End-point</th>
<th>Relative benefits</th>
</tr>
</thead>
<tbody>
<tr>
<td>ERA*</td>
<td>1994</td>
<td>Enoxaparin</td>
<td>458</td>
<td>R, C, B</td>
<td>Clinical and angiographic restenosis</td>
<td>-2% (p=ns)</td>
</tr>
<tr>
<td>REDUCE*</td>
<td>1996</td>
<td>Reviparin</td>
<td>612</td>
<td>R, PC, B</td>
<td>6 months death and MI plus revascularization</td>
<td>-4% (p=ns)</td>
</tr>
<tr>
<td>FACT*</td>
<td>1997</td>
<td>Nadroparin</td>
<td>354</td>
<td>R, PC, B</td>
<td>3 months angiographic restenosis</td>
<td>-6% (p=ns)</td>
</tr>
<tr>
<td>ENTICES*</td>
<td>1998</td>
<td>Enoxaparin</td>
<td>123</td>
<td>R, C</td>
<td>30-day death, MI, revascularization, and stent thrombosis</td>
<td>-25%</td>
</tr>
</tbody>
</table>

LMWH: low-molecular-weight heparin; PTCA: percutaneous transluminal coronary angioplasty; R: randomized; B: blinded; C: controlled; PC: placebo-controlled; ns: statistically not significant

Table 2. Overview of National Investigators Collaborating on Enoxaparin (NICE) 4 Study

<table>
<thead>
<tr>
<th>Inclusion criteria (patients)</th>
<th>PCI (excluding planned rotational atherectomy) for acute coronary syndromes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study design</td>
<td>Multicenter, open-label</td>
</tr>
<tr>
<td>Treatment regimen</td>
<td>Enoxaparin 0.75 mg/kg intravenous bolus, followed by abciximab 0.25 mg/kg intravenous bolus and 12-hour infusion (0.125 µg/kg/min)*</td>
</tr>
<tr>
<td>Primary end-point</td>
<td>Major and minor bleeding post-procedure and need for transfusion</td>
</tr>
<tr>
<td>Secondary end-points</td>
<td>Composite of death, MI, urgent revascularization at 30 days post-PCI, creatine kinase (CK) and CK-MB elevation at 30 days post-PCI</td>
</tr>
<tr>
<td>Results (%): first 310 patients</td>
<td>Hemorrhage</td>
</tr>
<tr>
<td></td>
<td>Major (0)</td>
</tr>
<tr>
<td></td>
<td>Minor (2.9)</td>
</tr>
<tr>
<td></td>
<td>Transfusion (0.6)</td>
</tr>
<tr>
<td></td>
<td>Death/MI/urgent revascularization (2.3)</td>
</tr>
</tbody>
</table>

*No further heparin of any type was administered after the procedure and vascular access sheaths were removed 4 hours after the enoxaparin bolus

PCI: percutaneous coronary intervention; MI: myocardial infarction

Fig. 1. Major bleeding incidence with or without events related to CABG and transfusion requirements up to 30 days post-PCI in the NICE 1 and NICE 4 trials.
comparison of the NICE 1 trial with the stent plus placebo subgroup (UFH 100 U/kg) of the EPISTENT trial (Figs 3 and 4) provides valuable insights, as both trials are comparable in size, and the definition of major and minor hemorrhage used in both are similar. Major non-CABG bleeding events, ischemic adverse outcomes, death, and need for urgent revascularization at 30 days were similar in both. Hence, it can be concluded that enoxaparin 1 mg/kg IV during PCI is as safe and effective as the contemporary experience utilizing a weight-adjusted heparin (UFH).

The NICE 4 trial: This trial was the first large-scale experience with the combination of an LMWH and a platelet Gp IIb/IIIa antagonist during PCI. Patients undergoing PCI with a Food and Drug Administration (FDA), USA-approved device (except rotational atherectomy) were administered enoxaparin 0.75 mg/kg as an IV bolus followed by a standard dose of abciximab (0.25 mg/kg IV bolus followed by 0.125 µg/kg/min to a maximum of 10 µg/kg). The reduced dose of enoxaparin was chosen to simulate the weight-adjusted reduction in heparin dose used in both the EPISTENT17 and EPILOG18 trials. Approximately 800 patients with an average age of 63 years were enrolled in 11 centers; multivessel PCI was performed in 52%, and stent deployment in 86%. Vascular sheaths were removed 4 hours following the enoxaparin bolus, and periprocedural ACT was not monitored. The primary end-point of NICE 4 was the incidence of major or minor bleeding and need for transfusion, secondary end-points being (i) clinical (death, MI, urgent revascularization), and (ii) biochemical changes (CK, CK-MB elevation) in hospital and up to 30 days’ post-PCI. (Table 2).

Remarkably, there was no major non-CABG bleeding in the first 557 patients and the final analysis revealed a meager 0.2% incidence. The need for transfusion was also negligible. Comparing NICE 4 with the EPILOG trial (low-dose weight-adjusted heparin 70 U/kg plus abciximab) and the EPISTENT trial (stent plus abciximab) cohorts (Fig. 5), it was observed that a combination of low-dose enoxaparin 0.75 mg/kg and abciximab was safe and associated with a low incidence of non-CABG related bleeding. Addition of abciximab to 0.75 mg/kg of enoxaparin bolus was
associated with a reduction of periprocedural ischemic events in the NICE 4 trial compared to the NICE 1 trial. Interestingly, abciximab-associated thrombocytopenia was lower in NICE 4 than in studies using abciximab plus UFH regimens. This might be related to the fact that enoxaparin is less likely than UFH to cause platelet activation or aggregation, or that thrombocytopenia may result from an interaction between abciximab and certain anticoagulants.  

The NICE 1 and NICE 4 trials demonstrated the safety and efficacy of enoxaparin alone and in combination with abciximab for procedural anticoagulation. The NICE 3 study\textsuperscript{16} investigated the use of enoxaparin with one of the three Gp IIb/IIIa antagonists (abciximab, tirofiban, eptifibatide) in patients with ACS (including PCI). It aimed to assess the safety of this combination in the catheterization laboratory with respect to bleeding and practicality of usage.

A total of 660 patients were enrolled with rest angina of less than 24 hours' duration at 46 clinical centers in Canada and the United States. All the patients received IV enoxaparin 1 mg/kg b.d., aspirin 162–325 mg/day, and a Gp IIb/IIIa antagonist assigned by the institution at a standard dose. Clinical outcomes in NICE 3 were comparable to those of prior studies—the combination of enoxaparin and Gp IIb/IIIa antagonist did not result in excess major non-CABG bleeding events (Table 3). In addition, the study showed that additional UFH was not required for the study population treated with enoxaparin and a Gp IIb/IIIa antagonist during coronary intervention, and patients on combination therapy could safely undergo PCI.

**Table 3. NICE 3 study findings: enoxaparin and Gp IIb/IIIa antagonist for patients with ACS including PCI (n=616)**

<table>
<thead>
<tr>
<th>In-hospital clinical outcomes</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>0.3</td>
</tr>
<tr>
<td>MI</td>
<td>3.4</td>
</tr>
<tr>
<td>Urgent revascularization</td>
<td>2.1</td>
</tr>
<tr>
<td>Death/MI/urgent revascularization</td>
<td>5.7</td>
</tr>
<tr>
<td>Bleeding</td>
<td>27.9</td>
</tr>
<tr>
<td>Major</td>
<td>4.5</td>
</tr>
<tr>
<td>Minor</td>
<td>25</td>
</tr>
<tr>
<td>Transfusion</td>
<td>10.5</td>
</tr>
<tr>
<td>Non-CABG</td>
<td>1.9</td>
</tr>
</tbody>
</table>

Gp: glycoprotein; ACS: acute coronary syndrome; PCI: percutaneous coronary intervention; MI: myocardial infarction; CABG: coronary artery bypass grafting

**Enoxaparin and Ticlopidine after Elective Stenting (ENTICES)\textsuperscript{10} (Table 4)**

Enoxaparin has been shown to be beneficial in patients requiring coronary stent implantation, and its use in combination with other antiplatelet regimens in stenting interventions was evaluated in this trial. One hundred twenty-three patients scheduled for elective intracoronary stenting were randomized (in a 2:1 ratio) to a combination of enoxaparin, ticlopidine, and aspirin; or to a conventional regimen of warfarin, UFH, dextran, dipyridamole, and aspirin. The composite clinical end-point of death, MI, stent thrombosis, CABG, repeat PTCA, and stroke at 30 days was significantly reduced in enoxaparin-treated patients than in the conventionally treated group. The incidence of vascular complications and major hemorrhage requiring transfusion was much less in enoxaparin recipients. This trial suggested that a modified antithrombotic regimen incorporating both antiplatelet and anticoagulant drugs may offer improved outcomes compared to anticoagulant therapy alone.

**Intracoronary LMWH**

In the POLONIA study,\textsuperscript{19} 100 patients from 4 centers with single lesions (single-vessel coronary artery disease) were randomized to enoxaparin 10 mg administered intramuscularly prior to stent implantation, or systemic heparinization with 100 U/kg of UFH. Follow-up angiography at 6 months was performed in all but one patient. The results showed that local delivery of enoxaparin resulted in significant reduction in the...
incidence of restenosis and the revascularization rate compared with systemic heparinization. A few other trials are also currently evaluating the comparison of local delivery of enoxaparin before stenting with stenting alone.

Safety Considerations

The most common adverse effects reported are hemorrhagic complications. In most cases, these are minor bleeds, e.g., injection site ecchymosis, as would be expected with subcutaneous injections. In the ESSENCE study, for example, minor bleeding was significantly more common in patients receiving subcutaneous enoxaparin 1 mg/kg twice daily, than those receiving IV UFH (18.4% v. 14.2% at 30 days; p<0.001). There were no significant differences between the 2 treatment groups regarding the incidence of major hemorrhage. Similarly, when safety results from other large clinical trials are considered, major bleeding was reported in <6.5% of patients with CAD treated with enoxaparin 1 mg/kg twice daily or 40 mg once daily. Thus, there does not appear to be an increased risk of major bleeding with enoxaparin therapy in patients with ACS.

The other important concern is regarding reversibility of anticoagulant action. Unlike heparin, the action of LMWH can only be partially reversed with protamine (50%). The use of fresh frozen plasma to replenish coagulation factors has been advocated for LMWH.

Timing of PCI

The validated, weight-adjusted dose of enoxaparin to treat unstable angina patients also seems to be suitable for PCI within 8 hours of the last injection. In the study of “Percutaneous coronary intervention after subcutaneous enoxaparin pre-treatment in patients with unstable angina pectoris”, carried out in the department of cardiology and the haemostasis laboratory of the University Hospital, Paris, France a total of 451 consecutive patients with UA/NQMI were treated for at least 48 hours with subcutaneous enoxaparin (1 mg/kg every 12 hours), cycled at 6 a.m. and 6 p.m. Two hundred ninety-three patients underwent a coronary angiography within 8 hours of the morning.
LMWH injection, followed by immediate PCI in 132 patients. PCI was performed without monitoring of coagulation and without any additional bolus of UF/LMWH heparin. There were no in-hospital abrupt closures or urgent revascularization needed in the PCI group. The incidence of death/MI rates in the PCI group was much lower than in those not undergoing catheterization. The 30-day major bleeding rate in the PCI group was also less than in those not undergoing catheterization. Sheath removal was done with manual or pneumatic compression more than 10 hours after the morning injection of enoxaparin. Importantly, enoxaparin was not restarted after PCI and the patients left the hospital the next morning.

This study convincingly shows that PCI can be performed safely within 8 hours in patients treated with LMWH, particularly enoxaparin, without additional anticoagulation. Whether the time window can be extended to 12 hours is a matter of debate and is being currently evaluated in the PEPCI trial (Pharmacokinetic Study of Enoxaparin in Percutaneous Coronary Interventions). Presumably, an additional bolus of anticoagulant may be beneficial in procedures performed between 8 and 12 hours of the last dose of the LMWH.

Role of Monitoring

The role of coagulation monitoring with the use of LMWH has also been evaluated in the study from France mentioned above. Anti-Factor Xa activity was measured from samples collected immediately before catheterization in all patients undergoing PCI. However, anti-Factor Xa measurements, obtained retrospectively, were not used for decision-making during PCI. During the period of medical stabilization before catheterization, in elderly patients and those with renal failure, anti-Factor Xa activity was measured 4 hours after the third injection, and the dose of enoxaparin adjusted, aiming at a target value of 0.5–1.0 U of anti-Factor Xa. The anti-Factor Xa activity at the time of catheterization was >0.5 IU/ml in 97.6% of patients, and it was stable over the 8-hour period after the injection of enoxaparin. The aPTT was also measured prior to catheterization and there was a weak but significant correlation with anti-Factor Xa activity.

From the above study, we can conclude that anti-Factor Xa activity need not be measured routinely before PCI done within 8 hours of the last dose of enoxaparin. However, in elderly patients and those with renal failure receiving a reduced dose of enoxaparin, anti-Factor Xa measurements may be beneficial.

Pilot studies are on for monitoring of LMWH in the setting of UA. A panel of assays to measure the tissue factor clotting time (TiFaCT) is being developed. The tests provide a functional measure of tissue factor, including its interaction with platelets and plasma components. The results can be obtained in 15 min–2 hours.

The issue of sheath removal following PCI has been addressed in the NICE 4 trial, in which the vascular sheath was removed 4 hours after the enoxaparin bolus dose without any increased incidence of puncture site complications. In the study reported from France mentioned above, the vascular sheath was pulled out >10 hours after the last enoxaparin injection.

Conclusions

In present day practice, when interventional cardiology is making rapid progress every day, it is worthwhile considering safer and easier adjunctive medications during the procedure. While UFH has been a trusted companion of interventionists for years, LMWH can offer an easier and assuring alternative of anticoagulation without compromising efficacy. The role of LMWH as an intracoronary injection for the prevention of stent complications is under evaluation and, if established, would certainly be a powerful weapon for the prevention of stent thrombosis. It is debatable whether the benefits demonstrated with enoxaparin can be extended to other LMWH. The US FDA classifies each LMWH as a distinct drug that cannot be interchanged with another. In the ESSENCE and TIMI-IIB studies, a combination of enoxaparin plus aspirin was more effective than that of UFH and aspirin. Inversely, in the FRIC study, dalteparin plus aspirin did not demonstrate such superiority. Evidence is also accumulating regarding the role of enoxaparin as an antithrombotic in the treatment of acute MI. Selection of an individual LMWH for a particular indication should reflect the level of evidence for a the agent in that condition. Thus, at present, evidence-based considerations favor the use of enoxaparin in the antithrombotic regimen of patients undergoing PCI.

References

unfractionated heparin for unstable coronary artery disease. Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q-Wave Coronary Events Study Group. JAMA 1997; 278: 1447–52
10. Zidar JP. Enoxaparin and ticlopidine after elective stenting, the ENTICES trial. Am J Cardiol 1998; 82: 29L–32L
Echocardiographic Anatomy of Atrial Septal Defect: “Nomenclature of the Rims”

Savitri Shrivastava, S Radhakrishnan
Department of Congenital and Pediatric Heart Disease, Escorts Heart Institute and Research Centre, New Delhi

The accuracy of diagnosis of atrial septal defect (ASD) by two-dimensional (2-D) echocardiography is well established, and has been utilized in clinical practice for almost two decades. However, following the easy availability of various devices for the closure of ASD, a detailed anatomy of the ASD and the rims around the defect has assumed great importance. Two-dimensional echocardiography, both transthoracic (TTE) and transesophageal (TEE), can clearly show the anatomy and is used for selecting cases for device closure of the ASD. During the procedure of device closure, TEE serves as the most important investigation for proper placement of the device. However, there is some confusion regarding the nomenclature of the various rims of ASDs, e.g. the rim in relation to the aorta has been variously called anterior, posterior, and inferior. We propose that for clarity, uniformity and mutual communication the rims should be designated according to the structure they are related to, e.g. superior vena caval (SVC), inferior vena caval (IVC), atrioventricular (AV) septal (rim at the crux), aortic and atrial rims (rim of the superior wall of the atrium near the right upper pulmonary vein). The gross anatomic details...
of an ASD with all the above-mentioned rims are depicted in Fig. 1.

The SVC and IVC rims are best visualized on TTE in the subcostal sagittal view (Fig. 2a), and on TEE in the basal long-axis view (Fig. 2b). The AV septal and atrial rims are best visualized on TTE in the subcostal coronal view (Fig. 3a), and on TEE in the 4-chamber view (Fig. 3b). The aortic rim is best seen on TTE in the parasternal short-axis view (Fig. 4a) and on TEE in the basal short-axis view (Fig. 4b). The rim between the IVC and SVC, located to the right and posterior aspect of the fossa ovalis, is not important in determining the success of transcatheter closure, and hence has not been considered.

References
Unusual Migration of Proximally Detached Pacemaker Lead into the Coronary Sinus

S Anandaraja, N Naik, R Yadav, R Juneja, KK Talwar
Department of Cardiology, All India Institute of Medical Sciences, New Delhi

A 72-year-old man had been implanted in 1976 with a unipolar VVI pulse generator in the right pectoral pocket for symptomatic complete heart block. The patient subsequently received a new pulse generator and pacing lead (both bipolar) in 1991 when the previous generator had exhausted its battery. This time, the pacemaker was placed in the left pectoral pocket. The previous generator was removed although the pacemaker lead was capped and retained. In 1996, the patient required a new pulse generator, which was connected to the bipolar pacing lead. In 1998, there was a fracture of this bipolar pacing lead resulting in pacing failure. Attempts to remove this lead by manual traction were unsuccessful, and it was severed at its entrance into the venous system and sutured to the pacemaker pocket. Hence, all the pacemaker leads implanted so far had been retained.

In December 2001, the unipolar lead retained in the right pectoral pocket spontaneously extruded through the skin. A local physician tried to extract this lead by traction. This, however, resulted in fracture of the lead, and a part of its distal end was retained, anchored to the right ventricular wall. Six months later, the patient had pacemaker extrusion from his left pectoral pocket after local trauma to the pacemaker pocket. The pulse generator was removed and the infected lead detached, proximally cut near its entrance into the venous system and retained in the pacemaker pocket. After a week of antibiotic therapy the patient was taken up for pacemaker implantation from the right pectoral side. However, the superior vena cava (SVC) was blocked and collateral channels connected the innominate vein to the SVC. It was noticed that the bipolar lead that had been detached and retained in the pocket a week back had slipped into the SVC while the previously implanted permanent pacemaker lead had also got detached from the pocket and was lying freely in the right atrial cavity. A left subclavian angiogram (by a catheter inserted from the femoral vein) demonstrated a collateral channel draining into the SVC-right atrial junction. Pacemaker lead implantation was attempted from this site at a second sitting, which was successful and without any untoward effect. Fluoroscopy repeated during this period.
on different days showed a marked migration of these detached pacemaker leads. Sites of migration included the inferior vena cava (IVC) and the coronary sinus (Fig. 1a and b). The patient was advised surgical extraction of the pacemaker leads, which he refused.

Proximal detachment of the pacemaker lead from its pectoral pocket is a rare complication that produces lead migration. This usually occurs if there is concomitant infection or if the leads are cut short and allowed to retract.\(^1,2\) Although such leads are usually secure, it is not unusual for sutures to cut through in the presence of local infection. This allows the lead to slip into the vascular cavity from where it is prone to migration. Such leads usually migrate into the IVC or the hepatic veins. This preferential localization of pacing leads to the lower half of the body is probably related to their higher specific gravity due to their metallic content. However, body position also plays a role in lead migration and these leads can migrate to unusual sites. Lead migration into the main and peripheral pulmonary arteries is reported in the literature.\(^1,2\) In one report, the free end of the lead perforated the atrial septum and caused cerebral embolism.\(^4\)

In our patient, the lead migrated to various sites and radiological examination showed the leads to lie coiled in the right atrial cavity, at the SVC-right atrial junction, within the IVC and hepatic vein, at different points in time. Migration was also noted deep within the coronary sinus at one juncture. To the best of our knowledge, migration into the coronary sinus has not been described previously. Such extensive migration of the lead is likely to produce complications. There have even been case reports of sudden death when patients with proximally detached pacing leads were treated only medically. Although autopsy findings are not available in these reports, it can be presumed that death was related to lead migration. Leads can conceivably perforate thin-walled structures, such as the right atrium and coronary sinus, thereby producing lethal hemopericardium.

Our patient had other lead-related complications. These included spontaneous extrusion of one of the pacemaker leads 26 years after its implantation. The patient also developed thrombosis of the SVC and, as collateral channels were adequate, he did not have any evidence of the SVC syndrome. The retained leads also interfered with appropriate sensing due to their electrical activity, and the pacemaker was programmed to VOO mode to ensure regular pacing.

Extraction of functionless pacemaker leads can be accomplished by transvenous techniques or surgically. A success rate of 94%–98% has been reported with transvenous techniques.\(^3,6\) Recently, the North American Society for Pacing and Electrophysiology (NASPE) has come up with guidelines for the extraction of functionless transvenous pacing and defibrillator leads.\(^7\) According to the recommendations, a retained lead that poses an immediate/imminent threat to the patient is a class I indication for lead extraction. As lead extraction devices are not available in our country, the patient was advised surgical extraction of these leads, which he refused.

References

Letters to the Editor

Tissue Doppler Echocardiography: A Need for Review

I read with great interest the article “Tissue Doppler Echocardiography: Principles and Applications” by Sengupta et al. I am concerned about the increasing number of papers on tissue Doppler echocardiography (TDE) appearing in leading medical journals. Tissue Doppler echocardiography is a clear case of misuse of technology. It could turn out to be the greatest hoax in cardiology. Doppler is best suited to study the direction of free-moving objects. In the case of echocardiography it is mainly used to study free-moving blood cells (blood flow). It is the direction of motion that is important; velocity measurements are secondary. A comparison of flow Doppler [color flow mapping (CFM)] and TDE will make things clear.

Doppler studies are primarily for the study of the direction of motion. The “red shift” in astronomy, for example, shows the stars moving away from us, indicating an expanding universe. Calculation of velocities is supplementary. The key point to note is that Doppler studies require a priori knowledge of the direction of motion. In blood flow there is a definite direction of flow and Doppler can detect any aberration in this. For example, we have prior knowledge of the direction of blood flow in the circuit—pulmonary veins→left atrium→left ventricle→aorta. Suitably directed Doppler interrogation can study and detect any deviation in this circuit. Myocardial motion is complex and not amenable to Doppler studies. In cardiac motion there are translational, rotational, and deformational movements. Besides, many tissues near the heart move—due to transmitted cardiac motion, vessel pulsation, respiratory motion, and involuntary muscle movements. Doppler interrogation at one point will represent the resultant of all these movements. At a particular point we can never predict the resultant vector. Even if known, the resultant is accurately recorded only if it is in the line of the Doppler beam. This is due to the inherent problem of directional bias. It is like measuring the length of a twisted rod with a straight ruler. Cardiac motion becomes more complicated in the presence of wall motion abnormalities. Blood flow is simple and suitable for Doppler study. Here the projectile motion of free-moving blood cells in one direction at an instant is studied.

In flow Doppler there are definite “points of interrogation”, which are the normal and abnormal orifices. In TDE there are no such definite points. In flow Doppler there is a unique unidirectional flow in one part of the cardiac cycle at the current interrogation points. For example, in mitral valve Doppler interrogation, the unique directional signal is obtained only in diastole. If there is a signal in systole it becomes abnormal. In TDE the to-and-fro motion (systole and diastole) of a tethered interconnected syncytium of myocytes is imaged. Such information is useless. This can even otherwise be seen and analyzed by B-mode imaging. While in flow Doppler higher velocities are studied, TDE is used to study lower velocities, i.e. to study hypofunctioning myocardial segments. Lower velocities are difficult to appreciate. Higher velocities are easier to appreciate with the help of aliasing and variance. Thus, hypofunction is difficult to analyze. The derivations from flow Doppler allow us to get orifice size, amount of flow, and pressure gradients, which are clinically of great importance. Thus, Doppler studies are best suited to study flow.

Color flow mapping allows us to “see” what we cannot see with ultrasonic “eyes”, hence it is of great value. In TDE we see more or less what we already see by B-mode. Hence its value is marginal. In CFM the anatomic landmarks are intact as the color is superimposed on the B-mode image. In TDE the B-mode is eliminated and the entire “picture” is Doppler information resulting in a fuzzy image, and different anatomic regions are difficult to determine. Tissue Doppler has been a disappointing imaging modality in clinical practice. This is due to the basic flaw in the application of the principles of Doppler. Doppler is best suited for flow studies and applying it to tissue motion is unreasonable. In flow Doppler the tissue “noise” is suppressed and flow is displayed. In TDE it is the other way round. It is like suppressing the PQRST waves in an electrocardiogram and displaying the “noise”. Besides, TDE is ultrasensitive and so the information gathered is almost useless (too much false-positive information). In fact, excellent cardiac waveforms can be obtained by placing the sample volume even outside the cardiac region! Once the foundation of a modality is wrong, all derivations tend to be wrong.

It is time to look at TDE more realistically. As a new modality of imaging it appears exciting. However, its real clinical utility is doubtful. TDE does not give any additional information over conventional modalities. Due to the mentioned deficiencies it could even give misleading information. Making diagnostic decisions based on this faulty application of technology should be unacceptable to the scientific cardiologist.
We read with great interest the views and concerns expressed in the letter regarding the use of tissue Doppler imaging (TDI). While we greatly admire the author's intelligent analysis of Doppler and its principles, we disagree on the technical contents cited in the letter that argue against the clinical use of TDI. Ever since the start of basic unidimensional echocardiography, it was known that cardiac motion was a complex combination of rotation, translation, and deformation in a three-dimensional (3-D) format, and its resultant vector was difficult to estimate. However, measures of cardiac motion and function on M-mode or two-dimensional (2-D) echocardiography were standardized and became invaluable tools for providing diagnostic and prognostic information. It was not the absolute 3-D cardiac motion or displacement that was quantified by these techniques but how these parameters changed predictably with disease. The use of Doppler with regard to tissue motion or strain, like earlier techniques, till date has centered not on quantifying the absolute displacement or true vector of cardiac motion but how an altered velocity profile predicts the presence of disease or provides reliable prognostic information.1,2

The limitation of Doppler in not providing the true velocity vector holds true for both blood flow and tissue motion. Blood flow in the heart and blood vessels has a complex profile. Red blood cells have a steady flow component and a series of oscillatory flow components. The mean flow has a parabolic profile while the pulsating component causes an oscillatory profile, which varies between parabolic and blunt. At curves the velocity profiles are disturbed giving rise to secondary flows, which persist for a finite distance.3 Doppler, when used for flow imaging, does not show all these components. The color data and spectral velocities merely represent a part of the true velocity vector in the direction of the transducer. Thus, in this regard, application of Doppler for blood flow has the same limitation as its use in tissue motion. On the contrary, TDI has a superior signal-to-noise ratio than the corresponding blood flow technique, thereby requiring fewer echoes for the estimation of mean velocities at each pixel location.4

Studies with sonomicrometry (which uses the principle of speed of sound through the cardiac tissue) have already been carried out for providing veracity of data, and this is a direct proof that information obtained by tissue Doppler is correct and scientifically valid.5 The reasons for sustained clinical and research interest in recent years resulted from the unique ability of TDI to provide rapid, incremental information not available currently by any other technique. Some of the areas where the use of TDI has been a clear advantage and which are incontrovertible are listed below.

1. A-mode, M-mode and real-time B-mode detect the motion of tissue boundaries, which is simply displayed over the screen. TDI detects and measures the motion of weaker and more complex echoes from within the layers of the myocardial wall.1,6 Velocity gradients are known to exist in different layers of the myocardium, which are altered in diseased states, and can be detected by TDI.1

2. Use of TDI and strain-rate imaging have already been shown to be superior to conventional real-time B-mode imaging for the interpretation of regional wall motion abnormalities.6,7 Distinguishing hypokinesis and akinesis or dyskinesis by conventional echocardiography has wide interobserver variability. Routine use of TDI and strain-rate imaging makes this job simple and quantitative.2,7

3. Longitudinal motion of the mitral valve annulus by M-mode has been used for assessing systolic and diastolic LV function. This information is now readily available by pulsed Doppler TDI and strain-rate imaging.1,2

4. Very high temporal resolution (<4 ms) have provided an insight into a number of physiologic and pathologic short-lived events during the cardiac cycle, particularly in relation to the understanding of myocardial ischemia and its detection. Assessment of segmental viability by post-systolic thickening or strain is now an invaluable tool in clinical practice.2,4 Similarly, estimation of regional and global isovolumic phases, and ejection and...
filling periods is possible within a single cardiac cycle from a single point of sample volume, even without the use of an ECG and phonocardiogram. This is the only technique that provides temporal data of both phases of the cardiac cycle simultaneously.

5. Tissue velocity imaging is an invaluable tool for the assessment of diastolic dysfunction, and can easily differentiate normal from pseudonormal patterns of diastolic dysfunction. Compared to hemodynamic flow Doppler parameters, it is relatively load-independent and does not fuse even at high heart rates.1

6. Strain and strain-rate imaging may cause problems in clinical use because of noise, angle-dependence and segments being syncytium, but this seems to be the right direction in which to proceed.2 Strain-rate imaging data obtained from Doppler ultrasound has good agreement with that obtained from magnetic resonance tagging.8

7. TDI has a distinct advantage with regard to the assessment of right ventricular function, which is difficult otherwise because of the complex geometry.9

8. Several well-conducted studies have shown that the requirement for resynchronization therapy in heart failure, optimizing benefits, and follow-up is much better with tissue velocity imaging compared to conventional parameters.10

The clinical applications of TDI are expanding and, despite a learning curve, more and more people are willing to use it. Some of the benefits listed above are obvious, the most important being its role in making echocardiographic techniques and measurements quantitative and less operator-dependent. It certainly is not a hoax, nor confined to research laboratories alone. Regular use will change skeptics into converts.

References


3. Evans DH, McDicken WN. Doppler ultrasound physics, instrumentation and signal processing. 2nd ed. West Sussex: John Wiley and Sons; 2000. pp. 5–26

4. Evans DH, McDicken WN. Doppler ultrasound physics, instrumentation and signal processing. 2nd ed. West Sussex: John Wiley and Sons; 2000. pp. 345–347


Partho P Sengupta, Jagdish C Mohan and Natesa G Pandian

GB Pant Hospital,Delhi,India and Tufts University, Boston,USA
Hypertension and Cancer Mortality: Is There a Place for Antioxidant Interventions?

The potential association between hypertension and cancer mortality has been extensively studied over the past several years but many aspects of this issue remain obscure. A recently published meticulous meta-analysis of previously published data concluded that hypertension is associated with an increased mortality from cancer, particularly renal cell carcinoma. Even though the clinical implications have not been clearly established, it is reasonable to assume that elucidation of the underlying pathophysiologic mechanisms could lead to the development of effective therapeutic strategies.

Notably, oxidative stress seems to play an important role in the pathophysiology of various disease states such as hypertension and cancer. Several parameters, which possibly contribute to the evolution of malignancy in hypertensives, have been associated with oxidative stress. In particular, the apoptotic process, which controls cellular growth, can be triggered by intracellular redox imbalance caused by oxidant stimuli. Furthermore, it is well known that oxidative stress leads to deregulation of calcium metabolism. It has been proposed that the accumulation of this ion leads to activation of several mitogens and oncogenes. In addition, various vasoactive neurohormones implicated in the pathogenesis of hypertension, such as angiotensin II, catecholamines, and insulin, apart from growth-like effects, have been shown to deteriorate antioxidant status. Presumably, the observation that diuretics increase cancer risk might be explained by the fact that the resulting rise in angiotensin II due to volume depletion exerts significant mitogenic and oxidative effects. Finally, factors such as aging, smoking, obesity, and diabetes, which are often related with hypertension, have also been found to induce oxidative stress.

In a recent “hypothesis” paper, Gago-Dominguez et al. proposed that lipid peroxidation, which is increased in obese and hypertensive subjects, is the mechanism responsible, at least in part, for the increased risk of renal carcinoma in such individuals. To the best of our knowledge, the hypothesis that oxidative stress contributes to increased cancer mortality in hypertensives has not yet been tested. In several observational studies, plasma concentrations of antioxidant vitamins were inversely associated with cardiovascular and cancer mortality. On the other hand, the evidence in randomized interventional studies that antioxidant vitamin supplementation can reduce cardiovascular and cancer mortality is scanty or nonexistent. Despite these unpromising results, direct evidence is lacking regarding the impact of antioxidant status on increased cancer risk observed in individuals with elevated blood pressure.

It is worth noting that besides pure antioxidants, several cardiovascular and antihypertensive drugs have been proposed to have intrinsic antioxidant properties. These include carvedilol, propranolol, nebivolol, captopril, losartan, calcium-channel blockers, statins, trimetazidine, aspirin, and others. Moreover, it has been suggested that the anti-inflammatory action of some of these drugs correlates with their antioxidant capacity. It is prudent to assume that most of these drugs act on components of neurohormonal activation or have metabolic and anti-inflammatory action. As previously mentioned, neurohormonal processes are able to induce oxidative stress by themselves. Thus, the study of their effect on oxidative stress in conjunction with cancer mortality appears to be difficult because their indirect “antioxidant effect” may confound their intrinsic free-radical scavenging capacity. Despite these difficulties, we believe that such medications may serve as valuable tools in the research of antioxidant interventions in this setting. Well-designed, prospective studies in the near future may further elucidate the association between these two major diseases, and delineate the role of antioxidant interventions.

References


Panagiotis Korantzopoulos
Laboratory of Biological Chemistry, University of Ioannina Medical School, Ioannina, Greece

Dimitrios Papaioannides
Department of Medicine
Arta General District Hospital
Arta, Greece
In-Stent Restenosis Treated With Stent-Based Delivery of Paclitaxel Incorporated in a Slow-Release Polymer Formulation

K Tanabe et al. TAXUS III Trial Investigators. Circulation 2003; 107: 559-564

Summary
The TAXUS III trial was a single-arm, 2-center study evaluating the feasibility and safety of a paclitaxel-eluting stent for the treatment of in-stent restenosis (ISR). It enrolled 28 patients with ISR with a lesion length of $\leq$30 mm, 50%-99% diameter stenosis in vessels with a diameter between 3 and 3.5 mm. Patients with acute myocardial infarction, poor ejection fraction (<30%), recent stroke, renal dysfunction, or contraindication to antithrombotics were excluded from the present study. The stent used was TAXUS NIRx paclitaxel-eluting stent (Boston Scientific Corporation, USA), with a total load of 1.0 $\mu$g/mm² of paclitaxel incorporated into a slow-release copolymer carrier system that gives biphasic release an early burst over the first 48 hours followed by slow release over the next 10 days. Predilatation was performed in all cases, and post-dilatation was performed when necessary. All the stents were 15 mm long and 3–3.5 mm in diameter. During the procedure, ACT was kept at $>250$ s, and standard antiplatelet regimen was followed post-procedure. Angiographic and intravascular ultrasonographic (IVUS) follow-up was performed at 6 months, and clinical follow-up at 6 months and 1 year. There were clinical, angiographic, and IVUS-based end-points. Angiographic follow-up was available in 25 patients, and IVUS follow-up in 17. The major adverse cardiac event (MACE) rate was 29% (6 patients; 1 non-Q-wave myocardial infarction, 1 coronary artery bypass grafting, and 6 target lesion revascularization (TLR)). Two patients underwent revascularization for restenosis in the gap between 2 paclitaxel-eluting stents, 1 for restenosis for a bare stent implanted at edge dissection, 1 for anginal symptoms but no restenosis (diameter stenosis of 32.5%), and in 2 patients not for restenosis but for incomplete stent apposition/expansion as detected on IVUS study. One patient had target vessel occlusion but required no intervention as there were no symptoms. Binary angiographic restenosis occurred in 4 patients (16%). One patient had restenosis of a bare stent implanted to cover edge dissection due to implantation of a paclitaxel-coated stent, and 2 patients had restenosis in the gap between 2 paclitaxel-eluting stents. Thus, of the 4 restenoses, only 1 occurred in the area of paclitaxel delivery. The diameter stenosis at follow-up was 30.8%, with an average in-stent late loss of 0.54 mm. Late loss at the proximal and distal edges was 0.20 and 0.11 mm, respectively. Of 17 patients undergoing IVUS, the volume of neointimal hyperplasia was 20.3±23.1 mm³. There was no evidence of positive or negative remodeling in the 6 patients undergoing TLR. Thus, paclitaxel-eluting stent implantation appears to be safe and potentially effective in the treatment of ISR.

Comments
In the current era, use of stents has improved the safety and success of percutaneous coronary interventions (PCI) and even reduced the restenosis rate (BENESTENT and STRESS trials). However, their use has also brought about the complex and difficult-to-manage problem of ISR and repeat TLR. Several pharmacologic and mechanical approaches have been tried to overcome the problem of ISR but they have limitations. Plain balloon angioplasty for ISR leads to a re-restenosis rate of 30%-85%, depending on whether it is a focal restenosis or diffuse ISR. Similarly, directional coronary atherectomy (re-restenosis rate 60%), and excimer laser (TLR 41%) have not been of much benefit. Rotablation and the use of cutting balloon may have some theoretical advantage but large studies to prove their efficacy are not available. Only radiation therapy has been found to be consistently useful till date. A number of double-blind clinical trials using gamma sources (SCRIPPS, WRIST, GAMMA-1) and a beta source (START, INHIBIT) have reported a striking efficacy in preventing re-restenosis in patients with established ISR (17%-34%). A major problem with brachytherapy, however, has been late stent thrombosis and late restenosis. Implantation of a new stent in the irradiated segment and withdrawal of clopidogrel/ticlopidine have been correlated with late thrombosis. Preliminary evidence from trials using prolonged antiplatelet regimens (>3 months) have suggested a marked reduction in this complication. Another major problem with brachytherapy is the edge effect. Careful analysis has suggested that these edge effects may represent a “geographic miss” of radiation and this problem can be substantially ameliorated with careful attention to registering adequate doses of radiation throughout the instrumented segment of the coronary artery. Furthermore, brachytherapy is less accessible, and its delivery requires special handling. In this context, stent-based local drug delivery have revolutionized the field of PCI. Smith et al. reported use of sirolimus-eluting stents in 15 patients with ISR; at 4 months, MACE occurred in 6.7% (1/15) cases. One patient died suddenly, and late occlusion occurred in another. In-stent late loss was 0.02 mm, and on IVUS, neointimal hyperplasia was 7.8±0.03 mm². In the present study using paclitaxel-coated stents, although the technical re-restenosis rate is 16%, actual restenosis occurred in only 1 patient. Similarly, the occurrence of late loss (0.54 mm) and neointimal hyperplasia (20.3 mm²) was low. However, these studies are too small and do not have a placebo arm. Nevertheless, it does seem that drug-eluting stents may be of use in the therapy of ISR.
Major Outcomes in High-Risk Hypertensive Patients Randomized to Angiotensin-Converting Enzyme Inhibitor or Calcium-Channel Blocker v. Diuretics

The ALLHAT Collaborative Research Group. JAMA 2002; 288: 2981–2997

Summary

The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) was a randomized, double-blind, active-controlled, clinical trial conducted with a view to determine which antihypertensive treatment decreased the risk of coronary artery disease (CAD) or other cardiovascular disease (CVD) events. It enrolled 33 357 hypertensive subjects, both men and women, ≥55 years of age, with at least one other risk factor for CAD from 623 North American centers. The patients were randomized to receive chlorthalidone 12.5–25 mg/day (n=15255), amlodipine 2.5–10 mg/day (n=9048), or lisinopril 10–40 mg/day (n=9054), and followed up for 8 years. The primary end-point was a combination of CAD deaths plus nonfatal myocardial infarction (MI). The secondary end-points were all-cause mortality, stroke, combined CAD end-point (CAD death, nonfatal MI, coronary revascularization, or angina requiring hospitalization), and combined CVD (combined CAD end-point, stroke, treated angina without hospitalization, CHF and peripheral arterial disease). At a mean follow-up of 4.9 years, the primary outcome of CAD death plus nonfatal MI was not different in any of the treatment groups. Compared with chlorthalidone (6-year rate, 11.5%), the relative risks (RRs) were 0.98 (95% CI: 0.90–1.07) for amlodipine (6-year rate, 11.3%) and 0.99 (95% CI: 0.91–1.08) for lisinopril (6-year rate, 11.4%). Similarly, all-cause mortality was also not different. Chlorthalidone was more effective in controlling systolic BP as compared to amlodipine and lisinopril (p<0.05 for both). On the other hand, amlodipine was more effective in lowering the diastolic BP (p<0.01). Among the secondary end-points, occurrence of CHF was commoner in the amlodipine group as compared to chlorthalidone group (10.2% v. 7.7%, RR 1.38; 95% CI: 1.25–1.52). Similarly, combined CAD end-points (33.3% v. 30.9%, RR 1.10; 95% CI: 1.05–1.16), stroke (6.3% v. 5.6%, RR 1.15; 95% CI: 1.02–1.30), and CHF (8.7% v. 7.5%, RR 1.19; 95% CI: 1.07–1.31) were all higher in the lisinopril group compared to chlorthalidone group. The authors concluded that diuretics are superior to amlodipine or lisinopril in reducing the cardiovascular morbidity and are much less expensive.

Comments

For decades, the search for an ideal antihypertensive has been on. An ideal antihypertensive is one which not only controls the blood pressure but also reduces cardiovascular morbidity and, even more importantly, mortality, without causing side-effects. The cost of drug therapy is also important, especially because it has to be continued lifelong. Classically, diuretics and beta-blockers have been considered drugs of first choice, primarily because of their effect in reducing mortality. However, these drugs are not without side-effects, and are besiegled with the problems of diuresis, impotence, and depression, as well as dyslipidaemia and metabolic abnormalities. Angiotensin-converting enzyme inhibitors (ACE-I) have emerged as a credible alternative because of their efficacy and ability to prevent complications such as the progression of renal disease and stroke. However, till date, no large study has shown reduction in overall mortality with ACE-I. Calcium-channel blockers (CCB), on the other hand, though efficacious, have actually shown increased mortality with the use of short-acting ones. Unfortunately, very few large studies have undertaken head-to-head comparison of various antihypertensive agents. In this context, the ALLHAT study is a landmark one. The major finding of this study was a striking and unequivocal null result in reducing the primary end-point, i.e. CAD death plus nonfatal MI (except doxazocin which was discontinued earlier on in the study). Because of the large number of subjects involved in the study, the mortality benefit with diuretics, if at all, is likely to be very small. However, in the context of reduction of cardiovascular morbidity, therapy with chlorthalidone does seem superior to that with amlodipine or lisinopril. In fact, chlorthalidone was found to be superior to even lisinopril in reducing 6-year CHF rates (8.7% v. 7.7%; CI: 1.07–1.31), a risk reduction of 1.19. However, despite being path-breaking, the study is still fraught with certain limitations. The blood pressure control achieved was not similar in all the groups (SBP was better controlled with chlorthalidone, while DBP was better controlled with amlodipine). Newer antihypertensive agents such as ramipril, angiotensin receptor blockers, selective aldosterone antagonists, and beta-blockers have not been studied. The most important message from this study is that, as of now, thiazide-type diuretics should still be considered first-line therapy because of their excellent efficacy, low long-term morbidity and mortality rates, and low cost.
Long-Term Effects of Spinal Cord Stimulation and Coronary Artery Bypass Grafting on Quality of Life and Survival in the ESBY Study


Summary

Electrical Stimulation versus Coronary Artery Bypass Surgery in Severe Angina Pectoris (ESBY) was a randomized, prospective, open-comparison study of coronary artery bypass grafting (CABG) and spinal cord stimulation (SCS) in patients with severe angina despite optimal pharmacologic treatment. Prior to ESBY study, SCS was used in patients for whom revascularization was not possible. In ESBY study patients were enrolled if angina was not controlled with anti-anginal agents, and the patients were eligible for CABG with an increased but acceptable risk (as per the ACC/AHA, 1991 indications). Patients enrolled did not have acute myocardial infarction in the past 6 months, and were intelligent enough to manage the SCS device. The mean Higgins score (scoring system for estimation of preoperative risk) was 4.2. The SCS device was implanted under local anesthesia. The long-term outcome regarding quality of life and survival of those 104 patients included in ESBY study (1992–1995) was investigated. The quality of life was assessed by the Nottingham health profile (NHP) and quality of life questionnaire (angina pectoris). The quality of life at 6 months had shown significant improvement compared to the run-in (p<0.001). This result persisted even up to 4.8 years of follow-up. In the CABG group, however, there was a deterioration during the postoperative observational period. Within 6 months of randomization, 1 patient in the SCS group and 7 in the CABG group died. At 3 and 5 years, there was no significant difference in mortality between the two groups. Three years after randomization, 84.9% in the SCS group and 76.5% in the CABG group were alive. At 5 years, 75.5% in the SCS group and 68.6% in the CABG group were alive. Thus, spinal cord stimulation as well as CABG offered long-lasting improvement in quality of life and survival up to 5 years was comparable between the groups.

Comments

SCS or epidural spinal electrical stimulation (ESES) has been used for treatment of refractory angina. The ESBY study was published in 1998 with 6 months of follow-up, and had shown no difference between the CABG and SCS arms. The present study is a long-term follow-up of the ESBY patients. The mortality rate in this study was similar to that seen in the angina subpopulation of the Swedish Council on Technology Assessment in Health Care patients. As compared with 0.8% mortality seen in CASS trial or 16% observed in the ECSS study, the mortality is higher in the present study. However, the patient population of the ESBY study does not match that of CASS/ECSS studies. The survival data in the study showed equivalent survival in both the arms with equal improvement in the quality of life. As it is a long-term follow-up study, the placebo effect will not be seen as it decreases with time. However, the exact mechanism of benefit is unknown. The antianginal effect is secondary to an anti-ischemic effect, which in turn seems to be due to a reduction in myocardial oxygen consumption; however, a redistribution of coronary blood flow cannot be excluded. Thus, it seems that SCS, being noninvasive and less traumatic, may be a therapeutic alternative for patients with severe angina and high risk for bypass surgery. At present, SCS treatment is costly and technically more demanding, thereby limiting its use. Further prospective studies are needed to compare SCS and revascularization to establish this as an alternative treatment in patients with refractory angina.
Eplerenone, a Selective Aldosterone Blocker, in Patients With Left Ventricular Dysfunction After Myocardial Infarction


Summary

Eplerenone is an aldosterone antagonist that selectively inhibits the mineralocorticoid receptors, leaving the glucocorticoid, progesterone or androgen receptors unaffected. Its selective action is beneficial in preventing side-effects such as sexual dysfunction and gynecomastia that are encountered with the nonselective blockade provided by spironolactone. This study is a multicenter, international, randomized, double-blind, placebo-controlled trial that included patients with acute myocardial infarction (time to randomization 3–14 days) and left ventricular dysfunction (LVEF <40%) with clinical heart failure, except in diabetics in whom the symptoms of heart failure did not have to be demonstrated. Exclusion criteria were the use of potassium-sparing diuretics, a serum creatinine level of 2.5 mg/dl or above, and a serum potassium concentration of >5 mmol/L. The potassium level was monitored on subsequent follow-up visits. Six thousand six hundred forty-two patients were randomized to eplerenone (25 mg/day initially, titrated to a maximum of 50 mg/day; 3319 patients), or placebo (3313 patients). The study continued until 1012 deaths occurred. At baseline, the 2 groups were not significantly different and were receiving optimal medical therapy including ACE inhibitors or angiotensin-receptor blockers (87%), beta-blockers (75%), aspirin (88%), and diuretics (60%).

The primary end-points were death from any cause and death from cardiovascular causes, or first hospitalization for a cardiovascular event including heart failure, recurrent acute myocardial infarction (AMI), stroke, or ventricular arrhythmia.

In the mean follow-up period of 16 months, 478 deaths occurred in the eplerenone group (14.4%) and 554 deaths in the placebo group (16.7%) (relative risk [RR] 0.85; p=0.008). Of these deaths, 407 in the eplerenone group and 483 in the placebo group were attributed to cardiovascular causes (RR: 0.83; p=0.005), which included sudden cardiac death, acute myocardial infarction, and heart failure. The reduction in risk of sudden death from cardiac causes was statistically significant (RR 0.79; p=0.03). There was a relative reduction of 15% in the risk of hospitalization for heart failure and there were 23% fewer episodes of hospitalization in those receiving eplerenone compared to placebo. The rate of death from any cause or any hospitalization was 8% lower in the eplerenone than in the placebo group (RR: 0.92; p=0.02).

During the study period, 493 patients in the placebo group and 528 patients in the eplerenone group discontinued the drug. There was a significantly greater increase in the serum creatinine concentration in the eplerenone group than in the placebo group, but the difference was clinically small. Serious hyperkalemia occurred in 5.5% of patients in the eplerenone group, as compared with 3.9% of patients in the placebo group. The incidence of hyperkalemia was more in patients with a baseline creatinine clearance of <50 ml/min. Though there were 12 hospitalizations for serious hyperkalemia in the eplerenone group, there were no deaths. Three patients in the placebo group were admitted because of hyperkalemia and there was 1 death. In conclusion, the study showed that eplerenone significantly reduces morbidity and mortality in patients with AMI and LV dysfunction.

Comments

The Randomized Aldactone Evaluation Study (RALES) proved the importance of aldosterone antagonists in the management of patients with heart failure. In addition to reducing mortality by 30%, small doses of spironolactone resulted in an improvement in the ejection fraction and enhanced treatment tolerance. It has been shown that patients with heart failure have high levels of plasma aldosterone because of increased production and decreased hepatic clearance. Sustained aldosterone levels promote endothelial dysfunction and oxidative stress in the vasculature and also organ fibrosis. The beneficial effect on ventricular remodeling is evidenced by this study, in which the relative risk of death was reduced by 15% and the risk of hospitalization was also reduced by 15%. The reduction in cardiovascular mortality is mainly due to 21% reduction in the rate of sudden death due to cardiac causes. An important point in the EPHESUS trial is that patients were already receiving optimal therapy (ACE inhibitors in 87% and beta-blockers in 75%). In RALES, beta-blockers were used only about 11%, although ACE inhibitors were given to 94%. One-year mortality among the placebo group was higher in RALES (25%) as compared with EPHESUS (13.6%). This difference in mortality may reflect the more severely depressed systolic function in patients enrolled in RALES (LVEF averaged 25% in RALES as compared to 33% in EPHESUS). Taken together, these 2 trials of aldosterone blockade have enrolled more than 8000 patients with systolic dysfunction and symptoms of heart failure, and have shown that the addition of aldosterone antagonists to these patients can substantially reduce overall mortality and rate of sudden death. Currently, the guidelines of the American College of Cardiology and American Heart Association specify that the use of spironolactone for patients with mild-to-moderate heart failure has not been tested. After the RALES and EPHESUS, their beneficial role in the management of heart failure is quite evident, with just a little extra effort to monitor the potential side-effects, especially hyperkalemia. Further studies would determine whether this class of drugs will prove as efficacious in patients with less severe symptoms or in those with heart failure due to diastolic dysfunction.
May 1–3, 2003, 18th International Meeting on Clinical Cardiology, Athens, Greece
Contact: Dr. P. Toutouzas
Chairman, Organizing Committee
Department of Cardiology
University of Athens, Greece
Tel: 0106401477
Fax: 0106401478

June 21–24, 2003, Heart Failure Update 2003, Strasbourg, France
Contact: European Society of Cardiology
The European Heart House
2035 Route des Colles, Les Templiers - BP 179
Sophia Antipolis Cedex 06903, France
Tel: 33 4 9294 7600
Fax: 33 4 9294 7601
e-mail: webmaster@escardio.org

June 25–28, 2003, 14th Asian Pacific Congress of Cardiology (APCC), Singapore, Singapore
Contact: Dr. Michael Lim, Chairman, 14th APCC
The Secretariat, 302, Orchard Road
# 16-04, Tong Building, Singapore 238862
Republic of Singapore
Fax: 65 836 0436
e-mail: enquiry@14apcc.com

September 16–21, 2003, Transcatheter Cardiovascular Therapeutics 2003, Washington, D.C., USA
Contact: The Course Directors
55 East 59th Street, 6th Floor
New York NY 10022-1112, USA
Tel: 1 212 434 6300
Fax: 1 212 434 6386
e-mail: info@crf.org

October 26–30, 2003, 69th Annual Scientific Assembly, American College of Chest Physicians, Orlando, Florida, USA
Contact: American College of Chest Physicians
3300 Dundee Road, Northbrook IL 60062, USA
Tel: 1 847 498 1400
Fax: 1 847 498 5460

November 2–5, 2003, 76th Scientific Session, American Heart Association (AHA), Orlando, Florida, USA
Contact: American Heart Association
7320 Greenville Avenue, Dallas TX 75231, USA
Tel: 1 214 373 6300
Fax: 1 214 373 3406

December 4–7, 2003, 55th Annual Conference of Cardiological Society of India, Kolkata, India
Contact: Dr. Asok Kumar Kar, Organizing Secretary
Indian Heart House
P-60, CIT Road, Scheme VIIM,
Kankurgachi, Kolkata 700 054, India
Fax: 033 355 6308
e-mail: csi@cal2.vsnl.net.in

November 7–10, 2004, 77th Scientific Session, American Heart Association (AHA), New Orleans, Louisiana, USA
Contact: American Heart Association
7320 Greenville Avenue, Dallas TX 75231, USA
Tel: 1 214 373 6300
Fax: 1 214 373 3406