Cardiac Amyloidosis - An Update

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Amyloidosis is a rare, mysterious and serious disorder. The extracellular deposition of seemingly homogenous and amorphous material actually represents the expression of very diverse pathologies. All amyloid fibrils share apple green birefringence under polarized light with Congo-red staining, and are arranged in beta-pleated structure on electron microscopy. More than 21 proteins have been identified that may give rise to amyloid in vivo including light chain immunoglobulins, transthyretin, acute phase reactant - protein A, fibrinogen Aα, apolipoprotein A etc. There are similarities and differences in the clinical manifestations of amyloidosis resulting from different precursor proteins. An accurate diagnosis of the type of amyloid has now become important as therapy for some forms of amyloidosis is emerging, and also the prognosis varies amongst different amyloidoses. Exciting progress is being made in our understanding of the process of amyloidogenesis, mechanisms of tissue damage due to amyloidosis, in genetics of amyloidosis and related areas raising the hope of effective treatment of the disease. However, a cure for all patients with amyloidosis is still afar.

At a clinical level, systemic amyloidosis is a disease with protean manifestations and the diagnosis is often delayed in the era of compartmentalized care. An early diagnosis may facilitate therapy before the end organ damage is severe. Cardiac involvement is the cause of death in nearly 50% of patients with systemic amyloidosis. In this article, we highlight the selected aspects of cardiac amyloidosis from a clinical standpoint and review the recent progress in the treatment of amyloidosis.

Types of Systemic Amyloidosis

The classification and terminology of amyloidosis is sometimes confusing. The deposits of AL amyloid, ATTR amyloid and AA amyloid result in the so-called primary, familial/senile amyloidosis, and secondary amyloidosis respectively. The commonly occurring types of systemic amyloidoses are shown in Table 1. Cardiac involvement most often results from the deposition of fragments of light chain immunoglobulins (primary or AL amyloidosis) produced by the clone of plasma cells in the bone marrow with or without multiple myeloma. Familial amyloidosis results from deposition of amyloid derived from mutant transthyretin. Transthyretin (previously called prealbumin) is a soluble plasma protein involved in the transport of thyroxine and vitamin A. Given sufficient time, the normal transthyretin may also get deposited in the heart, as in elderly with senile amyloidosis. Cardiac involvement in amyloidosis secondary to inflammatory disorders, like rheumatoid arthritis, Crohn’s disease, tuberculosis, or leprosy is very rare. Acidosis leads to significant heart failure in a minority. Transthyretin amyloidosis is universally present in the heart of patients above 80 years of age, but leads to significant heart failure in a minority. Transthyretin amyloidosis is universally present in the heart of patients above 80 years of age, but leads to significant heart failure in a minority. Transthyretin amyloidosis is universally present in the heart of patients above 80 years of age, but leads to significant heart failure in a minority. Transthyretin amyloidosis is universally present in the heart of patients above 80 years of age, but leads to significant heart failure in a minority. Transthyretin amyloidosis is universally present in the heart of patients above 80 years of age, but leads to significant heart failure in a minority. Transthyretin amyloidosis is universally present in the heart of patients above 80 years of age, but leads to significant heart failure in a minority. Transthyretin amyloidosis is universally present in the heart of patients above 80 years of age, but leads to significant heart failure in a minority.

Cardiac Amyloidosis

In the primary or AL amyloidosis, cardiac involvement at presentation is seen in nearly 30% of patients, but eventually occurs in the majority. Typical patient of cardiac amyloidosis is an older (> 40 years) man with dominant right-sided heart failure and evidence of multi-system involvement i.e. nephrotic syndrome, orthostatic hypotension, or carpal tunnel syndrome. The pathognomonic features of amyloidosis like macro glossia and easy bruising (Raccoon eyes resulting from trivial trauma) occur in only 10-15% of patients with primary
amyloidosis. Marked hepatomegaly or weight loss despite edema suggests gastrointestinal involvement and is a poor prognostic sign. Absence of systemic hypertension despite renal disease may be seen with systemic amyloidosis. Orthostatic hypotension due to autonomic neuropathy occurs in 40% of patients. Resting hypotension (systolic blood pressure < 100 mmHg) occurs in nearly 15% of patients, and amyloid-induced hypoaldosteronism or hypothyroidism as a cause of hypotension may remain unrecognized. The combination of restrictive cardiomyopathy and peripheral neuropathy is also found in other diseases like sarcoidosis, hemochromatosis, lymphoma, carcinomatosis and Fabry's disease. Recurrent pleural effusions may occur due to pleural amyloidosis, but is seen usually in the presence of associated cardiac amyloidosis. Nail dystrophy, testicular enlargement, or hoarseness of voice are seen in 5 - 10% of patients.

Cardiac amyloidosis accounts for nearly 10% of non-ischemic cardiomyopathies. It is estimated that 25% of myocardial mass is replaced with amyloid by the time the patient has clinical heart failure. The typical picture is that of a rapidly progressive congestive heart failure (CHF) due to restrictive cardiomyopathy, but systolic dysfunction occurs later in the course of the disease. Dilated cardiomyopathy is seen in only 5% of patients and occasionally cardiac amyloidosis may masquerade as hypertrophic cardiomyopathy. Typical angina may occur due to deposition of amyloid in intramural vessels and a pseudoinfarct pattern on electrocardiogram may mislead toward atherosclerotic coronary artery disease (CAD). However, atherosclerotic CAD may coexist. Unstable angina, myocardial infarction (MI), and silent ischemia in a patient with amyloidosis may also occur due to obstructive intramural amyloidosis or very rarely, epicardial obstructive amyloidosis as well.

Sudden cardiac death accounts for 30% to 50% of all cardiac deaths in systemic amyloidosis and may be due to ventricular arrhythmias, atrioventricular block, or acute electromechanical dissociation. Atrial fibrillation (AF) is found in 10-20% of cardiac amyloidosis, due to atrial enlargement, atrial infiltration or congestive heart failure. Atrial thrombi are described even in sinus rhythm related to an impairment of atrial emptying or deranged clotting factors. Thickened valves and valvular regurgitations are seen on echocardiography, but are not clinically apparent. Pericardial tamponade or pulmonary artery hypertension due to systemic amyloidosis are very rare.

Investigations
Anemia is uncommon without associated myeloma. Thrombocytosis and hypogammaglobulinemia are helpful pointers seen in a minority of AL amyloidosis. Low voltage in the limb leads on electrocardiogram in the presence of increased left ventricle (LV) mass is highly suggestive of cardiac amyloidosis, but has a sensitivity of 63 - 80%. The sensitivities of commonly used investigations for cardiac amyloidosis are shown in Table 2.

Table 2. Sensitivity of diagnostic tests in cardiac amyloidosis

<table>
<thead>
<tr>
<th>Test</th>
<th>Finding</th>
<th>Sensitivity (%)</th>
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<tbody>
<tr>
<td>Electrocardiography</td>
<td>Low Voltage</td>
<td>63 - 80</td>
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<td></td>
<td>Q Waves</td>
<td>60 - 93</td>
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<tr>
<td>Echocardiography</td>
<td>IVS thickening</td>
<td>87</td>
</tr>
<tr>
<td></td>
<td>Sparkled appearance</td>
<td>45 - 87</td>
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<tr>
<td></td>
<td>IAS thickening</td>
<td>40 - 60</td>
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<tr>
<td></td>
<td>Valve thickening</td>
<td>65</td>
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<tr>
<td></td>
<td>Biventricular dilation</td>
<td>45</td>
</tr>
<tr>
<td></td>
<td>Pericardial effusion</td>
<td>45</td>
</tr>
<tr>
<td></td>
<td>Restrictive pattern on Doppler</td>
<td>35 - 50</td>
</tr>
<tr>
<td>Biochemistry</td>
<td>Urine/Serum monoclonal protein</td>
<td>80 - 90</td>
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<tr>
<td>Tissue biopsy</td>
<td>Abdominal fat pad aspiration</td>
<td>80</td>
</tr>
<tr>
<td></td>
<td>Rectal biopsy</td>
<td>70 - 85</td>
</tr>
<tr>
<td></td>
<td>Bone marrow biopsy</td>
<td>50 - 56</td>
</tr>
<tr>
<td></td>
<td>Abdominal fat pad with bone marrow</td>
<td>90</td>
</tr>
<tr>
<td></td>
<td>Skin biopsy</td>
<td>50 - 90</td>
</tr>
<tr>
<td></td>
<td>Endomyocardial biopsy</td>
<td>100*</td>
</tr>
<tr>
<td>Radionuclide imaging</td>
<td>99Tc pyrophosphate scintigraphy</td>
<td>23</td>
</tr>
</tbody>
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* If at least 3 samples tested, occasionally negative; IVS: interventricular septum; IAS: interatrial septum; Tc: technetium. Adapted and modified from Ref. 30.

Echocardiography: Echocardiogram remains a very important tool for the diagnosis of amyloidosis. Typically, increased thickness of left ventricular walls in the absence of secondary causes like hypertension is seen. A granular sparkling appearance of myocardium is seen, but it cannot be qualitatively differentiated from the speckling seen occasionally in hypertrophied hearts from other causes. Dilated atria, interatrial septal hypertrophy (> 7 mm), small pericardial effusion, thickened valves, and thickened right ventricular free wall are also seen. Such an echocardiographic picture in the clinical context is considered diagnostic even without an endomyocardial biopsy. Further, the echocardiographic picture correlates with clinical severity and prognosis. Ventricular septal thickness more than 15 mm is considered a poor prognostic sign. These echocardiographic findings are seen in nearly 70% of patients with AL amyloidosis. Transmural and pulmonary venous Doppler findings progress from abnormalities suggestive of impaired relaxation to those of severe restrictive pattern as the severity of the disease progresses. Pulmonary venous A wave reversal duration that exceeds the mitral inflow A wave duration suggests that the LV end-diastolic pressure is greater than 15 mmHg, and this finding is seen in nearly all patients with amyloidosis, the magnitude of difference is higher in patients exhibiting restrictive pattern.
measure of systolic and diastolic function, is abnormal in both the left\textsuperscript{35} and right ventricles\textsuperscript{36} in cardiac amyloidosis, and is shown to be an independent marker of prognosis in some studies.\textsuperscript{35}

Tissue Doppler imaging (TDI), strain rate imaging, and ultrasonic tissue characterization may be useful in the early diagnosis of cardiac amyloidosis.\textsuperscript{33,37} TDI measured E wave velocities at lateral (≤12 cm/s) and medial (≤10 cm/s) mitral annulus have a good overall accuracy, but are not independent of age and LV hypertrophy. Age independent color TDI velocities like, early isovolumetric relaxation-mean myocardial velocity (IVR-MMV) accurately identify cardiac involvement even in patients with borderline or no LV thickening.\textsuperscript{38} These parameters help in the early diagnosis of cardiac involvement, but are seen in other hypertrophied hearts as well. Recently, a distinct serrated pattern of myocardial velocity profile on color-coded TDI has been reported in the ventricular septum and the posterior wall in patients with advanced amyloidosis.\textsuperscript{39} Such a pattern is highly specific for amyloidosis and is not observed in hypertensive LV hypertrophy or hypertrophic cardiomyopathy. It is proposed that the serrated pattern results from inhomogeneity of segments with regards to thickening, probably related to amyloid deposition.\textsuperscript{39}

Strain and strain rate imaging are shown to be more sensitive than TDI in identifying early amyloid involvement of the heart. Basal strain and basal peak systolic strain rate identify patients with cardiac involvement and CHF.\textsuperscript{40} An early impairment in systolic function, as identified by strain and strain rate imaging, precedes the onset of CHF and the onset of reduced fractional shortening.\textsuperscript{40} Ultrasonic tissue characterization using cycle-dependent variation of myocardial integrated backscatter (CV-IB) is shown to be a better predictor of clinical outcome in cardiac amyloidosis than the other standard echocardiographic measures.\textsuperscript{41}

Familial Amyloidosis

Familial amyloidosis commonly results from the deposition of transthyretin derived-amyloid (ATTR amyloidosis) in various organs.\textsuperscript{8} The mutant transthyretin is inherently more amyloidogenic, more than 60 such mutations have been described.\textsuperscript{32} In familial amyloidosis, neuropathy, and renal manifestations predominate and cardiac involvement is seen in only 25% of patients. The clinical picture of familial cardiac amyloidosis differs somewhat from AL or primary amyloidosis, but is not sufficiently distinct to make a diagnosis solely on the clinical grounds.\textsuperscript{8} A family history may not be available in nearly 30 - 50% of patients with familial amyloidosis, and late onset of the disease is common in them as well.\textsuperscript{4} The onset and severity of manifestations vary with specific mutation. Some mutations may result mainly in cardiac amyloidosis e.g., Ile122 mutation. This transthyretin mutation (Ile122) is seen in up to 4% of black population, and may be responsible for the higher prevalence of heart failure in elderly blacks.\textsuperscript{43} Similar cases may be present in India as well. Normal echocardiographic findings, better preserved electrocardiographic voltages, and a dominant conduction system disease have been described with some mutations of transthyretin.\textsuperscript{4,8} The distinction between AL or primary, and familial cardiac amyloidosis is important since liver transplantation can cure familial amyloidosis by providing normal transthyretin.\textsuperscript{44}

Senile Amyloidosis

Previously considered benign local deposits in the heart of the elderly, senile amyloidosis is now known to be widespread and occasionally responsible for CHF.\textsuperscript{4,5} The deposits result from normal or wild transthyretin and are universally present in the heart of patients above 80 years of age. In patients with senile amyloidosis, amyloid causes CHF in 10 - 20% of patients.\textsuperscript{24,45} Since the age of presentation may overlap in various forms of systemic amyloidoses, a definite diagnosis cannot be made on the basis of age alone. Cardiovascular findings including echocardiography may not be able to distinguish senile amyloidosis from primary or familial amyloidosis.\textsuperscript{46,47} However, macroglossia and other systemic involvement do not occur in senile amyloidosis; but carpal tunnel syndrome may occur in both.\textsuperscript{9} Thus in senile amyloidosis, abdominal fat aspirates are negative, no light chains are seen in serum/urine, bone marrow biopsy is normal, and no mutation in transthyretin gene is detected. It is important to recognize senile amyloidosis since the median survival in senile amyloidosis is 5 years, in contrast to only 5 months in primary amyloidosis.\textsuperscript{8}

Isolated Atrial Amyloidosis

Isolated atrial amyloidosis (IAA) is very commonly found histologically in people in the ninth decade, and results from atrial natriuretic peptide (ANP) deposition. The contribution of IAA in the pathogenesis of AF in the elderly is not clear. In a study of 245 patients undergoing open heart surgery for valvular or coronary heart disease, biopsy evidence of ANP amyloid deposition in the right atrial appendage correlated with prevalence of persistent AF, and the association was independent of the age of patients.\textsuperscript{10} IAA may play a role in the genesis of idiopathic AF in the elderly, but the question remains to be better studied.
Approach to the Diagnosis of Cardiac Amyloidosis

After the clinical suspicion, the most appropriate initial screening test would be immunofixation of serum and urine for monoclonal protein spikes. The presence of abnormal light chain suggests the diagnosis of primary (AL) amyloidosis. Routine serum electrophoresis alone is inadequate for this purpose, and is negative in 50% of patients. A negative immunofixation test alone will not rule out amyloidosis, as it can occur in non-secretory amyloidosis (10% of AL amyloidosis) or in other forms of amyloidosis (familial or senile amyloidosis).

The confirmation of amyloidosis requires some tissue biopsy (fat pad aspirate or other tissues). A bone marrow biopsy is required to characterize the monoclonal gammopathy and usually more than 5% plasma cells are found in primary amyloidosis. Fat pad aspiration and bone marrow biopsy together can identify amyloid in 90% of AL amyloidosis patients. Endomyocardial biopsy is extremely sensitive, but is often not required. However, endomyocardial biopsy is always required in isolated cardiac involvement, which may be seen rarely with AL amyloidosis (4%), and more frequently with senile or familial amyloidosis.

On histopathology, the pattern of arrangement of amyloid deposits may be of help in distinguishing primary from senile amyloidosis. A vascular pattern is more common in primary amyloidosis, whereas an interstitial nodular pattern is more common in senile cardiac amyloidosis. However, the confirmation of the type of amyloid on tissue biopsy requires staining with antibody to κ, λ, or transthyretin or serum amyloid protein A, but these are not widely available.

The diagnosis of familial amyloidosis requires demonstration of abnormal transthyretin. Isoelectric focusing of the serum identifies the variant forms of transthyretin. Further, the distinction between familial and senile amyloid requires genetic studies for mutation in transthyretin gene (the senile amyloid being normal transthyretin).

Further, the quantitative studies of volume of amyloid deposit have been described. The amyloid P scan utilizes labeling of amyloid P component (which is present in all amyloid fibrils) with 123-iodium, and such quantitations have been found useful for monitoring therapy. Unfortunately, these scans are unsuitable for cardiac amyloidosis. Recently, the measurement of amyloidogenic serum-free light chain (FLC) concentration has been utilized as a measure of amyloid load. A 50% decrease in FLC is associated with stabilization or regression of amyloid deposits, with potential for extended survival.

Prognosis

Majority of deaths in patients with systemic amyloidoses include secondary to cardiac involvement. The major cardiac prognostic factors are clinical CHF, LV ejection fraction less than 50% and ventricular septal thickness more than 15 mm. Syncope, exercise capacity, VO₂max, and right ventricular dilatation are also shown to be independent factors determining survival. The prognosis depends on the type of amyloidosis, and the number and extent of organ involvement. AL amyloidosis has the worst prognosis with a median survival of one to two years. The survival in familial transthyretin amyloidosis varies with the type of mutation and the age of diagnosis, but may be as high as 15 years.

Recently, prognostication using serum markers like ANP and brain natriuretic peptide (BNP) have been utilized. A N-terminal pro-BNP level of 152 pmol/L indicates heart involvement, and is a marker of myocardial dysfunction and of heart toxicity caused by amyloidogenic light chains. Cardiac troponins (Trop T and Trop I) are modestly elevated in patients with advanced cardiac amyloidosis. Trop T provides a better prediction of survival than does Trop I. Median survival was worse for patients with detectable levels of Trop T than that for those with undetectable values (6 months v 22 months). Recently, troponins and pro-BNP are incorporated into a staging system for assessing the eligibility for stem cell transplantation, and both identify high risk group.

Treatment

Symptomatic treatment: Management of cardiac failure in patients with amyloidosis is difficult. Usually larger doses of diuretics are required and careful monitoring for dyselectrolytemia is essential. Digoxin avidly binds to amyloid fibrils and drug toxicity may occur at therapeutic levels. Digitalis should only be used in selected patients in atrial fibrillation to control heart rate. High incidence of sudden death in patients treated with digoxin has been reported. Angiotensin-converting enzyme inhibitors should be used cautiously because of orthostatic hypotension and associated renal disease. Calcium channel blockers bind to amyloid fibrils, and therapy with these agents results in exacerbation of heart failure. Nitrates are effective in relieving angina. Utility of β-blockers is not known in amyloidosis. Midoaldrine, an alpha agonist, is very useful for orthostatic hypotension in amyloidosis. Aspirin and anticoagulation are indicated in atrial fibrillation, atrial dilation, atrial standstill, and documented thromboembolism. However, anticoagulants should be used cautiously as systemic amyloidosis may be
associated with coagulation abnormalities predisposing to clotting or bleeding.27

Patients with symptomatic bradycardia should receive a permanent pacemaker implantation. In contrast to AL amyloidosis, familial and senile amyloidosis are associated with a high prevalence of conduction disturbances. The atrial and ventricular pacing threshold may be higher than usual in some patients.42 Treatment of ventricular arrhythmia in cardiac amyloidosis is not standardized, and the safety of antiarrhythmic agents is not well known. Perhaps an implantable defibrillator may be indicated as in other cardiomyopathies, but the decision is more difficult due to poor prognosis in amyloidosis.

**Specific treatment:** Resolution of secondary amyloidosis with the control of the offending inflammatory disorder in the secondary (AA) amyloidosis led to the hope that amyloidosis may be treatable, if diagnosed before the advent of irreversible organ damage.44 Progress in the treatment of multiple myeloma has led to similar therapy for patients with primary (AL) amyloidosis as both are basically similar disorders. After many painstaking trials, high-dose melphalan with autologous stem cell therapy (ASCT) has shown remarkable success in selected patients of primary amyloidosis.64,65 In a recent case-control study involving 63 patients, high-dose melphalan with ASCT was associated with better 4-year survival rates (71%) than conventional therapy (41%).66

However, patients with cardiac amyloidosis do not tolerate high-dose melphalan with ASCT therapy.67 A procedural mortality of 20% or more is reported, and the mortality rises to almost 100% in patients with advanced, symptomatic cardiac amyloidosis.64 With high-dose melphalan, a 20% occurrence of second malignancy is reported. Further, the benefits are seen after a median duration of 1 year and many cardiac patients may not survive that long enough.64 An aggressive approach of heart transplantation followed by ASCT has been tried.68 The studies of high-dose melphalan with ASCT have included relatively less sicker patients and with the proposed selection criteria, only a minority of AL amyloidosis patients are eligible for high-dose melphalan with ASCT.64 Alternatively, oral melphalan and prednisolone in patients too sick to undergo stem cell transplant have also been found useful.69 It is remarkable that 5% of patients with AL amyloidosis have survived beyond 10 years with chemotherapy.70 In another multicentric trial of primary amyloidosis involving 93 patients, high-dose dexamethasone induction, followed by dexamethasone and alpha interferon maintenance therapy had achieved hematologic complete remissions in 24% of patients and resulted in a median survival of 31 months.71

These studies have shown that amyloidosis is not an inert, irremovable substance, and a decrease in as much as 2 mm septal thickness in patients was associated with remarkable symptom relief. In patients with severe CHF, heart transplantation has been done, but the results are less than encouraging.72 Recurrence of amyloid in the transplanted heart is seen73 and peri-procedural mortality remains high (20%). It may be considered after careful selection of many variables. Of course, liver transplantation that supplies normal transthyretin (instead of mutant thyretin synthesized in patients with TTR amyloidosis) is the treatment of choice for familial amyloidosis.44 Several hundreds of patients have undergone this procedure with relief of symptoms. Intriguingly, sometimes cardiac amyloidosis has progressed after liver transplantation in these patients74 possibly due to precipitation of normal transthyretin-induced amyloid on the seeding set up by the mutant variety previously.75

With better understanding of the mechanisms of amyloidosis, several other lines of therapy are being tried.6 Disintegration of amyloid fibril by compounds like iodinated anthracycline 4-iodo-4-deoxydoxorubicin has been shown in experimental animals and in a small clinical study.76 Decreasing the fibrillogenesis of amyloid precursor protein using small molecules that bind to the protein or interfere with the process of aggregation are being actively pursued. Further, drugs that displace fundamental cofactors important for amyloidogenesis like serum amyloid P (a substance found in all amyloid fibrils in addition to the precursor proteins) favors the dissolution of amyloid fibrils. Phase II trials of such compounds have recently been completed.6

Immunotherapy using monoclonal antibodies against appropriate peptides may inhibit the process of amyloidogenesis or increase its resorption.77 Trials with amyloid reactive antibodies are being planned. Immunomodulation with thalidomide is not tolerated by patients with primary amyloidosis.78 Etanercept, a tumor necrosis factor α-antagonist is well tolerated, but produces limited benefits in cardiac amyloidosis.79 Etanercept therapy resulted in a 10% decrease in septal thickness in a few patients. A combination of these approaches is expected to bring changes in the management of patients with cardiac amyloidosis.

However, the majority of patients with cardiac amyloidosis do not benefit from these therapies. An earlier diagnosis, when the disease burden is not high and the organ damage is not severe, may allow greater benefits of treatment. In conclusion, increased awareness of cardiac amyloidosis is warranted for early diagnosis. Advances in the understanding and treatment of amyloidosis are raising expectations of curative therapy in the future.
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Statins: Much More than Just A Lipid-Lowering Therapy

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Clinical studies have clearly demonstrated that reduction of plasma cholesterol, particularly cholesterol transported in low-density lipoproteins (LDL), lowers the risk of cardiovascular events for both primary and secondary prevention. Significant cholesterol reductions may be produced by the 3-hydroxy-3-methylglutaryl (HMG)-CoA reductase inhibitors, commonly named as statins. It is implicit that the beneficial effect of statins on coronary events is related to their hypocholesterolemic properties. However, the immediate product of HMG-CoA reductase, mevalonic acid, is not only the substrate for cholesterol synthesis but also the precursor of isoprenoids and other metabolites involved in different cellular pathways of atherogenesis and thrombosis. As a consequence, statins have the potential to result in pleiotropic effects, which are independent of cholesterol reduction and may explain many of the direct antiatherosclerotic and antithrombotic properties of these compounds.

Better understanding of the various pleiotropic effects of statins has prompted a new surge of interest in their use to treat and/or prevent a wide range of chronic and life-threatening disorders. Among the disorders targeted for statin therapy are ventricular arrhythmias, peripheral arterial disease (PDA), idiopathic dilated cardiomyopathy, cancer, osteoporosis, and even depression. Their effectiveness in treating these and other disorders suggest that the benefits of statins may not be limited to cholesterol lowering and that indications for the drugs’ use may extend to patient populations not considered traditional candidates for this therapy.

Statins as Antiarrhythmic Therapy

Recently, it has been proposed that statins reduce the incidence of arrhythmias in patients with atherosclerotic heart disease. According to a substudy of the Antiarrhythmic Versus Implantable Defibrillators (AVID) trial, in patients with atherosclerotic heart disease treated for ventricular tachycardia/ventricular fibrillation (VT/VF) with implantable cardioverter defibrillators (ICDs), the use of statins and other lipid-lowering agents (e.g. fibric acid derivatives and bile acid resins) significantly reduced the probability of VT/VF recurrence. In addition, lipid lowering therapy was associated with significant reduction in both cardiac mortality and all-cause death in a larger cohort of patients treated with either ICDs or antiarrhythmic drug therapy.

A recent study suggests that the antiinflammatory effects of statins can reduce the recurrence of atrial fibrillation (AF) in patients who undergo successful cardioversion. This study was based on the hypothesis that inflammation, evidenced by high levels of C-reactive protein, can induce AF and promote its persistence. Siu et al. found that after 2 years of follow-up, patients treated with statin therapy for high cholesterol had a significantly lower AF recurrence rate than the patients not on lipid lowering therapy (40% vs. 84%, respectively; p=0.007). The benefits observed in patients on statin were observed early, and persisted throughout the follow-up period.

The results of the above studies do not necessarily confirm a direct antiarrhythmic effect associated with statin therapy. However, both groups of authors attribute their findings to the slowing of atherosclerotic plaques, which lowers the risk of plaque rupture, “thereby preventing the ischemia-induced electrophysiologic effects that predispose to VT/VF.” Further, as AF in patients with coronary artery disease (CAD) is proposed to be caused by atrial ischemia, it is possible that in these patients, the beneficial effect of statin therapy in preventing AF may be mediated through its effects on the progression of CAD. Also, in addition to this indirect antiarrhythmic effect, statins may exhibit direct antiarrhythmic effects by modulating the fatty acid composition and physiochemical properties of cell membranes, with resultant alterations in transmembrane ion channel properties. Moreover, statins have multiple pleiotropic effects (independent of lipid lowering). They decrease the messenger ribonucleic acid (mRNA) levels for interleukin-8, monocyte chemotactant protein-1, plasminogen activator inhibitor-1, endothelin-1 and increase the levels of thrombomodulin and endothelial nitric oxide synthase (eNOS). Statins also act on G-proteins (small GTPases, Rho, Rac, Cdc 42). This
leads to reduced eNOS mRNA degradation and higher eNOS protein levels and activity.\textsuperscript{14} In addition, by scavenging free radicals and reactive oxygen species statins prevent nitric oxide degradation and preserve endothelial function.\textsuperscript{14} All these mechanisms result in improved endothelial function leading to coronary vasodilation, increased coronary blood flow and less myocardial ischemia with reduced likelihood of AF.

**Statins and Peripheral Arterial Disease**

According to a recent randomized, double-blind, parallel-design study by Mohler et al.,\textsuperscript{15} atorvastatin achieved greater improvement in pain-free walking time and participation in physical activity in patients with intermittent claudication than did inactive placebo.\textsuperscript{15} The authors assessed the effects of low- and high-dose atorvastatin on maximal walking time (MWT). They randomised 354 patients with intermittent claudication caused by PAD to 1 of 3 regimens: atorvastatin 10 mg/day, atorvastatin 80 mg/day, or placebo for 1 year.

After 1 year of atorvastatin therapy, MWT did not change significantly. However, the time in which patients could walk without pain improved by 63\% (81±15 sec) in patients receiving atorvastatin 80 mg/day, whereas the placebo group exhibited only 38\% improvement (39±8 sec), which was similar to the group receiving atorvastatin 10 mg/day. In post hoc analyses performed to determine whether smoking status or LDL-cholesterol (LDL-c) influenced the results, investigators found that neither variable had a response in overall MWT or pain-free walking time. They noted, however, that there was a slight trend toward greater improvement in patients with LDL-c levels >123 mg/dl. According to investigators, such improvements in pain-free walking time are consistent with those achieved with other approved pharmacotherapies.

Physical activity questionnaires reported significant improvement in physical activity with both doses of atorvastatin compared with placebo, but no significant differences were seen between the groups on the quality-of-life questionnaires. Although not adequately powered to assess the effect of atorvastatin on vascular events in patients with PAD, fewer vascular events occurred in the atorvastatin group versus placebo (1.3\% v. 7.9\%). Mohler et al.\textsuperscript{15} attributed their findings to several potential mechanisms, including a reduction in plaque size associated with statins, which may improve blood flow in the large arteries of the legs, and an increase in endothelium-dependent vasodilation.

In another randomized controlled trial, McDermott et al.\textsuperscript{16} demonstrated that, in persons with and without PAD, statin use is associated with superior leg functioning compared with no statin use, independent of cholesterol levels and other potential confounders. Their findings support the findings of the Scandinavian Simvastatin Survival Study (4S) which concluded that subjects randomized to simvastatin had a 38\% reduction in new or worsening claudication compared with subjects randomized to placebo over a median follow-up of 5.4 years (p=0.008).\textsuperscript{17}

The beneficial effects of statins in PAD may be attributed to increased production of nitric oxide in the endothelium, which has local vasodilatory properties in addition to antithrombogenic, antiproliferative, and leukocyte-adhesion inhibiting effects.\textsuperscript{18,19} Other mechanisms by which statins favorably influence lower limb ischemia include enhancement of endothelium-dependent relaxation,\textsuperscript{20} inhibition of platelet function,\textsuperscript{21} and inhibition of endothelin-1, a potent vasoconstrictor and mitogen.\textsuperscript{22} Reduction of vascular inflammation may be an additional mechanism by which statins are associated with better functioning in patients with PAD. Statin-associated reduction of inflammatory cytokines could improve blood flow, regress atherosclerosis, or improve end-organ function (such as skeletal muscle).\textsuperscript{23}

**Statins and Non-ischemic Cardiomyopathy**

The antiinflammatory properties of statins may confer greater benefit than just reducing the risk of AF. The results of a recently published randomized controlled trial by Node et al.\textsuperscript{24} suggest that the antiinflammatory effects of statin therapy result in improved neurohormonal imbalance and cardiac function and may benefit patients with symptomatic, non-ischemic dilated cardiomyopathy. The study involved 63 patients (average age, 54 years) with symptomatic non-ischemic dilated cardiomyopathy [New York Heart Association (NYHA) class II-IV; left ventricular ejection fraction (LVEF) <40\%] who were randomized to either simvastatin (5 mg/day, increased to 10 mg/day at 4 weeks; n=24) or placebo (n=27). Patients with a history or evidence of ischemic heart disease were excluded from the study.

Over the course of 14 weeks of treatment, the use of simvastatin was associated with significantly improved functional capacity compared with placebo (39.1\% v. 16\% of patients had an improved functional status; p<0.01). Reductions in NYHA class also translated into significant improvements in LVEF from baseline to follow-up (34\%±3\% to 41\%±4\%; p<0.05), which were predominantly due to a
decrease in LV end-systolic volume. Investigators reported that there were positive correlations between changes in ejection fraction and reductions in circulating inflammatory cytokines, suggesting that "statins may improve cardiac function, in part, by modulating the inflammatory state."

These findings, according to investigators, indicate that statins may be therapeutically useful in patients with non-ischemic congestive heart failure in whom statins may not otherwise be indicated.24

**Statins and Neuroinflammatory Disorders**

Clinically, there is emerging evidence that statins have beneficial effects in patients with multiple sclerosis, Alzheimer's disease, and ischemic stroke.25 Recent studies indicate that statins have immunomodulatory properties,25,26 statins decrease the migration of leukocytes into the central nervous system, inhibit major histocompatibility complex class II and costimulatory signals required for activation of proinflammatory T cells, induce a T(H)2 phenotype in T cells, and decrease the expression of inflammatory mediators in the central nervous system, including nitric oxide and tumor necrosis factor alpha.25,26 These immunomodulatory effects can either inhibit or reverse chronic and relapsing experimental autoimmune encephalomyelitis, a model of multiple sclerosis,25,27,28

Data from epidemiologic trials indicate that statins may have some protective effect against the development of Alzheimer's disease.29 However, at present, available evidence does not lend credence to the use of statins in the general non-demented population without hyperlipidemia.

**Statins and Psychological Well-Being**

Challenging the premise that the use of statins increases the risk of depression, two recent studies have associated long-term use of statin with a reduced risk of depression in patients with CAD.30,31 Young-Xu et al.30 assessed the psychological well-being of 590 patients with underlying CAD who were classified into groups according to frequency of statin use (continuous statin use (n=140), intermittent statin use (n=219), or no use of any cholesterol-lowering drugs (n=231).30 The mean age at entry for the 3 groups was 64, 66, and 70 years, respectively. At study enrolment, the researchers recorded the patients' sociodemographic, psychological, and clinical status. Patients completed annual follow-up questionnaires, including the Kellner Symptom Questionnaire, which is used to measure depression, anxiety, and hostility.

After an average follow-up of 4 years (maximum follow-up, 7 years), comparison of psychometric scores between patients using statins continuously and patients not using cholesterol-lowering drugs showed that statin use was associated with lower risk of abnormal scores for depression, anxiety, and hostility. Investigators also noted that intermittent statin use was not associated with the same beneficial effects. In addition, the risk of mental illness continued to decline with each additional year of treatment. The progressive reduction observed in continuous statin users over the 7-year study period also seemed to be independent of the cholesterol-lowering effect of the drug or baseline cholesterol levels. Although it requires additional study, Young-Xu and colleagues hypothesize that the "penetration of the blood-brain-barrier by the lipophilic statins accounts for most of the observed impact on psychological well-being."30

The findings of another study yielded results similar to those reported by Young-Xu and colleagues. Yang and colleagues31 found that statin use was associated with reduced risk of depression, especially in long-term users and in patients with pre-existing CAD. These investigators identified patients with newly treated depression, who needed either hospitalization or referral, and patients with first-recorded diagnosis of suicidal behavior. They found that neither lipid-lowering therapy (LLT) nor untreated hyperlipidemia was associated with an increased risk of depression. In fact, the risk of depression actually decreased with statin therapy; risk of depression was 60% less in individuals using statins than in hyperlipidemic individuals not using LLT. The use of non-statin LLT yielded a similar, but weaker effect. In addition, the risk of suicidal behavior in individuals using statins did not differ significantly from the risk in other groups, according to the authors.

The investigators observed that use of statin was inversely associated with depression but such an association was not likely to be directly causal because there is no known pharmacological mechanism for this effect. However, they suggested that a possible explanation could be an indirect effect of statins on the risk of depression through improved quality of life due to decreased incidence of cardiovascular events or more health consciousness and compliance among patients having longer lipid-lowering treatment.31

**Statins and Cancer**

Statins have been shown to inhibit proliferation and to induce apoptosis in a variety of tumor cells.32 They have
also been found to display antitumor effects against melanoma, mammary carcinoma, pancreatic adenocarcinoma, fibrosarcoma, glioma, neuroblastoma, and lymphoma in animal tumor models resulting in retardation of tumor growth, and/or inhibition of the metastatic process. In pre-clinical studies statins have also been demonstrated to potentiate the antitumor effects of some cytokines and chemotherapeutics. The molecular mechanisms underlying antitumor activity of statins have not been fully elucidated but interference with the function of Ras and Rho family GTPases, inhibition of the activity of certain cyclin-dependent kinases (CDK), and activation of CDK inhibitors, all seem to participate in this activity. Phase I trials of statins in humans have demonstrated myotoxicity as their main dose-limiting toxicity, and phase II trials in various tumor types are ongoing to evaluate their efficacy.

Future directions in the development of the statins as anticancer agents include combinations with chemotherapeutic or other molecular-targeted agents, combinations with radiotherapy, maintenance therapy in minimal disease status, and as chemopreventive therapy.

Statins and Osteoporosis

Statins have been linked to a reduction in the incidence of fractures in elderly patients. In a recent study, Bauer et al. analyzed statin use and fracture rates in 4 large prospective studies of older women taking statin therapy for hyperlipidemia (the Study of Osteoporotic Fractures, the Fracture Intervention Trial, the Heart and Estrogen/Progestin Replacement Study, and the Rotterdam Study). They also conducted 2 cumulative meta-analyses consisting of data from 8 observational studies and 2 clinical trials that reported statin use and documented fractures.

The investigators found interesting, yet somewhat conflicting results. After adjusting for multiple factors, such as age, body mass index, and estrogen use among statin users in each of the 4 prospective studies, a trend toward fewer hip and non-spine fractures was observed. Similar reductions in risk were reported in the meta-analysis of observational studies; statin use was associated with an estimated 57% reduction in hip fracture, and an estimated 31% reduction in non-spine fracture. However, these proposed protective effects of statins were not observed in the meta-analysis of clinical trials. Based on their findings, investigators called for controlled trials specifically designed to test the effect of statins on skeletal metabolism and fracture.

Statins and Age-Related Maculopathy

Age-related maculopathy (ARM) is the leading cause of irreversible vision loss among older adults in the Western world. Based on the presence of similar risk factors, some suggest that the pathophysiology of ARM and cardiovascular disease have similar causal pathways and, therefore, both groups of patients may benefit from the same drug treatment. Two recent studies assessing the impact of statin therapy in patients with ARM draw opposing conclusions.

Results from a nested case-control study suggest that statin use is associated with a significant risk reduction of ARM. In their study, McGwin and associates identified 550 incident cases of ARM and compared them to 5500 age-matched patients (controls). Compared with controls, ARM patients had a significantly higher incidence of diabetes, hypertension, cardiovascular and cerebrovascular disease; however, there were no differences between the 2 groups with respect to lipid metabolism disorders or arterial disease. Investigators found that 70% of ARM patients were less likely to have received and filled a statin prescription relative to controls, regardless of whether statin use was current or occurred more than 6 months before the ARM diagnosis. In addition, the results remained consistent after adjusting for other medical conditions, such as those listed above. Similar findings were noted when assessing non-statin LLT.

Compared with non-statin LLT, the use of only statins was associated with a significant risk reduction; the same results held true when statin and non-statin users were combined, but there was no significant association for non-statin users alone. Interestingly, with the exception of cardiovascular and cerebrovascular disease, the risk-reduction effects of statin therapy on ARM were stronger in the presence of an existing medical condition than in its absence. However, the investigators cautioned against presuming this association to represent a cause-and-effect relation; future research will also be required to address this issue. On the other hand, an earlier study conducted by van Leeuwen and colleagues concluded that the use of LLT did not change a patient’s risk of developing ARM. Their conclusions were based on data collected from 4822 patients who were followed at mean intervals of 2.0 and 6.5 years. Of these patients, 457 used cholesterol-lowering drugs for ≥1 day, and 419 incident cases of ARM were identified throughout the course of the study.

Compared with patients who had never used a cholesterol-lowering drug, the risk of ARM did not differ for those who had used cholesterol-lowering drugs at any
time, be it for 1 month, 1-12 months, or > 1 year. Based on their findings the authors suggested that the lack of an association between LLT and ARM makes a protective effect of statins unlikely.

Conclusions

Statins are currently the most effective method to pharmacologically decrease total plasma cholesterol levels. Apart from the well known LDL and cholesterol lowering effect, statins have been postulated to exert beneficial effects due to so-called ‘pleiotropic’ or ‘non-lipid’ effects. However at present although the clinical implications of these beneficial ‘non-lipid’ effects seem promising yet properly designed, large, multi-center, prospective, controlled trials are needed to validate the use of statins for indications other than primary and secondary prevention of vascular diseases.

References

Mortality and Morbidity of Acute ST Segment Elevation Myocardial Infarction in the Current Era

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Department of Cardiology, Christian Medical College, Vellore

Background: The mortality rate of acute myocardial infarction has come down considerably in the past three decades. In view of paucity of literature on this issue, present study was done to find out the in-hospital mortality and 30-day event rate in patients with acute ST segment elevation myocardial infarction presenting to a tertiary care hospital in India.

Methods and Results: Consecutive patients (n=1320) with the diagnosis of acute ST segment elevation myocardial infarction admitted in our institution were included in this study. The in-hospital mortality and 30-day event rates (mortality, reinfarction, recurrent angina and heart failure) were analyzed. The mean age of study population was 56±13 years. There were 1106 (83.8%) males and 214 (16.2%) females; 569 (43.1%) patients were smokers, 504 (38.2%) patients had hypertension, 531 (40.2%) patients were diabetic and 154 (11.7%) patients had past history of myocardial infarction. Anterior wall infarction was present in 752 (57%) patients, 517 (39.1%) patients had inferior wall infarction, 324 (39.6%) patients had associated right ventricular or posterior wall infarction and 51 (3.9%) patients had antero-inferior infarction; 1093 patients (82.8%) received thrombolytic therapy while 227 patients were not thrombolysed due to various reasons. Of the total 1320 patients, 223 (16.9%) patients died during in-hospital stay while 1097 patients were discharged from the hospital in stable condition after a mean stay of 5.3±3.4 days. Thirty-day event rates of death, reinfarction and recurrent angina following hospital discharge was 18.8% (134/715 patients) and 36 (5%) patients presented with heart failure.

Conclusions: The in-hospital mortality rate of acute ST segment elevation myocardial infarction in a tertiary care hospital is 16.9%, which is higher compared to reports from the West. (Indian Heart J 2004; 56: 210–214)

Key Words: Myocardial infarction, Mortality, Coronary artery disease
Methods

Between March 1999 and July 2003, patients who were diagnosed to have acute STEMI and admitted to our hospital were included in this study in a prospective manner. Patients who had non-ST elevation myocardial infarction (MI) and unstable angina were excluded from the present analysis.

Patients’ baseline characteristics such as age, gender, hypertension, diabetes mellitus, and smoking status were recorded. History of previous MI and angina pectoris were also assessed. All patients received standard clinical care including monitoring of vital functions in a coronary care unit during the initial hospital stay and thrombolytic treatment was given as per eligibility. We used 1.5 million units of streptokinase over 1 hour for the thrombolytic therapy.

Following criteria was used for the definition of STEMI: chest pain of >20 min duration and ST segment elevation >1 mm in at least two standard limb leads or >2 mm in at least two contiguous precordial leads or the presence of left bundle branch block in the electrocardiogram (ECG). STEMI was later confirmed by the elevation of cardiac enzymes either with CK-MB or troponin-I.

Besides in-hospital mortality, the occurrence of reinfarction, development of heart failure, cardiogenic shock and other important in-hospital complications were recorded. At 30-day follow-up, outcome variables recorded were death, reinfarction, recurrent angina and heart failure.

The diagnosis of post-infarction angina was based on presence of chest pain suggestive of ischemia occurring 24 hours after infarction while the reinfarction was defined as re-elevation of CK-MB above the upper limit of normal and increase by at least 50% of the previous value or by the presence of new Q waves in the ECG. Diagnosis of heart failure was based on Framingham criteria.

Statistical analysis: All data were analyzed using SPSS Software (7.5 version). Categorical variables were compared by the likelihood ratio \( \chi^2 \) test or Fisher’s exact test. Continuous variables are presented as mean ± SD and were compared by one-way ANOVA or unpaired t test. Baseline demographic features, treatment received, inhospital and 30-day event rates were evaluated using logistic regression. A probability value of <0.05 was considered statistically significant.

Results

Clinical presentation: Over a 4-year period, 1320 patients were admitted to our institution with a diagnosis of acute STEMI. Their clinical and demographic characteristics are summarized in Table 1. Most of the patients were male with a mean age of 56±13 years. The mean duration between symptom onset and hospital admission was 10.8±12.4 hours. Females presented to hospital later than the males; 53% of the males presented to hospital within 6 hours of onset of symptoms, while 42% of females were admitted to hospital within 6 hours of chest pain. Prevalence of diabetes mellitus and hypertension was higher in females than in males, while less number of females had previous history of MI.

| Location of infarction, Killip class and therapy: More than half of our patient population had anterior wall MI; of that almost equal proportion of patients had anteroseptal and extensive anterior wall MI; 517 (39.2%) patients presented with inferior wall MI of which 324 (24.5%) patients had associated right ventricular or posterior wall involvement and 51 (3.9%) patients had antero-inferior MI. Males had high prevalence of anteroseptal MI while inferior wall with associated right ventricular MI was common in females. Most of the patients presented with Killip class I, while 103 patients presented with Killip class IV. Overall 82.8% of patients received thrombolytic therapy and 7 patients underwent percutaneous coronary intervention as an alternative to thrombolysis (Table 2).

| In-hospital events: The mean duration of hospital stay was 5.4±3.2 days for anterior wall MI patients, 5.1±3.7 days for inferior wall MI, and 6.1±3.2 days for patients who had antero-inferior MI; 223 (16.9%) patients died during hospital stay. The mortality was 25.2% for females, which was significantly higher when compared with males.

<table>
<thead>
<tr>
<th>Table 1. Baseline characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Variables</td>
</tr>
<tr>
<td>Age (years)</td>
</tr>
<tr>
<td>Time delay from onset of symptoms to hospitalization (hours)</td>
</tr>
<tr>
<td>Overall</td>
</tr>
<tr>
<td>&lt; 6 hours</td>
</tr>
<tr>
<td>7-12 hours</td>
</tr>
<tr>
<td>&gt;13 hours</td>
</tr>
<tr>
<td>Smoking</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
</tr>
<tr>
<td>Hypertension</td>
</tr>
<tr>
<td>Past MI</td>
</tr>
<tr>
<td>Family history of IHD</td>
</tr>
</tbody>
</table>

Values in parentheses are percentages

* Statistically significant; MI: myocardial infarction; IHD: ischemic heart disease
(15.3%). The main cause of death was cardiogenic shock/pulmonary edema or pump failure in both male and females followed by cardiac asystole. Males had higher incidence of death due to ventricular arrhythmias than females. Other important in-hospital complications are shown in Table 3. In the multivariate analysis, the most significant variables for the mortality were, cardiogenic shock and Killip class III and IV.

30-day follow-up: 30-day follow-up data was available for 715 patients. Of these, 124 (17.3%) patients presented with recurrent angina, 36 (5%) patients developed heart failure, and 9 (1.3%) patients had reinfarction. One patient had died during this period.

Discussion

In our study, mortality rate during hospitalization with acute STEMI was 16.9%. Though this is considerably higher than what has been reported from randomized clinical trials, it compares well with the observational data from the West.7-10 We feel that there is an urgent need at the national level to bring this mortality further down.

Symptom onset to hospitalization: In our study, there was an inordinate delay in presenting to the hospital; the mean duration between symptom onset and hospitalization was 10.8±12.4 hours. This delay was mainly due to lack of emergency transport facilities and failure to recognize the seriousness of the problem. In the Western studies, the mean duration of delay ranges from 3 to 4 hours. In the GRACE registry and GUSTO IIb trial, the mean time delay was only 2-4 hours.11-13 Hence there is a need to improve transport facilities and patient education in our country to reduce this time delay.

Duration of hospital stay: The duration of hospital stay with STEMI was 5.3±3.4 days in our study, which is comparable with the data from other developed countries. In ENACT study,14 the total hospital stay was 7.9 days in UK/Ireland and 12.6 days in Eastern Europe.

In-hospital mortality: The overall in-hospital mortality rate was 16.9% in our study. In the randomized trials on fibrinolysis for STEMI,4,6 the reported mortality ranged from 4% to 7%. As per CREATE registry15 data from India, mortality rate was 7.9% at tertiary care centers for acute coronary syndrome which included both, patients with

**Table 2. Location of myocardial infarction and therapy**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Overall n (%)</th>
<th>Males n (%)</th>
<th>Females n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Killip class</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>772(58.5)</td>
<td>600(61.2)</td>
<td>172(52.3)</td>
</tr>
<tr>
<td>II</td>
<td>320(24.2)</td>
<td>253(26.3)</td>
<td>67(21.1)</td>
</tr>
<tr>
<td>III</td>
<td>125(9.5)</td>
<td>105(11.0)</td>
<td>20(6.3)</td>
</tr>
<tr>
<td>IV</td>
<td>101(7.8)</td>
<td>78(8.3)</td>
<td>23(7.1)</td>
</tr>
<tr>
<td>Other therapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspirin</td>
<td>1225(92.8)</td>
<td>1032(93.3)</td>
<td>213(90.2)</td>
</tr>
<tr>
<td>ACE inhibitor</td>
<td>791(60.0)</td>
<td>665(60.1)</td>
<td>126(58.9)</td>
</tr>
<tr>
<td>Beta blockers</td>
<td>863(65.4)</td>
<td>729(65.9)</td>
<td>134(62.6)</td>
</tr>
<tr>
<td>Nitrate</td>
<td>430(32.6)</td>
<td>364(32.9)</td>
<td>66(30.8)</td>
</tr>
<tr>
<td>Heparin</td>
<td>886(67.1)</td>
<td>749(67.7)</td>
<td>137(64.0)</td>
</tr>
<tr>
<td>Temporary pacing</td>
<td>105(8.0)</td>
<td>81(7.3)</td>
<td>24(11.2)</td>
</tr>
<tr>
<td>ExtAWMI</td>
<td>1290(98.8)</td>
<td>986(98.9)</td>
<td>304(91.5)</td>
</tr>
<tr>
<td>PWMI</td>
<td>195(14.8)</td>
<td>163(14.7)</td>
<td>32(15.0)</td>
</tr>
</tbody>
</table>

**Table 3. Morbidity and mortality data**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Total n (%)</th>
<th>Males n (%)</th>
<th>Females n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality rate</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall mortality</td>
<td>223 (16.9)</td>
<td>169 (15.3)</td>
<td>54 (25.5)</td>
</tr>
<tr>
<td>Cause of death</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asystole</td>
<td>59(26.5)</td>
<td>41(24.2)</td>
<td>18(33.3)</td>
</tr>
<tr>
<td>VT/VF</td>
<td>91(40.8)</td>
<td>68(40.2)</td>
<td>23(42.6)</td>
</tr>
<tr>
<td>Mortality in age subsets (years)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤44</td>
<td>5/114 (4.4)</td>
<td>5/102 (4.9)</td>
<td>0/12 (0)</td>
</tr>
<tr>
<td>45-54</td>
<td>21/313 (6.7)</td>
<td>21/287 (7.3)</td>
<td>0/26 (0)</td>
</tr>
<tr>
<td>55-64</td>
<td>85/453 (18.8)</td>
<td>62/380 (16.3)</td>
<td>23/73 (31.5)</td>
</tr>
<tr>
<td>&gt;75</td>
<td>71/313 (22.7)</td>
<td>51/243 (21.0)</td>
<td>20/70 (28.6)</td>
</tr>
<tr>
<td>In-hospital complications</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LV dysfunction</td>
<td>324 (24.5)</td>
<td>263 (23.8)</td>
<td>61 (28.5)</td>
</tr>
<tr>
<td>Post-MI angina</td>
<td>176 (13.3)</td>
<td>148 (13.4)</td>
<td>28 (13.1)</td>
</tr>
<tr>
<td>Reinfarction</td>
<td>61 (4.6)</td>
<td>46 (4.2)</td>
<td>15 (7.0)</td>
</tr>
<tr>
<td>Infarct extension</td>
<td>39 (3.0)</td>
<td>32 (2.9)</td>
<td>7 (3.3)</td>
</tr>
<tr>
<td>Cardiogenic shock</td>
<td>38 (2.9)</td>
<td>34 (3.1)</td>
<td>4 (1.9)</td>
</tr>
<tr>
<td>VSD</td>
<td>13 (1.0)</td>
<td>11 (1.0)</td>
<td>2 (3.5)</td>
</tr>
<tr>
<td>VSD</td>
<td>21 (1.6)</td>
<td>16 (1.4)</td>
<td>5 (3.2)</td>
</tr>
<tr>
<td>Bleding</td>
<td>11 (0.8)</td>
<td>10 (0.9)</td>
<td>1 (0.4)</td>
</tr>
<tr>
<td>Percarditis</td>
<td>86 (6.7)</td>
<td>77 (7.0)</td>
<td>11 (5.1)</td>
</tr>
<tr>
<td>30-day event rates</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>556/715 (77.8)</td>
<td>482/615 (78.4)</td>
<td>74/133 (55.6)</td>
</tr>
<tr>
<td>Angina pectoris</td>
<td>124715 (17.3)</td>
<td>101/615 (16.4)</td>
<td>23/133 (17.3)</td>
</tr>
<tr>
<td>Heart failure</td>
<td>36/715 (5.0)</td>
<td>31/615 (6.4)</td>
<td>5/133 (3.6)</td>
</tr>
<tr>
<td>Reinfarction</td>
<td>9/715 (1.3)</td>
<td>7/615 (1.1)</td>
<td>2/133 (1.5)</td>
</tr>
</tbody>
</table>

Values in parentheses are percentages

*Statistically significant; VT: ventricular tachycardia; VF: ventricular fibrillation; LV: left ventricle; MI: myocardial infarction; MR: mitral regurgitation; VSD: ventricular septal defect

Values in parentheses are percentages

* Statistically significant; MI: myocardial infarction; ASMI: anteroseptal MI; ExtAWMI: extensive anterior wall MI; IWMI: inferior wall MI; RVMI: right ventricular MI; PWMI: posterior wall MI; ACE: angiotensin-converting enzyme.
unstable angina and AMI. However, in non-randomized trials, especially in the registry data, the reported mortality is usually higher. In a study published in Scotland,\textsuperscript{16} the case fatality following AMI was 22.2% in a group of 11,778 patients. In the MITRA and MIR registries data\textsuperscript{17} from Germany, the overall mortality was 15%.

**Gender and age:** Women had higher prevalence of hypertension, diabetes mellitus and higher in-hospital mortality than men (25.2% v. 15.3%, p<0.001). The demographic characteristics and mortality rate in females in our study match the report from Trappolini et al.\textsuperscript{18} In their study, the overall mortality rate during hospitalization was 24.4% for women and 13.2% for men; women were significantly older than men, had higher prevalence of hypertension and diabetes mellitus, and thrombolytic therapy was prescribed less often in them. In the MONICA project\textsuperscript{19} also diabetes mellitus was more common in women and they had higher in-hospital mortality (21.2% v. 12.7%). In our study, the in-hospital mortality in patients above 75 years of age was 32.3%. In the study by Ruiz-Bailen et al.\textsuperscript{20} the mortality was 17.7% in patients between age of 75-84 years and 25.8% in patients more than 84 years of age.

**Reasons for high mortality:** The higher mortality observed in our patients can have several reasons. Firstly, most of our patients received only thrombolytic therapy and primary percutaneous coronary angioplasty was done only in few patients. Secondly, our hospital being tertiary care center, there could be a referral bias in the enrolment of patients. Patients who are sicker may be referred from primary and secondary level hospitals to our institution. However, this higher mortality compared well with the observational data from the West.\textsuperscript{13}

**Post-infarct angina:** We have no data in our country regarding incidence of angina following MI. In our study, we found that 13% of patients had post-infarction angina and 5% had reinfarction. In GRACE registry, post-infarct angina was observed in 14% patients and 3% patients had reinfarction. In the SPRINT trial,\textsuperscript{21} the prevalence of post-infarct angina and reinfarction was 9% and 4% respectively. Thus, the incidence of post-infarct angina and reinfarction in our country is comparable to the published data.

**Cardiac failure:** Cardiac failure is one of the most important complications that is observed during the first month of MI. In our study, heart failure was observed in 24.5% of patients during hospital stay, while in the GRACE registry this was observed in 18% of patients. Spencer et al.\textsuperscript{22} reported heart failure in 20.4% of the 606,500 patients with AMI during hospitalization and 8.6% patients developed heart failure thereafter.

**30-day event rates:** In our study, 30-day event rates of death, reinfarction and recurrent angina following hospital discharge was 18.1%. In the Western studies, these outcomes were in the range of 4-22%\textsuperscript{,23,24} In a study by Capewell et al.\textsuperscript{25} the reported case fatality was 22.2% at 30-day, while the SPRINT trial reported a 30-day mortality of 10.8%.\textsuperscript{21}

**Limitations of the study:** The number of patients with STEMI in our study is very small compared to published trials from the West. Secondly, our data is only from one center from South, hence our results are not generalizable. We also had a number of patients lost to follow-up during the study period. The mean hospital stay was shorter in our study population due to early discharge of uncomplicated patients. It is likely that we might have missed a few mechanical complications like ventricular septal defect and papillary muscle rupture.

**Conclusions:** To the best of our knowledge, this is the first acute STEMI segment elevation myocardial infarction registry data from a single tertiary care center in India looking at the in-hospital mortality and 30-day event rates. Though our results are comparable to the Western data, there is an urgent need to bring down this mortality. Enormous effort is, therefore, required to educate the public regarding heart attacks and there is an urgent need to establish heart attack centers/hospitals across the country that serve only the MI patients. We still need large well-designed prospectively performed registries in patients with AMI.

**Acknowledgements**

We are extremely thankful to Mr. Selva Raj for helping and guiding us in statistical analysis.

**References**

Mahaim and Winston first described tracts connecting the atrioventricular (AV) node and the ventricular myocardium as well as discrete connections from fascicles to the ventricles. Mahaim conduction is characterized by gradual increase in the AV interval simultaneous with the development of a left bundle branch block (LBBB) and shortening of the His-ventricular (HV) interval in response to atrial overdrive pacing. It was long believed that Mahaim accessory pathways represent nodofascicular or nodoventricular connections. However, recent evidence from electrophysiologic studies, surgery and catheter ablation has established that right atriofascicular fibers crossing the tricuspid annulus are responsible for Mahaim conduction, while nodoventricular fibers are uncommon. Several reports have described the successful ablation of these pathways using radiofrequency (RF) energy. The present report describes the characteristics of automatic ‘Mahaim’ accelerated rhythm arising during the RF ablation of these pathways.

Methods

Study population: The study population comprised of 18 patients, who on electrophysiological testing had a pre-excited tachycardia of an LBBB pattern with short ventriculo-atrial (VA) and long AV intervals, and were found to have an accessory pathway exhibiting only antegrade conduction, with long antegrade conduction time and decremental conduction properties. There were 9 males and 9 females in age range 15 to 49 years (mean 28.2±12.4 years). None of the patients had structural heart disease on echocardiography.

Electrophysiological study: All patients underwent electrophysiological testing after an informed written consent. Quadrupolar catheters were placed in the right
ventricular (RV) apex, the His bundle (HB) position and, the high right atrium. A decapolar catheter was positioned in the coronary sinus. The HB catheter was used to record right bundle (RB) and HB potentials from distal and proximal poles, respectively. In case both could not be recorded, an additional catheter was introduced to record RB potentials.

Programmed electrical stimulation was performed using atrial and ventricular extrastimuli and overdrive pacing. An LBBB morphology tachycardia was inducible in all the patients. The criteria for the presence of Mahaim fiber conduction included (a) baseline antegrade pre-excitation with LBBB morphology or normal conduction (Fig. 1), (b) increasing ventricular pre-excitation associated with an increasing AV interval and a short HV interval with atrial incremental pacing or decremental atrial extrastimulation (Fig. 2) and, (c) a reciprocating tachycardia with the same LBBB pre-excitation morphology and the RB electrogram preceding HB activation during antegrade pre-excitation (Fig. 3). After the diagnosis of Mahaim accessory pathway was established, the mapping was performed using a 7 F steerable ablation catheter with a 4 mm tip (EP technologies or Cordis Webster).

The entire tricuspid annulus was mapped during sinus rhythm with position of catheter tip confirmed in left anterior oblique (LAO) and right anterior oblique (RAO) position.
projections. The Mahaim (M) potentials were carefully searched in all these areas. A Mahaim potential was considered as a discrete deflection between A and V with the interval between the accessory potential (AP) and V remaining constant during the AV delay produced by atrial pacing. If potentials were not recorded, then pacing was performed from several sites along the tricuspid annulus and the site with the shortest stimulus to delta interval was targeted for ablation. The distal insertion was targeted for ablation in one patient.

**Radiofrequency ablation:** RF energy was delivered at the site recording M potentials \( (n=15) \) or site with shortest stimulus to delta wave duration \( (n=3) \). The temperature was set at 65°C and the power at 50 W. The energy was applied during sinus rhythm for 10 sec and was continued for 60 sec only if extrasystoles or brief accelerated rhythm that probably originated in the accessory pathway (QRS morphology identical to fully pre-excited QRS complexes, early ventricular activation at RV apex and early retrograde activation of the right bundle) – labeled as ‘Mahaim’ automatic rhythm was noted. At the completion of the RF lesion, atrial/ventricular incremental pacing/extrastimulation were performed to look for Mahaim conduction or induction of other tachycardias.

**3-Dimensional electroanatomical mapping:** In a patient with two previously failed attempts at ablation, mapping was performed using 3-dimensional electroanatomical mapping system (CARTO™, Biosense Webster). The tricuspid annulus was tagged all around and a careful search for M potentials was attempted along the annulus. However, despite extensive mapping, potentials were not recorded at any site. The catheter was then positioned at distal RB, RV mid septum and RV apical sites and a ventricular activation map was constructed during atrial pacing. The site of earliest ventricular activation was then targeted for ablation.

**Results**

**Electrophysiological characteristics:** In all patients, the electrophysiological study revealed that the accessory pathway had an atrial origin located along the right free wall and right atria was a critical component of the macro reentrant circuit during tachycardia. An LBBB morphology tachycardia was inducible on atrial/ventricular extra-stimulation in all patients with RB potential preceding the HB potential.

Six additional narrow QRS tachycardia were induced in 5 patients (4 - AV nodal reentry tachycardia, 1 - orthodromic tachycardia with concealed left lateral accessory pathway and 1 - concealed right posteroseptal accessory pathway).

**Recording of accessory potentials:** Potentials consistent with accessory pathway activation were recorded in 15 of the 18 patients (Fig. 4). An accessory pathway origin was confirmed by demonstrating a constant relationship between the AP and subsequent QRS complex during antidromic tachycardia or atrial pacing. These potentials were sharp deflections with an isoelectric line between the AP and the ventricular electrogram, resembling the HB potential.

**Stimulus to QRS interval mapping:** In three patients where AP could not be recorded, pacing from the mapping catheter was performed all along the tricuspid annulus to reach a site with the shortest stimulus to QRS interval, which was then targeted for ablation. Ablation was not successful in any of these patients.

**Mapping of the distal insertion site:** The distal insertion site was mapped during atrial pacing using the 3D electroanatomical mapping in one patient. The earliest site was found to be on RV apico-septal region just beyond the RB potential. Several attempts at RF ablation at this site resulted in only temporary interruption of the accessory pathway conduction.
Radiofrequency catheter ablation: The accessory pathway was successfully ablated in 15 patients. The accessory pathway potentials were recorded in all these patients; the site of ablation was the tricuspid annulus. In the remaining 3 patients where potentials could not be recorded, ablation was unsuccessful despite using other mapping techniques including electroanatomical mapping.

Mahaim-accelerated beats or rhythm were noticed during RF energy delivery in all patients where potentials were recorded; the presence of this rhythm also correlated with a successful procedure (Fig. 5). The lesion was continued till it resulted in complete abolition of these accelerated beats. In 2 patients residual conduction was noted after completion of these lesions; however, another lesion at the same site resulted in complete interruption in both. In all patients where potentials could be recorded, the RF energy was delivered during sinus rhythm and was continued only if these accelerated beats were noticed within 10 sec of the delivery of RF energy.

The success of the ablation was demonstrated by absence of pre-excited complexes on atrial pacing and inability to induce the tachycardia or single ventricular echo complexes by atrial or ventricular stimulation. The location around the tricuspid annulus of the successful ablation site or the site recording the AP is illustrated in Fig. 6.

One patient had a concealed left lateral accessory pathway which was successfully ablated by the retrograde aortic approach. Another patient had a concealed right posteroseptal accessory pathway, which was successfully ablated near the os of the coronary sinus. AV nodal reentrant tachycardia was inducible with atrial extrastimulation in 4 patients, all of whom underwent an additional successful slow pathway ablation.

Follow-up: Long-term follow-up has ranged from 6 to 60 months (mean 18±16 months). There were no further episodes of tachycardia, and none of the successfully treated patients received anti-arrhythmic drug therapy. Of the 3 unsuccessfully treated patients, one is asymptomatic on verapamil, the other 2 have had occasional episodes on a combination of beta-blockers and disopyramide.

Discussion

There are several reports in the literature on ablation of Mahaim accessory pathway guided by accessory pathway potentials. In present series, a distinct accessory pathway activation potential was recorded close to the anterolateral, lateral and posterolateral tricuspid annular sites, this was a high frequency potential of short duration similar to HB potential. The recording of AP was associated with high degree of success similar to the experience described by McClelland et al. The catheter ablation of these pathways is not easy. As they do not conduct retrogradely, they have decremental conduction properties. So mapping during pre-excitation to look for a short AV interval is not useful and because they insert close to or into right bundle branch, targeting distal insertion may not eliminate tachycardia. The most significant breakthrough was made by McClelland et al with the description of accessory pathway potential mapping.
This report describes the presence of accelerated automatic beats during RF ablation in patients where the potentials were recorded with success. The accelerated and irregular rhythm that was observed during ablation had a morphology identical to that seen during pre-excitation. Similar observations have been reported by McClelland et al. in 11 of 23 patients,7 Grogin et al.12 in 1 of 4 patients and Sternick et al.13 in 4 of 5 patients. The response to heating of a decrementally conducting tract appears analogous to the junctional rhythm associated with ablation of the slow pathway. The mechanism of this rhythm is more of the nature of enhanced automaticity.

From a practical viewpoint the rhythm appears to be a sensitive and specific marker of success. Since Mahaim accessory pathways are uncommon, to compute the sensitivity and specificity of this rhythm may be difficult. On the other hand, this response to heating adds to the list of characteristics that atriofascicular pathways share with AV node. Both demonstrate long conduction times, decremental conduction in response to extrastimuli, Wenckebach pattern conduction block, and conduction block in response to adenosine. Mahaim-accelerated rhythm also assumes importance as a marker of success, like the junctional acceleration noted during the slow pathway ablation.

Conclusions: High success rates are obtained by using AP as the target for ablation of atriofascicular pathways. Occurrence of ‘Mahaim’ automatic rhythm during RF ablation seems to predict the success of the procedure.

References
Assessment of Right Ventricular Diastolic Function: Does It Predict Post-Operative Course in Tetralogy of Fallot

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**Background:** In some cases of tetralogy of Fallot the post-operative course is characterized by episodes of low cardiac output, elevated central filling pressures and prolonged ventilation and inotropic support. This may be due to impaired diastolic function of the right ventricle despite preservation of biventricular systolic function.

**Methods and Results:** Sixty-four consecutive patients (mean age 7.06±4.9 years) undergoing repair of tetralogy of Fallot were prospectively studied to assess right ventricular diastolic function. ‘Restrictive physiology’ was defined as presence of laminar antegrade diastolic pulmonary artery flow (A wave) throughout the respiratory cycle, which was coincident with atrial systole. Right ventricle restriction was present in 45/64 (70%, Group 1) patients and absent in 19/64 (30%, Group 2) patients. There was a marked inspiratory augmentation of the pulmonary artery A wave velocity, flow integral and duration. Transtricuspid flow revealed significantly lower peak E velocity, lower E/A ratio, shorter E deceleration time and higher A velocity time integral in those with right ventricular restriction. Biventricular systolic function and transmitral flow were normal in all patients. Those with restrictive physiology had significantly longer mean intropoe support duration, longer ventilation and chest drainage times. Correspondingly, the mean intensive care unit stay (56.7±9.3 v. 34.7±5.38 hours, p<0.01) and mean hospital discharge time (9.3±2.3 v. 6.2±0.5 days, p <0.001) was also significantly longer in group 1.

**Conclusions:** Right ventricular restriction (as seen by laminar antegrade diastolic pulmonary artery flow throughout the respiratory cycle) exists in a significant subset of patients with tetralogy of Fallot following operative repair. Following surgery, such patients have higher inotropic requirement, longer ventilation times and longer hospital stay.

**(Indian Heart J 2004; 56: 220–224)**

**Key Words:** Tetralogy of Fallot, Echocardiography, Diastolic function

In most cases of tetralogy of Fallot (TOF) the post-operative course is uncomplicated. However in some patients, the course is characterized by episodes of low cardiac output, elevated central filling pressures with consequent pleural effusions and ascites, and requirement of prolonged ventilation and inotropic support. Despite preservation of biventricular systolic function, impaired diastolic function of the right ventricle (RV) is considered to be responsible for such a clinical picture. It has been documented that abnormalities of RV diastolic function exist in some patients following operative repair of TOF.\(^1\)\(^,\)\(^2\) Often these abnormalities have been shown to be transient, and are known to resolve within a few weeks.\(^1\) The aim of the study was to prospectively study patients undergoing repair of TOF between January 2001–December 2002 and to assess the RV diastolic function by serial echocardiography performed immediate post-operatively and at 12 weeks, and see if it correlates with post-operative recovery.

**Methods**

All patients were studied with transthoracic imaging using a 5 or 7.5 MHz transducer interfaced with a Hewlett-Packard Sonos 5500 echocardiography system. An M-mode imaging of the left ventricular cavity was performed in all patients followed by a detailed pulsed Doppler examination which included: (i) transtricuspid and trans...
mitral flow characteristics at the level of the tips of the valve leaflets in apical 4-chamber view (ii) superior vena caval (SVC) Doppler profile (1-2 cm proximal to the RA) and (iii) pulmonary artery (PA) systolic and diastolic Doppler flow with the sample volume placed at the midpoint between the pulmonary valve leaflets and bifurcation. This included measurement of peak velocity, integral and duration of antegrade systolic and diastolic PA flow, and duration of pulmonary regurgitation (PR). PR was graded according to standard criteria. While recording the transtricuspid and transmitral flow, the respective E- and A-velocity, velocity time integral (VTI), deceleration time (EDT or ADT) and duration were noted in each case.

Measurements were taken for simultaneous ECG and respiratory motion recordings, with minimal filtering at a paper speed of 100 cm/s. Three consecutive inspiratory and expiratory cycles were recorded and analyzed by planimetry and the values were averaged. Assessment of SVC flows were made with special reference to presence or absence of retrograde diastolic flow.

**Definition of restrictive physiology:** This was defined as presence of laminar antegrade diastolic PA flow throughout the respiratory cycle, which was coincident with atrial systole (Fig. 1).

**Surgical technique:** All patients were operated by a single surgeon (NG), using median sternotomy with aortic and bicaval cannulation with right-angled canulae, SVC and IVC snuggers. All patients were cooled to 28-32°C and blood cardioplegia with external ice slush was used. Ventricular septal defect (VSD) closure and infundibular resection were performed through right atrium in all cases, using Dacron patch and continuous prolene. Main or branch PA enhancement was performed during re-warming without cross-clamp on beating perfused heart. Closure of patent foramen ovale (PFO) or atrial septal defect (ASD) was performed routinely.

**Results**

The study population included 64 patients (mean age 7.06±4.9 years, range 1-27 years; mean weight 17.3±4.9 kg, range 9-36 kg) of which 43 (74%) were males. A transatrial VSD closure with infundibular resection and pulmonary valvotomy was performed in all cases, while patch enhancement of main pulmonary artery was performed in 46/64 (72%) cases. No patients had a significant residual RV outflow tract obstruction (gradient >20 mmHg) or a residual intracardiac shunt following the surgery.

**Right ventricular restriction:** Defined as laminar antegrade diastolic PA blood flow coincident with atrial systole, present in both inspiration and expiration (Fig. 1), it was present in 45/64 (70%, Group 1) patients and absent in 19/64 (30%, Group 2) patients. The A wave in the PA flow (marker of RV restriction) accounted for 24-35% of the total antegrade PA Doppler flow integral. A significant inspiratory augmentation of the A wave velocity, VTI and A wave duration was observed consistently (Table 1). PR was noted in all 64 patients; it was trivial to mild in 58 (90%) patients, and moderate in 6 (10%) cases. The duration of PR was significantly shorter in those with RV restriction (248.6±48.5 ms) than those without it (298±21.7 ms) (Table 1).

**Table 1. Pulmonary artery Doppler characteristics in those with (Group 1) versus those without (Group 2) restriction**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Group 1</th>
<th>Group 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>A wave velocity (I)</td>
<td>0.46±0.13</td>
<td>NA</td>
</tr>
<tr>
<td>A wave velocity (E)</td>
<td>0.33±0.08</td>
<td>NA</td>
</tr>
<tr>
<td>A wave duration (I)</td>
<td>184.3±13.66</td>
<td>NA</td>
</tr>
<tr>
<td>A wave duration (E)</td>
<td>130.08±12.7</td>
<td>NA</td>
</tr>
<tr>
<td>A wave integral (I)</td>
<td>2.58±0.55</td>
<td>NA</td>
</tr>
<tr>
<td>A wave integral (E)</td>
<td>1.51±0.42</td>
<td>NA</td>
</tr>
<tr>
<td>Systolic velocity</td>
<td>1.72±0.33</td>
<td>1.78±0.15</td>
</tr>
<tr>
<td>Systolic integral</td>
<td>8.14±1.6</td>
<td>7.23±0.85</td>
</tr>
<tr>
<td>PR duration (I)</td>
<td>248.6±48.5</td>
<td>298±21.7</td>
</tr>
<tr>
<td>PR duration (E)</td>
<td>165.7±36.7</td>
<td>279.8±19.8</td>
</tr>
</tbody>
</table>

All values marked (*) are significant (p <0.05) when inspiratory values are compared to those in expiration. All velocities are in cm/s and duration in ms.
SVC flow: Satisfactory SVC flow recordings were possible in 45/64 (70%) cases. All cases with evidence of RV restrictive physiology had reversal of SVC flow with atrial systole (retrograde SVC flow) while this was not seen in any case without RV restriction. Also, those with RV restriction, more often had predominant diastolic antegrade systolic flow in the SVC flow recordings (30/45 cases with restrictive physiology, v. 2/19 patients without RV restriction).

Transtecuspid flow (Table 2): Transtecuspid flow was reliably measured in 60/64 patients while in 4 patients such an analysis was not possible because of transtecuspid summation. Those with restrictive physiology had significantly lower peak E velocity and shorter transtecuspid E deceleration time as compared to those with no restriction with the difference persisting in expiration as well. Comparison of transtecuspid VTIs revealed that those with restriction had significantly higher A VTI. Although the E VTI was slightly lower in these patients, it was not statistically significant. Biventricular systolic function and the transmitral E and A velocity patterns were normal in all patients.

Comparison of patients with and without RV restriction (Table 3): The mean age, weight, hemoglobin (Hb), packed cell volume (PCV) and platelet counts were comparable among patients with and without restrictive physiology. The mean Nakata index (239.4±82.0 v. 252.1±102.4), mean z value (0.83±0.64 v. 0.82±0.54), cardiopulmonary bypass (CPB) time (101.46±19.3 v. 112.0±28.8 min) and mean aortic cross clamp time (ACC: 65.54±15.86 v. 60.1±8.71 min) were comparable among the two groups. There was no correlation between the use of transannular patch (TAP) with the incidence of RV restriction. Of the 46 patients who received TAP, 25 had RV restrictive physiology, while 21 did not.

The mean inotrope duration (16.2±2.1 v. 10.3±1.9 hours, p<0.02), mean ventilation time (18.8±4.3 v. 8.43±5.03 hrs, p<0.05) and mean chest drain time (34.6±2.5 v. 19.7±6.16 hours, p<0.04) were significantly longer in those with RV restriction group. Correspondingly, the mean ICU stay was much longer in group 1 (56.7±9.3 v. 34.7±5.38 hours, p<0.01). The mean hospital discharge time was also significantly longer in those with RV restriction (9.3±2.3 v. 6.2±0.5 days, p<0.001). Overall 3/64 (4%) patients died (2 due to sudden ventricular fibrillation, and 1 due to septicemia). All 3 patients had documented RV restrictive physiology.

Hospital stay: Based on mean hospital stay, the patients were divided into two groups (Group 1, <10 days, n=48; Group 2, >10 days, n=16). The mean age, weight, z value, CPB time and ACC times were comparable among the two groups. As expected, patients with longer hospital stay had longer ventilation and chest drainage times and consequently longer ICU stay.

The marker of RV restrictive physiology (the A wave in the antegrade PA Doppler flow) was observed to be significantly different among these two groups. Those with longer hospital stay had significantly higher pulmonary A velocity (0.60±0.19 v. 0.31±0.18 cm/s, p<0.01) and higher pulmonary A VTI (2.85±0.5 v. 1.82±1.17, p<0.01) recorded in the antegrade PA flow. Amongst all transtecuspid flow variables, only EDT was discriminatory, being significantly longer in patients with RV restriction.
patients following repair of TOF, and have also been observed in patients with RV restrictive physiology. The hemodynamic basis of this is RV end-diastolic pressure exceeding PA diastolic pressure leading to antegrade PA diastolic flow. Presence of retrograde flow in SVC and shorter tricuspid deceleration of early rapid filling velocity are also consistent with RV restrictive physiology.

We observed that in our patient population, despite normal biventricular systolic function and normal transmitial flow patterns, abnormalities of RV diastolic function existed in 70% (45/64) of patients, which is much higher than what is reported by previous studies. This was evident from the presence of laminar antegrade diastolic PA flow throughout the respiratory cycle, coincident with atrial systole. Those with a restrictive physiology also had abnormal tricuspid flow patterns, as shown by lower peak E velocity, lower E/A velocity ratio, significantly shorter EDT and higher A VTI. The SVC flow recordings revealed retrograde flow (coincident with atrial systole) and predominant antegrade diastolic flow only in patients with RV restriction.

The higher incidence of RV diastolic dysfunction in our patients as compared to that reported in other studies could be because of the fact that our patients were older (mean age 7.06±4.9, range 1-27 years) as compared to those in the other studies. The older the patient, longer would be the duration for which the RV is subjected to chronic pressure overload and hypoxia, possibly leading to higher incidence of RV diastolic abnormalities.

In-hospital course: Patients with a restrictive physiology had more adverse in-hospital course with a significantly longer need for inotropic support, longer ventilation and chest drain times, and longer ICU stay. The mean hospital stay was also longer in such patients (9.3±2.3 v. 6.2±0.5 days, p<0.001).

On comparing patients with respect to hospital stay (<10 days, n=48 v. >10 days, n=16), variables like age, weight, Hb, pre-operative aortic saturation, mean RA and RV end-diastolic pressure, z value, CPB time and ACC times were similar. As expected, patients with longer hospital stay had longer ventilation and chest drainage times and consequently longer ICU stay. Patients with longer hospital stay had significantly shorter tricuspid EDV, higher pulmonary A velocity and higher pulmonary A VTI recorded in the antegrade PA flow, highlighting the fact that restrictive RV physiology may lead to prolonged hospital course and more adverse outcome following surgical repair in cases of TOF.

Follow-up echocardiography: At 4 weeks following hospital discharge, all patients with immediate RV restrictive physiology continued to show persistent RV diastolic dysfunction. At 12 weeks, most (30/35, 86%) patients...
continued to show persistent RV diastolic dysfunction. No patient developed new onset RV restriction at follow-up (i.e. absent RV restriction at discharge and developing it subsequently on the follow-up echocardiographic study).

In contrast, Cullen et al\(^1\) reported resolution of RV restrictive pattern in 13/17 patients at a follow-up of 2 weeks. It is possible that the widely different age groups of the patient populations in the two studies are responsible for this observation. Older patients’ RV may be subjected to more chronic pressure overload and hypoxia, leading to a degree of endomyocardial fibrosis,\(^10\) which could explain more chronic pressure overload and hypoxia, leading to a lack of recovery of RV function at 12 weeks follow-up. Persistence of RV restrictiv physiology late after TOF repair has also been reported in other studies.\(^2,9\) Though Norgard et al.\(^9\) reported that use of TAP was more often associated with RV restrictive pattern, our observation was that the use of TAP did not correlate with presence of RV restrictive physiology.

Though the exact mechanisms of RV restriction are not clear, various theories have been postulated. These include inadequate operative RV protection (due to its anterior location),\(^10-12\) and chronic hypoxemia leading to down-regulation of antioxidant defences and resultant oxygen free-induced injury.\(^13,14\) Chaturvedi et al.\(^15\) demonstrated that following surgical repair of TOF, acute RV restrictive physiology was associated with severe iron loading of transferrin and post-operative oxidative stress.

**Conclusions:** Abnormalities of RV diastolic function exist in a significant proportion of patients undergoing TOF repair. Presence of laminar antegrade diastolic PA flow throughout the respiratory cycle, coincident with atrial systole is an accurate marker of RV restriction in these cases. Such patients have longer requirement for ventilatory support, with prolonged ICU and hospital stay. Pre-operative factors like age, weight, Hb, aortic saturation, mean RA and RV end-diastolic pressure, z value, CPB time and ACC times did not correlate with presence of RV restrictive physiology. Follow-up serial echocardiographic studies at 12 weeks demonstrated that these abnormalities were still present in 86% of the patients. Whether long-term follow-up studies would reveal further resolution of these abnormalities needs to be explored further.

**References**

Anticoagulation Protocol and Early Prosthetic Valve Thrombosis

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Background: Prosthetic valve thrombosis is a major cause of morbidity and mortality following heart valve replacement with a mechanical valve.

Methods and Results: 538 patients who underwent mechanical valve replacement between April 1999 and June 2003 were included in the study. They were divided into two groups. Group A (n=245) consisted of patients who underwent mechanical valve replacement between April 1999 and June 2001. Anticoagulation was started on the first post-operative day and consisted of only oral nicoumalone. Group B (n=293) consisted of patients who underwent mechanical valve replacement between July 2001 and June 2003; enoxaparin was started six hours following surgery in addition to oral nicoumalone which was started on first post-operative day. Fifteen (6.1%) patients in group A developed early prosthetic valve thrombosis at an interval of 4.33±0.97 months (range 3-6 months) following surgery. Ten had prosthetic valve thrombosis in the mitral position and five had prosthetic valve thrombosis in the aortic position. In group B, six (2.1%) patients developed early prosthetic valve thrombosis at a median interval of 4.58±0.9 months (range 3.5-6 months) in the mitral position (p=0.01).

Conclusions: Addition of enoxaparin to the anticoagulation regime in the immediate post-operative period significantly reduces early prosthetic valve thrombosis. (Indian Heart J 2004; 56: 225–228)

Key Words: Valvular heart disease, Anticoagulants, Prosthetic valve thrombosis

Prosthetic valve thrombosis (PVT) is a major cause of morbidity and mortality following heart valve replacement with a mechanical valve. Thrombotic and bleeding complications represent 57% to 92% of all valve-related complications in patients with mechanical aortic prostheses and 55% to 79% in patients with mechanical mitral prostheses.1 The incidence of prosthetic valve thrombosis is 0.1% to 5.7% per year according to the type of the valve, its location and the adequacy of anticoagulation.2 Thrombotic complications are more common in the first few months following operation.3 Anticoagulation with coumarin derivatives alone in the early post-operative period may be unreliable as their action is apparent only after 24-48 hours after initiation of therapy.1 Proper initiation and maintenance of anticoagulation in the early post-operative period may prevent these complications. Enoxaparin is a low-molecular weight heparin (LMWH) which has been successfully used to treat acute deep vein thrombosis and in patients with acute non-Q-wave myocardial infarction and unstable angina pectoris.4 It has also been used as a substitute therapy to maintain anticoagulation in patients in whom oral anticoagulants are contraindicated.3 Because of an observed high incidence of prosthetic valve thrombosis in patients receiving oral anticoagulants alone, we evaluated the role of enoxaparin added to the anticoagulation regime to prevent early prosthetic valve thrombosis.

Methods

Patient population: The patient population (n=538) consisted of two groups - Group A and Group B. Group A consisted of 245 survivors (of 256) who underwent mechanical valve replacement in the mitral and/or aortic position between April 1999 and June 2001. Of these 166 (68%) patients were male and 79 (32%) patients were female. Mean age was 34.5±6.8 years (range 14-56 years). Ninety-five (38.8%) patients underwent mitral valve replacement (MVR), 67 (27.3%) patients underwent aortic valve replacement (AVR) and 83 (33.9%) patients underwent double valve replacement (DVR); 118 (48.2%) patients were in atrial fibrillation before operation, 78
(69%) of these were in sinus rhythm post-operatively. Median valve size for MVR was 31 mm (range 25-33 mm) and for AVR, it was 25 mm (range 19-31 mm).

Group B comprised of 293 survivors (of 308) who underwent mechanical valve replacement between July 2001 and June 2003. 189 (64.5%) were males and 104 (35.5%) were females. Mean age was 36.2±7.3 years (range 15-53 years); 124 (42.3%) patients underwent MVR, 87 (29.7%) patients underwent AVR and 82 (28%) patients underwent DVR; 165 (56.3%) patients were in atrial fibrillation before operation. Of these, 103 (62.4%) were in sinus rhythm post-operatively. Median valve size for MVR was 31 mm (range 27-33 mm) and for AVR, it was 25 mm (range 19-31 mm).

**Surgical technique:** All the patients were operated by the senior author (ASK) and the surgical technique for valve implantation was identical in both the groups. Standard techniques for valve implantation were used in these patients. In all patients, St Jude mechanical heart valve (St. Jude Medical Inc., Minn, USA) was implanted. In patients undergoing MVR, both the anterior and the posterior chordal apparatus of the mitral valve were retained. No separate surgical procedure was performed for patients in atrial fibrillation.

**Anticoagulation protocol:** In Group A, anticoagulation was started on the first post-operative day. Initially 4 mg nicoumalone was administered to these patients and the dose was later titrated to maintain an International normalized ratio (INR) of 2.5 to 3.5 for patients undergoing MVR and DVR, and 2 to 3 for patients undergoing AVR, as per the published guidelines for antithrombotic therapy in patients with prosthetic heart valves. In all patients, StJude mechanical heart valve (St. Jude Medical Inc., Minn, USA) was implanted. In patients undergoing MVR, both the anterior and the posterior chordal apparatus of the mitral valve were retained. No separate surgical procedure was performed for patients in atrial fibrillation.

**Follow-up:** In both groups of patients, cinefluoroscopy was carried out before discharge from the hospital to confirm normal prosthetic valve disc movements. After discharge, these patients were followed up after 7 days, 1 month, 3 months, 6 months and then at yearly intervals. At each outpatient visit, prothrombin time and INR values were measured and cinefluoroscopy was carried out. In case the cinefluoroscopy was abnormal, echocardiography was done to measure gradients across the prosthetic heart valves. If abnormal, patients were thrombolyzed with streptokinase or urokinase and repeat echocardiography and cinefluoroscopy were performed.

PVT was defined as any thrombus in the absence of infection, attached to or near an operated valve that occludes part of the blood flow path or that interferes with prosthetic valve function. Early PVT was defined as the one occurring within 6 months of surgery. All the patients in groups A and B were followed up for at least six months before they were declared free of early prosthetic valve thrombosis.

**Statistical analysis:** All the data were collected and systematically analyzed. Data are presented as frequency distribution and simple percentages. Descriptive statistics i.e. mean, median and standard deviation have been calculated for all the continuous variables. A valve-related event was defined as any episode of thromboembolism, hemorrhage, congestive heart failure, infective endocarditis, structural deterioration, significant gradients or prosthetic valve dysfunction as per the published criteria. Comparison between the two groups was made by the Chi-square test with Yates correction wherever applicable. p value <0.05 was considered significant.

### Results

Fifteen of the 245 patients in Group A developed early PVT at an interval of 4.33±0.97 months (range 3-6 months) following surgery (Table 1). Ten had PVT in the mitral position and five had PVT in the aortic position. Nine patients had undergone MVR, three had undergone DVR, two had undergone AVR and one patient had undergone

<table>
<thead>
<tr>
<th>S.No.</th>
<th>Surgery</th>
<th>Valve size (mm)</th>
<th>Affected valve</th>
<th>Interval (months)</th>
<th>INR</th>
<th>NYHA class</th>
<th>Peak gradient (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. MVR 25</td>
<td>M</td>
<td>3</td>
<td>2.8</td>
<td>II</td>
<td>10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. MVR 29</td>
<td>M</td>
<td>3</td>
<td>3.2</td>
<td>II</td>
<td>16.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. MVR 29</td>
<td>M</td>
<td>3</td>
<td>2.8</td>
<td>II</td>
<td>14</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. DVR 25 A, 31 M</td>
<td>M</td>
<td>3.5</td>
<td>2.6</td>
<td>II</td>
<td>22.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5. MVR 29</td>
<td>M</td>
<td>4</td>
<td>1.81</td>
<td>II</td>
<td>18.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6. DVR 25 A, 29 M</td>
<td>A</td>
<td>4</td>
<td>2.59</td>
<td>I</td>
<td>46</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7. AVR 27</td>
<td>A</td>
<td>4</td>
<td>1.63</td>
<td>II</td>
<td>53</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8. MVR 29</td>
<td>M</td>
<td>4.5</td>
<td>4.22</td>
<td>II</td>
<td>15.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9. AVR 31</td>
<td>A</td>
<td>4.5</td>
<td>2.8</td>
<td>II</td>
<td>68</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10. MVR 33</td>
<td>M</td>
<td>4.5</td>
<td>3.1</td>
<td>III</td>
<td>41</td>
<td></td>
<td></td>
</tr>
<tr>
<td>11. MVR 33</td>
<td>M</td>
<td>5</td>
<td>2.9</td>
<td>II</td>
<td>19.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12. DVR 19 A, 27 M</td>
<td>M</td>
<td>5</td>
<td>2.59</td>
<td>II</td>
<td>17.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>13. AVR 25</td>
<td>A</td>
<td>5</td>
<td>2.8</td>
<td>I</td>
<td>57</td>
<td></td>
<td></td>
</tr>
<tr>
<td>14. DVR 25 A, 31 M</td>
<td>A</td>
<td>6</td>
<td>3.2</td>
<td>II</td>
<td>72</td>
<td></td>
<td></td>
</tr>
<tr>
<td>15. MVR 31</td>
<td>M</td>
<td>6</td>
<td>3.1</td>
<td>I</td>
<td>16</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

INR: international normalized ratio; MVR: mitral valve replacement; M: mitral; DVR: double valve replacement; A: aortic; AVR: aortic valve replacement.
AVR with coronary artery bypass grafting. Target INR was less than satisfactory in two patients (Table 1). All these patients were successfully thrombolyzed with streptokinase and were not re-operated. None of these patients had atrial fibrillation or a large left atrium.

Six of the 293 patients in Group B developed early PVT at a median interval of 4.58±0.9 months (range 3.5-6 months) following surgery (Table 2). All six had thrombosis of the prosthesis in the mitral position. Four had undergone DVR and two had undergone MVR. Target INR was less than satisfactory in one patient. All the six patients were successfully thrombolyzed. However, one patient had another episode of PVT three months later. His INR at this time was 1.8 and this was attributed to non-compliance with the prescribed dosage of anticoagulants. None of these patients had atrial fibrillation or a large left atrium. None were reoperated.

One patient in group B developed excessive drainage from the mediastinal tubes 36 hours following surgery after two doses of enoxaparin. Further doses were discontinued and the drainage gradually became less. Apart from this, there were no bleeding complications in either group.

There were no statistically significant differences in the two groups with respect to age, sex, type of surgery performed, incidence of pre- and post-operative atrial fibrillation and median valve sizes. All these patients were operated by the senior author and the surgical technique was identical in both groups. However, the incidence of PVT was significantly lower in patients in group B as compared to those in group A (6/293 in group B vs 15/245 in group A, p=0.01). Since the only difference in the two groups was the introduction of enoxaparin sodium in group B, the lower incidence of PVT in this group was attributed to this change in the anticoagulation protocol.

Table 2. Profile of patients with prosthetic valve thrombosis in Group B

<table>
<thead>
<tr>
<th>S.No.</th>
<th>Surgery</th>
<th>Valve size (mm)</th>
<th>Affected valve</th>
<th>Interval (months)</th>
<th>INR</th>
<th>NYHA class</th>
<th>Peak gradients (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>DVR</td>
<td>29 A, 31 M</td>
<td>M</td>
<td>3.5</td>
<td>2.59</td>
<td>II</td>
<td>19</td>
</tr>
<tr>
<td>2.</td>
<td>MVR</td>
<td>33</td>
<td>M</td>
<td>4</td>
<td>2.02</td>
<td>II</td>
<td>13.8</td>
</tr>
<tr>
<td>3.</td>
<td>MVR</td>
<td>31</td>
<td>M</td>
<td>4</td>
<td>3.48</td>
<td>III</td>
<td>24.6</td>
</tr>
<tr>
<td>4.</td>
<td>DVR</td>
<td>19 A, 27 M</td>
<td>M</td>
<td>5</td>
<td>3.72</td>
<td>II</td>
<td>15</td>
</tr>
<tr>
<td>5.</td>
<td>DVR</td>
<td>23 A, 31 M</td>
<td>M</td>
<td>5</td>
<td>3.02</td>
<td>II</td>
<td>18.7</td>
</tr>
<tr>
<td>6.</td>
<td>DVR</td>
<td>23 A, 31 M</td>
<td>M</td>
<td>6</td>
<td>3.48</td>
<td>III</td>
<td>21.4</td>
</tr>
</tbody>
</table>

INR: international normalized ratio; MVR: mitral valve replacement; M: mitral; DVR: double valve replacement; A: aortic

Discussion

We postulate that thrombus formation on the prosthesis begins soon after heparin reversal following cardiopulmonary bypass. Therefore anticoagulation and prevention of platelet aggregation and thrombosis should begin in the immediate post-operative period. For mechanical valves, anticoagulation with coumarin derivatives is the most important factor affecting the incidence of both thrombotic and bleeding complications. Without coumarin derivatives, this incidence is 3 to 8 times higher in patients with mechanical valve prostheses. Addition of platelet inhibitors has reduced the incidence of thromboembolism in some series but not in others. As such, the advantage of coumarins plus platelet inhibitors in not clear.

Rough surfaces, large surface area, stagnant flow, narrow flow paths and turbulence increase thrombosis. Till the healing occurs, the projecting sewing rim of the prosthetic valve is a potential site of development and propagation of a thrombus which may later on progress to produce prosthetic valve thrombosis and dysfunction. In a recent study of 680 patients undergoing MVR, early PVT was shown to occur in as many as 9.4% patients. However, no such data is available from the Indian subcontinent.

Coumarin derivatives act by completely blocking vitamin K epoxide reductase so that less vitamin K is available to participate as a cofactor in the addition of gamma-carboxyglutamic acid residues to the vitamin K-dependent coagulation factors VII, IX, X, protein C and protein S. Because there is inhibition of these procoagulant factors with plasma half-life ranging between 5 to 100 hours, the establishment of anticoagulation is slow with these drugs.

LMWH has been successfully used for prevention and treatment of thromboembolism and in patients with unstable angina pectoris and in those with prosthetic heart valve where anticoagulation with oral anticoagulants is contraindicated as in pregnancy. It has also been used for long-term anticoagulation in patients with prosthetic heart valves who develop adverse reaction to oral anticoagulants. It has been established to be superior to unfractionated heparin because there is a low risk of bleeding and laboratory monitoring is minimal because of its bioavailability, longer half-life, dose-dependent clearance and decreased affinity to heparin-binding protein. The onset of action is almost immediate and this helps to provide anticoagulation cover till the effect of oral anticoagulants is established. The efficacy of enoxaparin in the prevention of early PVT has not been previously investigated. In present study it has certainly brought down the incidence of early prosthetic valve thrombosis. Because thrombi may
form on the sewing rim of the prosthetic valve in the early post-operative period, we believe that early therapy with enoxaparin is essential to prevent this complication.

**Study limitation:** A limitation of our study is that it is not a randomized trial. However, considering the fact that PVT is a dreaded complication following valve replacement, such a study may not be ethically justified specially when the benefits of addition of enoxaparin are clear.

**Conclusions:** Addition of enoxaparin to the anticoagulation regime in the early post-operative period prevents early prosthetic valve thrombosis. Our patients who undergo prosthetic valve implantation now routinely receive enoxaparin.

**References**

Lack of Association of Heart Rate Variability Parameters with Head-up Tilt-Test Responses in Patients with Syncope

Department of Cardiology, Uludag University School of Medicine, Turkey

Background: Neurocardiogenic syncope is the most common type of syncope. Head-up tilt testing is the investigation of choice for diagnosis of patients with neurocardiogenic syncope. In this study, we aimed to find out any association between heart rate variability parameters and type of tilt-test response in patients with syncope.

Methods and Results: Forty-nine cases with unexplained syncopal attacks were enrolled into our study and were grouped according to the tilt-test responses. Tilt test was performed in all patients after excluding other causes of syncope. In case of a negative basal tilt-testing, pharmacological tilt testing was performed after 30 min of 5 mg sublingual isosorbide dinitrate. Holter monitoring was done from the beginning of tilt testing up to two hours post-procedure. The heart rate variability parameters analyzed were the mean of all coupling intervals between normal beats, the standard deviation about the mean of all coupling intervals between normal beats, the mean of all 5-min standard deviations of mean of all coupling intervals between normal beats, the proportion of adjacent normal R-R intervals differing by >50 ms, the root mean square of the difference between successive RRs, and the standard deviation of 5-min mean of all coupling intervals between normal beats and ratio between low and high frequencies.

Conclusions: In 35 patients, the tilt-test was positive, 16 were cardioinhibitor type (Group 1), four cases had a vasodepressor type response (Group 2) and 15 were mixed type (Group 3). Fourteen patients had a negative test result. The heart rate variability measures did not significantly differ among the study groups. The heart rate variability measures were compared between the tilt-test negative (Group 4) and the tilt-test positive groups (Groups 1, 2 and 3) and no statistically significant difference was found. (Indian Heart J 2004; 56: 229–231)

Key Words: Tilt-test, Syncope, Arrhythmia

The pathophysiology of neurocardiogenic syncope is complex and not completely elucidated. Head-up tilt testing has become the diagnostic study of choice for the identification of patients with neurocardiogenic syncope. We studied heart rate variability (HRV) in patients of neurocardiogenic syncope and correlated it with tilt test results.

Methods
Forty-nine cases with unexplained syncopal attacks were enrolled into our study between November 2000 and December 2002 (32 female, 17 male; mean age, 34.8 ± 14.2 years). Tilt test was performed in all patients after excluding other causative factors of syncope. In case of having a negative basal tilt testing, pharmacological tilt testing was performed after 30 minutes of 5 mg sublingual isosorbide dinitrate. A Holter monitoring analysis was done from the beginning of tilt testing up to two hours post-procedure. The tilt-test positive group was divided into three groups according to the type of response to tilting. The group of patients with the cardioinhibitor, vasodepressor and mixed type responses constituted the Group 1, Group 2 and Group 3, respectively and the tilt-test negative patients constituted Group 4. HRV was evaluated by time and frequency analysis methods. The derived time domain indices were the mean NN (mean of all coupling intervals...
between normal beats), the standard deviation about the mean of all coupling intervals between normal beats (SDNN), the mean of all 5-min standard deviations of NNs (SD), the proportion of adjacent normal R-R intervals differing by >50 ms (pNN50), the root mean square of the difference between successive R-Rs (rMSSD), and the standard deviation of 5-min mean NN intervals (SDANN). The frequency domain indices i.e. ratio between low and high frequencies (LF/HF) was taken as a representative of sympathovagal modulation. Syncope was defined as the transient loss of consciousness. Our routine tilt-test was a drug-free tilt-test (80° for 30 min) and in case of negative result, was followed by repeat tilt-test after 30 min of sublingual 5 mg isosorbide dinitrate. A positive tilt-test was defined as the reproduction of clinical pre-syncope or syncpe, after either a drug-free or sublingual isosorbide dinitrate tilt-test accompanied by relative bradycardia (20% decrease in heart rate compared with baseline) and/or hypotension (systolic blood pressure <80 mmHg).

Data are expressed as mean ± SD. Mann-Whitney U test; Fisher’s Exact test were used for statistical analysis. A p value <0.05 was considered statistically significant.

**Results**

Tilt-test was positive in 35 patients, 16 were cardioinhibitor type (Group 1), 4 cases had a vasodepressor type response (Group 2) and 15 were mixed type (Group 3). Fourteen patients had a negative test result. The HRV measures did not significantly differ among the study groups. The HRV measures were compared between the tilt-test negative (Group 4) and the tilt-test positive groups (Groups 1, 2 and 3) and no statistically significant difference was found. In addition, comparisons were made according to the type of tilt-test response and again, no statistically significant difference in HRV parameters was found between the groups. The HR was 79.5±14.3 beats per min (bpm). The HR variables calculated in the tilt negative and the tilt positive groups are given in Table 1 and the results according to the tilt-test response types are given in Table 2.

**Table 1. Heart rate variability parameters in tilt test negative and tilt test positive groups**

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Tilt-test positive group</th>
<th>Tilt-test negative group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>35.5±2.5</td>
<td>33.2±4.2</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>77.4±2.0</td>
<td>84.8±4.8</td>
</tr>
<tr>
<td>pNN50 (%)</td>
<td>13.9±2.0</td>
<td>10.1±3.0</td>
</tr>
<tr>
<td>rMSSD (ms)</td>
<td>48.6±4.7</td>
<td>35.8±4.4</td>
</tr>
<tr>
<td>Variability index</td>
<td>3.37±0.2</td>
<td>2.8±0.2</td>
</tr>
<tr>
<td>SDANN (ms)</td>
<td>75.9±4.8</td>
<td>70.4±5.9</td>
</tr>
<tr>
<td>SDNN (ms)</td>
<td>99.3±6.6</td>
<td>111.8±14.0</td>
</tr>
<tr>
<td>SD (ms)</td>
<td>131.1±7.6</td>
<td>139.4±15.3</td>
</tr>
<tr>
<td>LF/HF</td>
<td>2.6±0.3</td>
<td>3.9±0.7</td>
</tr>
</tbody>
</table>

*All p values are >0.05

**Table 2. Heart rate variability parameters in different groups according to tilt-test response types**

<table>
<thead>
<tr>
<th>Group</th>
<th>Heart rate (bpm)</th>
<th>pNN50 (%)</th>
<th>rMSSD (ms)</th>
<th>Variability index</th>
<th>SDANN (ms)</th>
<th>SDNN (ms)</th>
<th>SD (ms)</th>
<th>LF/HF</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>77.5±2.9</td>
<td>11.3±2.4</td>
<td>42.6±3.1</td>
<td>3.0±0.2</td>
<td>67.8±4.0</td>
<td>79.8±6.1</td>
<td>109.6±7.9</td>
<td>2.8±0.5</td>
</tr>
<tr>
<td>2</td>
<td>74.4±3.7</td>
<td>16.4±6.1</td>
<td>55.3±14.3</td>
<td>3.6±0.8</td>
<td>73.5±13.8</td>
<td>90.6±24.5</td>
<td>127.1±29.1</td>
<td>1.6±0.1</td>
</tr>
<tr>
<td>3</td>
<td>78.1±4.5</td>
<td>15.6±3.4</td>
<td>52.6±9.4</td>
<td>3.6±0.5</td>
<td>84.2±9.0</td>
<td>119.8±10.0</td>
<td>152.2±11.4</td>
<td>2.7±0.4</td>
</tr>
</tbody>
</table>

*All p values are >0.05

**Discussion**

Since vasovagal syncope may occur due to imbalance between the components of the autonomic nervous system, it is logical to assess the parameters reflecting the tone of sympathetic or parasympathetic activity. However, Suzuki et al. demonstrated that continuous spectral analysis of the R-R intervals revealed increased vagal influence on the heart in tilt-induced syncope.

On development of the first pre-syncopal manifestations, HRV parameters in patients with positive head-up tilt-test were found to be significantly higher as compared with patients with negative test results, suggesting an increase of the parasympathetic autonomous tone during the development of the vasovagal syncope. In another study, patients with vasovagal syncope had no basic differences from normal subjects in autonomic nervous system activity.

We evaluated our cases with 2 hours of Holter monitoring and compared the cases for differences in autonomic profile. However, we did not gather data to see the changes in sympathovagal tone during the tilt test before and after the occurrence of syncope. Lazzieri et al. reported that vasodepressive patients had a peculiar
autonomic profile assessed by 24-hour HRV analysis and stated that the evaluation of the autonomic profile by 24-hour Holter recordings could be of value in the diagnosis of patients with syncope. However, the patterns of HRV and catecholamine changes were not significantly different in vasodepressor and control groups in the study by Prinz-Zaiss et al.\(^5\)

In the studies by Sneddon et al.\(^6,7\) and Kochiadakis et al.\(^8\) it was found that the mean values of HR and HRV indices did not differ significantly between normal subjects and patients with vasovagal syncope.\(^6,8\) Differences between syncopal patients and normal subjects may exist, at least around the time of a positive tilt-test, when the patients are presumably more prone to syncopal episodes. The timing of the HRV measurements in relation to the tilt-test is important and it seems from our study that timing could play an important role in the evaluation of HRV. By evaluating the HRV during the whole tilt-test and afterward for a total of two hours, we were unable to detect the changes during the phases of the test and syncopal episode.

In our study, we found no association between tilt-test responses of patients and HRV measures. Though the autonomic tone changes before and after syncope attacks, the HRV measures did not show the differences we expected, suggesting that the vagal tone does not have a significant impact on the type of neurocardiogenic syncope.

References

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Transcatheter Management of Patent Ductus Arteriosus in Sick Ventilated Small Infants

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Background: Large patent ductus arteriosus can present in infancy with congestive cardiac failure and superadded pulmonary infection can necessitate mechanical ventilation. Surgical intervention is traditionally indicated for this subset of patients. We present our experience of transcatheter coil closure of the patent ductus arteriosus in such infants.

Methods and Results: Five infants weighing between 960 gm and 4.1 kg, aged between 17 days and 3½ months were mechanically ventilated because of congestive cardiac failure with pneumonia. Echocardiography showed patent ductus arteriosus with a size of 1.8 to 4.2 mm and adequate ampulla. Bioprome-assisted coil delivery was done and successful patent ductus arteriosus closure was achieved in all. There were two instances of embolization of coils with successful retrieval and redeployment. All infants could be weaned off mechanical ventilation over the next 24-72 hours. A pre-term infant developed a Doppler gradient of 25 mmHg in the descending aorta that decreased to 12 mmHg five months later. There was no significant obstruction to pulmonary artery flow in any child. At three months follow-up, all the five infants were asymptomatic with no residual flow across the patient ductus arteriosus.

Conclusions: Transcatheter coil closure of moderate to large patent ductus arteriosus is possible in sick ventilated infants weighing below 5 kg. It may be a better alternative to surgery in selected cases in view of minimal morbidity.

Key Words: Heart failure, Catheter intervention, Congenital heart disease

Large patent ductus arteriosus (PDA) is known to cause congestive cardiac failure (CCF) in infancy. Superadded respiratory infection is not uncommon and it can result in respiratory insufficiency necessitating mechanical ventilation. In such a situation, interruption of the PDA becomes a necessity to break the cycle of CCF-pneumonia-CCF. Surgery is the standard treatment as the ducts are often large. The morbidities associated with surgical interruption can result in prolonged mechanical ventilation and intensive care unit (ICU) stay. Since 1992, with the availability of Gianturco embolization coils, coil closure of PDA has been performed widely. However, it is largely reserved for stable children with relatively small PDA. We present our experience in transcatheter closure of large PDA in five small infants who needed mechanical ventilation to control the CCF and pneumonia.

Methods
Gianturco embolization coils (Cook Inc., Bloomington, IN) were used in all (0.038" and 0.052", 4 mm-8 mm). Coils were delivered from the venous end using a 4-7 F Balkin contralateral sheath (Cook Inc., Bloomington, IN) with a 3 F or 5.2 F bioprome (Cook Inc.) and arterial puncture was avoided whenever possible. For controlled delivery, the coils were deployed with bioprome control as described previously. Residual flow across the duct, right pulmonary artery (RPA) and left pulmonary artery (LPA) flows were checked by echocardiography in the catheterization laboratory. All procedures were done under general anesthesia.

Results
The physiological and other features of the patients are shown in Table 1. Case 1 was being mechanically ventilated for CCF bronchopneumonia elsewhere. As there was no improvement with standard therapy, the infant was referred...
Kannan et al. Coil Closure of PDA in Sick Infants

All other children were admitted with respiratory distress and needed mechanical ventilation subsequently. Case 5 had sepsis with disseminated intravascular coagulation that needed stabilization for five days with supportive measures including a double volume exchange transfusion before considering transcatheter treatment. All other children underwent coil closure within 24-48 hours of intubation. Case 2 had an associated 9 mm atrial septal defect. Case 3 was a pre-term child with Klebsiella pneumoniae septicemia. The platelet count was 6900 per cmm and catheter closure was considered safer than surgical closure.

Case 1 needed 4 additional coils that were delivered from the arterial end. A 3 F bioptome was used to hold the coil in the pre-term child (Case 3) and 5.2 F bioptome was used in all other infants. Arterial access was obtained in Case 1 for delivery of additional coils and the femoral artery was inadvertently punctured in the pre-term child (Case 3). Arterial puncture could be avoided in all other infants. Embolization of coils occurred in two instances. In Case 2, the coils embolized to abdominal aorta after achieving a stable position, following endotracheal suction. A 10 mm Gooseneck snare (Microvena) was introduced from the venous end and passed across the ductus into the descending aorta. The tied end of the coils was snared, pulled back into the ductal ampulla and redeployed. In Case 5, two coils that were initially delivered simultaneously embolized to left pulmonary artery indicating that the duct size had been underestimated. The coils were snared out. One more coil was tied to the same mass and redeployment was successful. There was no procedure-related complication. Two infants had mild residual flow at the end of the procedure that disappeared within 36 hours. All infants could be extubated 48-72 hours after the procedure.

Case 3 developed a systolic Doppler gradient of 25 mmHg in the descending aorta following the procedure. There was no diastolic spillover of the gradient. The gradient had come down to 12 mmHg, five months later. No infant had any significant gradient across the branch pulmonary arteries. At 3-8 months follow-up, all the infants were asymptomatic with appropriate weight gain.

**Discussion**

Infants with large PDA run the risk of death due to CCF and recurrent respiratory infections are also not uncommon in them. Traditionally surgical management of the patent ductus has been advocated. However, surgery-related morbidities could lead to prolonged hospital stay, especially in sick infants with CCF who are ventilated for respiratory failure with superadded respiratory infection. Over the past few years, coil occlusion of PDA has become a standard treatment for small PDAs and has been shown to be successful even in larger ducts. The latter has been possible especially with the availability of thicker 0.052” coils.

Coil closure was successfully done in all five infants resulting in rapid recovery from the illness. One of the infants was a 960 gm weighing pre-term neonate. To the best of our knowledge, this is the smallest reported child to undergo transcatheter coil closure of the duct. We prefer

**Table 1. Physiological and other features of patients**

<table>
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<tr>
<th>Case</th>
<th>Age (weeks)</th>
<th>Weight (kg)</th>
<th>PDA size (mm)</th>
<th>Mean PA pressure (mmHg)</th>
<th>Qp:Qs</th>
<th>No. of Emboli- Arterial Fluoroscopy</th>
<th>No.</th>
<th>Arterial Fluoroscopy access</th>
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</table>

PDA: patent ductus arteriosus; PA: pulmonary artery; Qp: Qs: ratio of pulmonary blood flow to systemic blood flow.

**Fig. 1.**

A - Lateral view of the aortogram showing 3.4 mm patent ductus arteriosus with a relatively small ampulla. The small arrows indicate the posterior border of the trachea. B - Bioptome has been shown in the open position just after the release of the coil mass. C - The embolized coil in the abdominal aorta is held by the snare. D - The final position of the coil mass after its release from the snare.
the transvenous coil closure and avoid arterial punctures whenever possible. In three of five children, no arterial access was obtained. In the pre-term child, the femoral artery was accidentally punctured and in another child, arterial access was needed for additional delivery of coils.

Various techniques have been described to reduce the risk of embolization that include snare- or bioptome-assisted delivery. We modified the bioptome-assisted coil delivery technique for simultaneous delivery of multiple coils which was applied in these children. Except the pre-term child, others needed two or more coils for complete occlusion of the duct. In one infant, the coil mass embolized to the abdominal aorta, few minutes after the release. The coil mass was in a stable position within the ductal ampulla. This event occurred just after the vigorous endotracheal suctioning and it is possible that the suction catheter mechanically dislodged the coil mass. The coil was snared and delivered back across the ductus successfully without the need for additional arterial puncture.

Depending on the visual assessment of the ductal ampulla, we tailored the length of the coils delivered. Two potential problems of coil closure of large ducts are: left pulmonary artery stenosis and iatrogenic aortic coarctation. The pre-term child developed turbulent flow in the descending aorta with a Doppler gradient of 25 mmHg following coil closure. Five months later, the gradient had decreased to 12 mmHg. Aydogan et al. reported a similar experience where a child developed a pressure gradient of 47 mmHg following coil closure. Five months later, the gradient had decreased to 12 mmHg. Aydogan et al. also reported a similar experience where a child developed a pressure gradient of 47 mmHg following coil closure of PDA that decreased to 21 mmHg at follow-up.

We believe that coil occlusion has potential advantages over occlusive devices in small infants as the aortic retention disk of the device can protrude into the aorta. The recent introduction of the angled Amplatzer PDA occluder may overcome some of these limitations. Video-assisted thoracoscopic surgery has been shown to be effective and minimally traumatic even in small children. This facility is, however, not universally available.

Conclusions: Transcatheter coil closure of PDA is safe even in sick, mechanically ventilated infants. Biopptome assistance, usage of thicker coils, simultaneous delivery of multiple coils and tailoring the length of the coil contribute to the success of this procedure. Considering the much lesser morbidity compared with that of conventional surgical interruption by thoracotomy, coil closure might be superior in such a situation. However, only ducts with adequate ampulla are suitable for coil closure and this procedure needs certain degree of expertise.

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Focal Extra Strength of a Stent Causing Instent Hourglass Stenosis: An Unusual Complication

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We report an unusual complication of a 25 mm long stent, which did not expand at all for 1 mm in its proximal segment, while rest of the 24 mm length of the stent got fully expanded. Repeated attempts to expand the extremely focal unexpanded part of the stent at high pressure led to rupture of the stent balloon and its entrapment. We failed to retrieve the balloon using various techniques and the patient had to be sent for coronary artery bypass graft surgery. (Indian Heart J 2004; 56: 235–238)

Key Words: Stent, Coronary angioplasty, Coronary artery disease, Stents

A n underexpanded stent predisposes to both subacute thrombosis and restenosis. While such a problem can be addressed by dilating the underexpanded segment using high pressure coronary balloons, it is prudent to prevent this problem beforehand. The best way of prevention is by adequate pre-dilation with a balloon of proper size and by decalcifying the calcified lesions with rotablator (rendering the lesion more compliant), which allows proper expansion of the balloon. We report a case, where during pre-dilation of a lesion with an adequate-sized balloon at 6 atm, there was no waist, signifying no restraint from the vessel wall. However, during stent deployment a marked and extremely focal waisting of the stent balloon was noted (due to extremely focal unexpansion of the stent) producing an hourglass deformity of the stent which was noted at 6 atm and persisted even at a high pressure of 16 atm. Further increase in pressure in the stent balloon led to rupture of the balloon and its entrapment which could not be retrieved percutaneously despite using all the known techniques, forcing us to send the patient for emergency surgical retrieval of the stent along with the entrapped balloon followed by coronary artery bypass graft surgery (CABG).

Case Report

A 45-year-old hypertensive, non-diabetic male patient with history of exertional angina for six months had a 90%
concentric long lesion in the mid left anterior descending (LAD) artery (Fig. 1a) and a 75% eccentric lesion in the first obtuse marginal branch of the left circumflex (LCx) artery. The right coronary artery (RCA) was normal.

The lesion in LAD was crossed with a Luge wire (Boston Scientific, Scimed, France) and dilated with a 3×20 mm Maverick balloon (Boston Scientific, Scimed, France). The waist of the balloon disappeared completely at 6 atm (Fig. 1b). Following balloon dilation, there was 25% residual stenosis with TIMI II flow and a distal dissection. Hence a 3×25 mm balloon expandable stent (Tenax, Biotronik) was taken and positioned across the lesion. At 6 atm all but 1 mm segment of the stent balloon failed to expand producing an hourglass appearance which persisted even up to a high pressure of 16 atm (Fig. 1c). Further increase in the pressure (to 17 atm) resulted in the rupture of the balloon leaving an extremely focal unexpanded segment of the stent in its proximal part. At

Fig. 1a. Arrow showing lesion in LAD in left anterior oblique cranial view. b. Fully inflated balloon across the lesion in LAD. c. Focally unexpanded stent at high pressure of 16 atm. LAD: left anterior descending
this point of time, though the balloon could be advanced distal to the distal end of the stent, but it could not be pulled proximal to the proximal end of the stent because the profile of the distal portion of the balloon had become larger after bursting and got entangled in the focal, unexpanded portion of the stent (Fig. 2a). At this juncture the patient had TIMI I flow, chest pain and hemodynamic compromise. We intended to pass a second coronary guidewire through the center of the unexpanded portion alongside the shaft of the previous entrapped balloon and inflate a non-compliant coronary balloon (that can withstand higher pressures than stent balloons) at high pressure which was likely to expand the unexpanded segment and also disengage the previous entrapped balloon and improve coronary blood flow. So we passed a second Luge wire and over it a 3×20 mm Quantum balloon (Boston Scientific, Scimed, France) and inflated it to 18 atm. This resulted in quick restoration of blood flow, relief of chest pain and resumption of hemodynamics. However, following withdrawal of this balloon, the previously entrapped balloon rather than getting disengaged got further entrapped and started behaving as a balloon implanted

within the stent. At this juncture, the balloon could not be even advanced distally. This was because the wire had passed through the struts of the unexpanded segment of the stent and not through the center of the unexpanded stent. Thus, though the high pressure balloon could

Fig. 2a. Schematic diagram showing higher profile of the distal portion of the ruptured stent balloon entrapped within the unexpanded segment of the stent.

Fig. 2b. Part of the expanded balloon compressing the unexpanded segment of the stent due to passage of guidewire through its struts.

Fig. 2c. Schematic diagram showing further narrowing of the lumen of the unexpanded segment of the stent on inflating the second balloon which inadvertently passed through its struts.
overcome the strength of this unexpanded segment of the stent and expanded the stent through its struts creating a new opening within the stent, it further constricted the previously narrowed focal area of the stent thereby impacting the balloon within the stent (Figs 2b and 2c). This however, improved the coronary blood flow to TIMI III by compressing the higher profile ruptured balloon (Fig. 3).

The guiding catheter was then taken deep into the LAD within the stented segment and repeated attempts at withdrawal of the balloon using traction resulted in fracture of the shaft of the balloon catheter. The proximal shaft easily came out of the guiding catheter, while the balloon trapped distal to the underexpanded segment was still lying over the guidewire. We passed a 2 mm Amplatz gooseneck microsnare (Microvena, MN, USA) over this guidewire till the underexpanded segment of the stent and tried to snare out the fractured and entrapped balloon. After repeated attempts failed, the guiding catheter was again advanced till the underexpanded segment and a Cook’s flexible biopsy forceps (3F, 120 cm, Cook Group Company, USA) was advanced through the guiding catheter into the stented segment in an attempt to catch a portion of the shaft of the fractured balloon but failed to retrieve the balloon catheter. At this point of time, although the patient was hemodynamically stable and had a normally flowing LAD, the situation was precarious because of a focally unexpanded stent and a fractured and entrapped balloon within it. So we had no other option but to send the patient for urgent surgery to retrieve the stent with the entrapped balloon and complete the process of revascularization by bypass grafts. During surgery, the stent along with the entrapped and fractured balloon was successfully retrieved (Fig. 4) and the patient made an uneventful recovery.

**Fig. 3.** Left coronary angiogram showing TIMI III flow in LAD despite the presence of entrapped balloon within the focally unexpanded stent. LAD: left anterior descending

**Discussion**

In the last 2000 of our cases undergoing coronary angioplasty, this is the only one who had to be sent for an emergency CABG and that too in a hemodynamically stable state with TIMI III flow. There are reports in world literature of unexpanded stents due to slippage of stent from the balloon, prior to the placement of stent. Subsequently, either the distal or the proximal portion of the stent remained unexpanded, depending on whether the stent had slipped distal or proximal to the balloon.\(^1\) There are also reports of stent unexpansion due to rupture of stent balloon during stent implantation. This may occur in a calcified lesion or with a weak balloon. Such cases are usually managed by removing the ruptured balloon and subsequently expanding the stent with another balloon.\(^2\) Another way of tackling this type of complication is the usage of a power syringe to deliver a controlled powerful injection, which expands the leaking balloon with the shear force of injection in cases of pinhole rupture. This was used to expand the Palmaz-Schatz stent in a case of renal angioplasty where the stent remained unexpanded because of balloon rupture.\(^3\)

However, to the best of our knowledge there is no report in world literature of focal unexpansion of a stent in a situation like the one described above. The balloon was fully expanded before stent implantation in the artery and the waist of the balloon had disappeared completely at 6 atm. Hence, any particular lesion characteristic like calcification cannot explain the focal unexpansion of the stent. The most probable mechanism was a manufacturing defect in the stent. Tenax (Biotronik) is a tubular slotted stent, which contains multiple segments connected by 0.75 mm long articulations. We hypothesize that one set of articulations all along the circumference of the stent contained extra metal which made this focal segment relatively stronger than the rest of the stent and prevented it from expanding.
even at high pressure of 16 atm. This focal band of metal ring produced focal pressure on the stent balloon resulting in its rupture.

The purpose of this report is to make the operators and stent companies aware of this type of complication, which may jeopardize the success of a commonly performed interventional procedure like stent implantation.

**Conclusions:** If such a situation like the one described occurs in the catheterization laboratory one should not overzealously try to expand the stent by inflating the stent balloon at or near the rated burst pressure, which may result in rupture of balloon and its entrapment as occurred in our case. Rather, one should attempt to expand the stent with non-compliant balloons which can withstand pressure higher than the stent balloon. One should be careful to avoid bursting of the balloon, which may lead to its entrapment as occurred in our case and thus force even a hemodynamically stable patient for emergency surgery.

**References**

Apical Hypertrophic Cardiomyopathy with Apical Necrosis and Aneurysm Formation

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Apical hypertrophic cardiomyopathy, characterized by giant T-waves and spade-shaped left ventricular cavity is prevalent in Oriental people, particularly the Japanese. We report an asymptomatic case of apical hypertrophic cardiomyopathy progressing to myocardial necrosis and aneurysm formation because of the chronic myocardial ischemia at the apex. (Indian Heart J 2004; 56: 239–241)

Key Words: Hypertrophic cardiomyopathy, Myocardial aneurysm, Angiography

A pical hypertrophic cardiomyopathy (HCM), a variant of HCM, is rare in the West but more common in oriental people, especially in the Japanese. It is characterized by the presence of giant T-waves and a spade-shaped left ventricular (LV) cavity on ventriculography. Transthoracic echocardiography (TTE) is a useful tool for the diagnosis, but sometimes its value is limited due to the poor echocardiographic window and presence of artifacts. Therefore, other diagnostic modalities, like contrast echocardiography and cine magnetic resonance imaging (MRI), have emerged as more confirmative tools. Apical HCM usually has benign prognosis although some serious cardiovascular complications such as myocardial infarction, ventricular tachycardia and syncope are also reported.6

We report a case of asymptomatic apical HCM complicated by apical necrosis and aneurysm formation found on the routine chest X-ray check-up in a young man.

Case Report

A 29-year-old man was referred to our institution from a local clinic for the evaluation of abnormal chest X-ray found on a routine check-up. He had no complaints of dyspnea, chest pain or palpitation. He was not a smoker but had a family history of sudden cardiac death of his uncle in adulthood. Physical examination revealed a blood pressure of 116/70 mmHg and pulse rate of 80 beats per min. There was no heart murmur or gallop and the lung was clear. The chest X-ray in the posteroanterior view demonstrated a focal curvilinear calcific density at the phrenic area. The calcific density was located anteriorly in the left lateral position (Figs 1A and 1B). Under the fluoroscopy, round-shaped calcific density was noted at LV apical area (Fig. 1C). This suggested local pericardial calcification or a calcified tumor. The electrocardiogram (ECG) revealed inverted T-waves in leads V2-V6, II, III and avF. Echocardiography showed symmetric apical hypertrophy with systolic obliteration of the LV cavity and an ejection fraction of 66%. On the apical area of the hypertrophied myocardium, a saccular cystic structure with thin wall was noted and the luminal surface was irregular without thrombus. Color flow showed systolic in-flow and diastolic out-flow to the aneurysm. Left ventriculography revealed a bottle gourd-shaped LV due to

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a saccular aneurysm at the apex. During diastole, the apical aneurysm communicated with the LV and the hypertrophied apical muscle obliterated the LV apex and separated the aneurysm from the LV cavity (Figs. 2A and 2B). Coronary angiography showed no stenotic lesion but the distal segment of left anterior descending artery (LAD) was deviated to the septum because of the aneurysm. $^{99m}$Tc-sestamibi myocardial perfusion single-photon emission computed tomography (SPECT) showed increased wall thickness at the LV apex with a focally fixed perfusion defect, but the aneurysm did not show any uptake of the tracer (Fig. 3). Signal-averaged ECG and 24-hour ECG monitoring did not show any abnormal finding. The patient was discharged on coumadin to prevent thrombosis in the aneurysm. During the 2-year follow-up period, the patient remained asymptomatic.

**Discussion**

HCM shows variable clinical presentations, prevalence, morphology and prognosis depending on the race. Apical HCM, first described in Japan, is a rare form of HCM with an apical distribution of hypertrophy and has been regarded as an atypical phenotype of non-obstructive HCM more prevalent in Japanese people. According to Kitaoka et al., apical HCM is seen in 15% of Japanese and 3% of American patients of HCM. Usually it is considered as a benign condition and is detected incidentally like in present case.

TTE is a useful diagnostic tool for HCM, but poor visualization of the endocardial border of the LV apex is a limiting factor for the diagnosis of the apical HCM. Further, in our patient, the endocardial border of the aneurysm was not clearly seen in the TTE. Contrast echocardiography and MRI are considered as useful and accurate diagnostic modalities. HCM with midventricular obstruction and apical hypertrophy can induce apical aneurysm formation though the exact mechanism of aneurysm formation is not known. In a case of mid-ventricular obstruction reported by Harada et al., coronary angiogram showed no stenotic lesion in the epicardial coronary artery supplying the apex, but myocardial perfusion imaging showed a fixed defect in the LV apex. Our patient also showed no narrowing of the major coronary arteries but there was a perfusion defect in the aneurysm. Apical HCM can show a resting "Solar Polar" map pattern and a relative apical ischemia on stress images even in the absence of epicardial coronary artery obstruction. The mismatch between fixed epicardial blood supply, and huge muscle mass can lead to sustained myocardial ischemia and necrosis. In this young patient, long-standing myocardial ischemia and necrosis led to the severe calcification seen on the routine chest X-ray and fluoroscopy.

The apical aneurysm can be complicated with serious arrhythmias i.e. ventricular tachycardia and may require antiarrhythmic medication or implantable defibrillator to prevent sudden cardiac death. Thin-walled aneurysms can increase in size in a short period and should be considered for aneurysmectomy. In rare cases, thrombosis can occur in the aneurysm which in turn causes systemic embolization. Therefore, anticoagulation therapy is needed for patients with large aneurysms to prevent systemic thromboembolism.

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Stenting Stenosed Aortopulmonary Collateral Arteries in Pulmonary Atresia with Ventricular Septal Defect

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We present two cases of pulmonary atresia with ventricular septal defect who were not suitable for corrective surgery due to absent or hypoplastic native pulmonary arteries and were quite symptomatic following shunt surgery. We dilated and stented stenosed aortopulmonary collaterals as palliative procedure with improvement in oxygen saturation, and significant symptomatic relief. (Indian Heart J 2004; 56: 242-244)

Key Words: Pulmonary atresia, Stents, Congenital heart disease

Pulmonary atresia with ventricular septal defect (PA-VSD) has major abnormalities in the size and distribution of pulmonary arterial tree. The pulmonary blood supply may be through patent ductus arteriosus (PDA) or well developed collaterals from the aorta. These collaterals are stenotic in nearly 60% of cases. The stenosis may be discrete or long and may progress with time.1 The stenosis may be congenital or acquired. Stenosis of collateral arteries may develop progressively and thereby cause a decrease in pulmonary blood supply. We present two cases of PA-VSD who were not suitable for corrective surgery in view of absent or hypoplastic pulmonary arteries (PAs); they improved symptomatically after dilation and stent implantation of stenosed major aortopulmonary collateral arteries (MAPCAs).

Case Reports
Case 1: An 8-year-old boy with PA-VSD presented with worsening cyanosis and dyspnea. He had undergone modified Blalock-Taussig (BT) shunt on the right and left sides at 1 and 7 years of age, respectively. His oxygen saturation was 50%. Echocardiography did not show any native PAs. The subclavian ends of BT shunts were seen; but distal ends were not visualized.

Angiography was done to define the pulmonary artery anatomy to decide the feasibility of corrective surgery. It showed patent shunts, from right subclavian artery to an aortopulmonary collateral supplying the upper lobe of the right lung and left subclavian artery to an aneurysmally dilated part of left upper pulmonary artery. Aortogram showed two MAPCAs supplying the right lung; the upper MAPCA was smaller and supplied the right upper lobe to which the right BT shunt had been done; lower MAPCA was larger, and supplied the right middle and lower lobes. This lower MAPCA had long segment, proximal stenosis. The left lung had multiple small collaterals supplying it. Pulmonary venous wedge angiography did not show native PAs.

The patient was taken up for palliative surgery in view of his symptomatic status. The shunt on the left was taken down and 6 mm Goretex tube was interposed between the left subclavian artery and one of the collaterals to left lung. Patient did not improve symptomatically and oxygen saturation remained at 50%.

As a palliative procedure, we decided to dilate the stenosed right lower MAPCA to improve the systemic saturation. Angiography showed tight narrowing at the origin (Fig. 1). The ostium was intubated with a 6 F renal guiding catheter. The lesion was crossed with 0.018", SV5, 300 cm wire. The lesion was pre-dilated with a 4 mm x 2 cm Opta-Pro balloon at 6 atm pressure. The lesion was stented with 5 mm x 18 mm Genesis stent at 12 atm pressure (Fig. 2). The result was good, with rapid clearance of contrast on check angiography. Patient improved symptomatically, and systemic saturation was stable at 71%.

Case 2: A 5-year-old girl was diagnosed to have PA-VSD. She had tiny confluent PAs and a large MAPCA supplying the right lung. There was a large MAPCA to the left lung. She underwent unifocalization of the right-sided MAPCAs and modified BT shunt on the same side at the age of 3 years.

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She presented after 2 years with easy fatiguability. Oxygen saturation was 70%. Angiogram showed functioning BT shunt filling hypoplastic PAs. The unifocalized right-sided MAPCA supplied right lung with good arborization. There was a large MAPCA to the left lung which divided into 2 branches, both having proximal stenoses (Fig. 3). Since PAs were hypoplastic, she was considered unsuitable for complete repair. So we decided to dilate the stenosed branches of left MAPCA as a palliative...
procedure to improve oxygen saturation. Stenosis in the upper branch was crossed with a 0.018\" SV5, 300 cm wire and stented with 6x18 mm Genesis stent at 14 atm pressure. There was significant residual stenosis in the midpoint of MAPCA, hence it was post-dilated to 20 atm pressure. Angiogram still showed mild stenosis in the mid segment. Stenosis in the lower branch was dilated and stented with 5x18 mm Genesis stent (Fig. 4). The distal MAPCA pressure improved from 12/9 mmHg (mean 10 mmHg) to 20/9 mmHg (mean 12 mmHg) in the upper MAPCA, and from 12/4 mmHg (mean 8 mmHg) to 27/17 mmHg (mean 12 mmHg) in the lower MAPCA after stenting. The oxygen saturation improved to 90%.

Discussion

PA-VSD has variable pulmonary blood flow. The blood supply is either through a PDA or through MAPCAs. Many of these collaterals are stenosed or hypertensive which pose a problem in management. The feasibility for corrective surgery depends on the size of native PAs. In patients with PA-VSD who are not suitable for corrective surgery due to unsuitable pulmonary artery anatomy, various palliative procedures have been tried, such as BT and central aortopulmonary shunts. Transcatheter palliation has been achieved in symptomatic patients by dilating and stenting the stenosed aortopulmonary collaterals.\(^5\) In patients who are symptomatic following shunt surgery, symptom relief and improvement in oxygen saturation have been seen following dilation and stenting of the restrictive shunts.\(^3\)\(^5\)\(^6\) Balloon expandable and self expanding stents have been used successfully in stenting the stenosed MAPCAs.\(^3\)\(^6\) Luc et al.\(^7\) have reported successful redilation of stenosis in collaterals which were resistant to high pressure initial dilatation, by using cutting balloon. Pettersen et al.\(^5\) have reported successful stenting of a right coronary to PA fistula to augment pulmonary blood flow. In neonates, stenting of closing ductus arteriosus has been done to maintain pulmonary blood flow.\(^5\)\(^9\)

Our first patient had undergone 3 shunts and still remained symptomatic, although all the shunts had been patent. The shunts had failed to provide adequate increase in systemic saturation, as they were between the systemic arteries and smaller aortopulmonary collaterals. Native pulmonary arteries did not grow after the shunts. So he was thought to be unsuitable for complete repair. Hence we dilated and stented the larger collateral, which otherwise would have needed another surgery involving lots of dissection to reach the collateral. Fortunately this right-sided collateral was large with good arborization and supplied the right middle and lower lobes. After stenting, the diameter of the MAPCA increased from 2.3 to 4.7 mm at the stenotic segment with improvement in oxygen saturation. Second patient also was not suitable for corrective surgery. The unifocalized right-sided MAPCAs with shunt on right side was working well. But the native PAs had not grown well. The major MAPCA on left side had multiple stenoses which were quite distal from the hilum. It would have been difficult surgically to address those stenotic lesions through mid sternotomy approach. So as a palliative procedure, a decision was taken to dilate and stent the collateral. Sometimes MAPCAs can be quite difficult to dilate. In our second patient, in spite of dilating with 20 atm high pressure balloon, there was narrowing in the mid segment. Such resistant lesions have been described earlier.\(^7\) In both of our patients improvement has been achieved by combination of various strategies such as shunt procedures and endovascular stenting of MAPCAs. We accept that this is just a palliation, and patients may become symptomatic again over a period of time.

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A young primiparous lady presented with drug-refractory atrial tachycardia which had led to cardiomyopathy. Three attempts with electrical cardioversion were also unsuccessful. She was rescued by radiofrequency ablation. (Indian Heart J 2004; 56: 245–247)

Key Words: Radiofrequency ablation, Tachyarrhythmia, Pregnancy

In pregnancy, significant changes occur in the hormonal and hemodynamic state of women that make them more susceptible to arrhythmias. Palpitations are frequently reported and the usual cause is sinus tachycardia. The incidence of paroxysmal supraventricular tachycardia is increased during pregnancy and tends to recur with each pregnancy, whereas atrial fibrillation and ventricular tachycardia are rarely seen. We describe a case of atrial tachycardia that became incessant during pregnancy, leading to cardiomyopathy. We performed successful radiofrequency (RF) ablation of the atrial tachycardia, hitherto unreported in the pregnant state.

Case Report

A 24-year-old primigravida was referred at 6 months of pregnancy for uncontrolled symptomatic atrial tachycardia. History of episodic rapid palpitations predated her pregnancy by 6 months. They were infrequent, abrupt in onset and termination, without giddiness or syncope. She was not on any treatment for the same. However, after conceiving, the palpitations had increased in frequency and duration. On presentation, she had associated breathlessness on exertion of one month duration. An attempt was made to control the ventricular rate by pharmacologic means. Injection adenosine, metoprolol, diltiazem and verapamil were tried but there was no success. Synchronized 200 J DC cardioversion was then attempted, but to no avail. She was then loaded with intravenous amiodarone and DC cardioversion on amiodarone was again tried. However, this was also unsuccessful and she continued to be in tachycardia, although the rate had slowed from 240 beats per min (bpm) to 166 bpm.

On clinical examination, the pulse was 166 bpm; jugular venous pressure was raised; her systolic blood pressure (BP) was 90 mmHg. There was tender hepatomegaly. An S₃ gallop was heard. The electrocardiogram was suggestive of atrial tachycardia with cycle length (CL) of 360 ms with an upright p-wave in lead II, equiphasic p in lead III and inverted p in lead V₁ (Fig. 1). The echocardiogram revealed generalized hypokinesia and left ventricular ejection fraction (LVEF) of 22%. The tachycardia rate decreased on amiodarone and propafenone (CL 460 msec), but her symptoms of breathlessness persisted; she was in NYHA class III by this time. A third attempt at cardioversion was given but that was only transiently effective in restoring sinus rhythm. A pelvic ultrasound revealed normal fetal growth and development. Since the tachycardia was intractable and had led to congestive heart failure, we decided to ablate the tachycardia in spite of her pregnant status.

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Fig. 1. Surface ECG at presentation suggesting atrial tachycardia. Note the upright p-wave in lead II, and inverted in V₁.
The electrophysiology procedure was performed after shielding the abdomen against radiation. Two electrode catheters were placed, one in the right ventricle and the other for mapping in the right atrium. Both bipolar as well as tip unipolar signals from the mapping catheter were recorded. A Webster thermocouple medium curve catheter with Stockert ablator was used for RF ablation. Mapping demonstrated the low crista region in the right atrium to be the site of origin of tachycardia with local activation preceding the onset of the p-wave by 20 ms (Fig. 2a). RF energy at this site did terminate the tachycardia abruptly. However, after few minutes there was a recurrence of atrial tachycardia at a rate of 140 bpm and the morphology of the p-wave of this tachycardia was slightly different from the first atrial tachycardia. Mapping of the second slower persistent tachycardia revealed earliest atrial activation 1 cm higher than the previous site. At this site the endocardial activation was 29 ms ahead of the p-wave and there was low amplitude fractioned signal with a QS pattern in the unipolar distal RF signal (Fig. 2b). RF energy immediately terminated the second incessant tachycardia and sinus rhythm was restored (Fig. 3). No tachycardia was inducible thereafter. Low-dose fluoroscopy was used and the fluoroscopy time was 4 min.

After 2 days, she had a recurrence of atrial tachycardia with a rate of 110 bpm but this tachycardia spontaneously terminated after a few minutes. Her symptomatic status improved. She had an uneventful delivery at term by caesarian section. The child was healthy. Short episodes of
well-tolerated atrial tachycardia at a rate of 110-116 bpm
continued for a few days and then disappeared sponta-
neously.

On 6 months follow-up after ablation she was in sinus
rhythm without any medications. Clinical examination was
normal. Chest radiogram revealed normal cardiac size
(Fig. 4). Repeat echocardiogram showed normal LVEF of
50%. Her child was growing normally. At one year after
delivery, she continues to be asymptomatic.

Discussion

Atrial tachycardias result from abnormalities of impulse
formation or conduction in atrial tissue. They usually tend
to cluster along the crista terminals in the right atrium
and from within a pulmonary vein in the left atrium.
Underlying mechanism of atrial tachycardia is most often
abnormal automaticity. This may be from a single or multiple
foci. The majority arise from single focus; multiple
foci are present in 10-15 % of patients.3

Automatic atrial tachycardias are often poorly res-
ponsive to long-term medical treatment and are sometimes
incessant. These tachycardias have been associated
with tachycardia-induced cardiomyopathy which is
frequently reversible after termination of tachycardia.4,5 RF
ablation has been successfully applied to the treatment of
tachyarrhythmias of atrial origin. The immediate success
rate of atrial tachycardia ablation has been somewhat lower
(90%) than that for atrioventricular (AV) nodal reentrant
and AV reentrant tachycardia.2 The recurrence rate is also
generally higher. Successful ablation of one site
occasionally leads to the appearance of atrial focus at a
different site.

Acute treatment of atrial tachycardias for pregnant
women is same as that for other patients. However, chronic
drug therapy during pregnancy should be reserved for only
the frequent, hemodynamically significant arrhythmic
episodes. For rate control, digoxin and beta-blockers are the
drugs of choice. For long-term therapy, beta-blocking
agents with beta-1 selectivity are first-line drugs; class IC
agents (flecainide) or the class III drugs (sotalol) represent
effective therapeutic alternatives.6 Flecainide is commonly
used for conversion to sinus rhythm in patients of atrial
tachycardia. However, its safety in pregnancy is not proved.
It has been classified under category C (studies in animals
have revealed adverse effects on the fetus; no controlled
studies in humans available; should be used only if the
potential benefit justifies the potential risk to the fetus).7 It
has a negative ionotropic effect and can cause or worsen
heart failure. It is also not readily available. Amiodarone is
not safe for the fetus.

RF ablation poses the hazard of radiation on the fetus. Standard fluoroscopy could deliver 1-2 Rads/min, and high
level fluoroscopy or cine as much as 5-10 Rads/min. The
amount of radiation scattered to the uterus and absorbed
by the embryo is <5% of the radiation absorbed by the
directly radiated tissue. Current recommendations related
to intrauterine radiation exposure suggest that with
exposure to <5 Rads, the patient can be reassured of a very
low likelihood of risk. With 5-10 Rads, the patient should
be counseled regarding low risk of problems; and with 10-
15 Rads during the first six weeks, termination of pregnancy should be considered.7

RF ablation performed as the therapeutic challenge in this case was to balance the hazards of the procedure with the ill effects associated with the cardiomyopathy secondary
to incessant tachycardia. While immediate success was
achieved by RF ablation, the patient continued to have atrial
tachycardia but at a much slower rate, probably due to the
hormonal and hemodynamic milieu of pregnancy. After
the delivery, she remained in sinus rhythm and the
cardiomyopathy disappeared with the ejection fraction
rising to 50% within 6 months.

Atrial tachycardia in pregnancy poses therapeutic
challenges. Incessant tachycardias resulting in tachy-
cardiomyopathy may require RF ablation. Interestingly,
these results may be influenced by the pregnant state.

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Torsade de Pointes in a Case of Pheochromocytoma - An Unusual Presentation of an Uncommon Disease

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We report the case of a middle aged lady with dilated cardiomyopathy, presenting with recurrent syncope due to torsade de pointes. Further evaluation revealed that she had a pheochromocytoma which caused the arrhythmia. (Indian Heart J 2004; 56: 248–249)

Key Words: Dilated cardiomyopathy, Ventricular arrhythmia, Pheochromocytoma

Patients with pheochromocytoma are known to have various cardiac complications including arrhythmias, heart failure, myocardial infarction and cardiomyopathy. QT prolongation has been reported in these patients and can predispose to serious ventricular arrhythmias resulting in syncope and cardiac death in the worst cases. We report here the case of a lady who was diagnosed to have dilated cardiomyopathy and had episodes of syncope in the past, which worsened with the initiation of β-blocker therapy. Torsade de pointes was detected on Holter monitoring and further evaluation revealed the etiology to be the presence of a pheochromocytoma.

Case Report

A 36-year-old lady presented to us with history of breathlessness on exertion (NYHA class II), fatigue, loss of weight and fearfulness of 2 years duration. She also had two episodes of syncope in this period for which a computerized tomography (CT) of brain was done which was found to be normal. There was no family history of sudden cardiac death. On examination her blood pressure was 140/90 mmHg and heart rate was 120 beats per min. Cardiovascular examination was unremarkable. Hematologic findings were normal. Serum electrolytes were as follows: sodium 140 mmol/L, potassium 4 mmol/L, calcium 9.2 mg%, phosphorus 3.6 mg%, magnesium 1.99 mg%. Fasting blood glucose, urea, creatinine, liver and thyroid function tests were all normal. Her baseline electrocardiogram (ECG) showed a QTc interval of 551 msec (Fig. 1). The echocardiogram revealed global hypokinesia with an ejection fraction of 34%. Chest X-ray revealed a cardiothoracic ratio (CTR) of 60% with mild pulmonary venous congestion. Based on the above findings a diagnosis of dilated cardiomyopathy was made and she was started on β-blockers, angiotensin-converting enzyme (ACE) inhibitors and diuretics. Four days later she presented to the emergency services with palpitation followed by syncope. She was very agitated and her blood pressure was 200/120 mmHg. There were no clinical features suggesting secondary hypertension. Dose of β-blocker was increased. Over the next 3 days she reported a paradoxical increase in the number of syncopal episodes. Her Holter monitoring revealed torsades de pointes (Fig. 2), hence she was admitted in the coronary care unit. She had multiple episodes of torsades which did not respond to intravenous magnesium. Since she had a prolonged QTc on ECG, possibility of a congenital long QT syndrome (LQTS) was considered (no acquired causes hitherto being found) and the dose of the β-blocker was further increased. She was found to have paroxysmal rise in blood pressure associated with sweating and panic attacks. Escalation in β-blocker dose was associated with an increase in arrhythmogenicity.

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Fig. 1. Baseline electrocardiogram showing QTc of 551 ms.
possibility of a pheochromocytoma was considered as the cause of an acquired LQTS. An ultrasound abdomen revealed a 4×3 cm echogenic mass in the left adrenal region. Her 24-hour urine vanillylmandelic acid (VMA) excretion was 14.2 mg in 2140 ml. A CT scan and 131-meta iodo benzyl guanidine scintigram confirmed the diagnosis. She was started on α-blockers and her β-blocker dose was tapered. Her arrhythmias decreased in frequency with progressive α-blockade. She was operated and the biopsy confirmed the diagnosis. Her post-operative period was uneventful. Two weeks after surgery her echocardiogram showed an improvement in ejection fraction from 34% to 45%.

Discussion

We report here a rare case of torsade de pointes occurring in a patient with pheochromocytoma. In pheochromocytoma complications such as heart failure, myocardial infarction and arrhythmias have been described. Though several cardiac arrhythmias have been reported, the occurrence of torsades in pheochromocytoma is rare; only a few case reports are available in literature.

Torsades occurring in pheochromocytoma is interesting in the sense that this is a completely reversible condition following the tumor removal. However, long QT interval in this condition may persist as long as six years after surgery.

In our patient, β-blocker therapy initiated for her dilated cardiomyopathy actually caused an increase in the frequency of arrhythmias and syncope. Further increase in the dose of β-blocker to control the blood pressure caused an unusual increase in the frequency of arrhythmias. Though β-blockers are used in the treatment of congenital LQTS, they are contraindicated in acquired LQTS. This is because the bradycardia produced by these agents can precipitate a torsades. Besides, β-blockers are known to decrease the outward potassium current. This increases the susceptibility of an individual with an acquired LQTS to arrhythmias as it is the rapid component of the delayed rectifier potassium outward current that is most commonly affected. By blocking the β-receptors in our patient with pheochromocytoma, the α-receptor stimulation continued unabated. Alpha adrenergic stimulation prolongs the action potential. However, animal studies have shown that α-adrenergic stimulation triggered ventricular arrhythmias only when the myocardial potassium channels were blocked, thus mimicking a congenital LQTS or a repolarization abnormality.

Conclusions: QT prolongation can occur in patients with pheochromocytoma and may give rise to dangerous arrhythmias like torsades. It would be advisable to evaluate patients with dilated cardiomyopathy who also have high blood pressure to exclude secondary causes of hypertension. Our case illustrates that pheochromocytomas can be a rare, reversible cause of torsade de pointes.

References

Eptifibatide-Induced Profound Thrombocytopenia

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We report a case of profound thrombocytopenia, 2 hours following eptifibatide therapy which got reversed within 12 hours of discontinuation of eptifibatide. (Indian Heart J 2004; 56: 250-251)

Key Words: Thrombocytopenia, Eptifibatide, Coronary angioplasty

Acute profound thrombocytopenia is not commonly seen in patients receiving eptifibatide. Immunologic mechanisms are proposed for etiopathogenesis of thrombocytopenia which are reversible. Other causes of thrombocytopenia should also be ruled out in such cases. The standard treatment is discontinuation of the offending drug and providing supportive measures.

Case Report

A 54-year-old hypertensive lady underwent elective coronary angiogram due to crescendo angina. This revealed 90% stenosis in distal circumflex artery and therefore, percutaneous coronary intervention (PCI) with eptifibatide cover was planned. During the procedure she received a total of 11,000 units of intravenous heparin and two boluses of intravenous eptifibatide 180 mcg/kg, 10 min apart followed by infusion at the rate of 2 mcg/kg/min. Activated clotting time (ACT) was kept around 250 sec. A 3×18 mm sirolimus-eluting stent was successfully deployed. She had mild gum oozing which was treated with cold saline gargles. Her baseline platelet count was 2,32,000 per cmm. Two hours post-procedure, her platelet count dipped to 4,000 per cmm. Repeat heparinized sample to rule out pseudothrombocytopenia also revealed platelet count of 6,000 per cmm. Eptifibatide therapy was discontinued, antiplatelet drugs (asprin and clopidogrel) were withheld, intravenous dexamethasone 8 mg 8 hourly was started and 2 units each of platelet concentrate and platelet apheresis were transfused, which raised the platelet count to 35,000 per cmm. Over next 12 hours, the platelet count stabilized at 1,26,000 per cmm, and remained so till 48 hours post-procedure. She developed petechial spots on the back as well as large ecchymotic patches on the right forearm and left leg 12 hours post-PCI (Fig. 1). No other hematological sequelae was noted. At 6 weeks follow-up, she is doing well with no recurrence of thrombocytopenia.

Discussion

Drug-induced acute profound thrombocytopenia is defined as a decrease in platelet count to below 20,000 per cmm within 24 hours of exposure to the drug. In our patient, normal baseline platelet count and other hematological parameters (prothrombin time, red and white blood cell count) ruled out bone marrow dysfunction, non-immune and immune thrombocytopenia as a cause of thrombocytopenia. Pseudothrombocytopenia was ruled out by manually examining peripheral smear (heparinized sample). Resolution of thrombocytopenia within 24 hours ruled out clopidogrel as a cause of thrombocytopenia and
A acute profound thrombocytopenia associated with abciximab has been well described. However, this complication has not been commonly reported in association with eptifibatide. The incidence of acute thrombocytopenia with eptifibatide in PURSUIT trial was 4.9% for platelet count <100,000 per cmm, 0.5% for severe thrombocytopenia (platelet count <50,000/cmm) and 0.1% for profound thrombocytopenia (platelet count <20,000/cmm). The close temporal relationship to administration and the resolution of the adverse reaction on discontinuation of the offending drug support the likelihood that the profound acute reversible thrombocytopenia in our patient was due to eptifibatide.

Several hypotheses have been proposed to explain the mechanism of glycoprotein (Gp) IIb/IIIa inhibitors causing thrombocytopenia. Some patients have pre-formed antibodies to ligand-induced binding sites (LIBSs) which are normally not exposed on the surface of the platelets. Binding of Gp IIb-IIIa inhibitors to the receptors on the platelets induces conformational changes that expose the LIBSs which leads to binding of anti-LIBSs antibodies causing platelet clearance by reticulo-endothelial (RE) system. This endorses the response of this subset of patients to steroid treatment therapy. Another possible mechanism is increased P-selectin expression with abciximab that causes paradoxical activation and aggregation of platelets.

Patients receiving parenteral Gp IIb/IIIa inhibitors should be monitored for development of thrombocytopenia within the first 24 hours of drug administration, and for patients receiving abciximab therapy, a platelet count at 2 to 4 hours after the start of therapy is recommended. If detected, true thrombocytopenia should be confirmed and all potential causes should be evaluated. If Gp IIb/IIIa inhibitor is the likely culprit for thrombocytopenia, the infusion should be stopped. Aspirin should be withheld only in patients with high risk for bleeding and whose platelets are <20,000 per cmm. The threshold for platelet transfusion is not clear, but it is suggested that transfusion should be considered for: (i) patients with platelet count below 20,000 per cmm, (ii) patients scheduled for surgery, (iii) patients with bleeding complications, and (iv) patients with other active medical problems such as fever. Use of intravenous immunoglobulin does not show immediate benefit, nor does it offer additional benefit over patients receiving platelet transfusion alone. Further supportive treatment of patients with profound thrombocytopenia includes bed rest, use of stool softeners, avoidance of intramuscular injections and monitoring of platelet counts every 12 hours until the condition improves.

References
Rheumatic carditis is the only clinical manifestation of rheumatic fever (RF) which results in a residual, permanent damage. The virulence of RF is directly related to the presence of carditis. Long after RF has subsided it is possible to examine a patient and make a positive diagnosis of past RF, based on the classical mitral and/or aortic valve disease. The other manifestations of RF – arthritis, chorea, subcutaneous nodules and erythema marginatum – do not leave residual clinical signs, nor do they cause any long-term morbidity value. The significance of these manifestations lies only in their ability to help in the diagnosis of acute RF.

Magnitude of Carditis

Rheumatic fever is a clinical diagnosis and may or may not be associated with carditis. Rheumatic carditis has been reported to occur in 14% to 99% patients of acute RF (Fig. 1). Such a wide difference in its prevalence is due to a number of factors.

The carditis in the initial attacks of RF is generally mild and remains unrecognized. RF has a tendency for recurrences in the absence of secondary prophylaxis. Recurrences tend to have mimetic features, that is, the manifestations seen in the initial attack tend to occur again in subsequent attacks. Patients who have carditis in the first attack will have it again in the subsequent attacks causing further damage to the heart. After the second or third attack, the patient becomes symptomatic from cardiac damage and seeks medical help. The system of periodic medical check-up during infancy and childhood does not exist in many countries. Since the previous cardiac findings are not known it is extremely difficult to be sure whether it is the first attack or a recurrence in an individual patient, specially because patients seek help only after they become symptomatic from cardiac involvement. In the absence of history indicative of past RF, the symptomatic patient is labeled as having the first attack of RF and severe carditis. This would obviously raise the prevalence rate of carditis in analysis of reported data from large series.

With the availability of echocardiogram as an investigative tool, a new subset of carditis is being recognized, namely subclinical carditis. The only physical finding which can be considered as being diagnostic for rheumatic carditis is the presence of mitral and/or aortic valve regurgitation in an acute attack of RF. If a murmur of mitral and/or aortic valve regurgitation is not made out clinically, the patient is labeled as not having carditis. Utilizing echocardiographic evaluation, a very sensitive investigation, presence of mitral valve disease not audible clinically, that is, subclinical carditis has been recognised. It is well known that a minimal physiological mitral regurgitation can be identified in normal people by echo-Doppler. Hence, before labeling abnormal mitral regurgitation by echo-Doppler, it must be beyond the normal limits. As such, use of echocardiogram is likely to overdiagnose presence of carditis. Combining clinical and echocardiographic data in the diagnosis of rheumatic endocarditis in the recent resurgence of RF in the United States, carditis was diagnosed in 90% or more patients with acute RF. Out of 74 children with acute RF, clinical carditis was present in 53 (71.6%) and by echocardiogram in an additional 14 (18.9%) cases giving a total of 90.5% with carditis. Thus 18.9% patients had subclinical carditis. In another study, carditis was clinically diagnosed in 20 (50%)
patients and by echocardiographic evaluation in another 18 (45%) of 40 children with acute RF. Thus carditis was present in 95% patients of whom in 45% it was subclinical. This has not been substantiated in a study from India wherein echo-Doppler did not add to the diagnostic yield over clinical examination. Since recurrences have mimetic features, most of those clinically undiagnosed as carditis will become definite carditis after a second or third attack of RF due to further damage to the valve tissue in the absence of echocardiographic evaluation in the first attack. The wide difference in the reported prevalence of carditis in the first attack could thus be related to clinically undiagnosed carditis in the first attack which becomes apparent after recurrences of acute RF. With the availability of echo-Doppler providing significant additional diagnosis of subclinical carditis, most of the past data regarding the frequency of carditis in acute RF is now difficult to accept. However, this statement does not imply that echo-Doppler be made an integral part of the Jones’ criteria for the diagnosis of carditis. Declining auscultatory skills in the West has been cited as one of the reasons for the clinical and echocardiographic discrepancy. Studies are needed for comparing the sensitivity and specificity of auscultatory findings with echo-Doppler findings. It remains to be determined as to how many of the subclinical carditis cases actually go on to develop frank carditis. Such data may be difficult to obtain since not giving secondary prophylaxis would be unethical.

**Rheumatic Pancarditis**

Rheumatic pancarditis means that the patients have pericarditis, myocarditis and endocarditis. Rheumatic carditis is a pancarditis and an early manifestation. As a rule, by the time a patient seeks help carditis is already present. Almost 80% of patients who develop carditis will have features of carditis within the first two weeks of the onset of RF. Less than 20% patients develop features indicative of carditis after the first two weeks. This data is from pre-echocardiogram era. Since patients could have subclinical carditis that may become apparent later on, it is possible that a higher number of patients actually have onset of carditis within the first two weeks of the onset of RF as suggested by the echo-Doppler findings.

**Pericarditis**

Rheumatic pericarditis is relatively less common clinically and is present in up to 15% patients. Precordial pain and an evanescent friction rub may be present. The electrocardiogram may show changes of pericarditis but lacks sensitivity and specificity. There are usually no features of significant effusion or tamponade. Patients with pericarditis always have findings of an underlying mitral valve and/or aortic valve regurgitation which could be difficult to make out at times, because of the pericardial friction rub. However, once the friction rub subsides, the murmurs become obvious. If there is no murmur of valvulitis after the friction rub has subsided, the diagnosis of rheumatic carditis and RF can be excluded. Since pericarditis neither results in tamponade nor constriction and clears up without leaving a residue, its limited clinical significance lies in the fact that it provides clear cut evidence for the presence of active carditis as well as active RF. Pericarditis does not occur in the absence of clinical findings indicative of valvulitis.

**Myocarditis**

The diagnosis of rheumatic myocarditis has traditionally been made on the basis of soft first sound, third sound gallop (S₃, or protodiastolic gallop), cardiomegaly, Carey Coomb’s murmur and congestive cardiac failure. As of today it is clear that none of these clinical findings are due to myocarditis per se. Soft first sound, S₃ gallop, cardiomegaly and congestive cardiac failure are due to an acute hemodynamic overload on the left ventricle from acute/ subacute mitral and/or aortic regurgitation.

The delayed diastolic mitral murmur known as Carey Coomb’s murmur is due to a large diastolic flow under pressure due to acute mitral regurgitation across inflamed mitral leaflets. Carey Coomb’s murmur is not heard in the absence of mitral regurgitation. There is nothing novel about the Carey Coomb’s murmur in terms of the etiology of mitral regurgitation since any cause of significant mitral regurgitation would result in a delayed diastolic flow murmur across the mitral valve. Hence all of the clinical findings supposed to be indicating myocarditis are actually due to acute mitral regurgitation. The investigations for documenting the presence of myocarditis indicate that in RF myocyte damage is insignificant and plays no part in the morbidity and mortality of rheumatic carditis. Markers of myocardial damage in the form of troponin I, myoglobin and CPK-MB were evaluated in patients with acute rheumatic carditis with and without cardiomegaly or congestive cardiac failure. The markers of myocardial damage remained normal in spite of clinically active carditis. In another study troponin I was evaluated in patients with acute RF with and without carditis and in patients with scarlet fever without RF. While the antihist
antibodies and antistreptolysin ‘O’ were elevated, the troponin I was insignificantly elevated in 18% patients with acute RF. The authors concluded: “the presence of low troponin I levels throughout the course of RF, especially in the face of active carditis, argues against significant cardiomyocyte injury”.

Echocardiographic assessment of myocardial function based on ejection fraction indices in patients with acute RF with and without carditis, with and without mitral regurgitation and in the presence of congestive cardiac failure has been found to be normal. Normal myocardial contractility in the presence of left heart failure is against muscle damage per se playing a significant role in precipitating congestive cardiac failure.

Myocardial biopsies performed during acute rheumatic carditis failed to improve upon the clinical diagnosis for the presence or absence of active carditis. It was concluded that myocardial biopsies do not add to the clinical diagnosis of active carditis due to paucity of myocardial damage.21

The lesions of active myocarditis are primarily perivascular and interstitial without evidence of cellular myocardial necrosis on histological evaluation which is against the concept of rheumatic myocarditis causing ventricular dilation.22

Pathological studies indicate that the inflammatory cells are localized to subendocardial, subepicardial and perivascular connective tissue with little myocyte damage.23 Aschoff nodules, the pathognomonic marker of rheumatic myocarditis, are localized strictly to perivascular area leaving the rest of the myocardium both in terms of the myofibers as well as the connective tissue normal. Aschoff nodules, which were felt to reflect myocardial damage have not been found by immunohistochemical studies to indicate presence of myocardial damage. Immunohistological studies indicate that Aschoff nodules have no cells of myocardial origin, are negative in staining for actin with HHF-35 monoclonal antibodies and the giant cells (owl eye/Anitschkow) are negative for myosin, myoglobin and desmin but positive for vimentin, which is of mesenchymal origin.24 In patients with acute RF, active carditis and congestive cardiac failure, not responding to medical management, mitral valve replacement has been shown to be life-saving. It results in prompt relief from congestive failure and decrease in heart size inspite of clinical evidence for ongoing carditis.25

Thus evaluation of markers of myocardial damage – (troponin I and CPK-MB), echocardiogram, histopathology, immunohistology and surgical management indicate that in the so-called rheumatic myocarditis, there is insignificant myocardial damage and it plays little role, if any, in the morbidity and mortality associated with RF.

Endocarditis

Rheumatic endocarditis is the diagnostic hallmark of rheumatic carditis in acute RF. It is represented by involvement of mitral and/or aortic valve causing mitral and/or aortic regurgitation. Mitral valve involvement occurs in 92% to 95% cases of whom about 20% to 25% also have aortic valvular disease. Isolated aortic valve disease is seen clinically in approximately 5% to 8% patients. However, pathological evaluation indicates presence of mitral valve disease even in the clinically diagnosed isolated aortic valve disease.26

Mitral and/or aortic valve disease results in an acute onset of mitral or aortic valve regurgitation. It is the severity of the mitral or aortic regurgitation which results in left heart failure, soft first sound, third sound gallop and cardiomegaly. Follow-up data on secondary prophylaxis indicates that in our country, disappearance of established mitral regurgitation occurs in about 15% patients although figures from the West have documented disappearance of cardiac findings in more than 50% patients. However, it needs to be emphasized that disappearance of the murmur does not mean that the patient has a normal heart. If a recurrence occurs, the valvular damage would suddenly appear as a severely damaged valve. Both mitral and aortic valve disease cause progressively worsening regurgitation. Over a period of time they would result in left ventricular dysfunction compromising the functional capacity of the patient.

Thus, of the three components of rheumatic pancarditis – pericarditis, myocarditis and endocarditis – two, that is pericarditis and myocarditis have no long-term morbidity. The damage is limited to valvular tissue, subepicardial, subendocardial and perivascular connective tissue adjacent to vascular endothelial tissue. The valvular tissue is made of connective tissue covered by endothelium. It has no muscle tissue and no blood vessels. It appears that the primary damage in RF is to the endothelium, the underlying connective tissue damage is unfortunate.

Rheumatic endocarditis leading to mitral and/or aortic regurgitation thus determines the morbidity and mortality of rheumatic carditis. Research in the pathogenesis of RF, needs to be directed toward valvulitis rather than myocarditis, which plays no role in the adverse outcome following rheumatic carditis.
Acknowledgements

The authors wish to thank Mrs. Lata Joshi for the help in preparing the manuscript.

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Isolated Congenital Muscular Left Ventricular Diverticulum in an Adult

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A 45-year-old hypertensive male patient referred for routine echocardiographic evaluation was found to have a digitiform accessory chamber communicating with the apex of the left ventricle (LV) through a narrow neck. The accessory chamber was contracting synchronously along with the LV in systole and its wall had similar acoustic properties as the ventricular wall. Color Doppler illustrated blood entering the diverticulum from the LV during diastole and flowing out during systole. There were no other congenital defects. Transesophageal echocardiogram (TEE) could better delineate the diverticulum (Fig. 1). Left ventriculography confirmed our echocardiographic findings showing a multilobulated contractile diverticulum originating from the apex (Figs 2a and 2b). Selective coronary angiography was normal. Twenty-four hour Holter monitoring did not reveal any episode of ventricular tachycardia.

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Three types of congenital LV diverticula have been reported in literature. The first type, described by Cantrell et al. in 1958 is a part of a syndrome of cardiac anomalies (ventricular and atrial septal defects, pulmonary stenosis/atresia and LV diverticulum) and midline thoracoabdominal defects. In the second type, the LV diverticula are usually subvalvular and basal, being intimately related to the mitral and aortic valves producing regurgitation. The third type, first described by Hoeffel et al. comprised of only isolated diverticulum, usually arising from the LV apex and till now only 20 such cases have been reported in world literature. Our patient falls in the third type described by Hoeffel et al. While diverticula described by Cantrell et al. and Hoeffel et al. contain all the three cardiac layers and are classified as muscular, those arising near the atrioventricular valves have predominantly fibrous tissue and are classified as fibrous type. Failure of normal midline fusion of paired primitive mesoderm in combination with abnormal fusion of the cardiac loop to the yolk sac before its descent is believed to result in development of muscular ventricular diverticulum.

The natural history and management of patients with isolated congenital LV diverticula is not well defined. There is no agreement in the literature regarding the best therapeutic approach. Some advocate resection in all cases, even in asymptomatic patients, to prevent risk of complications like heart failure, infective endocarditis and ventricular tachyarrhythmias (sometimes causing sudden death). However, others recommend a conservative approach in asymptomatic patients with close follow-up. We preferred the conservative approach advising the patient to come for periodic follow-up and take antibiotic prophylaxis against endocarditis in high-risk situations.

References
Migration Accelerates Development of Metabolic Syndrome - An Interesting Pedigree

Indian migrants living in the UK, USA, Canada, Fiji, Mauritius, South Africa, Malaysia etc. have been reported to have a higher prevalence of diabetes, coronary artery disease (CAD), particularly premature CAD and dyslipidemia compared to the native populations.1-3 The common link seems to be genetic background, psychosocial stress and alterations in lifestyle consequent to migration.4 The ensuing biochemical and molecular changes due to the above factors accelerate the process of atherosclerosis at a comparatively young age. A similar phenomenon also seems to be operative when young people move from rural locations to urban towns in native country itself.5 Though this hypothesis appears logical, it may be too simplistic and deserves in-depth anthropological, psychosocial and molecular studies.

We recently came across a family whose first generation elders had migrated from a rural area to a metropolis about 75 years ago. Many of the second, third and fourth generation migrant siblings exhibited central obesity and other clinical manifestations of metabolic syndrome and cardiovascular (CVS) and allied disorders.6 This prompted us to report the pedigree of migrant family. The diagnosis of metabolic syndrome was based on the presence of central obesity, raised blood pressure (130/85 mmHg) and high fasting blood sugar (110-125 mg/dl).

The index case in the pedigree is a 61-year male who belongs to the third generation of the migrant family (Fig. 1). Following migration from eastern part of Uttar Pradesh to a metropolis of Eastern India by first generation subjects there was a quantum jump in the economic prosperity in second generation as evident by additional land purchase at home. Male members in second generation used to chew tobacco, were doing less laborious job and had waist-hip ratio (WHR) of >0.9 indicating central obesity. All second generation male subjects developed type-2 diabetes mellitus and two of them subsequently died because of CVS or allied disorders. These findings heralded the beginning of metabolic syndrome in second generation male members. The index case, who belongs to third generation also had developed central obesity (WHR 1.01) and hypertension at an early age which was followed by type-2 diabetes mellitus indicated by raised fasting and postprandial blood sugar (160 mg/dl and 300 mg/dl respectively). He subsequently developed CAD which was detected to be triple vessel disease on angiography and had elevated triglycerides (164 mg/dl), low high-density lipoprotein (HDL) cholesterol (34 mg/dl), raised low-density lipoprotein (LDL) cholesterol (144 mg/dl) and a high comprehensive lipid tetrad index (20837.64). His sister too had central obesity, type-2 diabetes mellitus and died of sudden cardiac death at 58 years of age. These findings suggest metabolic syndrome in third generation subjects.

Fig. 1. Rural to urban migration and metabolic syndrome. ■: index case SCD: sudden cardiac death

SES: socio-economic status; T2DM: type-2 diabetes mellitus; HTN: hypertension; CVA: cerebrovascular accident; CAD: coronary artery disease; BPH: benign prostatic hypertrophy; DVD: double vessel disease; TVD: triple vessel disease; CAG: coronary angiography; CABG: coronary artery bypass grafting; CLTI: comprehensive lipid tetrad index; BMI: body mass index; WHR: waist-hip ratio
The most striking feature was observed in fourth generation where both male members were found to have central obesity (WHR 0.96), frontal and crown balding at an early age of 30 and 25 years respectively. Both of them have pre-diabetes. Their elder female siblings had increased WHR (1.03 and 0.95) indicating upper segment obesity. These observations point toward the presence of metabolic syndrome in fourth generation siblings also.

Going back to the history of migration by first generation people, it was revealed by the index case that poor socioeconomic conditions and social upheaval at home town about 75 years ago forced the male members from rural area to move to metropolis for better job opportunities. The first generation subjects in the metropolis opted for cheap accommodation; kept consuming Khaini (mixture of tobacco and chuna i.e. lime, taken sublingually) but left hard labour and did not exercise at all. Their food habits changed from coarse fiber-rich diet, “clarified ghee” to refined polyunsaturated vanaspati oil and carbohydrates. Besides tobacco, lack of exercise, sedentary habits and faulty diet accelerated accumulation of fat around the waist leading to central obesity and diabetes mellitus. These lifestyle changes and the genetic proclivity for syndrome-X made them prone to hypertension and CAD compared to their counterparts in rural environment.

The above pedigree is an evidence supporting the hypothesis that migration from rural area to metropolis accelerates the development of metabolic syndrome in next generation. Remedial lifestyle steps comprising of cessation of smoking and/or tobacco products, adoption of some form of active exercise and use of fiber-rich, low-fat diet may help in mitigating the onset of metabolic syndrome and thus prevent the premature CAD.

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Non-Pharmacological Therapy of Hypertension: Practical Limitations

Lifestyle modifications can reduce blood pressure to some extent but significantly reduce other cardiovascular risk factors. These should be strongly advised to all hypertensives. We should, however, realize some practical limitations.

For primary prevention of hypertension, weight loss, restricted sodium intake, reduced alcohol consumption and regular exercise have documented efficacy. Stress management, fish oils, calcium, magnesium, micronutrients and fiber have limited or unproven efficacy.

**Weight reduction:** (i) Obesity is one of the most refractory disorder of medicines, (ii) Odds of recovering from most forms of cancer are substantially better than those for controlling excess fat, (iii) Maintenance of significant weight loss is difficult for most of the obese people.

**Restricted sodium intake:** (i) It is not practical for persons living away from home i.e. in hostels or persons involved in touring job, (ii) Even for those who live with the family, it is not practical for a long time to have two vegetables with different amount of salt. Usually the patient compromises to eat what is prepared for rest of the family, (iii) Old, non-earning and dependents have to compromise with what is served to them, (iv) Severe salt restriction makes the diet unpalatable.

**Reduction in alcohol consumption:** (i) Prevention and Treatment of Hypertension (PATH) study has shown that reduction in alcohol consumption from 6 drinks to 2 drinks per day did not have any favorable effect on blood pressure and incidence of cardiovascular events over a 2-year period.

**Physical exercise:** (i) Regular exercise for 30-60 min/day is difficult for persons working >12 hours a day to earn their living. It is also not practical for middle-aged and elderly hypertensives with osteoarthritis.
Stress management: It is easier said than done. It is very difficult, if not impossible, to change personality and reactivity. Relaxation techniques are neither practical for the majority of hypertensives nor they are effective in maintaining a significant long-term effect.

Diet: Dietary Approaches to Stop Hypertension (DASH) advocates diet rich in fruits, vegetables and low fat dairy products. The study involved only 8-11 weeks of intervention feeding. It is therefore not clear if the observed blood pressure reduction will be sustained over longer time. This is important because adherence to a particular diet is unlikely to decline with time. The study was conducted in individuals with high normal or stage 1 hypertension. Effects in patients with higher levels of blood pressure are not clear. A diet rich in potassium, magnesium and protein cannot be advised to patients with impaired renal functions. Large sections of poor population cannot afford DASH diet which stipulates 4-5 servings of fruits, 4-5 servings of vegetables and 2-3 servings of low-fat dairy foods per day. Knowledge about “equals” or “alternates” needs the help of a trained nutritionist.

Other limitations: (i) Lifestyle modifications are more effective in reducing systolic blood pressure. Effect on diastolic blood pressure is not very impressive. Except for significant weight reduction and strict salt restriction, other modifications can reduce systolic blood pressure only up to 5 mmHg. The patient, therefore, feels discouraged if he does not understand that the main target of these lifestyle modifications is to reduce total cardiovascular risk and not a significant reduction in blood pressure. (ii) Successful implementation needs discussion by the clinician which is not easy since clinician is always short of time. Convincing other family members and ensuring their involvement in patient care. Even then, many patients do not act upon the advice, (iii) Modifications are still more difficult to maintain. Initially there is weight loss but then it creeps upwards. Physical activity increases with training but slack off with time. Sodium intake is effectively reduced at first but gradually returns toward baseline. Successful maintenance needs a network of paramedical staff for constant follow-up and encouragement. (iv) Lifestyle modifications alone may not be effective in attaining blood pressure goal in large number of patients; it helps few patients with mild or labile hypertension. (v) Even if blood pressure goal is achieved, most of the benefit is tapered off by the end of 3 years and most of the patients will need drug therapy to maintain blood pressure level. (vi) There is no convincing data that lifestyle modifications alone can reduce morbidity and mortality. Drugs have been shown to provide this benefit.

The fact that the efficacy and value of blood pressure reduction in preventing cardiovascular complications with pharmacologic agents could be demonstrated even in patients at low risk calls into question the current emphasis on delaying drug therapy even in low risk individuals.

To conclude, all hypertensives should be encouraged to adopt lifestyle modifications with clear understanding that the main aim of these modifications is to reduce total cardiovascular risk and that their impact on blood pressure may not be great. These should be primarily adjunctive to drug therapy in hypertensives since so many well tolerated, cheap, effective and single daily dose agents are available and it has been shown that lowering blood pressure with drugs reduces morbidity and mortality. Cost of nutrition and exercise regimens are greater than drug therapy. Lifestyle measures should never unnecessarily delay the initiation of drug treatment or detract patients or clinicians from compliance with drug treatment.
Kawasaki Disease

Since its first description in Japan about 35 years ago, Kawasaki disease (KD) has been reported worldwide. It is now believed to be the commonest vasculitic disorder seen in children. It has replaced rheumatic heart disease as the commonest cause of acquired heart disease in the West. Although an infectious etiology is suspected based on the epidemiology and clinical features, a definitive causative agent has still not been identified. KD is an acute medium vessel panarteritis without any evidence of chronicity. During recovery, inflammation subsides but leaves behind vessel panarteritis without any evidence of chronicity. This difficulty is further compounded by absence of any diagnostic test for this disease. However, it is important to make a diagnosis in the acute phase because treatment during this phase with intravenous immunoglobulin (and acetylsalicylic acid) results in significant reduction in coronary complications.

Features such as thrombocytosis and periungual desquamation, which are said to be virtually pathognomonic of KD, are seen only in the subacute phase. Hence clinical diagnosis may be relatively easy in this phase but the patient may not benefit even if intravenous immunoglobulin is administered because coronary vasculitis would have already developed.

Majority of children with KD remain undiagnosed in India. It is our contention that since KD is not being diagnosed properly in our country, majority of the affected patients are at present being left untreated thereby rendering them liable to coronary complications later in life. It is entirely possible that such cohort of untreated children with KD would grow up to develop coronary artery disease (CAD) as adults. These untreated children may therefore be contributing to the total load of CAD encountered by our cardiologists. As a corollary, some of the young adults with MI in our country, who have no risk factors for CAD and no family history either of a similar ailment, could be representing such untreated children with KD.

References


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Contrast-Induced Nephropathy and Cardiac Surgery

We read with great interest the excellent article, ‘Contrast-Induced Nephropathy [CIN]’ by Narang et al. The Cardiac surgeon shares with his cardiology colleague the challenges posed by a patient with renal impairment who needs a coronary artery bypass graft (CABG) surgery. The problem gets compounded when the nephropathy is contrast-induced and the patient needs an urgent surgery, for example after a failed percutaneous coronary intervention (PCI) or unfavorable anatomy with unstable hemodynamics.

Post-operative renal failure remains a serious complication of CABG surgery even in a patient with normal renal parameters. The rate of post-operative renal failure varies between 1% and 30%, and the mortality between 7% and 38%. When post-operative renal failure is severe enough to require dialysis, the magnitude of mortality rate goes up to 60 to 100%. The causes of renal failure are: pre-existing undetected renal artery arteriosclerosis, peri-operative low cardiac output, hypotension, hyperperfusion, hypothermia, exogenous nephrotoxins (aminoglycosides, diuretics, contrast media), and endogenous nephrotoxins (free plasma hemoglobin, myoglobin, free radicals, proinflammatory cytokines, activation of the complement, coagulation, fibrinolytic and kallikrein cascade). Radiocontrast agent administration less than 48 hours before surgery is an independent preoperative predictor of renal dysfunction.

Percutaneous transluminal coronary angioplasty (PTCA) has been associated with unfavorable acute and long-term effects in patients with renal failure possibly because of the presence of more complex lesions with diffused disease and extensive calcification, smaller diameter vessels, high incidence of diabetes mellitus, multivessel disease and increased prothrombotic risk. An emergency CABG for failed angioplasty A such, entails a high mortality especially in patients with renal impairment.

As outlined by Narang et al the cardiologist is in the unique position of preventing CIN following the principles they have mentioned. Care of these high risk patients in whom emergent surgery is indicated because of unstable hemodynamics after PCI or unfavorable coronary anatomy mandates the development of innovative techniques and strategies to minimize the deleterious effects of surgery to reduce morbidity and mortality. Quite often because of the exigency of the situation the cardiac team may be unaware that CIN has developed until after the surgery is over. While there are no clear cut guidelines for the optimum management of such high risk patients in whom surgery cannot be delayed, based on experience and previous reports the following measures are suggested.

An off pump procedure using previously described techniques is employed in majority of cases. This not only maintains pulsatile flow (the beating heart is still the best model of pulsatile perfusion) but also avoids exposure to an extracorporeal circuit and so a reduction in inflammatory cytokine response. It maintains normothermia and decreases the need for inotropes. Off pump surgery reduces the likelihood of acute renal failure in patients with normal renal function and also in those with pre-operative nondialysis-dependent renal insufficiency undergoing CABG.

Other preventive measures to avoid a further deterioration in renal function with CPB are: Keeping optimum perfusion pressure; avoidance of all nephrotoxic drugs; maintenance of adequate hydration and filling pressures, optimal hemodynamics and cardiac output guided by a pulmonary artery thermodilution catheter or a continuous cardiac output catheter; use of mannitol, frusemide and dopamine - efficacy unproven; prophylactic perioperative hemodialysis; a low threshold for starting hemodialysis post-operatively relying on clinical sense and a combination of the following indications - a rising serum
creatinine and/or serum potassium level—without a fixed cut off point, deterioration of oxygenation and a rise in pulmonary artery pressures.

The goal of improved patient outcome warrants further joint efforts of the cardiovascular surgeon, cardiologist, cardiac anesthetist, intervention, and nephrologist.

References

Academy of Cardiology at Mumbai: International and Indian Fellowships

Academy of Cardiology at Mumbai invites applications for above fellowships (one each) beginning January 2005 from eligible candidates. Applications along with detailed curriculum vitae and two letters of support from seniors in the profession should be sent to Academy of Cardiology, 102 Kirti Manor, S.V. Road, Santacruz (W), Mumbai - 400 054 by October 15, 2004.

Eligibility: D.M. or D.N.B (Cardiology) from recognized centers and age 35 years or below. The fellowship will provide funding for training in interventional/non-invasive cardiology in prestigious centers up to one year. The interviews for selection will be conducted by Academy.

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**Selected Summaries**

**Enoxaparin versus Unfractionated Heparin in High-Risk Patients with Non-ST Segment Elevation Acute Coronary Syndromes Managed with an Intended Early Invasive Strategy**

**Summary**

The Superior Yield of the New strategy of Enoxaparin, Revascularization and Glycoprotien IIb/IIIa Inhibitors (SYNERGY) trial was a prospective, randomized, open label trial, enrolling 9978 high-risk acute coronary syndrome (ACS) patients from 467 centers. It aimed at demonstrating efficacy and safety of enoxaparin compared to unfractionated heparin (UFH) in a group of patients with high risk ACS, due for early invasive/interventional therapy. Inclusion criteria included patients with ACS presenting within 24 hours of onset of ischemic chest pain and at least two of the following risk factors: age >60 years, elevated troponin or CPK levels, and ST segment changes on ECG. Overall, there was no difference in the baseline characteristics between the two groups. Average age was 68 years. Most were male and most were asymptomatic (87%) at the time of enrollment. Time from onset of pain to enrollment was about 15 hours. Overall 92% of patients underwent coronary angiography, within mean of 21 hours after randomization; 47% underwent PCI and surgical revascularization was performed in 19% patients. More than half were administered Gp IIb/IIIa antagonists during procedure, but interestingly only two-third patients received thienopyridines. The primary end point of all-cause mortality and non-fatal myocardial infarction (MI) during the first 30 days occurred in 14% patients in enoxaparin arm versus 14.5% in UFH arm demonstrating that while enoxaparin was not superior to UFH, it was also not inferior. On the other hand bleeding complications were significantly increased in enoxaparin group (9.1% v. 7.6%, p=0.08). However, major bleeding was not increased in enoxaparin group (2.7% v. 2.2%, p=0.08) with no increase in need for blood transfusion (17% v. 16%, p= 0.16). The increased bleeding risk in enoxaparin arm could be pinned down to excess bleeding related to coronary artery bypass grafting (CABG)-related events. Three-fourth of the patients in SYNERGY trial had received pre-randomization antithrombins and 12% patients in enoxaparin arm and 4% patients in UFH arm underwent post-randomization crossover. When cofounders (pre-randomization or post-randomization crossovers) were excluded, enoxaparin was associated with reduction in hazard for primary end point (0.82%) and no increase in TIMI bleeding hazard (1.06).

**Comments**

Several large randomized clinical trials of ACS have demonstrated superior efficacy of enoxaparin over UFH, without increased risk of bleeding. Superiority of enoxaparin over UFH may be due to several limitations of the later; a narrow therapeutic window, poorly predictable kinetics, paradoxical platelet activation and most importantly, inability to inhibit clot-bound thrombin. In this context enoxaparin, by virtue of higher anti-factor Xa/anti-IIa factor ratio does away with most of these limitations. Further, because of convenience of use, enoxaparin therapy becomes even more attractive. With the availability of new interventional devices and pharmacological adjuncts particularly Gp IIb/IIIa antagonists, there is a need to redefine the role of enoxaparin in patients of ACS due for invasive management. The inability to monitor the activity of enoxaparin during the PCI procedure leaves many interventional cardiologists feeling out of control, with some justification to it. Indeed, in a study Montalescot et al. have reported underanticoagulation (anti Xa levels <0.5 IU/ml) in 8% patients contributing to a markedly increased risk of death plus non-fatal MI at the end of 30 days in these patients. This has led to a widespread strategy of discontinuation of enoxaparin prior to PCI and replacing it with UFH intra-procedure. In this context SYNERGY trial shows that enoxaparin was not superior to UFH in high-risk patients of ACS due for invasive strategy. There could be several reasons for it. Firstly, in SYNERGY trial patients were not only given heparin, but also other potent antithrombinics like thienopyridines and particularly Gp IIb/IIIa antagonists and more importantly they underwent PCI, so the benefit of enoxaparin over UFH could not get manifest as much as it would have been otherwise. Secondly, the time to PCI after randomization was just 22 hours (after which ischemic events anyway markedly decrease) i.e. there was not enough time for enoxaparin to show its benefit over UFH in contrast to older studies. But most likely reason for this lack of efficacy seems to be the trial design, which led to a lot of pre-randomization and post-randomization issues. More than 75% patients were on antithrombinics prior to randomization and nearly 10% underwent post-randomization crossover. It was in these patients that efficacy of enoxaparin was not manifest. In those patients where post-randomization crossover occurred compared to where it did not, the primary end point was 18.5% versus 13.9%. Moreover there was a higher risk of bleeding too in these patients (requirement for blood transfusion more than doubled, 31.5% v.15.2%).

The Synergy Trial Investigators. JAMA 2004; 292: 45-54
A Randomized Trial of Rescue Angioplasty versus a Conservative Approach for Failed Fibrinolysis in ST Segment Elevation Myocardial Infarction


Summary
The Middlesbrough Early Revascularization to Limit INfarction (MERLIN) trial was a randomized, multicentric trial based in UK which compared the strategy of emergency invasive intervention (rescue angioplasty) with conservativetreatment in patients with failed thrombolysis. The trial enrolled 307 patients with ST elevation myocardial infarction (STEMI) who had failed to respond to thrombolytic therapy and had presented within 10 hours of onset of symptoms. Failed thrombolysis was defined as failure of ST segment elevation to have resolved in the worst lead by 50% as compared with pre-treatment ECG or absence of accelerated idioventricular rhythm, 60 min after the institution of thrombolysis. Streptokinase was the primary thrombolytic agent used in 95% patients. Overall, the baseline characteristics were similar in both thegroups. In the rescue angioplasty arm, the mean time from onset of chest pain to coronary angiography (CART) was about 5½ hours. Angioplasty was attempted mostly in patients who had less than TIMI 3 flow (82/88 patients) but also in some patients who had TIMI 3 flow but significant residual stenosis (19/61 patients). Overall, about two-third patients in rescue arm underwent angioplasty and 85% (130/153) patients achieved TIMI 3 flow. Four patients did not undergo CART, 5 patients were considered unsuitable for percutaneous coronary intervention (PCI) and 5 patients had failed PCI. Half of the patients received stents but glycoprotein (Gp) IIb/IIIa antagonists were used in only 5 (3.3%) patients. The primary end point of all-cause mortality was similar in the rescue and conservative groups (9.8% v. 11%, p=0.7). However, the composite secondary end point of death, infarction, stroke, congestive heart failure (CHF) and clinically driven subsequent revascularization within 30 days was lower in rescue group (37.3% v. 50%, p=0.02) primarily due to lesser rate of subsequent revascularization (6.5% v. 20.1%, p<0.01). Furthermore, reinfarctions and CHF were also less common in the rescue group (7.2% v. 10.4%, p=0.03 and 24.2% v. 29.2% respectively, p=0.3) but not statistically significant. On the other hand, strokes and need for blood transfusions were more common in the rescue group (4.6% v. 0.6%, p=0.03 and 11.1% v. 1.3%, p<0.001). There was no difference in left ventricular (LV) function assessment at 30 days between 2 arms. Regional wall motion abnormality (RWMI) was 1.52 in the rescue group versus 1.58 in conservative group. The only univariate predictor of all-cause mortality by 30 days was anterior MI. Multivariate logistic regression analysis revealed that predictors for composite secondary end points were anterior MI, female gender and conservative treatment.

Comments
Several small studies, most of them observational ones, have reported the utility of rescue angioplasty in patients with failed thrombolysis. In RESCUE study, 151 patients with acute anterior MI and TIMI grade 0/1 flow showed a reduction in composite end point of death or CHF at 30 days favoring the rescue angioplasty arm (6.4% v. 16.6%, p<0.05). In a subsequent large meta-analysis (n=2433), Ellis et al. demonstrated a high success rate in angioplasty arm with favorable results persisting beyond 1 year in patients with moderate/large MI. One-year survival was 92% for rescue arm versus 87% for conservative arm (p=0.001). On the other hand, TAMI I trial demonstrated that immediate angioplasty for TIMI grade 2 flow was not beneficial probably because of highly thrombogenic milieu engendered by potent plasminogen activators via the thrombin liberated from dissolved occlusive clot. MERLIN study is unique in several respects. Firstly, streptokinase was the thrombolytic agent (v. tpa in most other studies) used in majority of patients. Secondly, failed thrombolysis was defined only on ECG parameters with no consideration for ischemic pain. Thirdly, it included all types of MI (and not just higher risk patients with anterior MI) and finally, the mortality was extremely high in both the arms, to the tune of 10% in comparison to conventional angioplasty/thrombolysis trials (2-5%). This trial showed that though there was an improvement in combined end points of death/re-infarction/stroke/subsequent reinfarction/CHF (RR 12.7%), there was no improvement in primary end point of all-cause mortality at 30 days. Furthermore, the small improvement in combined end points itself was driven almost entirely by lesser rates of subsequent revascularizations in rescue arm (RR 13.6%), implying the futility of the primary procedure itself. In other words, there was no benefit of angioplasty in rescue arm, which anyway could be offered on elective basis if required, saving on the cost and logistics of the procedure. Additionally, there was an increased risk of developing disabling strokes and more requirement of blood transfusion in rescue group. However, the present study had several limitations. It was underpowered for assessment of all-cause mortality. Secondly, the high mortality in both the arms was surprising and at variance with all other trials. Whether it was a chance matter, or related to choice of thrombolytic i.e. streptokinase, is unclear. The failure of ST segment to settle despite patent IRA may itself reflect a high-risk situation probably indicating reperfusion injury, hemorrhagic infarction or microvascular obstruction.
Drug-Induced Atrioventricular Block: Prognosis after Discontinuation of the Culprit Drug

Summary
This study from Israel deals with a common yet clinically important condition of atrioventricular (AV) block. Its aim was to find out whether beta-blockers or calcium channel blockers merely unmask the presence of serious AV conduction problems or are themselves the cause of AV block. The authors analyzed the clinical course and definitive management of 169 consecutive patients with second or third degree AV block. The patients were excluded if their AV block was secondary to acute myocardial infarction, vasovagal syncope, digitalis toxicity or radiofrequency ablation. The patients treated with class I and class III antiarrhythmic drugs were also excluded. The level of block (nodal or infranodal) was defined by electrocardiographic criteria; no electrophysiological study was done. Of the 169 patients enrolled, 92 (54%) patients (mean age 78±9 years) were either on beta-blockers (n=62) or were receiving non-dihydropyridine calcium channel antagonists - verapamil or diltiazem or receiving both groups of medicines (n=13). The rest of the 77 patients (mean age 78±5 years) out of the 169 enrolled were not on any incriminating drug therapy. The patients were classified under drug-related AV block—if the block resolved upon discontinuing the offending drug and did not recur in the three weeks follow-up period. AV blocks that resolved within 48 hours but recurred in the subsequent three weeks follow-up period were classified as not caused by drugs. The baseline clinical and electrocardiographic characteristics including the level of block were similar in patients with AV block related to drugs and in the group not receiving such drugs. The culprit drug was discontinued in 79 (86%) of the 92 patients, 32 (41%) of whom experienced spontaneous resolution of AV block within 48 hours. In comparison, only 18 (23%) patients, who had not received such medication, experienced spontaneous resolution (p=0.014). However, there was a relapse of the AV block (within the following 3 weeks) in 56% of the 32 patients who had experienced spontaneous resolution in their drug-related blocks. Spontaneous relapse of AV block also was seen in 36% patients who originally had block in absence of any drug therapy. The presence of ECG characteristics suggesting AV block at level of AV node during drug therapy was found to be a poor predictor of causation. Therefore the authors concluded that drug-related AV block ‘truly caused by the drugs’ occurred only in 15% of patients presenting with AV block while receiving beta-blockers, or calcium channel blockers (diltiazem and verapamil). The other important observation was that the majority would persist with the block despite the discontinuation of medication. More ominously, there is a strong likelihood of recurrence of the block, even if it resolves initially, when the medications are discontinued.

Comments
The AHA/ACC guidelines for permanent pacing have listed as class III, with level of evidence B— the AV block expected to resolve and unlikely to recur (e.g. drug toxicity)—thereby recommending that for drug-induced AV block, a pacemaker implantation by evidence and/or general agreement, is not indicated. Based on the guidelines the general management worldwide is to discontinue the culprit drugs while patients are being monitored in the hospital. However, the present study consisting mainly of elderly patients with structural heart disease indicates that AV block will most likely persist despite discontinuation of the implicated drug therapy. There was resolution of AV block shortly after drug discontinuation in 41% of cases. However, 23% of AV blocks also resolved in those who had not received medications. And there was a 56% recurrence of AV block after its resolution following drug discontinuation in the short follow-up of three weeks. All this points toward the suspicion that there was underlying AV conduction disease in the first place and that the drugs—beta-blockers and calcium channel blockers merely unmask the disorder. Improvement in AV block upon cessation of culprit drugs may be coincidental and is often transient.

The study has limitations in being restricted mainly to the elderly (mean age around 78 years) with infranodal conduction disease. Also, no electrophysiological studies were performed to ascertain the site of block. The dosage relation to the occurrence of AV block with the beta-blockers and calcium channel blockers was also not determined because of the less number of patients. However, this study has important implications for clinicians in the management protocol for drug-related AV block. It suggests that the course of such patients despite discontinuation of the culprit medication is not benign as made out by existing ACC/AHA guidelines. Chances of improvement are not certain and the recurrence of blocks despite early improvement makes it important to carefully monitor these patients. An electrophysiology test at this stage may probably help in the decision to implant a permanent pacemaker, that would eventually be required by a majority, as shown in this study.

Randomized, Double-Blind, Placebo-Controlled Trial of Oral Sirolimus for Restenosis Prevention in Patients with In-Stent Restenosis


Summary
Several trials including the RAVEL study and the subsequently published series of SIRIUS trials have demonstrated the efficacy of sirolimus-eluting stents in reducing the restenosis rates in de novo coronary artery lesions. However, their role in managing in-stent restenosis (ISR) has not been evaluated in clinical trials. Sirolimus is a macrolide immunosuppressant that inhibits proliferation of smooth muscle cells and thus decreases the restenosis rate after angioplasty. Oral sirolimus has also shown to slow the accelerated arteriopathy following cardiac transplant. The Oral Sirolimus to Inhibit Recurrent In-stent Stenosis (OSIRIS), a randomized, double blind, placebo-controlled trial was conducted with the objective of evaluating the efficacy of oral sirolimus treatment with two different dosing regimens for prevention of restenosis in patients with ISR. 300 patients who had either angina or exercise-induced ischemia in the presence of angiographically significant ISR were randomized to either of the three treatment arms - placebo, usual dose or high dose sirolimus groups. Exclusion criteria were: acute coronary disease, presence of severe infections or significant renal failure. All patients were pre-treated with oral sirolimus for 2 days prior to angioplasty. In the high-dose group, 24 mg was given over 3 days compared with 8 mg in the usual dose group. After the percutaneous coronary intervention (PCI), a maintenance dose of 2 mg/day was given for 1 week (day 4 to 10) in both the arms. Blood levels were determined on day three i.e. the day of the procedure. The primary endpoints were angiographic stenosis defined as diameter stenosis of $\geq 50\%$. Secondary end points were the combined incidence of death and myocardial infarction and target vessel revascularization (TVR) during 1-year follow-up.

Repeat angiography was performed in 88.4% of patients at a median time interval of 206 days. Angiographic restenosis rate was reduced by 48% in the high-dose sirolimus group with a restenosis rate of 22.1% ($p<0.005$). The placebo group had a restenosis rate of 42.2% and the usual dose sirolimus group had angiographic restenosis rate of 38.6%. The minimal lumen diameter was highest (1.66±0.62 mm) in the high-dose group (1.37±0.69 mm in the usual dose group and 1.35±0.61 in the placebo group). A significant correlation between the sirolimus blood level on the day of PCI with the late lumen loss was observed at follow-up ($p<0.001$). There was a significant reduction in the white blood cell and thrombocyte count; however there were no clinical consequences of either leukopenia or thrombocytopenia. At 1-year clinical follow-up, because of restenosis TVR was necessary in 25.5% of placebo group, 24.2% in the usual dose group and in 15.2% of the high-dose group ($p<0.08$). The combined rate of death or myocardial infarction (MI) at 1 year was 1%, 3% and 2% respectively in the three groups.

Comments
Sirolimus has antiinflammatory and antiproliferative properties besides being an effective immunosuppressant. Sirolimus-eluting stents have found widespread acceptance after several randomized trials demonstrated lower rates of restenosis. However, the high cost of coated stents is a big deterrent especially in the third world countries such as ours. Moreover, as of now sirolimus-eluting stents have not been approved for use in many conditions, with little data of its use in situations such as chronic total occlusion and for in-stent restenosis. Hence alternative means to prevent restenosis are still being investigated. Brachytherapy was a promising means toward decreasing ISR. However, disappointingly the early benefit seen with brachytherapy is lost later on, as seen in studies with longer follow-up. This study is the first randomized trial with oral sirolimus that assessed the benefit of its short-term administration in prevention of restenosis. Two previous non-randomised trials have addressed this issue. In the study by Brara et al, there was no clinical benefit achieved in 22 cases of ISR. In the ORAR trial, a trend toward lower restenosis rates was observed following coronary stenting in de novo lesions. The explanation for the remarkable benefit seen in the present study may be the administration of loading dose of sirolimus 2 days prior to intervention, unlike in the 2 previous studies mentioned. Moreover, the maximum benefit was seen with higher dose of sirolimus, than in the previous studies. This had decreased the restenosis rate by 48% whereas the usual dose showed a decrease of only 9% from that observed with placebo. The importance of the loading dose was further confirmed by a significant correlation between the sirolimus blood levels on the day of the intervention and the late lumen loss.

This study also showed that the drug was well tolerated as compared with previous studies probably because only short duration (10 days) of therapy was used. The clustering of 5 patients in the 2 sirolimus groups who died during the follow-up period is also of some concern in this trial, although it appears that oral sirolimus was not the cause of these deaths. This being the first randomized trial with oral sirolimus, further trials with longer follow-up are obviously needed addressing the issue of optimal dosage, safety profile and duration of treatment.
## Calendar of Conferences/CSI Executive Committee

### October 10, 2004, 4th Mid Term Conference on Preventive Cardiology, CSI, Uttar Pradesh Chapter, Jhansi
- **Contact:** Dr Praveen Jain
  - Lifeline Hospital
  - Kanpur Road, Jhansi 284 128 UP
  - Tel: 0517-232 0183, 283 983
  - Fax: 0517-232 0553
  - e-mail: lifeline_hospital@rediffmail.com

### October 31 - November 3, 2004, 6th Asia-Pacific Congress of Cardiovascular and Interventional Radiology, New Delhi
- **Contact:** Dr Sanjiv Sharma, Convener
  - Department of Cardiac Radiology
  - All India Institute of Medical Sciences
  - New Delhi 110 029
  - Tel: 2659 4759
  - Fax: 011-2658 8663, 2658 8641
  - e-mail: meetisv@vsnl.com; meetisv@yahoo.com

### December 2-5, 2004, 56th Annual Conference of the Cardiological Society of India, Bangalore
- **Contact:** Dr CN Manjunath, Organising Secretary
  - #40, 4th Floor, Lakshmi Complex
  - Opposite Vasi Vilas Hospital
  - KR Road, Bangalore 560002
  - Fax: 91-080-6704483
  - Tel: 9844006659
  - e-mail: csibr@vsnl.net
  - or
  - Dr PC Manoria, President-Elect
  - E-5/103, Arera Colony, Bhopal 462016
  - Tel: 9827074602
  - Fax: 91-0755-2532405
  - e-mail: pmanoria@hotmail.com

### February 18-20, 2005, International Summit on CAD and Cardiovascular Interventions, Mumbai
- **Contact:** Dr Satyavan Sharma
  - Bombay Hospital and MRC
  - Room No. 104, 1st Floor MRC
  - 12, New Marine Lines
  - Mumbai 400 020
  - Tel: 91 22 2205 4532
  - e-mail: drsharma@bom3.vsnl.net.in and drsatyavan@vsnl.net

### February 24-27, 2005, 2nd World Congress of Interventional Cardiology, Mumbai
- **Contact:** Dr Lekha Adik Pathak
  - Memdil, Linking Road
  - Santacruz (W), Mumbai 400 034
  - Tel: 91 22 26490262
  - e-mail: lekha_p@vsnl.net

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