Prehospital Thrombolysis: A Reappraisal

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Last three decades have witnessed revolutionary changes in the management of patients with ST-elevation acute myocardial infarction (AMI). Despite the advances in pharmacological and interventional treatment, the magnitude of morbidity and mortality from AMI remains quite substantial. It is widely acknowledged that the key factor in the successful treatment of AMI by thrombolytic therapy is the time elapsed between the onset of symptoms and initiation of therapy. A meta-analysis of 22 trials, including more than 50000 patients, showed maximal effectiveness of thrombolytic therapy within the first hour of symptom onset (the golden hour), whereas the benefit was reduced by nearly 50% in the subsequent hour (the Boersma's curve). An estimated 65, 37, 26 and 29 lives are saved per 1000 patients when treated with thrombolytic therapy within 0-1, 1-2, 2-3 and 3-6 hours respectively. If the patients of AMI can be identified and treated very early after the onset of symptoms, the infarction process can essentially be aborted. Although these data have been recognized for nearly a decade, time-to-thrombolysis in major recent clinical trials still remains stalled at approximately 2.5 to 3 hours after the onset of symptoms.

Reasons for delay in the treatment of AMI by thrombolytic therapy include: patient delay, ambulance response time, transportation to hospital, and door to needle time. Public awareness, comprehensive community planning and rapid diagnosis of AMI in the emergency department may partly reduce the delay. However, the time delay factor that is most vulnerable is the transportation time to the hospital. This time can be unacceptably long in rural or congested urban areas. A recent study from a tertiary care hospital of northern India showed that prehospital delay was the most important factor in delayed administration of thrombolytic therapy. Only a third of the patients could reach the hospital within two hours of onset of symptoms. Additional delay of one hour in administering the thrombolytics resulted in only a few patients actually receiving thrombolysis within the first two hours.

Who Should Give Prehospital Thrombolysis?
The obvious step in the continuing effort to shorten time-to-treatment and thus to achieve maximal myocardial salvage is the use of prehospital thrombolysis. Although, this paradigm shift in the treatment of AMI to the prehospital setting rather than in the emergency department of a hospital sounds interesting, yet it raises several clinical, medico-legal and logistical issues.

Where to Initiate Prehospital Thrombolysis?
Thrombolytic therapy was given on domiciliary basis (at home of the patient) by the general practitioner in the early trials of prehospital thrombolysis. However, home setting is not equipped to handle complications related to the patient’s ischemic state, co-morbidities, or to reperfusion therapy. Further, valuable time is lost at home if rescue angioplasty is required. At present, prehospital thrombolysis is advised to be initiated in a fully equipped ambulance of the emergency medical services (EMS) en route to the hospital.
Choice of Agent for Prehospital Thrombolysis

Various factors need to be considered regarding the choice of agent for prehospital thrombolytic therapy. These include ease of drug administration, its efficacy, potential for adverse reactions, cost, and storage. Streptokinase (first generation thrombolytic agent) is not an ideal option for a paramedic-initiated prehospital thrombolysis. It has to be administered as an infusion and carries risk of allergic reactions and hypotension. Similarly, anistreplase (APSAC) though given as a bolus injection, has similar risks of allergic reactions. Alteplase [tissue-type plasminogen activator (t-PA), a second generation thrombolytic agent] has high safety and efficacy profile, but need for administration as an infusion makes it less attractive in the prehospital setting.

New third generation thrombolytic agents which are predominantly derivatives of alteplase include: reteplase (recombinant plasminogen activator, r-PA), tenecteplase (TNK-mutant of alteplase), and lanoteplase (novel-plasminogen activator, n-PA). Reteplase has a great potential for prehospital administration. The advantages of this drug in the prehospital treatment are manifold. It is administered as a bolus injection. Since early reocclusion of the infarct-related artery had been observed with single bolus administration, it is currently given as double boluses of 10 U each, 30 min apart. The drug-dosing pattern is standard irrespective of the body weight of the patient making its use simple in the prehospital scenario. An additional advantage of this drug may be its role in facilitating percutaneous coronary intervention (PCI). Since the first bolus is given in the prehospital setting, the hospital staff has a choice of the treatment regimen to follow; a second dose of reteplase or PCI once the patient arrives in the hospital. If the patient is still not in the hospital within 30 min, the other bolus can be given. This concept is being tested in the Pre-hospital Administration of Thrombolytic Therapy with Urgent Culprit Artery Revascularization (PATCAR) pilot study. Presently, it appears that reteplase may be considered as the 'drug of choice' for prehospital administration. Another thrombolytic agent, tenecteplase, has relative long plasma half-life that allows for a single bolus application. Lanoteplase has plasma half-life 10 times that of alteplase and therefore can be administered as single bolus. But higher incidence of hemorrhagic stroke has been reported with this drug. Thus, the third generation thrombolytic agents are likely to replace current thrombolytic therapy regimen in near future. Reteplase and tenecteplase are ideal agents to be used in setting of prehospital administration. However, a much higher cost and non-availability remain major issues in the developing countries.

Prehospital Compared with In-hospital Thrombolysis

Several randomized trials have compared the feasibility and efficacy of prehospital initiation of thrombolytic therapy with in-hospital treatment (Table 1). Besides routine contraindications to thrombolytic therapy, patients having cardiogenic shock, altered consciousness, atrioventricular or bundle branch blocks, advanced age and symptoms of more than 6 hours duration have been excluded in majority of the trials of prehospital thrombolysis. Individually, each of the trials favored prehospital thrombolysis; but there was

<table>
<thead>
<tr>
<th>Study (year)</th>
<th>No. of patients</th>
<th>Thrombolytic agent</th>
<th>Provider</th>
<th>Time-to-thrombolysis in min (from symptom onset)</th>
<th>Result Prehospital (No./Total)</th>
<th>Result In-hospital (No./Total)</th>
<th>Odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Castaigne et al. (1989)</td>
<td>100</td>
<td>Anistreplase</td>
<td>Mobile care unit</td>
<td>131</td>
<td>180</td>
<td>3/57</td>
<td>3/43</td>
</tr>
<tr>
<td>Schofer et al. (1990)</td>
<td>78</td>
<td>Urokinase</td>
<td>Mobile care unit</td>
<td>85</td>
<td>137</td>
<td>1/40</td>
<td>2/38</td>
</tr>
<tr>
<td>Roth et al. (1990)</td>
<td>116</td>
<td>Alteplase</td>
<td>Mobile care unit</td>
<td>94</td>
<td>137</td>
<td>4/72</td>
<td>3/44</td>
</tr>
<tr>
<td>GREAT study (1992)</td>
<td>311</td>
<td>Anistreplase</td>
<td>Domiciliary</td>
<td>101</td>
<td>240</td>
<td>11/163</td>
<td>17/148</td>
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<tr>
<td>EMIP trial (1993)</td>
<td>5469</td>
<td>Anistreplase</td>
<td>Mobile care unit</td>
<td>130</td>
<td>190</td>
<td>251/2750</td>
<td>284/2719</td>
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<tr>
<td>MITI study (1993)</td>
<td>360</td>
<td>Alteplase</td>
<td>Paramedics</td>
<td>92</td>
<td>120</td>
<td>10/175</td>
<td>15/175</td>
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<tr>
<td>Morrison et al. (meta analysis) (2000)</td>
<td>6434</td>
<td>Pooled data</td>
<td>Pooled data</td>
<td>104</td>
<td>162</td>
<td>Pooled data</td>
<td>Pooled data</td>
</tr>
</tbody>
</table>
no statistically significant survival benefit. This dampened the initial enthusiasm for prehospital thrombolysis. However, a meta-analysis of 6 major randomized trials involving more than 6,000 patients showed that time-to-treatment from the onset of symptoms was reduced by 58 min with prehospital thrombolysis (varying between 33 min in urban population to 130 min in rural population). This led to 17% relative risk reduction in the hospital mortality. The absolute risk reduction of 2% translated into one life saved for every 62 patients of AMI treated in the prehospital setting. Similarly, Boersma et al. reported that one hour reduction in treatment time with prehospital initiation of thrombolysis resulted in benefit of 21 lives saved per 1000 patients treated within 3 hours from onset of symptoms (p=0.002). These data resulted in resurrection of prehospital thrombolysis and paved the way for testing newer, third generation thrombolytic agents.

**Impact on Time Delay with Prehospital Administration of Newer Thrombolytics**

The Early Retavase-Thrombolysis In Myocardial Infarction (ER-TIMI)-19 trial tested the feasibility of bolus thrombolytic agent (reteplase) and evaluated the time saved (ER-TIMI)-19 trial tested the feasibility of bolus thrombolytic agent (reteplase) and evaluated the time saved (ER-TIMI)-19 trial tested the feasibility of bolus thrombolytic agent (reteplase) and evaluated the time saved (ER-TIMI)-19 trial tested the feasibility of bolus thrombolytic agent (reteplase) and evaluated the time saved (ER-TIMI)-19 trial tested the feasibility of bolus thrombolytic agent (reteplase) and evaluated the time saved (ER-TIMI)-19 trial tested the feasibility of bolus thrombolytic agent (reteplase) and evaluated the time saved. Prehospital initiation of thrombolysis resulted in time saving of 32 min (31 min prehospital v. 63 min in-hospital, p<0.0001). By 30 min after first medical contact, there was 10-fold increase in the proportion of patients receiving prehospital thrombolysis (49% v. 5%, p<0.0001). At one hour, 97% patients received the prehospital reperfusion therapy in comparison to less than half in controls (p<0.0001). In a recently published study from a district hospital, tenecteplase took 10.5 min less time to prepare than standard treatment of streptokinase or t-PA (p<0.001). Also, after the introduction of tenecteplase, the percentage of patients receiving thrombolysis within 30 min increased from 58% to 76% (p< 0.01). This data may have significant implications for the practice of prehospital administration of this drug.

**Impact of Adjuvant Therapy with Prehospital Thrombolysis**

Intravenous unfractioned heparin (UFH) either as bolus or bolus followed by infusion has been used as an adjuvant to thrombolytic therapy in prehospital setting. The low molecular weight heparin (LMWH), being more convenient to use, seems more suitable for prehospital administration. Safety and efficacy of tenecteplase with LMWH, enoxaparin was earlier demonstrated in the in-hospital (ASSENT-3) trial. The ASSENT-3 PLUS trial was designed to extend the same findings in the prehospital setting. Though the primary efficacy end points tended to be lower with LMWH (14.2% v. 17.4%; p=0.08), there was increased risk of stroke (2.9% v. 1.3%, p=0.026) and intracranial hemorrhage (2.20% v. 0.97%, p=0.047) as compared to UFH. This occurred exclusively in the older population (>75 years). The increased risk for bleeding was augmented in the prehospital compared with in-hospital setting of earlier ASSENT-3 trial. Remarkably, UFH was safe in elderly patients in either prehospital or in-hospital settings. So, pending results of future studies of dose modification of enoxaparin, only UFH is recommended as an adjunctive therapy to newer thrombolytics in the prehospital setting.

**Aborted Infarction- “The Ultimate Myocardial Salvage”**

The expression “aborted infarction” was first used to describe the patients treated very early in the Myocardial Infarction and Triage Intervention (MITI) trial. It was found that 40% of all patients treated within 3 hours of onset of symptoms had no evidence of infarction as measured by thallium scan at 30 days follow-up. Minimal infarct size of less than 10% was noted in additional 35% patients. The key factor influencing these results was the early treatment through prehospital triage and not necessarily prehospital administration of thrombolytic therapy. Few recent reports have focused on the impact of prehospital thrombolysis on the incidence of aborted infarction. Aborted infarction was defined on the basis of ECG criteria (subsiding of cumulative ST segment elevation and depression to <50% of the level at presentation), together with a rise of creatine kinase less than twice the upper limit of normal. As expected, the median time-to-treatment was shorter by approximately one hour in the prehospital group compared to in-hospital group (97 min v. 153 min, p<0.05). Prehospital thrombolysis was associated with a four-fold increase of aborted infarction compared with in-hospital therapy (17.1% v. 4.5%, p<0.05). Stepwise logistic regression analysis revealed that time-to-treatment of ≤ 2 hours was an important predictor of aborted infarction (p=0.005). Thrombolysis within one hour of onset of symptoms was administered to 19% patients of prehospital group compared to only 3% in the in-hospital group. In comparison to established AMI, patients with aborted infarction had a significantly lower 30-day (1.0% v. 9.2%, p<0.01) and 1-year mortality (2.2% v. 11.6%, p< 0.01).
Comparing Prehospital Thrombolysis with Primary Percutaneous Coronary Interventions

Several meta-analyses of randomized trials have consistently shown the superiority of primary PCI over in-hospital thrombolysis, even when it required transportation to other hospitals for PCI.\(^{30,31}\) Since several trials have clearly shown gain in time-to-treatment with prehospital compared to in-hospital thrombolysis, it is logical to compare PCI with thrombolytic therapy in the prehospital setting. Comparison of Angioplasty and Prehospital Thrombolysis In Acute Myocardial Infarction (CAPTIM) trial randomized 840 patients presenting within 6 hours from onset of symptoms to either prehospital thrombolysis with accelerated alteplase or primary angioplasty.\(^{24}\) Despite the gain of an hour with prehospital thrombolysis, there was no difference in 30 days in the primary composite triple end point of death, non-fatal MI, and non-fatal disabling stroke (8.2% for thrombolysis v. 6.2% for PCI, \(p=0.29\)).\(^{24}\)

A subgroup analysis of this trial determined the impact of time-to-treatment after onset of symptoms (<2 hours, early v. >2 hours, late) on the clinical outcomes in patients assigned to either prehospital thrombolysis or primary PCI.\(^{32}\) Time-to-treatment after onset of symptoms was consistently shorter by an hour in the thrombolysis group than in the PCI group (difference of 55 min among patients randomized before 2 hours, \(p<0.0001\) and of 63 min among patients randomized after 2 hours, \(p<0.0001\)). There was a strong trend toward lower 30-day mortality with prehospital thrombolysis for patients randomized <2 hours from onset of symptoms (2.2% thrombolysis v. 5.7% PCI, \(p=0.058\)) whereas no difference in survival was seen in patients randomized later (5.9% v. 3.7% respectively, \(p=0.47\)).\(^{32}\) In other words losing one hour to implement a strategy of hospital transfer for primary PCI has a different impact on survival when patients are seen early as opposed to being seen late. Also, in the <2 hours group, the incidence of cardiogenic shock was less frequent with thrombolysis (1.3% v. 5.3%, \(p=0.032\)); this was largely due to lower incidence of shock developing during transport to the hospital. Probably one hour delay imposed by primary PCI contributed to the development of cardiogenic shock in patients presenting early with their symptoms when maximum myocardial salvage is feasible. Beyond 2 hours, the rates of cardiogenic shock were very low, and similar in both the groups (0% with thrombolysis v. 0.5% with PCI).\(^{32}\) Thus, primary PCI fails to show superiority over thrombolysis in a small but important subgroup of patients who can receive thrombolysis within first two hours after the onset of symptoms.

Rational approach

Clearly, patients with contra-indication to thrombolytic therapy or in cardiogenic shock should be considered for primary PCI. In situations where facility of PCI is not readily available (in rural or remote areas, or at odd hours of day) or where transit time is significantly higher, thrombolytic therapy at point of first medical contact (if feasible, prehospital) should be given. Based on the Boersma's equation and its proposed modification,\(^{33}\) the following rationale can be drawn.\(^{34-40}\)

(a) Patients presenting within 2 hours from onset of symptoms: These patients are the ideal candidates for prehospital administration of thrombolytic therapy. Primary PCI should be considered only if patient reaches hospital within this time frame without thrombolysis. However, a large registry data showed that only 8% of patients actually receive primary PCI within 2 hours of symptom onset due to combination of delays in patient presentation and those inherent to interventional strategy.\(^{41}\)

(b) Patients presenting between 2–6 hours from the onset of symptoms: The effect of thrombolytic therapy weans off with time as the aging thrombi become more resistant to lysis. In comparison, primary PCI is far least-time-dependent in achieving reperfusion and salvaging ischemic myocardium. Given this superiority of PCI over thrombolytic therapy, patients presenting between 2–6 hours from the onset of symptoms should be considered for PCI even if it involves transfer to other hospital. The controversy of initiating thrombolysis for patients who are being shifted to other institutions for PCI is a subject of ongoing trials. Recent report from the National Cardiovascular Data Registry of American College of Cardiology highlighted the need of thrombolysis in patients who require transport to other institutions for PCI. Patients transferred on thrombolytic therapy had lower rate of mortality post-PCI (3.2% v. 5.8%, \(p<0.0001\)) perhaps due to lesser rate of occluded infarct-related artery prior to PCI (24.7% v. 49.2%, \(p<0.0001\)) in comparison to patients transferred without thrombolytic therapy.\(^{42}\) However, large scale randomized trials are needed to support this contention.

(c) Patients presenting beyond 6 hours from the onset of symptoms: Little myocardial salvage is expected beyond 6 hours, especially if the chest pain and ST segment elevation has settled. These patients have only modest benefit from thrombolytic therapy and are not candidates for prehospital thrombolysis. These patients may be
considered for coronary angiography and revascularization to achieve patent infarct-related coronary artery (open artery hypothesis), though the merits of this approach are still contentious.

The Future “Pharmacoinvasive” Approach

The advantages of thrombolysis and primary PCI may be complementary and not mutually exclusive. In the CAPTIM trial all AMI patients (whether they received prehospital thrombolysis or were destined for primary PCI) were shifted to a center with access to emergency or rescue angioplasty. About 70% of the patients treated by prehospital thrombolysis underwent PCI up to day 30, and 33% had urgent PCI (26% labeled “rescue PCI” because of persistent ischemia).24 Need for subsequent angioplasty in substantial number of cases seems to indicate that all patients receiving thrombolysis (prehospital or in-hospital) should undergo early elective angiography and, if required, coronary revascularization. However, there is no consensus on this approach at present, as the reported trials have given conflicting results. Few randomized trials have found facilitated angioplasty either inferior to or no better than primary PCI.43 In contrast, some recent studies on thrombolytic therapy support this contention.44 If future studies also support this concept, the management strategy for patients presenting early may change to prehospital administration of thrombolysis in ambulance (as this will even gain more time in these early hours) along with shifting the patient straight to tertiary care for elective or rescue angioplasty. The ongoing pilot study, PATCARE, is specifically designed to address this issue in both the urban and rural population.

Prehospital Thrombolysis: the Indian Context

The concept of prehospital thrombolysis appears particularly relevant to India. The population is predominantly rural and patients have to travel long distances to avail medical facility. Even in the urban areas tertiary care centers are few in number and travel time may be long due to various factors including congestion. Although these circumstances seem to warrant an urgent need for prehospital thrombolysis program, it will require tremendous infrastructure support. Nevertheless, future developments in this direction would be useful not only in achieving the maximum benefits of thrombolytic therapy to all patients of AMI but such networks will also serve as models of health care in the community.

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Remodeling in Systolic Heart Failure: Therapeutic Implications

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In the last three decades, there has been an explosion in our knowledge in the understanding of the pathophysiology of systolic heart failure. It is now recognized that adverse ventricular remodeling is the major mechanism for systolic heart failure. That neurohormonal activation causes progressive remodeling has been also established. Considerable advances in the management of this syndrome have also occurred based on the understanding of these pathophysiologic mechanisms. This brief review attempts to discuss the morphologic and functional changes in ventricular remodeling, the adverse effects of neurohormonal activation and the therapies with reverse remodeling effects that have been documented to be of benefit for the management of systolic heart failure.

Remodeling

Ventricular remodeling is characterized by increase in its size and mass, altered shape and impaired pump function. There is an increase in both end-systolic and end-diastolic ventricular volumes but the magnitude of increase in end-systolic volume is greater than that of end-diastolic volume resulting in reduced ejection fraction. Ventricular mass is considerably increased but, very often, ventricular wall thickness remains unchanged or may be reduced. As the cavity is disproportionately enlarged, the cavity-mass ratio is substantially increased. Furthermore, as there is little or no change in left ventricular (LV) wall thickness, global wall stress is increased.

Changes in ventricular geometry and shape also contribute to progressive ventricular remodeling. Although shortening of both longitudinal and circumferential muscle fibers is impaired, enlargement along transverse axis is usually greater than that along the long axis; thus ventricle becomes globular and more spherical in shape. This alteration in the LV shape and geometry is an important contributing factor in the pathogenesis of secondary mitral regurgitation which causes further ventricular enlargement and worsening mitral regurgitation.

Dyssynchrony i.e., abnormal sequence of contraction and relaxation and regional wall motion abnormalities frequently accompany remodeling. Although regional wall motion abnormalities are most frequently observed in patients with ischemic cardiomyopathy, in approximately 30% of patients with non-ischemic dilated cardiomyopathy (DCM), LV regional wall motion abnormalities occur. Left bundle branch block (LBBB) or intraventricular conduction defects of LBBB type with prolonged QRS duration are the principal mechanisms of dyssynchrony. In a substantial number of patients with or without ischemic heart disease (IHD), however, dyssynchrony may occur in absence of QRS prolongation.

Dyssynchrony is associated with early contraction of one region at the time of low systolic load which is then stretched later in systole as the other regions contract. Dyssynchrony leads to a further increase in end-systolic volume and wall stress which decreases mechanical and energetic efficiency. Systolic heart failure is associated with eccentric hypertrophy characterized by the lengthening of myocytes with little change in the myocyte width. In contrast to concentric hypertrophy, which is associated with increased protein synthesis, in eccentric hypertrophy there is probably a reduction in protein degradation.

The histopathologic changes in remodeling are partly related to the etiology of DCM. IHD is the most common cause of systolic heart failure. It appears that a threshold degree of systolic dysfunction is required to initiate remodeling. Clinical and experimental studies suggest that a reduction in ejection fraction to 40% or less is more likely to be associated with remodeling. This degree of reduction in ejection fraction is more likely to occur in larger and anterior infarctions. Remodeling may occur despite adequate recanalization of the infarct-related artery. It has been reported that in approximately 20% of patients, after the first infarct and without evidence of overt ischemia or heart failure, left ventricle continues to dilate and severe LV global and regional dysfunction occurs. The histopathologic changes begin almost concurrently in the infarcted/ischemic and the remote non-infarcted segments.

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In the infarcted segments, myocyte necrosis, myocyte lengthening and disruption of the collagen network are associated with infarct expansion. The changes in the extracellular matrix are probably due to increased activity of matrix metalloproteinases. Subsequently, there is replacement fibrosis. In the non-infarcted remote myocardium, myocyte hypertrophy and myocyte loss probably occurs simultaneously. Disproportionate increase in myocyte length compared to increase in cross sectional area is observed during remodeling in ischemic cardiomyopathy. There are also changes in the extracellular matrix architecture allowing the non-infarcted segments to expand as well. Altered activity of the matrix metalloproteinases enzymes has been implicated for the derangement of the matrix in the non-infarcted segments. There is also fibroblast proliferation and fibrosis which contributes to systolic and diastolic dysfunction. The features of adverse remodeling in systolic heart failure are summarized in Table 1.

There are multiple potential mechanisms for myocyte loss after the initial insult. Both ischemic necrosis and enhanced programmed cell death (apoptosis) cause myocyte loss. Increased global myocardial oxygen demand and consumption and diminished coronary flow reserve may occur not only in patients with ischemic cardiomyopathy but also with non-ischemic DCM. In post-infarct patients, coronary flow reserve appears to be impaired in the infarcted and in the remote non-infarcted segments, not only during the acute phase of infarction but for considerably long time after the initial insult. Endothelium-dependent and endothelium-independent coronary flow reserve is markedly attenuated both in patients with and without atherosclerotic coronary artery disease (CAD). Metabolically mediated coronary flow response is also impaired. Thus myocardial ischemia may result from an imbalance between myocardial oxygen demand and supply that can produce myocyte necrosis and apoptosis. In patients with congestive heart failure due to DCM with or without CAD, troponins and CK-MB may be elevated indicating myocardial injury. It should be appreciated that elevated troponins also indicate poor prognosis in patients with systolic heart failure.

The mechanisms of ventricular remodeling in non-ischemic DCM are poorly understood. "Non-ischemic" DCM encompasses many etiologies including hypertensive heart disease, diabetic cardiomyopathy, valvulopathic cardiomyopathy and inflammatory cardiomyopathy. The common functional derangement in these various types of cardiomyopathies is impaired systolic function as indicated by reduced ejection fraction. In hypertensive cardiomyopathy, it has been suggested that excessive hypertrophy may be associated with increased oxidative stress that may cause myofibrillar loss and impaired myocardial contractile function and may initiate ventricular remodeling. In diabetic cardiomyopathy, hyperglycemia, insulin resistance and microvascular dysfunction may be associated with both systolic and diastolic dysfunction.

In inflammatory DCM, it has been suggested that in the genetically predisposed subjects, cardiac autoimmunity may develop following viral myocarditis that may cause cross-reactive auto antibodies-mediated impairment of contractility and also cytotoxic T-lymphocytes-mediated myocytolysis. The net result is impairment of pump function and remodeling. In some patients with viral myocarditis, viral persistence and viral replication may be associated with disturbed myocardial metabolism and disruption of dystrophin and perpetuation of inflammation causing impairment of contractility and remodeling.

Direct cytotoxic effects of the neurohormones and cytokines are other mechanisms of myocyte loss. Stimulation of the neurohormones particularly of angiotensin II is associated with activation of cytokines leading to increased generation of inducible nitric oxide synthase and oxygen-free radicals. Cytokines are produced in various cell systems including macrophages, endothelial cells and myocytes. Many cytokines, tumor necrosis factor -alpha (TNF-α) in particular, are increased in patients with advanced heart failure. TNF-α exerts a negative inotropic effect. Oxidative stress characterized by an imbalance between oxygen-free radicals and antioxidant defense mechanism is disturbed, and is an important mechanism of myocyte loss and progressive ventricular remodeling.

Myocardial stretch may induce hypertrophy by stimulation of the sarcolemmal Na/H exchanger system as well as activation of neurohormonal systems. The potential contributing factors for progressive ventricular remodeling are summarized in Table 2.
Table 2. Contributing factors of adverse ventricular remodeling

<table>
<thead>
<tr>
<th>Infarct size</th>
<th>Reduced ejection fraction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased wall stress (mechanical stretch)</td>
<td>Regional and systemic neurohormonal activation:</td>
</tr>
<tr>
<td>– Angiotensin II, norepinephrine, aldosterone,</td>
<td>Endothelins, vasopressin</td>
</tr>
<tr>
<td>Cytokine activation (TNF-α, interleukins)</td>
<td>Inducible nitric oxide synthase/nitric oxide production</td>
</tr>
<tr>
<td>Increased oxidative stress</td>
<td>Activation of mechano sensitive ion channels</td>
</tr>
<tr>
<td>Ischemia</td>
<td>Continued myocytes loss (necrosis), apoptosis</td>
</tr>
</tbody>
</table>

Neurohormonal Activation

Neurohormonal activation has been established to be an important mechanism for ventricular remodeling and progression of heart failure. The neurohormonal systems are stimulated even before the development of clinical heart failure. In patients with overt clinical heart failure, activation of these neurohormones continues. Neurohormonal activation appears to be initiated by myocyte/myocardial and global and regional left ventricular dysfunction including increased wall stress. Myocyte and myocardial remodeling associated with neurohormonal activation result in decreased bioenergetics, altered Ca\(^{2+}\) handling, abnormal architecture and fetal gene induction.

The neurohormonal systems that are activated in systolic heart failure can be broadly categorized into those that promote vascular and cardiac remodeling and those that have the potential to cause reverse remodeling. Some of the neurohormones that can cause adverse remodeling or reverse remodeling are described in Table 3.

Table 3. Neurohormones that are increased in systolic heart failure with remodeling and reverse remodeling effects

<table>
<thead>
<tr>
<th>Adverse remodeling</th>
<th>Reverse remodeling</th>
</tr>
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<tbody>
<tr>
<td>Plasma renin</td>
<td>Vasoactive intestinal peptides</td>
</tr>
<tr>
<td>Angiotensin II</td>
<td>Calcitonin gene-related peptide</td>
</tr>
<tr>
<td>Catecholamines</td>
<td>Substance P</td>
</tr>
<tr>
<td>Neuropeptide Y</td>
<td>Adrenomedulin</td>
</tr>
<tr>
<td>Aldosterone</td>
<td>Natriuretic peptides (ANP, BNP)</td>
</tr>
<tr>
<td>Endothelins</td>
<td>Urotensin</td>
</tr>
<tr>
<td>Cytokines (TNF-α, interleukin-6)</td>
<td>Growth hormones</td>
</tr>
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<td></td>
<td>Prostaglandins</td>
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</table>

In systolic heart failure, both tissue and circulating renin-angiotensin systems are activated. Plasma renin activity and circulating angiotensin levels are higher in patients with overt heart failure than in patients with asymptomatic LV systolic dysfunction. The deleterious effects of angiotensin II are primarily mediated by activation of angiotensin subtype 1 (AT\(_1\) ) receptors. Angiotensin II (AT\(_2\) ) causes peripheral vasoconstriction and decreases arterial compliance which increase LV systolic load causing further impairment of systolic function. In addition, AT\(_2\) promotes cell migration, myocyte and vascular smooth muscle cell (SMC) hypertrophy, atherothrombosis and inflammatory responses via stimulation of proinflammatory mediators and cytokines. AT\(_2\) also promotes programmed cell death (apoptosis) of the endothelial cells and vascular SMC via activation of AT\(_1\) and AT\(_2\) receptors and of myocytes via activation of AT\(_2\) receptors. AT\(_2\) also stimulates myocardial fibroblast growth and fibrosis. It also possesses direct cytotoxic effects on cardiac myocytes.

Sympathetic nervous system is activated even before overt clinical heart failure develops. In heart failure, circulating norepinephrine levels are increased. Increased norepinephrine spillover rate, increased muscle sympathetic activity and decreased heart rate variability indicate marked stimulation of systemic sympathetic nervous system. Not only systemic sympathetic activity but also cardiac and renal adrenergic activities are enhanced in patients with systolic heart failure. Stimulation of sympathetic nervous system produces peripheral vasoconstriction, increases systemic vascular resistance and LV afterload. Activated sympathetic nervous system promotes cardiac and vascular remodeling and stimulates cytokines and renin angiotensin system. In patients with overt heart failure, there is approximately 40-fold increase in myocardial norepinephrine release indicating a marked increase in cardiac adrenergic activity.

Myocardial energy demand and oxygen consumption increase which can enhance myocardial ischemia. Catecholamines also promote myocardial necrosis and apoptosis by their direct cytotoxic effects. Increased sympathetic activity is associated with downregulation of myocardial β\(_1\) adrenergic receptors which may decrease contractile response. Renal sodium excretion is impaired which contributes to fluid retention and worsening congestive heart failure. Increased adrenergic activity is a potent stimulus for vascular SMC and myocytes hypertrophy and fibroblast growth. It also promotes atherothrombosis and inflammatory response.

In patients with systolic LV failure, aldosterone levels are increased independent of activation of renin angiotensin system. Aldosterone and its receptor and the enzyme 11B-hydroxy steroid dehydrogenase, necessary for selective
binding of aldosterone are present in target tissues such as heart and blood vessels.\textsuperscript{21,22} Aldosterone concentrations in the myocardium are increased after myocardial infarction and heart failure.\textsuperscript{23} Aldosterone exerts a number of deleterious effects such as a decreased arterial compliance which increases LV systolic load and can cause hemodynamic deterioration. Aldosterone also impairs endothelial function and promotes cardiac hypertrophy. It potentiates the sympathetic nervous system activity and reduces the conversion of $\text{AT}_1$ to $\text{AT}_2$. It also causes parasympathetic inhibition and $\beta$-receptor dysfunction. It produces sodium and water retention and electrolyte imbalance which promote the risk of arrhythmias. More importantly, aldosterone has been demonstrated to promote fibroblast growth and fibrosis which may contribute to myocardial and vascular remodeling. Aldosterone also exerts prothrombotic effect.

Endothelins, the peptides with vasoconstrictive, proliferative, prothrombotic and proinflammatory effects are elevated in systolic heart failure.\textsuperscript{24} Endothelins by activation of endothelin A receptors promote vascular SMC and cardiac myocyte hypertrophy and production of various growth factors. Increased expression of endothelin in the myocardium in heart failure has been observed and thought to contribute to adverse remodeling.\textsuperscript{25,26}

Arginine vasopressin that also possesses vasoconstrictive and proliferative effects is elevated in patients with LV systolic dysfunction with or without overt clinical heart failure.\textsuperscript{27,28} Decreased arterial blood volume resulting from heart failure activates cardiac and sino-aortic baroreceptors and mediates increased release of vasopressin. The vasoconstrictive effect of vasopressin is due to activation of the vasopressin 1a receptors and its anti-diuretic effect is mediated through activation of the vasopressin 2 receptors.

The counter regulatory neurohormones with potential to prevent or attenuate ventricular remodeling are also activated in patients with LV systolic dysfunction even before overt clinical heart failure develops. Brain or B-type (BNP), atrial or A-type (ANP) natriuretic peptides, prostaglandins and bradykinins possess vasodilatory and anti-proliferative effects and are elevated in systolic heart failure.\textsuperscript{1,29} Increased production of these neurohormones particularly of the natriuretic peptides may counteract the deleterious effects of the remodeling promoting neurohormones. If a balance between these two counter regulatory systems can be maintained, probably adverse remodeling can be attenuated. An excessive stimulation of the pro-remodeling neurohormones, however, is likely to cause continued remodeling and progressive heart failure.

### Etiology and Prognosis of Systolic Heart Failure

The most common cause of systolic heart failure resulting from ventricular remodeling is atherosclerotic CAD. About 70% of patients with systolic heart failure have IHD (Table 4). However, ventricular remodeling causing systolic heart failure can occur in absence of atherosclerotic CAD. Chronic non-ischemic DCM including familial, genetic, and peripartum cardiomyopathies, inflammatory cardiomyopathy, valvulopathic cardiomyopathy, hypertensive heart disease and toxic cardiomyopathy cause systolic heart failure in approximately 30% of patients (Table 4).

#### Table 4. Etiology and risk factors of systolic heart failure

<table>
<thead>
<tr>
<th>Etiology</th>
<th>Risk Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ischemic heart disease</td>
<td>Hypertension, diabetes, obesity, hyperlipidemia and smoking</td>
</tr>
<tr>
<td>Non-ischemic dilated cardiomyopathy</td>
<td></td>
</tr>
<tr>
<td>Unknown etiology</td>
<td></td>
</tr>
<tr>
<td>Familial and genetic cardiomyopathy</td>
<td></td>
</tr>
<tr>
<td>Congenital, i.e. non-impacted myocardium</td>
<td></td>
</tr>
<tr>
<td>Immunologic</td>
<td></td>
</tr>
<tr>
<td>Valvulopathic</td>
<td></td>
</tr>
<tr>
<td>Inflammatory</td>
<td></td>
</tr>
<tr>
<td>Toxic</td>
<td></td>
</tr>
</tbody>
</table>

The risk factors for ischemic DCM are similar to those of CAD namely advancing age, hypertension, diabetes, obesity, hyperlipidemia and smoking (Table 4). The risk factors for non-ischemic DCM are variable and related to its etiology in patients with “idiopathic” and familial dilated cardiomyopathy. However, mutations of a number of genes have been recognized.

Remodeling is associated with worse prognosis.\textsuperscript{30} In patients with IHD, larger LV end-diastolic and end-systolic volumes are associated with higher mortality.\textsuperscript{31,32} In patients with acute myocardial infarction (AMI), the risk of developing heart failure and mortality increases with increasing end-systolic volume despite reperfusion therapy.\textsuperscript{33,34}

### Reverse Remodeling

The morphologic and functional features of reverse remodeling have not been well characterized. An increase in ejection fraction alone should not be used to define reverse remodeling. Decrease in mass, normalization of ventricular shape, regression of fibrosis and improvement of hemodynamics including a decrease in wall stress should be considered as features of beneficial reverse remodeling. An acute decrease in ventricular volume or an increase in
Ejection fraction is not necessarily translated into long-term benefit and improved prognosis.

**Therapeutic Approach for Prevention and Attenuation of Remodeling**

In patients with ischemic cardiomyopathy, as the infarct size and the degree of depression of LV systolic function are the major determinants of remodeling, limiting the infarct size should be considered as an essential therapeutic goal. In patients with AMI early, effective and adequate reperfusion of the ischemic myocardium is the best strategy to decrease the extent of myocardial injury and preserve LV systolic function. When thrombolytic therapy or percutaneous coronary interventions are instituted within 60 to 90 min of the onset of ischemic symptoms in patients with ST-elevation myocardial infarction, LV ejection fraction and end-systolic and end-diastolic volumes frequently remain in the normal range. However, application of such early reperfusion therapy is impractical in most clinical circumstances. In patients with unstable angina also, revascularization can result in normalization of the regional wall motion abnormalities and ejection fraction.

In patients with chronic IHD, regional and global left ventricular wall motion abnormalities can occur due to presence of hibernating myocardium. A substantial reduction in ejection fraction and an increase in end-systolic and diastolic volumes may occur in patients with significant hibernating myocardium. It has been postulated that the contractile dysfunction of the hibernating myocardium increases the workload of the non-infarcted remote myocardial segments that undergo initially, compensatory hypertrophy. Increased workload, regional wall stress and filling pressures may increase metabolic requirements of these segments to such an extent that these segments can be relatively ischemic and the process of remodeling is initiated. Progressive ventricular dilatation and reduction of ejection fraction leads to heart failure. Thus, the mechanisms of remodeling in patients of chronic IHD are very similar to those with AMI. It should be appreciated that the prevalence of chronic heart failure is rising with increasingly successful treatment and reduced mortality of acute coronary syndromes. It is apparent that revascularization of hibernating myocardium will emerge as an important therapy not only for treatment of chronic heart failure in patients with CAD but also to prevent or attenuate remodeling in such patients.

Many uncontrolled studies have reported that successful revascularization surgery improves regional wall motion abnormalities and ejection fraction. The incidence and magnitude of functional recovery following coronary artery bypass graft surgery (CABG) depends on a number of factors such as patient selection, myocardial protection during surgery, perioperative myocardial injury and adequacy of revascularization.

Nevertheless, revascularization should be considered in all appropriate patients with hibernating myocardium. Many therapies have been shown to reduce the risks of reinfarction and development of heart failure and should be considered in all appropriate patients. The antiplatelet agents (aspirin, clopidogrel), angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blocking agents, beta adrenergic blocking agents, aldosterone antagonists and 2-hydroxy-3 methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) have been demonstrated to be of benefit.

In patients with acute coronary syndromes, cooling therapy, anti-inflammatory agents, glucose-insulin-potassium, partial free fatty acid oxidation inhibitors and drugs to improve microcirculation have the potential to reduce the extent of myocardial injury. Other pharmacologic agents to decrease myocardial ischemia, necrosis and apoptosis such as inhibition of pro-apoptotic and promotion of anti-apoptotic pathways and to preserve ventricular function and architecture of extra-cellular matrix (e.g. modulation of matrix metalloproteinase enzymes) are under investigations. Surgical interventions to attenuate ventricular remodeling besides revascularization (e.g. cell implantation, LV ventricular assist devices and ventricular constraining devices) are also under investigations. It is very likely that a few of these therapies will find clinical application. The therapies of potential benefit to prevent or retard ventricular remodeling in patients with IHD are summarized in Table 5.

**Reverse Remodeling Therapy**

A number of pharmacologic agents have been shown to produce reverse remodeling and some of them have been shown to improve not only the clinical status but also the prognosis. Many prospective clinical trials have documented their beneficial effects. Other studies have documented that many conventional treatments such as diuretics and digitalis may not be beneficial for the long-term treatment of systolic heart failure.

Diuretic therapy alone may promote ventricular remodeling, probably due to activation of renin-angiotensin-aldosterone and sympathetic nervous systems. Thus, diuretic therapy, although frequently...
Table 5. Treatment strategies to prevent or retard ventricular remodeling in ischemic heart disease

<table>
<thead>
<tr>
<th>Strategy</th>
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<tbody>
<tr>
<td>To limit infarct size and preserve systolic function</td>
</tr>
<tr>
<td>Early and adequate reperfusion of ischemic myocardium:</td>
</tr>
<tr>
<td>Thrombolytic therapy, percutaneous coronary intervention, surgical revascularization</td>
</tr>
<tr>
<td>Adjunctive therapy i.e. myocardial cooling, glucose-insulin-potassium, partial free fatty acid oxidation inhibitors, agents to improve micro circulation, anti-inflammatory drugs, presently in experimental stage.</td>
</tr>
<tr>
<td>To decrease the risks of recurrence of infarction, remodeling and development of heart failure</td>
</tr>
<tr>
<td>Antiplatelet agents i.e. aspirin, clopidogrel</td>
</tr>
<tr>
<td>Angiotensin inhibition therapy: ACE inhibitors or angiotensin receptor blocking agents</td>
</tr>
<tr>
<td>Adrenoreceptor blocking agents: carvedilol, metoprolol</td>
</tr>
<tr>
<td>Aldosterone antagonists - eplerenone</td>
</tr>
<tr>
<td>Statins</td>
</tr>
<tr>
<td>Therapies designed to improve myocardial function and structure i.e. regulation of matrix metalloproteinase activity, cell implantation therapy under investigation</td>
</tr>
<tr>
<td>To decrease myocyte loss</td>
</tr>
<tr>
<td>Pharmacologic treatment of myocardial ischemia</td>
</tr>
<tr>
<td>Revascularization in patients with hibernating myocardium</td>
</tr>
<tr>
<td>Angiogenesis and therapies designed to prevent or attenuate, apoptosis under investigation</td>
</tr>
</tbody>
</table>

required to relieve congestive symptoms should not be used for the long-term management of congestive heart failure. Treatment with digitalis improves symptoms and LV function of patients with systolic heart failure.59 However, a prospective randomized trial has shown that it does not improve survival.60 Furthermore, digitalis therapy may increase the risk of arrhythmic death if serum digoxin level is high (>1.2 ng/ml). On the other hand, addition of digoxin to ACEIs may decrease morbidity such as rate of hospital admissions for treatment of heart failure. Thus, low-dose digoxin treatment along with ACEIs may provide some benefits in the long-term management of patients with symptomatic LV failure.

Long-term use of ACEIs results in decrease of end-systolic and end-diastolic volumes and mass of LV and an increase in its ejection fraction.57,61,62 These beneficial reverse remodeling effects are observed in patients with ischemic or non-ischemic DCM. Reverse remodeling occurs not only in patients with overt clinical heart failure but also in patients with asymptomatic LV systolic dysfunction.

The ACEIs relieve symptoms of heart failure, improve exercise tolerance and quality of life in the majority of patients although the magnitude of improvement is variable. Beneficial changes in systemic, renal and coronary hemodynamics may also occur with ACEIs. The most consistent systemic hemodynamic effect is reduction in right atrial and pulmonary capillary wedge pressures, although cardiac output tends to increase in a substantial proportion of patients.63 There is also a significant decrease in arterial pressure and systematic vascular resistance. The magnitude of decrease in pulmonary artery pressure and pulmonary vascular resistance is also variable.

The ACEIs reduce myocardial oxygen consumption.64 A primary coronary vasodilatory effect of ACEIs has also been demonstrated. Despite a reduction in coronary artery perfusion pressure, coronary blood flow tends to increase. Coronary sinus venous oxygen content increases supporting primary coronary vasodilatory effect. Concurrent decrease in myocardial oxygen demand and increase in coronary blood flow may ameliorate myocardial ischemia and decrease the risks of myocytes necrosis, apoptosis, adverse remodeling and progression of heart failure. ACEIs improve endothelial function and can stabilize atherothrombotic plaque. AT₂ inhibition may increase tissue plasminogen activity and decrease plasminogen activator inhibitors. These changes have been thought to be the principal mechanisms for the reduction of the incidence of myocardial infarction with AT₂ inhibition therapy. In addition to blockade of angiotensin II, ACEIs improve bradykinin-mediated endothelial function, as ACEIs decrease degradation of bradykinins.

Prospective randomized clinical trials have also documented a substantial survival benefit of ACEIs in patients with chronic systolic heart failure.65,66 In patients with acute myocardial infarction, ACEIs improve short-term and long-term prognosis.67 AT₂ (Subtype 1) receptor blocking agents also attenuate ventricular remodeling. There is an increase in LV ejection fraction along with a decrease in LV end-diastolic volume.68 Angiotensin receptor blocking agents also decrease morbidity and mortality of patients intolerant to ACEIs.69,70

Complete angiotensin blockade with combined ACEIs and AT, blocking agents have been shown to decrease the risks of cardiovascular deaths and morbidity such as rates of hospital admission for congestive heart failure, non-fatal myocardial infarction and stroke in patients with mild to moderately severe systolic heart failure.69,71 Very few patients with severe heart failure (NYHA class IV) have been treated with combination therapy. Hypotension and deteriorating renal function are limitations of combination therapy, particularly in patients with severe heart failure and relative hypotension. Combination therapy should not be considered as treatment of refractory hypotensive heart failure patients.

The aldosterone antagonists attenuate adverse
ventricular remodeling. A substantial reduction occurs in LV end-diastolic and end-systolic volumes and LV mass.\textsuperscript{71} It also reduces collagen turnover and myocardial fibrosis.\textsuperscript{72} Aldosterone antagonists increase nitric oxide bioavailability, improve endothelial vasodilatory function and decrease conversion of vascular AT\textsubscript{1} to AT\textsubscript{2}.\textsuperscript{73} In patients with heart failure, there is also a decrease in norepinephrine and BNP levels. Thus, aldosterone antagonists not only decrease the deleterious remodeling effects of aldosterone, directly by blocking the aldosterone receptors but also by their anti-angiotensin and anti-adrenergic effects. Other potential beneficial effects of aldosterone are improved vascular compliance and decreased myocyte hypertrophy. In patients with severe systolic failure, there is a significant reduction in the risk of total mortality, cardiovascular mortality and sudden cardiac death.

These benefits were observed in patients who remained symptomatic despite treatment with digitalis, diuretics and ACEIs.\textsuperscript{74} In post-infarction patients with LV systolic dysfunction adequately treated with reperfusion therapy and ACEIs as well as β-blockers, addition of eplerenone, an aldosterone antagonist without anti-androgenic effect, reduces the risk of total mortality and the risk of development of heart failure, as also the risk of sudden cardiac death.\textsuperscript{75}

The combination of hydralazine and isosorbide dinitrate has also been demonstrated to produce reverse remodeling effects in patients with mild to moderate systolic heart failure. The LV ejection fraction increases significantly during chronic use of hydralazine-isosorbide combination therapy. In VHEFT II heart failure trial, the magnitude of increase in LV ejection fraction and improvement in exercise tolerance with hydralazine - isosorbide dinitrate combination was greater than that with enalapril.\textsuperscript{76}

Hydralazine - isosorbide combination also improves hemodynamic characterics by substantially increasing the cardiac output and stroke volume and reducing the right atrial and pulmonary capillary wedge pressures.\textsuperscript{76} It also provides survival benefit in patients with heart failure although the magnitude of survival benefit is less than that with ACEI, enalapril.\textsuperscript{75,77} It should be appreciated that hydralazine - isosorbide therapy is poorly tolerated by patients with severe, refractory hypotensive heart failure patients.

It is now well documented that chronic long-term β-blocker therapy is associated with reverse remodeling. There is a decrease in end-systolic and end-diastolic volume as well as in LV mass and an increase in the sphericity index.\textsuperscript{78,80} A number of prospective randomized controlled studies have documented that chronic β-blocker therapy improves survival of patients with mild, moderate and even severe heart failure.\textsuperscript{81-83} Chronic β-blocker therapy is associated with a reduction in the risk of sudden cardiac and heart failure death. Bisoprolol, a selective β-blocker with vasodilating property, metoprolol XL, a slow release, long-acting selective β-blocker and carvedilol, a non-selective β-blocker which also has alpha antagonist property, all have been shown to improve prognosis and survival of these patients. Chronic β-blocker therapy substantially improves functional class and exercise tolerance. However, clinical improvement becomes evident only after a few weeks of treatment. Furthermore, signs and symptoms of heart failure may worsen due to worsening hemodynamics, during initiation of β-blocker therapy. Adjustment of diuretic therapy is often required to decrease congestive symptoms and signs during initial titration of β-blockers in the treatment of systolic heart failure. Short-acting immediate release metoprolol has been found to be less effective than carvedilol in reducing the risk of mortality.\textsuperscript{84} It is preferable therefore to use those β-blockers that have been investigated in clinical trials. However, it should be emphasized that β-blocker therapy should not be instituted in patients who are unstable or in cardiogenic shock. More severe the heart failure is, lower should be the initial dose of a β-blocker and the dose should be titrated gradually. Beta-blocker therapy is not contraindicated in patients with mild to moderate chronic obstructive lung disease, advancing age or diabetes. Indeed, these patients derive more benefit from β-blocker therapy.

It should be appreciated that angiotensin inhibition therapy, β-blocker therapy and aldosterone antagonists provide incremental benefit in reduction of the risks of mortality and morbidity. These benefits are observed irrespective of age, gender, race and ethnicity and both in patients with ischemic and non-ischemic dilated cardiomyopathy. Thus, ACEIs and or AT\textsubscript{1} receptor blocking agents, β-blockers and aldosterone antagonists should be considered as essential initial therapy for patients with systolic heart failure irrespective of severity of symptoms and etiology.

In addition to these therapies with proven benefits, other pharmacologic agents with a potential benefit should also be considered in the routine management of patients with systolic heart failure particularly due to ischemic cardiomyopathy. Anti-platelet therapy with aspirin or clopidogrel or both, reduce the risks of adverse cardiovascular events. The HMG co-enzyme reductase inhibitors (statins) have been shown to decrease the risks of adverse cardiovascular events and also development of...
heart failure. It is thus preferable to add anti-platelet and statin therapy to the pharmacologic armamentarium for managing systolic heart failure.

A number of other pharmacologic agents have been investigated to improve prognosis of patients with systolic heart failure based on their favorable hemodynamic and neuroendocrine effects. Long-acting, relatively vasoselective dihydropyridine calcium channel blockers have not been shown to improve mortality or morbidity. The positive inotropic agents such as dobutamine, dopamine and ibopamine increase mortality. The inodilators like milrinone, amrinone, enoximone and vesiarninone may improve symptoms, but also increase mortality.\(^ {85}\) In general, pharmacologic agents which increase myocardial cyclic AMP, enhance the risk of arrhythmias and sudden cardiac death. However, short-term use of phosphodiesterase inhibitors has been proposed as a pharmacologic bridge to β-blocker therapy.\(^ {86}\)

The newer neurohormonal modulators also have failed to meet the expected promise. In prospective randomized clinical trials, the use of intravenous prostacyclin, TNF-α antagonists, endothelin antagonists and vasopeptidase inhibitors all have been associated with increased mortality or morbidity.\(^ {1,87}\) Only intravenous B-type natriuretic peptide (brain natriuretic peptide) has been shown to produce favorable hemodynamic and clinical responses in patients with decompensated systolic failure.\(^ {88}\) However, the impact of BNP therapy on ventricular remodeling has not been adequately investigated. Pentoxiphyllin, which reduces production of TNF-α can increase LV ejection fraction and exercise capacity of patients with non-ischemic DCM. However, adequate prospective studies have not been performed to assess its impact on the prognosis of patients with systolic heart failure.

Amiodarone, a type III anti-arrhythmic drug, decreases heart rate both in sinus rhythm and in atrial fibrillation. It possesses anti-adrenergic, systemic and coronary vasodilatory properties.\(^ {89}\) It also exerts a mild negative inotropic effect. In in vitro studies, amiodarone has been shown to possess protective effect against oxidative stress-induced myocytes loss. A modest decrease in total mortality with oral low-dose amiodarone therapy is associated with a significant increase in LV ejection fraction, particularly of patients with non-ischemic DCM.\(^ {90}\) Low-dose oral amiodarone (200 mg, two to three times daily) is effective in some unstable heart failure patients who are not candidates for immediate β-blocker therapy. Amiodarone is also the anti-arrhythmic drug of choice in patients with systolic heart failure. Pharmacologic treatment of symptomatic systolic heart failure is summarized in Table 6.

**Table 6. Pharmacologic treatment of symptomatic systolic heart failure**

<table>
<thead>
<tr>
<th>Initial therapy</th>
</tr>
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<tbody>
<tr>
<td>Angiotensin-converting enzyme inhibitors</td>
</tr>
<tr>
<td>Angiotensin receptor blocking agents in patients intolerant to</td>
</tr>
<tr>
<td>angiotensin-converting enzyme inhibitors</td>
</tr>
<tr>
<td>β-blockers</td>
</tr>
<tr>
<td>Diuretics to relieve congestive symptoms</td>
</tr>
<tr>
<td>Digitalis in selected patients</td>
</tr>
<tr>
<td>Patients with persistent symptoms</td>
</tr>
<tr>
<td>Aldosterone antagonists</td>
</tr>
<tr>
<td>Combination of angiotensin-converting enzyme inhibitors and α-adrenergic blocking</td>
</tr>
<tr>
<td>agents in selected patients</td>
</tr>
<tr>
<td>Amiodarone in selected patients</td>
</tr>
<tr>
<td>β-type natriuretic peptide in selected patients with decompensated heart failure</td>
</tr>
<tr>
<td>Non-glycosidic inotropic agents (may improve symptoms, but increase mortality)</td>
</tr>
<tr>
<td>Prostaglandins, endothelin antagonents, vasopeptidase inhibitors (may increase mortality)</td>
</tr>
</tbody>
</table>

Non-pharmacologic interventions such as chronic resynchronization therapy, with or without defibrillator has been reported to attenuate ventricular remodeling and to improve prognosis.\(^ {91,92}\) LV assist devices also have the potential for improving prognosis of patients with refractory heart failure.\(^ {93}\) Ventricular volume reduction therapy, revascularization and LV reconstruction, mitral valve repair, myoblast implantation and gene therapy are under investigation. Cardiac transplantation is an established treatment for end-stage refractory heart failure, which improves quality and quantity of life. The non-pharmacologic therapy for refractory heart failure is summarized in Table 7.

**Table 7. Non-pharmacologic therapy of refractory heart failure**

<table>
<thead>
<tr>
<th>Chronic resynchronization therapy (bi-ventricular pacing) with or without implantable cardioverter defibrillator</th>
</tr>
</thead>
<tbody>
<tr>
<td>LV assist device</td>
</tr>
<tr>
<td>Cardiac transplantation</td>
</tr>
<tr>
<td>LV revascularization, reconstruction (under investigation)</td>
</tr>
<tr>
<td>Mitral valve repair, myoblast implantation and gene therapy (under investigation)</td>
</tr>
</tbody>
</table>

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Chatterjee Remodeling in Systolic Heart Failure


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Control of Rate versus Rhythm in Rheumatic Atrial Fibrillation: A Randomized Study

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Background: Patients with rheumatic heart disease and atrial fibrillation incur significant morbidity and mortality. It is not known which approach, rate control or maintenance of sinus rhythm might be most appropriate. The present study was undertaken to compare the strategy of ventricular rate control versus maintenance of sinus rhythm in rheumatic atrial fibrillation, and to evaluate the role of amiodarone in this patient population.

Methods and Results: We prospectively studied 144 patients with chronic rheumatic atrial fibrillation in a double-blind protocol—rhythm control (group I: 48 patients each with amiodarone - group Ia; and placebo - group Ib) and compared the effects with the ventricular rate control (group II) by diltiazem (n=48, open-label). Direct current cardioversion was attempted in group I. The mean age of the study population was 38.6±10.3 years, left atrial size was 4.7±0.6 cm, atrial fibrillation duration was 6.1±5.4 years, and 72.9% patients had undergone valvular interventions. At 1 year, 45 patients with sinus rhythm in group I compared to 48 patients in group II demonstrated significant increase in exercise to sinus rhythm time, had improvement in functional class and quality of life score. There was no difference in hospitalization rates, systemic bleeds or incidence of thromboembolism. Five patients died in group II but none in group I (p=0.02). In group I, 73/87 (83.9%) patients converted, and 45/86 (52.3%) patients maintained sinus rhythm at 1 year. Conversion rates were 38/43 (88.4%) with amiodarone versus 34/44 (77.3%) with placebo (p=0.49); corresponding rate for maintaining sinus rhythm was 29/42 (69.1%) versus 16/44 (36.4%), p=0.008 respectively.

Conclusions: Maintenance of sinus rhythm appeared to be superior to ventricular rate control in patients with rheumatic atrial fibrillation in terms of an effect on mortality and morbidity. Sinus rhythm could be restored in the majority and amiodarone was superior to placebo in this regard. (Indian Heart J 2004; 56: 110-116)

Key Words: Atrial fibrillation, Amiodarone, Rheumatic heart disease

Atrial fibrillation (AF) is associated with the risk of thromboembolic complications in 4-5% per year in patients without rheumatic heart disease (RHD)\textsuperscript{1-5} and about 17-18% in the presence of rheumatic valvular heart disease.\textsuperscript{6,7} AF is also associated with symptoms of palpitation, shortness of breath at rest and during exercise and may have deleterious effects on ventricular function and overall survival.\textsuperscript{8} In the Indian subcontinent, RHD still accounts for significant number of hospital admissions and one-fourth of patients with rheumatic valvular heart disease have AF.\textsuperscript{9}

Pharmacological Intervention in Atrial Fibrillation (PIAF)\textsuperscript{10} trial suggested that maintenance of sinus rhythm (SR) leads to symptomatic improvement in patients with AF. However, this does not provide any mortality benefit as evaluated by the AFFIRM study.\textsuperscript{11} These studies were primarily conducted in patients with non-rheumatic AF and the issue of rate versus rhythm control has not been critically evaluated in the setting of RHD.

Amongst all anti-arrhythmic drugs evaluated for AF, amiodarone has shown most promising results with successful conversion and maintenance of SR achieved in 50–70% of patients.\textsuperscript{12-14} There have been no randomized trials evaluating the role of amiodarone in chronic rheumatic AF and thus, a prospective, randomized trial in
patients with RHD and chronic AF was undertaken to evaluate the benefits of ventricular rate control versus those of restoration and maintenance of SR. The study, Control of Rate versus Rhythm Control in Rheumatic Atrial Fibrillation Trial (CRRAFT), was thus designed to address two specific issues in patients with RHD and chronic AF. The first aim was to evaluate whether restoration and maintenance of SR had a significant clinical advantage compared to the persistence of AF with only control of ventricular rate. The second aim was to evaluate the role of amiodarone compared to placebo in the restoration and maintenance of SR.

**Methods**

**Patients:** All patients with RHD who had AF and were referred to the Cardiology Clinic of the King Edward VII Memorial Hospital, Mumbai, a tertiary referral center and University Hospital, were eligible for entry into the study, provided they had another electrocardiogram (ECG) done at least 3 months earlier, which also showed the presence of AF. Exclusion criteria included AF of <3 months duration, left atrial size >6.0 cm on echocardiography, valvular heart disease with hemodynamic compromise necessitating surgery, valvular surgery or balloon valvotomy in the past two months, pregnancy and any contra-indications to the use of amiodarone. The study period was over two years, from March 1998 to May 2000.

**Sample size:** Sample size was calculated assuming a 60% success in conversion to SR with amiodarone and 30% for placebo, based on published studies in non-rheumatic AF. 14-16 Forty-eight patients were required to be randomized in each treatment group to achieve an 80% power at 95% confidence levels.

**Randomization and interventions:** All patients who consented to participate in the study (protocol approved by the institutional ethical committee) were randomized in an open design to either the rate control (group I) or the rhythm control (group II) in a ratio of 1:2.

**Rhythm control arm (group I):** Patients who entered the rhythm control group were further randomized in a double-blind design to receive either amiodarone or placebo for conversion to SR. The objective in these patients was to restore and maintain SR by drug therapy with electrical conversion, wherever required.

**Amiodarone arm (group Ia):** Forty-eight patients received 200 mg of amiodarone thrice daily for the first 10 days followed by a maintenance dose of 200 mg once daily thereafter.

**Placebo arm (group Ib):** Forty-eight patients received inert placebo tablets in a schedule identical to that in the amiodarone group.

**Rate control arm (group II):** Forty-eight patients randomized to this group received 90 mg sustained release diltiazem twice daily to maintain the resting ventricular rate below 90 beats/min, and less than 130 beats/min with activity. No attempt to restore SR with drug therapy or electroversion was made in these patients.

In all the three groups Ia, Ib and II, the need for additional drug therapy was left to the discretion of the recruiting physician.

After 8 weeks of drug therapy, ECG was recorded and conversion to SR noted. Patients who remained in AF were subjected to DC cardioversion as an out-patient procedure with up to three synchronized, monophasic DC shocks of 200J, 360J and 360J respectively, using intravenous midazolam or propofol for sedation. In patients who failed conversion at the first attempt, a second attempt was made at 12 weeks. Patients who failed to convert to SR after 2 consecutive attempts were classified as primary failure. Patients who achieved SR were followed up at 3, 6, 9 and 12 months. Patients who had recurrence of AF after the initial restoration of SR were subjected to up to 2 further attempts at DC cardioversion, but not more than 3 attempts in all. Failure to maintain SR till the 12-month follow-up visit after initial development of SR was considered as secondary failure.

All patients were subjected to a detailed physical examination, echocardiography, and treadmill exercisetest (Bruce protocol) for effort tolerance. NYHA class and quality of life (QOL) were assessed at baseline. The QOL score was assessed by modifying the questionnaire from the Minnesota scale. The scoring was: 1 - worse, 2 - fair, 3 - good, 4 - very good and 5 - excellent. Patients were followed up at 3, 6, 9, 12 months and specifically evaluated for the development of new symptoms, change in previous symptoms, concomitant drug use, adverse effects of drugs, and maintenance of rhythm and rate by ECG. All patients received oral anticoagulation with warfarin and the prothrombin time was monitored regularly; INR was maintained at 3-4 in patients with metallic prosthetic valves and between 2-3 with no metallic prosthesis. Treadmill exercise test, NYHA functional class and QOL assessments were repeated at the end of 12 months in all patients in the ventricular rate control arm and in those who maintained SR in the rhythm control arm. In addition, patients in the rhythm control arm were monitored for side effects of amiodarone therapy with liver, thyroid, and lung function.
tests and ophthalmologic slit lamp examination at 3 and 9 months of follow-up. ECG was performed at every visit.

**Study outcomes:** For the rate control versus rhythm control part of the study, differences in effort tolerance assessed by treadmill exercise time (Bruce protocol), NYHA class, QOL score, thromboembolic and bleeding complications, hospitalization rates, and deaths were compared between the rate control group and patients in rhythm control group, who maintained SR for the 12 months of follow-up. For comparison of efficacy of amiodarone and placebo in achieving rhythm control, restoration and maintenance of SR at 12 months follow-up was considered the primary end point. Other end points considered were spontaneous conversions - defined as conversion to SR without electrical cardioversion, primary and secondary failure.

**Statistical analysis:** Student's t test, chi-squared test and Fisher's exact test were used to compare baseline characteristics and outcomes in the various treatment groups. Differences between variables which could predict successful maintenance of SR in the rhythm control arm were initially evaluated by univariate methods, and then subjected to multiple logistic regression analysis to identify variables which independently correlated with maintenance of SR. The data were analyzed using EpiInfo (version 6, World Health Organization, Geneva) and WINKS (Version 4.62, Texasoft Inc.) software packages.

**Results**

A total of 144 consecutive patients who consented to participate in the study were recruited. There were 79 females and 65 males, aged 38.6±10.3 years; they had chronic AF for an average of 6.1±5.4 years (range 1–25 years) and the mean left atrial size was 4.7±0.6 cm (range 3.7–5.8 cm). One hundred and thirty patients had mitral valve disease, 14 had combined mitral and aortic valve disease and 4 had only aortic valve disease. One hundred and twenty-one valvular interventions had been performed in 105/144 (72.9%) patients—closed mitral commissurotomy in 13, open mitral commissurotomy in 19, balloon valvuloplasty in 11, mitral valve replacement in 70, and aortic valve replacement in 8.

**Baseline characteristics:** The baseline characteristics in the three groups with respect to age, sex, duration of AF, NYHA class, QOL score, exercise time, LA size, LV ejection fraction, and valvular interventions performed were similar (Table 1).

<table>
<thead>
<tr>
<th>Table 1. Baseline characteristics in the three treatment groups</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td>Amiodarone</td>
</tr>
<tr>
<td>------------------</td>
</tr>
<tr>
<td>No. of patients</td>
</tr>
<tr>
<td>Age (years)</td>
</tr>
<tr>
<td>Sex (M:F)</td>
</tr>
<tr>
<td>AF duration (years)</td>
</tr>
<tr>
<td>NYHA class</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>QOL score</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Exercise time (min)</td>
</tr>
<tr>
<td>LA size (cm)</td>
</tr>
<tr>
<td>EF (%)</td>
</tr>
<tr>
<td>Past surgery (%)</td>
</tr>
<tr>
<td>Prosthetic valves</td>
</tr>
</tbody>
</table>

AF: atrial fibrillation; NYHA: New York Heart Association; QOL: quality of life; LA: left atrial; EF: ejection fraction

**Rate control versus rhythm control:** To determine whether maintenance of SR was superior to persistence of AF with control of ventricular rate. 45/86 patients in group I who maintained SR at 1 year follow-up were compared to 48 patients with AF in group II. The baseline characteristics of these two groups were comparable in terms of age, sex, duration of AF, NYHA functional class, QOL score, left atrial size and left ventricular ejection fraction on echocardiography and effort tolerance as assessed by treadmill exercise testing.

During the 12-month study period, 10 patients in group I (6 in amiodarone subgroup and 4 in placebo subgroup) and 8 patients in group II were lost to follow-up and were excluded from analysis. The change in duration of treadmill exercise time over pretreatment values was significantly longer in patients in group I (SR group) (2.6±1.9 min) compared to that in group II (rate control group) (0.6±2.5 min). Moreover patients in SR showed an improvement in NYHA class and QOL scores compared to the rate control group (Table 2). Hospitalization rates, incidence of bleeding and thrombosis were similar in both the groups (Table 2). There were 5 deaths during the 12-month study period, all in the rate control group. Three patients died because of
choked prosthetic valve (due to pannus formation in 2 and thrombosis in 1), one died of progressive heart failure and one due to presumed bacterial endocarditis. All five patients had metallic prosthetic valves. Thus, the relative risk of death in the rate control group was 12.4 times that in the SR group (95% CI 5.3 to 29).

### Table 2. Outcomes in rate versus rhythm group

<table>
<thead>
<tr>
<th></th>
<th>Rhythm (n=45)</th>
<th>Rate (n=40)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improvement in exercise time (min)*</td>
<td>2.6±1.9</td>
<td>0.6±2.5</td>
<td>0.001</td>
</tr>
<tr>
<td>NYHA class*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Improved (≥1 class)</td>
<td>27</td>
<td>7</td>
<td>0.0014</td>
</tr>
<tr>
<td>Same</td>
<td>16</td>
<td>24</td>
<td></td>
</tr>
<tr>
<td>Worsened (≥1 class)</td>
<td>2</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Quality of Life score*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Improved (≥1 class)</td>
<td>39</td>
<td>20</td>
<td>0.033</td>
</tr>
<tr>
<td>Same</td>
<td>6</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>Worsened (≥1 class)</td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Deaths</td>
<td>0</td>
<td>5</td>
<td>0.023</td>
</tr>
<tr>
<td>Hospitalization*</td>
<td>4</td>
<td>6</td>
<td>0.51</td>
</tr>
<tr>
<td>Bleeding*</td>
<td>1</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Thrombosis*</td>
<td>1**</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

* These parameters were assessed at baseline and at the end of 12 months in patients who survived (n=35, rate control arm)
** Transient ischemic attack

### Table 3. Efficacy of amiodarone versus placebo in maintenance of sinus rhythm

<table>
<thead>
<tr>
<th></th>
<th>Amiodarone (n=48)</th>
<th>Placebo (n=48)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SR restoration (3 months)</td>
<td>38</td>
<td>34</td>
<td>0.49</td>
</tr>
<tr>
<td>SR maintenance (1 year)</td>
<td>29</td>
<td>16</td>
<td>0.008</td>
</tr>
<tr>
<td>Primary failure</td>
<td>5</td>
<td>10</td>
<td>NS</td>
</tr>
<tr>
<td>Secondary failure</td>
<td>8</td>
<td>18</td>
<td>0.006</td>
</tr>
<tr>
<td>Lost to follow-up</td>
<td>6</td>
<td>4</td>
<td>NS</td>
</tr>
</tbody>
</table>

SR: sinus rhythm

### Fig. 1. Maintenance of sinus rhythm at 1-year follow-up.

Rhythm control—amiodarone versus placebo: To evaluate whether amiodarone was superior to placebo in restoration and maintenance of SR, 48 patients were randomized to receive amiodarone (group Ia) and 48 patients received placebo (group Ib). During the first 8 weeks of initiation of therapy, 9 patients in group Ia and 2 in group Ib had converted to sinus rhythm (p=0.03) without need for electrical cardioversion. Restoration of SR at 3 months and the primary failure rate was similar in both the groups (Table 3). However at one-year follow-up significantly more patients on amiodarone maintained SR and also there were fewer secondary failures in these patients (Table 3 and Fig. 1). The number of attempts at electrical conversion to maintain SR was significantly less in the amiodarone as compared to placebo group (1.4 v. 2.1, p=0.01). There were no deaths in either subgroup. Hospitalization was required in 4 and 8 patients respectively in the amiodarone and placebo groups. The drug was withdrawn in 3 patients in the amiodarone group: 2 had severe bradycardia and 1 had significant hypothyroidism. One other patient on amiodarone developed mild hypothyroidism but the drug was continued. Two patients in the placebo arm had their drug withdrawn, one because of intolerance and the other because of worsening congestive heart failure. These patients were included in the analysis as intention to treat. None of the patients in the placebo group had bradyarrhythmias or thyroid dysfunction. No abnormalities in the lung function tests or corneal deposits affecting vision were noted in either of the treatment groups.

Of the 86 patients in the rhythm control arm of the study who completed one year follow-up, the group of 45 patients who maintained SR till the end of the study period were compared with the 41 patients who failed to maintain SR (Table 4). Patients who maintained SR were more likely to have QOL scores ≥3 at baseline. Age, sex, duration of AF prior to enrollment, left atrial size, left ventricular ejection fraction and prior valvular surgery did not correlate with the likelihood of maintaining SR. On multiple logistic regression, the only two variables that correlated with successful maintenance of SR at 12 months were treatment with amiodarone (OR = 2.5, 95% CI 0.59 to 10.8, p = 0.013) and QOL score at baseline ≥3 (OR = 0.41, 95% CI 0.18 to 0.92, p = 0.035).

**Additional medications:** In the rate control arm 5
patients required higher dose of diltiazem and 6 patients required addition of digoxin for adequate control of ventricular rate. In the SR arm, 13 patients required additional rate control drugs, 10 in the placebo group and 3 in the amiodarone group. Eight patients were given diltiazem, 3 required combination of diltiazem and digoxin and 2 required combination of digoxin and atenolol for adequate rate control.

### Discussion

Atrial fibrillation can adversely affect hemodynamics specially in patients with valvular heart disease. The absence of atrial systole (atrial kick) and a rapid ventricular rate with relative shortening of diastole can increase left atrial pressure, worsen pulmonary venous congestion and compromise cardiac output. Moreover, stasis of blood in the left atrial appendage predisposes to development of thrombi and embolic complications. All of these can presumably be corrected by restoration of SR. However, it is not yet clear whether restoration and maintenance of SR improves effort tolerance, QOL and reduces morbidity and mortality in patients with AF in the setting of rheumatic heart disease.

Our study shows that at the end of 12 months follow-up period, patients who maintained SR had improvement in their NYHA symptomatic class, QOL scores, and also had lower mortality than patients in whom only control of ventricular rate was attempted. Of the 5 patients who died, death in one was due to prosthetic valve thrombosis, and in another due to progressive heart failure. In patients with prosthetic heart valves, presence of AF may carry an incremental risk for thromboembolism, which may be reduced with SR. Of the other three deaths, two were due to choked prosthetic valves through pannus formation and one due to presumed bacterial endocarditis, and these could not be attributed directly to AF.

The PIAF trial evaluated the benefits of SR and was performed in patients with persistent AF, predominantly in the non-rheumatic valvular heart disease patients. There was significant improvement in the effort tolerance in SR group, as objectively assessed by 6-min walk test. However the subjective assessment by the QOL score was not different between the SR and AF groups. A larger number of hospitalizations were required in the rhythm arm but the majority (67%) of admissions were for electrical cardioversion and not because of any ill effects of SR or amiodarone. In our study, electrical cardioversion was performed as an outpatient procedure and was not considered as hospitalization. The objective assessment of effort tolerance in our study showed improvement similar to that in the PIAF study. The AFFIRM study concluded that the rhythm control strategy offered no survival advantage over the rate control strategy. This is contrary to our results, primarily because of the different patient population studied; our study was conducted in patients with RHD and AF and the mean age was much younger (39 years v. 70 years). Also the means to achieving SR seems equally important than the rhythm itself. In the AFFIRM study the anti-arrhythmic drug used to achieve SR was left to the discretion of the treating physician and in the current study amiodarone was the only drug used.

In patients with valvular heart disease, it is generally considered difficult to maintain SR, with or without antiarrhythmic drug therapy. Most studies with rheumatic AF addressing the issue of SR restoration have been surgical series undergoing Cox’s maze procedure and its variations during the valve surgery. They report a high success rate in maintaining SR in 70–80% patients. We found that with the electrical cardioversion protocol followed in this study, 84% of patients could be converted to SR. However, in the absence of any antiarrhythmic drug, only 36% patients maintained SR. If treated with amiodarone, 69% patients maintained SR; nearly 21% of

<table>
<thead>
<tr>
<th>Predictor</th>
<th>SR at 1 year (n=45)</th>
<th>AF at 1 year (n=41)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>37.5±11.2</td>
<td>40.4±10.6</td>
<td>0.7</td>
</tr>
<tr>
<td>Sex (M:F)</td>
<td>20:25</td>
<td>21:20</td>
<td>0.4</td>
</tr>
<tr>
<td>AF duration (years)</td>
<td>5.8±5.5</td>
<td>6.3±6.2</td>
<td>0.4</td>
</tr>
<tr>
<td>NYHA class</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>8</td>
<td>13</td>
<td>0.3</td>
</tr>
<tr>
<td>II</td>
<td>34</td>
<td>27</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>3</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Quality of life score ≥3</td>
<td>35</td>
<td>10</td>
<td>0.001</td>
</tr>
<tr>
<td>LA size (cm)</td>
<td>4.7±0.7</td>
<td>4.9±0.7</td>
<td>0.21</td>
</tr>
<tr>
<td>LV ejection fraction (%)</td>
<td>55.6 (6.9)</td>
<td>56.1±6.2</td>
<td>0.77</td>
</tr>
<tr>
<td>Prior valvular intervention</td>
<td>35</td>
<td>28</td>
<td>0.80</td>
</tr>
<tr>
<td>Exercise time (min)</td>
<td>5.7±2.7</td>
<td>7.0±2.6</td>
<td>0.047</td>
</tr>
<tr>
<td>Electric cardioversions</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>27</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>9</td>
<td>15</td>
<td>0.001</td>
</tr>
<tr>
<td>3</td>
<td>1</td>
<td>22</td>
<td></td>
</tr>
<tr>
<td>Spontaneous conversion</td>
<td>9</td>
<td>1</td>
<td>0.025</td>
</tr>
<tr>
<td>Amiodarone treatment</td>
<td>29</td>
<td>13</td>
<td>0.018</td>
</tr>
</tbody>
</table>

Note: On multiple logistic regression analysis, successful maintenance of SR at 12 months correlated with QOL score (p=0.035, OR=0.41; CI 0.18-0.92) and treatment with amiodarone (p=0.013, OR=2.5; CI 0.59-10.8): SR: sinus rhythm; AF: atrial fibrillation; LA: left atrial; LV: left ventricular; QOL: quality of life.
patients on amiodarone converted to SR without the need of electrical cardioversion. The relatively larger randomized CTAFT (Canadian Trial of Atrial Fibrillation) trial revealed that 65% patients on amiodarone maintained SR as opposed to 37% patients on sotalol or propafenone. Earlier non-randomized and smaller randomized trials have shown similar efficacy with amiodarone13–14 in patients with non-rheumatic AF. Our study suggests that amiodarone may be equally effective in restoring and maintaining SR in patients with non-rheumatic origins of AF as well as those with chronic rheumatic AF with hemodynamically insignificant valvular heart disease.

To determine whether it is possible to identify which patients will maintain SR for prolonged periods, we compared the baseline characteristics in patients who did and who did not maintain SR. Multivariate analysis revealed that the two predictors of successful maintenance of SR were QOL at baseline and the use of amiodarone. Previously published studies have found that left atrial size may be one such predictor.19 In our study patients with LA size above 6 cm were excluded.

**Study limitations:** It is possible that the drug (diltiazem or amiodarone) itself influenced the outcome rather than the rhythm (sinus or atrial fibrillation). However this is less likely since the entire SR group, inclusive of patients on placebo, derived the same benefits as those of amiodarone. Further, the study is relatively small with a relatively higher drop outs and therefore larger studies will be needed to corroborate the findings especially those relating to mortality. The deaths in the rate control group were due to choked prosthetic valves, infective endocarditis and heart failure, which could be chance finding and cannot be directly attributed to AF.

**Conclusions:** It is possible to restore and maintain SR in about 36% patients of AF due to RHD with electrical cardioversion alone. Addition of amiodarone increases the success rate to 69%; patients who received amiodarone also required fewer attempts at electrical conversion than those who did not. The data suggest that it might be beneficial to restore and maintain SR because it improves the symptoms (NYHA class), QOL scores, effort tolerance, and possibly lowers mortality rate when compared to patients in whom AF is allowed to persist with a controlled ventricular rate. The data supports the notion that most patients with rheumatic AF should be given the benefit of conversion to SR. After 8 to 12 weeks of amiodarone therapy, those who do not convert to SR, should be subjected to electrical cardioversion.

**Acknowledgement**

The authors acknowledge M/s Sanofi Synthe laboratories India Ltd. for their limited financial grant for this study.

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Carotid Intima-Media Thickness and Brachial-Ankle Pulse Wave Velocity in Patients with and without Coronary Artery Disease

Ravi R Kasliwal, Manish Bansal, Kartikeya Bhargava, Hansa Gupta, Sharad Tandon, Vinayak Agrawal
Department of Cardiology, Escorts Heart Institute and Research Centre, New Delhi

Background: Carotid intima-media thickness and pulse wave velocity are non-invasive markers of atherosclerosis and have been shown to reliably predict presence and extent of atherosclerotic vascular disease. However, studies examining their association with each other have shown inconsistent results. Hence it was sought to assess correlation between carotid intima-media thickness and pulse wave velocity in patients with and without coronary artery disease.

Methods and Results: Sixty-four patients with angiographically proven coronary artery disease and 84 age-matched individuals without coronary artery disease but having one or more conventional cardiovascular risk factors were included in the study. Individuals with established cerebrovascular disease and peripheral vascular disease were excluded from the study. Carotid intima-media thickness of far wall was measured at three predefined sites (distal common carotid, carotid bifurcation and proximal internal carotid artery) on each side. Brachial-ankle pulse wave velocity was measured non-invasively using VP 1000 (Colin Corporation) automated ABI/PWV analyzer. There was no significant difference in gender and presence of cardiovascular risk factors in the two groups. Mean and maximum carotid intima-media thickness and brachial-ankle pulse wave velocity were all significantly higher in coronary artery disease patients as compared to patients without coronary artery disease (0.842 v. 0.657 mm, p <0.0001; 1.076 v. 0.795 mm, p <0.0001; 1708.63 v. 1547.26 cm/s, p <0.0004 respectively). There was a significant correlation between brachial-ankle pulse wave velocity and both mean and maximum carotid intima-media thickness in patients with coronary artery disease (r =0.47, p <0.0001 and r=0.41, p < 0.0008 respectively) but not in individuals without coronary artery disease (r=0.01 and -0.1 respectively).

Conclusions: Presence of significant correlation between carotid intima-media thickness and brachial-ankle pulse wave velocity in patients with coronary artery disease but absence of the same in individuals without major atherosclerotic vascular disease suggests that the correlation between carotid intima-media thickness and brachial-ankle pulse wave velocity becomes stronger with increasing extent of atherosclerosis. (Indian Heart J 2004; 56: 117-122)

Key Words: Pulse wave velocity, Coronary artery disease, Ultrasonography
aspects of atherosclerosis have shown inconsistent results. Differential influence of non-atherosclerotic vascular changes on these two parameters has been said to be the major reason for this discrepancy. More data is needed to correctly understand the underlying pathophysiological process. Hence, we conducted this study to assess the correlation between carotid IMT and arterial PWV in patients at high risk of having atherosclerosis and in those with established CAD.

**Methods**

A total of 148 individuals from inpatient and outpatient departments of the institute were included in the study. They were divided into two groups: with CAD (n=64) and without CAD (n=84). The CAD group comprised of randomly selected subjects who had undergone coronary angiography for various reasons and were found to have significant CAD on angiography (≥50% luminal stenosis in at least one major epicardial coronary artery). The non-CAD group comprised of age-matched individuals without any history suggestive of CAD, who had one or more conventional cardiovascular risk factors and had attended cardiology outpatient of our institute for routine checkup. Exercise stress electrocardiography was performed in these subjects to exclude presence of asymptomatic significant CAD. The cardiovascular risk factors taken into consideration for the selection of these individuals included diabetes mellitus, hypertension, dyslipidemia, family history of premature CAD and smoking. Diabetes mellitus was defined as a fasting blood glucose level of ≥126 mg/dl, or non-fasting blood glucose level ≥200 mg/dl or pharmacological treatment for diabetes. Hypertension was defined as systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg or self-reported use of antihypertensive medications. Dyslipidemia was defined as low-density lipoprotein (LDL) level >130 mg/dl, or high-density lipoprotein (HDL) <40 mg/dl, or triglycerides (TG) >200 mg/dl. Family history was considered to be positive if there was occurrence of a coronary event, before the age of 55 years in a first degree male relative or before 65 years in case of a first degree female relative. Current smoking was considered a conventional risk factor.

Exclusion criteria included presence of occlusive disease of carotid or lower limb arteries, whether symptomatic or asymptomatic, diagnosed on the basis of ultrasonography (USG)/Doppler, angiography or any other imaging modality. An ankle-brachial index <0.9 on either side was also considered to be a marker of significant peripheral vascular disease and such patients were excluded from the study. Patients with prior coronary artery bypass grafting (CABG) and/or percutaneous transluminal coronary angioplasty (PTCA) were also excluded from the study.

All subjects gave informed written consent and underwent clinical evaluation, biochemical tests and measurement of carotid IMT and brachial-ankle PWV (baPWV). Clinical evaluation included detailed history regarding presence and duration of conventional cardiovascular risk factors mentioned above, blood pressure recording, assessment of cardiovascular status and height and body weight measurements. Biochemical tests included fasting and post-prandial blood sugar, and fasting lipid profile.

Carotid IMT measurement was done using high resolution B-mode scanning with 7.5 MHz linear phased-array transducer attached to Sonos 5500 USG machine.

IMT was taken as the distance between the leading edge of the first echogenic line of the far wall of carotid artery (lumen-intima interface) and leading edge of the second echogenic line (media-adventitia interface). Measurements of the IMT were made at end-diastole (peak of R wave of ECG) at three segments on each side i.e. distal 1 cm of common carotid artery just before bifurcation, carotid bifurcation itself and proximal 1 cm of internal carotid artery. Maximum detectable IMT excluding plaques was recorded for each carotid segment. Six measurements were thus obtained for each subject. Mean and maximum of these six values were used for further analysis. A single observer who was unaware of the clinical status of the subjects took all the measurements.

Brachial-ankle PWV was measured using an automated machine—VP 1000 (Colin Corporation®) ABI/PWV analyzer. The machine records pulse wave contours in different arterial segments on the basis of volume plethysmography. The patient was asked to lie supine and sphygmomanometer cuffs, which were attached to the machine, were tied around both the arms just above the elbows and both the legs just above the ankles. The cuffs are automatically inflated and deflated and pulse wave contours in both the brachial and both the posterior tibial arteries were recorded simultaneously. Pulse transit time between brachial and ankle regions was calculated from these pulse wave recordings. Dividing the distance between these segments with the pulse transit time gives the PWV for that particular segment. Average of the baPWVs obtained for either side was used for further analysis. Reproducibility of the technique has already been established and the machine has been approved by US FDA for this purpose.
To assess the reproducibility of both IMT and PWV measurement in the present study, 60 subjects (30 each without and with CAD) were examined on two separate occasions. The coefficients of variation were 3.2%, 4.1% and 3.9% for mean carotid IMT, maximum carotid IMT and baPWV respectively in non-CAD patients and 3.9%, 3.7% and 4.5% respectively in CAD patients.

**Statistical analysis:** The statistical analysis was done on SPSS 10.0 for windows. All values were expressed as mean±SD or as percentages. The demographic data and risk factors were compared between the groups using chi-square and student’s t test wherever appropriate. Unpaired student’s t test was used to assess the presence of any difference in measured parameters in the two groups. Pearson’s correlation was used for assessing relationship between carotid IMT and baPWV. A p value <0.05 was considered as statistically significant.

**Results**

The baseline characteristics of the study groups are shown in Table 1. There was no statistically significant difference between the two groups with respect to age, gender and prevalence of various conventional cardiovascular risk factors.

The mean and maximum carotid IMT and baPWV in the two groups are shown in Table 2. Both the mean and maximum carotid IMT were significantly higher in CAD group (0.842±0.119 mm and 1.076±0.186 mm, respectively) as compared to the non-CAD group (0.657±0.057 mm and 0.795±0.138 mm, respectively; p value <0.0001 for both). Similarly baPWV was also significantly higher in CAD group (1708.63±344.01 cm/s) as compared to non-CAD group (1547.26±193.3 cm/s; p <0.0004).

The relationship between mean and maximum IMT and baPWV in the two groups is depicted in the Table 3 and Figs 1-4. A significant correlation was found between baPWV and both mean and maximum carotid IMT in patients with CAD (r=0.47, p=0.0001 and r=0.41, p <0.0008 respectively) but not in individuals without CAD (r=0.01, p=0.8931 and r=0.1, p <0.3658 respectively). Multivariate analyses showed that the association between carotid IMT and baPWV in CAD patients was independent of sex, age, mean blood pressure, diabetes, dyslipidemia, family history of premature CAD and smoking habits (p <0.012 for mean carotid IMT and baPWV and 0.037 for maximum carotid IMT and baPWV).

**Table 1. Clinical characteristics in the two groups**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Non-CAD group (n= 84)</th>
<th>CAD group (n= 64)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>49.54 ± 5.1</td>
<td>50.56±6.4</td>
<td>0.287</td>
</tr>
<tr>
<td>Male</td>
<td>64 (76.2)</td>
<td>55 (85.9)</td>
<td>0.139</td>
</tr>
<tr>
<td>Hypertension</td>
<td>48 (57.1)</td>
<td>36 (56.3)</td>
<td>0.914</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>20 (23.8)</td>
<td>12 (18.8)</td>
<td>0.459</td>
</tr>
<tr>
<td>F/h/o premature CAD</td>
<td>36 (42.9)</td>
<td>20 (31.3)</td>
<td>0.149</td>
</tr>
<tr>
<td>Smoking</td>
<td>20 (23.8)</td>
<td>16 (25.0)</td>
<td>0.867</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>52 (61.9)</td>
<td>32 (50.0)</td>
<td>0.148</td>
</tr>
</tbody>
</table>

Values in parentheses are percentages

CAD: Coronary artery disease

**Table 2. Carotid IMT and baPWV in the two groups**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Non-CAD group</th>
<th>CAD group</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean carotid IMT (mm)</td>
<td>0.657±0.057</td>
<td>0.842±0.119</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Max carotid IMT (mm)</td>
<td>0.795±0.138</td>
<td>1.076±0.186</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Mean baPWV (cm/s)</td>
<td>1547.26±193.3</td>
<td>1708.63±344.01</td>
<td>0.0004</td>
</tr>
</tbody>
</table>

IMT: intima-media thickness; baPWV: brachial-ankle pulse wave velocity

**Fig. 1.** Correlation between mean carotid intima-media thickness (IMT) and brachial-ankle pulse wave velocity (baPWV) in non-coronary artery disease group. Pearson’s correlation coefficient r=0.01, p <0.8931

**Table 3. Correlation between carotid IMT and baPWV in the two groups**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Non-CAD group</th>
<th>CAD group</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Carotid IMT and baPWV</td>
<td>r = 0.01, p = 0.8931</td>
<td>-0.1, p = 0.3658</td>
<td></td>
</tr>
<tr>
<td>Max Carotid IMT and baPWV</td>
<td>r = 0.47, p &lt;0.0001</td>
<td>0.41, p = 0.0008</td>
<td></td>
</tr>
</tbody>
</table>

r: Pearson's correlation coefficient; CAD: coronary artery disease; IMT: intima-media thickness; baPWV: brachial-ankle pulse wave velocity
with which it can be performed and its ability to allow direct visualization of ongoing atherosclerotic process. For these reasons carotid IMT measurement has become an integral component of a wide variety of cardiovascular research. On the other hand, application of arterial stiffness measurement in clinical research has remained very limited due to cumbersome nature of the available techniques for assessment of arterial stiffness and complexity of the arterial pathophysiology. Several non-invasive parameters have been developed that allow relatively easy assessment of arterial stiffness i.e. distensibility coefficient, elastic modulus, pulse wave velocity etc. Of these parameters, measurement of arterial PWV is of particular interest because it can provide information about central aortic stiffness, which is of the greatest importance as far as cardiovascular risk assessment is concerned. In majority of the studies, aortic PWV is measured as carotid-femoral PWV using applanation tonometry because of the ease of application. However, applanation tonometry itself is associated with certain technical problems related mainly to the correct application of the sensors. The automated machine VP-100 (Colin Corporation®), which measures PWV on the basis of volume plethysmography, circumvents these problems and has made the process very simple. The technique just involves tying sphygmomanometer cuffs to both arms and legs and the machine automatically calculates baPWV. Though baPWV differs from central aortic PWV, which has been the preferred parameter for assessing arterial stiffness, an excellent correlation between

Discussion

Development of new non-invasive tools for detection of subclinical atherosclerosis such as carotid IMT, PWV, brachial artery flow-mediated vasodilatation etc. has added a new dimension to cardiovascular research and clinical cardiology practice. Carotid IMT measurement in particular, has generated a lot of interest due to the ease
these two techniques has been previously shown.\textsuperscript{17,18} Hence, ease of measurement makes baPWV a reliable and preferable substitute of central aortic PWV for research purpose as well as for clinical application.

Several studies in past have attempted to evaluate association between atherosclerosis and arterial stiffness.\textsuperscript{10-16} Some studies found good correlation between the two,\textsuperscript{10,13-15} while others could not demonstrate such a relationship.\textsuperscript{11,12,16} Relatively few studies have used PWV as a marker of arterial stiffness.\textsuperscript{12-16} In the Rotterdam study, association of carotid-femoral PWV with several parameters of atherosclerosis including common carotid IMT was studied.\textsuperscript{13} An excellent correlation was found between PWV and all parameters of atherosclerosis. Taniwaki et al.\textsuperscript{14} studied the correlation of carotid-femoral PWV and carotid IMT in diabetic and non-diabetic individuals. Significant correlation was found between the two in both the groups but the relationship was steeper in diabetics. Similarly in Cardiovascular Health Study\textsuperscript{15} involving elderly patients, aortic PWV was found to be positively associated with increased common carotid intima-media thickness. On the other hand, Zureik et al.\textsuperscript{16} in their study of 564 healthy individuals did not find any independent association between carotid-femoral PWV and carotid IMT but a significant independent association was shown to exist between carotid-femoral PWV and carotid plaques.

Several explanations have been proposed for the lack of association between carotid IMT and arterial stiffness observed in various studies. Arterial stiffness is influenced by a number of factors in addition to atherosclerosis i.e. age, blood pressure, diabetes, smoking etc.\textsuperscript{19} These factors may increase arterial stiffness directly as well as through initiation of atherosclerotic process. The effect of atherosclerosis itself on arterial stiffness and vice versa is not very well understood. It appears that atherosclerosis may decrease arterial stiffness in the initial stages but in later stages increases it.\textsuperscript{11} Furthermore, it has been suggested that in the initial stages carotid IMT too, is influenced by non-atherosclerotic factors such as shear stress on the vessel wall.\textsuperscript{20}

\textbf{Limitations:} Our study is limited by the small sample size. Larger studies are needed to confirm our findings and also to evaluate relative values of carotid IMT and PWV, individually and jointly, in cardiovascular risk stratification of asymptomatic ‘at risk’ individuals.

\textbf{Conclusions:} We have found an excellent correlation between carotid IMT and arterial PWV in patients with CAD but no correlation was found between these two parameters in patients who did not have any significant atherosclerotic vascular disease (i.e. no carotid, coronary or peripheral vascular disease). These findings provide further evidence to support the hypothesis that atherosclerosis increases arterial stiffness only in late stages and that arterial PWV predominantly reflects atherosclerosis only when it is relatively advanced.

\section*{References}
\begin{enumerate}
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**Terminalia Arjuna Reverses Impaired Endothelial Function in Chronic Smokers**

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*Division of Cardiology, Department of Medicine, Mahatma Gandhi Memorial Medical College and Maharaja Yashwant Rao Hospital, Indore*

**Background:** Smoking, largely through increased oxidative stress, causes endothelial dysfunction which is an early key event in atherosclerosis. Smoking cessation and antioxidant vitamin therapy are shown to have beneficial role by restoring altered endothelial physiology. The present study was aimed to determine whether *Terminalia arjuna*, an Indian medicinal plant with potent antioxidant constituents, would improve endothelial dysfunction in smokers.

**Methods and Results:** Eighteen healthy male smokers (age 28.16±9.45 years) and equal number of age-matched non-smoker controls participated in the study. The baseline brachial artery reactivity studies were performed using high frequency ultrasound according to standard protocol under identical conditions to determine endothelium-dependent, flow-mediated dilation and endothelium-independent nitroglycerine-mediated dilation. The two groups were matched regarding age, body mass index, blood pressure, serum cholesterol, mean resting vessel diameters and post-occlusion flow velocities (all p=NS). While flow-mediated dilation was significantly impaired amongst smokers compared to controls (4.71±2.22 v. 11.75±5.94%, p <0.005), the nitroglycerine-mediated dilation was similar in the two groups (20.35±3.89 v. 19.68±3.74%, p=NS). Subsequently the smokers were given *Terminalia arjuna* (500 mg q8h) or matching placebo randomly in a double blind cross-over design for two weeks each, followed by repetition of brachial artery reactivity studies to determine various parameters including flow-mediated dilation after each period. There was no significant difference as regards vessel diameter and flow velocities between the two therapies. However, the flow-mediated dilation showed significant improvement from baseline values after *Terminalia arjuna* therapy but not with placebo (9.31±3.74 v. 5.17±2.42%, p <0.005)

**Conclusions:** Smokers have impaired endothelium-dependent but normal endothelium-independent vasodilation as determined by brachial artery reactivity studies. Further, *Terminalia arjuna* therapy for two weeks leads to significant regression of this endothelial abnormality amongst smokers. *(Indian Heart J 2004; 56: 123–128)*

**Key Words:** Endothelial dysfunction, Smoking, Terminalia arjuna

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**Original Article**

**Background:** Smoking is a major cardiovascular risk factor and is associated with impaired endothelium-dependent vasodilation, a key early event in atherogenesis.1-3 The cause of endothelial dysfunction in smokers is not known, but it has been attributed to increased oxidative stress that may reduce the bioavailability of endothelium-derived nitric oxide (NO), leading to impairment in vasodilatory function.4-5 The smoking-related endothelial dysfunction is potentially reversible after withdrawal from active or passive smoking.1-6 Further, the use of antioxidant vitamin C or vitamin E is associated with short-term improvement in endothelial dysfunction in smokers but does not show sustained beneficial effect.7-9 The short-term beneficial effects of vitamin C on vascular reactivity have also been demonstrated in other conditions associated with endothelial dysfunction and increased oxidative stress such as coronary artery disease (CAD), hypertension, diabetes and dyslipidemia.10-13

*Terminalia arjuna*, an Indian medicinal plant, used as bark extract, has been reported to have significant anti-failure and anti-ischemic properties.14,15 The mechanism of this benefit is not precisely known but could be related to potent antioxidant constituents present in *Terminalia*...
Terminalia arjuna causing improvement in endothelial dysfunction seen in CAD and heart failure. We aimed to determine whether endothelium-dependent, flow-mediated vasodilation (FMD) in brachial artery is impaired in healthy young chronic smokers and whether it is reversible with Terminalia arjuna therapy.

**Methods**

Eighteen (age 28.16±9.45 years) healthy, normotensive, non-diabetic, normo-lipidemic, chronic smokers (≥10 cigarettes/bidies for ≥2 years) with negative family history for cardiovascular disease and diabetes mellitus and equal number of age-matched controls participated in the study. They underwent thorough physical examination and routine laboratory evaluation. A standard questionnaire was used to obtain information about smoking, diabetes, dyslipidemia and hypertension and also the family history of these diseases. All subjects gave informed consent for participation in the study. The study protocol was approved by the institutional ethic committee.

Subjects with hypertension (BP ≥140/90 mmHg), diabetes, dyslipidemia (serum cholesterol ≥220 mg/dl), hepatic, renal or cardiovascular disease, malignancy, and psychiatric disorders were excluded from the study.

**Study design:** The subjects and controls underwent baseline brachial artery reactivity studies using standard protocol to determine endothelium-dependent and endothelium-independent vasodilation. Subsequently, the subjects were randomly given Terminalia arjuna extract (500 mg q8h) or visually matching placebo capsules for two weeks in a double blind cross-over design with a wash out period of at least two weeks between the therapies. The brachial artery reactivity studies were repeated at end of each therapy period to determine endothelium-dependent vasodilation. The brachial artery studies were carried out by a single operator who was blind to the smoking status or the therapy given to the subjects.

**Evaluation of Brachial Artery Reactivity**

Subject preparation and baseline measurements: Subjects and controls fasted for at least 8 hours, did not exercise or ingest substances that might affect flow-mediated dilation such as caffeine, high fat food, and vitamin C. The subjects continued to smoke throughout the study period except for four hours prior to brachial artery reactivity studies to avoid acute confounding effects of smoking on the FMD results.

Ultrasonographic studies were performed using 7.5 MHz linear array transducer (Image Point, Hewlett-Packard, USA) by a single ultrasound operator with intra observer variability of ≤3%. The subjects were positioned supine with the arm in a comfortable position for imaging the brachial artery above the antecubital fossa in the longitudinal plane (approximately 4 cm above bifurcation). A segment with clear anterior and posterior intimal interfaces between the lumen and vessel wall was selected for continuous two-dimensional gray-scale imaging.

Endothelium-dependent, flow-mediated dilation: To create flow stimulus in the brachial artery, a sphygmomanometric cuff was first placed on the forearm. A baseline rest image was acquired, and diameter measurements were taken from the vessel-lumen interface on the posterior wall to the vessel-lumen interface of the anterior wall three times and average diameter was obtained. Thereafter, arterial occlusion was created by inflating blood pressure cuff to at least 50 mmHg above systolic pressure for 5 min.

The longitudinal image of the artery was recorded continuously for 30 sec before to 2 min after cuff deflation. A mid-artery pulsed Doppler signal was obtained upon immediate cuff release and no later than 15 sec after cuff deflation to assess hyperemic velocity. The post-occlusion diameters were recorded three times during 45–60 sec following deflation and average diameter was obtained. The end of response to reactive hyperemia was followed by repeating measurements 15 min after recovery period. All brachial artery diameters were measured at the onset of R waves in the electrocardiogram corresponding to the end-diastole. The FMD of brachial artery was expressed as the percentage change in the arterial diameter from baseline to 45 to 60 sec after deflation of the cuff. Maximal hyperemic velocities were obtained within the first 15 sec after deflation and compared with the velocities obtained during baseline scanning.

Endothelium-independent vasodilation: The endothelium-independent vasodilation, reflecting vascular smooth muscle cell function, was determined by measuring the brachial artery diameters and flow velocities 3-4 min after sublingual nitroglycerine (0.5 mg) administration.

**Preparation of Terminalia arjuna extract:** The bark was crushed to a coarse powder, 20-40 mesh size, and then repeatedly extracted with 90% v/v alcohol at boiling temperature till complete exhaustion. This was followed by extraction with water at 70°C for 2 hours. Both alcoholic and aqueous extracts were concentrated separately at 55–60°C and vacuum extracted to a syrupy consistency.
After uniform mixing, further drying was carried out at 60°C under vacuum conditions. The dried material was powdered to a mesh size of 80–100 and capsulated.

**Statistical analysis:** The baseline demographic and brachial artery parameters between smokers and non-smoking controls were compared using unpaired t test. The differences in brachial artery diameters, FMD and blood flow velocities amongst smokers following *Terminalia arjuna* and placebo therapies compared to baseline parameters were analyzed using one-way analysis of variance (ANOVA) test. The difference in nitroglycerine-mediated dilation (NMD) amongst smokers and controls were analyzed using unpaired t test. The p value <0.05 was taken as statistically significant.

**Results**

**Baseline characteristics:** The demographic and various brachial artery parameters amongst healthy smokers and non-smoking controls are given in Table 1. The two groups were well-matched regarding age, body mass index (BMI), blood pressure and serum cholesterol levels. The smokers showed significantly lower endothelium-dependent dilation (FMD) compared to controls, but endothelium-independent dilation at baseline, indicating presence of endothelial dysfunction, was similar in controls and smokers.

**Brachial artery reactivity:** The brachial artery parameters in smokers obtained at baseline and at the end of *Terminalia arjuna* and placebo therapies are shown in Table 2. There was a significant improvement in FMD following *Terminalia arjuna* therapy but not with placebo (p<0.005).

**Table 1. Baseline characteristics of healthy smokers and non-smokers**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Smokers (n=18)</th>
<th>Non-smokers (n=18)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographic characteristics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>28.16±9.45</td>
<td>26.17±5.79</td>
<td>NS</td>
</tr>
<tr>
<td>Body mass index (BMI) (kg/m²)</td>
<td>23.08±2.71</td>
<td>22.13±1.81</td>
<td>NS</td>
</tr>
<tr>
<td>Blood pressure (mmHg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>119±5.54</td>
<td>118±11±6.15</td>
<td>NS</td>
</tr>
<tr>
<td>Diastolic</td>
<td>77.56±4.09</td>
<td>75.88±6.07</td>
<td>NS</td>
</tr>
<tr>
<td>Serum cholesterol (mg/dl)</td>
<td>180.44±16.67</td>
<td>186.6±15.27</td>
<td>NS</td>
</tr>
<tr>
<td>Brachial artery characteristics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vessel diameter (mm)</td>
<td>4.05±0.62</td>
<td>3.86±0.45</td>
<td>NS</td>
</tr>
<tr>
<td>Blood flow velocity (cm/s)</td>
<td>96.11±15.77</td>
<td>103.8±32.30</td>
<td>NS</td>
</tr>
<tr>
<td>% change in velocity (post-occlusion)</td>
<td>69.38±24.49</td>
<td>60.32±24.72</td>
<td>NS</td>
</tr>
<tr>
<td>Flow-mediated dilation (%)</td>
<td>4.71±2.22</td>
<td>11.75±5.94</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>Nitroglycerine-mediated dilation (%)</td>
<td>20.35±3.89</td>
<td>19.68±3.74</td>
<td>NS</td>
</tr>
</tbody>
</table>

**Table 2. Brachial artery reactivity amongst smokers following therapy (n=18)**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Baseline</th>
<th>Placebo</th>
<th><em>Terminalia arjuna</em></th>
<th>p value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basal lumen diameter (mm)</td>
<td>4.05±0.62</td>
<td>4.03±0.60</td>
<td>4.16±0.58</td>
<td>NS</td>
</tr>
<tr>
<td>Flow velocity (cm/s) (%)</td>
<td>69.38±24.49</td>
<td>68.44±19.02</td>
<td>71.33±21.67</td>
<td>NS</td>
</tr>
<tr>
<td>Flow-mediated dilation (%)</td>
<td>4.71±2.22</td>
<td>5.17±2.42</td>
<td>9.31±3.74</td>
<td>&lt;0.005</td>
</tr>
</tbody>
</table>

---

**Drug tolerance and side effects:** There were no significant differences in resting heart rates, blood pressure or any other clinical parameters during *Terminalia arjuna* therapy compared to baseline values. No untoward effects were noticed, or reported by study subjects on questioning during *Terminalia arjuna* or placebo therapy periods.
Discussion

Cigarette smoking is an established risk factor for cardiovascular disease and the leading preventable cause of CAD and death.27 The impaired endothelium-dependent vasodilation denoting endothelial dysfunction, prelude to atherosclerosis, occurs with active or even passive smoking and with chronic or acute exposure, is dose-dependent and potentially reversible.1,18-20 The precise mechanisms causing altered vascular reactivity are not fully understood, and may be complex. However, increased oxidative stress, related to large amounts of free radicals present in the cigarette smoke such as superoxide anion and hydroxyl radicals, that may reduce the bioavailability of NO released from the endothelium, remains the most important contributor.21,22 Preserved NO bioavailability is an important protective mechanism in the vessel wall, as it has anti-platelet, anti-adhesive and anti-proliferative effects in addition to its role as a vasodilator.23 NO is released by normally functioning endothelium and its release is responsible for endothelium-dependent arterial relaxation which can be induced by increasing flow and shear stress.23

Smoking also causes alpha-adrenergic receptor-mediated coronary vasoconstriction24 and is associated with increased plasma levels of endothelin-1 (ET-1), soluble vascular cell adhesion molecule-1 (sVCAM-1), soluble intercellular adhesion molecule-1 (sICAM-1) and E- and P-selectins which play pivotal role in the pathogenesis of atherosclerosis and might represent the connective links between smoking, endothelial dysfunction and atherosclerosis.25 Detection of brachial artery abnormalities may serve as surrogate marker to reflect changes in coronary vascular bed.26 The current research shows that endothelial dysfunction, related to various cardiovascular risk factors, is modifiable. Control of risk factors such as smoking, hypertension, elevated LDL cholesterol, diabetes, hyperhomocysteinemia has potential to improve endothelial functions.

Epidemiologic studies have shown that plasma levels of antioxidant nutrients such as vitamin C and E, are significantly lower in smokers compared to non-smokers.27 Vitamins C and E have been shown to attenuate the impairment of endothelium-dependent vasodilation related to smoking with associated improvement in the antioxidant status.7,9,17 Improvement in endothelial dysfunction among smokers was noticed in the forearm vasculature after-intra arterial infusion of water-soluble antioxidant vitamin C28 and in the brachial artery after intravenous vitamin C infusion.9 The beneficial effect of vitamin C supplementation was associated with a decrease in thiobarbituric acid reactive substances (TBARS) as an index of oxidative stress. Oral vitamin E (alpha-tocopherol, 600 IU daily) supplementation for four weeks in chronic smokers prevented the transient further impairment of endothelial dysfunction after acute smoking while it showed no effect on chronic endothelial dysfunction. The attenuation of transient endothelial dysfunction after acute smoking correlated with an improvement of the antioxidant status under vitamin E supplementation.9

The oral vitamin C therapy led to short-term improvement in endothelial dysfunction in smokers but it had no long-term beneficial effect.7 Similarly, increasing the bioavailability of NO by L-arginine or tetrahydrobiopterin administration in smokers has been shown to improve endothelium-dependent vasodilation.2,5,9

The young, healthy chronic smokers participating in our study showed significantly impaired endothelium-dependent FMD compared to no-smoking controls suggesting presence of chronic endothelial dysfunction related to smoking. These observations are consistent with several other published reports.1,3,5,18 We have demonstrated that two week’s treatment with Terminalia arjuna but not placebo, reverses smoking-related endothelial dysfunction in our subjects. This benefit is similar to the reported reversal of endothelial dysfunction amongst smokers with use of antioxidant vitamins C and E.7,9,17 The study participants continued smoking while on Terminalia arjuna or placebo therapy to remove any beneficial effect of smoking cessation confounding the study results.

The baseline brachial artery diameter, which is the strongest determinant of FMD, did not differ significantly during Terminalia arjuna or placebo therapies thus ruling out any confounding effect of baseline diameter to the observed FMD. The finding of impaired endothelium-dependent dilation (FMD) with preserved endothelium-independent dilation indicates smoking-related endothelial dysfunction in the study subjects.

Terminalia arjuna contains antioxidant constituents such as flavones (arjunolone), tannins and oligomeric proanthocyanidins (OPCS). The other constituents include glycosides : arjunetin, arjunoseide I-IV; acids : arjunic acid, arjunin, gallic acid, ellagic acid; minerals : calcium, magnesium, zinc, copper; colouring matter and essential oils.10

In animal experiments, intravenous administration of Terminalia arjuna extract led to dose-dependent decrease in blood pressure and heart rate that was thought to be centrally mediated.31 There was enhancement of aortic...
prostaglandin E2-like activity following isoproterenol-induced ischemia in rabbits pretreated with Terminalia arjuna. This was associated with increase in the threshold for myocardial ischemia and ventricular arrhythmia. The drug is known to have no significant effect on heart rate, blood pressure and cardiac output in healthy volunteers but causes an increase in cardiac output and blood pressure and a decrease in heart rate in patients with a failing heart. The mechanism of reversal of smoking-related endothelial dysfunction with Terminalia arjuna is unknown. Although we have not measured any improvement in its antioxidant status during Terminalia arjuna therapy amongst smokers, this appears to be the most likely mechanism. Extrapolating the results of present study, the improvement in endothelial dysfunction with Terminalia arjuna therapy could possibly explain its anti-ischemic and anti-failure properties documented in previous studies. This study subjects tolerated Terminalia arjuna well with no significant untoward effects which correlates with our previous experience. This short-term study was not designed to answer the question whether the beneficial endothelial effects of Terminalia arjuna are short-lived or sustained.

Acknowledgements

We thank Prof. LK Mathur, Department of Biostatistics, MGM Medical College, Indore for the statistical analysis and Mrs. Prasanna Nair for the secretarial assistance.

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Prevalence of Coronary Artery Disease in Patients with Rheumatic Heart Disease in the Current Era

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**Background:** This study was undertaken to determine the prevalence of coronary artery disease in patients with rheumatic heart disease undergoing valve surgery.

**Methods and Results:** Consecutive patients with rheumatic heart disease (n=376) who were above the age of 40 years, and scheduled for valve surgery underwent diagnostic coronary angiogram to delineate coronary arteries. The patients were divided into three groups based on valve involvement (mitral valve, aortic valve, and combined aortic and mitral valve). Significant coronary artery disease was considered to be present if one or more coronaries showed 50% or more luminal stenosis. There were 287 (76.3%) males and 89 (23.7%) females. The mean age of the study population was 51.2±8.2 years. Eighty-nine (23.8%) patients had typical chest pain, 116 (30.6%) patients had atypical chest pain and 171 (45.5%) patients had no chest pain. Hypertension was noted in 88 (23.4%) patients, 65 (17.3%) patients had diabetes, 98 (26.1%) patients were smoker, and 66 (17.6%) patients had dyslipidemia, and 15 (4.0%) patients gave past history of myocardial infarction. Of the total 376 patients, 46 (12.2%) patients were found to have significant coronary artery disease. In patients with mitral valve disease the prevalence was 13.5% (13/96), while it was 15.3% (19/124) in patients with aortic valve disease and 9% (14/156) in those with combined mitral and aortic valve disease.

**Conclusions:** Our results suggest that the overall prevalence of coronary artery disease in a group of patients with rheumatic heart disease undergoing valve surgery in the current era is 12.2%. This prevalence is much lower than the figures reported earlier in the Western literature. (*Indian Heart J* 2004; 56: 129-131)

**Key Words:** Coronary artery disease, Prevalence, Rheumatic heart disease

Coronary angiography is usually done routinely for patients with valvular heart disease prior to their valve replacement surgery, if there is suspicion of coronary artery disease (CAD) or if the person is above the age of 40 years. With improvement in health, sanitation and education, the prevalence of rheumatic heart disease (RHD) has come down significantly in India. However, due to rapid industrialization, lifestyle modifications and change in dietary habits, the prevalence of CAD has increased in the past four decades. The prevalence rate of CAD in India has been recently estimated to be 11%. The aim of the present study was to find out the prevalence of CAD in the current era, in a group of patients with established RHD who were undergoing valve replacement surgery.

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**Methods**
Consecutive patients with RHD (n=376), above the age of 40 years, who had undergone coronary angiography were included in the present study. Coronary angiography was performed after informed written consent. This study was done over a period of four years from 1998 to 2002. All patients were evaluated for the presence of chest pain and symptom class. Established risk factors for CAD such as diabetes mellitus, systemic hypertension, smoking and dyslipidemia were evaluated. Previous history of myocardial infarction and coronary artery bypass surgery was also recorded.

Cardiac catheterization and coronary angiography was performed by femoral approach using Judkins' technique. A coronary artery luminal diameter reduction of ≥50% in one or more arteries was considered to have significant CAD. Patients were divided into three groups namely; Group I: mitral valve disease, Group II: aortic valve disease, Group
III: combined mitral and aortic valve disease.

Statistical analysis: All data were analyzed using SPSS (9.0 version) software. Continuous variables were analyzed and expressed as mean±SD and difference in frequency distribution of risk factors were tested using chi-square analysis. A p-value <0.05 was considered significant.

Results

Patients' characteristics: There were 376 patients; 287 (76.3%) were males and 89 (23.7%) females. The mean age of the study population was 51±8 years. Females were slightly older than males but the difference was statistically non-significant. Baseline characteristics of the study population are shown in Table 1. Males had higher prevalence of systemic hypertension and smoking habits.

Patients were categorized depending on the presence or absence of chest pain; typical chest pain was observed in 89 patients. Of them, 27 had CAD, giving a prevalence of 30.3%. Of the 116 patients with atypical chest pain 12 patients had CAD, giving a prevalence of 10.3%; 171 patients gave no history of chest pain and 9 of these patients had CAD, giving a prevalence of 5.3%. Typical chest pain was most often seen in males while most of the females did not have history of chest pain.

<table>
<thead>
<tr>
<th>Table 1. Baseline characteristics</th>
<th>Total (n=376)</th>
<th>Male (n=287)</th>
<th>Female (n=89)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>51.2±8.2</td>
<td>51.4±8.2</td>
<td>50.4±7.8</td>
<td>0.86</td>
</tr>
<tr>
<td>Chest pain (typical)</td>
<td>89 (23.8)</td>
<td>76 (26.5)</td>
<td>13 (14.6)</td>
<td>0.01*</td>
</tr>
<tr>
<td>Chest pain (atypical)</td>
<td>116 (30.6)</td>
<td>94 (32.7)</td>
<td>22 (24.7)</td>
<td>0.09</td>
</tr>
<tr>
<td>No chest pain</td>
<td>171 (45.5)</td>
<td>117 (40.8)</td>
<td>54 (60.6)</td>
<td>0.001*</td>
</tr>
<tr>
<td>Hypertension</td>
<td>88 (23.4)</td>
<td>73 (25.4)</td>
<td>15 (16.9)</td>
<td>0.06</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>65 (17.3)</td>
<td>51 (17.8)</td>
<td>14 (15.7)</td>
<td>0.4</td>
</tr>
<tr>
<td>Smoking</td>
<td>98 (26.1)</td>
<td>94 (32.8)</td>
<td>4 (4.5)</td>
<td>0.001*</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>66 (17.6)</td>
<td>52 (18.1)</td>
<td>14 (15.7)</td>
<td>0.37</td>
</tr>
<tr>
<td>Past MI</td>
<td>15 (4.0)</td>
<td>14 (4.9)</td>
<td>1 (1.1)</td>
<td>0.09</td>
</tr>
</tbody>
</table>

Values in parentheses are percentages
MI: myocardial infarction; * statistically significant

Table 2. Distribution of valve lesions and coronary artery disease

<table>
<thead>
<tr>
<th>Valve involved</th>
<th>Total No. of patients</th>
<th>No. (%) of patients with CAD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mitral valve</td>
<td>96</td>
<td>13 (13.5)</td>
</tr>
<tr>
<td>Aortic Valve</td>
<td>124</td>
<td>19 (15.3)</td>
</tr>
<tr>
<td>Combined</td>
<td>156</td>
<td>14 (9.0)</td>
</tr>
<tr>
<td>Total</td>
<td>376</td>
<td>46 (12.2)</td>
</tr>
</tbody>
</table>

Values in parentheses are percentages
CAD: Coronary artery disease

CAD and RHD prevalence: The patients were divided into three groups based on valve involvement as stated above. The prevalence of CAD in these groups is shown in Table 2. In patients with mitral valve disease, the prevalence was 13.5% and in the group with aortic valve disease it was 15.3%, while the overall prevalence was 12.2%.

Discussion

In our study the prevalence of significant CAD in a group of patients undergoing valve replacement was 12.2%, which is much lower than what has been reported in the Western literature.

The overall prevalence of CAD in patients undergoing valve replacement ranges from 5% to 50%. Sarano et al.7 studied the prevalence of coronary atherosclerosis in a group of 601 patients with non-ischemic valvular regurgitation going for surgery. The prevalence of CAD in this study group was 35.6%. In patients with aortic valve disease the prevalence of CAD is in the range of 17-30%6-10 and for mitral valve disease it ranges from 22-50%3,4,8-11-14 (Tables 3 and 4). In our study, we found the prevalence of CAD in patients with mitral valve disease to be 13.5% and for those with aortic valve disease it was 15.3%. The overall prevalence of associated CAD did not differ amongst patients with mitral and aortic valve disease.

Table 3. Reported prevalence of coronary artery disease in mitral valve disease

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>No. of patients studied</th>
<th>Reported prevalence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Befeler et al.3</td>
<td>1970</td>
<td>26</td>
<td>50</td>
</tr>
<tr>
<td>Lacy et al.11</td>
<td>1977</td>
<td>67</td>
<td>32</td>
</tr>
<tr>
<td>Baxter et al.4</td>
<td>1978</td>
<td>82</td>
<td>22</td>
</tr>
<tr>
<td>Saltups4</td>
<td>1982</td>
<td>100</td>
<td>23</td>
</tr>
<tr>
<td>Chun et al.12</td>
<td>1982</td>
<td>82</td>
<td>26</td>
</tr>
<tr>
<td>Czer et al.13</td>
<td>1984</td>
<td>56</td>
<td>27</td>
</tr>
<tr>
<td>Mattina et al.14</td>
<td>1986</td>
<td>96</td>
<td>28</td>
</tr>
<tr>
<td>CMC Vellore</td>
<td>2003</td>
<td>96</td>
<td>13.5</td>
</tr>
</tbody>
</table>

Table 4. Reported prevalence of coronary artery disease in aortic valve disease

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>No. of patients studied</th>
<th>Reported prevalence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coleman &amp; Soloff6</td>
<td>1970</td>
<td>77</td>
<td>17.7</td>
</tr>
<tr>
<td>Harris et al.9</td>
<td>1975</td>
<td>69</td>
<td>23.2</td>
</tr>
<tr>
<td>Baxter et al.4</td>
<td>1978</td>
<td>47</td>
<td>17</td>
</tr>
<tr>
<td>Saltups4</td>
<td>1982</td>
<td>100</td>
<td>30</td>
</tr>
<tr>
<td>Vandeplas et al.31</td>
<td>1988</td>
<td>192</td>
<td>24</td>
</tr>
<tr>
<td>Ravi Kishore et al.6</td>
<td>1988</td>
<td>106</td>
<td>5.6</td>
</tr>
<tr>
<td>CMC Vellore</td>
<td>2003</td>
<td>124</td>
<td>15.3</td>
</tr>
</tbody>
</table>
Our results are similar to a study from India by Ravi Kishore et al. They also found the prevalence of CAD to be 5.6% in a group of patients who underwent coronary angiogram for aortic valve disease prior to surgery.

Our study done in Indian population suggests a lower prevalence of associated CAD compared to Western data. There could be several reasons for the low prevalence of CAD in our population; firstly, patients with RHD usually come from poorer socioeconomic status and it is likely that the prevalence of CAD in this group is lower; secondly, it is possible that RHD is in some way protective of CAD.

Limitations: Several limitations of our study need to be emphasized (i) the number of patients studied are small and a large study involving thousands of patients may give the realistic prevalence, (ii) our report is from the southern part of India and this may not be applicable across the nation; hence we suggest that under the auspicious of Cardiology Society of India, a registry may be formed to collect these data prospectively across the nation, and (iii) our diagnosis of CAD is based on coronary angiography, which has its own limitations.

Conclusions: Our results suggest that in patients with rheumatic heart disease the overall prevalence of associated coronary artery disease is less when compared with Western data.

References
Background: Transcatheter closure of coronary artery fistulas has emerged as a successful alternative to surgery. We describe various techniques and short-term findings in 15 patients who were taken up for transcatheter closure of these fistulas.

Methods and Results: Fifteen patients (aged 2–55 years; 12 males) with coronary artery fistulas underwent percutaneous transcatheter closure between June 1997 and December 2002. Site of origin of these fistulas were: right coronary artery in 7, left anterior descending coronary artery in 4, left main coronary artery in 2 and left circumflex coronary artery in 2 patients. Drainage site of these fistulas were: right ventricle in 9, right atrium in 4 and pulmonary artery in 2 patients. Out of these 15 fistulas, 14 were congenital and one was iatrogenically produced following inadvertent cutting balloon angioplasty of a septal perforator in a patient with chronic total occlusion of left anterior descending coronary artery. Various occlusion devices used to close these fistulas were: conventional metallic coils in 10, floppy tips of coronary angioplasty guidewires in 2, Amplatzer duct occluder in 1 and Amplatzer septal occluder in 2 patients. One of our patients had a coronary artery fistula draining by two openings into the right atrium, both of which were successfully closed using 2 Amplatzer duct occluders. Check angiogram after the procedure revealed complete occlusion in 13 (86.6%) and small residual flow in 2 patients. Follow-up studies at 3–55 months (mean 18 months) showed complete abolition of shunt in all patients with no evidence of recanalization leading to recurrence of shunt.

Conclusion: Transcatheter closure of coronary artery fistulas is feasible and safe in the anatomically suitable vessels. Use of floppy tips of coronary angioplasty guidewires reduces the cost of the procedure significantly, which is an important consideration in developing countries like India. (Indian Heart J 2004; 56: 132-139)

Key Words: Coronary artery fistulas, Coil embolization, Amplatzer device

Coronary artery fistulas (CAF) are rare congenital anomalies. Their incidence is estimated to be 0.2%–0.4% of all congenital cardiac defects. These fistulas may be congenital or acquired and may communicate with a cardiac chamber, coronary sinus, vena cava, pulmonary artery or pulmonary vein. More than 90% of these fistulas open in right-sided cardiac chambers. They generally connect to a cardiac chamber through a single lumen but multiple lumens with diffuse and complex connections may also occur. CAF have to be closed to prevent complications like myocardial ischemia, congestive heart failure, infective endocarditis, aneurysm formation and rarely, rupture.

Until recently, surgical correction was the only option available for closure of these fistulas. But in recent years, transcatheter closure of these fistulas has become a therapeutic option for anatomically suitable vessels. The use of gelfoam, polyvinyl alcohol foam, detachable balloons, coils and a variety of other devices has been reported. We report our short-term findings and various techniques of closure of these coronary fistulas in 15 patients, who were taken up for transcatheter closure.

Methods

Patient characteristics: Between June 1997 and December 2002, 15 patients in the age range 2–55 years (mean 22.6 years) underwent transcatheter closure of various types of CAF. There were 12 males and 3 females. Fourteen patients had congenital CAF while in one patient, with chronic total occlusion of left anterior descending (LAD) artery, a fistula was produced inadvertently by cutting balloon angioplasty of a septal perforator resulting in its communication with the right ventricle (RV). All patients underwent full cardiac evaluation, including
medical history, physical examination, electrocardiogram (ECG) and echocardiogram.

Out of 14 patients with congenital CAF, 5 were symptomatic (36%) with dyspnea on exertion in two, effort angina in 2 and recurrent hemoptysis in 1 child with tetralogy of Fallot (TOF). All these patients had clinically significant large fistulas producing either symptoms or a typical continuous murmur of grade IV/VI.

**Electrocardiogram:** On the initial ECG, 4 patients had evidence of left ventricular (LV) strain, 1 patient had right ventricular conduction delay and the child with TOF had typical ECG findings of the anomaly. All other patients had normal ECG.

**Echocardiogram:** CAF could be detected by color Doppler echocardiography in all the patients. All the patients had a jet width of ≥ 3 mm on color Doppler. Five patients (all symptomatic) showed chamber dilation and 3 showed reversal of flow in the descending aorta. A part from 1 child with TOF, none of the patients had any other associated congenital cardiac anomaly. Echocardiograms showed normal ventricular function and normal wall motion in all patients (ejection fraction: 61.4±8%; fractional shortening: 31±6%).

**Catheterization data:** All patients were taken up for cardiac catheterization to determine the anatomy of the fistula and feasibility of transcatheter closure. The median Qp/Qs prior to occlusion was 1.5 (range 0.8-2.2) and post-occlusion was 1.0.

**Angiographic data:** Selective coronary angiography was performed to demonstrate the anatomy of the CAF. Once the general anatomy was defined, the fistulous connection was entered from the arterial end with either an end-hole catheter or side-hole balloon-tipped catheter (Berman type, Arrow International, Reading, MA). A selective injection was then performed with or without balloon occlusion to delineate precisely the diameter of the fistula, its drainage site and identify all distal coronary branches. Seven patients had origin of the fistula from the right coronary artery (RCA), 4 from the LAD, 2 from the left main coronary artery (LMCA) and 2 from the left circumflex (LCx) coronary artery. Drainage site of these fistulas were: RV 9, right atrium (RA) 4 and pulmonary artery (PA) 2. In all the patients, fistula drained by a single opening except in one patient where the fistula was draining into the RA by two openings.

After properly mapping the angiographic details, patients were evaluated for suitability of transcatheter closure by various occlusion devices by taking into consideration the number and location of drainage sites, ability to cannulate the distal part of fistula and proximity of coronary branches to the optimal occlusion site. Special care was taken to avoid interference of flow by a device into any visible coronary artery. Selection of devices was based on anatomical features of the fistula. Coils were used to close smaller fistulas (diameter <4 mm at site of drainage), while devices were used to close larger fistulas. Though patients with more than one drainage site are usually referred for surgery, but one of our patients with fistula draining by two openings was taken up for transcatheter closure as the patient did not give consent for surgical closure and persuaded us to attempt transcatheter closure, which seemed feasible.

**Transcatheter closure techniques:** Heparin was administered (75–100 units/kg) after obtaining arterial and venous access. Prophylactic antibiotics were also administered to all the patients. Antegrade and retrograde approaches were used as per the requirement.

Retrograde approach: In patients, with the fistula size < 4 mm at site of drainage, retrograde approach was used for coil placement. Its placement was always attempted at the insertion of the fistula into the cardiac chamber. End-hole steerable catheters like the right/left Judkin's catheter or multipurpose catheter was used for access to the mouth of the fistula and to stabilize position for coil delivery. Depending on the anatomy of the fistula, coils were delivered in the distal part of fistula using additional catheters like Tracker catheter (Target Therapeutics, Fremont, CA, USA: lumen diameter 0.018” to 0.025”) passed through the guiding catheter deep into the fistula if the feeding vessel was very tortuous or delivered directly through the guiding catheter into the distal part of the fistula.

Coils chosen had a helical diameter approximately 20% larger than the maximum vessel diameter as the larger diameter coil results in a non-orderly lie of the coil, preventing alignment with the vessel and thereby promoting occlusion. Coil length was determined by the amount that would fit in the fistula without protruding into the origin of the last coronary branch, even if only partially coiled. If additional coils were needed for occlusion, smaller helical diameters were selected because these coils would easily become entrapped within the initial large coil. After placing the catheter tip in the distal part of the feeder vessel just proximal to its drainage side, presellected coil was loaded into the catheter with the stiff end of the pusher wire. The wire was then reversed and the soft tip was used to advance the coil through the catheter and deliver it into the vessel for occlusion. Delivery was performed carefully under...
fluoroscopy. While Gianturco coils (0.038" and 0.035") were used in 6 patients with congenital CAF, 0.018 platinum microcoils (Target Therapeutics, Fremont, CA, USA) were used in 3 patients delivered through the 3 F Tracker catheter. In 1 patient, the microcoils became jammed in a partially delivered state within the 3 F Tracker catheter because the catheter course involved multiple curves. In this patient, no attempt was made to remove the catheter from this position as the coils often embolize on retracting the catheter. In this patient high pressure injection of saline by a smaller syringe was used to complete delivery of the coils. Fibered platinum microcoils were also used in a patient with coronary artery perforation draining into the right ventricle. The Tracker catheter was advanced over a 0.014" angioplasty guidewire up to the distal end of the septal artery. Before introducing coils into the microcatheter, a coil pushing wire was advanced through the Tracker catheter to assess stability of the catheter position. After confirming stability of the Tracker catheter, the stiff proximal end of the coil pusher wire was used to advance the coil approximately one-fourth of the catheter length while the distal floppy end was used to advance the coil through the rest of the catheter and deliver the coil into the septal artery (Figs 1a, 1b).

Antegrade approach: This technique was used in patients with fistula size at site of drainage ≥ 4 mm, in whom occlusion of fistula by devices (like Amplatzer devices) were planned. After engaging the feeding vessel with the guiding catheter, the fistula was crossed using 0.035" exchange length (260 cm) guidewire (Cook) and snared in the RV or RA (Microvena, Minnesota, USA). The exchange wire was then exteriorized out of the femoral vein forming an arteriovenous wire loop. The advantages of using the venous route are that it avoids potential damage to the femoral artery, allows use of larger catheters and affords a straighter catheter course. Amplatzer septal occluder of 4 mm and 6 mm were deployed successfully in 2 patients (Figs 2a, 2b). One patient, in whom the fistula was draining by two openings into RA, was successfully occluded by deploying two Amplatzer duct occluders of 14/12 mm and 12/10 mm size respectively (Figs 3a, 3b). None of the patients showed any residual shunt following deployment of the Amplatzer devices.

**Use of non-conventional coils where feeding vessel was highly tortuous - new techniques:** Two patients had coronary artery to pulmonary artery fistula. But in both of these patients, the feeding arteries were exceedingly tortuous and it was not possible even to negotiate a 0.014" coronary angioplasty guidewire or a support catheter deep into the fistulous tract. Therefore in these patients, we adopted new technique for coil delivery. In the first patient, a 3 F support Tracker catheter was stabilized at the proximal end of the feeding artery and then floppy tips of used sterilized coronary angioplasty guidewires (each 1-2 cm in length) were pushed one at a time into the proximal end of the feeding artery with the help of hard end of a coronary angioplasty guidewire. After packing the feeding artery...
proximal part (Fig. 5a). We were unable to negotiate the highly flexible Tracker catheter over a 0.014" Luge wire through the bend. So we thought of placing coils proximal to the bend. However we failed to achieve stability of the Tracker catheter—a prerequisite before delivering coils. Therefore, after withdrawing the Tracker catheter, we passed a 2×20 mm over-the-wire balloon (Ranger, Boston Scientific, Scimed Inc, USA) over the Luge wire (Boston Scientific, Scimed Inc, USA) just proximal to the hairpin bend and inflated it, which resulted in stability of the system. As the Ranger balloon has an internal diameter of 0.014", so options available to us were to pass either 0.010" platinum microcoils or floppy tips of coronary angioplasty guidewires (diameter 0.014"). To make the procedure cost-effective, we decided to use floppy tips of used coronary
angioplasty guidewires sterilized by ethylene oxide. Like in our previous patient, we pushed pieces of floppy tips of coronary angioplasty guidewires through the central lumen of the balloon successively into the bend segment of the feeder artery with the hard end of the exchange length Luge wire (Fig. 5b). After packing the feeder vessel with four such wires, check angiogram revealed TIMI-1 flow. One hour later, check angiogram revealed complete occlusion of the feeder vessel with all the wires lying in situ (Fig. 5c). Following occlusion, the child did not have any further episode of hemoptysis. Mean fluoroscopy time was 40.6 min (range 19.4-104.6 min).

Fig. 4(a). Right coronary angiogram showing conus artery to pulmonary artery (PA) fistula. (b) Check angiogram showing complete occlusion of the fistula after packing it with coronary angioplasty guidewires.

Fig. 5(a). Right coronary angiogram showing right coronary artery to pulmonary artery fistula along with the hairpin bend in the proximal portion of the feeder vessel. (b) Arrow shows a wire being placed in the tortuous segment; double arrow shows a second wire being pushed through the balloon shown by arrowhead. (c) Check angiogram showing complete occlusion of the fistula with arrow showing all wires lying in situ.
Results

Origin of the fistula from the left coronary artery was more common than from the RCA. All fistulas drained into the right side of the heart. Conventional coils (Gianturco type 0.038" Spring coils (6); 0.035" micro-coils (8); 0.018" fibered platinum microcoils (8)) were placed in 10 patients (all patients requiring multiple coils; mean number of coils per patient 2.2), floppy tips of coronary angioplasty guidewires in 2, Amplatzer duct occluder in 1 and Amplatzer septal occluder in 2 patients. While all the Amplatzer devices were deployed anterogradely, coils in all the patients were deployed retrogradely. An arteriovenous wire loop facilitated antegrade delivery of the devices. One patient had two openings of the fistula draining into right atrium, both of which were closed successfully using 2 Amplatzer duct occluder devices. Cineangiogram following occlusion device deployment demonstrated complete occlusion in 13 (86.6%) patients and trivial residual flow in 2 (13.4%) patients who underwent conventional coil embolization. None of the patients had to be taken up for recatheterization on follow-up.

Procedural complications included transient arrhythmias in 3 patients and minor ST-T changes in 2 patients. There were no major complications like coil migration, dissection of native coronary arteries or of the feeding vessel, myocardial infarction, death, stroke or infection.

Follow-up: All the patients have been followed up clinically and by echocardiography at three monthly intervals during the first year after transcatheter closure and thereafter at six monthly intervals. While all the patients completed at least three months of follow-up, 3 patients were lost to follow-up after one year. All patients have been asymptomatic with no clinically audible murmurs. Echocardiography at the end of three months showed complete occlusion in 14 with persistence of trivial shunt in 1 patient. However, this patient showed complete occlusion at the end of six months. On follow-up echocardiography, none of the patients has shown recanalization of the fistula with recurrence of shunt. There has been no evidence of coil migration or device displacement/fracture.

Discussion

First description of CAF was given by Krause in 1865. These are classified as primary and secondary. Primary fistulas occur in association with congenital heart lesions such as pulmonary atresia with intact ventricular septum or as an isolated lesion in an otherwise normal heart. Acquired CAF can occur as a result of intracardiac congenital heart operations or following transcatheter interventions like myocardial biopsy and coronary angioplasty. They mostly originate from the RCA and drain into the right heart or PA. Bilateral fistulas originating from right and left coronary arteries account for only 5% of all fistulas and tend to terminate in the pulmonary artery. Congenital CAF rarely (3%) drain into the left heart and when present, are usually iatrogenically produced following a surgical procedure or percutaneous coronary intervention.

Currently there are three management options available for these fistulas. First, small asymptomatic coronary artery fistulas may be managed conservatively, not only because small and hemodynamically inconsequential coronary artery fistula generally run a benign course but also because small coronary artery fistula may close spontaneously. The second therapeutic option is surgical closure of the coronary artery fistula. Though surgical management is safe and effective with a high closure and survival rate, but chances of myocardial infarction or recurrence are always there. Furthermore, surgery requires a median sternotomy and sometimes cardiopulmonary bypass. The third therapeutic option is percutaneous transcatheter closure. In our opinion, the majority of these fistulas can and should be addressed by percutaneous techniques initially, even if staged procedure is ultimately required. Surgery should be limited to the fistulas with large branch vessels that could be compromised following placement of occlusion devices or the coronary fistulas with multiple communications without a single narrow restrictive drainage site into a cardiac chamber or patients with associated complex congenital cardiac defects that require correction. Till now, largest series of transcatheter closure of CAF have been published by Armsby et al. where 33 patients were taken up for transcatheter closure. Beside this report, transcatheter closure of CAF has been reported in another 64 patients (excluding single case reports) since 1982.

Armsby et al. reported 39% of patients to be asymptomatic. In our series, 36% of patients were asymptomatic at the time of intervention. Origin from the left coronary artery was more common than from the right one (66.6% in Armsby series and 53.3% in our series).

Transarterial device delivery was performed in 33 patients in Armsby series of 35 procedures which included coils in 28, umbrella devices in 6 and Grifka vascular occlusion device in 1. In rest of the reported cases CAF were closed by coils in 48, detachable balloon in 10, umbrella device in 2, covered stent in 1, combination of detachable balloon with coils in 2 and Amplatzer duct.
occluded in 2. Complete occlusion was reported in 82% of the cases in series by Armsby et al.20 while it was 86.4% in our series.

There was one procedure-related death in world literature, involving a symptomatic 76-year-old man with a large coronary artery fistula arising from a diffusely diseased LAD and draining into a PA. Death resulted from embolization of a coil to the LMCA and subsequently its dissection.21 In Armsby series,20 there was a single instance of unretrieved coil embolized to a PA and fistula dissection. In our series, there were no major complications like coil embolization perhaps because of certain precautions we had taken: (i) selecting oversized coils (20% greater in diameter than the maximum diameter of the fistula), (ii) assessing stability of the delivery catheters before coil embolization, (iii) using floppy ends of coil pushing wires for final delivery of the coils from the delivery catheter instead of the hard end which sometimes causes displacement of the tip of the delivery catheter leading to improper position of the coils and then embolization, (iv) use of high pressure small syringes to deliver partially jammed microcoils in the Tracker catheter instead of trying to withdraw the catheter which often causes embolization of the coils, (v) avoiding use of coils in fistula having diameter >4 mm, thus eliminating not only the need of multiple coils but also their risk of migration. Follow-up data have shown that the patients were asymptomatic with no long-term morbidities.

The use of transcatheter techniques as the primary therapeutic option reduces hospital stay, improves recovery time, eliminates the need for thoracotomy and is cost effective. It can be performed easily in patients who satisfy the following criteria: (i) absence of multiple fistula, (ii) a single drainage site, (iii) absence of large branch vessels, and (iv) safe accessibility to the coronary artery supplying the fistula. Use of non-conventional coils like floppy tips of catheterization laboratory, (b) no requirement of any special delivery system, (c) high technique of deployment, and (e) cost-effectiveness.

Conclusions: Transcatheter closure of coronary artery fistulas is safe and feasible in anatomically suitable vessels. Comparison of our results with other published series has shown similar efficacy and safety. Use of non-conventional coils like floppy tips of used coronary angioplasty guidewires in developing countries like ours can reduce the cost of procedure significantly. However, the choice of device and technique for any patient is based on many factors like cost, familiarity of the operator with the different approaches, and most importantly on the anatomic characteristics of the fistula as discussed.

References
**Effect of Smoking on QT Interval, QT Dispersion and Rate Pressure Product**

K Singh
Department of Physiology, Post Graduate Institute of Medical Sciences, Rohtak

**Background:** Smoking may predispose to ventricular fibrillation and sudden cardiac death by altering ventricular recovery time dispersion indices. However, effect of acute smoking on QT interval and QT dispersion in chronic smokers has not been studied so far.

**Methods and Results:** Effect of cigarette smoking on ventricular recovery time dispersion indices and rate pressure product (product of heart rate and systolic blood pressure) was investigated in 25 chronic smokers and compared with 25 age- and sex-matched non-smoker controls. There was increase in R-R interval (p<0.05), corrected QT interval, QT dispersion (p<0.001) and rate pressure product (p<0.05) in chronic smokers at baseline (before smoking) compared to non-smoker controls. On cigarette smoking, there was further increase in heart rate, blood pressure, QT dispersion and rate pressure product (p<0.001) with reduction in R-R interval (p<0.05) in chronic smokers compared to non-smoker controls.

**Conclusions:** Our observations indicate that there may be some relationship between prolonged ventricular recovery time dispersion indices and ventricular fibrillation and sudden cardiac death associated with smoking. (Indian Heart J 2004; 56: 140–142)

**Key Words:** QT interval, Smokers, Sudden death

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**Cigarette smoking is a major risk factor for development of coronary heart disease (CAD),** acute myocardial infarction (AMI), and sudden cardiac death (SCD). QT interval and QT dispersion (QTd) reveal regional heterogeneity of repolarization with consequent possibility of sudden death. Smoking has unfavourable influence on autonomic balance, which is an important determinant of QT interval and QT dispersion.

The present study investigated the effect of acute smoking on QT interval, QT dispersion and rate pressure product (RPP), in chronic smokers.

**Methods**

The study population included 25 men who were chronic smokers (mean age: 34±7.3 years). They were compared with 25 non-smoker men in the same age group (control group) (mean age: 31.6±9.1 years). A detailed history of smoking was obtained from each smoker according to Fagerstrom Scale. This scale uses the number of cigarettes smoked per day, duration of habit and intensity of craving for cigarettes. Subjects with hemoglobin level <10 gm%, arterial hypertension, organic heart disease, chronic obstructive pulmonary disease, diabetes mellitus, deranged renal function or drug intake or any other factor affecting QT interval were excluded from the study.

Subjects were asked to abstain from smoking two hours prior to the tests. Recording was performed in the morning hours (always at the same hour of the day). Subjects were asked to smoke two cigarettes (Red and White Marcitch nonfilter) within 10 min (range 5.2–7.5 min; average 5.36 min). Each cigarette was smoked to a butt length of 4.2 cm (total length 6.7 cm). Data were collected in smokers and in non-smoker controls, before and after smoking. Complete procedure was explained to the subjects to avoid any anxiety or apprehension.

Electrocardiogram (ECG) was obtained in a quiet room, with a comfortable temperature (22°C–25°C) at a speed of 25 mm/sec with calibration of 10 mm/mv. Every subject had a light breakfast without any caffeinated beverages (coffee and tea) on the morning of the study. In the hours preceding the study, all subjects continued their usual daily activity and avoided any physical exercise. Variables were measured manually in lead II. QT interval and R-R interval of at least 2 sinus beats (range 1–3) were measured. QT interval was measured from beginning of Q wave to end T.
wave, where it merges with isoelectric line. Only clearly defined tracings were analyzed. Data were excluded if there was any change in QRS-T morphology. Bazett’s formula was used to correct QT interval (QTc) for heart rate. QTd was defined as the difference between maximum and minimum QT values. RPP, which is an index of myocardial oxygen consumption was also calculated (heart rate × systolic blood pressure/100).

**Statistical analysis:** Results were expressed as mean ± SD. Statistical analysis was done using paired and unpaired $t$ test. A $p$ value <0.05 was considered significant.

**Results**

Subjects (chronic smokers) smoked 7 to 30 (mean 14.5±9.2) beedis/cigarettes daily for 2–15 years (mean 10.6±5.9 years) and mean age at which they started smoking was 18.4±2.2 years, with quetelet index (body mass index in kg/m²) of 24.2±2.0 in smokers v. 24.1±4.0 in controls. R-R interval (p <0.05), ventricular recovery time dispersion indices (QTc, QTd) (p<0.001) and RPP (p <0.05) were increased at baseline (before smoking) in chronic smokers compared to controls. Heart rate (HR) and blood pressure (BP) in both the groups are given in Table 1.

Cigarette smoking increased, HR (p <0.001), BP (diastolic (p<0.001) more than systolic (p<0.01)), QTc, QTd and RPP (p <0.001) and reduced R-R interval (p<0.05) in chronic smokers compared to non-smoking controls (Table 1, Figs 1 and 2).

**Table 1. Comparison of parameters between non-smokers and smokers (before and after smoking)**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Non-smokers</th>
<th>Smokers before smoking</th>
<th>Smokers after smoking</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (beats/min)</td>
<td>72.4±15.1</td>
<td>66.1±19.7 NS</td>
<td>83.5±9.6***</td>
</tr>
<tr>
<td>Blood pressure (mmHg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>124.9±14.9</td>
<td>120.0±11.0</td>
<td>134.8±9.2***</td>
</tr>
<tr>
<td>Diastolic</td>
<td>76.9±12.8</td>
<td>80.8±12.7</td>
<td>91.0±10.5***</td>
</tr>
<tr>
<td>R-R interval (ms)</td>
<td>760±88.1</td>
<td>810±22.4</td>
<td>724±43.2†</td>
</tr>
<tr>
<td>QTc interval (ms)</td>
<td>396±19.5</td>
<td>456±47.1***</td>
<td>453.3±41.0</td>
</tr>
<tr>
<td>QTd interval (ms)</td>
<td>29.1±18.0</td>
<td>46.6±11.5***</td>
<td>65.3±10.4***</td>
</tr>
<tr>
<td>Rate pressure product</td>
<td>86.0±3.4</td>
<td>90.9±10.2*</td>
<td>106.0±6.09***</td>
</tr>
</tbody>
</table>

Comparison between non-smokers and smokers (before smoking): *p<0.05, **p<0.01, ***p<0.001; NS: non-significant
Comparison between smokers (before and after smoking): **p<0.05, ***p<0.01, ****p<0.001; NS: non-significant

**Discussion**

Underlying triggering mechanism for ventricular fibrillation and sudden cardiac death caused by smoking is not clear. QTc and QTd evaluate the non-homogeneity of ventricular recovery time and thus serve as a powerful determinants of susceptibility to ventricular tachycardia and/or fibrillation in clinical studies. This study was carried out in chronic male smokers to avoid any gender difference in QTc. Present study has shown that chronic smoking is associated with prolonged QTc and prolonged QTd in healthy subjects. These findings are in agreement with that of Ileri et al. in habitual smokers. However, effect of acute smoking on QT interval and QT dispersion in healthy smokers have not been studied so far.
Previous studies have shown the influence of autonomic nervous system on QT interval. Chronic smoking augments the autonomic sympathetic tone. Changes in autonomic tone may affect QTc and QTd through depolarization and repolarization kinetics of myocardial cells. It has also been reported to be prolonged in patients with primary autonomic failure.

Long-term effect of smoking in healthy subjects has been reported to be associated with increased perfusion heterogeneity at rest induced by interplay of regional endothelial dysfunction and autonomic dysregulation. These mechanisms may lengthen the QTc and QTd in habitual smokers.

It has been demonstrated that brief sympathetic nerve stimulation and rapid catecholamine injection increases QT interval. Smoking acutely increases plasma catecholamine and cardiac nonepinephrine spillover. QT interval changes are strongly influenced by circulating catecholamines. A cute smoking further increases the QTd, as found in our study. Moreover, exposure to tobacco smoke also increases myocardial oxygen demand as is evident by raised RPP in smokers. They have elevated myocardial work as both HR and BP are increased acutely by smoking. Oxygen supply is further reduced by direct vasoconstriction of coronary bed and by alteration of aortic elastic properties which adversely affect left ventricular performance and thus may alter QTd. Ischemic heart disease is also associated with prolonged QT interval.

Conclusions: Smoking augments sympathetic myocardial stimulation which promotes mechanisms responsible for ventricular fibrillation including reentry, increased automaticity and triggered activity. Raised RPP and QTd have also been linked to increased incidence of angina, fatal and non-fatal myocardial infarction and sudden cardiac death.

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Coronary Angioplasty in a Case of Quadriostial Origin of Coronary Arteries from Right Aortic Sinus

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We report a case in which all three coronary arteries were originating from the right aortic sinus via separate ostia, and angioplasty of the normally arising right coronary artery was performed. In addition, the conal artery also originated separately from the right sinus leading to a quadriostial origin of the coronaries. A combination of anteriodiastal septal course of the left anterior descending artery and retroaortic course of left circumflex artery is an unusual coronary anomaly and was noted in this case. (Indian Heart J 2004; 56: 143-146)

Key Words: Anomalous coronary artery, Coronary artery disease, Angioplasty

Despite their rarity, anomalous coronary arteries are not exempt from obstructive disease, and may require revascularization. Anomally arising left coronary artery (LCA) from the right aortic sinus [with separate ostia for left anterior descending artery (LAD) and left circumflex artery (LCx)] is a rare entity. We present a case of monocuspal origin of all three coronary arteries via separate ostia from the right aortic sinus, where angioplasty of the normally arising right coronary artery (RCA) was performed. In addition, the conal artery also originated separately from the right sinus leading to a quadriostial origin of the coronaries from the right aortic sinus. The rarity of the condition and the unusual course of the LAD and LCx form the basis of this presentation.

Case Report
A 60-year-old male presented with a history of recent onset angina (NYHA class II-III). The resting electrocardiogram (ECG) was normal and echocardiography revealed a hypokinetic RCA territory with an overall normal left ventricular (LV) function. The patient was taken up for coronary angiography. However, the LCA could not be cannulated despite use of multiple catheters. Suspecting an anomalously arising LCA, we proceeded to cannulate the RCA using a regular Judkin right 4 F catheter. The RCA was a dominant vessel, with 100% occlusion just beyond the mid-segment (Fig. 1). The catheter was disengaged from the RCA ostium and rotated slightly counterclockwise which hooked an anomalously arising LAD from the right aortic sinus, that followed a caudal and anterior course, consistent with a septally coursing LAD (Fig. 2). The LAD was free of any significant disease. A slight clockwise rotation of the catheter hooked a separately arising conus branch of the RCA from the right aortic sinus (Fig. 3).

Despite repeated attempts, the LCx origin was not clearly profiled, though it was apparent that it was not arising from the left aortic sinus. A pigtail catheter was used to perform an aortic root angiogram, which profiled the LCx also arising from the right aortic sinus. An AL1 catheter was employed to cannulate the RCA. As mentioned above, a...
slight counterclockwise torque to this disengaged the catheter from the RCA and profiled a separate origin of the LAD. Midway between the origins of the LAD and RCA, the LCx origin was profiled (Fig. 4). The LCx followed a retro-aortic course (taking a caudal and posterior loop), which is common for an anomalously arising LCx from the right aortic sinus. The LCx also gave rise to a diagonal branch before coursing off posteriorly in the left atrioventricular (AV) groove. Hence our case represented a “quadriostial” origin from the right aortic sinus, with separate origin of the conal artery, RCA, LAD and LCx. The course of the arteries is depicted in Fig. 5.
Subsequently percutaneous transluminal coronary angioplasty (PTCA) and stenting of the RCA was performed using AL1 guiding catheter. The lesion was crossed with 0.014" intermediate coronary guide wire, predilated with a 3 x 20 mm balloon and a 3.5 x 24 mm NIR Express stent was deployed with excellent result.

Discussion

Anomalous origin of coronary arteries is rare, seen in 1% of patients undergoing cardiac catheterization. Often the anomalies are of anatomic interest only, or may be associated with congenital heart disease. However, coronary atherosclerosis is not uncommon in such patients and coronary angioplasty, if required, poses a technical challenge. In addition, the anatomical course of such anomalous arteries, is of interest to the angiographer, and needs careful delineation and understanding.

Anomalously arising coronary arteries may take the form of the artery arising from the non-corresponding aortic sinus, or from the ascending aorta above the sinotubular ridge, the latter occurring most often in cases of anomalously arising RCA.

It may be useful to classify such patients based on (i) the number of coronary ostia present, and (ii) the course followed by the coronary arteries.

It is important to find out if there is a single coronary artery (arising either from the left or the right coronary sinus) or there are separate origins of the anomalously arising coronary arteries. This information is vital because performance of angioplasty through a single coronary ostium may be potentially hazardous and needs extra caution. An anomalously arising left main coronary artery (LMCA) may involve takeoff as a branch from the RCA itself (single coronary ostium of RCA and LMCA) or from separate ostium from the right aortic sinus (two coronary ostia—one each for LMCA and RCA). Origin of the LAD and LCx separately from different ostia in the right aortic sinus (thus leading to three separate ostia) is a rarely reported anomaly.

Hence, depending on the number of coronary ostia present, this anomaly may be classified as Type I (one coronary ostium), Type II (two coronary ostia) and Type III (three separate ostia, as in our case) (Fig. 6). Type I is the commonest of these, while Type III is the rarest anomaly (all 3 coronary arteries arising from the right aortic sinus by 3 separate ostia).

When the LMCA arises from the anterior, right coronary sinus of Valsalva (whether by single or separate ostia), it may follow either of the four described courses, (i) Interarterial course—the LMCA passes between the aorta and the pulmonary artery or between the aortic valve and the right ventricular (RV) infundibulum immediately adjacent to the pulmonary valve. This is consistent with a cranial and posterior loop of the anomalously coursing artery, (ii) Anterior free wall course—wherein the artery crosses anterior to the free wall surface of the RV outflow tract (RVOT). The anomalous artery describes a cranial and anterior loop, (iii) Retroaortic course—the artery passes posterior to the aorta in the transverse pericardial sinus, taking a caudal and posterior loop, and (iv) Septal course—the artery runs an intramuscular course through the infundibulum (conal septum) across the floor of the RVOT, inscribing a caudal and anterior loop.

In our case the LAD followed a septal course because as is evident in the RAO view (Fig. 2a) the initial course was forward and downward, followed by a slight upward and leftward course before dividing into its branches. The LAD thus inscribed a caudal and anterior loop. The arterial course—the LMCA passes between the aorta and the pulmonary artery or between the aortic valve and the right ventricular (RV) infundibulum immediately adjacent to the pulmonary valve. This is consistent with a cranial and posterior loop of the anomalously coursing artery, (ii) Anterior free wall course—wherein the artery crosses anterior to the free wall surface of the RV outflow tract (RVOT). The anomalous artery describes a cranial and anterior loop, (iii) Retroaortic course—the artery passes posterior to the aorta in the transverse pericardial sinus, taking a caudal and posterior loop, and (iv) Septal course—the artery runs an intramuscular course through the infundibulum (conal septum) across the floor of the RVOT, inscribing a caudal and anterior loop.

A presentation as in our case i.e. all three coronary arteries arising separately (along with a separate ostium for the conal artery) leading to a quadriostial origin, is an arterial course—the LMCA passes between the aorta and the pulmonary artery or between the aortic valve and the right ventricular (RV) infundibulum immediately adjacent to the pulmonary valve. This is consistent with a cranial and posterior loop of the anomalously coursing artery, (ii) Anterior free wall course—wherein the artery crosses anterior to the free wall surface of the RV outflow tract (RVOT). The anomalous artery describes a cranial and anterior loop, (iii) Retroaortic course—the artery passes posterior to the aorta in the transverse pericardial sinus, taking a caudal and posterior loop, and (iv) Septal course—the artery runs an intramuscular course through the infundibulum (conal septum) across the floor of the RVOT, inscribing a caudal and anterior loop.

In our case the LAD followed a septal course because as is evident in the RAO view (Fig. 2a) the initial course was forward and downward, followed by a slight upward and leftward course before dividing into its branches. The LAD thus inscribed a caudal and anterior loop. The artery thus inscribed a classic caudal and anterior loop.

The characteristic retroaortic course of the LCx artery, was confirmed by its initial posterior and downward course, which was then followed by a leftward course just beneath the aortic valve (as seen in the LAO view, Fig. 5). The artery thus inscribed a classic caudal and posterior loop.

A presentation as in our case i.e. all three coronary arteries arising separately (along with a separate ostium for the conal artery) leading to a quadriostial origin, is an

Fig. 6. Schematic representation of origin of coronaries from right coronary sinus via single or multiple ostia.
extremely rare entity. Apart from the uniqueness of the origin, the subsequent course of the arteries, with the LAD running a septal intramyocardial course, and the LCx following a retroaortic course is another extreme rarity. Dollar and Roberts' reported such a case at autopsy, which was, however, Type I (with only a single coronary ostium). All the reported cases of LAD following a septal intramyocardial course and the LCx following a retroaortic course have been diagnosed at necropsy and only one of these belonged to the Type III variety (i.e. with separate origins for LAD and LCx).

In literature there are several case reports of successful coronary angioplasty of anomalously arising RCA (from the left sinus or the ascending aorta above the sinotubular ridge) as well as that of anomalously arising LCA. However most cases of angioplasty to anomalous LCA involve either a single coronary artery (Type I) or an anomalous LCx arising from the RCA. We have not come across any report where successful angioplasty and stenting has been performed (either of the normally arising RCA or the anomalously arising LAD or LCx) in a case with separate coronary ostial origin of LAD and LCx from the right aortic sinus.

This report is special due to a variety of reasons. Firstly it reports a relatively rare anomaly—origin of the LAD and LCx from two separate ostia in the right aortic sinus. In such a situation an intramyocardial septal course for LAD and a retroaortic course for LCx diagnosed ante mortem is even more of a rarity. In most of such reported cases with separate origins for LAD and LCx, though the LCx followed a retroaortic course, the LAD either followed an interarterial or anterior free wall course.

Secondly, the presence of a separate ostium for the conal artery was responsible for the presence of four coronary ostia in this patient. To the best of our knowledge, there is no such report in English literature describing four separate coronary ostia diagnosed ante mortem. The only similar available report was of a case with hypertrophic cardiomyopathy that was diagnosed at necropsy. Finally, the procedural and technical details of performing a successful coronary angioplasty and stenting (albeit in the normally arising RCA) in such a case have not yet been reported. The choice of a stable guiding catheter along with usage of extra support angioplasty wires in such cases cannot be overemphasized.

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Balloon Valvuloplasty of Stenosed Carpentier-Edwards Bioprosthesis at Pulmonary Position

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Bioprostheses frequently become calcified and stenosed, especially when implanted in younger patients. The general recommendation in such cases is to repeat surgery. Balloon valvuloplasty has hitherto been attempted with mixed success. Calcification and limitation of the balloon size due to the valve ring can lead to suboptimal long-term results. We report a case where balloon dilation of the stenosed bioprosthesis at pulmonary position was successfully performed with good immediate result. Cardiac catheterization after 3 years showed only a minimal increase (5 mmHg) in the gradient. (Indian Heart J 2004; 56: 147-149).

Key Words: Bioprosthetic valve, Pulmonary stenosis, Balloon dilatation

Bioprosthetic valves are generally used in older patients when extended longevity is not expected. Over time, they frequently become calcified and stenosed and hence, are not used commonly in children. Once stenosed, surgical replacement is recommended. Balloon dilation of stenosed bioprosthesis is controversial. We report a case of balloon dilation of stenosed Carpentier-Edwards bioprosthesis at pulmonary position where sustained reduction of gradient over three years was obtained.

Case Report

A 20-year-old male presented with history of effort intolerance, atypical chest pain and giddiness of six months duration. He was evaluated nine years ago for breathlessness and a cardiac murmur, which had been documented since early childhood. Echocardiography and cardiac catheterization had revealed large subaortic ventricular septal defect (VSD) with 50% override of aorta, absent pulmonary valve, moderate pulmonary regurgitation (PR) and labile infundibulum. Per-operative findings in 1990 were suggestive of tetralogy of Fallot with dysplastic, widely incompetent pulmonary valve. Dacron patch closure of the VSD, pulmonary valve replacement with size 21A Carpentier-Edward’s Bioprosthesis and right ventricular (RV) outflow repair with pericardial patch was performed. The patient had an uneventful recovery and was asymptomatic till six months prior to the present admission. Physical examination revealed a tall, well-built individual. There was no cyanosis or clubbing. Apex beat was in the 5th left intercostal space 1 cm inside the mid clavicular line. The first heart sound was normal and the second heart sound was single. There was a grade 4/6 ejection systolic murmur in the pulmonary area. Echocardiogram showed a thickened and restricted opening of the bioprosthetic valve with a gradient of 90 mmHg and a small residual VSD with left to right flow.

The therapeutic options of repeat surgery and mechano-prosthesis insertion, or balloon valvuloplasty were explained to the patient and relatives. As the patient was unwilling for repeat surgery, it was decided to attempt balloon valvuloplasty and he was taken up for cardiac catheterization. The stenosed pulmonary valve was crossed with 5 F end-hole balloon catheter. An exchange wire was placed in the left pulmonary artery (LPA). A 7 F Cournand catheter was kept deep in LPA. A 0.025” floppy tip spring coil wire of Inoue balloon was placed in the main pulmonary artery (MPA). The pre-procedure gradient across the pulmonary bioprosthesis was 100 mmHg. A 4 x 10 mm peripheral balloon was used to predilate the lesion. Then a 20 mm Inoue balloon (Fig. 1) was placed across the prosthetic pulmonary valve and was serially dilated at 18 mm, 19 mm and 20 mm. The limitations of the procedure were the degenerated, calcified bioprosthesis valve and enclosed ring. The gradient was reduced from 100 to 50 mmHg. The post-procedure echocardiogram also showed a gradient of 50 mmHg. The patient withstood the
procedure well and was discharged on the third day.

The patient was re-evaluated three years later. He had NYHA class II symptoms. Echocardiography showed a gradient of 65 mmHg across the prosthetic valve. As the patient was unwilling for surgery, it was decided to re-evaluate the patient by cardiac catheterization. The prosthetic valve was crossed using Berman catheter. The gradient across the valve was 55 mmHg compared to the 50 mmHg post-procedure 3 years ago. It was decided to redilate the valve as the patient still had moderate residual stenosis. The stenosed prosthetic valve was dilated with 20 mm Mansfield balloon. Although full dilation was restricted by the valve ring, the gradient came down to 40 mmHg.

As the valve ring was restricting further expansion and the part of the balloon inside the ring was fully dilated, it was decided to accept the results.

**Discussion**

Bioprosthetic valves have been used for valve replacement and surgical reconstruction of the right ventricular outflow tract. They have a lower risk of thromboembolism and hemolysis, are easier to insert and have relatively more durability. Carpentier-Edwards bioprosthesis is generally recommended for aortic valve replacement in patients older than 70 years, in patients 61 to 70 years when extended longevity is not anticipated and for mitral valve replacement, in patients older than 70 years. Bioprostheses, especially if inserted at a younger age, frequently become calcified and stenosed.

Valved conduits or bioprosthetic valves, when used for congenital cyanotic defects, may need replacement at a later date due to the patient growth or due to valve/conduit failure. Essentially, all conduits need replacement by 10 years but porcine bioprosthesis in the tricuspid position has been shown to have actuarial freedom rate from structural deterioration of 47.1±19.1% at 10 years.

The risk of surgical replacement of conduit or bioprosthesis is low. However, balloon dilation of bioprosthetic conduits has been advocated to delay the need for surgical intervention. Zeevi et al. reported success in 3 of 9 patients and Lloyd et al. in 3 of 6 patients with stenosed conduits. Surgery was avoided or postponed in 8 of 11 patients in a study by Ensing et al. Low pressure balloon dilation of stenotic conduits or homografts was attempted by Sohn et al. with only partial and transient success. Similar partial benefit has been reported for bioprosthesis in tricuspid valve position also. Slama et al. reported 2 cases with immediate hemodynamic improvement, but both patients required valve replacement at 14 and 21 months of follow-up, respectively.

Even though procedural success (defined as more than 50% reduction in peak gradient or a 50% increase in the diameter of the stenotic area) is obtained in the immediate post-procedural phase, the long-term benefit is only partial and ill sustained. Bashore and O’Laughlin likened it to ‘ballooning between a rock and a hard place’. Factors that contribute to the high incidence of suboptimal long-term benefits are (a) lack of understanding of the causes of bioprosthesis and homograft failure, (b) dense calcification, (c) limitation of balloon size by the valve ring, and (d) the presence of multiple levels of obstruction within the conduit.

The cause of bioprosthesis and homograft failure due to degeneration is poorly understood and very little research has been directed towards preventive aspects. Calcification of bioprosthetic conduit can be attributed to the inability of devitalised cells to maintain a low intracellular content of free calcium in the presence of high extracellular calcium. A more labile calcium homeostasis in children than in adults may explain more frequent occurrence of calcification in children. Cuspal and commissural calcification renders the cusps rigid, and held in a semi-closed position, which prevents the balloon from exerting its full radial force and may induce balloon rupture.

Dilations with high pressure balloons may be the answer to part of the problem. Dilatation with high pressure balloons may relieve the waist of the balloon, resulting in a more successful dilation. In conduit obstruction, balloon-expandable stents have been utilised with greater success.

Our case is different from the few reports available on
balloon valvuloplasty of stenosed Carpentier-Edwards bioprosthetic valve at pulmonary position. The immediate procedural success could be sustained over a three year period in spite of the presence of calcified, degenerated bioprosthesis with the use of Inoue balloon. Repeat balloon dilation definitely postponed the ultimately inevitable surgery.

Thus, balloon dilation of stenosed bioprosthetic valves is possible with good procedural success. Unlike the other reports, in our patient the benefit could be sustained over three years.

References
Right Ventricular Pacing via Left Superior Vena Cava

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Negotiating the pacing lead into the right ventricle via left superior vena cava, at times, can be difficult. We report two such cases in which pacing leads were introduced into the right ventricle via left superior vena cava, with the help of stylet tip shaped into a large pigtail loop. (Indian Heart J 2004; 56: 150-151)

Key Words: Pacing, Left superior vena cava, Arrhythmia

Pacing lead insertion into the right ventricular (RV) apex via left superior vena cava (SVC) has been rarely reported. We describe two cases of RV pacing lead insertion via left SVC-coronary sinus-right atrium route. In the first case a tined bipolar ventricular lead was introduced and in the second case, a bipolar active fixation screw-in lead was placed. The pacing leads could be easily introduced into right ventricle with the help of a stylet tip shaped into a large pigtail loop.

Case Reports

Case 1: An 81-year-old male presented with recurrent giddiness and presyncope and was found to be in atrial fibrillation with ventricular rate of 40 beats per min. A diagnosis of atrial fibrillation with complete heart block was made and single chamber ventricular permanent pacemaker implantation was planned. An extrathoracic left subclavian venipuncture was performed. The course of guide wire suggested presence of left SVC draining into coronary sinus that was subsequently confirmed by contrast injection under fluoroscopy. A bipolar tined steroid eluting lead (St Jude's Medical E 1450 T) was inserted via left SVC into the right atrium. With a stylet shaped to a large pigtail loop, the lead could be negotiated into the RV apex with little difficulty. The optimum lead parameters obtained were: R wave 19.8 mV, threshold 0.5 V, and resistance 519 ohms. An interrogation at 3 months and 1 year showed normal functioning of the pacemaker.

Case 2: A 50-year-old female had undergone prior surgical closure of sinus venosus type atrial septal defect with rerouting of right upper pulmonary vein into left atrium in 1984. Few days after surgery, she was detected to have infarction of upper lobe of the right lung due to right upper pulmonary vein obstruction for which she underwent lobectomy. Recently, she presented with history of presyncope, and electrocardiogram revealed intermittent atrial flutter with fast ventricular rate. During sinus rhythm she was having slow heart rate of less than 40 beats per min. Atrial flutter was thought to be scar-related; a radiofrequency ablation was attempted, which was unsuccessful. A diagnosis of brady-tachy syndrome was made and single chamber ventricular permanent pacemaker implantation was planned. Contrast injection in the upper limb veins showed blocked right SVC and presence of left SVC draining into the right atrium via coronary sinus (Fig.1). Extrathoracic subclavian venipuncture was performed in the left side and a bipolar steroid eluting active fixation screw-in ventricular lead (Medtronic Capsure 4068) was introduced into the right atrium via left SVC and coronary sinus (Fig. 2). A stylet was shaped to a large pigtail loop with an additional curve anteriorly to facilitate lead entry into the right ventricle. With this pre-shaping of the stylet, the lead could be easily introduced into the right ventricle. The lead was screwed at right ventricular apex and optimum lead parameters were obtained: R wave 13.8 mV, threshold 0.8 V and resistance 624 ohms.

Discussion
Due to its rarity, there is no large series on RV pacing lead insertion via left SVC, reported in the literature. However, several case reports of the pacing lead insertion via left SVC into the right atrium and right ventricle have been published in the literature. There is also a case report of insertion of defibrillator lead into the right ventricle via left SVC.

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SVC. There is no standard procedure for easy and effective negotiation of the pacing lead into the right ventricle via left SVC - coronary sinus route. Negotiating the pacing lead via left SVC into the right ventricle is challenging and at times difficult due to its anatomical location and relationship of coronary sinus ostium and right ventricular inflow. By shaping the stylet into a large pigtail loop with an additional curve anteriorly at the distal end, we found it easier to introduce the lead into right ventricle. However, in case RV lead cannot be placed, the left ventricle can be paced via a left ventricular vein draining into the coronary sinus.

We recommend a detailed echocardiographic study to exclude left SVC and if doubt exists, a left forearm vein contrast injection under fluoroscopy may be done. In the presence of left SVC it is advisable to do a right-sided approach for better stability of the pacing lead. In cases, where the right-sided SVC is absent like in our second patient, it may be worth preshaping the stylet, as we did, to negotiate the lead into the right ventricle. A large loop may b eleft in the right atrium for greater stability so as to support the lead by the right atrial free wall to decrease the tension over the lead. An active screw-in fixation lead may prevent lead tip displacement.

References

Supravalvular Aortic Stenosis and Coronary Ostial Stenosis in Homozygous Familial Hypercholesterolemia

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Patients with homozygous familial hypercholesterolemia exhibit severe hypercholesterolemia, cutaneous and tendon xanthomata, and premature atherosclerosis from childhood. A rare presentation of this condition with supravalvular aortic stenosis and coronary ostial stenosis is described. (Indian Heart J 2004; 56: 152–154)

Key Words: Supravalvular aortic stenosis, Coronary ostial stenosis, Familial hypercholesterolemia

Familial hypercholesterolemia (FH), the commonest and most severe form of monogenic hypercholesterolemia, was the first genetic disease of lipid metabolism to be characterized clinically and studied at a molecular level.1 This morbid condition affects not only the coronary arteries, but also the aortic root, particularly the aortic valve (hypercholesterolemic valvulopathy).2 The development of aortic stenosis and aortic root involvement are grave prognostic factors in these patients.

Case Report

A 22-year-old man, born of consanguineous marriage, presented with multiple cutaneous swellings since infancy, and effort angina (NYHA class II) of one-year duration. On examination, arcus juvenilis was evident in both eyes. The facies was otherwise normal. He had tuberous xanthomata over the gluteal region and Achilles tendon xanthomata (Fig. 1). All peripheral pulses were equally palpable. Blood pressure was normal and equal in both the right and left arms. On cardiac auscultation, the aortic component of the second heart sound was normal in intensity. There was no ejection click. A loud (grade 4/6) mid-systolic murmur was heard at the right second intercostal space. A faint, early diastolic murmur of aortic regurgitation was also heard. Fundus examination did not reveal any abnormality.

Serum total cholesterol was 480 mg/dl, low-density lipoprotein cholesterol (LDL-c) 418 mg/dl, triglyceride 160 mg/dl, and high-density lipoprotein cholesterol (HDL-c) 30 mg/dl. Serum calcium level, liver function, renal function and thyroid function tests were normal. Severe supravalvular aortic stenosis (peak gradient of 86 mmHg) was demonstrated on echocardiography. The aortic sinuses were markedly thickened and echogenic, but the aortic valve remained mobile. Mild aortic regurgitation was present. The patient also had concentric left ventricular (LV) hypertrophy, normal LV systolic function and diastolic dysfunction.

On cardiac catheterization, there was a pressure gradient of 80 mmHg at the supravalvular level on pullback from the left ventricle. Aortic angiography revealed funneling of the aortic root, hourglass supravalvular stenosis, partial obliteration of the sinuses of valsalva and non-obstructive plaques in the descending thoracic aorta (Fig. 2). Selective coronary angiography showed significant stenosis of the right coronary artery (RCA) ostium (Fig. 3). Left coronary system was normal. There was mild plaquing of the left...
internal carotid artery while the rest of the carotid-vertebral arterial system was normal.

Clinical examination and fasting lipid profile in the other siblings were found to be normal. The patient's father had expired due to alcoholic cirrhosis and the mother was unavailable for screening.

Discussion

Patients with FH have extremely high serum cholesterol levels and may develop advanced atherosclerotic plaque before 10 years of age. The plaque formation can occur at unusual sites, including the ascending aorta and around the coronary ostia. These atheromata can interfere with aortic valve function and cause patients to present with angina, myocardial infarction, and even sudden death.

Magnetic resonance imaging (MRI) for detecting and characterizing aortic root atherosclerotic plaque and supravalvular aortic stenosis in FH patients has been reported.

Familial hypercholesterolemia is an autosomal dominant disease characterized by elevated LDL-c in the blood. The primary defect is a mutation in the gene for the receptor of plasma LDL. Individuals with two mutated LDL receptor alleles (FH homozygotes), although rare (approximately one in a million persons), are much more severely affected than those with one mutant allele (FH heterozygotes). The plasma levels of LDL-c are uniformly very high in FH homozygotes, despite modifications of diet, lifestyle or medications. Homozygotes with FH living in China, where the dietary intake of cholesterol and saturated fat is low, have plasma LDL-c levels similar to those of FH homozygotes living in Western countries. The severity of atherosclerosis is proportional to the extent and duration of elevated plasma LDL-c levels which is calculated as the cholesterol-year score.

Familial hypercholesterolemia was the most probable diagnosis in our patient in view of the extremely high LDL-c levels and the presence of tuberous and tendon xanthomata. Since the xanthomata developed in early infancy itself and the clinical response to maximum statin therapy was poor, it is likely that this patient had the homozygous form of the disease. It may also be noted that tuberous xanthomata and aortic valve/root involvement, although rarely seen in heterozygotes, are clinical pointers in favor of the homozygous phenotype.

The management of homozygous FH presents a major therapeutic challenge. Treatment includes lifestyle modification, cholesterol-lowering drugs and, in some cases, liver transplantation. Another effective therapeutic option for homozygous FH is LDL apheresis, a process by which the LDL particles are selectively removed from the circulation through extracorporeal binding. However, the procedure is time consuming and expensive and must be performed every 1–2 weeks. Although it retards the development of atherosclerosis, it does not prevent it, because of the recurrent hypercholesterolemia between procedures. Therefore, new therapies are urgently needed to treat the hypercholesterolemia of individuals suffering from homozygous FH.

Despite the improved prognosis resulting from medical treatment, most patients eventually require surgery for coronary revascularization and/or for valvular pathology. The combination of severe supravalvular aortic stenosis and coronary artery disease necessitates reconstruction of aortic root and coronary artery bypass grafting – a daunting procedure with high operative risk. Our patient...
has been put on maximal medical therapy with statins and bile acid sequestrants and is awaiting surgery.

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Unruptured Sinus of Valsalva Aneurysm Presenting as Acute Coronary Syndrome

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An unusual presentation of sinus of Valsalva aneurysm causing right ventricular outflow tract obstruction and presenting as acute coronary syndrome is reported. A 38-year-old lady presented with ischemic chest pain, probably due to embolization from an unruptured sinus of Valsalva aneurysm. (Indian Heart J 2004; 56: 155–157)

Key Words: Sinus of Valsalva aneurysm, Myocardial ischemia, Coronary embolization

Sinus of Valsalva aneurysm (SVA) may be either congenital or acquired. An unruptured SVA is usually asymptomatic and hence often goes undetected. Rarely, it may present with myocardial ischemia.1,2 We report an unusual case of SVA causing right ventricular outflow tract (RVOT) obstruction and presenting as acute coronary syndrome.

Case Report

A 38-year-old lady was admitted to the emergency services of our hospital with history of chest pain associated with sweating and palpitation of 5 hours duration. There were no obvious coronary risk factors nor history of previous thromboembolic episodes. She was not taking oral contraceptive pills. She was detected to have systolic murmur on a routine medical examination and presumptive diagnosis of pulmonary stenosis was made 6 months back. She had not undergone any further evaluation for the murmur. On examination she had a grade III/VI ejection systolic murmur that was best heard in left third intercostal space.

A 12-lead electrocardiogram revealed ST segment elevation in inferior and lateral leads and there was moderate elevation of serum CPK and MB fraction. She was diagnosed as a case of acute coronary syndrome, but was not thrombolyzed. A two-dimensional echocardiogram revealed an unruptured SVA arising from the right aortic sinus, obstructing the RVOT with peak instantaneous gradient of 40 mmHg. She underwent cardiac catheterization and angiography. Right ventriculography showed a filling defect in RVOT with a gradient of 35 mmHg across it. Left ventriculography showed posterobasal hypokinesia and aortic root angiography showed a large unruptured SVA (Fig.1). Her coronary angiogram revealed a normal left coronary system. The right coronary artery (RCA) had a high origin and its terminal branches (posterior descending artery [PDA] and posterior left ventricular artery [PLV]) were abruptly cut off (Fig. 2) suggesting embolic occlusion. However, the thrombus was dislodged during subsequent contrast injections and later entire PDA and PLV branches could be visualized flowing normally (Fig. 3).

The patient underwent elective surgical repair of the unruptured SVA on cardiopulmonary bypass (CPB) and

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Fig. 1. An unruptured sinus of Valsalva aneurysm.
moderate hypothermic perfusion. The aortic valve was tricuspid and leaflets were normal. The RCA had a high origin. There was a large unruptured SVA from the right aortic sinus. There was no evidence of thrombus or ulcer in the aneurysmal sac. The defect was repaired with an expanded PTFE patch. Patient had an uneventful recovery and postoperative echocardiogram did not reveal any residual defect.

Discussion

An unruptured SVA is usually silent and is likely to be missed unless echocardiogram is performed, which in fact should be a part of routine work up of acute coronary syndrome. Transesophageal echocardiography (TEE) was not performed in this case although it is an important investigation for establishing the source of thrombus by showing echogenic contrast. The most frequent complication of SVA is a rupture, most commonly into right atrium or ventricle. Rarely it may present with RVOT obstruction, conduction disturbances, embolic episodes, infective endocarditis and myocardial ischemia.

Regueiro et al. found in literature 44 cases of SVA complicated by myocardial infarction or ischemia. The SVA was arising from the left aortic sinus in 28 cases, the right aortic sinus in 12 cases and both left and right sinus in 4 cases. The commonest mechanism of ischaemia is by compression of the coronary artery by sheer size of the aneurysm or stretching of the coronary artery across the surface of the aneurysm. Less commonly spontaneous coronary dissection may result in myocardial ischemia. Myocardial infarction following dobutamine stress test has been reported due to expansion of the aneurysm by dobutamine injection and stretching of the coronary artery. SVA has been reported as a potential source for cerebrovascular and systemic embolization. However, there is no reported case of coronary embolism from SVA, though acute myocardial infarction resulting from a thrombus in normal SVA has been reported. We did not find any thrombus in the SVA, but the angiographic picture of cut off of PDA and PLV, which cleared off during subsequent contrast injections, with an otherwise smooth and normal coronary tree, was highly suggestive of embolic etiology of myocardial ischemia. The patient was a relatively young premenopausal lady in normal sinus rhythm, with no evidence of atherosclerosis or coagulation disorder. In this background, embolization of the RCA is the most likely cause for her myocardial infarction. In this case, SVA was a potential source of an embolus and there is a strong clinical evidence that the embolus lodged in the terminal branches of the RCA originated from the SVA. Further, the high origin of RCA could have theoretically facilitated the embolization of thrombus into it.

The other feature of this case was the SVA causing RVOT obstruction, which is well known and adequately reported in the literature. However, co-existence of the two presentations makes the case an unusual one.

References

Difficult Percutaneous Transvenous Mitral Commissurotomy: A New Technique for Left Atrium to Left Ventricular Entry

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Percutaneous transvenous mitral commissurotomy using Inoue balloon is an effective procedure for the management of patients with juvenile mitral stenosis. Inability to cross the mitral valve by the Inoue balloon catheter is one of the important reasons for failure of the procedure. We describe a new technique, facilitating left atrium to left ventricular entry using double loop of Inoue balloon catheter in a child with small left atrium.

Key Words: Mitral valvuloplasty, Juvenile mitral stenosis, Inoue balloon

Case Report

An 8-year-old male child weighing 14 kg with height of 110 cm and body surface area of 0.63 m² presented with history of dyspnea on exertion (NYHA class III) of two years duration. His pulse rate was 92 beats per min, regular, blood pressure was 90/60 mmHg and respiratory rate 22 breaths per min. He had a grade III/III left parasternal heave, a right ventricular apex, loud first heart sound, accentuated pulmonary component of the second heart sound, a rumbling mid-diastolic murmur at apex with presystolic accentuation, a grade IV/VI pansystolic murmur at the lower left parasternal area and bibasal fine crepitations. Echocardiographically calculated mitral valve area by planimetry and pressure half-time was 0.5 cm², with a mean gradient of 23 mmHg across the mitral valve and Wilkin’s mitral valve score of 6/16. The LA measured 2.8 cm in parasternal long-axis view. The right atrium (RA) and right ventricle were markedly dilated. There was severe tricuspid regurgitation on Doppler color flow and right ventricular systolic pressure was estimated to be 110 mmHg by tricuspid regurgitation jet.

After obtaining informed consent from the parents, the patient was taken up for PTMC through the right femoral venous route. Through right femoral arterial access, a 5 F pig-tail catheter was positioned at the aortic root. A 0.032 J-tipped exchange length teflon guidewire was positioned in the superior vena cava and then a 7 F Mullin’s dilator (Bard, Ireland) was introduced over it. The teflon guidewire was removed and Brockenbrough septal puncture needle was advanced in the Mullin’s dilator. The septal puncture was assisted by transthoracic echocardiography (TTE) in addition to fluoroscopic guidance because of the more vertical position of the atrial septum. The septal puncture site was dilated with an Inoue dilator. The first difficulty was encountered during advancement of the 20 mm Inoue balloon (Toray, Tokyo, Japan) into the LA across the septal puncture site. The length of the stretched balloon (lower profile) was more than the vertical LA dimensions (owing to the small LA size) (Fig. 1). Hence, the whole length of the Inoue balloon in its low profile stretched position (with
the stretcher fully advanced) could not be advanced into the LA (Fig. 2). Taking the stretcher fully out at this position used to result in a destretched and a higher profile Inoue balloon getting trapped at the septal puncture site and thus the balloon could not be advanced over the coiled wire into the LA (Fig. 3a). So we dilated the septal puncture site with a 14 F dilator, but still failed to advance the destretched balloon fully into the LA. To overcome this difficulty, the stretcher was partially advanced so that the length of the now partly stretched slightly lower profile balloon was almost equal to the vertical dimension of the LA and the balloon could be advanced into the LA with its tip pointing upwards (Fig. 3b).

However, the real problem came while trying to negotiate the balloon across the mitral valve. At this point, the balloon tip with the stylet in was much above the level of the mitral orifice (Fig. 4). The usual practice of gently pulling down the balloon to bring its tip at the level of the
mitral valve and counterclockwise rotation of the stylet to direct the balloon tip into the mitral orifice resulted in repeated entrapment of the proximal part of the unstretched balloon at the septal puncture site due to small size of the LA (Fig. 5). Though the tip of the Inoue balloon made bobbing movements at the mitral orifice (as if the balloon is ready to enter the LV), the balloon shaft could not be advanced over the stylet across the mitral valve due to entrapment of the proximal part of the unstretched balloon. With the balloon tip at the mitral orifice, the stylet was taken out and coiled wire could be easily advanced through this balloon into the LV. However, the balloon could not be advanced over the coiled wire as it was trapped at the septal puncture site. Effort to improve the profile of the balloon with the help of the stretcher, so that it could be advanced over the coiled wire, resulted in jumping out of the coiled wire from LV to LA, the moment the balloon was partly stretched with the stretcher. The coiled wire per se could easily be re-negotiated from LA to LV with the help of the Mullin’s dilator. However, repeated attempts to advance the Inoue balloon catheter over the coiled wire into the LV met with failure.

Ultimately, with the coiled wire free in the LA, the Inoue balloon catheter was advanced over the coiled wire to make two loops, so that after completing one full circle in excess of the usual lie of Inoue balloon catheter, the tip of the Inoue balloon was now pointing at mitral valve orifice. At this juncture, the coiled wire could be easily passed into the LV (Fig. 6) and the Inoue balloon catheter could also be easily negotiated over it into the LV, as the Inoue balloon was free and not entrapped at the atrial septum (Figs 7 and 8). The mitral valve was then successfully dilated by giving two dilations (Fig. 9). After completing the procedure, the same maneuver could easily be repeated as many times as we tried, authenticating its feasibility and ruling out an accidental/incidental advancement of the balloon over the wire.

Discussion

Several series of PTMC in children have been published, establishing it as a safe and effective procedure with a low
In this report we describe an 8-year-old child, in whom crossing of the mitral valve with Inoue balloon was not possible using the previously described techniques because of the superior septal puncture and small size of the LA. Therefore, we had to use an innovative method and make a double loop of the Inoue balloon catheter inside the LA to facilitate LA to LV entry. Crossing of the mitral valve is an important and a vital step in the PTMC procedure. When conventional method fails, other techniques have been described for facilitating LA to LV entry like the reverse loop technique and the straight balloon technique. The Inoue balloon itself may be negotiated into the LV using reverse loop technique or else an entry to the LV with a wire is first achieved using one of the following methods (i) taking the help of the balloon floatation catheter (Swan-Ganz) which can be advanced into the LV or even beyond into the aorta and exchange length wire of a desired diameter can be passed through the Swan-Ganz catheter lumen and Swan-Ganz catheter withdrawn, (ii) with the help of either a Mullin's sheath (or only dilator) or an angled catheter like right Judkin's catheter, an exchange length wire can be passed into the LV. Once the exchange length wire has entered the LV or aorta, rest of the procedure can be accomplished over the wire with the help of either Inoue balloon or non-Inoue type balloons (single or double balloon techniques). However it is a good practice to take a partly inflated Swan-Ganz/Inoue balloon over the wire across the mitral orifice to rule out an inadvertent inter-chordal track of the wire, so as to avoid injury to the subvalvular apparatus during the PTMC, which can result in mitral regurgitation.

In the present case, none of the above techniques were applicable. There was no difficulty in entering the LV with the coiled wire. However, the Inoue balloon could not be advanced over it as with every attempt to take the balloon across the mitral orifice (with stretcher partially elongating the balloon), the coiled wire straightened out and jumped into the LA. The small LA size made it difficult for the Inoue balloon.
balloon to enter into the LV, as part of the destretched balloon was entrapped in the atrial septum when the LA to LV entry was tried. To free the balloon from the atrial septum a double loop inside the LA was made. This maneuver was possible because of the small height of the patient, with enough length of the balloon shaft lying outside the body. Another way of making the balloon free could have been to enlarge the atrial septal defect so as to allow free movement of the balloon across the septal puncture site. We tried this by upsizing the dilation of septal puncture site with 14 F Inoue dilator. However, dilation of the atrial septum with balloon (which is likely to create a larger septal defect) was not attempted. This was due to apprehension of right to left shunting in the immediate post-PTMC period. Theright ventricular pressure being supra-systemic (which is likely to take sometime before it regresses), a severe tricuspid regurgitation is likely to result in right ventricle to LA shunt if a larger residual atrial septal defect with low LA pressure exists after successful PTMC.

This case highlights a new method of LA to LV entry in children with small LA. However, this method can be used only in those patients in whom sufficient length of the balloon shaft is available for making a double loop inside the LA.

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Role of Oxidative Stress in Coronary Heart Disease

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Over the last several decades, it has become amply evident that oxidative stress plays a significant role in the pathogenesis of coronary atherosclerosis and its complications. Relatively recent studies have demonstrated an association between increased oxidative stress and diabetes, hypertension, cigarette smoking and dyslipidemia, which are well known risk factors for atherosclerosis. Indeed, it appears that oxidative stress both promotes and is induced by vascular disease and risk factors that lead to vascular disease.

What is oxidative stress? How is oxidative stress generated and removed? What are the effects of oxidative stress on cells? How is oxidative stress related to coronary heart disease? Perhaps more importantly, what are the currently available therapies against oxidative stress and their therapeutic effects? This article will answer these questions.

Oxidative Stress and Reactive Oxygen Species

Oxidative stress has consequences for cells as a result of one of three factors: (i) an increase in oxidant generation, (ii) a decrease in anti-oxidant protection, or (iii) a failure to repair oxidative damage. Oxidative stress-mediated cell damage occurs, in part, via reactive oxygen species (ROS). ROS are produced continually in most tissues and are part of normal cell functions, and their generation may increase in vascular disease, such as atherosclerosis, when enhanced formation of ROS may be pathogenic.

ROS include molecules like hydrogen peroxide; ions like the hypochlorite ion; radicals like the hydroxyl radical; and the superoxide anion which is both ion and radical. Radicals (also called “free radicals”) are a cluster of atoms that contain an unpaired electron in their outermost orbit of electrons. This is an extremely unstable configuration, and radicals quickly react with other molecules or radicals to achieve the stable configuration. Once formed, ROS participate in a number of reactions, yielding additional free radicals such as hydrogen peroxide (causing a positive feedback), peroxynitrite, or hypochlorous acid. In the vascular system, the formation of ROS from endothelial cells, smooth muscle cells (SMCs) and macrophages seems to be of major relevance in atherogenesis, in part due to their reaction with nitric oxide (NO). NO, perhaps the most important endothelium-derived vasorelaxing factor, is scavenged by ROS. NO reacts with ROS to yield peroxynitrite, which can rearrange to form nitrate and the highly reactive OH radical, which is toxic to tissues and cells. Important pathophysiological consequences of enhanced ROS formation in the vascular system are: (i) attenuation of endothelium-dependent dilation, resulting in disturbed organ perfusion and systemic hypertension, (ii) induction of cellular damage and inflammation, (iii) induction of apoptosis, and (iv) initiation of several intracellular signaling processes. The main source of ROS in vivo is aerobic respiration taking place in mitochondria, although ROS are also produced by peroxisomal oxidation of fatty acids, microsomal cytochrome P450 metabolism of xenobiotic compounds, stimulation of phagocytosis by pathogens or lipopolysaccharides, arginine metabolism, and tissue-specific enzymes.

Antioxidants

Under normal conditions, numerous cellular antioxidant systems exist to defend against oxidant stress and maintain the redox balance of the cell. ROS are cleared from the cell by enzymatic systems including superoxide dismutases (SODs), catalase, and glutathione peroxidase, or the non-enzymatic system including alpha-tocopherol (vitamin E), ascorbic acid (vitamin C), glutathione, and uric acid. SODs convert two superoxide anions into one molecule of hydrogen peroxide and oxygen each, and catalase catalyzes the decomposition of hydrogen peroxide into water and oxygen, leading to the removal of superoxide anion. Glutathione peroxidase plays an important role as defense mechanism in mammals, birds and fish against oxidative damage by catalyzing the reduction of a variety of hydroperoxides, using glutathione as the reducing substrate. For example, glutathione peroxidase reduces...
hydrogen peroxide to water by oxidizing glutathione (GSH) to its oxidized form (GSSG), and the reduction of the oxidized form of glutathione (GSSG) is then catalyzed by glutathione reductase. Through the glutathione redox cycle, ROS is removed from cells. In addition to its role as a substrate in GSH redox cycle, glutathione, as well as uric acid, also act as a direct endogenous scavenger of hydroxyl radicals. Ascorbic acid scavenges free radicals and reduces them into hydrogen peroxide, which can be further catalyzed by catalase to form water and oxygen. Alpha-tocopherol can transfer a hydrogen atom with a single electron to free radicals, thus removing the radicals before they can interact with cell membrane proteins or generate lipid peroxidation.

Excessive production of ROS, outstripping endogenous antioxidant defense mechanisms, is referred to as oxidative stress. The major damage to cells results from the ROS-induced alteration of macromolecules such as polyunsaturated fatty acids in membrane lipids, essential proteins and DNA.7

**Stimuli for Increased ROS Generation**

ROS production is induced under several pathological conditions by various stimuli. Risk factors for atherosclerosis, such as hypertension and hyperlipidemia, are also associated with increased generation of ROS, and it is likely that cigarette smoking and diabetes mellitus share oxidative heritages.8 Increasing evidence shows that ischemia-reperfusion, which frequently occurs in narrowed atherosclerotic arteries, increases ROS generation.9 At the molecular level, signaling in response to pro-atherogenic agents requires as well as causes generation of ROS.9 Proatherogenic agents comprise a large variety of molecules. It has been identified that cytokines, including tumor necrosis factor-γ (TNF-γ), interferon-γ (IFN-γ), interleukin-1,-6 (IL-1, IL-6), and angiotensin II (Ang II), stimulate intracellular generation of ROS. High levels of low-density lipoprotein (LDL), especially in the form of oxidized low-density lipoprotein (ox-LDL), have also been shown to increase intracellular ROS generation.13 In addition, growth factors, such as platelet-derived growth factor (PDGF) and epidermal growth factor (EGF) as well as vascular endothelial growth factor (VEGF), and hormones, such as insulin, all greatly induce intracellular ROS generation.14,15

The mechanism for the generation of intracellular ROS appears to involve multiple enzyme systems mainly comprised of, but not limited to, NADPH oxidases, amine oxidase, oxalate oxidase and peroxidases. The NADPH oxidases have emerged as an important source of ROS in vascular cells. The generation and activity of NADPH oxidases are regulated by many of the stimuli mentioned above.16

**Oxidative Stress in Atherosclerosis**

Oxidative stress has been identified throughout the process of atherogenesis, beginning at the early stage when endothelial dysfunction is barely apparent.17 As the process of atherogenesis proceeds, inflammatory cells, as well as other constituents of the atherosclerotic plaque release large amounts of ROS, which further facilitate atherogenesis. Fig. 1 demonstrates various steps where oxidative stress could be involved in atherogenesis. In general, increased production of ROS may affect four fundamental mechanisms that contribute to atherogenesis: oxidation of LDL, endothelial cell dysfunction, vascular SMCs, growth and monocytes migration.18

A number of studies suggest that ROS oxidize lipids and that the oxidatively modified LDL is a more potent pro-atherosclerotic mediator than the native unmodified LDL.19 The suggestion is based on the observations that high plasma levels of ox-LDL are present in patients with atherosclerosis and that antibody to ox-LDL is detected in plasma of most patients with atherosclerosis.20 Strong evidence in favor of a pro-atherosclerotic role for ox-LDL comes from a number of studies demonstrating the noxious effects of ox-LDL on various components of the arterial

![Oxidative stress and atherogenesis](image-url)
wall. For example, ox-LDL causes activation of the endothelial cells lining the arterial wall, resulting in the expression of several adhesion molecules that facilitate the adhesion of monocytes/macrophages.\textsuperscript{21} ox-LDL also activates inflammatory cells and facilitates the release of a number of growth factors from monocytes/macrophages.\textsuperscript{22,23} Vascular SMCs exhibit intense proliferation when exposed to ox-LDL.\textsuperscript{23} ox-LDL enhances the formation of matrix metalloproteinases (MMPs) in vascular endothelial cells and fibroblasts,\textsuperscript{24} thus setting the stage wherein oxidative stress leads to rupture of a soft plaque. In addition, ox-LDL upregulates the expression of its endothelial receptor LOX-1 and other scavenger receptors mainly expressed on macrophages/monocytes. The increased expression of these receptors is responsible for the uptake of ox-LDL and the formation of foam cells, which is an early step in atherogenesis.

The term endothelial dysfunction has been used to refer to several pathological conditions, including altered anti-coagulant and anti-inflammatory properties of the endothelium, impaired modulation of vascular growth, and dysregulation of vascular remodeling.\textsuperscript{25} However, an important characteristic of endothelial dysfunction is impaired synthesis, release, and activity of endothelium-derived NO. Studies from several laboratories have demonstrated that endothelial NO inhibits several processes involved in atherogenesis. For example, it mediates vascular relaxation and inhibits platelet aggregation, vascular SMC proliferation, and endothelium-leukocyte interactions. Inactivation of NO by superoxide anion limits the bioavailability of NO and leads to nitrate tolerance, vasoconstriction, and hypertension as well as atherosclerosis.\textsuperscript{26} It has also been shown that ROS can rapidly destroy bioactive NO in bovine coronary arteries and induce atherosclerosis.\textsuperscript{27} Studies in our laboratory have identified that ox-LDL, by increasing ROS production, induces apoptosis in human coronary artery endothelial cells.\textsuperscript{28}

Proliferation of vascular SMCs is a characteristic feature of atherosclerosis, and ROS can induce vascular SMC growth. The increase in SMC growth by ROS occurs as a result of stimulation of the expression of fibroblast growth factor (FGF) and fibroblast growth factor receptor-1 (FGFR-1), insulin-like growth factor-1 (IGF-1) and insulin-like growth factor-1 receptor (IGF-1R) as well as epidermal growth factor receptor (EGFR).\textsuperscript{29–32} Also, there is increasing evidence that ROS generation, via NADPH oxidase activation, plays a critical role in Ang II-induced vascular SMC proliferation and hypertrophy.\textsuperscript{33} Several studies show that ROS may induce vascular SMC death by either apoptosis or necrosis,\textsuperscript{34} but this process, which occurs in the final stage of atherosclerosis, requires large amount of ROS.

Increased adhesion of monocytes to endothelial cells has been linked to the development and progression of atherosclerosis in humans. One study has shown that the effect of increased concentration of glucose on monocyte adhesion to endothelial cells is due to the increased production of ROS.\textsuperscript{35} A number of studies have shown that ROS upregulate the expression of intercellular adhesion molecule-1 (ICAM-1),\textsuperscript{36} vascular cell adhesion molecule-1 (VCAM-1),\textsuperscript{36,37} monocyte chemoattractant protein-1 (MCP-1),\textsuperscript{38} P-selectin,\textsuperscript{39} L-selectin,\textsuperscript{40} E-selectin\textsuperscript{37} and platelet endothelial cell adhesion molecule-1 (PECAM-1)\textsuperscript{41} in vascular endothelial cells. Expression of these molecules is critical in the adhesion of monocytes to endothelial cells. Other studies have shown that induction in arterial wall of heme-oxigenase, which scavenges ROS, may lead to the attenuation of monocyte adhesion,\textsuperscript{42} and may represent a regulatory mechanism to counter the effects of ROS.

**ROS-Mediated Signal Transduction Pathways**

A large body of literature has linked oxidative stress with atherosclerosis and with virtually all aspects of atherosclerotic lesion development culminating in an acute coronary event. Although the observations discussed above implicate ROS as a stimulus for the expression and release of several pro-atherogenic and inflammatory mediators, less is known regarding the specific intracellular signaling pathways by which ROS act.\textsuperscript{43}

Some recent studies suggest that the function and activity of intracellular signals are regulated by ROS. These studies link the cellular oxidative state to specific mitogen-activated protein kinases (MAPKs), such as p38 kinase\textsuperscript{44} and to extracellular signal-regulated kinase 1/2 (ERK 1/2),\textsuperscript{44} as well as the c-Jun N-terminal kinase (JNK)\textsuperscript{44} signaling pathway.

Although MAPK plays a central role in ROS-mediated signal transduction in cardiovascular diseases, other protein kinases are also involved in ROS-mediated changes in vascular cells.\textsuperscript{44} Protein tyrosine kinases are among the intracellular mediators that may be rapidly activated by many stimuli including ROS. To date, there is no direct evidence showing that ROS stimulates receptor tyrosine kinases; however, three mechanisms have been proposed by which ROS could activate tyrosine kinases. First, tyrosine kinases may be activated by ROS directly by altering protein–protein interactions dependent on sulfhydryl groups. Second, inhibition of phosphotyrosine phosphatases (PTPases) may be another important mechanism by which ROS may activate tyrosine kinases. All PTPases contain a
redox-sensitive cysteine at their active site, and oxidation of the sulfhydryl group inactivates the PT Pase. Since many tyrosine kinases are inactivated by PT Pases, oxidation of PT Pases would stimulate tyrosine kinases. Third, oxidation has been shown to stimulate proteolysis of regulatory proteins that may inhibit tyrosine kinase activation. Several tyrosine kinases are activated by ROS, and the Src family of kinases have been described most frequently.44

Phospholipases may also be activated by ROS.44 At least three important phospholipases have been shown to be activated by ROS in vascular cells, including phospholipase A2,45 phospholipase C46 and phospholipase D.47 Phospholipase A2 is likely activated by increases in intracellular calcium caused by ROS. It is important to note that many lipids generated by phospholipase A2 may themselves generate ROS through the action of monooxygenases. Phospholipase C is a calcium-dependent phospholipase that hydrolyzesPIP2 to generate IP3 and diacylglycerol. Although there are no published findings to suggest that ROS directly activate phospholipase C, generation of ROS may be an early event in growth factor-dependent signaling and activation of phospholipase C. Phospholipase D has been shown to be stimulated by H2O2, fatty acid hydroperoxides, and 4-hydroxynonenal in endothelial cells. Further studies are required to elucidate the mechanisms by which phospholipases are activated.44

In addition to regulating enzyme activity, ROS participate in signal transduction by generating classic second-messengers (calcium and lipid mediators) that transmit signals to intracellular mediators in both the cytoplasm and nucleus.44 Other important mediators of the ROS-sensitive signaling pathway are small G proteins. Based on experiments with recombinant p21 Ras in vitro, it was shown that ROS directly promote guanine nucleotide exchange on p21 Ras.48 This leads to an increased population of active p21 Ras-GTP, resulting in increased availability of p21 Ras to its downstream targets.49

The final step in the ROS-mediated signaling pathway usually involves the activation of transcription factors, which are proteins that are transported to the nucleus upon activation and trigger target gene expression. Nuclear factor-κB (NF-κB) is an inducible transcription factor that is a likely target for ROS signal transduction. NF-κB is a heterodimer containing a 50kDa and a 65kDa subunit (termed as p50 and p65). There are two forms of NF-κB in the cell, an inactive form in the cytosol and an active form in the nucleus. Cytosolic NF-κB can be activated by a variety of stimuli including cytokines, physical stress such as ultraviolet and ionizing radiation, and ROS, such as H2O2. The recognition sequence for NF-κB is present in genes, such as E-selectin, VCAM-1 and ICAM-1, whose expression causes monocyte adhesion to endothelial cells.50

In addition to NF-κB, activator protein-1 (AP-1) also appears to be activated by ROS. Regulation of AP-1 by ROS has been shown to involve p38 MAPK and ERK1/2 as well as JNK in vascular SMCs.51 Other transcription factors such as hypoxia-inducible factor-1 (HIF-1) and early growth response-1 (Egr-1) may also be involved in ROS-mediated pro-atherogenic events in vascular SMCs and endothelial cells.52, 53 Fig. 2 outlines the ox-LDL and Ang II-induced ROS signaling pathways.

Hyperlipidemia-induced Oxidative Stress and Atherosclerosis

It has long been identified that hyperlipidemia is a major inducer of oxidative stress and plays a pivotal role in atherogenesis in susceptible animals and humans.54–56 In hyperlipidemic patients, the enrichment of triglycerides and the high apo-B cholesterol levels suggest the presence of abnormally high levels of LDL particles.57 Also, elevated levels of ox-LDL in plasma of patients with atherosclerosis further suggest the importance of ox-LDL in hyperlipidemic patients. Increasing evidence has shown that ox-LDL is not only a marker of oxidative stress, but itself can induce oxidative stress in vascular tissues.58,59 A large body of

![Fig. 2. Both Ang II and ox-LDL may induce oxidative stress in endothelial cells by activating their specific receptors: AT1R and LOX-1. The increased ROS, which is produced from NADPH oxidase, may activate phospholipases (PLA2, PLC and PLD), mitogen-activated protein kinases (p38 kinase, ERK1/2 and JNK), and protein tyrosine kinase, leading to the activation of transcription factors such as NF-κB, AP-1, HIF-1 and Eg-1. This results in the expression of target genes including leukocyte adhesion molecules, metalloproteinases, and AT1R as well as LOX-1.](image-url)
literature has confirmed a central pro-atherogenic role of ox-LDL in vascular cells.\(^{21-24}\) It has been recently shown that ox-LDL induces pro-atherosclerotic NADPH oxidase expression and superoxide anion formation in human vascular endothelial cells,\(^{60}\) and this may be one mechanism by which ox-LDL stimulates ROS generation and the resultant endothelial dysfunction as well as atherosclerosis.

Since hyperlipidemia is a major risk factor for atherosclerosis, therapies directed at modulating hyperlipidemia may have anti-atherogenic effect. As mentioned, both probucol and 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors are effective lipid lowering agents. Clinical studies in humans show that these agents can significantly reduce the plasma LDL-cholesterol level. The LDL cholesterol-lowering effect may be responsible for their anti-atherosclerotic effects. However, a large number of studies have demonstrated that their anti-atherosclerotic effects are due not only to their lipid-lowering property, but also to their direct anti-oxidant effect.\(^{61,62}\) HMG-CoA reductase inhibitors in particular provide endothelial stabilization through mechanisms that go beyond their primary lipid-lowering effect. The improvement of endothelial dysfunction induced by ox-LDL may be secondary to a reduction in the production of free radicals that might result in an increase in endothelial NO synthase (eNOS) expression and activity.\(^{62}\) In addition, HMG-CoA reductase inhibitors have been shown to reduce the susceptibility of LDL to oxidation.\(^{63}\) These data provide indirect evidence supporting an anti-oxidant effect of these agents, independent of their lipid-lowering effect.

The effects of ox-LDL on vascular tissues are mediated by specific receptors on monocytes/macrophages and SMCs.\(^{64}\) Uptake of ox-LDL through these receptors leads to foam cell formation, SMC proliferation and migration and neointima formation. The inhibition of these scavenger receptors indeed is associated with a reduction in atherosclerosis.\(^{65}\)

Recently a novel lectin-like receptor for ox-LDL (LOX-1 or OLR1) has been identified on endothelial cells that lack the traditional receptors seen on monocytes/macrophages and SMCs. The effects of ox-LDL on endothelial biology, such as apoptosis, expression of adhesion molecules and release of metalloproteinases appear to be mediated largely through LOX-1.\(^{21,23,28}\) Notably, HMG-CoA reductase inhibitors such as simvastatin and atorvastatin inhibit the endothelial uptake of ox-LDL and reduce the upregulation of endothelial ox-LDL receptor LOX-1, and upregulate the expression of eNOS.\(^{21,66}\) All these effects may complement the inhibitory effect of statins on ROS generation described above.

**Angiotensin II (Ang II)-induced Oxidative Stress and Atherosclerosis**

Besides hyperlipidemia, hypertension is another important risk factor in atherogenesis. There is activation of renin-angiotensin system (RAS) in many hypertensive patients. Activation of RAS with the formation of Ang II and subsequent activation of Ang II receptors, mainly type I receptors (AT1R), has been implicated in atherogenesis.\(^{67}\) Ang II can exert multiple pro-atherogenic effects on vascular endothelial cells and SMCs by activating AT1R. For example, Ang II upregulates the expression of inflammatory factors such as P-selectin and MCP-1, resulting in the adhesion of monocytes and other inflammatory cells.\(^{68}\) Ang II enhances the uptake of ox-LDL and the biosynthesis of cholesterol in macrophages, leading to formation of foam cells.\(^{69,70}\) Ang II upregulates LOX-1 gene and protein expression in cultured human coronary artery endothelial cells, and enhances the noxious effects of ox-LDL, both via AT1R activation.\(^{69}\) Ang II induces apoptosis of human coronary artery endothelial cells.\(^{71}\) Angiotensin II-induced oxidative stress and proatherosclerotic effects as well as MAPK activation in response to Ang II in mice endothelial cells; a similar effect has also been identified in human endothelial cells.\(^{75}\)

There is rapidly growing evidence in favor of the idea that Ang II-induced oxidative stress plays an important role in Ang II-mediated cellular responses. This is further supported by the data that PPAR-γ ligands, which are potent anti-oxidants, may attenuate Ang II-induced ROS generation and monocytes adhesion to human coronary artery endothelial cells.\(^{58}\) An in vivo study also shows that the pro-atherogenic effect of intravenous infusion of Ang II is attenuated by co-infusion of vitamin C, another widely used anti-oxidant.\(^{76}\) Taken together, Ang II-induced oxidative stress is an important mechanism by which this neurohormone induces many of its pro-atherogenic effects. This idea is further supported by several in vitro and in vivo findings showing that blockade of RAS by AT1R blockers, such as losartan and candesartan, attenuates Ang II-induced oxidative stress and proatherogenic effects as well in some species.\(^{77-79}\)
Interaction between Hyperlipidemia and RAS Activation: Role of ROS

Since hyperlipidemia and hypertension are major risk factors for coronary heart disease, and both are often present in the same patient, it is thought that an interaction between hyperlipidemia and RAS activation exists. This interaction may not only explain the frequent coexistence of hyperlipidemia and hypertension, but may play an important synergistic role in the pathogenesis of atherosclerosis. This idea is based on the data that Ang II and ox-LDL co-localize in macrophages in the atherosclerotic plaque and the fact that the concentration of ox-LDL co-localize in macrophages in the atherosclerosis. This idea is based on the data that Ang II and ox-LDL co-localize in macrophages in the atherosclerotic plaque and the fact that the concentration of ox-LDL is increased in atherosclerotic arteries of hyperlipidemic humans and monkeys. Experimental data suggest that the effects of Ang II and ox-LDL on atherogenesis are not independent. Accumulating data from recent experimental and clinical studies suggest that the pathways by which Ang II and ox-LDL lead to vascular disease may frequently overlap. Common pro-atherogenic effects of hyperlipidemia and Ang II are shown in Table 1.

Table 1. Common effects of hyperlipidemia and RAS activation in atherosclerosis

- Both stimulate formation and release of reactive oxygen species (ROS).
- Both degrade or decrease endothelial nitric oxide synthase expression, and hence decrease endothelium-dependent vasodilation.
- Both cause activation of redox-sensitive transcription factor NF-κB.
- Both are pro-inflammatory (cause expression of adhesion molecules and cytokines, upregulate gene for monocyte chemoattractant protein-1, and induce monocyte adhesion).
- Both cause apoptosis (programmed cell death).

Experimental studies have shown that hyperlipidemia enhances RAS activity. A number of recent studies in hyperlipidemic human atherosclerotic tissues have confirmed the upregulation of ACE and AT1R, particularly in the regions that are prone to rupture. Importantly, these same areas show extensive inflammatory cell deposits, macrophage accumulation and apoptosis. In vitro studies have shown that incubation of vascular SMCs with ox-LDL increases expression of the AT1R. It has also been observed that ox-LDL increases mRNA and protein for AT1R in human coronary artery endothelial cells and that activation of the redox sensitive transcription factor NF-κB plays a critical role in this process.

Further, there is generally a linear relationship between plasma LDL-cholesterol concentration and AT1R expression in endothelial cells and statin-mediated downregulation of AT1R expression has also been shown in vascular SMCs.

On the other hand, RAS activation may enhance hyperlipidemia-mediated atherogenesis. The role of Ang II in promoting atherosclerotic lesions in apolipoprotein-E (apo-E) deficient mice has been recently examined. Daugherty et al. showed that 1-month infusion of Ang II enhances the severity of aortic atherosclerotic lesions compared to placebo. In vitro experiments also show that Ang II treatment may facilitate ox-LDL-induced vascular SMC proliferation. As further evidence for the role of Ang II in hyperlipidemia-mediated atherogenesis, ACE inhibitors as well as AT1R blockers have been shown to decrease the progression of atherosclerosis in a variety of hyperlipidemic animals. Consistent with the concept of slowing progression of atherosclerosis, these agents also decrease the markers of inflammation and LDL oxidation in the atherosclerotic regions. The inhibition of atherosclerosis by these agents suggests that the anti-atherosclerotic effects of RAS inhibitors may be due, at least in part, to direct inhibition of LDL oxidation and other actions of Ang II in the vessel wall.

Other studies demonstrate that the expression of ox-LDL receptor LOX-1 is stimulated by Ang II, while the expression of Ang II receptor AT1R is stimulated by ox-LDL in endothelial cells. This provides direct evidence supporting the interaction between ox-LDL and RAS activation in coronary endothelial cells.

Ang II and ox-LDL interact synergistically in the context of oxidative stress. This idea is based on following considerations. First, there are striking similarities between the effects of Ang II and ox-LDL, especially those related to ROS production, in vascular endothelial cells and SMCs as well as in animal models. Second, the blockade of AT1R normalizes the activity of NADPH oxidase and reduces macrophage infiltration and atherosclerotic plaque area in animals fed a high-cholesterol diet. Third, Ang II and ox-LDL together exert a cumulative cell injurious effect, and importantly, anti-oxidant such as vitamin E can attenuate the injurious effect of ox-LDL and Ang II.

Both the inhibition of RAS with ACE inhibitors or AT1R blockers and the treatment of hyperlipidemia with statins have been shown to be effective in reducing endothelial dysfunction, monocyte adhesion and SMC migration as well as atherosclerosis. In a recent study, we observed that the concurrent treatment of hyperlipidemia with rosuvastatin and inhibition of RAS with candesartan had a synergistic anti-atherogenic effect in high cholesterol diet-fed apo-E deficient mice. We also observed the expression of LOX-1...
and several inflammatory mediators such as MMP-1, MMP-2, MMP-9, CD40, and the activation of p38 MAPK were markedly upregulated in these mice. Although rosuvastatin or candesartan, separately had modest inhibitory effects, the combination therapy showed total blockade of these pro-atherogenic effects. These innovative studies confirm the interaction between hyperlipidemia and RAS activation, and also imply that oxidative stress and inflammation play a critical role in atherogenesis.

Fig. 3 shows our current understanding of the interaction between RAS and hyperlipidemia. It is particularly important to note that both mediators share common pathways resulting in activation of the cell injury and atherosclerosis.

**Anti-oxidant Therapies in Atherosclerosis**

Since ROS are widely known to be involved in the progression of atherosclerosis, it is not surprising that anti-oxidant therapies are one of the most effective and promising strategies against atherogenesis. To date, there are at least five anti-atherosclerotic agents that have exhibited anti-oxidant effects, albeit to varying degrees (1) probucol; (2) HMG-CoA reductase inhibitors; (3) AT1R blockers and ACE inhibitors; (4) vitamins E and C; and (5) peroxisome proliferator-activated receptor-γ (PPAR-γ) ligands.

Probucol is a modestly potent LDL-lowering agent with powerful anti-oxidant properties that effectively inhibits the oxidative modification of LDL independent of its lipid-lowering effect. By exerting anti-oxidant effect, it may inhibit VCAM-1 and MCP-1 expression and inhibit human aortic SMC proliferation as well as atherogenesis. The HMG-CoA reductase inhibitors, also known as statins, are potent lipid-modifying agents. There is overwhelming evidence from clinical studies that reducing plasma LDL levels with statins results in a markedly lower risk of cardiovascular events related to atherosclerosis. Recent studies in patients with established CAD show that these agents can cause a modest regression of atherosclerotic lesions. It has been suggested that the anti-atherosclerotic effect of statins may be dependent on their LDL-lowering effect, among which is their ability to decrease ROS generation.

Vitamins E and C have been demonstrated to reduce the progression of atherosclerosis in animal models, but this effect is not consistently observed. Clinical studies show that while these anti-oxidant vitamins do not reduce endpoints related to atherosclerosis, they improve endothelial function by increasing local NO bioavailability and, therefore, endothelium-dependent vasodilation.

AT1R blockers and ACE inhibitors are widely used to treat patients with hypertension and/or congestive heart failure by blocking the effect of Ang II or its formation. Recent studies show that Ang II is also a strong stimulus for ROS generation, and AT1R blockers as well as ACE inhibitors inhibit the expression of pro-atherogenic factors by decreasing ROS production in vascular endothelial cells and in animal models. A large number of studies have provided direct evidence showing the anti-atherosclerotic effects of these agents. Experimental studies from our laboratory showed that statins and AT1R blockers exert synergistic effects on the inhibition of atherosclerotic lesions in the apo E knockout mice placed on a high cholesterol diet.

The ligands of PPAR-γ, a member of the nuclear receptor super-family, were initially developed to affect glucose and lipid metabolism. These agents, such as rosiglitazone and pioglitazone, are widely used in the treatment of type II diabetes. Recently, PPAR-γ ligands have been identified as potent anti-oxidants. By suppressing NADPH oxidase expression and reducing intracellular ROS production, these agents inhibit the expression of several pro-atherogenic proteins and apoptosis in vascular endothelial cells and SMCs. Experimental studies show that thiazolidinediones, a potent PPAR-γ ligand, reduces the size and number of atherosclerotic lesions in the vessel wall by...
modulating foam cell formation and inflammatory responses of macrophages. A recent study shows a significant vascular protective effect of PPAR-γ ligand rosiglitazone in hypercholesterolemic rabbits, most likely by the attenuation of oxidative stress, and this endothelial protective effect of rosiglitazone may reduce leukocyte accumulation in vascular walls and contribute to its anti-atherosclerotic effect. Work in our laboratory suggests that another ligand, pioglitazone, decreases TNF-α-mediated apoptosis in human coronary artery endothelial cells by reducing ROS formation. Thus, PPAR-γ ligands have the potential for the treatment of atherosclerosis and type II diabetes.

Conclusions

Increased production of ROS, exceeding the ability of the body to combat it, is considered oxidative stress. By activating several signal transduction pathways, oxidative stress exerts noxious effects on cells of the vessel wall and leads to the initiation and progression of atherosclerosis culminating in acute events, such as acute coronary syndrome and stroke. Inhibition of ROS generation and function is a potential therapy to attenuate the extent of atherosclerosis and its sequence. Two major risk factors involved in human atherosclerosis, hyperlipidemia and RAS activation, stimulate ROS generation and interdependently induce atherogenesis. The concurrent therapy directed at modulation of these two major risk factors may synergistically block oxidative stress and resultant atherogenesis and its complications.

Acknowledgements

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A 45-year-old man presented with breathing difficulty of one month duration. He was euglycemic and normotensive, and had no history of myocardial infarction or angina. On clinical examination his jugular venous pressure was elevated and S3 gallop was present. His ECG showed pathological q waves in inferior leads and poor progression of R waves in anterior chest leads. Chest X-ray revealed cardiomegaly with cardiothoracic ratio of 17/28. His abdominal ultrasonography was normal. He was advised echocardiography to assess the left ventricular function.

Echocardiogram revealed three cystic structures of various sizes in the left ventricle (Figs 1-3). These cysts were seen in apical four-chamber, long axis and short axis views. These cysts were well circumscribed, had a thin wall and echolucent core. Based on these characteristic findings, we made a diagnosis of blood-filled cyst of heart, which is a rare condition.

Blood-filled cyst of the heart was first described in 1844 by Elsasser. Houser et al. first reported the use of echocardiography for detection of intracardiac blood-filled cyst in 1983. Cyst wall consists of endothelial cells and a thin layer of fibrous tissue that contains non-organised blood or serosanguinous fluid. The echocardiographic appearance of these cysts (well-circumscribed mass with a thin wall and echolucent core) is characteristic and has since been confirmed by several echocardiographic-pathologic correlations.

Intracardiac blood-filled cysts are typically asymptomatic, usually congenital in origin, seen predominantly in infants. These cysts have been described on the mitral valve, papillary muscles and aortic valve as
well as in the atrialized portion of right ventricle in a patient with Ebstein anomaly. Recently acquired blood-filled cyst after mitral and tricuspid valve surgery has been reported in a 68-year-old woman.

The cysts regress spontaneously in most of the patients and are rare in adults. However, cyst's growth has also been reported. The potential complications include valve dysfunction, left ventricular outflow tract obstruction, and embolic stroke. There is no consensus regarding the optimal management of asymptomatic cysts. Roberts et al. have proposed that the cyst should be removed routinely to exclude malignancy and avoid the potential risk of embolism.

Our patient presented with left ventricular dysfunction and was started on anti-failure treatment. Coronary angiogram followed by surgical removal of the cysts has been advised.

References
Adverse Interactions between Low-Dose Aspirin/ Warfarin and Garlic/Ginkgo biloba

Most people believe that herbal medicines are harmless and therefore their use as self-prescribed drugs for different disorders with or without prescription drugs is on the rise. At times, adverse effects of herbal medicines and their undesirable interactions with prescription drugs occur that often go unnoticed. In fact, use of herbal medicines is neither enquired and recorded in drug history while making diagnosis nor are the patients advised against their indiscriminate concurrent use with prescription drugs. Various reports have confirmed that the prescribers are often unaware about the concurrent use of herbal medicines with prescription drugs.

In India, the herbal medicines which are used widely include garlic, ginseng and ginkgo biloba. Garlic is used for hyperlipidemia, hypertension and prevention of heart diseases; ginseng for physical, mental and sexual weakness and ginkgo biloba for improving mental concentration, diabetes mellitus-related circulatory disorders and impotence. The most common adverse effect of these herbal drugs is bleeding. Bleeding complications including cerebral and post-operative bleeding have been reported after use of garlic, ginseng and ginkgo. These case reports suggest that appropriate precautions are essential with the use of herbal medicines before surgery. It has been recommended that garlic and ginkgo should be discontinued at least 7 days and ginkgo biloba should be discontinued at least 3 days before surgery.

Garlic has been reported to inhibit aggregation of platelets by inhibiting synthesis of both cyclo-oxygenase (Cox)-mediated thromboxane A2 (TXA2) and platelet activating factor (PAF). It also prevents blood coagulation, reduces blood viscosity and enhances fibrinolytic activity.

Ginseng has been reported to inhibit platelet aggregation by inhibiting synthesis of Cox-mediated TXA2.

Ginkgo biloba has vasorelaxant action. It contains ginkgolide B which inhibits the binding of PAF to its receptors on platelet membranes, resulting in reduced platelet aggregation. It also increases bleeding time. Intraocular bleeding due to interaction between low-dose aspirin and ginkgo biloba has also been reported. Aspirin in low dose leads to selective blockade of synthesis of Cox-mediated TXA2, which inhibits platelet aggregation without inhibiting synthesis of PGI2 which prevents platelet aggregation. Ginkgo biloba inhibits PAF-mediated platelet aggregation. With their concurrent use, bleeding may occur due to enhanced antiplatelet activity.

Though no interaction between garlic/ginseng and low-dose aspirin has been reported, yet there is potential for interaction because garlic also inhibits Cox-mediated and PAF-mediated platelet aggregation whereas ginseng inhibits Cox-mediated platelet aggregation. Moreover, the possibility of underreporting due to inadequate adverse drug reaction (ADR) monitoring also exists.

Ginseng has been reported to reduce effectiveness of warfarin, if taken concomitantly. Various reports also suggest that garlic and ginkgo biloba may cause hemorrhage due to increased effectiveness of warfarin.

The patients who are at increased risk of adverse interactions with garlic, ginseng and ginkgo biloba include patients with bleeding disorders, those who have a tendency to undergo surgery, those on low-dose aspirin/other antiplatelet drug and warfarin/other anticoagulants. These patients need to be advised to avoid consumption of ginseng and ginkgo biloba. Since the use of garlic as ingredient of food or spice is quite prevalent, it will be wise if these patients avoid extra garlic supplements.

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Use of Cardiac Resynchronization Therapy in the Context of Electrocardiographic Criteria Needs Reconsideration

I read with interest the article by Gupta et al. on the proportion of patients given cardiac resynchronization therapy (CRT) as per present electrocardiographic (ECG) criteria. However, using ECG criteria as a yardstick for such therapy has outlived its utility and is only partially relevant. Many patients who do not have an ECG duration >150 ms, are also candidates for CRT. In a recent article by Bader et al., the presence of intraventricular (but not interventricular) asynchrony was identified as an independent predictor of severe cardiac events, irrespective of the width of QRS and left ventricular ejection fraction (LVEF). Intraventricular dysynchrony can be easily measured using M-mode echocardiogram to find the posterolateral left ventricular wall activation delay (Q-LW), from QRS onset to maximal left ventricular posterolateral wall inward movement, recorded from the apical four-chamber view with the M-mode cursor positioned at 1 cm below the mitral annulus on the lateral wall of the left ventricle. Intraventricular asynchrony is identified when Q-LW exceeds Q-E (QRS onset to beginning of transmitial filling interval) and Q-LW is above 9.9 corrected units (corrected units = measured interval in ms/ R-R interval). Dividing their patients into two groups with QRS duration >120 ms or <120 ms, Achilli et al. demonstrated a significant clinical and functional benefit with CRT in patients with QRS width ≤120 ms. Recent articles by Blazek et al., Yu et al., and Breithardt et al. have all demonstrated that a large number of patients with QRS duration ≤120 ms have intraventricular dysynchrony and could be candidates for CRT. I therefore feel that looking at the width of QRS as a marker for CRT would exclude many patients who could benefit from CRT. It is time we revise the criteria about who will benefit from CRT based only on QRS.

References

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Reply
We thank Dr UK Patnaik for interest in our article. This study was done only to look at the ECG manifestations as seen in the group of patients with congestive cardiac failure presenting to a tertiary care center with left ventricular ejection fraction less than 40%.

One of the critical questions is how one should select patients with heart failure for biventricular pacing. The criteria for selection of patients for cardiac resynchronization therapy (CRT) is dependent on patient’s symptomatic class, sinus rhythm, conduction delay on the ECG and the demonstration of inter- and intra-ventricular dyssynchrony. Different studies have used different thresholds for QRS duration ranging from more than 150 to more than 120 ms in the COMPANION trial. But a great deal of the problem with QRS duration is that it does not reflect the underlying level of mechanical dyssynchrony.

The way to assess mechanical dyssynchrony can be through M-mode echocardiography on tissue Doppler imaging. Tissue Doppler imaging identifies intraventricular dyssynchrony easily. The following basis has been used in the study by Ghio et al., using Tissue Doppler imaging. Regional pre-ejection period was measured from the beginning of QRS to the beginning of positive component of the regional systolic velocity. Intraventricular dyssynchrony is considered to be present when there is absolute difference of greater than 50 ms between the two segments at basal or at medium level.

In addition, Tissue Doppler helps to identify responders to CRT, better than left bundle branch block in ECG. Mechanical dyssynchrony also identifies higher risk of cardiac events, independent of the QRS width and left ventricular ejection fraction.
Dr Patnaik is correct in pointing out that we must use mechanical criteria before selecting patients for CRT, rather than relying on QRS width. Our study did not look at the mechanical dysynchrony and we only looked at the prevalence of ECG changes in group of patients with heart failure.

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Intraoperative Endocardial Ablation of Chronic Atrial Fibrillation along with Mitral Valve Surgery using High Frequency Ultrasound with a Ball-tipped Harmonic Scalpel Probe

Alternative energy sources for the surgical ablation of chronic atrial fibrillation (AF) have found frequent mention in recently published literature. Their primary aim is to afford a shortcut to replicate Cox Maze III lesions, without going through the rigmarole of its complex cut-and-sew protocol. Such currently available surrogate applications/devices include: (i) Thermaline or Cobra malleable multielectrode surgical ablation system with fluid-cooled and bipolar options (Boston Scientific Corporation, San Jose, California, USA), (ii) the Cardioblate saline-irrigated cooled-tip radiofrequency (RF) ablation pen, also available in an extra length (XL) as well as bipolar design (Medtronic Inc, Minneapolis, Minnesota, USA), (iii) bipolar RF energy, (iv) ordinary unipolar surgical electrocautery, (v) helium or argon-based cryosurgical ablation, (vi) Flex (AFx Inc, Fremont, California, USA)
microwave catheter ablation system, (vii) Optimaze (CardioFocus Inc, Norton, Massachusetts, USA) malleable laser tip surgical ablation system, (viii) IRK-151 (Messerschmidt-Bolkow-Blohn, Germany) infrared energy coagulator, and (ix) ultrasonic waves delivered through a balloon catheter.

We used a new option, high frequency ultrasound with a ball-tipped Harmonic scalpel (Ethicon Endo-Surgery, Cincinnati, Ohio, USA) probe for intraoperative endocardial ablation of chronic AF along with mitral valve procedures in 24 patients. Harmonic scalpel high frequency ultrasonic generator was used for the intraoperative creation of Maze III lesions. For this purpose we obtained a 5 mm ball-tipped coagulator probe (Fig.1) compatible with the generator. Coagulation occurs when the probe, vibrating at 55,000 Hz, couples with protein and denatures it by the process of coaptive coagulation, at relatively low temperatures. The extent of tissue coagulation is easily controlled and can be balanced by varying power, tissue tension, and grip force/pressure. The generator has five power levels for adjustment of the intensity of tissue coagulation. The ultrasonic vibration remains the same at all power levels. It produces less lateral tissue thermal damage and does not involve passage of any electrical energy to or through the patient. The generation of negligible amount of smoke ensures clearer visibility of the lesion lines.

Cardiopulmonary bypass (CPB) was instituted with standard aortic and direct bicaval cannulation. The superior and inferior venae cavae were snugged and the classical right atrial Maze III incisions including excision of the appendage, were executed on a beating heart. The right atrial lesions for RF maze ablation were then applied with the ball-tipped Harmonic probe by suitably adjusting the power level and the duration of application in accordance with the nature and thickness of the tissue.

![Fig. 1. The Harmonic ball-tipped probe.](image)

On completion of the right atrial subset of lesions, the aorta was cross-clamped and an appropriate dose of normothermic blood cardioplegia was infused to arrest the heart. A standard longitudinal left atriotomy was done along the interatrial groove, and thrombi, if any, were evacuated. The left atrial appendage was then amputated at its base. The resultant gap as well as the atriotomy were utilized to apply the Maze-replicating left atrial endocardial lesions with the Harmonic probe. The amputated appendage base was repaired, cold cardioplegia infused and ice-slush put in the pericardial cradle to cool the heart. The core temperature was maintained at around 35°C throughout the procedure, essentially using a ‘warm body and cold heart’ protocol. The mitral valve procedure was then completed, left atriotomy repaired and the aorta unclamped after deairing followed by gradual disconnection from CPB.

Our study group comprised 24 (15 female) patients, aged 26 to 53 (average 35.28) years, suffering from mitral valve disease (stenosis, regurgitation or mixed) with chronic AF (known duration > 6 months), operated upon over an 8-month period. The patients underwent open mitral valvotomy (3 cases, all with left atrial clot) or mitral valve replacement (21 cases including 5 with left atrial clot) along with Harmonic Scalpel AF ablation as described. All our patients could be weaned off CPB without defibrillation. None required pacemaker support although a pacing wire is routinely attached to both right atrium and right ventricle. All patients converted to sinus rhythm on the table. At the end of 12 weeks, 19 (79.2%) patients had sinus rhythm and a regular atrial rhythm was present in the rest. None had AF or flutter. None required pacing at any stage.

In cardiothoracic surgery, the Harmonic Scalpel generator and accessories ordinarily find use in harvesting the internal mammary and radial arteries for myocardial revascularization as well as for lysis of dense adhesions in reoperations. Acquisition of this unit in our institution unfolds the opportunity to harness high frequency ultrasonic energy for the intraoperative creation of Maze III lesions.

Studies on return of atrial transport function, sustenance of sinus rhythm, regression of left atrial size and other parameters to evaluate the efficacy of this technique are on and will constitute the basis of a subsequent detailed report.

**References**


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A Randomized Trial Comparing Myocardial Salvage Achieved by Coronary Stenting versus Balloon Angioplasty in Patients with Acute Myocardial Infarction considered Ineligible for Reperfusion Therapy


Summary

STOP-AMI, a German study, was undertaken to evaluate the role of percutaneous coronary interventions (PCI) in patients with acute myocardial infarction (AMI) who were ineligible for thrombolysis. The patients were considered ineligible for thrombolysis if they had either non-ST segment elevation MI, presented late (>12 hours but <48 hours after onset of symptoms), or if they had any contraindication to thrombolysis. Patients enrolled in the study were randomized to either plain balloon angioplasty (POBA) or coronary stenting. However, coronary stenting was allowed in the POBA group, if the result of balloon angioplasty was considered suboptimal i.e. TIMI flow <3, dissection, significant residual thrombus or residual diameter stenosis ≥50%. Before performing the procedure, patients received an intravenous injection of 1000 MBq 99m Tc sestamibi required for baseline scintigraphic study. Single photon emission computed tomography study was done 6 hours after the injection of radionuclide and follow-up scintigraphy study done at 7–14 days. The primary end point of the study was salvage index (ratio between the degree of myocardial salvage and initial perfusion defect) and the secondary end point was 6 months mortality. Out of 611 patients, 305 were enrolled in stent arm and 306 in POBA arm. The baseline characters were similar in the two groups. Nearly one-third (30.4%) patients in POBA group subsequently required stents. Abciximab was used in 90.3% patients. A salvage index of 0.53 was achieved with PCI, which was comparable in both the arms (stent arm 0.54 v. POBA arm 0.50, p=0.20). At the end of one month, mortality (stent arm 5.6% v. POBA arm 4.9%, p=0.71), target vessel reocclusion rates (stent arm 2%, v. POBA arm 1.3%, p=0.75) and major bleeding (stent arm 1.3%, v. POBA arm 2.0%, p=0.76) were similar in both the groups. During 6-month follow-up, mortality (stent arm 8.2% v. POBA arm 9.2%, p=0.69), combined incidence of death or MI (10.5% in both), CABG (stent arm 2.3% v. POBA arm 2.0%, p=0.77) and repeat PTCA rates (stent arm 8.2% v. POBA arm 10.5%, p=0.34) were also similar. Thus, the authors concluded that patients of AMI, ineligible for thrombolysis may greatly benefit from PCI, but the benefit seems comparable whether a plain balloon angioplasty is done or additional stents are implanted.

Comments

Patients with AMI who are considered ineligible for thrombolysis should logically be considered for primary PCI. If the reason for ineligibility is non-ST elevation MI, where risks of thrombolysis clearly outweigh its benefit, there is a great value in clarifying the underlying coronary anatomy with angiography and then offering angioplasty, if suitable. On the other hand, if reason for ineligibility is late presentation, several trials have shown that benefits of open artery achieved by PCI are sustained even if the procedure is performed within days (time independent) unlike with thrombolysis where the benefit rapidly declines as time of administration increases. Even in patients considered ineligible due to contraindication to thrombolytic therapy, PCI may be better because of more predictable anti-thrombotic response with use of abciximab along with weight-adjusted heparin. Indeed, the present study has shown that use of PCI in these patients leads to a considerably myocardial salvage (salvage index 0.53) with a very acceptable clinical outcome. Another contentious issue has been the role of abciximab and use of stents during these procedures. Certainly, they increase the cost of the procedure, but whether they provide incremental benefit which justifies the cost, has to be established. Theoretically, stents reduce the problem of acute thrombosis and restenosis, but can increase the problem of slow/no re-flow phenomenon. Even in the situation of ST segment elevation AMI, the data is at best controversial. The Stent PAMI trial showed that although stents reduced the rates of ischemia and restenosis, the intermediate term results and the late mortality were actually higher as compared to POBA. On the other hand CADILLAC trial showed that not only the combined end points of death, reinfarction, disabling stroke and target vessel revascularization (TVR) were lower in stent group, but the rates of restenosis and reocclusion of IRA were also lower. This difference may be due to newer generation stents and greater operator experience in the enrolling center. In the present study, however, there was no benefit from the use of stent. However, the primary end point was assessed within 30 days, whereas with most other studies it is assessed at 6 months. Arguably, the benefits of stents increase with time. Another reason of difference could be that even in POBA group, nearly one-third of patients crossed over to receive stents.
Impact of Sirolimus-Eluting Stents on Outcome in Diabetic Patients


Summary

The SIRIUS (SIRolImUS-coated Bx velocity balloon-expandable stent) trial is a randomized double blind trial that compared 1058 patients who had received either a drug (sirolimus)-eluting or a bare metal stent (BMS). The present substudy is an analysis of the diabetic patients which comprised 26% of the whole cohort, to determine the effect of sirolimus-eluting stent (SES) in them compared with non-diabetic patients. Out of these 279 diabetics, 131 patients received SES and 148 received BMS. The SIRIUS trial included symptomatic patients with myocardial ischemia having a single de novo native coronary artery lesion between 15 and 30 mm in length. These patients were randomly assigned to either SES or BMS in a 1:1 double blind manner. The SES contained 140 µg of sirolimus/cm² of stent surface area within a copolymer matrix. The stented patients were followed up at 30 days, and then at 3 monthly intervals. The primary end point was target lesion failure (TVF) that was defined as occurrence of cardiac death, myocardial infarction or target lesion revascularization (TLR). All major adverse cardiac events (MACE) were evaluated in in-hospital, out-of-hospital and at 270 days. There was no difference in in-hospital event rates and early and late stent thrombosis rate between diabetics and non-diabetics, with and without SES. In diabetic patients, MACE at 270 days were 25% with SES compared to 9.2% with BMS (p < 0.001) and 16.5% and 6.5% (p < 0.001) respectively, in non-diabetic patients. Moreover, the primary end point of TVF was significantly reduced with SES compared to BMS in both the groups (diabetics: 27% with BMS v. 12.2% with SMS and non-diabetics: 18.6% v. 7.7% respectively; p < 0.001). This reduction in the primary end point was chiefly due to lower rates of TLR (22.3% with BMS v. 6.9% with SES in diabetics, and 14.1% v. 2.9% respectively in non-diabetics; p < 0.001).

Also the event (TLR and MACE)-free survival rates were better in the diabetic patients with SES compared to BMS. Angiography was performed in 67% of the diabetic patients and 66% of the non-diabetic patients at 8 months. There was significantly less late loss both in-stent and in-segment (including 5 mm proximal and distal margins) and restenosis rates in SES compared to BMS group in both diabetics (17.6% v. 50.5%) and non-diabetics (6% v. 30.7%). Moreover, the pattern of restenosis was predominantly focal with SES in both diabetics (80% of all restenosis) and non-diabetics (94%). The insulin-requiring diabetics (IRD) fared worse even after SES compared to non-insulin-requiring diabetics (NIRD), with high in-segment restenosis rate of 35% in IRD compared to 12.3% in NIRD patients. Those with IRD had no statistically significant benefit in restenosis rates (SES:35% v. BMS:50%), MACE and TLR with SES compared to BMS.

Comments

Diabetes alters the function of endothelial cells, smooth muscle cells and platelets causing an overall arterial dysfunction that translates into a more severe coronary artery disease and up to 4 times increase in the cardiovascular mortality. Outcomes after percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG) are worse in patients with diabetes mellitus. In a recent meta-analysis of 4000 patients, there was a higher restenosis rate of 55% v. 20% in non-diabetics. This higher rate of restenosis is mainly due to increased neo intimal hyperplasia seen in diabetics. The entry of drug-eluting stents has rekindled hopes of effective PCI strategy as these have antiproliferative properties to deal with the menace of an exaggerated intimal response. Several trials with sirolimus-coated stents like the RAVEL, SIRIUS, the NEW SIRIUS, and e-SIRIUS have shown a consistent reduction in the restenosis rates. The diabetic subsets studied in these randomized controlled trials have shown a reduction in the stent late loss (6-8 months) of almost 80% and similar reduction in TLR of around 70%. However, these subsets comprised a small number, for example in RAVEL there were only 19 diabetic patients who received SES and 45 in the NEW SIRIUS. In this substudy of SIRIUS there were 131 diabetics who received an SES compared with 148 who received BMS. There was no difference in the in-hospital MACE and early stent thrombosis between the two groups and overall there was a 63% relative reduction of MACE in diabetic patients compared with a 61% reduction in non-diabetics. Angiographic follow-up revealed that there was a reduction in the incidence of in-segment angiographic restenosis rate in diabetic patients by 65% compared with 80% in non-diabetic patients. Moreover, the restenosis pattern was predominantly focal in SES in both groups, that is, more amenable to repeat PCI. It was seen that the NIRD patients fared much better than IRD patients. In fact, IRD patients receiving SES had an outcome similar to NIRD patients getting BMS. The reason why IRD patients do not benefit much by SES is difficult to pinpoint– these patients may require higher sirolimus dose concentration or balloon-injured portions may need to be covered adequately by the stents. However, only 38 insulin-dependent patients received SES which is too small a number to be certain. This study, it should be remembered, is a non-randomized subset analysis, and randomized large scale trials are required to confirm the findings of this study. The diabetic patients specially NIRD benefit from implantation of SES which is safe, and associated with a lower early as well as late restenosis rate.
Comparison of Intensive and Moderate Lipid Lowering with Statins after Acute Coronary Syndromes

Christopher P Canon et al. PROVE IT - TIMI22 Study N Engl J Med 2004; 305: 1495-1504

Summary
Pravastatin or Atorvastatin Evaluation and Infection Therapy (PROVE IT) trial compared the clinical outcomes of standard regimen of lowering low-density lipoprotein (LDL) cholesterol to 100 mg/dl with 40 mg of pravastatin and intensive regimen of lowering LDL cholesterol to 70 mg/dl with 80 mg of atorvastatin, in patients with acute coronary syndromes. 4162 patients with either acute myocardial infarction (AMI) or unstable angina (USA) in the preceding 10 days, were enrolled at 349 sites in eight countries. Patients had to be in a stable condition with a total cholesterol of ≤240 mg/dl (≤200 mg/dl in case they were already on statin treatment). The patients continued to receive the standard medical treatment, and no other lipid lowering agent was permitted. Eligible patients received 40 mg of pravastatin or 80 mg of atorvastatin daily in a double-blind, double dummy fashion. Patients were followed up at 30 days and then at 4 monthly intervals for 18 to 36 months (average follow-up of 24 months). The primary end point was a composite of death from any cause, AMI, USA requiring hospitalization, revascularization (after 30 days of randomization) and stroke. The study was designed as a time to event study (i.e. time from randomization until the first occurrence of a component of the primary end point) to establish the non-inferiority of pravastatin. The baseline median LDL cholesterol in the two groups was 106 mg/dl, which fell to 95 mg/dl in the standard dose pravastatin group and 62 mg/dl in the high dose atorvastatin group (p<0.001). With 40 mg pravastatin, the mean reduction of LDL cholesterol was minimal in patients who were already on statins while atorvastatin decreased the levels by an additional 32% (p<0.001). In those patients who had not received statin during prior index acute coronary event, the LDL reduction was 22% with pravastatin and 51% with atorvastatin at 30 days (p<0.001). The Kaplan-Meier estimates of rates of primary composite end point at two years were 26.3% in the pravastatin group and 22.4% in the the intensive therapy atorvastatin group, reflecting a reduction in hazard ratio of 16% in favor of atorvastatin (p=0.005). This benefit was seen as early as 30 days and continued thereafter on the follow up. There was a 28% reduction in rate of death from any cause (p=0.06), 14% reduction in the need for revascularization and 29% reduction in the incidence of USA requiring hospitalization (p=0.02). Stroke rate was low and did not differ in two groups. The benefits of intensive lipid lowering were seen in all the pre-specified subgroups, including diabetics, elderly, prior statin user and those with HDL levels below 40 mg/dl. The only subgroup that showed greater benefit was the one with patients having LDL cholesterol of 125 mg/dl at baseline, in which there was a 34% risk reduction for all-cause mortality or major cardiovascular events compared with 7% among patients with baseline LDL cholesterol of <125 mg/dl.

Comments
The Scandinavian Simvastatin Survival Study (4S) published a decade back first confirmed that statins improved survival. The Heart Protection Study, the largest ever statin trial, confirmed the benefit of statins in reducing the incidence of coronary events irrespective of baseline LDL level. This study showed that patients with a baseline LDL cholesterol of 100 mg/dl, the accepted target according to the current NCEP guidelines, benefited as much as those with higher levels. This raised issues like whether more intensive lipid lowering was preferable the currently recommended to and also whether the benefits of statins were solely attributable to their lipid lowering or whether their anti inflammatory and plaque stabilizing property also contribute to their effectiveness. The present trial has shown that among patients with acute coronary syndrome, a more intensive lipid lowering resulted in a lower risk of death, or a major cardiovascular event than does a moderate degree of lipid lowering. The drugs had a good safety profile with rare liver enzyme abnormalities (1.1% with pravastatin v. 3.3% with atorvastatin) and equally uncommon myalgia or creatine kinase elevation (2.7% pravastatin v. 3.3% atorvastatin). Another recent trial, Reversing Atherosclerosis with Aggressive Lipid Lowering using intravascular ultrasound also demonstrated the superiority of 80 mg of atorvastatin over 40 mg of pravastatin in limiting the progression of atherosomatous burden in coronary arteries. Both these trials have demonstrated that the recommended LDL level of 100 mg/dl is not optimal and that atherosclerotic progression and clinical outcomes are further improved by a more aggressive lipid lowering regimen. The question of the mechanism of the beneficial effect – whether it is due to stabilizing the vulnerable plaque and preventing rupture, or due to a generalised anti-inflammatory effect of the drug is still open to debate. It appears logical from the result of this trial to start aggressive statin therapy immediately after acute coronary syndrome and to continue lowering of LDL to levels <100 mg/dl so as to confer further and substantial benefit to such patients.
Calendar of Conferences/CSI Executive Committee

August 28–29, 2004, 6th Annual Conference of the Pediatric Cardiac Society of India, Bangalore, India
Contact: Dr Sunita Maheshwari
Organizing Secretary
e-mail: pcsi2004@yahoo.com

October 31 - November 3, 2004, 6th Asia-Pacific Congress of Cardiovascular and Interventional Radiology, New Delhi, India
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, India
Contact: Dr C N Manjunath, Organizing Secretary
#40, 4th Floor, Lakshmi Complex
Opposite Vasi Vilas Hospital
KR Road, Bangalore-560002
Tel: 9844006659
e-mail: csiblr@vsnl.net
or
Dr PC Manoria, President-Elect
E-5/103, Arera Colony, Bhopal-462016
Tel: 9827074602
Fax: 91-755-2532405
e-mail: pmanoria@hotmail.com

February 18–20, 2005, International Summit on CAD and Cardiovascular Interventions, Mumbai, India
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, India
Contact: Dr Lekha Adik Pathak
Memdil, Linking Road
Santacruz (W), Mumbai-400 034
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e-mail: lekha_p@vsnl.net

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