Aspirin Resistance: Myth or Reality?

Sandeep Singh, SS Kothari, VK Bahl
Department of Cardiology, All India Institute of Medical Sciences, New Delhi

Aspirin is the cornerstone of antiplatelet therapy in cardiovascular medicine. Its role in the secondary prevention of vascular events has been proven beyond any doubt. A recently published meta-analysis of 287 randomized trials of antiplatelet therapy by the Antithrombotic Trialists' Collaboration has shown a significant reduction in the combined end-point of any serious vascular event in a cohort of high-risk patients with atherothrombotic diseases. However, a substantial proportion of patients manifest “breakthrough” events despite regular intake of aspirin. It is estimated that one in eight high-risk patients suffers from the recurrence of a vascular event within the next 2 years despite regular daily aspirin therapy. Also, by using different methods of measuring platelet activity, several studies have demonstrated marked individual variations in the response to treatment with aspirin. Based on the clinical and laboratory evidence of reduced or absent response to treatment with aspirin in some patients, the concept of “aspirin resistance” has emerged, and has caught the attention of both professionals and the mass media.

Is there a Standardized Definition of Aspirin Resistance?

Unfortunately, aspirin resistance remains a poorly defined term. There are conflicting reports on the incidence and clinical relevance of this phenomenon as this term is being used to describe a number of different phenomena. These include the inability of aspirin to either protect individuals from thrombotic complications; or failure to cause prolongation of bleeding time, or inhibit platelet aggregation ex vivo, or inhibit platelet thromboxane formation. Perhaps a clinical definition of aspirin resistance as the failure of the drug to prevent an ischemic event despite regular intake of appropriate doses is the most relevant for practising physicians. It is well known that platelet inhibition is not a uniform process, and considerable inter- and intra-individual variations exist in the antiplatelet effect of aspirin. This mandates functional and biochemical in vitro tests to individualize treatment, and possibly identify the subgroup of patients at risk for future vascular events.

Are Reliable and Reproducible Tests Available to Diagnose Aspirin Resistance?

Traditionally, platelet function has been assessed by measuring platelet aggregation in platelet-rich plasma using an optical aggregometer. This test is widely available, and has been used in many investigational studies. However, it is neither reproducible nor user friendly. Based on this method, 5% and 24% of patients with stable cardiovascular disease on aspirin therapy (325 mg/day for at least a week) were defined as “resistant” and “semi-responders”, respectively.

Recently, simpler and more rapid tests of platelet function have been developed. Whole-blood aggregometry is more user friendly as it eliminates the step of preparing platelet-rich plasma. However, the results of this test have not correlated well with those from optical aggregometry. In clinical practice, PFA-100 (Dade Behring, Deerfield, Illinois) is the most appealing test at present for the assessment of platelet function. It is a semi-automated analyzer developed to allow the rapid assessment of platelet function using whole blood. The results are easily reproducible, and correlate well with the results of optical aggregometry. A nonspecific measure of platelet function is the assessment of bleeding time. Other less extensively studied tests include the platelet aggregate ratio, the platelet reactivity index, and the rapid platelet function assay (RPPA). Recently, urinary 11-dehydrothromboxane B2 levels (a stable metabolite of thromboxane A2 [TxA2]) has been used as a marker of suppression of thromboxane formation with aspirin therapy. Since the levels reflect both platelet and nonplatelet sources of thromboxane generation, this test lacks specificity. Collectively, these techniques identify an inadequate response to aspirin in 5%–60% of patients with various vascular atherothrombotic diseases. It is difficult to assess which of these techniques is the most accurate and specific measure of aspirin resistance, unless the results are supported by direct comparison with the clinical outcome.

Correspondence: Professor VK Bahl, Department of Cardiology, All India Institute of Medical Sciences, New Delhi 110029, India.
e-mail: vkbahl2002@yahoo.com
Can Aspirin Resistance be Classified?

To better understand the mechanisms of aspirin resistance and its therapeutic implications, Weber et al.8 classified aspirin resistance into 3 distinct types using simple biochemical tests, and functional in vitro studies (Table 1). In aspirin responders, an oral intake of 100 mg/day of aspirin for 5 days resulted in more than 95% inhibition of thromboxane synthesis, and also in the inhibition of collagen-induced platelet aggregation measured in vitro. In “type I resistance” (pharmacokinetic type), there was no inhibition of either thromboxane synthesis or collagen-induced platelet aggregation with oral aspirin intake for 5 days. However, both these parameters were remarkably altered by the in vitro addition of 100 µm of aspirin in the platelet-rich plasma. This suggests that there may be considerable variation in pharmacokinetics with low-dose aspirin. In “type II resistance” (pharmacodynamic type), both the platelet functions were altered neither by the oral intake of aspirin, nor by the in vitro addition of 100 µm of aspirin. The mechanism of this type of resistance is unclear but may relate to genetic polymorphism of the enzymatic pathway, and its sensitivity to aspirin. In “type III resistance” (pseudoresistance), oral treatment resulted in the inhibition of thromboxane synthesis. However, this was not accompanied by the expected inhibition of platelet aggregation in response to collagen. The lack of effect of platelet aggregation in response to collagen despite thromboxane synthesis was not corrected by the addition of aspirin in vitro. This is labeled as pseudoresistance, since aspirin did exert its putative effect of inhibition of platelet thromboxane synthesis but failed to alter another important in vitro antiplatelet effect. Perhaps, in some patients with aspirin resistance, there is increased sensitivity of platelets to collagen.14 The clinical relevance of this variant is not clear. Whether this alteration as measured under artificial in vitro conditions will reflect an impaired antithrombotic effect of aspirin in vivo is not known.14 It is proposed that patients with type I resistance may benefit from increasing the dose of aspirin. In addition, patients with types II and III resistance may benefit from other antiplatelet drugs. However, the clinical significance of this classification has not been tested yet. Only prospective follow-up studies in patients with aspirin resistance, and their clinical correlation, can effectively resolve this issue.

Does Aspirin Resistance have any Clinical Significance?

A few long-term follow-up clinical studies have suggested that aspirin resistance is indeed clinically important13,15–18 (Table 2). Grotemeyer et al.,15 in a cohort of 180 patients with stroke, found that nearly 30% of patients were aspirin nonresponders. At a follow-up of 2 years, major clinical vascular end-points were significantly higher in this group as compared to aspirin responders (40% vs. 4.4%, p<0.0001). Similarly, in 100 patients undergoing peripheral balloon angioplasty, Mueller et al.16 reported an 87% higher risk of reocclusion on follow-up in patients who failed to show an appropriate response to aspirin. Grundmann et al.17 found that an aspirin nonresponder status was seen in 34% of patients with recurrent cerebrovascular ischemic events, despite regular use of aspirin for more than 60 months.

Two recently published studies have highlighted adverse outcomes with aspirin resistance in a larger cohort of patients, and after a longer follow-up period. Eikelboom et al.,13 in a subgroup analysis from the population of the Heart Outcomes Prevention Evaluation (HOPE) trial, reported higher adverse outcomes at a follow-up of 5 years in patients showing aspirin resistance. Urinary

<table>
<thead>
<tr>
<th>Table 1. Typological classification of aspirin resistance*</th>
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<tbody>
<tr>
<td>Oral aspirin treatment (100 mg/day, 5 days)</td>
</tr>
<tr>
<td>Platelet thromboxane inhibition</td>
</tr>
<tr>
<td>Aspirin responders</td>
</tr>
<tr>
<td>Type I resistance (pharmacokinetic)</td>
</tr>
<tr>
<td>Type II resistance (pharmacodynamic)</td>
</tr>
<tr>
<td>Type III resistance (pseudoresistance)</td>
</tr>
<tr>
<td>Addition of in vitro aspirin (100 µm)</td>
</tr>
<tr>
<td>Platelet thromboxane inhibition</td>
</tr>
<tr>
<td>Aspirin responders</td>
</tr>
<tr>
<td>Type I resistance (pharmacokinetic)</td>
</tr>
<tr>
<td>Type II resistance (pharmacodynamic)</td>
</tr>
<tr>
<td>Type III resistance (pseudoresistance)</td>
</tr>
<tr>
<td>*Adapted from Weber et al.8</td>
</tr>
</tbody>
</table>


concentration of 11-dehydrothromboxane B₂ was measured as a marker of in vivo thromboxane generation. The adjusted odds for the composite end-point of myocardial infarction (MI), stroke or vascular death increased with each increasing quartile of 11-dehydrothromboxane B₂ levels. Patients in the highest quartile (indicating incomplete suppression of TxA₂, and thereby aspirin resistance) had a 1.8-fold higher risk of composite end-points than those in the lowest quartile. Similarly, there was a 2-times higher risk of MI and 3.5-times higher risk of cardiovascular death in the groups, respectively. This strong and graded association of adverse outcome, and laboratory evidence of aspirin resistance, was independent of conventional risk factors for atherothrombotic vascular diseases. Gum et al. highlighted the natural history of aspirin resistance among stable patients with cardiovascular disease over a mean follow-up period of 679 ± 185 days. In this prospective, blinded study of 326 patients, aspirin resistance was associated with a significantly increased risk of composite end-points of death, MI or cerebrovascular accident (CVA) as compared to aspirin-responsive patients (24% v. 10%, respectively; p = 0.03, hazard ratio 3.12). Stratified multivariate analysis showed aspirin resistance to be a significant independent predictor of long-term major adverse outcome. However, the laboratory markers of aspirin resistance were assessed only at baseline, and it is well known that the efficacy of aspirin, as judged by laboratory tests, shows temporal and biological variations. Despite this limitation, it appears from the results of these studies that a substantial number of patients may not be obtaining the intended antiplatelet effects of daily aspirin therapy.

What are the Possible Mechanisms of Aspirin Resistance?

Aspirin blocks the formation of TxA₂, a potent vasoconstrictor and platelet agonist by irreversibly inhibiting the enzyme platelet cyclo-oxygenase (COX). COX has two isoforms of clinical relevance; COX-1 isoenzyme is expressed in mature human platelets. The therapeutic efficacy of aspirin in atherothrombotic vascular disease has been clearly attributed to its inhibition of COX-1 activity. Importantly, in the low doses necessary to achieve platelet inhibition, aspirin does not inhibit endothelial cell prostaglandin synthesis, particularly prostacyclin I₂, which is a potent vasodilator. COX-2 isoenzyme plays a dominant role in the processes of inflammation and cancer. Aspirin acts as an anti-inflammatory agent due to the inhibition of COX-2 activity at higher doses. Although much is currently known about effect of aspirin on platelets, the mechanism by which some patients are resistant to this effect has not been clearly established.

Extrinsic factors: Several extrinsic factors can modify the ability of aspirin to inactivate platelets. Smoking, higher lipid levels, and conditions associated with an increased platelet turnover have been shown to influence the antiplatelet effect of aspirin. Although low-dose aspirin is expected to inhibit COX-1 completely, some patients may
require higher doses to achieve the desired antiplatelet effect. In patients with stroke, Helgason et al.\(^5\) reported the effect of dose escalation of aspirin in nonresponders as judged by aggregation studies. An initial 25% incidence of aspirin resistance (daily dose 325 mg) fell to 8% with dose escalation up to 1300 mg. However, a recently published meta-analysis does not support this contention, and it may not be practical in many patients due to gastrointestinal side-effects.\(^1\)

Certain drug interactions, especially with non-steroidal anti-inflammatory drugs (NSAIDs), may play a role in secondary aspirin resistance. Both aspirin and NSAIDs are very commonly prescribed drugs, and it seems likely that many patients may be taking both chronically. There is a likelihood of competitive interaction between these drugs, as both act by inhibiting the COX enzyme. However, unlike aspirin, NSAIDs are reversible inhibitors of this enzyme. It has been shown that NSAIDs (e.g. ibuprofen) block the long-lasting antiplatelet effect of aspirin, leading to modulation of its cardioprotective effect, and may even lead to secondary aspirin resistance in patients who are aspirin responders initially.\(^2\),\(^3\) This is due to the competitive inhibition of the active site within the COX-1 channel by an NSAID, thereby impeding access of aspirin to its target.\(^2\) Also, there is now evidence of unfavorable long-term clinical outcomes resulting from this drug interaction.\(^2\),\(^7\)\(^–\)\(^10\) MacDonald and Wei\(^2\) recently reported a cohort of patients on secondary prophylaxis with aspirin, and highlighted that concomitant administration of ibuprofen was associated with a significant increase in the all-cause mortality as well as cardiovascular mortality on long-term follow-up. The absence of COX-2 in mature human platelets explains why selective COX-2 inhibitors (coxibs) do not inhibit the effects of low-dose aspirin on platelet function in comparison with ibuprofen.\(^2\),\(^7\)\(^–\)\(^9\) These drugs would logically seem preferable to ibuprofen when patients taking aspirin for cardioprotectiveness require chronic treatment with NSAIDs.

**Intrinsic factors:** There are several proposed intrinsic mechanisms resulting in aspirin resistance. The pivotal role in the pathogenesis of aspirin resistance is played by the failure of to adequately suppress TxA\(_2\) synthesis despite therapy.\(^1\),\(^11\) Although aspirin inhibits COX-1 nearly 170 times more potently than COX-2, the latter isoenzyme has been implicated in the genesis of aspirin resistance.\(^10\) For a long time it has been believed that mature platelets contain only COX-1 isoenzyme. However, recent evidence, though still controversial, has shown that platelets do contain COX-2 mRNA.\(^12\),\(^13\) The degree of COX-2 expression varies among patients, and certain patients may have higher levels of COX-2 expression, especially during stress.\(^4\),\(^12\) Since low-dose aspirin is ineffective in inhibiting the COX-2 enzyme, this mechanism could provide an alternate pathway for platelet-mediated thromboxane production in patients treated with aspirin, and may result in aspirin resistance.

Besides platelets, the nucleated cells (monocytes/macrophages) have also been implicated in the mechanisms of aspirin resistance. These cells are also rich sources of TxA\(_2\), ranking behind platelets in the potential for synthetic capability.\(^11\) However, compared to anucleate platelets, these cells have the capacity to regenerate the enzyme. This regenerated, uninhibited COX-1 in nucleated cells produces prostaglandins which are shunted to the platelets, bypassing platelet COX-1 for the production of aspirin-insensitive/resistant thromboxane. In addition to COX-1-mediated generation, these nucleated cells can also synthesize their own TxA\(_2\) through COX-2, which remains uninhibited at low doses of aspirin.\(^7\),\(^11\) Unlike COX-1, which is constitutively expressed, COX-2 expression in nucleated cells is augmented 10–20-fold by inflammatory stimuli.\(^7\),\(^11\) The TxA\(_2\) synthesized by these nucleated cells may in turn activate platelets, thereby initiating a chain reaction.\(^11\) Upregulation of COX-2 has been demonstrated in atherosclerotic tissue. The macrophages residing in the atherosclerotic plaque may significantly contribute to the pool of TxA\(_2\) that is not inhibited by low doses of aspirin, potentially leading to aspirin resistance and acute coronary syndromes. Even erythrocytes have been shown to be prothrombotic and to enhance platelet reactivity. This cell-to-cell interaction is not consistently blocked by aspirin in all patients, and may provide an alternative pathway for thrombus formation.\(^14\)

Genetic differences may also be responsible for the variable effect of aspirin in different patients. First, polymorphism or mutations of the COX-1 gene makes, which it relatively resistant to the action of aspirin may provide a molecular basis for aspirin resistance. There is a possibility that single nucleotide polymorphisms (SNPs) of COX-1 exist, and affect the sensitivity of the individual to the inhibitory action of aspirin.\(^3\) SNPs are believed to be the mediators of phenotypic variation and form the genetic basis for the altered response of a drug. Secondly, genetic differences in the glycoprotein IIb/IIIa receptor complex may also be responsible for the varying effect of aspirin in different patients. The glycoprotein IIb/IIIa receptor is the final common pathway for platelet activation. A frequent polymorphism involving Leu33 to Pro substitution defines P1A\(_1\) and P1A\(_2\) alleles, respectively. Although the evidence is conflicting, most studies indicate that P1A\(_1\) carriers not only have enhanced platelet activation by agonists but are
also less responsive to the antithrombotic effects of aspirin. However, it is not well known at present to what extent these actions of aspirin influenced by glycoprotein IIb/IIIa polymorphism contribute to the clinical efficacy of this drug and to resistance to its actions.4,10

How should Aspirin Resistance be Managed?

There are no specific treatment guidelines once aspirin resistance is diagnosed. Certain strategies may help reduce the risk of thrombotic complications in the presence of possible aspirin resistance. Assessing a patient’s compliance, and the appropriate dose of the drug, are simple and important initial measures. The optimal dose of aspirin has been controversial in the past. There is no convincing evidence that the antithrombotic effect of aspirin is dose related.11 In a recent meta-analysis, high doses of aspirin (500–1500 mg/day) were found to be no more effective than low doses (75–150 mg/day) for a reduction in the incidence of vascular events in high-risk patients.1 High-dose aspirin may also be associated with a higher incidence of potential side-effects, and therefore may not be practical. As newer agents that work by different mechanisms are now available, one must explore how these agents can be best used to maximize the benefit from antiplatelet therapy. Unlike aspirin, clopidogrel inhibits platelet aggregation via the ADP receptors, and therefore may represent an important therapeutic alternative for patients with aspirin resistance. In fact, recent trials have demonstrated the superior clinical benefit of clopidogrel, and the combination of clopidogrel with aspirin compared with aspirin alone.15–17 These studies make it apparent that alternative antiplatelet agents will play a significant role in the treatment of cardiovascular diseases. It is possible that the clinical benefits of clopidogrel, and other agents similar to it, would be even more pronounced in patients who are aspirin resistant.18 However, it is not clear whether the superiority of a combination of clopidogrel and aspirin over aspirin is due to clopidogrel compensating for aspirin nonresponders.17 Interestingly, resistance to the effects of clopidogrel with an adverse clinical outcome has been reported recently.18,19 So, should a combination of antiplatelet therapy be accepted in every high-risk patient for secondary prophylaxis to reduce vascular events? The answer to this question is not clear yet, as the implications of this will be significant in terms of side-effects and cost, especially in developing countries.40 The combination of aspirin plus clopidogrel versus aspirin alone in both secondary prevention and high-risk primary prevention is being studied in the ongoing CHARISMA (Clopidogrel for High Atherothrombic Risk and Ischemic Stabilization Management and Avoidance) trial.41

What are the Future Implications?

Platelet COX-1 has long been an accepted target for aspirin therapy because of the synthesis of large quantities of TxA2, and its pivotal role in the pathogenesis of acute cardiovascular syndromes. Perhaps it is now time to consider COX-2 as an additional target for treatment since it is also a rich source of TxA2. Evidence is beginning to accumulate that COX-2 may be an important contributory factor in plaque instability and rupture. However, selective COX-2 inhibition without concomitant low-dose aspirin in patients requiring secondary prophylaxis may be associated with an increased risk of an acute cardiac event.31 This thrombogenic effect of coxibs, though controversial, has been attributed to reduced PGI2 synthesis in the face of unopposed TxA2 production, thereby necessitating adjuvant aspirin therapy. Another potential target that needs to be considered is the platelet TxA2 (TP) receptor. These receptor antagonists have a potential advantage over aspirin since several eicosanoids, including nonenzymatically synthesized isoprostanoids, which have a potential role in atherovascular diseases, act by stimulating the TP receptors. Besides platelets, the monocytes/macrophages also manifest these receptors. Therefore, TP receptor antagonists may have a significant therapeutic benefit in preventing not only the progression of atherosclerosis but also acute cardiovascular events associated with it. Perhaps the ideal future therapeutic approach might be a combination of a TP receptor antagonist and a selective COX-2 inhibitor.31

Unanswered Questions

There is strong evidence now that a substantial number of patients fail to show the anticipated response to aspirin therapy, and that the phenomenon of aspirin resistance does exist. Still, several questions remain unanswered at present. The target population that needs screening remains unidentified. Racial variation in aspirin resistance remains unknown. The quantum of clinical benefits that could accrue with the diagnosis of aspirin resistance remains to be quantified. These questions appear clinically important, and the answers will be forthcoming in the future. Despite the known limitations of aspirin, at present, the appropriate use of this simple, inexpensive drug is unlikely to be replaced as a first-line antiplatelet agent.
References


Stress Echocardiography for the Diagnosis of Coronary Artery Disease

Eugenio Picano
Istituto di Fisiologia Clinica, CNR, Pisa, Italy

In patients with known or suspected coronary artery disease (CAD), diagnosis and risk stratification can be aided by noninvasive tests for myocardial ischemia. The scientific use of stress echocardiography started twenty years ago and, for at least a decade, it has been considered a method of established usefulness. Guidelines for choosing from the different stress testing approaches have been published, but the use of these tests by physicians varies widely according to the diagnostic yield, cost, and convenience.

Some general principles should be considered before choosing a test. First, no single test or strategy has proven to be superior in all respects. Second, all published research has consistently shown that stress testing with radionuclide scintigraphy and echocardiography provides more information than exercise electrocardiography alone. However, the fact that a test provides more information does not mean that it is the most appropriate one. Other important issues to be considered include whether the additional information is sufficient to change patient care in ways that would be expected to improve outcome.

Third, regardless of which test is used, a normal test result should never be considered a guarantee that the patient does not have CAD or is at no risk of developing cardiovascular events. The rational diagnostic approach can be divided into four successive steps, progressing from the clinical picture to an exercise ECG, and then to an imaging stress test; in highly selected cases, testing for coronary vasospasm can be considered.

Step 1: Clinical Picture
A simple ECG and resting echocardiography can integrate the clinical picture sufficiently to identify patients with a higher probability of severe disease warranting coronary angiography. In such patients, the good cardiologist needs hardly any help to identify patients who need coronary angiography. Patients who should be referred directly for coronary angiography include those with myocardial infarction (MI) associated with ischemic, mechanical, or arrhythmic complications (such patients should be referred early after the MI), patients with unstable angina not alleviated by maximal therapy, or those with malignant arrhythmias associated with spontaneous episodes. The guidelines from the American College of Cardiology and American Heart Association consistently indicate exercise ECG as the appropriate first test in the initial assessment of a patient with known or suspected stable CAD who is capable of exercising and has an interpretable baseline ECG. Exercise ECG is of little diagnostic value in patients with particular ECG abnormalities at rest, including left bundle branch block (LBBB), electronically paced ventricular rhythm, and ST segment depression >1 mm. In such patients, and in patients who are...

Table 1. Indications for the use of stress imaging rather than exercise electrocardiography

<table>
<thead>
<tr>
<th>Coronary angiography first</th>
<th>EET first</th>
<th>Stress imaging first (rather than exercise electrocardiography)</th>
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<tbody>
<tr>
<td>Complicated myocardial infarction</td>
<td>After uncomplicated myocardial infarction</td>
<td>Complete LBBB</td>
</tr>
<tr>
<td>Unstable coronary syndromes after maximal therapy</td>
<td>Stable chest pain syndrome</td>
<td>Electronically paced ventricular rhythm</td>
</tr>
<tr>
<td>Aborted sudden death, etc.</td>
<td>Capability of exercising</td>
<td>More than 1 mm ST segment depression on resting ECG</td>
</tr>
<tr>
<td></td>
<td>No contraindications to exercise testing</td>
<td>Unable to exercise</td>
</tr>
<tr>
<td></td>
<td>Interpretable ECG</td>
<td>Poor left ventricular function if viability is critical</td>
</tr>
</tbody>
</table>

Source: Modified and adapted from the guidelines developed by the American College of Cardiology, the American Heart Association, the American College of Physicians, and the American Society of Internal Medicine.

ECG: electrocardiography; LBBB: left bundle branch block; EET: exercise electrocardiography test

Correspondence: Dr Eugenio Picano, Istituto di Fisiologia Clinica, CNR, Via Moruzzi 1, 56123 Pisa, Italy, e-mail: picano@ifc.cnr.it
unable to exercise, and/or have poor left ventricular function if viability is critical, noninvasive testing with some form of imaging is indicated by default.5

**Step 2: Exercise ECG Stress Test**

High feasibility, excellent safety record, ease of application, and low cost make exercise ECG a first-line tool for screening patients with known or suspected CAD. The likelihood of precipitating acute MI or death while conducting this test is about 1 in 2500.6 Compared to stress echocardiography and stress single-photon emission computed tomography (SPECT), the cost of exercise ECG is at least two and five times lower, respectively.7 In addition, exercise ECG provides information not only on the coronary reserve, but also on cardiovascular efficiency (i.e., the way in which the coronary reserve can be translated into external work). Both these variables (coronary reserve and cardiovascular efficiency) concur in determining exercise tolerance and, therefore, the quality of life.8 A negative exercise ECG is associated with a 99.3% survival at 5 years’ follow-up in patients with normal resting function.9 Survival is only slightly lower in patients with previous MI. It is hard to believe that one can improve on this extraordinarily good prognosis with any form of intervention. Therefore, in a patient capable of adequate physical effort and with an interpretable ECG, exercise ECG should be the first step in the diagnostic sequence: in a patient showing negativity for both ECG criteria and chest pain at a maximal load, exercise ECG should also be the last step (Fig. 1). Exercise ECG can also show a high-risk response (Fig. 1), which includes at least one of the following findings:10 (i) early positivity (with an exercise time of <4 min); (ii) prolonged positivity with slow recovery (>8 min); (iii) marked positivity (>3 mm of ST segment depression or ST segment elevation in the absence of resting Q waves); (iv) global ST segment changes; (v) associated hypotension that may indicate either left main or advanced triple-vessel CAD over underlying left ventricular dysfunction; and (vi) reproducible malignant arrhythmias. In patients with these or other markers of adverse prognosis, angiography is warranted without further imaging tests (Fig. 1).

**Step 3: Stress Imaging Testing**

Exercise ECG positivity at an intermediate-to-high load, negativity at a submaximal workload, or negativity in the presence of chest pain warrants a stress echocardiography test. The latter should establish the diagnosis of ischemia with a higher reliability, and should define its extent and severity. A negative stress echocardiography test makes the presence of a prognostically important organic CAD unlikely. The excellent outcome associated with this response does not support the decision to proceed with coronary angiography.

A positive stress echocardiography test identifies the group of patients at higher risk, in whom coronary angiography is warranted (Fig. 1). However, stress echocardiography positivity should be titrated, as the associated risk of mortality may range between 2% and 20% per year, depending on the time, space, extent, severity, recovery of inducible wall motion abnormalities, and concomitant therapy at the time of testing (Table 2).

While choosing an imaging technique,7 stress echocardiography should be preferred for logistic and economic reasons.7 In fact, guidelines now accept that the information provided by perfusion scintigraphy and stress

![Fig. 1. Flowchart showing the stage at which the patient should be considered for coronary angiography.](image)

Table 2. Stress echocardiography risk titration

<table>
<thead>
<tr>
<th>Risk</th>
<th>Low (2% per year)</th>
<th>High (20% per year)</th>
</tr>
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<tbody>
<tr>
<td>Dose/workload</td>
<td>High</td>
<td>Low</td>
</tr>
<tr>
<td>Resting EF</td>
<td>&gt;50%</td>
<td>&lt;40%</td>
</tr>
<tr>
<td>Anti-ischemic therapy</td>
<td>Off</td>
<td>On</td>
</tr>
<tr>
<td>Coronary territory</td>
<td>LCx/RCA</td>
<td>LAD</td>
</tr>
<tr>
<td>Peak WMSI</td>
<td>Low</td>
<td>High</td>
</tr>
<tr>
<td>Recovery</td>
<td>Fast</td>
<td>Slow</td>
</tr>
<tr>
<td>Positivity of baseline</td>
<td>Homozonal</td>
<td>Heterozonal</td>
</tr>
<tr>
<td>Dyssynergy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ESV increase peak stress</td>
<td>No</td>
<td>Year</td>
</tr>
</tbody>
</table>

ESV: end-systolic volume; EF: ejection fraction; LCx: left circumflex artery; RCA: right coronary artery; LAD: left anterior descending artery
Instead of a pharmacologic stress echocardiogram, it may be wise to choose an exercise echocardiogram in patients with an ambiguous positive result during exercise ECG at a workload of \( \leq 6 \) min. Such a patient (typically, a middle-aged hypertensive woman with ST segment depression at a peak rate pressure product below 20 000) may have either angiographically normal or severely diseased coronary arteries. Exercise echocardiography has the advantage of being the safest test besides being highly feasible and less technically demanding for low levels of exercise.

### Step 4: Testing for Vasospasm

The possibility of testing for coronary vasospasm should be considered only after complete negativity of maximal exercise stress testing or imaging stress testing at the end of the diagnostic evaluation. Testing for vasospasm is the

### Table 3. Stress echocardiography: which test for which patient

<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th>Exercise</th>
<th>Dipyridamole</th>
<th>Dobutamine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inability to exercise</td>
<td>3</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Contraindication to exercise</td>
<td>3</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Positive EET at ( \leq 6 ) min of exercise in hypertensives, women, those with baseline ECG changes</td>
<td>1</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Asthmatic patient</td>
<td>2</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Under theophylline therapy</td>
<td>1</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Severe hypertension</td>
<td>3</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Well-controlled hypertension</td>
<td>2</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Relative hypotension</td>
<td>1</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Ventricular ectopy</td>
<td>1</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>2nd–3rd degree AV block</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Suboptimal acoustic window</td>
<td>3</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Evaluation of anti-ischemic therapy efficacy</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Unstable carotid disease</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Permanent pacemaker</td>
<td>Pacemaker stress echocardiography</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1: especially indicated; 2: relatively contraindicated; 3: contraindicated; EET: exercise electrocardiographic test; AV: atrioventricular
last resort if chest pain is present and a coronary origin is sought. Before angiography, coronary vasospasm can be suspected in patients with angina at rest, particularly at night or in the early morning, and good or extremely variable effort tolerance. After angiography, the suspicion of spasm should be raised if the coronary arteries are normal or mildly diseased, “paradoxically” in conflict with severe ischemia (Fig. 3).

Clinically, the suspicion of vasospasm is also high in patients with syncopal angina11–14 or aborted sudden death.15,16 In susceptible patients, coronary vasospasm can be triggered by noncardiological medications, such as the chemotherapeutic agent 5-fluorouracil in patients with cancer,17–19 or sumatriptan in those with migraine,20,21 or bromocriptine, which is also given for coronary vasospasm. EET: exercise electrocardiographic test.

Fig. 3. Flowchart showing the stage at which the patient should be considered for coronary vasospasm. EET: exercise electrocardiographic test.
Tuberculous pericardial effusion usually presents as a slowly progressive febrile illness. When it presents as acute pericarditis or cardiac tamponade, the diagnosis is more likely to be delayed or missed.\(^1\)\(^2\) With specific anti-tuberculous therapy, the prognosis is excellent.\(^1\) Confirmation of the tuberculous etiology currently depends on: histopathologic study of the pericardium or other tissue; demonstration of acid-fast bacilli in the pericardial tissue; culture of *Mycobacterium tuberculosis* (MT) from pericardial tissue or fluid; the presence of tuberculosis elsewhere in the body;\(^1\) or response to a specific treatment.\(^3\)

The spread of tuberculosis to the pericardium resulting in an effusion is most often from the mediastinal glands.\(^6\) Characteristically, in tuberculous adenitis the lymph nodes have a soft caseating center, seen as hypodense central areas on computed tomography (CT) studies;\(^7\) often, there is coalescence of the adjacent glands, resulting in “matting”.\(^8\) Gland enlargement regresses or clears with specific treatment.\(^9\) There have been no systematic studies of mediastinal lymph glands in tuberculous pericardial effusion, even though tuberculous mediastinal glands found at autopsy have been reported.\(^1\) In a review of consecutive autopsies in 1956, 275 cases with tuberculosis, of which 7 had pericarditis, were reported. The authors concluded that caseous mediastinal lymph glands were the usual focus for pericardial involvement.\(^10\) We, therefore, planned a prospective study using chest CT for the detection and follow-up of mediastinal lymph glands in patients with proven tuberculous pericardial effusion. We also

**Background:** Tuberculous pericardial effusion is most often due to the spread of tuberculosis from the mediastinal lymph glands; however, no attempt has yet been made to study these glands. We studied the mediastinal glands in proven tuberculous pericardial effusion patients and hypothesized that the findings may be of use in the etiological diagnosis of pericardial effusion.

**Methods and Results:** We studied 45 patients with large pericardial effusion or tamponade. All underwent chest computed tomographic studies that were reviewed by radiologists blinded to the diagnosis. Of these 45 patients, 27 had tuberculosis and 18 had viral or idiopathic effusion. Pericardial biopsy was done in 25/27 and tuberculin skin test in 22/27 patients with tuberculosis, and all received specific treatment. In patients with tuberculosis the skin test measured 17±3.3 mm. All 27 had mediastinal lymph glands ≥10 mm in size. The mean size of the mediastinal glands was 19.5±8.6 mm and the mean number was 2.5±1.2. The aortopulmonary glands were the most frequently enlarged (63%), and hilar the least often (14.8%). The glands showed a hypodense center in 52% of the patients. On follow-up of 15.8±10.4 months, glands were not seen in 80.9%, and were smaller in size in 19%; none had a hypodense center. Marked lymphadenopathy was not seen in any patient with viral/idiopathic pericardial effusion. Two had glands ≤5 mm in size.

**Conclusions:** Only patients with tuberculosis had substantial mediastinal lymph gland enlargement and not those with viral or idiopathic pericardial effusion. Such glands disappeared or regressed on treatment. In the appropriate clinical context, marked nonhilar mediastinal lymphadenopathy on chest computed tomographic studies along with a strongly positive tuberculin skin test could be of value in the noninvasive diagnosis of pericardial effusion due to tuberculosis. (Indian Heart J 2003; 55: 228–233)

**Key Words:** Mediastinal lymph glands, Pericardial effusion, Tuberculosis
hypothesized that the findings may be of value in the etiologic diagnosis of pericardial effusion. Patients with viral/idiopathic pericardial effusion served as controls.

**Methods**

Patients with large pericardial effusion (sum of anterior and posterior echo-free space >20 mm) or suspected to have cardiac tamponade were transferred to our tertiary care centre. Echocardiographic examination, if done earlier, was repeated. Cardiac tamponade was diagnosed when there was right ventricular diastolic collapse or right atrial compression lasting more than one-third of the cardiac cycle on M mode and two-dimensional echocardiography, or an inspiratory decrease in mitral and aortic flow velocities in the range of 40%, with a reciprocal inspiratory increase in flow velocities across the tricuspid and pulmonary valves.11

After a full clinical evaluation, urgent or deferred pericardial aspiration was performed to our tertiary care centre. The technique used has been described in detail earlier.12,13 A biopsy could not be taken in the viral/idiopathic pericardial effusion group when there was no pericardial thickening. The pericardial fluid was analyzed for protein and lactic dehydrogenase, and for culture for MT. Each biopsy consisted of 4–8 pieces of tissue. The tissue was processed for culture and histopathologic examination using special stains. A definitive diagnosis of tuberculous pericardial effusion was made, based on the presence of necrotizing granuloma and demonstrable acid-fast bacilli. In the absence of acid-fast bacilli, a presumptive diagnosis of tuberculous pericarditis was suggested.

Chest X-rays were studied, particularly for the presence of enlarged lymph glands, evidence of tuberculosis, and pleural effusion. After pericardial aspiration, a chest CT examination was done after a few days, since it had to be done at the radiology department of another hospital. The CT scans were interpreted by radiologists (JMC, RMH) blinded to the diagnosis. One or more chest CT studies were repeated during the follow-up. These were performed using a Sytec 3000 GE machine. An initial pre-contrast study was done with 10 mm thick slices at 10 mm intervals from the apex. Then, 100 ml of nonionic contrast (Iohexol–Omnipaque 300, Nycomed) was injected as a bolus through a cannula and the study repeated. Particular attention was paid to the appearance of the pericardium. Lymph glands, when seen, were studied for their site/s, size, hypodense central areas, coalescence or matting of adjacent glands, and the presence or absence of calcification. When individual glands could not be clearly separated, the size of the group was measured. Otherwise, the largest size was noted in either the transverse or anteroposterior axis. Lung fields were studied for any infiltration, fibrosis, cavitation or calcification.

All patients suspected to have tuberculous pericardial effusion underwent a tuberculin skin test (purified protein derivative) before discharge from the hospital and the area of induration was recorded in millimeters. This was inadvertently not done in the other groups.

The diagnosis of tuberculous pericardial effusion was based on the demonstration of characteristic tuberculous granulomata in the pericardium or other tissue, with or without acid-fast bacilli; culture of MT from the pericardial tissue or pericardial fluid; or the presence of a tuberculous focus on the chest X-ray or chest CT scan.4,5 The diagnosis of viral pericardial effusion was based on the clinical picture, and the presence of a raised viral antibody titer. When the antibody titer was not raised, a diagnosis of idiopathic pericardial effusion was made. Viral and idiopathic pericardial effusion were grouped together for analysis.5

There are numerous classifications for the mediastinal lymph nodes. We have used a simplified grouping that corresponds to the findings on conventional chest CT scans.14,15 This grouping includes the internal mammary, paratracheal, aortopulmonary, hilar, subcarinal, posterior mediastinal, and paracardiac glands. On chest CT scan, lymph glands are seen as oval or round structures, with or without central or eccentric radiolucent fat. As per convention, glands that were 10 mm or more in size were considered to be enlarged.15 On follow-up, normal glands did not change in size.

This study included 45 patients. None were seropositive for human immunodeficiency virus. Only those patients in whom pericardial aspiration was performed and chest CT scan was done were included in the study. None of the patients with these criteria were excluded. There were 16 males and 11 females, 16–70 years of age (mean 36.4±12.8 years). History of contact with tuberculosis was present in 6 patients (22.2%).

**Statistical analysis:** SPSS 10.0 (Chicago, Illinois) and Instat (Graph Pad Software, San Diego) were used for statistical analysis. Student’s t test or Fisher’s exact test was used to compare variables. The McNemar test was used to compare the results before and after treatment, and p values ≤0.05 were considered significant.

**Results**

**Tuberculous pericardial effusion:** Pericardial rub was
heard in 51.8% of patients. Peripheral lymph gland involvement (axillary, not those from which a biopsy was taken) was present in 2 patients, and 19 (70.3%) presented with cardiac tamponade.

The mean cardiothoracic ratio was 62.2%±7.9%. Pulmonary lesions consistent with tuberculosis were found in the chest X-ray or chest CT scan of 6 patients. The amount of fluid at first aspiration ranged from 150 to 1500 ml (mean 584±352.2 ml). Analysis showed the protein content to be 53.4±9.8 g/L, and lactic dehydrogenase 989±640.7 units. *Mycobacterium tuberculosis* was cultured from the pericardial fluid or tissue in 8/25 patients (32%).

The tuberculin skin test was done in 22 patients. Induration ranged from 9 to 22 mm (17±3.3 mm).

**Diagnosis of tuberculous pericardial effusion:** A diagnosis of tuberculosis was made in 23 patients from the biopsy specimens (22 pericardial, 1 pleural). Twelve of them had tuberculous granulomata with acid-fast bacilli, and 11 had similar granulomata without demonstrable bacilli. Two other patients had nonspecific findings on biopsy; in one of them MT was cultured from the pericardial fluid. Three patients were presumptively diagnosed from the associated pulmonary tuberculosis. All the 27 patients also responded to anti-tuberculous therapy.

**Chest CT scan:** Chest CT scan was performed in all the 27 patients. Pericardial thickness ranged from 2 to 9 mm (4.76±2.06 mm). There was no calcification. Pleural effusion was found in 56% of the patients.

**Mediastinal lymph glands on chest CT scan before treatment:** Mediastinal lymph glands ≥10 mm in size were found in all the 27 patients. Gland size varied from 10 to 50 mm (mean 19.5±8.6 mm) and the number of anatomic glands from 1 to 5 (mean 2.5±1.22), in varying combinations. The aortopulmonary glands were the most frequently enlarged (63%); followed by paratracheal (51.8%); carinal (40.7%); pre-tracheal (25.9%); and hilar (14.8%). The glands showed a hypodense center in 52% of the patients, while matting of the adjacent glands was seen in 57.7%. The enlarged glands could not be seen on plain chest X-ray taken after pericardiocentesis.

**Treatment:** All the 27 patients underwent anti-tuberculous treatment with a combination of ethambutol (15 mg/kg/day) for 3 months, and isoniazid acid hydrazide (5 mg/kg/day) and rifampicin (10 mg/kg/day) for 9 months. One patient with a multidrug-resistant strain of MT developed constrictive pericarditis and needed pericardiectomy after 2 months of treatment. Multidrug-resistant tuberculosis is difficult to manage. This patient was treated with a combination of injection streptomycin, ciprofloxacin, clarithromycin and prothionamide, and was doing well at 12-month follow-up. She has been advised to continue therapy for 24 months. Two other patients underwent a pericardiectomy at 2 and 3 months after the start of therapy, respectively.

**Follow-up:** Three patients were lost to follow-up and 3 needed a pericardiectomy. The remaining 21 patients were followed up for 4–48 months (15.8±10.4 months). All were doing well. Substantial changes in the mediastinal lymph glands, pericardial thickness and pleural effusion were seen on follow-up (Table 1). Figure 1 shows pericardial thickening and pleural effusion before and after anti-tuberculous treatment.

<table>
<thead>
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</tr>
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<tr>
<td>Number of patients</td>
<td>27</td>
<td>21*</td>
<td>–</td>
</tr>
<tr>
<td>Mediastinal lymph glands on chest CT scan</td>
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<td>4*</td>
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<td>Glands on chest CT scan with hypodense center</td>
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<td>&lt;0.001</td>
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<tr>
<td>Pericardial thickness in mm on chest CT scan</td>
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<td>2.06±0.54</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pleural effusion</td>
<td>15</td>
<td>Nil</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*3 patients had pericardiectomy and 3 were lost to follow-up; all 4 had regressed in size
CT: computed tomography

**Fig. 1.** Chest computed tomography frames of a patient taken before treatment and after pericardiocentesis (left). Note the pleural effusion (PL) and thickened pericardium (P) with strands in the pleural space. After treatment (right) the pleural effusion has disappeared and the pericardium is barely seen. V: vertebra; H: heart

**Mediastinal lymph glands on follow-up:** Enlarged glands were no longer seen in 17 of the 21 patients (80.9%), and were smaller in the remaining 4 (19%). None of the glands showed a hypodense center. Regression and disappearance of the enlarged glands following treatment are shown in Figs 2 and 3.
There were 6 patients with viral pericardial effusion and raised antibody titers; this group comprised 4 patients with raised Coxsackie B5 and 2 with raised Picornavirus titers. Twelve patients without raised titers were labeled as having idiopathic pericardial effusion. All 18 were grouped under viral/idiopathic pericardial effusion. Eleven of the 18 had cardiac tamponade. Pericardial biopsy was done in 6/18 patients. Of these, 4 showed acute fibrinous changes, 1 had lymphocytic infiltration, and 1 nonspecific changes. All patients in the viral/idiopathic group also underwent a chest CT scan and none had mediastinal lymph gland involvement. Of these patients, 4 showed acute fibrinous changes, 1 had lymphocytic infiltration, and 1 nonspecific changes.

All patients in the viral/idiopathic group also underwent a chest CT scan and none had mediastinal lymph gland enlargement >10 mm. Two patients had paratracheal glands measuring around 5 mm. Of these patients, 17 could be followed up and were doing well.

Discussion

Pathology and spread of tuberculosis to the pericardium: The pericardium may be involved in many ways in tuberculosis. In rare cases, there may be direct spread from tuberculous pneumonia. The pericardium can be seeded in miliary tuberculosis and, in such instances, other organ systems dominate the presentation. Direct extension from an infected visceral layer of the pleura or a rib is rare. Most often, the spread of tuberculosis to the pericardium is from the breakdown of infection in the mediastinal lymph glands, particularly those at the tracheobronchial bifurcation. Spread occurs over those lymph channels that merge at points where the parietal pericardium and the pleura separate. A large effusion is most often found with adenitis; when the effusion is due to hematogenous seeding, little fluid is found.

Tuberculosis and regional lymph glands: Tuberculous lesions in the body are classically associated with regional adenitis. These glands usually have soft caseating centers and there is matting of the adjacent glands. As the disease clears, the adenitis resolves with or without calcification. Enlarged mediastinal lymph glands in association with tuberculous pericardial effusion has been noted earlier. Rooney et al. performed autopsy in 10 of 11 patients with tuberculous pericardial effusion, and all (100%) had mediastinal lymph gland involvement. In a report from India, right scalene node biopsy was done in 41 patients with pleural effusion (right in 18 and left in 23), and 6 with pericardial effusion. The nodes were palpable in only 2 patients. Biopsy showed evidence of tuberculosis in 23/41 with pleural effusion, and in all 6 with pericardial effusion.

Mediastinal lymph glands in tuberculous pericardial effusion: Enlarged glands were not seen on routine chest X-ray examination even after pericardiocentesis, probably because of the site/s of enlargement. Our study showed that all the 27 patients with tuberculous pericardial effusion had marked mediastinal lymph gland enlargement on chest CT scan. On follow-up, 17 of 21 patients no longer had enlarged glands, and the glands were smaller in the remaining 4. None of the glands showed a hypodense center or matting on follow-up. On the other hand, glands were not enlarged in any of the 18 patients with viral or idiopathic pericardial effusion.

Studies on human cadavers have shown that the lymphatic drainage of the pericardium is mainly to the anterior mediastinal, tracheobronchial, latero-pericardial, and posterior mediastinal lymph nodes, and not to the hilar nodes. Pericardial effusion associated with mediastinal adenopathy is seen in other conditions, such as malignancy, lymphomas, sarcoidosis, etc. In these conditions, there is prominent involvement of the hilar nodes. In tuberculous pericardial effusion, the hilar group was the least often enlarged and not seen on routine chest X-ray. Chest CT scan was done in our patients after pericardial aspiration, since this investigation had to be done at another hospital, and
28/45 patients had tamponade. We have had other patients with large effusions who underwent chest CT scan before pericardiocentesis. The mediastinal gland areas were not obscured by the effusion. This would be particularly relevant for those who do not have hemodynamic compromise and do not need pericardiocentesis.

**Diagnosis of tuberculous pericardial effusion:** The delay from admission to diagnosis was a mean of 5.2 weeks in one report, while in another, the diagnosis was made in 17% of the patients only at autopsy. In a recent report of 30 patients with cardiac tamponade from India, in 60% the cause was tuberculosis. On echocardiography, the presence of irregular pericardial thickening and strands in the pericardial fluid favor the diagnosis of a tuberculous etiology, and intrapericardial masses which resolved on treatment have also been described. Tuberculous pleural involvement has been reported to be 50% at autopsy. Radiologic pleural effusion was seen in 56% of our patients with tuberculous pericardial effusion. The tuberculin skin test, which is not diagnostic in itself, was positive in all the patients in one series, and was >10 mm in 239/240 patients in another report, being >15 mm in 78%. The skin test was strongly positive in all our patients who were tested, measuring 17±3.3 mm.

The confirmation of a tuberculous etiology currently depends on a histopathologic study of the pericardium or other tissue, culture of MT from the pericardial tissue or pericardial fluid, the presence of tuberculosis elsewhere in the body, or the response to a specific treatment. However, the pericardial biopsy may show nonspecific findings. Strang et al., while reporting on patients with tuberculous pericardial effusion, found that out of the 49 patients in whom MT was cultured at the same time as conducting the pericardial biopsy, pericardial histologic changes “characteristic of tuberculosis” were present in only 35/49 (71%), while 14/49 patients (29%) had nonspecific findings. In our study, 2/25 biopsies showed nonspecific findings. This difference may be due to the number of samples obtained at biopsy. Asymptomatic patients without hemodynamic compromise do not require pericardiocentesis except for diagnostic purposes.

The diagnosis of tuberculous pericardial effusion in our study was not based on enlarged mediastinal lymph glands or a positive skin test. The diagnosis was made from histologic changes or culture of MT or the presence of pulmonary tuberculosis. All the patients responded to a specific treatment.

**Limitations of this study:** Since it was not possible to repeat chest CT scans at pre-set intervals, we were unable to determine how long it takes for the enlarged glands in tuberculosis to regress. The tuberculin skin test should have been done in all the patients.

**Conclusions:** All patients with tuberculous pericardial effusion had marked mediastinal lymph gland enlargement on chest CT examination. These were not seen on plain chest X-ray examination. On anti-tuberculous treatment, these glands disappeared or regressed. None of the patients with viral or idiopathic pericardial effusion had similar gland enlargement. When done, the tuberculin skin test was positive in all the patients with tuberculous pericardial effusion. None of the patients was seropositive for human immunodeficiency virus infection.

It appears that under the appropriate clinical circumstances, when other conditions likely to result in mediastinal adenopathy, such as malignancy or lymphoma, are not under consideration, the demonstration of marked nonhilar mediastinal lymph gland enlargement along with a positive tuberculin skin test could suggest a tuberculous etiology for pericardial effusion. This could be particularly useful when there is no hemodynamic compromise necessitating pericardial aspiration.

**Acknowledgments**

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**References**

A Tertiary Care Hospital-Based Study of Conventional Risk Factors Including Lipid Profile in Proven Coronary Artery Disease

Pravin K Goel, BB Bharti, CM Pandey, Uttam Singh, Satyendra Tewari, Aditya Kapoor, Naveen Garg, Nakul Sinha

Departments of Cardiology and Biostatistics, Sanjay Gandhi Post Graduate Institute of Medical Sciences, Lucknow

Background: The prevalence and mortality rates of coronary artery disease have been known to be higher in the Indian than the Western population. Most data on lipid levels in Indians have been obtained from studies on migrant Asian Indians. There are insufficient data on lipid profile and other conventional risk factors in Indian patients living within India.

Methods and Results: The study included 2656 consecutive patients who underwent coronary angiography between March 1998 and February 2002. Of these, 2399 subjects had angiographically proven coronary artery disease (group 1) while 257 had normal coronary arteries (group 2). Lipid values were measured in the fasting state on the morning the coronary angiography was done. Patients receiving lipid-lowering agents, those having renal, hepatic or thyroid disorders, patients presenting within 8 weeks after acute myocardial infarction, and patients who were taking noncardiac drugs that affect the lipid profile were excluded from the study. Other conventional risk factors were also recorded. In subjects with coronary artery disease and normal coronary arteries, the levels of mean total cholesterol recorded were 178.5±42.1 mg/dl v. 154.1±40.2 mg/dl (p<0.001), high-density lipoprotein cholesterol 30.6±9 mg/dl v. 27.3±6.8 mg/dl (p<0.001), low-density lipoprotein cholesterol 109.8±35.4 mg/dl v. 93.6±33.9 mg/dl (p<0.001), and triglyceride 190.7±95.4 mg/dl v. 157.6±73.5 mg/dl (p<0.001), respectively. In subgroup analysis by age, the younger coronary artery disease group (<40 years) had significantly higher total and low-density lipoprotein cholesterol levels than the older group (>40 years), viz. 194.6±51.4 mg/dl v. 176.3±40.2 mg/dl (p<0.001), and 118.3±39.6 mg/dl v. 108.7±36.1 mg/dl (p=0.001). Triglyceride levels were not significantly different [211.7±105.1 mg/dl v. 187.8±93.6 mg/dl (p=ns)], being equally high in both subgroups and, although high-density lipoprotein cholesterol levels were different, this difference was minimal, being equally low in both [32.7±9.5 mg/dl v. 30.3±9.0 mg/dl (p=ns)]. In the subgroup analysis of those with coronary artery disease, diabetics had significantly lower total cholesterol [174±41.1 mg/dl v. 180.4±42.4 mg/dl (p<0.001)] and low-density lipoprotein cholesterol levels [105.8±34 mg/dl v. 111.5±35.8 mg/dl (p<0.001)] than non-diabetics, whereas triglyceride and high-density lipoprotein cholesterol levels were not significantly different, triglycerides being equally high in both [186.2±95.5 mg/dl v. 192.5±95.2 mg/dl (p=ns)], and high-density lipoprotein equally low in both [30.9±9.3 mg/dl v. 30.5±9 mg/dl (p=ns)]. The commonest associated conventional risk factor in diabetics was hypertension and, in the younger age group (<40 years), it was smoking and a positive family history of premature coronary artery disease.

Conclusions: We conclude that in north Indians, coronary artery disease occurs at much lower levels of total cholesterol and low-density lipoprotein cholesterol than other populations, and high triglyceride and low high-density lipoprotein levels are more of a universal phenomenon in this population. Younger patients have a more atherogenic lipid profile than the older subgroup with coronary artery disease, and smoking and a family history of premature coronary artery disease are the most common associated risk factors. Total cholesterol levels seem to play a lesser role in the occurrence of coronary artery disease in diabetics, the presence of which is in itself overwhelming for the occurrence of coronary artery disease. (Indian Heart J 2003; 55: 234–240)

Key Words: Coronary artery disease, Risk factor, Lipid profile

Correspondence: Dr Pravin K Goel, Department of Cardiology, Sanjay Gandhi PGIMS, Lucknow 226014.
A dramatic increase in the prevalence of coronary artery disease (CAD) is predicted in the next 20 years within the Indian subcontinent, due to rapid changes in demography and lifestyle consequent to economic development. Although CAD is declining in the West, its prevalence is steadily rising in India. The prevalence of CAD is four-fold higher in urban India and two-fold higher in rural India than in the United States.

The prevalence of conventional risk factors such as smoking, hypertension, and diabetes mellitus is not different in south Asians as compared with other ethnic groups. Lipid patterns, however, are known to vary with dietary habits, which could be different in diverse ethnic groups and geographical locations. Thus, south Asians are noted to have higher triglyceride (TG) levels, low concentration of high-density lipoprotein cholesterol (HDL-c), increased visceral fat, and higher insulin resistance as more prevalent risk factors. While total cholesterol (TC) levels have been observed to be lower in CAD patients of Indian origin when compared to their counterparts in the West. Most such studies have been based on migrant Indians and a few reports from south India. There are insufficient data on lipid levels in patients with known CAD from Indians living within India, and especially north India. We, therefore, planned a broad-based study of serum lipid patterns and other conventional risk factors in patients with proven CAD in north India.

Methods

The study group constituted consecutive patients presenting between March 1998 and February 2002 for coronary angiography at a tertiary care center in north India for typical or atypical chest pain or post-myocardial infarction assessment. They were classified into group 1 (subjects with definite CAD on angiography, n=2399) and group 2 (subjects without CAD, i.e. with angiographically normal coronary arteries, n=257). Details of risk factors, including family history of premature CAD, hypertension, smoking, and diabetes mellitus were recorded. Patients already taking antihypertensive medication or those in whom the average of two blood pressure readings at least five minutes apart in the sitting posture was >140/90 mmHg were labeled as hypertensive. Diabetes mellitus was diagnosed to be present if a patient had a definite history of diabetes mellitus with records of treatment, or fasting plasma glucose ≥126 mg%/ or two-hour post-load glucose ≥200 mg/dl, based on the guidelines of the American Diabetes Association, 2000. A smoker was defined as a person regularly smoking cigarettes/beedis (tobacco rolled in Diospyros melanoxylon leaf) or who had stopped smoking within the past one year. A family history of premature CAD was defined as myocardial infarction or sudden death before the age of 55 years in the father or any other male first-degree relative, or before the age of 65 years in the mother or any other female first-degree relative.

Lipid measurement: The lipid values of all the patients were measured in a fasting state on the morning of the day the coronary angiography was done. Patients receiving lipid-lowering agents or having renal, hepatic or thyroid disorders, or those presenting within 8 weeks of acute myocardial infarction, and patients taking noncardiac drugs which affect the lipid profile (such as steroids) were excluded from the study. Fresh fasting samples (after 12 hours of overnight fasting) were used for the estimation of lipid profile. Lipid profile included TC, TG, HDL-c and very low-density lipoprotein cholesterol (VLDL-c) measured by the enzymatic method (autoanalyzer, Technicon RX. XT). The reagent was added to the serum according to the method described in the kits. The concentration of cholesterol in the samples was directly proportional to the intensity of the red complex (red quinon), which was measured at 500 nm. The concentration of TG in the sample was directly proportional to the intensity of the purple-colored complex formed during the reaction, which was measured at 546 nm. For HDL-c measurement, the chylomicron, VLDL-c, and low-density lipoprotein cholesterol (LDL-c) subfractions in the serum were separated by precipitation with phosphotungstic acid, magnesium chloride and, after centrifugation, the cholesterol in the HDL fraction, which remains in the supernatant, was assayed using the enzymatic cholesterol method. VLDL-c was estimated by dividing the TG levels by a factor of 5. LDL-c was obtained by subtracting the sum of VLDL-c and HDL-c fractions from TC by applying the Friedewald formula. The ratios of TC to HDL-c and of LDL-c to HDL-c were also calculated.

Subgroups: Patients with proven CAD were further divided into two subcategories. The first subgroup analysis was based on the age of the patients, i.e. age ≤40 years v. >40 years. The second subgroup analysis was based on the presence or absence of diabetes mellitus.

Statistical analysis: All data were entered prospectively in a computerized database. Analysis was done with the SPSS statistical software (9.0 version). Continuous data were presented as mean±SD. Discrete data were compared by the Chi-square test and continuous data with the Student’s t test. Test of proportion was done to compare...
the risk factors between the two groups, i.e. diabetic v. non-diabetic and age ≤40 years v. >40 years.

**Results**

The demographic profile of the study groups is given in Table 1. There was no significant difference in age between the groups with and without CAD (53.4±10.2 years v. 52.7±8.0 years). Males dominated both the groups, with 87.7% in group 1 and 73.9% in group 2 (p<0.001). Hypertension was present equally in both the groups (49.9% in group 1 v. 44.7% in group 2, p=ns). Other risk factors, including smoking, diabetes mellitus, and family history of CAD, were significantly higher in group 1 (p<0.001, p<0.05, and p=0.003, respectively).

Table 2 shows the lipid profile analysis of the two groups. The mean TC was 178.5±42.1 mg/dl (p<0.001), HDL-c 30.6±9.1 mg/dl v. 27.3±6.8 mg/dl (p<0.001), LDL-c 109.8±35.4 mg/dl v. 93.6±33.6 mg/dl (p<0.001), and TG 190.7±95.4 mg/dl v. 157.6±73.5 mg/dl (p<0.001) in those with and without CAD, respectively. Thus, all lipid fractions, viz. TC, HDL-c, LDL-c, and TG were significantly higher in group 1 but there was no significant difference in the TC to HDL-c and LDL-c to HDL-c ratios. On the whole, however, both TC and LDL-c lipid fraction levels were within the normal range and HDL-c levels were lower than normal in both the groups, with TG levels higher than normal in both groups. TG values had a markedly skewed distribution in patients with CAD with a skewness level of 1.08 v. 0.78 in non-CAD patients. This was seen as the mean TG level (190.7 mg/dl) which was much higher than the median value (170 mg/dl).

**Subgroup analysis of patients with age ≤40 years v. >40 years:** Table 3 shows the stratification of proven CAD patients into young and those more than 40 years of age and their lipid profiles. Young CAD patients (≤40 years) had significantly higher levels of TC, LDL-c, and HDL-c than the older patients (>40 years), viz. TC 194.6±51.4 mg/dl v. 176.3±40.2 mg/dl (p<0.001), LDL-c 118.3±39.6 mg/dl v. 108.7±36.1 mg/dl (p<0.001), and HDL-c 32.7±9.5 mg/dl v. 30.3±9 mg/dl (p=ns), respectively. However, there was no significant difference in TG levels between the two groups, viz. 211.7±105.1 mg/dl in those ≤40 years and 187.8±93.6 mg/dl in those >40 years. Test of proportion performed using age group (≤40 years v. >40 years) for conventional risk factors showed smoking to be the most common associated risk factor in patients in the younger age group (Table 4).

**Subgroup analysis by presence or absence of diabetes mellitus:** Table 5 shows the lipid profile in CAD patients stratified into diabetics and non-diabetics. Diabetic patients had significantly lower TC and LDL-c levels than non-diabetics, viz. TC 174.0±41.1 mg/dl v. 180.4±42.4 mg/dl.

**Table 1. Demographic profile of the study population**

<table>
<thead>
<tr>
<th>Age (mean±SD years)</th>
<th>Group 1 With CAD (n=2399)</th>
<th>Group 2 Without CAD (n=257)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male (%)</td>
<td>53.4±10.2</td>
<td>52.7±8.0</td>
<td>ns</td>
</tr>
<tr>
<td>Smoker (%)</td>
<td>210.4 (87.7)</td>
<td>190 (73.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>848 (35.4)</td>
<td>38 (14.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes mellitus (%)</td>
<td>1198 (49.9)</td>
<td>115 (44.7)</td>
<td>ns</td>
</tr>
<tr>
<td>Family history of premature CAD (%)</td>
<td>255 (10.6)</td>
<td>11 (5.1)</td>
<td>0.003</td>
</tr>
</tbody>
</table>

Values in parentheses are percentages

CAD: coronary artery disease; ns: not statistically significant

**Table 2. Lipid profile of the study population**

<table>
<thead>
<tr>
<th>Lipid profile</th>
<th>Group 1, n=2399 (mg/dl, mean±SD)</th>
<th>Group 2, n=257 (mg/dl, mean±SD)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TC</td>
<td>178.5±42.1</td>
<td>154.1±40.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HDL-c</td>
<td>30.6±9.1</td>
<td>27.3±6.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LDL-c</td>
<td>109.8±35.4</td>
<td>93.6±33.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TG</td>
<td>190.7±95.4</td>
<td>157.6±73.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TC/HDL-c</td>
<td>6.1±1.6</td>
<td>6.1±1.5</td>
<td>ns</td>
</tr>
<tr>
<td>LDL/HDL-c</td>
<td>3.8±1.1</td>
<td>3.8±1.1</td>
<td>ns</td>
</tr>
</tbody>
</table>

TC: total cholesterol; HDL-c: high-density lipoprotein cholesterol; LDL-c: low-density lipoprotein cholesterol; TG: triglyceride; ns: not statistically significant

**Table 3. Lipid profile of patients with CAD (group 1) of age ≤40 years v. age >40 years**

<table>
<thead>
<tr>
<th>Lipid profile</th>
<th>Age ≤40 years (n=287) (mg/dl, mean±SD)</th>
<th>Age &gt;40 years (n=2112) (mg/dl, mean±SD)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TC</td>
<td>194.6±51.4</td>
<td>176.3±40.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HDL-c</td>
<td>32.7±9.5</td>
<td>30.3±9.0</td>
<td>ns</td>
</tr>
<tr>
<td>LDL-c</td>
<td>118.3±39.6</td>
<td>108.7±36.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TG</td>
<td>211.7±105.1</td>
<td>187.8±93.6</td>
<td>ns</td>
</tr>
</tbody>
</table>

**Table 4. Other conventional risk factors in CAD patients grouped by age: test of proportions**

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>Age ≤40 years (n=287)</th>
<th>Age &gt;40 years (n=2112)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension (%)</td>
<td>91 (32)</td>
<td>110 (52)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Family history of premature CAD (%)</td>
<td>56 (20)</td>
<td>199 (9)</td>
<td>&lt;0.001**</td>
</tr>
<tr>
<td>Diabetes mellitus (%)</td>
<td>38 (13.2)</td>
<td>678 (32)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Smoking (%)</td>
<td>34 (47)</td>
<td>714 (34)</td>
<td>&lt;0.001**</td>
</tr>
</tbody>
</table>

Values in parentheses are percentages

*significant in favor of age ≤40 years; **significant in favor of age >40 years.
performed between the two groups (diabetics observed in some of the other Indian studies.14–16 Mohan with CAD and those without, were much less than those other studies.14–16 However, lipid levels in our patients both CAD—an observation which is not dissimilar from that in the lack of a uniform assay technique, which has resulted measurement in India are not uncommonly hampered by in the occurrence of CAD in Indian patients, including the genetic predisposition.

In our study, serum HDL-c levels were significantly higher in CAD patients than in those without CAD [30.6±9.1 mg/dl v. 27.3±6.8 mg/dl (p<0.001)], a paradox indeed. However, this needs to be seen in the light of the absolute difference being only 3 mg/dl, which may not have any clinical relevance, and statistical significance might have been achieved only because of the larger numbers. Also, contrary to the expectation, the levels were not lower in CAD patients, suggesting this to be a phenomenon secondary to the higher TC levels per se in this group rather than a primary change, HDL-c being a subcomponent of TC. In fact, both groups, i.e. those with and without CAD, had HDL-c levels much lower than normal (<40 mg/dl). Hence, a low HDL-c level is probably more of a
constitutional association with our ethnic background (genetic basis) than secondary to any environmental factor. Previous studies had shown that as HDL levels increase, the risk of CAD decreases. Mean HDL-c in Asian Indian men is on average 5 mg/dl lower than in white men, and 15 mg/dl lower than in black and Japanese men. The Framingham data suggested an optimal HDL-c level >52 mg/dl in men and >66 mg/dl in women, which probably may not apply to our patients who, as shown by us, have much lower levels even in the absence of disease.

Mean LDL-c levels in our study were significantly higher in patients with CAD than those without CAD [109.8±35.4 mg/dl v. 93.6±33.9mg/dl (p<0.001)] with a mean difference of 16.7 mg/dl. However, 40% of patients with CAD had LDL-c levels of <100 mg/dl and 77.9% fell in the range of LDL-c <130 mg/dl. Populations with low LDL-c are known to have a low incidence of CAD, and raised LDL-c has been recognized as a primary risk factor for CAD by the National Cholesterol Education Programme (NCEP); this was reaffirmed by the ATP-III groups. Gupta et al. reported no significant difference in LDL-c levels among patients with angiographically documented CAD and the normal Indian population. The CADI study showed that LDL-c levels did not differ among Asian Indians with or without CAD. In our study, LDL-c levels, though somewhat higher in the CAD than in the nonCAD group, were well within the normal range in both groups.

Mean TG levels in our study were significantly higher in patients with CAD than those without CAD [93.6±33.9 mg/dl v. 157.6±73.5 mg/dl (p<0.001)], but the mean levels were in the high range even in those without CAD (157 mg/dl). Of our patients without CAD, 35.8% in fact had TG levels >199 mg/dl. Hypertriglyceridemia was not found to be an important risk factor for CAD in the Framingham study. The role of TG as an additional risk factor in epidemiologic studies is, however, gaining prominence. It has been shown that it is of greater importance in people with low HDL-c levels and in women. Mehta et al. suggested that hypertriglyceridemia has been associated with high plasma levels of tissue plasminogen activator inhibitor and may therefore be an important factor underlying the pathogenesis of CAD. Our study suggests that, as a whole, TG levels are probably higher in our patients and may be a more important contributor to CAD risk than high LDL-c and TC levels. Krishnaswami et al. observed a similar finding in a study on Indian patients from south India.

Diabetic v. non-diabetic patients with CAD: In our study, diabetes with CAD were found to have significantly lower TC and LDL-c levels than non-diabetic patients with CAD. This may indicate that high TC and LDL-c levels do not as such form an important risk factor for the occurrence of CAD in patients who are already diabetic, or one may conclude that the presence of diabetes per se is so overwhelming that patients develop CAD with diabetes even with normal or low levels of cholesterol. TG and HDL-c levels were not different within the two groups; TG was equally high and HDL-c equally low in both diabetic and non-diabetic subjects. This is possibly related to the inherent tendency of our ethnic group as seen in the ethnic group analysis. In the Framingham population, TG levels were higher and HDL-c levels lower in diabetics when compared to non-diabetics but TC and LDL-c levels did not differ.
between the groups. The MRFIT data also showed no significant difference in TC levels between diabetic and non-diabetic individuals. A study by Ramachandran et al. had shown that the lipid profile of diabetic CAD patients had a higher concentration of TC, TG, LDL-c, LDL-c/HDL-c ratio, and a lower concentration of HDL-c, which is in contrast to our finding. However, because for any lipoprotein level a diabetic will have CAD more frequently than a non-diabetic, it may not be unusual to observe what we have found.

Test of proportion showed that the diabetic subgroup had a significantly higher prevalence of hypertension (65% v. 44%, p<0.001) and lesser incidence of smoking. but there was no difference in a positive family history of premature CAD in both the groups. This, however, could be explained by the high prevalence of hypertension in diabetic patients.

Limitations: The present study was conducted retrospectively, and the patients’ clinical and laboratory data were analyzed by different persons, which might have influenced the study results. Also, patients already receiving lipid-lowering agents were excluded from the study protocol, which might have excluded some patients (both with and without CAD) with truly high lipid levels and thereby influenced the results.

Conclusions: North Indians develop CAD at lower levels of cholesterol than other populations. Hypertriglyceridemia is a widely prevalent risk factor for CAD. HDL-c is universally low in this patient subgroup. The ATP-III guidelines for the management of dyslipidemia are in urgent need of modification for the Indian population, because as per the current guidelines, a larger majority of our patients with CAD would not fall in the category recommended for drug treatment. Younger patients have a more atherogenic lipid profile than older patients. Hypertension is a strong risk factor in diabetic patients for the occurrence of CAD but a family history of premature CAD and smoking are the strongest associations in the younger population.

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Carotid Artery Stenting With Filter Protection

PC Rath, G Lakshmi, Manoj Agarwala, Sunil Kumar, PS Rao, Sitaram, Michel Henry
Apollo Heart Institute, Hyderabad

Background: Neurologic events associated with distal embolization of debris during percutaneous carotid artery stenting complicate the procedure. Filter devices for cerebral protection potentially reduce the risk of embolization and other neurologic events. We studied the feasibility, safety, and efficacy of carotid artery stenting with a filter device.

Methods and Results: Between January 2002 and January 2003, a total of 22 consecutive patients (30 lesions) who had >70% diameter stenosis of the internal carotid artery underwent carotid artery stenting with filter protection at our institute. The mean age of the patients was 64±9 years; 14 were men and 8 women, and 15 had neurologic symptoms. A stent was successfully implanted in 29 lesions. It was possible to position a filter device in all the 29 lesions. Neurologic complications during the procedure, in the hospital, and at 30-day clinical follow-up occurred in 2 patients. One patient suffered a minor stroke that resolved within 24 hours. None of the patients had a major embolic stroke. There was one death from intracerebral hemorrhage related to hyperperfusion and the use of a glycoprotein IIb/IIIa inhibitor.

Conclusions: Filter protection during carotid artery stenting seems technically feasible, safe, and effective. In the present study, the incidence of embolic neurologic events was low. (Indian Heart J 2003; 55: 241–244)

Key Words: Carotid artery disease, Stents, Protection device

Correspondence: Dr PC Rath, Director Cathlab and Interventional Cardiology, Apollo Heart Institute, Jubilee Hills, Hyderabad 500033. e-mail: drpcrath@hotmail.com

Methods
Between January 2002 and January 2003, CAS using a filter protection device was attempted in 30 lesions in 22 consecutive patients at our center. All the patients had severe (>70%) stenosis of the internal or common carotid artery. Clinical and angiographic characteristics of the patients are listed in Table 1.

All the patients were premedicated with clopidogrel 75 mg once a day, and aspirin 150–325 mg once a day for a minimum of 7 days before the procedure. A single bolus of intravenous heparin (5000 units) was administered at the beginning of the procedure.

The filter system was deployed according to the manufacturer’s instructions. A glycoprotein IIb/IIIa inhibitor was used when indicated. Arterial blood pressure was monitored during the procedure and, if needed, modulated with nitrates or dopamine. All the patients were awake during the procedure. Atropine (0.6 mg) was routinely used before balloon dilatation. After the procedure, patients received clopidogrel for 1 month and aspirin was continued indefinitely.

A careful neurologic examination was performed before and after the procedure by a neurologist. Baseline computed
tomographic scan of the brain was performed in all the patients before the procedure, and imaging studies were appropriately utilized for determining occurrence of endpoints.

The primary end-points were: (i) technical success (angiographic and device success), and (ii) procedural and 30-day incidence of minor stroke, major stroke, myocardial infarction, and death.

**Carotid stenting procedure:** Percutaneous access was routinely gained through the femoral artery. A dedicated 7 or 8 F, 90 cm long guidewire catheter was advanced into the common carotid artery using a 0.035" guidewire. In cases in which this was difficult, special diagnostic catheters (Vitek, Simmonds 1 or 2), and 0.035" or 0.038" support wires were placed in the external carotid artery, and the guidewire catheter was then advanced into the common carotid artery.

Care was taken not to cross the lesion with the guidewire. Stenosis was crossed with a filter device that had a diameter matching that of the distal cervical internal carotid artery (ICA) (Fig. 1 a,b,c). Two different filter designs were used. These included 27 EPI filters (93%; Boston Scientific), and 2 Angioguard filters (6.8%; J&J Cordis). Filter deployment and retrieval was performed using dedicated catheters or sheaths. At the commencement of the procedure, the filter system was loaded into the delivery sheath. The system was then advanced through the guiding sheath, and across the target lesion into the distal ICA. The delivery sheath was withdrawn, and the filter was deployed, such that a position below the base of the skull was targeted. After the delivery catheter was removed, an angiogram was obtained to document blood flow through the filter, ascertain apposition of the device to the wall of the artery, and placement of the device distal to the target lesion (Fig.1 b). The filter guidewire was used to deliver the balloon and stent delivery catheters. Following completion of the procedure, the filter assembly was recovered using the retrieval sheath.

The filter device crossed the lesion in the initial attempt in 27 lesions (90%), and after gentle predilatation (using a 2 mm coronary balloon) in 2 lesions (6.6%). After positioning the filter, direct stent deployment was performed in 25 lesions (86.3%), and after predilatation with a 3.5 – 4 mm coronary balloon in 4 lesions (13.7%). Self-expandable stents (89.7% carotid Wallstent, Boston Scientific; 10.3% Smart stent. Cordis) were implanted. All the stents were postdilated at a medium–high pressure (8–12 atm) using 5 or 6 mm Gazelle or Bypass speedy (Boston Scientific) balloons.

**Filter device description:** The filter device consists of a nitinol skeleton or supporting wire with a polyurethane membrane that has pores ranging in diameter from 80 to 130 µm. The diameter of the filter ranges from 5 to 7 mm. The filters are connected to the distal end of a 0.014" wire with a floppy tip, which is used as a guidewire during the procedure. The closed filter is advanced through the lesion and opened in the ICA. At the end of the procedure, it is closed with the retrieval sheath, and removed from the vessel.

**Technical success:** Device success was defined as the successful placement and retrieval of the filter device. Successful stent deployment resulting in ≤30% residual diameter stenosis was defined as angiographic success.

**Stroke:** A minor stroke was defined as an arterio-occlusive brain infarction characterized by the sudden onset of a neurologic deficit that persisted for ≤24 hours. Patients should not be disabled. A major stroke as an arterio-
occlusive brain infarction characterized by the sudden onset of a neurologic deficit persisting for a minimum of 30 days.

A procedural event was defined as the occurrence of any clinical event during the procedure, from the time femoral arterial access was obtained until access site hemostasis was successfully achieved. The 30-day outcome was the composite incidence of the clinical end-points within the first 30 days.

**Statistical analysis:** The primary end-points were analyzed on an intention-to-treat basis. All values are expressed in mean±SD.

**Results**

The clinical and angiographic characteristics of the patients are summarized in Table 1. The mean age of the patients was 64±9 years (range 51–85 years); 2 patients (9%) were >80 years. Among a total cohort of 22 patients, 12 (54%) had substantial bilateral ICA stenosis. Bilateral carotid stenting was done in 8 patients (36%). CAS for bilateral lesions was done in the same sitting in 2 patients (25%), and in a staged manner (48 hours after the initial procedure) in 6 patients (75%). Fifteen patients (68%) had symptoms attributable to the treated lesion within 3 months before the procedure — 47% had transient ischemic attacks, 33% had stroke, and 20% had recurrent syncope and amaurosis fugax.

**Immediate outcome:** Procedural data and results are shown in Table 2. Angiographic success and successful filter placement and retrieval was achieved in 21 patients (95%).

In 1 patient (5%), failure to cross the lesion resulted in inability to place the filter. Gentle predilatation (using a 2 mm coronary balloon) was necessary in 2 lesions (6.6%) to facilitate filter placement. In these cases, severe stenosis was the cause of failure to cross the lesion with the filter in the initial attempt. There was no device failure following deployment, and all the filters were successfully retrieved in a completely collapsed condition. It required an additional maneuver, such as advancing the guider catheter close to the stent, and rotation of the filter device to retrieve the filter in 2 cases (7%).

Nonflow-limiting spasm that resolved after administration of nitroglycerin occurred in 4 vessels (13.4%); flow impairment due to occlusion of the filter, which resolved completely after removal of the filter, occurred in 2 filters (6.8%). In all these procedures, there were no associated clinical sequelae, no vascular dissections at the site of filter placement, and no procedural events.

One patient developed a minor stroke (4.5%). He developed hemiparesis in the treated territory 4 hours after the procedure. This patient also underwent additional stenting of a critical stenosis in the proximal common carotid artery near its ostium during the initial procedure. Angioplasty and stenting of this lesion was technically challenging, and required excessive maneuvering of the guide catheter, which increased the procedural time. Check angiogram, done 4 hours after the initial procedure, revealed patency of both the stents and total occlusion of the middle cerebral artery. Intra-arterial thrombolysis using 750 000 units of urokinase was given. The patient showed considerable improvement in symptoms soon after this, and recovered completely within 24 hours. There were no other embolic neurologic events.

**30-day outcome:** The overall combined rate of all strokes and deaths at 30 days was 9% (2 events). This included 1 minor stroke, and 1 death. One patient received abciximab before carotid angioplasty and stenting for a suspected thrombus in a critical lesion. She underwent stenting of both the carotid arteries during the same sitting. She developed a massive intraventricular/subarachnoid hemorrhage 2 days later and died within 48 hours from the onset of the event. This constituted the only neurologic death and was thought to be due to reperfusion injury resulting from the use of abciximab. All the remaining patients were asymptomatic with no neurologic events or myocardial infarction.

**Discussion**

Carotid artery stenting without distal protection has been
associated with embolic minor stroke rates of 2%–5%, and major stroke rates of 1%–1.5%. Neuroprotection using various distal protection strategies has been shown to reduce the risk of embolic events, particularly embolic major stroke by experienced groups in several series. Which is the best protection system is yet to be determined. Filter devices are well tolerated, are easy to use and, with them, antegrade flow is maintained, allowing visualization and more precise stent placement.

In our study, filter devices were well tolerated by all the patients. The present study demonstrates that the application of a filter protection system during CAS is feasible and safe. The crossing profile of the filter devices used in this study was favorable, resulting in successful placement in 96.6% of lesions. There were no complications related to the filters, and their routine use during CAS appears safe.

The embolic neurologic events in this study were low, and the event rate is comparable to the large series published recently. The minor stroke rate was 4.5%, and major stroke rate was 0%. The absence of major embolic events is notable. Reimers et al. also reported no major strokes during CAS using various filter designs in a series of 84 patients. Al-Mubarak et al., in a series of 162 patients pooled from 3 institutions, evaluated the Neuro Shield filter system. They also reported no major strokes. Our study confirms the results of the two series mentioned above evaluating various filter designs during CAS.

One neurologic death in a patient, who underwent bilateral CAS and received abciximab, underlines the importance of avoiding this drug as recommended by some authors, and particularly when bilateral stenting is done in the same sitting, as this carries a higher risk of reperfusion injury.

Limitations of the study: One limitation of this study is that histologic analysis of the particulate debris collected in the filter was not done. Hence, this study does not provide information on the type of embolic particles dislodged during CAS, and cannot confirm that the filters are actually effective. However the efficacy of filter devices in capturing at least 88% of embolized particles during the procedure of CAS has been well documented. Secondly, TCD monitoring was not done during the procedure. It would be important to study the degree of embolization that occurs while crossing the lesion with the device. The number of patients studied is not large enough to draw any conclusions on effectiveness of the use of filters during CAS. Nevertheless, it is a feasibility study, and a consecutive series from a single center.

In conclusion, cerebral protection with filter devices during CAS seems feasible, safe, and effective. Protection devices reduce the chances of cerebral embolization and associated neurologic events, particularly the major stroke rate during CAS.

References
Prevalence, Correlates, Awareness, Treatment, and Control of Hypertension in a Middle-Aged Urban Population in Kerala

Manu G Zachariah, KR Thankappan, Shiney C Alex, PS Sarma, RS Vasan
Achutha Menon Centre for Health Science Studies, Sree Chitra Tirunal Institute for Medical Sciences and Technology, Thiruvananthapuram

Background: Hypertension is an important cause of cardiovascular morbidity and mortality.

Methods and Results: We conducted a cross-sectional survey of 314 middle-aged subjects (163 men; age range 40–60 years, mean 49 years) in urban Thiruvananthapuram City, Kerala, to estimate the prevalence of hypertension, examine its correlates, and assess the degree of awareness, treatment, and control of high blood pressure. Blood pressure was measured by a nurse graduate using a mercury column sphygmomanometer and a standardized technique. We used multivariable analyses to examine the sociodemographic and clinical correlates of hypertension. The overall prevalence of hypertension in our sample was 54.5% (men 56.3%, women 52.3%). The factors associated with an increased prevalence of hypertension were higher body-mass index (odds ratio for a value in the top tertile of 2.33, 95% confidence interval: 1.2–4.4), and older age (odds ratio for the age group 55–60 years of 2.65, 95% confidence interval: 1.3–5.6). An occupation involving moderate or greater physical activity was inversely associated with the prevalence of hypertension (odds ratio 0.35, 95% confidence interval 0.13–0.94). Among hypertensives, 39% were aware of the condition, while 29% were treated with blood pressure-lowering medications. Adequate control of elevated blood pressure was achieved in only 30.6% of treated hypertensives. In our community-based sample, over half of all middle-aged individuals were hypertensive, but less than a third were under treatment. Adequate control of hypertension was achieved in less than a third of the treated individuals.

Conclusions: These observations re-emphasize the need for hypertension awareness programs targeting the general public and the increased use of opportunistic blood pressure screening, and underscore the importance of measures to increase the knowledge of current guidelines for the detection and treatment of hypertension among healthcare providers. (Indian Heart J 2003; 55: 245–251)

Key Words: Hypertension, Epidemiology, Prevalence

Cardiovascular diseases (CVD) account for nearly a third of all deaths worldwide. CVD are increasing in developing countries, and it has been estimated that CVD will be the major cause of morbidity and mortality in these countries by the year 2020. Consequently, the prevention of risk factors for CVD is a public health priority worldwide. Hypertension (HTN) is a premier risk factor for CVD, which is easily recognized if sought, and can be treated effectively. Treatment of high blood pressure (BP) has been consistently reported to reduce the risk of CVD. A recent meta-analysis of the prevalence of HTN in India suggested that the prevalence of HTN is increasing steeply in urban areas. A community-based investigation conducted in urban Jaipur reported a 30% prevalence of HTN (the age range of the sample population was 20–80 years). A recent epidemiological study compared the prevalence of HTN among women 20–64 years of age in 5 Indian cities. The investigators noted that the prevalence of HTN was highest (30.7%) in Thiruvananthapuram City in Kerala. We have previously reported a very high prevalence of HTN (52%) in an elderly sample population from Kerala. The high prevalence of HTN in Kerala compared to other parts of India may be related to the advanced stage of
epidemiological transition of the state. Given the high prevalence of HTN in the elderly in Kerala, and based on the insidious onset of the condition, we hypothesized that a considerable proportion of middle-aged individuals in Kerala are likely to be hypertensive. Accordingly, we performed a cross-sectional survey to assess the prevalence, correlates, awareness, treatment, and control of HTN in a sample of middle-aged individuals in urban Thiruvananthapuram City, Kerala.

Methods

Study site, and sample size: We chose the urban City Corporation Area of Thiruvananthapuram district (population 525,000 as per the 1991 Census) for our cross-sectional survey. We estimated that a random sample of 265 middle-aged individuals would yield a reasonably precise estimate of the prevalence of HTN.

Thus, if the true prevalence of HTN was 50%, our estimates could vary from 44% to 56%. Since we planned on a cluster sampling technique (rather than simple random sampling), we increased our estimated sample size to about 300 subjects.

Sampling method: We used multistage cluster sampling to identify subjects eligible for our investigation. According to the 1991 Census, there are 50 wards in the Thiruvananthapuram City Corporation Area. Initially, we selected 30 of these 50 eligible wards. To do so, we listed the population of each of the 50 wards and calculated the total cumulative population (N). This total cumulative population was divided by 30 (N/30) to obtain a sampling interval (n). Finally, a random number between 0 and n was chosen. The ward in which the total cumulative population exceeded the random number was selected as the first ward. Then the random number and the sampling interval were summed to identify the second ward. Subsequent wards were identified in the similar fashion for a total of 30. Each of these 30 wards constituted a cluster.

Next, we identified 10 subjects in the age group of 40–60 years (both inclusive) randomly from each ward (or cluster). Since there was more than one middle-aged subject in the last household of some of the clusters, our final sample exceeded 300: the final number was 314.

Household survey: One of the investigators (MZ, a nurse) conducted the survey from 23 December 1999 to 23 February 2000. The survey was performed in the late afternoon and evening to facilitate the participation of employed people. The survey had two principal components: the administration of a questionnaire and measurement of BP. Informed consent was obtained verbally from all the participants after explaining the purpose of the study.

Study questionnaire: The nurse administered a pre-tested structured questionnaire, which collected information on demographic characteristics, medical history, and information on lifestyle habits such as smoking, alcohol consumption, physical activity, tobacco chewing, use of “top-added” salt to meals, and the use of oral contraceptive agents. Participants were asked to report the highest level of education they had attained, and were categorized into 2 groups on this basis: those who had less than 10 years, and those who had 10 or more years of schooling.

Information on the participant’s household assets, and the type of house they lived in was collected using a previously validated questionnaire that generated numerical scores. Subjects were then categorized into 3 groups on the basis of socioeconomic status (lower, middle, and upper) based on the tertiles of the numerical scores.

Based on the information obtained regarding the physical activity involved in each participant’s occupation, individuals were divided into 3 groups: those with sedentary occupations; those with occupations involving mild-to-moderate physical activity; and those having occupations involving greater-than-moderate physical activity. For example, desk work at the office was classified as sedentary, maintenance of a garden at home, cooking, etc. were classified as mild-to-moderate physical activity, and labor-intensive work, such as quarry work, construction jobs, etc., was classified as greater-than-moderate activity. Nine unemployed subjects were included in the sedentary activity category.

Current smokers were defined as those who smoked cigarettes or bidis regularly, including during the period of the survey, while ex-smokers were those who had quit smoking prior to the survey.

Measurement of BP and anthropometry: Before the BP was measured, the investigator made sure that the subjects had not consumed any hot beverages, such as tea or coffee or smoked/chewed tobacco or undertaken vigorous physical activity within the 30 min preceding the household visit. If they had, then the measurements were postponed by 30 min. The nurse measured the BP of all the participants twice using a mercury column sphygmomanometer and a standard protocol. Both BP readings were obtained on the left arm of the seated subject using a cuff of an appropriate size, with the arm supported and the sphygmomanometer at the level of the heart. The first BP measurement was performed after collecting
demographic information (first part of the questionnaire), and ensuring that the participant had rested in a sitting position for at least 5 min. The BP cuff was inflated to 30 mmHg above the pressure at which the radial pulse disappeared, and then deflated slowly at a rate of 2 mm/s. Phases 1 and 5 of the Korotkoff sound were taken as indicative of systolic blood pressure (SBP) and diastolic blood pressure (DBP), respectively. Both SBP and DBP readings were recorded to the nearest 2 mmHg. The second BP measurement was taken after completing the study questionnaire. When the difference between the first and second BP readings was more than 4 mmHg for either SBP or DBP, a third measurement was obtained. The average of the readings of SBP and DBP was taken as the BP of the participant.

Body weight and height of all the participants were measured using a standardized protocol described previously. Weight was recorded to the nearest 0.5 kg, while height was measured to the nearest 0.5 cm. Body mass index (BMI) was computed as the weight in kilograms divided by the square of the height in meters.

Definitions of HTN, awareness of HTN, treatment and control: The HTN status of the subjects was assessed based on the criteria formulated by the World Health Organization–International Society of HTN (WHO–ISH) and the US Sixth Joint National Committee (JNC VI) report on the prevention, detection, evaluation, and treatment of high BP; SBP ≥140 mmHg or DBP ≥90 mmHg, or the use of antihypertensive medications. Recently published US guidelines (JNC VII) maintain the same definition of hypertension. This definition excludes hypertensives whose BP has reduced to a nonhypertensive range solely by the use of nonpharmacologic measures. A subject was said to be “aware” of HTN status if he/she reported a prior medication. Mean SBP and DBP increased with age but did not differ among men and women (Table 2).

Results

Characteristics of the study sample: Characteristics of the 314 study subjects are given in Table 1. About 60% of the participants were in the fifth decade of life and a third had attained more than 10 years of formal education. HTN was the commonest self-reported morbidity (23.2%). Over half of the women and nearly a third of the men were overweight (BMI 25 kg/m² or more). None of the women in our sample reported using oral contraceptives.

Prevalence of HTN and mean BP levels: In the sample population studied, 171 subjects (92 men and 79 women) were hypertensive, yielding an overall prevalence of 54.5% (95% CI: 49%–60%) (Table 2). Prevalence of HTN was similar in both the sexes (56.3%, 95% CI: 50.9%–61.9% in men compared to 52.3%, 95% CI: 46.8%–57.8% in women). Using an older criterion for HTN, i.e. BP >160/95 mmHg and/or use of antihypertensive medications, the prevalence of HTN was estimated to be 36% (95% CI: 30.7%–41.3%; 113 subjects, including 59 men and 54 women). The prevalence of ISH was 4.1% (95% CI: 1.9%–6.3%) among subjects who were not on antihypertensive medication. Mean SBP and DBP increased with age but did not differ among men and women (Table 2).

Classification of BP according to WHO grades: Table 3 displays the classification of BP according to WHO grades.
the sample was associated with increased odds of HTN (OR 2.33; 95% CI: 1.24–4.4). Prevalence of HTN was lower among subjects involved in occupations requiring a moderate or greater degree of physical activity (OR 0.35; 95% CI: 0.13–0.94).

Awareness, treatment, and control of HTN: Data on awareness, treatment, and control of HTN among hypertensives in our study sample are given in Table 5. Of the hypertensives, only 39% were aware of their HTN status. Less than a third of the hypertensives were on treatment, and less than a tenth of all hypertensive subjects (about a third of those on treatment) satisfied the criteria for controlled HTN. The use of alternate systems of medicine (Ayurveda or homeopathy) for the treatment of HTN was negligible in the present study. Awareness of HTN, and the treatment and control of the condition were similar in men and women. Awareness of HTN increased in the oldest age group and with a visit to a physician in the past year (Table 6). Current smokers were less aware of their HTN status.

Of the 73 subjects with self-reported HTN, actual HTN was detected in 66 (90%) during the survey. Thus the sensitivity of self-reported HTN was 90.4% while the specificity was 56.4%. Among the hypertensive subjects, 80% had visited a physician in the previous year, and 92% had their BP measured during the visit. Over half of all subjects with HTN were unaware of their condition despite having visited at least one physician in the past year.

Discussion

It is being increasingly recognized that high BP is an important public health problem in developing countries. In our cross-sectional study, we observed that over half of the middle-aged subjects were hypertensive according to the JNC VI–WHO criteria. Our data are consistent with the high prevalence reported among Indian middle-aged

Table 1. Characteristics of the study sample

<table>
<thead>
<tr>
<th>Variable</th>
<th>Men (n=163)</th>
<th>Women (n=151)</th>
<th>Total (n=314)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in years, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>40–44</td>
<td>35 (21.5)</td>
<td>48 (31.8)</td>
<td>83 (26.4)</td>
</tr>
<tr>
<td>45–49</td>
<td>51 (31.3)</td>
<td>52 (34.4)</td>
<td>103 (32.8)</td>
</tr>
<tr>
<td>50–54</td>
<td>30 (18.4)</td>
<td>31 (20.5)</td>
<td>61 (19.4)</td>
</tr>
<tr>
<td>55–60</td>
<td>47 (28.8)</td>
<td>20 (13.2)</td>
<td>67 (21.3)</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>49.7 (6)</td>
<td>47.6 (5)</td>
<td>48.7 (6)</td>
</tr>
<tr>
<td>Socioeconomic status, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lower</td>
<td>48 (29.4)</td>
<td>53 (35.1)</td>
<td>101 (32.2)</td>
</tr>
<tr>
<td>Middle</td>
<td>45 (27.6)</td>
<td>44 (29.1)</td>
<td>89 (28.3)</td>
</tr>
<tr>
<td>Upper</td>
<td>70 (42.9)</td>
<td>54 (35.8)</td>
<td>124 (39.3)</td>
</tr>
<tr>
<td>Education, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;10 years of schooling</td>
<td>71 (43.6)</td>
<td>40 (26.5)</td>
<td>111 (35.4)</td>
</tr>
<tr>
<td>Physical activity, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>98 (60.1)</td>
<td>17 (11.3)</td>
<td>115 (36.6)</td>
</tr>
<tr>
<td>Mild-to-moderate</td>
<td>45 (27.6)</td>
<td>124 (82.1)</td>
<td>169 (53.8)</td>
</tr>
<tr>
<td>&gt;Moderate</td>
<td>20 (12.3)</td>
<td>10 (6.6)</td>
<td>30 (9.6)</td>
</tr>
<tr>
<td>Smoking, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current</td>
<td>59 (36.2)</td>
<td>0 (0)</td>
<td>59 (18.8)</td>
</tr>
<tr>
<td>Past</td>
<td>41 (25.2)</td>
<td>0 (0)</td>
<td>41 (13.3)</td>
</tr>
<tr>
<td>Body-mass index (kg/m²), n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;25 kg/m²</td>
<td>114 (69.9)</td>
<td>71 (47.0)</td>
<td>185 (58.9)</td>
</tr>
<tr>
<td>25–30 kg/m²</td>
<td>38 (23.3)</td>
<td>58 (38.4)</td>
<td>96 (30.6)</td>
</tr>
<tr>
<td>≥30 kg/m²</td>
<td>11 (6.7)</td>
<td>22 (14.6)</td>
<td>33 (10.5)</td>
</tr>
<tr>
<td>1st tertile (&lt;22.8)</td>
<td>65 (61.1)</td>
<td>38 (36.9)</td>
<td>103 (32.8)</td>
</tr>
<tr>
<td>2nd tertile (22.8–25.9)</td>
<td>59 (55.7)</td>
<td>47 (44.3)</td>
<td>106 (33.8)</td>
</tr>
<tr>
<td>3rd tertile (≥25.9)</td>
<td>39 (37.1)</td>
<td>66 (62.9)</td>
<td>105 (33.4)</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>23.5 (4)</td>
<td>25.6 (4.4)</td>
<td>24.5 (4.3)</td>
</tr>
</tbody>
</table>

Values in parentheses are percentages, unless indicated otherwise. SD: standard deviation

Table 2. Prevalence of hypertension, and mean systolic and diastolic blood pressure in the study sample by age group and gender

<table>
<thead>
<tr>
<th>Variables</th>
<th>40–44 years</th>
<th>45–49 years</th>
<th>50–54 years</th>
<th>55–60 years</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension (%)</td>
<td>42.2</td>
<td>55.3</td>
<td>55.7</td>
<td>67.2</td>
<td>*0.004</td>
</tr>
<tr>
<td>SBP (mmHg) (SD)</td>
<td>130 (15)</td>
<td>135 (20)</td>
<td>140 (18)</td>
<td>140 (21)</td>
<td>**0.005</td>
</tr>
<tr>
<td>DBP (mmHg) (SD)</td>
<td>88 (9)</td>
<td>89 (12)</td>
<td>89 (9)</td>
<td>91 (11)</td>
<td>**0.4</td>
</tr>
</tbody>
</table>

*Chi-square test; **one-way ANOVA; *Chi-square trend test
SD: standard deviation; SBP: systolic blood pressure; DBP: diastolic blood pressure

Less than one tenth of our participants had “optimal” BP while a fifth had “normal” BP. A higher proportion of men had high normal BP (p=0.015). The distribution of BP grades was similar across the 4 age groups examined.

Correlates of HTN: The clinical and sociodemographic correlates of the prevalence of HTN are presented in Table 4. Increasing age and elevated BMI were associated with increased prevalence of HTN; the oldest age group examined (55–60 years) had higher odds of HTN (OR 2.65; 95% CI: 1.3–5.6), while a value of BMI in the top tertile for
Table 3. Distribution of blood pressure in the study sample by WHO grades of blood pressure

<table>
<thead>
<tr>
<th>Group</th>
<th>Optimal BP (n (%))</th>
<th>Normal BP (n (%))</th>
<th>High normal BP (n (%))</th>
<th>Hypertension n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total (n=314)</td>
<td>25 (7.96)</td>
<td>60 (19.1)</td>
<td>58 (18.5)</td>
<td>15 (4.8)</td>
</tr>
<tr>
<td>By gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males (n=163)</td>
<td>13 (7.97)</td>
<td>19 (11.7)</td>
<td>39 (23.9)</td>
<td>8 (4.9)</td>
</tr>
<tr>
<td>Females (n=151)</td>
<td>12 (7.94)</td>
<td>41 (27.2)</td>
<td>19 (12.6)</td>
<td>7 (4.6)</td>
</tr>
<tr>
<td>By age group</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>40–44 years (n=83)</td>
<td>6 (7.2)</td>
<td>27 (32.5)</td>
<td>15 (18.1)</td>
<td>4 (4.8)</td>
</tr>
<tr>
<td>45–49 years (n=103)</td>
<td>9 (8.7)</td>
<td>16 (15.5)</td>
<td>21 (20.4)</td>
<td>6 (5.8)</td>
</tr>
<tr>
<td>50–54 years (n=61)</td>
<td>4 (6.6)</td>
<td>9 (14.8)</td>
<td>14 (22.9)</td>
<td>1 (1.6)</td>
</tr>
<tr>
<td>55–60 years (n=67)</td>
<td>6 (8.9)</td>
<td>8 (11.9)</td>
<td>8 (11.9)</td>
<td>4 (6.0)</td>
</tr>
</tbody>
</table>

BP: blood pressure; SBP: systolic BP; DBP: diastolic BP; optimal BP: SBP <120 mmHg and DBP <80 mmHg; normal BP: SBP 120–129 mmHg and/or DBP 80–84 mmHg; high normal BP: SBP 130–139 mmHg or DBP 85–89 mmHg; grade 1 hypertension: SBP 140–159 mmHg or DBP 90–99 mmHg; grade 2 hypertension: SBP 160–179 mmHg or DBP 100–109 mmHg; grade 3 hypertension: SBP >180 mmHg and DBP ≥110 mmHg. When SBP and DBP fall into different categories, the higher category is selected to classify the individual’s BP status. For example, 145/100 is classified as grade 2 hypertension and 160/120 is classified as grade 3 hypertension.

Table 4. Correlates of hypertension

<table>
<thead>
<tr>
<th>Variables</th>
<th>Referent category</th>
<th>Beta (SE)</th>
<th>Odds ratio (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age group (55–60 years)</td>
<td>Age group (40–44 years)</td>
<td>0.98 (0.4)</td>
<td>2.65 (1.3–5.6)</td>
<td>0.009</td>
</tr>
<tr>
<td>BMI&gt;25.9 kg/m²</td>
<td>BMI&lt;22.8 kg/m²</td>
<td>0.85 (0.3)</td>
<td>2.33 (1.2–4.4)</td>
<td>0.007</td>
</tr>
<tr>
<td>Current occupation: Sedentary occupation</td>
<td>with &gt;moderate physical activity</td>
<td>–1.05 (0.49)</td>
<td>0.35 (0.13–0.94)</td>
<td>0.034</td>
</tr>
</tbody>
</table>

Variables considered in this model and not significant include sex, self-reported diabetes mellitus, socioeconomic status, and smoking status. Interaction between smoking and BMI was also considered but found insignificant.

Beta: regression coefficient in logistic models; SE: standard error of beta coefficient; BMI: body-mass index; CI: confidence interval

Table 5. Awareness, treatment, and control of hypertension

<table>
<thead>
<tr>
<th>Category</th>
<th>Hypertensives (n=171)</th>
<th>Treated hypertensives (n=49)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Aware (n)</td>
<td>Treated (n)</td>
</tr>
<tr>
<td>Total (n=171)</td>
<td>66 (38.6)</td>
<td>49 (28.7)</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men (n=92)</td>
<td>31 (33.7)</td>
<td>21 (22.8)</td>
</tr>
<tr>
<td>Women (n=79)</td>
<td>35 (44.3)</td>
<td>28 (35.4)</td>
</tr>
<tr>
<td>p value*</td>
<td>0.15</td>
<td>0.07</td>
</tr>
<tr>
<td>Age group</td>
<td></td>
<td></td>
</tr>
<tr>
<td>40–44 years (n=35)</td>
<td>13 (37.1)</td>
<td>9 (25.7)</td>
</tr>
<tr>
<td>44–49 years (n=57)</td>
<td>22 (38.6)</td>
<td>18 (31.6)</td>
</tr>
<tr>
<td>50–54 years (n=34)</td>
<td>12 (35.3)</td>
<td>8 (23.5)</td>
</tr>
<tr>
<td>55–60 years (n=45)</td>
<td>19 (42.2)</td>
<td>14 (31.1)</td>
</tr>
<tr>
<td>p value**</td>
<td>0.70</td>
<td>0.87</td>
</tr>
</tbody>
</table>

All values in parentheses are percentages.
†Uncontrolled severe hypertension indicates BP ≥180/110 mmHg; *Chi-square test; **Chi-square trend test
individuals in previous reports. The prevalence of HTN was similar in men and women, and increased with age and elevated BMI. It is noteworthy that nearly 40% of the subjects in our sample were overweight or obese, a figure that is surprisingly high for a developing country. A higher prevalence of HTN was noted in subjects with a sedentary occupation.

There was a striking lack of awareness of elevated BP among participants in our study; only 39% of hypertensives were aware of their condition, and it was adequately controlled in less than 10%. A concurrent study in Kerala among an elderly population showed that only 45% of elderly hypertensives were aware of their condition. Awareness, treatment, and control of HTN did not differ among men and women, perhaps due to the high level of education in both sexes in Kerala. Not surprisingly, a visit to a physician in the year preceding our survey was associated with increased awareness of HTN status. The low awareness about HTN among current smokers may indicate a marker of reduced overall health awareness in this group. Overall, the low levels of awareness among these middle-aged subjects, the majority of whom are in the work force, may be due to the “silentness” of the condition and a lack of regular health check-ups at the workplace. A low awareness of HTN, despite a visit to a physician in the previous year, may indicate a fluctuation of BP across visits, and/or inadequate attention paid by physicians to measuring BP and treating HTN.

It is disconcerting to note that the control of HTN was very poor even in a sample with more than 90% of the subjects reporting more than a primary level of education. Our observations are especially noteworthy because the survey was conducted in urban Thiruvananthapuram, well known for its wide network of public and private healthcare facilities, including tertiary-level referral centers. Unlike other developing countries or other states of India, availability of and accessibility to health facilities are less important factors in Kerala when evaluating HTN awareness, treatment or control. The reasons for the low level of treatment and control of HTN merit further investigation.

**Strengths and limitations of the study:** Our study sample was reasonably representative of middle-aged subjects in the Thiruvananthapuram City Corporation area. The use of a community-based sample, and the use of BP measurements obtained at the participants’ homes by a trained health professional are the strengths of our investigation. A major limitation is the use of single-occasion BP measurements to determine HTN status. Use of BP measured on a single occasion overestimates the prevalence of HTN; it is recommended that BP be recorded on multiple occasions before a diagnosis of HTN is made. This was not possible in the present study due to the restrictions of time and manpower resources. As such, the findings of our survey should be considered an upper estimate of the prevalence of HTN in the community sampled. An additional limitation is that physical activity was assessed based on the occupation of the subjects, and leisure-time activity was not considered.

**Conclusions and policy implications:** The high prevalence of HTN in the urban middle-aged population studied, and the low levels of awareness, treatment, and control identify an important public health problem in the area surveyed. Furthermore, the relationship of BP to vascular risk is a continuous one with no threshold down up to 115/70 mmHg. There are data to suggest that promotion of lower levels of BP down to this level may lower the vascular risk in the population. In this context, it is striking that less than a tenth of the sample population had optimal levels of BP. Our observations assume significance given that the middle-aged segment of a society is an important contributor to the economic productivity of the nation and individual families.
There is a need for strengthening health education programs in the general population, promoting HTN awareness, and emphasizing preventive measures such as lifestyle modification, regular exercise, and maintenance of optimal body weight. The only effective method for the diagnosis of HTN is BP screening of the population. In developing countries with limited resources, the promotion of opportunistic screening by physicians is the principal option. In Kerala, with its network of primary health centers, such opportunistic screening is readily achievable. Integrating HTN control in the primary healthcare program may be another option, whereby multipurpose health workers can be trained and utilized for the detection and monitoring of HTN. All such efforts must be coupled with continuing medical education programs for healthcare providers to promote awareness of the current guidelines for the diagnosis and treatment of HTN. It is important for healthcare providers to pursue contemporary goals of HTN treatment consistently and to motivate their patients to improve compliance.

Acknowledgments

We thank S Sivasankaran, Additional Professor of Cardiology, Sree Chitra Tirunal Institute for Medical Sciences and Technology, Thiruvananthapuram, for his help in training the nurse for taking measurements, and N Krishnaji for his assistance in developing the sampling scheme for the study.

References

Much of the recent research on the origin of atherosclerosis has concentrated on the interplay among lipid metabolism, cytokines, and cellular activity within the arterial wall. There is general recognition of the fact that the atherogenic potential of low-density lipoprotein (LDL) lies in its cholesterol moiety or its oxidized derivative. Although considerable evidence supports the involvement of inflammation and immunity in atherogenesis, the role of the immune system has been recently questioned following the finding that mice, either with severe combined immunodeficiency or lacking a thymus, nevertheless develop characteristic atherosclerotic lesions with monocyte infiltration. However, the pro-inflammatory cytokine interleukin-6 (IL-6) gene transcript has been shown to be expressed in atherosclerotic lesions as well as genetically hyperlipidemic rabbits. CD40 signaling was shown to increase the secretion of IL-6 by endothelial cells, and atherosclerotic lesions in mice could be reduced in size by inhibiting CD40 signaling. A direct relationship between apolipoprotein (Apo) E and IL-6 was revealed by the finding that IL-6 mRNA and protein are overexpressed in the atherosclerotic plaques of the Apo E-knockout mouse model of atherosclerosis. A new dimension was added to atherosclerosis research by the discovery of a novel cell surface cholesterol-specific sensor (designated receptor-Ck) which, through its signaling pathway, regulates genes involved in the cell cycle (c-fos, c-myc, cyclin E, p27); cell death (Bcl-2); cholesterol homeostasis [HMC-CoA reductase: Apo B-specific LDL receptor through proteolytic maturation of the 125 kDa sterol response element-binding protein (SREBP) with an affinity for the sterol regulatory sequence in these genes], and cytokine IL-6. Further, oxy-derivatives of cholesterol (25-OH cholesterol or 7-keto cholesterol), through their specific or intracellular receptor LXRα, have been shown to downregulate genes coding for c-myc and Bcl-2, leading to cellular apoptosis, as well as upregulate genes coding for 125 kDa SREBP, Apo E, CETP, and IL-8. Keeping in view these observations, an attempt was made to define a molecular link between cholesterol, cytokines, and atherosclerosis (Fig. 1). To confirm this hypothesis, the present study was directed towards understanding the inter-relationship between expression coupled with functional activity of receptor-Ck (reflected by the expression of various key genes that are regulated by this receptor) and the developmental stages of atherosclerosis of the arterial wall.
Methods

Specific antibodies against various gene products, such as SREBP, cyclin D, p27, and CD40, were obtained from Santa Cruz Biotechnology, USA. The polyclonal monospecific antibody against receptor-Ck was raised in our laboratory. All other reagents/chemicals used in the study were procured from Sigma Becton-Dickinson.

Aortas (n=25) were obtained from human subjects up to 60 years of age (after obtaining valid consent from legal guardians of the subjects declared dead because of accidental trauma, and on whom medicolegal post-mortem was carried out by the Forensic Medicine Department of our institute). The aortas were cut open to visualize grossly the various types of atherosclerotic lesions as well as normal intima/media tissue adjacent to these lesions. Half of the tissue specimens from normal tissue and the lesion site were processed for protein isolation, and the other half of both the types of tissue specimens were fixed in 10% neutral formaldehyde for morphologic study. The fixed tissues were processed for preparing paraffin blocks. The paraffin sections were 4 µ thick and stained with hematoxylin and eosin. On the basis of morphologic examination (Fig. 2), only those aortas (n=6) with all three features (normal, fatty streak, fibrofatty/fibrous lesion) in each aorta were selected for the gene expression study. The protein extract from each tissue was subjected to SDS-PAGE followed by the Western blot test. Immunodetection of the Western blots was carried out using specific antibodies against various gene products and employing the standard immunodetection procedure reported earlier. For comparison of gene expression between normal and atherosclerotic tissue from each aorta, the same amount of protein from each specimen of aorta was loaded on the electrophoresis gel.

Results

A gradual increase in receptor-Ck gene expression was observed from the normal to the developmental stages of an atherosclerotic (viz. fatty streak and fibrofatty lesion) arterial wall (Fig. 3). This increase in receptor-Ck gene expression was accompanied by a gradual increase in gene expression of the matured form of SREBP (47 kD), p27, IL-6, and CD40, as well as a gradual decrease in cyclin D gene expression from the normal to the developmental stages of an atherosclerotic arterial wall (Fig. 3). However, p27 was predominantly expressed in fibrous lesions (Fig. 3).
Cells from higher animals face the complex problem of not only sensing extracellular cholesterol but also the intracellular oxysterol pool, which arises as a result of either uptake through passive diffusion or Apo B/E-specific LDL-receptor or oxidation of cholesterol within the cells. Recent studies have identified these cholesterol sensors, designated receptor-C₁α, for extracellular cholesterol, and LxR-α for intracellular oxysterol. LxR-α has been shown to regulate SREBP gene transcription, and receptor-C₁α has been shown to regulate various genes involved in cholesterol homeostasis as well as cell death (Bcl-2) through proteolytic maturation of 125 kDa SREBP (giving rise to the 47 kDa transcription factor) having an affinity for the SRE sequence in their promoter region. It was found that inhibitors of the mevalonate pathway repressed LxR-α activity, and this repression was relieved by the addition of mevalonate or oxysterol.

Several studies have indicated that the presence of oxysterol in the LDL particle may be important for the production of atherosclerotic lesions, whereas other studies have claimed that the oxysterol derivatives of cholesterol are less atherogenic than native cholesterol. The direct atherogenic potential of cholesterol was unambiguously revealed by the finding that exposure of arterial smooth muscle cells to cholesterol, through an Apo B-specific LDL-receptor-independent pathway, displays most of the pathognomonic features of atherosclerosis observed at the cellular level. Further, receptor-C₁α has been shown to regulate cholesterol and DNA synthesis in HepG2 cells. The recent report that atherosclerotic lesions contain a substantial number of cells with characteristics of apoptosis, coupled with reports on the production of apoptotic events in human endothelial and smooth muscle cells by oxysterols, has provided a stimulus for research regarding the role of oxysterols in atherogenesis.

The oxysterol receptor LxR-α has been shown to down regulate genes coding for c-myc and Bcl-2 leading to cellular apoptosis, as well as upregulating genes coding for 125 kDa SREBP, Apo E, CETP and IL-8. Keeping in view these observations, an attempt was made to define how cholesterol and/or its oxyderivative (present in LDL) could create a specific cross-talk between their receptors, leading to the initiation of the atherogenic process at the cellular level (Fig. 1). According to this hypothesis, Apo E gene product (induced by oxysterol-dependent activation of LxR-α) has a dual function: (i) when Apo E is secreted alone, it inhibits LDL-cholesterol-dependent activation of receptor-C₁α, leading to the upregulation of genes coding for Bcl-2, cyclin D, and p27, as well as downregulation of genes coding for c-fos, c-myc, and IL-6; (ii) when Apo E is secreted together with cholesterol, it activates receptor-C₁α, leading to downregulation of genes coding for Bcl-2, cyclin D, and p27, as well as upregulation of genes coding for c-fos, c-myc, and IL-6. Hence, the presence of cholesterol and its oxyderivative in the modified LDL will result in transient activation/deactivation of receptor-C₁α-dependent genes, which will give rise to repeated cycles of growth with apoptosis, leading to a situation where apoptotic-deficient cells in the arterial wall would be selected, resulting in their accumulation and the formation of an oligoclonal atherosclerotic plaque. The results reported here (Fig. 3) conform with this hypothesis (Fig. 1). This hypothesis is further strengthened by the following findings: (i) nontransformed smooth muscle cells express Bcl-2 protein and induce apoptosis in these cells; (ii) therapeutic interventions to reduce IL-6 production are cardioprotective; (iii) atherosclerotic lesions could be reduced in size by inhibiting CD40 signaling; and (iv) studies of identical twins suggest a strong genetic component for premature coronary artery disease.

In conclusion, our observation suggests that receptor-C₁α, which defines a molecular link between cholesterol, cytokines, and genes involved in cell growth as well as death, may be of crucial importance in atherogenesis.

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Transcatheter Closure of Perimembranous Ventricular Septal Defect in a Patient With Situs Inversus and Dextrocardia

Vijay Trehan, Jamal Yusuf, Saibal Mukhopadhyay, UmaMahesh C Rangasetty, Ramesh Arora
Department of Cardiology, GB Pant Hospital, New Delhi

Successful transcatheter closure of a perimembranous ventricular septal defect with an Amplatzer device has been reported in patients with levocardia. We report a case in which the device could be deployed successfully in a child with isolated perimembranous ventricular septal defect with situs inversus and dextrocardia. (Indian Heart J 2003; 55: 256–258)

Key Words: Amplatzer device, Ventricular septal defect, Transcatheter closure

Ventricular septal defect (VSD) accounts for approximately 20% of all forms of congenital heart diseases. In the past 2 decades, significant advances have been made in the transcatheter closure of various left-to-right shunts such as atrial septal defect, VSD, patent ductus arteriosus, and coronary arterial fistula with various occlusive devices. The first successful transcatheter closure of a VSD was reported in 1987.

Transcatheter closure of a perimembranous VSD is technically more challenging than that of closing an atrial septal defect or patent ductus arteriosus. Its success necessitates the precise anatomic definition of the defect and its distance from the aortic valve. Though there have been many reports of successful closure of perimembranous VSDs (all with levocardia), we successfully closed an isolated perimembranous VSD in a patient with a malposed heart (situs inversus with dextrocardia).

Case Report

An 8-year-old girl had a history of frequent respiratory infections in early childhood. She was diagnosed to have a VSD in early infancy along with situs inversus and dextrocardia. Initially, she needed anticongestive treatment because of poor feeding and mild respiratory distress. She was managed conservatively till the past few months, when her parents complained that she had a moderately limited exercise tolerance. Chest X-ray showed a mild degree of cardiomegaly, and increased pulmonary vascular markings along with a right-sided apex of the heart. Electrocardiography showed inverted P and T waves in leads I and aVL along with negative QRS deflections, while the precordial leads (V1–V4) showed regression of the R waves with prominent S waves. Leads V5–V6 showed normal R wave progression. Transthoracic echocardiography showed situs inversus, dextrocardia with the left ventricle forming the apex, atrioventricular and ventriculo-arterial concordance, and a perimembranous VSD of 5.8 mm with a septal aneurysm. There were no other associated congenital defects. The defect was located 6 mm from the aortic valve. Color Doppler study revealed a peak systolic gradient of 45 mmHg across the VSD, and Qp/Qs ratio was found to be 1.8:1. Cardiac catheterization showed a pulmonary artery pressure of 50/20 mmHg with a mean of 30 mmHg and a pulmonary-to-systemic flow ratio of 1.9:1. In view of her continued symptoms and significant left-to-right shunt, transcatheter closure using an Amplatzer VSD occluder was planned.

Procedure: Transcatheter closure was performed under ketamine anesthesia. Left ventricular angiography was performed in the long-axis view (20° right anterior oblique view, 25° cranial), and the size of the defect at the left ventricular surface was measured in diastole (Fig. 1). The size of the VSD and its distance from the aortic valve were confirmed. The VSD was crossed using a 5 F Judkin’s right coronary curve catheter and a 0.035” exchange length Terumo wire (Terumo Corp, Japan). The wire was then
occluder (AGA Medical Corporation, Golden Valley, MN) attached to its delivery system was advanced through the Mullin’s sheath to the left ventricular apex. The left ventricular disc was then extruded and pulled with the long sheath into the left ventricular surface of the defect. While maintaining tension on the delivery cable, the right ventricular disc was also deployed (Fig. 2).

At this point, transthoracic echocardiography was done with color Doppler to determine the residual shunt, and whether the device was impinging on the aortic and tricuspid valves. After confirming that there was no impingement on either valve and no significant residual shunt, the device was released. A repeat left ventricular angiogram showed no residual shunt across the VSD (Fig. 3). A repeat hemodynamic study showed a pulmonary-to-systemic flow ratio of 1:1 and a pulmonary artery pressure of 39/17 mmHg. The total fluoroscopy time was 30 min, and the procedure time was 90 min. After 24 hours, repeat echocardiography showed that the device was in situ without any residual shunt. The patient was discharged on 75 mg aspirin once a day. At follow-up of 3 months, the patient is asymptomatic and her effort tolerance has improved.

Discussion

Closure has been described of muscular, perimembranous, postoperative, residual, and post-infarction VSDs.3–8 Despite being the most common congenital heart defect,
Transcatheter closure of VSD is an uncommon procedure in most tertiary centers, as it is technically challenging. Further, a perimembranous VSD should have a margin of at least 5 mm from the aortic valve before it can be taken up for transcatheter closure using an Amplatzer device.

Transcatheter closure of a perimembranous VSD requires the formation of a continuous arteriovenous loop for delivery of the device from the venous side. Much manipulation is required to pass a wire from the arterial side across the VSD into the right-sided chamber. The second challenge is the proper positioning of the device below the aortic valve, so that it does not impinge on the valve. As we have already closed 63 perimembranous VSDs in our center with a procedural success rate of 95.2%, we took up the challenge of trying to close a perimembranous VSD in a patient with dextrocardia. Recently published series of catheter closure of VSDs have shown a success rate of 90%–100%. In patients with levocardia, the perimembranous VSD is best profiled in the shallow LAO cranial view. We could profile the VSD in this patient with dextrocardia in the shallow RAO cranial view. Following this, a continuous arteriovenous loop was formed, and the device deployed successfully as described above.

To the best of our knowledge, this is the first case in the world literature in which a perimembranous VSD could be successfully closed using an Amplatzer muscular VSD occluder in a patient with dextrocardia.

References
Refractory Adenosine-Sensitive Congenital His Bundle Tachycardia: Response to Calcium-Channel Blockers

K Sharada, C Narasimhan, K Nageshwar Rao, B Soma Raju
Care Hospital, The Institute of Medical Sciences, Hyderabad

The congenital form of His bundle tachycardia is an uncommon pediatric arrhythmia. We report the case of a 7-year-old child with tachycardiomypathy. The incessant arrhythmia, detected in infancy, was resistant to amiodarone and beta-blockers. During electrophysiologic study, the tachycardia converted to sinus rhythm with intravenous adenosine and diltiazem. Subsequently, the child is maintaining sinus rhythm on oral verapamil. Calcium-channel blockers should be considered for the treatment of this arrhythmia, which is often resistant to multiple antiarrhythmic drugs. (Indian Heart J 2003; 55: 259–261)

Key Words: His bundle tachycardia, Calcium-channel blockers, Arrhythmia

Case Report

A 7-year-old female child was referred to the arrhythmia services at our institute for the evaluation of persistent tachyarrhythmia. She was born of nonconsanguineous parents and was the second of two siblings. Her elder sister was apparently normal. Our patient was symptomatic since the age of 1 year with marked breathlessness, and was found to have cardiomegaly on chest X-ray, and narrow QRS tachycardia on electrocardiogram (ECG). She was diagnosed as having dilated cardiomypathy with severe left ventricular dysfunction and atrial tachycardia. An echocardiogram performed at that time revealed global left ventricular (LV) hypokinesia and severe LV dysfunction. She was treated with digoxin, captopril, propranolol and amiodarone with improvement in symptoms and partial control of tachycardia rate.

At the time of admission, she had a respiratory rate of 20/min, her heart rate was 140 beats/min and blood pressure 100/70 mmHg. The mean jugular venous pressure was normal and the liver was not enlarged. Cardiac examination revealed a normal apical impulse, varying first heart sound, and LV third heart sound. The lungs were clinically clear. An ECG revealed a narrow QRS tachycardia at a rate of 140 beats/min with atrioventricular (AV) association (Fig. 1). She was taken up for electrophysiologic (EP) study in view of the incessant tachycardia with a possibility of tachycardiomypathy.

During EP study, the child was in tachycardia with a cycle length of 380 ms with ventriculoatrial association. Ventricular pacing dissociated the ventricular from the atrial electrograms without affecting His–His intervals (Fig. 2). Intravenous adenosine terminated the arrhythmia (Fig. 3), but the His bundle rate gradually warmed up to resume tachycardia again (Fig. 4). Intravenous metoprolol lengthened the tachycardia cycle length to 460 ms without

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**Correspondence:** Dr C Narasimhan, Care Hospital, The Institute of Medical Sciences, Exhibition Road, Nampally, Hyderabad 500001. e-mail: calambur@hotmail.com
converting to sinus rhythm. Intravenous diltiazem transiently converted the tachycardia to sinus rhythm with gradual resumption of the arrhythmia.

In view of the good response to intravenous adenosine and diltiazem, the child was started on oral verapamil at a dose of 2.0 mg/kg in three divided doses. A 24-hour Holter done one month later revealed good control of ventricular rate (mean heart rate 100 beats/min). At 6-month follow-up, the child was asymptomatic and had good biventricular function. She was mostly in sinus rhythm with occasional nonsustained junctional rhythm at a rate of 100 beats/min.

**Discussion**

HBT is a rare arrhythmia, peculiar to the pediatric age group. It is recognizable on surface ECG by a narrow QRS tachycardia with AV dissociation and a faster ventricular rate.\(^3\) The origin of the tachycardia is an automatic focus in the nodal tissue proximal to the bifurcation of the bundle of His.\(^4\) This arrhythmia has a primary or congenital form and an acquired form, which occurs postoperatively, particularly after congenital heart surgery.

The congenital form usually occurs in the first six months of life as a persistent arrhythmia, although sporadic cases have been detected *in utero.*\(^5\) In 60% of cases, it is associated with cardiomegaly or heart failure.\(^2\) A family history has been observed in 50% of patients.\(^1\) Histologic examination of the conduction system is reported to show diffuse hemorrhage and necrosis of the AV node/His bundle,\(^6\) and the presence of a constricting fibrosis around the main trunk of the bundle of His, which is similar in appearance to that found in congenital AV block.\(^7\)

The age at which the tachycardia presents is usually related to the ventricular rate, a higher rate (>250 beats/min) presents at an earlier age than that with a lower rate (<170 beats/min).\(^8\) The age at presentation is related more to the fast ventricular rate (>250 beats/min) than to the occurrence of congestive heart failure or impaired LV function. Despite advances in treatment, a mortality rate of 35% has been reported. The exact mechanism due to which death occurs is still unclear. Sporadic cases of sudden death have been attributed to the occurrence of paroxysmal complete AV block;\(^1,9\) it has been suggested that the same process of His bundle degeneration which causes tachycardia could later extend to cause AV block. Some cases have been attributed to the proarrhythmic effects of drugs used to control the arrhythmia.\(^10\)

HBT is unresponsive to synchronized cardioversion\(^3\) and, although difficult to treat medically, antiarrhythmic therapy is the treatment of choice. Treatment is indicated
in infants with symptoms, reduced ventricular function, or rapid heart rate. Digoxin is used to control the symptoms of congestive heart failure, and antiarrhythmic drugs are used to control the ventricular rate. Adequate rate control with antiarrhythmic drugs is reported to lead to improvement in ventricular function.

Various antiarrhythmic drugs have been used for the treatment of this rare condition. Amiodarone alone or in combination with beta-blockers (propranolol, sotalol), and class IC drugs (propafenone, flecainide) have all been used to control the arrhythmia. There is a paucity of information in the literature about the efficacy of calcium-channel blockers in this condition. In view of the good response to adenosine and intravenous diltiazem on EP study, our patient was started on oral verapamil, with which the tachycardia converted to sinus rhythm. Studies report the rarity of conversion to sinus rhythm even with a combination of antiarrhythmic drugs in these patients. Contrary to this, our patient reverted to sinus rhythm shortly after starting verapamil, and was doing well with no adverse effects at intermediate follow-up.

Though spontaneous cessation of tachycardia can occur, Sarubbi et al. reported that all 9 patients of HBT in their study continued to have arrhythmia and required antiarrhythmic drugs for rate control over a follow-up period of 2.6–21 years.

When drug therapy fails, AV junction ablation (transcatheter or surgical), with permanent pacemaker implantation has been used for intractable HBT. Alternatively, radiofrequency catheter ablation of the paraHisian region with selective targeting of the focus of junctional tachycardia while preserving AV conduction has been successfully performed for drug-refractory HBT. However, complete AV block is a potential complication and hence such therapy should be considered only after failure of medical treatment.

References
Stenting of a Large Thrombus-Containing Subclavian Artery Stenosis Using a Distal Protection Device

Sanjay Tyagi, UmaMahesh C Rangasetty, Upkar A Kaul
Department of Cardiology, GB Pant Hospital and Maulana Azad Medical College, New Delhi

Atheromatous obstructive lesions of the arch vessels that contain thrombi are at high risk for distal embolization during angioplasty. This can lead to catastrophic neurological complications. We report a case of acute-on-chronic ischemia of the left upper limb due to thrombus-containing subclavian artery stenosis. After placement of an intravascular filter device, angioplasty and stent implantation successfully relieved the stenosis without any complications. (Indian Heart J 2003; 55: 262–264)

Key Words: Endovascular therapy, Angioplasty, Distal protection

Percutaneous transluminal angioplasty and/or stenting has emerged as an alternative to surgery for patients with extracranial arch vessel obstruction. However, atherosclerotic debris or a thrombus released during angioplasty or stenting may lead to distal embolization and periprocedural brain ischemia or infarction.1 Experimental studies utilizing human carotid plaques have shown that embolic particles are released from them.2 In addition, transcranial Doppler studies have confirmed that multiple emboli are released during carotid, subclavian, and vertebral artery angioplasty.3,4 The risk of distal embolization would be much more in stenotic lesions containing a large thrombus. Over the past few years, distal protection devices have been used to capture and retrieve atherosclerotic material in carotid and coronary lesions (saphenous grafts and native).5 However, there is a scarcity of data on the use of distal protection devices in the stenting of subclavian artery stenosis containing a thrombus. Such devices protect against distal embolization. We report a case with severe subclavian artery stenosis containing a large thrombus, which necessitated the use of a distal protection device. Angioplasty and stent implantation could be performed successfully without any complications.

Case Report
A 65-year-old male, chronic smoker, nonhypertensive, and nondiabetic presented with a history of pain in the left upper limb after exercise for the past 6 months. The pain increased in severity, and the patient had developed rest pain for the past 15 days. He also developed a bluish discoloration of the fingertips of the left hand. The other limbs were not affected, and there was no history suggestive of coronary artery disease. On physical examination, the left upper limb was cooler, the left brachial and radial pulses were absent, and the fingertips were cyanotic. The other peripheral pulses were normal. Systemic examination was unremarkable. Routine biochemical, hematological, and lipid profile parameters were within normal limits. He underwent an arch aortogram and a selective angiogram of the left subclavian artery, which showed 90% stenosis in the first part with a large thrombus just distal to the obstruction (Fig. 1). The carotid and vertebral arteries were normal.

The patient was given a bolus of heparin 5000 units intravenously. The left subclavian artery was hooked with a 7 F Shuttle sheath (Cook Inc, Bloomington, IN, USA). The stenotic lesion was crossed with a Filter Wire Ex™ (Boston Scientific, Natick, MA, USA) along with its retrieval sheath. The distal part of the wire along with the filter was positioned in the vertebral artery on the left side, and the retrieval sheath removed (Fig. 2). Optimal positioning and apposition of the filter were confirmed in two orthogonal views by the injection of contrast. The lesion was predilated with a 3×15 mm coronary angioplasty balloon. Subsequently, a balloon-expandable Corinthian stent (Cordis Corp, FL, USA) measuring 7×15 mm was deployed at a pressure of 14 atm.

Check angiogram showed an optimal result with excellent dilatation of the stented segment (Fig. 3). A retrieval catheter was then passed over the filter wire into the vertebral artery to collapse the filter. Leaving 1 mm of the filter open, the system, i.e. the filter wire and the
On follow-up of 18 months, the patient continues to be asymptomatic. The arterial pulsations in the left arm are well palpable. The blood pressure in both arms continues to be the same.

**Discussion**

Occlusion of the subclavian or brachiocephalic artery accounts for approximately 17% of symptomatic extracranial cerebrovascular disease. Patients who have subclavian artery stenosis with thrombi need to be diagnosed early so that therapy can be started for disabling upper extremity ischemia and gangrene. The traditional therapy for subclavian arterial occlusive disease is a surgical bypass. A variety of surgical techniques have been used, including transthoracic procedures, carotid–subclavian bypass, and axillo-axillary bypass. However, even with less invasive, extra-anatomic, extrathoracic reconstruction, the morbidity and mortality are considerable. An analysis of published results shows that it is associated with a mortality rate of 2%±2% (0%–11%), stroke rate of 3%±4% (0%–14%), and an overall complication rate of 16%±11% (0%–43%).

Subclavian angioplasty has become the preferred mode of treatment for stenotic lesions. However, it has certain limitations, such as dissection in 10%–15% of cases, thrombosis in 2%–8%, and technical failure in 5%–12%. Distal embolization of plaque material or a thrombus into the vertebral artery resulting in neurological deficit has been reported in 1% of procedures. In the presence of a thrombus, the risk of distal embolization and stroke is greater.
Stents are increasingly being used in arch vessel angioplasty, and have been found to overcome some of the limitations of balloon angioplasty, thereby improving the acute and long-term outcomes. The use of stents may limit distal embolization by trapping debris between the stent and arterial wall. However, microembolization still occurs. Transcranial Doppler studies have shown evidence of multiple embolization during almost all carotid stenting procedures. Carotid angioplasty and stenting is associated with perioperative stroke rate of 3%–6% in most series, largely due to distal embolization. It has been shown in various studies that capturing these materials with a distal protection device leads to a reduction in neurological events. In a recent review of studies, the stroke and death rate within 30 days was found to be 1.8% in patients treated with a cerebral protection device compared with 5.5% in patients treated without a cerebral protection device. In the present case, there was a big thrombus in the proximal portion of the subclavian artery. Distal embolization into the vertebrobasilar territory could have led to disastrous consequences. The filter device retrieved thrombotic material, thereby avoiding neurological complications. Thrombolytic therapy to lyse the thrombus followed by angioplasty may be an option in such a case, but may be complicated by embolization of the thrombus or hemorrhage. Protected angioplasty and stenting, as used in this case, would seem to be a safer option.

There are three approaches to cerebral protection: distal balloon occlusion devices, distal filter devices, and proximal occlusion devices. Each approach has its inherent advantages and disadvantages. The FilterWire EX (Boston Scientific, Natick, MA, USA) used in this patient is a new filter device currently under clinical investigation. The FilterWire is unique in that it has an off-center filter mounted on a 0.014" guidewire. Because of the unique design of the fish-mouth filter opening, it is extremely flexible, and also has a low crossing profile (<3.5 F). The filter has bare holes of 80 µ that permit antegrade flow while providing distal protection. In addition, the nitinol framework, which supports the filter, provides circumferential contact with the arterial wall, thereby assuring complete apposition of the filter, even in diseased and tortuous vessels. Finally, this filter can be recaptured (collapsed) and retrieved using any standard peripheral balloon that is used for post dilatation. Recently, a multicenter experience using this filter in patients undergoing carotid artery stenting has been reported by Grube et al. Embolic material was retrieved in 74% of 36 procedures, with only 2 (5.7%) transient periprocedural neurological events, and 0% 30-day major adverse cardiac events. Flow reversal also could provide protection from atheroembolization during subclavian angioplasty to some extent. However, some cases do develop neurological complications following angioplasty. Transcranial Doppler studies have also shown microembolization during and immediately after subclavian angioplasty. Techniques to make the procedure safer need to be employed.

The present case demonstrates the innovative use of a distal filter protection device in the presence of a large thrombus in the subclavian artery to protect the posterior circulation from embolization during angioplasty. Reduction of embolization by the use of a distal protection device during carotid artery stenting, and our experience with this case, suggest that the use of a protection device should be considered for proximal subclavian artery interventions, especially those with a thrombus.

References

Sutureless Patch Repair of Post-Myocardial Infarction Left Ventricular Rupture

AR Raghuram
Apollo Hospitals, Chennai

Ventricular rupture following myocardial infarction is a serious clinical problem with a high mortality. A 60-year-old man with left ventricular rupture and cardiac tamponade following myocardial infarction was managed successfully by emergency surgery. An onlay patch of Teflon held in place by an adhesive without any sutures was used to repair the ruptured myocardium. (Indian Heart J 2003; 55: 265–267)

Key Words: Myocardial infarction, Ventricular rupture, Patch repair

Case Report

A 60-year-old man developed acute chest discomfort while traveling in a remote place. He was immediately shifted to a nearby town 4 hours away, where he was diagnosed to be suffering from acute anterolateral myocardial infarction. He was thrombolyzed and shifted to a city hospital after 12 hours. After 48 hours, he again developed chest pain with ST elevation in leads I, aVL, V5, and V6. Reinfarction was suspected and treated with eptifibatide infusion. Since he continued to have pain and showed signs of shock, he was shifted to our hospital.

An echocardiogram revealed evidence of ventricular rupture high in the lateral wall and cardiac tamponade. A coronary angiogram was done, which showed diffuse coronary disease with total occlusion of the first diagonal artery. The disease was not bypassable. Left ventricular function was adequate. He was immediately shifted to the operation theatre.

Hemodynamics were maintained with inotropes, and anesthesia was carefully induced. A midline sternotomy was done. The pericardium was tense and bluish. On opening the pericardium, about 600 ml of blood-stained fluid was drained, and the hemodynamics improved instantaneously. There was an acute infarct high up in the lateral wall near the left atrial appendage measuring about 2×3 cm. There was active oozing of blood from the area. The coronary arteries were diffusely diseased. The diagonal artery in the region of the myocardial rupture was small, diffusely diseased and not bypassable. An oval patch of Teflon measuring 4×6 cm was cut. The area was dried well by application of pressure with a gauze for 5 min. BioGlue (Cryolife International Inc. Kennesaw GA, USA) was applied to the dried area, and the Teflon patch placed over that area and held compressed for 10 min. On release of pressure, there was no oozing.

The chest was closed with a pericardial drain after placing epicardial pacing wires. Inotropes were withdrawn and the postoperative period was uneventful. At 6-month follow-up, the patient is doing well. Postoperative echocardiogram (Fig. 1) clearly revealed the patch with no pericardial collection, and adequate ventricular function.

Discussion

Autopsy studies indicate that 8%–20% of deaths following myocardial infarction are due to free-wall myocardial rupture. However, it is still a rare clinical condition to encounter for most cardiac surgeons, even those working in busy cardiac surgical centers. Thus, there is very little scope to formulate a standardized technique to manage this life-threatening emergency.

Pathologically, the endocardial defect is relatively small. However, blood seeps through the myocardium and oozes through multiple rents in the epicardium. This lesion is better described as a “bleeding hematoma” rather than a...
Mortality in this condition is as high as 25%–30%. Repair of these defects is not easy because it is not a simple rent in the myocardium surrounded by normal muscle all around. The edematous, friable tissue in the vicinity of the rupture does not hold sutures well.

The standard technique of repair consists of wide excision of the infarct on cardiopulmonary bypass (CPB) and ventricular reconstruction using a Teflon or Dacron patch. This is the technique of choice if the patient has an associated septal defect or mitral regurgitation needing simultaneous correction. It entails a long period of bypass in a sick patient and a great deal of bleeding from the sutured area once the patient is weaned away from the bypass. When the lesion is an isolated seeping hematoma of the free wall, it is best tackled by an off-pump approach using a Teflon, Dacron or pericardial onlay patch. Earlier reports described a technique of suturing the onlay patch to the surrounding healthy myocardium with running prolene sutures. Application of sutures on a beating heart in an edematous myocardium is technically demanding, and sometimes results in further extension of the tear. Another off-pump method is felt-buttressed mattress suturing of the defect when the necrotic area is small. This sounds simple but can be terrible when the surrounding tissues are edematous and friable. The bleeding may become uncontrollable if the tissues tear further and emergency CPB may be necessary to save the patient. If too wide an area is sutured and bunched up, it can distort the ventricular geometry.

The recent technique of sutureless patch repair using an adhesiver to fix the patch onto the defect and adjacent healthy myocardium has many advantages: (i) it can be done without CPB, thus avoiding bleeding complications; (ii) no suturing is required of friable edematous myocardium; (iii) the left ventricular geometry is preserved.

This technique was particularly useful in this patient because he was on antiplatelet medication until the time of presentation to the emergency department. His blood group was O-negative and availability of compatible blood was limited.

The adhesives available are: (i) fibrin glue; (ii) gelatin hydrogels; and (iii) synthetic cyanoacrylate monomers. Fibrin glue is completely biodegradable and nontoxic. It depends on the normal clotting mechanism to produce a stable fibrin matrix. The gelatin hydrogel contains a mixture of gelatin and resorcinol, which polymerizes on contact with formaldehyde. The long-term toxic effects of formaldehyde are a source of concern. Synthetic glues are monomers, which polymerize on contact with fluids in an exothermic reaction. Both Padro et al. and Lachapelle et al. have used synthetic glue. The cytotoxic and possible mutagenicity of these chemicals is probably reduced by acetylation.

Even though the sutureless patch technique is simple and easy, it may not be universally applicable to all cases of left ventricular rupture. When there is active squirting of blood from the torn site, it is not possible to use the adhesive because the glue is effective only when applied to a dry surface. A 5-year follow-up of sutureless patch repair by Padro et al. showed 100% survival.

Conclusions: Sutureless repair for left ventricular free-wall rupture is simple, effective, and easily reproducible. It is associated with a good clinical outcome.

References


An acquired aortopulmonary artery fistula is rare. We describe a case with an aortic arch aneurysm communicating with the main pulmonary artery. The diagnosis was made on the basis of transthoracic echocardiography and confirmed by transesophageal echocardiography. A post-mortem examination revealed the complete anatomy of the aneurysm and the aortopulmonary communication.

Key Words: Aortopulmonary fistula, Echocardiography, Aortic aneurysm

Case Report

A 76-year-old hypertensive woman was admitted with symptoms of worsening dyspnea on exertion of 4 weeks' duration, which was acute in onset and associated with paroxysmal nocturnal dyspnea. On examination, she was found to have anemia, a raised jugular venous pressure, and normal blood pressure. The peripheral pulses were normal.

Cardiovascular examination revealed a hyperdynamic left ventricular apex in the left 5th intercostal space in the mid-clavicular line. The pulmonary component of the second sound was loud. There was a harsh, pansystolic murmur heard all over the precordium, and a continuous murmur in the second and third intercostal spaces. There were extensive crepitations in both lung fields. Examination of the other systems were within normal limits.

Investigations revealed that the hemoglobin level was 9 g%; total and differential WBC counts were normal; blood urea was 36 mg% and serum creatinine 1.2 mg%. The serum lipid values were: total cholesterol 155 mg%, high-density lipoprotein cholesterol 40 mg%, low-density lipoprotein cholesterol 95 mg%, and triglycerides 96 mg%. All other routine investigations were within normal limits.

The ECG was within normal limits while chest X-ray revealed an aneurysm of the arch of the aorta with cardiomegaly. There was evidence of pulmonary edema and pulmonary venous congestion with bilateral pleural effusion (Figs 1a and 1b).

Transthoracic echocardiogram revealed a 6.5×7 cm aneurysm of the arch of the aorta layered with clots adjacent to the main pulmonary artery (MPA). A two-dimensional (2-D) echocardiogram showed a drop-out measuring 9–10 mm in the common wall formed by the aneurysm and pulmonary artery. Continuous-wave Doppler study showed a continuous flow across the defect with a gradient of 54/13 mmHg (Fig. 2). Color Doppler

Fig. 1. (a) Chest X-ray showing cardiomegaly with bilateral pleural effusion. An aneurysm of the arch of the aorta is seen, causing mediastinal widening; (b) a CT scan of the chest also demonstrates the aneurysm in planar imaging.
study revealed a shunt across the defect entering the MPA near its bifurcation, the direction of flow being perpendicular to the long axis of the MPA, the jet then hitting the opposite wall of the pulmonary artery and breaking into two—one towards the pulmonary valve and the other towards the right pulmonary artery (Figs 3a and 3b). The left ventricle was mildly dilated and hyperkinetic, the left atrium was enlarged, and there was moderate mitral and tricuspid regurgitation. The calculated pulmonary systolic pressure was 82 mmHg.

A transesophageal echocardiogram showed the large aneurysm with clots and a fistulous communication with a continuous signal in the pulmonary artery (Figs 4a and 4b). There was a spontaneous echo contrast in the aneurysm.

A CT scan of the thorax delineated a saccular aneurysm measuring 7×7×6 cm at the arch with the fundus pointing inferiorly. The aneurysm contained a thrombus and was free from the origin of the arch vessels (Figs 5a and 5b).

The patient was advised a coronary angiogram followed by repair of the aneurysm; however, the patient’s condition deteriorated during her hospital stay, and she could not be operated on due to financial reasons. A limited autopsy was conducted for clinical interest.

The autopsy showed the aneurysm to be adherent to the MPA (Fig. 6a) and there was evidence of hemorrhage in the wall of the aneurysm. The aneurysm was layered with clots (Fig. 6b), and a direct communication between the aneurysm and MPA (fistula) could be visualized (Fig. 7). Histopathologic examination revealed the aneurysm to be atherosclerotic and sections of the coronary artery showed calcific plaques.

Discussion

This case highlights a rare instance of an aortic aneurysm that ruptured into the pulmonary artery, leading to an acute left-to-right shunt with volume overload of the left
ventricle causing acute congestive heart failure. Clinically, the patient had features of pulmonary edema with mitral and tricuspid regurgitation associated with pulmonary hypertension. The continuous murmur pointed towards a fistula between the great vessels.

Acquired communication between the aorta and pulmonary artery has been reported as a rare complication of thoracic aortic aneurysms. A review of 4000 autopsy cases of thoracic aortic aneurysms revealed that only 3.7% of them ruptured into the pulmonary artery. Most of these aneurysms rupture to the right or anteriorly, which explains the low incidence of rupture into the pulmonary artery. Aortopulmonary artery fistula has been reported as a rare complication of aortic dissection. Other causes include Marfan syndrome, trauma, infections, inflammatory aortitis (giant cell arteritis), and syphilitic aortitis. The commonest cause, however, is atherosclerotic aneurysm. The cause in this case was atherosclerosis as shown by the pathologic findings. One case report of severe aortic stenosis with acquired aortopulmonary fistula presenting with pulmonary embolism, who underwent successful repair, has been published. A case report of an aortopulmonary fistula with paradoxical cerebral embolism delineated with magnetic resonance imaging of the heart has also been published. The anatomic location of the fistula was confirmed on pathologic examination, which also helped to indicate the probable mechanism of formation of the communication. Since the aneurysm was adherent to the MPA, erosion of the wall of the aneurysm must have predisposed to the fistulous communication without free rupture; the adhesion itself was possibly due to the chronic pressure effect of the aneurysm. A total of 108 cases of ante-mortem diagnosis of aortopulmonary fistulae due to various causes have been reported in the world literature till 1992 and, of them, a few cases have been successfully operated. However, no case of a similar nature has been reported in the Indian literature (specifically atherosclerotic). Surgical treatment was a viable option, since the patient was hemodynamically stable at presentation, but could not be carried out for financial reasons. Percutaneous intervention was ruled out since the aneurysm involved the arch (covered stent). Early diagnosis and prompt surgical intervention using profound hypothermia and total circulatory arrest are essential for a successful outcome, according to the published literature.

In conclusion, aortopulmonary fistula is a rare complication of thoracic aortic aneurysms, and echocardiography is essential to make an early diagnosis. Timely surgical intervention is necessary, without which the fatality rate is high. To the best of our knowledge, this is probably the first reported case of aortopulmonary fistula in the Indian literature.

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Hypertension is the most common major complication of Takayasu’s arteritis. In patients with renovascular hypertension, which is the most prevalent form of curable hypertension, drug therapy is often associated with the problem of partial control of blood pressure (BP), while multidrug therapy may result in side-effects and poor patient compliance. Carbon dioxide (CO₂)-guided intervention is useful for the endovascular treatment of renal artery stenosis, as the use of even a small volume of nonionic contrast medium can be associated with a marked deterioration in renal function in these patients. We report a patient with type II Takayasu’s arteritis affecting the single functioning kidney, who underwent an exclusive CO₂-guided renal angioplasty.

**Case Report**

A 28-year-old female with hypertension for 15 years gave a history of having undergone a left nephrectomy for uncontrolled hypertension 14 years back. She was on 3 antihypertensives at the time of presentation. Clinical examination revealed a BP of 204/108 mmHg, and a right renal artery (RRA) bruit. Her ESR was elevated (60 mm after 1 hour). Serum creatinine was 1.8 mg/dl (normal 0.8–1.4 mg/dl), and renal Doppler study revealed tight RRA stenosis.

**Procedure:** The right groin was cannulated with a 7 F Avanti sheath under local anesthesia, and 5000 IU of unfractionated heparin was administered. A 6 F pigtail angiography catheter was introduced, and positioned at the upper border of the first lumbar vertebra. The catheter was flushed with saline, and connected with a three-way stopper to the CO₂-delivery system (Fig. 1). The side port of the three-way stopper was connected to a pressurized cylinder with medical grade CO₂. The other port was connected to a 50 cc plastic, graduated collection syringe.

The pressurized gas cylinder was opened towards the collection syringe, the piston of which was fixed to accommodate the desired volume of gas. The three-way stopper was then turned to allow the gas, now under pressure in the syringe, to auto-inject into the pigtail catheter, and angiography performed in the digital subtraction mode at 12.5 frames/s. The nonselective aortogram using 30 ml of CO₂ delineated the gross anatomy, and the origin of the RRA (Fig. 2a).

The ostium of the RRA was engaged with a 7 F renal guiding catheter. A 0.018” Road Runner guidewire (Cook
Inc.) was gently manipulated across the lesion. Over this, a 4×20 mm Symmetry balloon (Boston Scientific Meditech) was negotiated, and the lesion predilated to a pressure of 6 atm. A postdilatation CO₂ angiogram done through the guiding catheter in the manner described above showed suboptimal results. A 5×16 mm premounted renal stent (Bridge X3, 75 cm, Medtronic AVE) was then positioned optimally across the lesion, and deployed at 12 atm. Post-deployment CO₂ injections showed a good flow of gas with preservation of all the segmental arteries (Fig. 2b). A pull-back pressure analysis showed abolition of the pre-existing gradient.

**In-hospital follow-up:** Following the procedure, the patient remained normotensive for 48 hours, requiring withdrawal of all antihypertensive medication. Subsequently, there was a transient elevation of mean BP, requiring partial re-institution of antihypertensive therapy. Serial serum creatinine estimations following the procedure showed a transient elevation to a maximum of 2.7 mg%. At discharge on the 4th day, the serum creatinine was 1.3 mg%, and the patient was normotensive.

**Discussion**

Involvement of the renal arteries with steno-obstructive lesions occurs in 34%–85% cases of arteritis. In the majority of these cases, the orifice and proximal segment of the renal arteries are involved, and these lesions may be localized or diffuse. Surgical revascularization to improve the renal blood flow is associated with considerable morbidity, mortality, postoperative complications, and cost. Renovascular hypertension resulting from Takayasu’s arteritis can safely be treated by renal angioplasty with excellent clinical results.

CO₂-guided intervention is a feasible and useful option in patients with renal artery stenosis, especially in those who have renal impairment. CO₂ as an arterial contrast agent was first used by Hawkins. CO₂ is 20 times more soluble than oxygen, and is eliminated from the blood in a single pass through the lungs. However, CO₂ reduces the cerebral blood flow, and its use should be restricted to organs below the diaphragm. CO₂ angiography produces suboptimal images, especially if bowel preparation has been inadequate, and there may be patient intolerance.

CO₂ can be injected either using a dedicated pump injector or by hand. As described, we used a custom-made CO₂ injector. Caridi et al. performed 29 renal angioplasties without stenting in 21 high-risk patients using CO₂ in whom 6 (29%) needed adjunctive conventional contrast. In a series by Kan et al., in which 11 renal arteries were treated in 10 patients, 9 arteries (82%) required additional contrast. Our patient received no contrast during the entire procedure.

It is worthwhile pointing out that post-procedure, the level of serum creatinine may remain elevated, as in this case, and this could be due to the ischemia caused by balloon occlusion or the sluggish flow induced by the gas.
in the renal segmental arteries. In our case, it was transient and improved with good hydration. Pre-discharge reduction of serum creatinine to levels lower than the baseline suggests that exclusive CO₂-guided intervention worked as a nephron-saving procedure in our patient. The use of CO₂ does not, however, obviate routine measures of renal protection, such as adequate pre-procedural hydration and the use of theophyllines. It is also prudent to have hemodialysis back-up, especially in cases with prolonged procedure time, and those requiring the adjunctive use of conventional contrast agents. The immediate and rapid reduction of BP followed by later elevation is not unusual after renal angioplasty, and may require partial re-institution of antihypertensive therapy.

In conclusion, CO₂ is a useful adjunct to conventional contrast-guided interventions, especially in patients with impaired renal function, which precludes the use of conventional contrast media. When used judiciously, CO₂ can minimize, and in some cases even replace, the use of conventional contrast agents.

Acknowledgments

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References

Off-Pump Coronary Artery Bypass Grafting in High-Risk Patients

R Ascione, A Ghosh, GD Angelini
Bristol Heart Institute, Bristol Royal Infirmary, Bristol, UK

In the past decade, off-pump coronary artery bypass (OPCAB) surgery has become an established surgical technique. The evidence available from a number of observational, case-matched, and prospective randomized studies suggests that elective OPCAB surgery reduces postoperative morbidity and organ dysfunction.1–5 Over the past few years, there has been an increasing profile of co-morbidity in patients presenting for coronary artery bypass surgery.6 Since off-pump coronary revascularization is conducted on the beating heart, it is a potentially more physiological method of maintaining the functional integrity of malfunctioning organs or systems. Therefore, high-risk patients should, in theory, benefit the most from revascularization on the beating heart. The aim of this review is to investigate the available literature on the efficacy of OPCAB surgery in high-risk patients.

OPCAB Surgery in High-Risk Patients

Since the re-advent of OPCAB surgery, many centers have carried out studies of variable scientific quality, ranging from prospective randomized trials and case-matched studies to observational reports. Many of these have focused on high-risk patients. The best of the latter, based on study design, size of the surgical population, and quality of the statistical analysis, have been discussed in this review.

Some of these studies were on high-risk patients, selected according to either a list of inclusion criteria, or recognized systems of preoperative risk stratification, whereas others focused on high-risk patients presenting with a specific organ dysfunction.

a. Overall high-risk patients: Our group recently investigated the incidence of early mortality and morbidity in 1570 consecutive high-risk patients undergoing only coronary artery bypass grafting (CABG) [332 (21.1%) underwent OPCAB surgery] selected on the basis of the following criteria: age >75 years, ejection fraction (EF) <30%, recent myocardial infarction (MI) (<1 month), current congestive cardiac failure, previous cerebrovascular accident (CVA), serum creatinine >130 µmol/L, respiratory impairment, peripheral vascular disease, redo surgery, and intraoperative endarterectomy.7 After adjustment for known prognostic factors, the majority of the variables investigated showed the benefits associated with OPCAB surgery. This was statistically highly significant for blood loss, transfusion requirement, and ICU and hospital stay.

Similar results were recently reported by Meharwal et al.8 who compared 1075 high-risk patients undergoing OPCAB surgery to 2312 similar patients undergoing conventional surgery. Selection criteria included poor left ventricular (LV) function (EF ≤30%), advanced age (>70 years), left main stenosis, acute MI, and redo coronary artery surgery. Patients undergoing OPCAB had significantly less intubation time, mean blood loss, atrial fibrillation, and requirement for prolonged ventilation. In similar studies, other workers have also found significant benefits associated with OPCAB surgery, including reduced mortality and perioperative MI.9

Some authors have focused on the elderly population, which is increasing the risk profile of patients requiring cardiac surgery, with an incidence of nonfatal complications ranging from 30% to 73%, and in-hospital mortality from 5% to 24%.10 Two recent retrospective reports11,12 have provided evidence supporting the use of OPCAB surgery in elderly patients undergoing myocardial revascularization, with a decreasing rate of major postoperative complications, including low-output syndrome, atrial fibrillation, blood usage, and shorter ICU and hospital stay.

b. High-risk patients with specific organ dysfunction

Poor LV function: Mohr et al.13 demonstrated good early and long-term results in 57 patients undergoing OPCAB surgery within 1 week of an acute MI, with an operative mortality of 1.7%, and a 5-year actuarial survival of 82%. Tugtekin et al.14 reported the in-hospital and 6-month outcome of 31 patients with severe LV dysfunction undergoing OPCAB surgery. Hospital survival was 93.5%. Intra-aortic balloon pump (IABP) was used in...
1 patient, and no additional events of perioperative MI or stroke were observed. The 6-month survival was 90%. In a similar study on 48 patients with severe LV dysfunction, Eryılmaz et al.\textsuperscript{16} reported an in-hospital mortality of 6.25%. Of the 45 survivors, 41 had improved NYHA status, LV fractional shortening, and EF at 1 year.

Recently, we investigated the outcome of 250 patients with preoperative LVEF <30% (74 off-pump, 29.6%).\textsuperscript{16} After adjustment for different surgical teams and propensity scores, no differences were found between the groups with regard to in-hospital mortality and morbidity. The only in-hospital outcome that showed a significant difference after adjustment was the need for intraoperative inotropic support, which was 2-fold higher in on-pump patients (odds ratio 5.1, 95% CI: 2.55–10.2, p<0.001). Goldstein et al.\textsuperscript{17} reported the early and mid-term outcome of 100 patients with baseline EF <30%. Observed mortality was 3% with a predicted mortality of 5.3%. The ratio of observed to expected mortality was 0.56. The incidence of adverse events compared favorably with that reported in the Society of Thoracic Surgeons database for all CABG patients regardless of LV function, and also to a concurrent CABG cohort. One-year survival was 85%, freedom from cardiac re-admission was 88% and relief from angina 83%.

One possible explanation of the results reported in these studies is that cardioplegic arrest is avoided. OPCAB surgery in elective patients has been found to be associated with reduced myocardial injury,\textsuperscript{5,18–20} arrhythmias, and requirement of inotropic support.\textsuperscript{5}

**OPCAB surgery and renal dysfunction:** The benefit of OPCAB surgery on renal function should be theoretically more evident in the presence of factors predisposing to renal failure, such as a raised preoperative level of serum creatinine and diabetes mellitus. In our study on 253 patients\textsuperscript{21} with preoperative serum creatinine >150 µmol/L (51 [20.1%] OPCAB surgery), a multiple logistic regression analysis showed cardiopulmonary bypass (CPB) inclusive of cardioplegic arrest to be an independent predictor of acute renal failure (ARF). This finding is supported by Magee et al.\textsuperscript{22} in a retrospective study on the influence of diabetes mellitus on mortality and morbidity. They found that diabetic patients undergoing OPCAB surgery had a significantly lower incidence of postoperative ARF when compared to patients undergoing conventional surgery.

Such findings are similar to those reported in elective patients undergoing specific assessment of renal function. In a randomized study\textsuperscript{23} on an on-pump group, we found markedly lower creatinine clearance values at 24 and 48 hours postoperatively compared to the preoperative levels, and a reduced urinary albumin/creatinine ratio and urinary N-acetyl-β-glucosaminidase activity compared to the off-pump group. Similar results were obtained by Loef et al. and Van Belleghem et al.,\textsuperscript{24,25} who demonstrated a greater increase in several markers of both glomerular and tubular damage after on-pump surgery compared to off-pump surgery.

**OPCAB surgery and neurological outcome:** Major neurological complications, reported to occur in 3.1% of patients, are responsible for 21% of the post-coronary bypass mortality rate, and prolong ICU and hospital stay.\textsuperscript{6} Such complications are associated with aortic manipulation, and a previous history of stroke.\textsuperscript{26} Patel et al.\textsuperscript{27} have recently reported the results of a series of 3770 patients (993 patients in the high-risk group) divided into 2 groups according to the baseline presence or absence of predictors of neurological events, such as previous stroke, carotid disease, peripheral vascular disease, and extensive calcification of the aorta. A logistic regression analysis showed that OPCAB surgery significantly reduced the incidence of stroke in predisposed patients. On the same lines, Bolotin et al.\textsuperscript{28} have reported that a no-touch aortic technique, only possible with OPCAB surgery by using arterial revascularization, is associated with a lower rate of neurological complications.

Using OPCAB surgery in elective patients, without avoiding aortic manipulation, reduces the release of S-100 protein seen in on-pump cases, but the effect on cognitive function remains controversial.\textsuperscript{29–31}

**OPCAB surgery and overweight patients:** In the past, obesity has been considered a major risk for coronary artery disease, and this condition is often associated with other risk factors, including diabetes, hypertension, and impaired respiratory function.\textsuperscript{34} A recent retrospective analysis of prospectively collected data performed at our institution on overweight and obese patients showed that off-pump surgery offered significant benefits, after adjustment for known prognostic factors, for intraoperative arrhythmias and inotropic use, and postoperative blood loss, transfusion requirement, chest infections, low cardiac output, use of IABP, arrhythmias, pulmonary complications, neurological complications including stroke, intubation time, ICU and length of hospital stay.\textsuperscript{11} These results were found even though the role of obesity as a risk factor for postoperative morbidity in patients undergoing coronary surgery has been questioned recently by the findings of several patient–cohort studies.\textsuperscript{36,37} Indeed, we recently found that obesity does not increase the risk of perioperative death and other adverse outcomes in patients undergoing CABG.\textsuperscript{35}
Conclusions
There seems to be a body of evidence in the literature suggesting that OPCAB surgery in high-risk patients reduces postoperative morbidity and organ dysfunction compared to conventional CABG with CPB and cardioplegic arrest.

There is consensus that OPCAB surgery results in a marked attenuation of the inflammatory response normally seen when CPB is used. This, together with the reported benefit on isolated organs, may allow a marked improvement in the quality of care and resource-saving while undertaking surgery of the ever-increasing elderly population presenting with co-morbidities.

This, in turn, indicates a need for a recognized teaching program that addresses genuine concerns about OPCAB surgery, the organization of dedicated audit systems of OPCAB surgery, and, not least, addressing the ethical issues of research projects designed to randomize patients to both techniques for “study purposes” only.

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Double-Orifice Mitral Valve

V Jacob Jose, Sunil Thomas Chandy, Bobby John
Department of Cardiology, Christian Medical College Hospital, Vellore

A 32-year-old female presented with class III exertional dyspnea. She gave a definite history of rheumatic fever. The echocardiographic features were suggestive of double-orifice mitral valve (DOMV) of the complete bridge type (Fig. 1a and b). The patient successfully underwent balloon mitral valvotomy. After diagnostic catheterization, balloon mitral commissurotomy was performed using over-the-wire technique with a JOMIVA 20 mm×4 cm balloon. Transseptal catheterization was done in the usual manner, under 30° right anterior oblique fluoroscopic view.1 A 7 F Swan–Ganz catheter was looped in the left atrium and negotiated across the medial orifice of the mitral valve into the left ventricle, facilitated by an 0.018” Road Runner wire. Through this a 0.035” Backup-Meier wire was negotiated into the left ventricle. A second Backup-Meier wire was used to cannulate the lateral orifice of the mitral valve. In order to do this a double-lumen catheter was advanced over the first Backup-Meier wire into the left atrium. A 0.032” guidewire was negotiated through the second lumen of the catheter into the left atrium. The double-lumen catheter was then withdrawn and a Swan–Ganz catheter advanced over this guidewire. Using a 0.018” Road Runner wire, the Swan–Ganz catheter was negotiated into the lateral orifice of the mitral valve. Further, the interatrial septum was dilated with a 14 F 50 cm long sheath. An over-the-wire technique with JOMIVA 20 mm × 4 cm balloon was used to dilate the lateral orifice. The end-diastolic gradient between the left atrium and left ventricle reduced from 14.9 mmHg to 2 mmHg. Since there was no significant residual gradient, the medial orifice was not dilated.

The first case of DOMV was reported by Greenfield in 1876. DOMV is a rare congenital anomaly of the subvalvar apparatus consisting of an accessory bridge of fibrous tissue, which divides the mitral valve into two orifices. In 85% of cases, the size of the orifice is not equal.2 DOMV usually occurs along with other cardiac anomalies, such as an atrial septal defect of the sinus venosus type, ventricular septal defect, patent ductus arteriosus, atrioventricular septal defect, coarctation of the aorta, and bicuspid aortic valve. Rarely, DOMV can be acquired following surgery for mitral valve prolapse.

Based on the echocardiographic studies, DOMV has been classified into three types by Trowitzsch et al.1 These are as follows:
1. Complete bridge type: Two separate complete orifices are visible from the leaflet edges all the way through the right. Both the orifices are circular, almost equal in size, and appear like a pair of spectacles.
2. Incomplete bridge type: A connection is seen between the anterior and posterior leaflets only at the leaflet edges, resulting in a double circle only at the leaflet level.

Correspondence: Professor V Jacob Jose, Professor and Head, Department of Cardiology, Christian Medical College Hospital, Vellore 632004
At the mid-basal level, the mitral valve appears normal.

3. Hole type: A single orifice is present at the leaflet level.

An additional smaller orifice is visible in one of the two commissures oriented roughly at a right angle to the main orifice.

Once this malformation is detected, differentiation of the various types in the parasternal and subxiphoid short-axis views can be done using accurate sweeping from the apex to the base of the ventricle. The apical 4-chamber view may be particularly useful in the hole type of defects because the 2 orifices cannot be reviewed in the short-axis view.\(^4\)

References


QRS Widening as a Marker of Dys-synchrony

We read with great interest the article “Cardiac resynchronization in heart failure” by JS Sra. Wide QRS duration has been considered a key criteria for selecting patients with congestive heart failure (CHF) for cardiac resynchronization therapy (CRT), as it has been suggested to be associated with marked RV-to-LV and intra-LV dys-synchrony. However, the correlation between QRS width and regional electromechanical LV dys-synchrony has not been completely clarified, and a high prevalence of LV systolic and diastolic asynchrony has also been found in patients with CHF and normal QRS duration. Hence, for a given QRS width there is considerable scatter in response to CRT-responsive patients with narrow complexes, and less responsive patients with wide complexes also exist. A study was done by Gasparini et al. in a large cohort of patients to assess the role of baseline QRS width (<150/≥150 ms) on clinical and echocardiographic parameters, hospitalization rates, and survival after CRT. In this study, 158 patients with CHF (121 men, mean age: 65 years, mean left ventricular ejection fraction (LVEF): 0.29%, mean QRS width:174 ms) underwent successful biventricular (BiV) pacemaker implantation, and were then followed up for a mean of 11.2 months. The patients were divided in 2 groups according to the basal QRS duration: the wide QRS (≥150 ms) (128 patients, 81%) and the narrow QRS group (<150 ms, 30 patients, 19%).

In the wide QRS group, the results were: (i) LVEF improved from 20% to 39% (p<0.0001); (ii) six-minute walk test improved from 311 to 463 m (p<0.0001); and (iii) the number of patients in NYHA classes III–IV decreased from 86% to 8% (p<0.0001).

In the narrow QRS group, the results were: (i) LVEF improved from 30% to 38% (p<0.0001); (ii) six-minute walk test improved from 370 to 506 m (p<0.0001); and (iii) the number of patients in NYHA classes III–IV decreased from 60% to 0% (p<0.0001).

The data showed that in patients with both wide and narrow QRS, BiV pacing substantially improved clinical parameters (NYHA class, six-minute walk test, quality of life, and hospitalization rate), and main echocardiographic indicators. Further, patients with narrow QRS had a better survival rate, rapidly regained LV function, and only a few patients remained in a higher NYHA class during follow-up. In another tissue Doppler study of 104 patients with bundle branch block, Garrigue et al. observed that 35% of patients with left bundle branch block (LBBB) had no interventricular dys-synchronization and 20% had no LV dys-synchronization. Despite fulfilling the “classic” criteria of wide QRS and LBBB, these patients are hardly candidates for CRT. Conversely, a sizable number of patients with right bundle branch block may present with mechanical anomalies, which might be corrected with CRT.

The results of recent investigations have prompted a reappraisal of the apparent correlation between conduction disorders and cardiac dys-synchronization. The new markers of asynchrony should be investigated and defined.

References

Vishal Bhatia and Boban Mathew
808, Potomac Avenue, Buffalo, New York USA 14209
Reply

We would like to thank Vishal Bhatia and Boban Mathew for their letter. Most studies in cardiac resynchronization have focused on conduction system disease involving left bundle branch block. Hopefully, future studies, including the one mentioned by the authors, will concentrate on other conduction system abnormalities and on studying patients with congestive heart failure without bundle branch block. However, large-scale double-blind studies will be needed to address this issue in detail.

Jasbir S Sra
University of Wisconsin Medical School-Milwaukee Clinical Campus, St Luke’s and Aurora Sinai Medical Centers
Milwaukee, USA

Brachial Artery Flow-Mediated Dilatation for Detecting Subclinical Atherosclerosis

I read with great interest the article on brachial artery flow-mediated dilatation (FMD) by Jadhav et al. The study involves the use of FMD, a promising, noninvasive tool for detecting subclinical atherosclerosis, which has potentially far-reaching implications. Hence, interpretation of such studies in the proper context is of utmost importance. However, there are several issues that have raised concerns about the methodology and statistical interpretation of the study.

The authors have taken an FMD cut-off value of 4.5% to identify the presence or absence of endothelial dysfunction, and have analyzed their data on that basis. This assumption is based on only one study, which was not large (122 subjects). Since endothelial dysfunction is influenced by many factors, it is inappropriate to uniformly apply the results of a particular study to all patient subgroups. This is clearly reflected in the wide range of FMD values obtained in different studies. In fact, even the recently published reports of the International Brachial Artery Reactivity Task Force on FMD and ACC/AHA expert committee on noninvasive tests of atherosclerotic burden have not mentioned any cut-off value for impaired FMD.

Even in the present study, the very high prevalence of endothelial dysfunction in subjects without coronary artery disease (CAD) possibly suggests that the cut-off value of 4.5% may not be applicable to this population subset. If this is actually so, one can imagine what the significance of the findings of the present study would be. It would have been better if the authors had plotted the receiver-operating characteristics (ROC) curve and calculated a cut-off value on their own. The authors are also requested to provide a summary of FMD values (mean, range, and standard deviation) obtained in their study that would be more informative, and would allow readers to be aware of spectrum in the Indian population.

The authors have not mentioned how the subjects were selected for the study. It appears that FMD was first assessed in patients with CAD and the results then compared with an equal number of controls without CAD. Since the positive and negative predictive values of the test directly depend on the prevalence of the disease being studied, these parameters can be calculated only when the entire study cohort represents a single group to which the results will be applicable. If the study involves two different groups of patients who are selected separately, these parameters cannot be calculated, because the prevalence of the disease in the entire cohort is no longer the same as in the actual population subset. For example, 50% of the subjects had CAD in the present study; hence, calculated positive predictive value (PPV) and negative predictive value (NPV) can be applied only to a population with an equally high prevalence of CAD, which is not the population to which this test will be applied. Thus, the calculation of PPV and NPV is statistically inappropriate in the present study.

The authors’ conclusion that FMD assessment can be a useful tool for the prediction of CAD is questionable, because they have obtained sensitivity (76%) and specificity (44%) values which suggest that this test is inferior to several other noninvasive tests available for the same purpose (including all the stress tests). A high odds ratio alone cannot be used for assessing the utility of a diagnostic tool.

There was a significant difference in the age of the subjects in the two groups. Even on multivariate regression analysis, age was the strongest predictor (stronger than FMD) of the presence of CAD, though it has not been mentioned in the report. It would have been better if age-matched subjects had been enrolled in the study.

Some of the p values mentioned in Tables 1 and 2 appear to be incorrect. These include p values for smoking, diabetes, and hypertension in Table 1, and for diabetes and hypertension in Table 2. Even the percentage value mentioned for the number of males in the non-CAD group is incorrect (Table 1). Of particular interest is the p value...
for the prevalence of smoking in the CAD and non-CAD groups (Table 1). The actual value would be <10^-8. Considering such a highly significant difference, it is very surprising that multivariate regression analysis did not show smoking to be an independent predictor of CAD.

References


Ravi R Kasliwal
Head of the Department
Non-Invasive Cardiology-Heart Stations
Escorts Heart Institute and Research Centre
New Delhi

Brachial Artery Flow-Mediated Dilatation in Prediction of Coronary Artery Disease in Indian Subjects

I would like to point out that in the article by Jadhav et al.1 the absence of a significant odds ratio for several established risk factors (Table 5) is because many of the factors are strongly correlated among themselves. A multiple logistic regression analysis using coronary artery disease (CAD) as a dichotomous outcome variable, and all the risk factors, including flow-mediated dilatation (FMD), as predictor variables, would have revealed these correlations. In turn, this would have suggested which factors could be dropped from the model, and which could be retained. Such an analysis would have revealed the contribution of each retained factor in the form of its regression coefficient and the odds ratio based on it.

Secondly, instead of using the previously published cut-off point of a 4.5% increase in FMD, they could have examined the receiver-operating characteristics (ROC) curves obtained by using the lower and higher cut-off points, just as Jose et al.2 did for pro-brain natriuretic peptide. This would have been a good opportunity to examine the validity of the 4.5% cut-off point in Indian patients.

The purpose of my comments is not to criticize the good work done by the authors, but to suggest how appropriate statistical analyses could have added more value to the study.

References


Arun Nanivadekar
C-2, Flushel Apts, 21 Road, Bandra (W), Mumbai

Reply

We sincerely express our thanks for the valuable inputs in both the letters in response to our article on endothelial dysfunction. We hope the following clarification may be pertinent to the issues addressed by Arun Nanivadekar and Ravi R Kasliwal.

The data submitted in Table 5 are, in fact, a multiple logistic regression analysis using coronary artery disease (CAD) as a dichotomous outcome variable, and all the risk factors, including flow-mediated dilatation (FMD), as predictor variables. The regression coefficient was deleted during review submission. Only age and FMD showed a significant correlation as shown in Table 1, reproduced here.

The studies on endothelial dysfunction utilizing the technique of FMD for the prediction of CAD have involved a small number of subjects. The study by Schroeder et al.1 on angiographically documented CAD is one of the best on the subject and widely quoted. We used the cut-off point of 4.5% based on their data, and this cannot be considered
inappropriate or inaccurate. Unfortunately, the Writing Group III report by Greenland et al. is a very short write-up on endothelial dysfunction with not much text on the practical aspects of the technique, including the cut-off value. Although no gold standard for the measurement of endothelial function exists, the measurement of flow-mediated dilatation (FMD) in the brachial artery assessed by Doppler ultrasonography is the most used method, and shows the most promise for clinical application. It is a well-tolerated, noninvasive, and low-risk procedure.

The area under the receiver-operating characteristics (ROC) curve, when an FMD value of 2.5% was used as a cut-off point for the diagnosis of CAD, was 0.62 (5% confidence interval: 0.52–0.71, p=0.018) as shown in Fig. 1. A cut-off value of FMD 2.5% had a sensitivity of 60% and specificity of 65% in the present study population. The AUC was marginally better than when FMD 4.5% was used as the cut-off value (AUC=0.60).

The mean FMD±SD in subjects without CAD was 4.8%±7.9% (range: 22%–25%), and in subjects with CAD 0.9%±10.8% (range: 45%–25%). It will be worthwhile mentioning here that subjects without CAD were not free of risk factors for endothelial dysfunction. In fact, the mean FMD value of healthy volunteers enrolled for the reproducibility study was 12.6%. If the group without CAD comprises completely healthy individuals, the sensitivity and specificity of the study will exceed 90%, and will be superior to the stress test and myocardial perfusion imaging, as already demonstrated by Schroeder et al. Prospective studies in angiographically documented, larger study populations will definitely improve the sensitivity and specificity of the present data.

The subjects of the study were enrolled consecutively as they presented to the hospital, and brachial artery FMD was performed as a part of the ongoing study. The number of subjects was equal in both the groups by chance and not decided upon while commencing the study. The calculation of sensitivity and specificity for the study is, therefore, not totally inappropriate. This also explains the difference in age in both the groups. We will be able to provide data on age-matched populations in both the subsets as the study progresses.

The p value in Table 1 is 0.012, the number of smokers among subjects with CAD being 6 and not 51, as erroneously mentioned. The corrected p values for hypertension and diabetes mellitus are 0.0111 and 1.00, and 0.215 and 0.015 in Tables 1 and 2, respectively. The error is regretted.

Smoking has surprisingly not been a risk factor in multiple logistic regression analysis for CAD in this study, possibly due to the smaller sample size. The lack of association of smoking with CAD has also been shown in the recent Chennai Urban Population Study from a selected population in south India. This does not in any way undermine the importance of an established risk factor but suggests that we look beyond it at other emerging risk factors.

References
primary prevention: noninvasive tests of atherosclerotic burden:
Writing Group III. Circulation 2000; 101: 16e–22e

Uday M Jadhav
Department of Non-Invasive Cardiology
MGM New Bombay Hospital
Vashi, Navi Mumbai

Sildenafil in Pulmonary Hypertension

The study reported by Bharani et al.1 had a crossover design. Therefore, the difference in the effects of sildenafil and placebo should have been analyzed by Analysis of Variance (ANOVA) rather than by the paired t test. In a crossover study, the factors are patients, treatments and periods. ANOVA separates the variation due to each factor, allowing the comparison of treatments after removing the variation due to periods and patients. Because the difference was large, the difference in the effects of sildenafil and placebo turned out to be statistically significant by the paired t test. Had it been modest, and had the period and patient effects been large, it could have been missed.

My purpose is not to criticize the good work, but to emphasize that matching the method of analysis to the design of the study can enhance the value of a research study.

Reference

Anil Bharani, V Mathew, A Sahu, B Lunia
Division of Cardiology
Department of Medicine
MGM Medical College and MY Hospital
Indore

Reply

We appreciate the interest shown by Arun Nanivadekar in our article.3 While the Analysis of Variance (ANOVA) provides the general answer regarding homogeneity of variance and homogeneity of means of given samples, the paired t test provides a specific answer to whether any significant difference exists between the means of the two samples. It is worth noting that the two essential conditions for application of the t test include (i) random selection of samples from the population; and (ii) the presence of homogeneity of variances in the samples. Before application of the paired t test on our data, the above conditions were fulfilled. One-way ANOVA essentially confirmed the homogeneity of variances in our samples and subsequent analysis using the paired t test showed that sildenafil therapy was significantly associated with improved exercise tolerance, decreased Borg dyspnea score, and decreased pulmonary artery systolic pressure. Further, treatment was the only variable in our study, the patients and periods were constant.

Reference

Arun Nanivadekar
C-2, Flushel Apts, 21 Road Bandra (W) Mumbai

Erratum

The authorship of the following original article (Indian Heart J 2003; 55: 152–157) should be read as follows:

Has the Prevalence of Rheumatic Fever/Rheumatic Heart Disease Really Changed? A Hospital-Based Study

TK Mishra, SN Routray, M Behera, UK Pattniak, C Satpathy
Department of Cardiology, SCB Medical College, Cuttack
A Comparison of Coronary Angioplasty With Fibrinolytic Therapy in Acute Myocardial Infarction


Summary

Primary percutaneous coronary intervention (PCI) is being increasingly recognized as the reperfusion therapy of choice in the treatment of acute myocardial infarction (AMI) with ST segment elevation. However, this facility is not widely available, which appears to negate the superiority of this strategy over fibrinolytic therapy. Delay in transportation of a patient from a local hospital to a center offering PCI is a major limitation. Whether PCI would still be better despite the time spent in transportation is an obvious question. The Danish Multicenter Randomized Study on Fibrinolytic Therapy versus Acute Coronary Angioplasty in Acute Myocardial Infarction (DANAMI-2) was a randomized trial conducted in 1572 patients with AMI who were randomized to treatment with accelerated intravenous alteplase or angioplasty. Of these, 1129 patients were enrolled at 24 referral hospitals, and 443 patients at 5 invasive treatment centers. Transfer to the nearest angioplasty center from the referral hospital was done within 3 hours. Patients randomized to fibrinolysis received alteplase. Heparin was given as a bolus of 5000 units intravenously followed by a 48 hour infusion. Aspirin and intravenous beta blockers were given to both the groups. Those randomized to the PCI arm received 10 000 IU of unfractionated heparin. The infarct-related artery was treated if it was totally occluded, if there was a culprit lesion with a diameter stenosis of more than 30%, or if there was < TIMI-3 flow. Stenting was attempted in all cases except when the vessel diameter was <2.0 mm. Only the infarct-related artery was tackled. Either ticlopidine or clopidogrel was given for a month after the procedure. Patients with symptoms for <12 hours and ST segment elevation were enrolled. Those with a contraindication to fibrinolysis, left bundle branch block, recent MI, previous coronary artery bypass surgery, renal failure, and metformin-treated diabetes were excluded. Also, high-risk patients with cardiogenic shock, severe heart failure, life-threatening arrhythmia, or those with a need for mechanical ventilation were excluded. At the time of the third interim analysis, in October 2001, it was clearly demonstrated that angioplasty was superior. Among patients at the referral hospital who were transferred to another center for PCI, or received fibrinolytic therapy on site, the primary end-point (a composite of death, reinfarction, or disabling stroke at 30 days) was reached in 8.5% of patients who were transferred for PCI as compared with 14.2% of those in the fibrinolytic group (p=0.002). Those patients admitted directly to invasive treatment centers had a similar outcome with 6.7% of the angioplasty group reaching the primary end-point compared with 12.3% in the fibrinolysis group (p=0.045). The difference in the 2 treatments arms was driven by a 75% reduction in the rate of reinfarction in the angioplasty group (1.6% v. 6.3% in the fibrinolytic group), whereas the rate of death or stroke was similar in both arms. Of the patients randomized to angioplasty at referral hospitals, 99% (559/567) were transferred and, of these, 96% within 2 hours after randomization. There were no deaths during transportation, though rhythm disturbances (atrial fibrillation in 14 patients, AV block in 13 patients, and VF in 8) were encountered.

Comments

This study confirms the superiority of angioplasty over fibrinolysis in patients with AMI. It proves that the benefit of treatment with primary angioplasty was the same for patients transferred from referral hospitals as for patients admitted directly to invasive centres. Transportation was found to be safe with no death reported. In fact, the time taken for transfer was found to be just 14% of the total time between onset of symptoms and start of treatment. Other established reasons for PCI in the setting of AMI include fibrinolytic failure and cardiogenic shock. Another emerging strategy to buy time is facilitated PCI (combination therapy with reduced-dose fibrinolytic agents and glycoprotein IIb/IIIa platelet inhibitors). Studies of facilitated PCI have shown promise; however, there is an increased risk of bleeding. In the DANAMI-2 study, the angiographic success rate (TIMI-3 flow) was 83%, which is similar to that from other experienced centers. This study suggests that primary PCI is worth the wait. However, future attempts to further improve the clinical outcome would involve shortening the time of transfer. Adjunctive medicines including facilitated PCI may further enhance the effectiveness of the procedure.
Estrogen Plus Progestin and the Risk of Coronary Heart Disease


Summary

Previous observational studies had reported a reduction in the risk of coronary heart disease (CHD) with the use of postmenopausal hormonal therapy. However, recent randomized trials have had contrary results. The Women’s Health Initiative (WHI) is a double-blind, randomized, primary prevention trial of estrogen plus progestin therapy compared with placebo in 16,608 postmenopausal women with intact uterus. One daily tablet containing 0.625 mg of oral conjugated equine estrogen and 2.5 mg of medroxyprogesterone acetate was given to the study group while the control group received a matching placebo. The women included in this trial were largely from a healthy population with only 4.4% of those recruited reporting previous CHD, stroke or transient cerebral ischemia. The baseline levels of cardiovascular risk factors (hypertension in 36%, hypercholesterolemia in 13%, diabetes in 4.4%, and 10.5% smokers) were also consistent with those in a generally healthy population of postmenopausal women. The primary end-point was nonfatal myocardial infarction (MI) or death due to CHD. This study contains information at an average of 5.6 years of follow-up for 15,582 women. In adjusted analysis, women on hormonal therapy had a 24% higher risk of CHD than those on placebo (hazard ratio 1.24, 95% confidence interval (CI): 1.00–1.54). The elevation in risk was most apparent at one year (hazard ratio 1.81). The hazard ratios were 1.28 for nonfatal MI and 1.1 for death due to CHD. No significant differences were observed with regard to coronary revascularization, hospitalization for acute coronary syndrome or congestive heart failure. No subgroup of women was found to be at a higher or lower risk for CHD. Women with risk factors for CHD including smokers, hypertensives, diabetics, or those with pre-existing CHD did not have any different risk of coronary events in either group. Neither did various other demographic or clinical characteristics, baseline lipid levels (except elevated LDL), and inflammatory and thrombotic biomarkers (including C-reactive protein, fibrinogen, etc.) identify a subgroup that benefited from hormonal therapy.

Comments

This study provides no evidence of cardiac protection with hormonal therapy among normally encountered healthy postmenopausal women. On the contrary, there was an increased risk of CHD in the women on estrogen plus progestin therapy, especially during the first year of the therapy. The slight apparent increase in risk occurred predominantly for MI with no difference in the risk for coronary revascularization, angina, or congestive heart failure. The absence of cardiac protection is consistent with recent findings from randomized trials. In the Heart Estrogen/Progestin Replacement Study (HERS) trial, estrogen plus progestin had no overall effect on the risk of recurrent coronary events after 4.1 and 6.8 years of follow-up. Moreover, the findings of an increased risk soon after starting therapy was similar in the two studies. In HERS, subgroup analysis suggested a possible reduction in the risk for CHD in those women who had an elevated baseline lipoprotein Lp(a) levels. The WHI study did not confer any added benefit in this group. Adverse outcomes early on in women on hormone replacement therapy (HRT) had also been suggested from earlier observational studies including the Coronary Drug Project and the Nurses Health Study. This early increased risk has been sought to be explained by a prothrombotic effect, increased serum inflammatory markers such as C-reactive protein and matrix metalloproteinase-9 (MMP-9) or due to the altered lipid profile (increased small low-density lipoprotein (LDL) sub-fracton).

Whether altering the dose of estrogen/progestin or using an alternative route, or the use of selective estrogen receptor modulators (SERMS), e.g., raloxifene, would provide a different perspective needs to be seen. But for now, HRT is best not recommended for cardiac protection in postmenopausal women.
Calendar of Conferences

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

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

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

November 14–15, 2003, 4th Annual Conference of Nuclear Cardiological Society of India, Vellore, India
Contact: Organizing Secretary
Department of Nuclear Medicine
Christian Medical College
Vellore, Tamil Nadu, India
Fax: 0416 2232103
e-mail: nuclear@cmcvellore.ac.in

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

January 9–11, 2004, Joint Meeting of International Society for Heart Research and International Academy of Cardiovascular Sciences, Lucknow, India
Contact: Prof VK Puri, Organizing Secretary
Department of Cardiology
CSM Medical University
Lucknow, India
Fax: 0522 225 5830
e-mail: vijaykumarpuri@hotmail.com

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

Announcement
“Apollo Telemedicine Networking Foundation and Anna University announce the commencement of four-week intensive certificate course on TELEHEALTH TECHNOLOGY. This course is aimed at doctors, engineers and technologists who wish to make use of information and communication technology in their practice. Full details are available at www.apollohospitals.com (Click on to Telehealth Course).” Contact: Prof. K Ganapathy, Medical Director, ATNF.

Academy of Cardiology at Mumbai—International and Indian Fellowships

Applications are invited for the Academy of Cardiology—International and Indian Fellowships (one each) beginning January, 2004 from candidates below 35 years of age and possessing DM or DNB Cardiology qualifications. Fellowships will provide funding for training in interventional/noninvasive cardiology at prestigious centers for a duration of up to one year. Interviews for the selection will be conducted by the Academy. Applications along with detailed curriculum vitae and two letters of support from seniors in the profession should be sent to the Academy of Cardiology, 102, Kirti Manor, SV Road, Santacruz West, Mumbai 400054 by September 30, 2003.