Coronary Slow Flow Phenomenon: An Angiographic Curiosity

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Cardiologists are familiar with the phenomenon of slow progression of angiographic contrast in the coronary arteries in the absence of stenosis in the epicardial vessels in some patients presenting with chest pain. The coronary slow flow phenomenon (CSFP), first described in 1972, remains scantily studied.1-3 This phenomenon should be distinguished from occurrence of slow flow in the context of coronary reperfusion therapy such as angioplasty or thrombolysis that is associated with different pathophysiological and clinical implications. Similarly, coronary slow flow associated with coronary artery spasm, coronary artery ectasia (CAE), myocardial dysfunction, valvular heart disease and certain connective tissue disorders involving coronary microvasculature is easy to understand.3,4 CSFP may occasionly also result from inadvertent air-embolism during angiography or may be due to an overlooked ostial lesion. However, it is not certain whether CSFP in the absence of any of these known causes represents merely an angiographic curiosity or has special physiologic or therapeutic implications. In this editorial we focus on the current knowledge regarding CSFP manifesting in the absence of any known etiology.

Incidence and Methods of Assessment

Overall, CSFP is observed in approximately one percent of the patients undergoing coronary angiography, specially in patients presenting with acute coronary syndrome (usually unstable angina). In the Thrombolysis In Myocardial Infarction (TIMI)-III A study, 4% of patients presenting as unstable angina but with normal/insignificant epicardial coronary artery disease (CAD) showed impaired angiographic filling suggestive of CSFP.5 Mangieri et al.6 reported an incidence of 7% of this phenomenon in patients suspected to have CAD, however the documentation of slow flow was visual without any objective criteria. Usually TIMI flow grade scheme is followed to assess coronary blood flow. It reflects the speed and completeness of the passage of the injected contrast through the coronary artery.7,8 This method is a qualitative way of assessing coronary flow and is limited by significant inter-observer variability. In contrast, corrected TIMI frame count (CTFC) is a more quantitative and reproducible index of coronary artery flow.9 It represents the number of cine frames required for contrast to reach the standardized distal coronary artery landmarks. CSFP is defined as CTFC greater than 2 standard deviations (SD) from normal published range for that particular vessel.9,10 In a retrospective study using these objective criteria of CTFC, as high as 25% of patients evaluated for typical angina or angina-like chest pain syndrome with normal epicardial coronary arteries showed this phenomenon.10

Clinical Profile

CSFP is more often seen in males who are current smokers.3,11 This is in contrast to “Syndrome X” which is predominantly a disorder of post-menopausal females.11 Patients with CSFP more often present with rest pains, requiring urgent hospital admission. Both resting electrocardiographic (ECG) abnormalities as well as positive exercise stress testing are more frequent in patients with CSFP as compared with patients having normal coronary flow.3 Myocardial perfusion scintigraphy shows reversible perfusion abnormalities in 30-75% of such patients.12,13 On long-term follow-up the clinical course is usually benign in patients with CSFP, although it is frequently punctuated with remitting, relapsing anginal episodes resulting in considerable impairment in quality of life.14 Over 80% of these patients experience recurrent chest pain and one-third of them require readmission for an acute exacerbation.3,15 Occasionally, patients may present with evidence of acute myocardial infarction.3,16 Recently, Atak et al.17 have reported abnormalities of corrected QT dispersion in patients with CSFP. Whether this predisposes to ventricular arrhythmias and sudden cardiac death in these patients is not clear.
Pathophysiology

The pathophysiological mechanisms of CSFP remain uncertain. The coronary circulation is traditionally considered as a two-tier model. The first tier consists of epicardial vessels, which are also referred to as "conductance vessels" as these do not pose any resistance to blood flow. The second compartment consists of "small vessels" of <400 µm ("resistive vessels") which primarily regulate myocardial blood flow in the absence of any significant obstructive epicardial stenosis.18

Is it a disease of small vessels?: “Small vessel dysfunction” has been typically implicated in the pathogenesis of CSFP since its first description.2 The evidence of affliction of small vessels comes from the results of histopathological examination of ventricular biopsy specimens in patients with CSFP.6-19 Mosseri et al.19 reported abnormalities of small coronary arteries along with myocardial hypertrophy and patchy fibrosis in the biopsy samples from right ventricle of six patients with CSFP. However, majority of these patients had concomitant diseases that could have induced these changes. Later, Mangieri et al.6 reported histopathological examination of left ventricular endomyocardial biopsy specimens in a more homogenous group of 10 patients of CSFP who did not have any other cardiac or systemic diseases. There was evidence of small vessel affliction i.e. endothelial thickening due to cell edema, capillary damage and reduced luminal diameter of the small vessels. Electron microscopy revealed irregular nuclear morphology and several indentations of the nucleolmma and pycnosis. But it is not certain whether slow flow leads to these histopathological changes or whether these changes cause slow flow, though the later appears more likely.12 Also, these fixed structural changes cannot explain the acute presentation in the majority of these patients. The clinical and angiographic variability implies a significant dynamic component to the coronary microvascular resistance. It is noteworthy that only a third of the patients with CSFP fulfilled the criteria on a repeat angiographic study.15 Thus CSFP lacks reproducibility. It is postulated that this dynamic increase in microvascular tone is due to "microvascular spasm" resulting in recurrence of symptoms. Exact mechanism for this dynamic response is not well elucidated. It is plausible that intermittent release of certain autacoids (neuropeptide-Y, endothelin-1, thromboxane-A2, etc.) mediate coronary vasoconstriction.15,20-22

Even invasive hemodynamic and metabolic parameters do not consistently suggest a uniform mechanism for CSFP. Resting hemodynamic parameters of heart rate, blood pressure or the double product fail to explain the occurrence of CSFP.13,15 The vasodilatory response of the microvasculature to provocative stimuli is less clear and has evoked mixed responses.15,23 Lower resting coronary sinus (CS) oxygen saturation has been observed in patients with CSFP as compared to controls for a similar myocardial oxygen demand.15 This implies a higher transcoronary myocardial extraction caused by the delayed resting coronary perfusion consistent with CSFP. Whether this delayed perfusion results in myocardial ischemia either during rest or during stress needs to be addressed. Yaymaci et al.24 investigated the presence of stress-induced myocardial ischemia in patients with CSFP by measuring two metabolic indicators of ischemia i.e. coronary arteriovenous oxygen content difference and lactate production. Although majority of patients developed anginal pain with atrial pacing, only few (17%) revealed evidence of metabolic ischemia. Thus, angina pectoris in most patients with CSFP does not originate from myocardial ischemia as demonstrated by metabolic parameters. However, of the subset of patients who showed evidence of metabolic ischemia, majority showed a perfusion defect using single photon emission computed tomography (SPECT) that anatomically correlated well with the vessel showing CSFP. These differences in patients with CSFP may be explained by the variability in the degree of coronary flow reserve (CFR), which, per say, is an indicator of microvascular function. Recently, Sezgin et al.25 reported evidence of endothelial dysfunction in patients with CSFP using simple method of measuring flow-mediated vasodilation (FMD) of the brachial artery. It has been suggested that FMD is predominantly due to endothelial release of nitric oxide (NO). There was a strong and inverse relationship between CTFC and percentage of FMD in patients with CSFP thereby suggesting that endothelial NO activity is impaired in these patients.25

Can we exclude epicardial coronary artery disease?

It is well appreciated that diffuse atherosclerosis may be present in angiographically normal appearing vessel. Further, macro- and microvascular disease may also coexist.26,27 A recent study investigated the significance of epicardial vessel affliction by studying coronary anatomy using intravascular ultrasound (IVUS) and measuring epicardial resistance using fractional flow reserve (FFR) in patients with CSFP.27 FFR is an index of resistance to flow along the epicardial vessel and is defined as the ratio of distal to proximal coronary pressures.18 In maximal hyperemia (e.g. adenosine-induced), FFR is independent from microvascular bed. If there is no resistance along the artery
as expected in normal epicardial artery, there is no pressure decline and FFR approaches unity. Surprisingly, a decline in the distal coronary pressure leading to significantly lower FFR value was seen in the patients exhibiting slow flow phenomenon. There was a strong negative correlation between CTFC and FFR. Interestingly, the patients showing perfusion defects using myocardial perfusion scintigraphy had significantly lower FFR values, signifying even higher epicardial resistance. There was diffuse intimal thickening and calcification throughout the epicardial arteries on IVUS. A negative correlation was observed between intimal thickness and FFR. It is postulated that decreased FFR levels are due to increased resistance in the epicardial coronary arteries resulting from diffuse atherosclerotic disease as demonstrated by IVUS.27

Thus, at present, the data are not sufficient to delineate the borders of this phenomenon. Whether it is due to involvement of predominantly macro- or microvasculature of the heart is not certain. It is hypothesized that CSFP may be a form of early phase of atherosclerosis in some patients. However, certain other factors may also contribute to CSFP.

Miscellaneous factors: It appears that CSFP may represent a heterogeneous group of disorders unified because of characteristic angiographic appearance. Slow flow has been characteristically seen in ectatic and aneurysmally dilated coronary arteries (dilated coronary filling has been reported in patients with cocaine use) because of characteristic angiographic appearance. Slow flow has been characteristically seen in ectatic and aneurysmally dilated coronary arteries (dilated coronary arteries) with proportionately more impairment of blood flow in these vessels with increasing coronary artery diameters.28 This is in accordance with the Hagen-Poiseuille's equation which states that resistance to flow within a tube depends on the dimensions of the tube and the viscosity of the fluid in it.29 However, the relationship of CSFP in relation to vessel diameter has not been well studied. Furthermore, importance of other rheological factors, blood viscosity, fibrinogen levels and hyperlipidemia (contributing to increased blood viscosity) in these patients has not been studied. Hematocrit and fibrinogen are the major determinants of blood viscosity. Increased blood viscosity leading to decrease in coronary blood flow reserve has been associated with hyperlipidemia and high fibrinogen levels.30,31 The therapeutic implications, if any, of these findings remain to be studied. Similarly, contribution of CSFP in patients with syndrome X has not been sharply delineated and these may represent overlapping phenomena.10 Other rare causes may be important in appropriate settings. For example, slow coronary filling has been reported in patients with cocaine use even in the absence of coronary artery spasm.31

Proposed mechanisms at molecular level: Endothelin-1 (ET-1) and NO are important molecules that modulate vasodilatory response to stress (rapid atrial pacing/exercise). Recently published studies have highlighted the imbalance between ET-1 and NO release in patients with CSFP as compared to controls with normal coronary flow.32,33 No significant difference in arterial and coronary sinus NO plasma levels was seen in the two groups, at baseline as well as after pacing. In contrast, basal plasma ET-1 levels were higher in patients with CSFP. Rapid atrial pacing resulted in significantly higher coronary sinus levels of ET-1 in patients with CSFP, which also correlated well with the CTFC. Furthermore, in patients with CSFP, coronary sinus ET-1 levels also increased significantly as compared to femoral artery ET levels. Even correlation of ET-1 levels and intimal thickness of coronary artery using IVUS has been reported.32 It is possible that CSFP results from imbalance of ET-1, a potent vasoconstrictor leading to deregulation of vascular tone even in the very early stages of plaque formation. More studies are required to unravel the molecular mechanisms of CSFP.

Treatment

There are no definite treatment modalities for patients with CSFP. Conventional antianginal therapy is of limited value in the chronic management in these patients.34 Nitrates are ineffective as their biotransformation to active metabolite is diminished due to deficiency of required enzymes in coronary microvessels as compared to larger epicardial coronary arteries.35,36 In contrast, dipyridamole may be effective due to its predominant action on the small vessels of diameter less than 200 µm. It blocks uptake of adenosine by both vascular endothelium and erythrocytes and prevents its conversion to inactive metabolites. This results in re-distribution of vascular resistances due to vasodilation of the small vessels.36,37 Mangieri et al.5 demonstrated the effectiveness of dipyridamole in acute setting during coronary angiography in patients with CSFP. Intracoronary administration of this drug relieved microvascular tone and accelerated contrast run-off in coronary arteries without changing the diameter of epicardial coronary vessels. As expected, intracoronary nitroglycerine failed to produce any beneficial effect in these patients. Demirkol et al.12 also observed improvement in myocardial perfusion with dipyridamole infusion using myocardial perfusion SPECT. Long-term oral therapy with dipyridamole was assessed by Kurtoglu and associates38 in an open-label fashion. Coronary flow returned to normal levels in majority of the vessels as adjudged by using CTFC. This was accompanied with complete relief from chest pain in two-
third of patients and decrease in symptoms in the remaining. Since this phenomenon, per say, is punctuated by remissions in clinical course, more data using case-control studies are required to confirm the above observations.

Conventional calcium L-channel blockers (diltiazem/verapamil) are of limited value in alleviating symptoms. This is perhaps due to absence of voltage-gated L-type calcium channels in microvessels, as shown by studies in the animal models.39 Instead, the microvascular tone may appear to rely on other types of voltage-gated calcium channels, possibly of the T-type.40 Mibefradil is a long-acting calcium T-channel antagonist that was approved by FDA in 1997 for the treatment of hypertension and chronic stable angina pectoris. Unfortunately the drug was voluntarily withdrawn shortly after its launch due to its numerous clinically relevant drug interactions.41 Recently, Beltrame et al.42 assessed the acute and long-term clinical benefits of mibefradil in patients with CSFP by exploring its beneficial effects on microvessels. There was significant acute angiographic improvement in coronary flow indices with this drug. CSFP was abolished in approximately three-fourth of the vessels at 30 min after the drug intake. This occurred without any significant changes in the epicardial vessel diameter or rate-pressure product. Interestingly, the improvement in flow indices occurred primarily in vessels with CSFP as compared to vessels with normal epicardial flow. In accordance with these acute angiographic results, long-term clinical benefits with this drug were also observed. In a randomized, double blind, placebo-controlled, cross-over study, there was substantial reduction in frequency of angina by 56% (p<0.001), episodes of prolonged angina by 74% (p<0.001), and sublingual nitrate consumption by 59% (p<0.01) along with improvement in physical quality of life (p=0.003).42 Since the drug has been formally withdrawn, these observations may stimulate further research with similar molecules. Recently, a three-dimensional pharmacophore model consisting of three hydrophobic regions, one hydrogen bond acceptor and one positive ionizable region has been hypothesized for T-type calcium channel blockers.42 Whether it acts as a valuable tool in designing new ligands for this group of drugs remains to be seen.

Thus, CSFP continues to intrigue the clinicians. It appears to represent a heterogeneous group of disorders. In some it may represent an early stage of atherosclerosis with endothelial dysfunction and in others it may indicate microvascular dysfunction or other unknown disorders. The prognosis appears good although symptoms tend to recur. Further advances in the understanding of pathophysiology mechanisms and treatment of CSFP are awaited.

References

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Mitral valve operations have typically been performed through a median sternotomy, which provides generous exposure and allows ample access to all cardiac structures. Over the past 10 years, improvements in endoscopic techniques have resulted in a dramatic increase in non-cardiac minimally invasive surgical procedures. Surgeons and patients have been enthused by the benefits and possibilities of minimally invasive heart valve surgery. Initially, standard endoscopic instruments were used but they proved to be ineffective. As a result, computer-enhanced instrument systems were developed. Advances in closed-chest cardiopulmonary bypass and myocardial protection as well as improved intracardiac visualization have hastened the shift toward efficient and safe minimally endoscopic cardiac surgery. Today, mitral valve surgery can be done through small incisions using either robotic or endoscopic assistance and has become standard practice for an increasing number of cardiac surgeons.

Evolution of Robotic Mitral Valve Surgery

Minimally invasive robotic-assisted cardiac surgery has evolved through graded levels of difficulty with increasingly less exposure. In mitral valve surgery, the progression to complete dependence on three-dimensional (3D)-assisted vision and telemanipulation has been a conscious step-wise evolution. Consequently, complex reconstructive mitral valve operations can be performed completely using a robotic interface. Thus far, surgical results have been encouraging and have hastened adoption of these less invasive methods.

Innovations in computer-assisted telemanipulation cardiovascular surgery occurred rapidly in the late1990s. By 1998, Carpentier et al.1 performed the first truly endoscopic mitral valve repair using an early prototype of the da Vinci™ (Intuitive Surgical, Sunnyvale, CA) surgical system. In May 2000, our group performed the first complete mitral valve repair in North America using the da Vinci™ system.2 In that operation a large P2 trapezoidal resection was done with the defect closed using multiple interrupted sutures followed by implantation of an annuloplasty band. Lange and associates in Munich were the first to perform a totally endoscopic mitral valve repair using only 1 cm ports and da Vinci™.3 Although we still use a 4 cm incision for assistant access, robotic technology has progressed to a point where totally endoscopic mitral valve surgery has become the operation of choice for patients having isolated mitral valve pathology.

Patient Selection

All patients with isolated degenerative mitral valve disease are now considered for a robotic mitral valve repair. In the development of a robotic mitral valve repair program, strict inclusion and exclusion criteria should be followed (Table 1). Patients with severely calcified mitral annuli are not suitable candidates. De-calcification methods will require further instrument development. However, moderate annular calcification alone does not preclude patients from undergoing a minimally invasive approach.

### Table 1. Robotic mitral surgery: exclusion criteria

- Previous right thoracotomy
- Renal failure
- Liver dysfunction
- Bleeding disorders
- Severe pulmonary hypertension
- Significant aortic or tricuspid valve disease
- Coronary artery disease requiring surgery
- Recent myocardial ischemia (<30 days)
- Recent stroke (<30 days)
- Severely calcified mitral valve annulus

Patients with poor lung function should undergo pulmonary testing to ascertain whether they will tolerate single lung ventilation. If they are not able to tolerate isolated lung ventilation, then cardiopulmonary bypass is first instituted for intrathoracic preparation. The preoperative transesophageal echocardiogram (TEE) remains the gold standard for peri-operative planning. It is important
to correlate the dynamic echocardiographic anatomy with both the Carpentier functional class and intraoperative pathology. Coronary angiography should be done preoperatively in patients who are over 40 years old, have a strong family history, or have symptoms of coronary artery disease.

Surgical Techniques

Pre- and post-operative transthoracic and TEE studies should be done in every patient. Patients are anesthetized and positioned with the right chest elevated to 30° and with the right arm tucked by the side. Single-lung ventilation is performed to facilitate pericardial, aortic, and cardiac exposure. Cardiopulmonary bypass is established at 28°C using femoral arterial inflow. Kinetic venous drainage is provided using both a 21-23 F femoral-to-right atrial and a right jugular vein (17 F) cannula. If the femoral artery is too small or atherosclerotic, either a Bio-Medicus™ (Medtronic, Minneapolis, MN) or Directflow™ (Cardiovascular, Inc., Somerville, NJ) transthoracic cannula can be placed via a right anterior 2nd interspace port.

A 4 cm inframammary incision is used and the chest is entered through the 4th intercostal space (ICS). Under direct vision, the pericardium is opened 2 cm anterior to the phrenic nerve and distracted laterally using transthoracic sutures. Antegrade cardioplegia is given by an aortic root needle/vent placed either under direct vision or videoscopically. To minimize intracardiac air entrainment, carbon dioxide is insufflated at 1-2 liters per min via a 14 gauge plastic catheter. For aortic occlusion, a transthoracic cross-clamp (Scanlan International Inc., Minneapolis) is passed through a 4 mm incision in the mid-axillary line, low enough so that there is no conflict with the left robotic arm. The transthoracic atrial retractor is placed just off the lateral edge of the sternum, avoiding the internal mammary artery.

Operative procedures are performed from the surgeon’s console (Fig. 2). Annuloplasty bands (Edwards Lifesciences, Irvine, CA) are used to support repairs or provide annular reduction. Leaflet resections, sliding-plasties, papillary muscle reconstructions, chord insertions or transpositions can be readily performed because of the 3D high magnification optics, camera mobility and flexible instrument manipulation within both the atrium and ventricle (Table 2). Each suture is placed and tied intracorporeally. After completion of the repair, robotic arms are removed, and the left atrium is closed under direct vision to decrease operative times. Standard de-airing and weaning procedures are performed under TEE control.

Clinical Results

East Carolina University sponsored a multi-center, phase II FDA trial that studied 112 da Vinci™ patients operated in 10 United States centers. Repairs included quadrangular resections, sliding-plasties, edge-to-edge approximations,
We recently published results of our first 38 mitral valve repairs with the da Vinci system. Patients were divided into two cohorts of 19 patients each (early experience and late experience) for data analysis and comparison. Total robotic time represented the exact time of robot deployment after valve exposure and continued until the end of annuloplasty band placement. This time decreased significantly from 1.9±0.1 hours in the first group to 1.5±0.1 hours in the second group (p=0.002). Concurrently, leaflet repair time reduced significantly from 1.0±0.1 hours to 0.6±0.1 hours (p=0.004). Also, the total operating time decreased significantly from 5.1±0.1 hours to 4.4±0.1 hours in the second group of patients. Further, both cross-clamp and bypass times decreased significantly with experience. Similar time trends were reported in a later publication that reviewed our subsequent da Vinci™ patients. The only time that did not change between the two groups was the annuloplasty band placement time. Most likely, this represents an inherent limitation in the current technology of tying suture knots. Even with extensive experience, the speed of suture placement is limited. For the entire group of 38 patients, the mean length of hospital stay was 3.8 days, with no difference between the two groups. For all patients in the study, 84% demonstrated a reduction of three or more grades in mitral regurgitation at follow-up. In the entire series there was no device-related complication or operative death. One valve was replaced at 19 days because of hemolysis secondary to a leak that was directed against a prosthetic chord.

### Table 2. Robotic mitral procedures (n=150)

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Count (Percentage)</th>
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<tbody>
<tr>
<td>Valve replacements</td>
<td>2 (1.3)</td>
</tr>
<tr>
<td>Valve repairs</td>
<td>148 (98.7)</td>
</tr>
<tr>
<td>Ring annuloplasty alone</td>
<td>36 (24.0)</td>
</tr>
<tr>
<td>Posterior leaflet resection</td>
<td>94 (62.7)</td>
</tr>
<tr>
<td>Sliding annuloplasty</td>
<td>25 (16.7)</td>
</tr>
<tr>
<td>Posterior/anterior cleft repair</td>
<td>1 (0.67)</td>
</tr>
<tr>
<td>Chordal replacements (GORE)</td>
<td>9 (6.0)</td>
</tr>
<tr>
<td>Chordal transfer</td>
<td>40 (26.7)</td>
</tr>
<tr>
<td>Alfieri</td>
<td>6 (4.0)</td>
</tr>
</tbody>
</table>

Values in parentheses are percentages.

and both chordal transfers and replacements. Leaflet repair and annuloplasty times had decreased to 37 and 39 min respectively, compared to an earlier phase I trial. Aortic cross-clamp and cardiopulmonary bypass times averaged 2.1 and 2.8 hours, respectively. There were little differences in operative times between centers. At one-month follow-up, transthoracic echocardiography (TTE) revealed that 9 (8.0%) patients had grade 2 mitral regurgitation and 6 (5.4%) of these had re-operations. Although the reoperative rate was of concern, the failed repairs were distributed across the group evenly and some centers had performed less than 10 robotic operations. There were no deaths, strokes, or device-related complications. This study demonstrated that multiple surgical teams could perform robotic mitral valve surgery safely early in the development of this technique albeit with a learning curve as far as operative times and repair results are concerned. The device was approved by FDA in November 2002 for use in mitral valve surgery.
To date, we have completed over 150 robotic mitral valve repairs with the da Vinci™ system. There has been one operative death (0.67%) from a protamine reaction but no device-related complications. In the entire series there have been two late deaths (1.3%) and we have reoperated on four (2.7%) patients for mid-term valve repair failures. Even at the 100th case we continued to see improving operative time data. No doubt this is related to improved robot set up and deployment times, closer team working relations, and surgeon experience. However, there are parts of this operation that can only be improved by new technology and not experience alone. We have found that by using alternative suturing techniques, such as nitinol U-clips™ (Coalescent Surgical, Sunnyvale, CA) anuloplasty band insertion times are reduced by 50% (Fig. 3). Improved methods for retraction and exposure as well as visioning need to be developed. Moreover, to achieve the greatest facility with robotics in mitral surgery, instrument arm sizes must be reduced and a greater variety of end-effector tips developed. As our group has trained over 250 surgeons to repair mitral valves using robotic techniques, we believe that the true benefits will emerge over a larger population and that many of these methods could become standard in the future.

Conclusions

The reported results suggest that robotic mitral surgery is well on the way to reality. Although operative philosophies, patient populations and surgeon abilities differ between centers, the compendium of recent results remains very encouraging. The advent of true three-dimensional vision with tactile instrument feedback will be the final bridge to truly “tele-micro-access” operations. Also, to perform these operations optimally, “extracorporeal” surgeons and engineers will need to improve methods by which instruments are manipulated by computers. Recent successes with direct vision, videoscopic, and robotic minimally invasive surgery all have reaffirmed that this evolution can be extremely fast, albeit through various pathways.

Technological advances are occurring at a rapid pace. In just a short span of six years, cardiac surgery has witnessed the incorporation of robotic tele-manipulative systems into the mitral surgeon’s armamentarium. Nevertheless, surgical scientists must continue to evaluate this technology critically in this new era of cardiac surgery. Despite enthusiasm, caution cannot be overemphasized. Surgeons must be careful as indices of operative safety, speed of recovery, level of discomfort, procedural cost, and long-term operative quality have yet to be defined fully. Traditional valve operations still enjoy long-term success with ever-decreasing morbidity and mortality, and remain our measure for comparison. Ultimately, telerobotic systems will continue to evolve, most likely creating a new paradigm for the way cardiac surgery is performed in the 21st century.

References

Background: Robotic telemanipulation surgery is a fast developing technique which allows totally
dissection and perfusion on both beating heart and arrested
heart.

Methods and Results: Between December 2002 and February 2004, 125 patients underwent robotic
enhanced coronary artery bypass surgery using the da Vinci telemanipulation system (Intuitive Surgical Inc.,
California). Eleven patients underwent totally endoscopic coronary artery bypass surgery. Of them, 9 were done
on beating heart while 2 were done on arrested heart. One hundred and fourteen patients had endoscopic
taking-down of internal mammary artery followed by minimally invasive direct coronary artery bypass in 63
patients and left anterolateral thoracotomy in 51 patients. The internal mammary artery mobilization time
was 42 min (35-74 min) while the left internal mammary artery to left anterior descending artery anastomosis
time ranged from 20 to 36 min for the totally endoscopic coronary artery bypass patients. In 1 patient, the right
internal mammary artery was anastomosed to diagonal artery totally endoscopically. The mean internal
mammary artery flow by Doppler measurement done in patients undergoing minimally invasive direct coronary
artery bypass was 64 ml/min. Seven patients required conversion to median sternotomy and coronary bypass
surgery on beating heart. The mean intensive care unit stay was 1.2 days and the mean hospital stay 4.5 days.
There was no in-hospital mortality. All 11 patients who underwent totally endoscopic bypass surgery had coronary
angiography done at 3 months interval which showed 100% patency in 10 patients while one patient had 50%
anastomotic narrowing for which coronary angioplasty was done in the same sitting.

Conclusions: Using telematic technology, a complete endoscopic anastomosis is possible in both single vessel
and suitable double vessel disease patients. The use of robotics is now extended to achieve complete myocardial
revascularization by harvesting both the internal mammary arteries and making a small thoracotomy for direct
anastomosis as well. (Indian Heart J 2004; 56: 622–627)

Key Words: Coronary artery bypass grafting, Coronary artery disease, Minimally invasive surgery

The ultimate goal of minimally invasive coronary artery
bypass grafting (CABG) is to perform the entire
anastomosis endoscopically. This is done by keeping the
following main concepts of minimally invasive surgery in
mind: firstly, to circumvent the deleterious effect of cardio-
pulmonary bypass (CPB); and secondly to minimize the
incision and surgical trauma. This also aims at reducing
patient’s morbidity, length of hospital stay and overall cost.
Minimally invasive direct coronary artery bypass (MIDCAB)
via a small minister anastomosis or a 2° left anterior
thoracotomy approach, also termed as endoscopic
atraumatic coronary artery bypass (EndoACAB), refers
to such approaches. The advancement in beating heart
surgery also aided these approaches. In patients for
multivessel revascularization where direct aortovenous
cannulation is not possible through a limited incision, the
Port Access system via formal approach (Heartport, Inc,
Redwood City, California, USA) is very helpful for
establishing CPB.

With the advent of robotically enhanced tele-
manipulation, the latest in minimally invasive technique
is now available thus permitting true closed chest totally
endoscopic procedures. Our institute initiated the robotic
programme using the da Vinci surgical system (Intuitive
Surgical Inc, California, USA) in December 2002. We re-
view our experiences with the use of da Vinci in performing
CABG using various minimally invasive approaches.

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Methods

Between December 2002 and February 2004, 125 patients underwent robotically enhanced CABG. Eleven patients underwent totally endoscopic coronary artery bypass (TECAB). Of them, 9 were done on beating heart while 2 were done on arrested heart using the Port Access system. Ten patients who underwent TECAB had single vessel left anterior descending (LAD) disease, while 1 patient had single vessel disease with additional proximal diagonal artery disease for which anastomosis was done using the right internal mammary artery (RIMA) on beating heart.

One hundred and fourteen patients underwent EndoACAB in which the skeletonized internal mammary artery was harvested in its entire length robotically and direct anastomosis was done either by MIDCAB (n=63) or using a small anterior thoracotomy incision (THORACAB) (n=51). All patients were informed about the procedure preoperatively and each patient gave a written informed consent; institutional review board permission was also obtained. The 125 patients (108 males, 17 females) were 58.4±8.0 years old (range: 34-78 years). The pre-operative demographic profile is listed in Table 1. Left ventricular ejection fraction (LVEF) was 54±2.8% and New York Heart Association (NYHA) class was 2.1±0.6. The pre-requisite for patients included for any robotic procedure were: those requiring CABG, age range 18-80 years and informed consent for the procedure.

Patients with significant co-morbidity including compromised pulmonary function tests, those requiring additional cardiac procedures, LVEF < 30%, associated ventricular or aortic aneurysm or those with significant peripheral vascular disease, thus making them unfit for Port Access procedures, were not considered for robotic surgery. Other pre-operative exclusion criteria included, body mass index (BMI) >35.0 kg/m², decompensated congestive heart failure (NYHA class III or IV), acute pulmonary edema, uncontrolled hypertension, any coagulopathy or history of acute myocardial infarction (MI) of <30 days duration.

Intraoperatively, if any of the following criteria were found, the procedure was converted to conventional CABG on beating heart i.e. systolic arterial pressure drop of >20% of baseline or <80 mmHg for >15 min or not responding to therapy, dense pleural or pericardial adhesions limiting visibility, intramyocardial LAD or target LAD diameter <1.5 mm previously not identified on coronary angiogram or inadequate visualization or malpresentation of target vessel such that it was not accessible via routine endoscopic ports.

Anesthesia for TECAB: After routine induction of anesthesia, patients underwent double lumen intubation for single right lung ventilation. Arterial cannulation was done using both radial and femoral arteries. Bilateral radial cannulation was done for invasive monitoring of the endoaortic occlusion catheter in patients who underwent TECAB on arrested heart. All patients had thermodilution pulmonary artery catheter monitoring and transesophageal echocardiography (TEE) for assessment of cardiac function and for positioning and monitoring the endoaortic catheter of the Port Access system.

The da Vinci Surgical System: The da Vinci telemanipulation system consists of a master console (Fig. 1) used by the operating surgeon for controlling the microinstruments which are mounted on the surgical cart which has three arms (slave unit, Fig. 2). The surgical assistant manages the change of instruments and positions of the arms and camera on the slave unit. Of the three arms, the left and right arms carry the microinstruments resembling the human wrist which correspond to the left and right

<table>
<thead>
<tr>
<th>Table 1. Pre-operative demographic profile (n=125)</th>
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<td>Age (range) (years)</td>
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<td>Male</td>
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<td>NIDDM</td>
</tr>
<tr>
<td>Hypertension</td>
</tr>
<tr>
<td>Smoking</td>
</tr>
<tr>
<td>COPD</td>
</tr>
<tr>
<td>LVEF</td>
</tr>
<tr>
<td>Stable angina</td>
</tr>
<tr>
<td>Previous MI</td>
</tr>
<tr>
<td>NYHA class (mean)</td>
</tr>
</tbody>
</table>

Values in parentheses are percentages
NIDDM: non-insulin dependent diabetes mellitus; COPD: chronic obstructive pulmonary disease; LVEF: left ventricular ejection fraction; MI: myocardial infarction; NYHA: New York Heart Association

Fig. 1. Robotic master console.
arms on the main console. The middle arm carries a stereo endoscope for three-dimensional vision seen at the console end. An additional video cart carries the light source, a continuous carbon dioxide (CO₂) insufflator, and a conventional two-dimensional monitor for viewing by the surgical team.

The video image from the camera is transferred to the master console, magnified (×10), and projected as a three-dimensional image for optimal visualization.

**Operative Technique for TECAB:** The approach for both left internal mammary artery (LIMA) and the RIMA can be done from the left pleural cavity. The patient is placed in supine position with the left chest elevated to about 30°. The landmarks such as suprasternal notch, xiphoid and 2nd to 6th ribs are marked. After ensuring single right lung ventilation the camera cannula with CO₂ insufflator port is inserted in 4th or 5th intercostal space close to the anterior axillary line and chest is insufflated with warm CO₂ at 37°C. After insertion of the endoscope, two ports are placed under visual control to accommodate the two robot arms, usually in the 2nd and 6th intercostal space. LIMA is harvested, skeletonized right from its origin from left subclavian artery upto its bifurcation using a 30° angled endoscope facing upward (Fig. 3). Unipolar cautery is used at low intensity for the LIMA branches. RIMA can be approached via the same ports after creating a retrosternal mediastinal plane and opening the right pleura. The pericardium is then opened using the same endoscope with a 30° down angulation for visualization of the LAD and its target site for anastomosis. If TECAB is proposed on arrested heart then the Port Access system is used to initiate CPB and infusion of antegrade cardioplegia into the aortic root via the Port Access Endo clamp provides reliable cardiac arrest.

In the case of beating heart surgery once the internal mammary artery (IMA) is harvested, the endostabilizer is inserted via a 4th port in the xiphoid area under endoscopic vision. The patient is thereafter heparinized and the IMA prepared for anastomosis. Throughout the procedure, the CO₂ pressure is kept between 10-14 mmHg depending on the working space, at the same time monitoring the systolic pressure for any hemodynamic instability.

Once the LAD is opened the anastomosis is done either by using continuous endoscopic suture or by using endoclips (US Surgical Corp., Connecticut, USA) (Fig. 4). After completion of anastomosis the endoaortic occlusion catheter is deflated and patient weaned from CPB. Heparin is reversed using protamine and a single chest tube is placed via the xiphoid port which is guided into the left pleural cavity.

In patients for whom MIDCAB or EndoACAB was performed to LAD the approach was either via a small...
ministernotomy or a 2.5" left anterior thoracotomy incision after a robotic takedown of skeletonized LIMA. Once the anastomosis was completed, but prior to protamine reversal, the LIMA flow was checked by Doppler flow method for all patients.

**Results**

Of the 125 patients who underwent robotic enhanced CABG, 11 patients underwent TECAB. Nine TECAB were done on beating heart of which 8 were for single vessel LAD disease and 1 was done for single vessel disease in which RIMA was anastomosed to diagonal and LIMA to LAD on beating heart. In 114 patients, the LIMA or RIMA was harvested robotically in a skeletonized fashion. Of these, 51 underwent THORACAB via a small left anterior thoractomy incision. In TECAB patients the total operating time was 208±36 min in which, the LIMA was mobilized in 42 min (range: 35-74 min) and the LIMA to LAD anastomosis time ranged from 20-36 min. The LIMA mobilization time range was same for the other patients. Table 2 shows the various intraoperative parameters. Seven patients had to be converted to conventional CABG. None of these were from the TECAB group. Of these 5 patients had dense pleural adhesions and 2 patients developed hemodynamic instability not responding to medical treatment. In both patients there was a fall in systolic blood pressure with a rise in pulmonary artery pressure and a fall in oxygen saturation which was due to high CO2 insufflation pressures. There was no electrocardiographic (ECG) ST-T change or arrhythmia and once the patient was put back to two-lung ventilation, all hemodynamic parameters became stable. All 7 patients had regular sternotomy and CABG was done on beating heart. No conversion for any hemodynamic instability has, however, been done in the last 90 cases.

The post-operative parameters are summarized in Table 3. One patient developed superficial infection of the anterior thoracotomy site which responded to antibiotics. Three patients who had undergone MIDCAB were re-explored for bleeding. Re-exploration was done via the same limited incision. In two patients the bleeding was from mammary branch; however, in the third patient no specific bleeding site was found. There was one mortality in the non-TECAB group. This patient, a known case of choledolithiasis, had undergone MIDCAB, and developed fulminating gall stones pancreatitis post-operatively.

Follow-up data is summarized in Table 4. All the patients who underwent TECAB had an angiogram on follow-up at 3 months. Of the 11 TECAB patients, there was 100% anastomotic patency (Fig. 5) in 10 patients while one patient had 50% anastomotic narrowing for which angioplasty was done at the same sitting. All 7 patients who have completed one-year follow-up are symptom-free during regular physical activity.

**Discussion**

The treatment of single vessel coronary artery disease is generally non-surgical. However, when surgery is indicated in patients with double vessel disease and a suitable anatomy, one always wants the least invasive procedure.

### Table 2. Intra-operative data

<table>
<thead>
<tr>
<th>Parameter</th>
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<th>Range (min)</th>
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<tr>
<td>OR time</td>
<td>208 ± 36</td>
<td>190 - 296</td>
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<tr>
<td>CPB time</td>
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<td>-</td>
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<tr>
<td>Cross clamp time</td>
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<td>-</td>
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<tr>
<td>IMA mobilization time (TECAB)</td>
<td>42</td>
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<td>LAD identification/dissection time</td>
<td>1.7</td>
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<td>LIMA-LAD anastomosis time (TECAB)</td>
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</tr>
<tr>
<td>RIMA-diag anastomosis time (TECAB)</td>
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<td>-</td>
</tr>
<tr>
<td>IMA flow (MIDCAB)</td>
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<td>36-78 ml/min</td>
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<td>Pulsatility index (MIDCAB)</td>
<td>2.1</td>
<td>1.4-3.6 (N=5)</td>
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<td>Conversion to median sternotomy and OPCAB (MIDCAB)</td>
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Table 3. Post-operative data

<table>
<thead>
<tr>
<th>Parameter</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Total ventilation time (hours)</td>
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</tr>
<tr>
<td>Chest tube drainage (ml)</td>
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<td>ICU stay (days)</td>
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<td>Hospital stay (days)</td>
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<tr>
<td>Peri-operative MI (CPK-MB &gt; 10% of CPK at 6 hours post-operative sample)</td>
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<td>New onset atrial fibrillation</td>
<td>Nil</td>
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<tr>
<td>Wound infection</td>
<td>1</td>
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<tr>
<td>Mortality</td>
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</tbody>
</table>

ICU: intensive coronary unit; MI: myocardial infarction

Table 4. Follow-up data

<table>
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<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration (1-14 month)</td>
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<tr>
<td>Late mortality</td>
<td>Nil</td>
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<tr>
<td>Recurrence of angina</td>
<td>Nil</td>
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<tr>
<td>Patient follow-up TECAB</td>
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<tr>
<td>Rest</td>
<td>92.6%</td>
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<tr>
<td>Post-operative angiogram (3 month)</td>
<td>11</td>
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<tr>
<td>LIMA - LAD patency</td>
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</tbody>
</table>

LIMA: left internal mammary artery; TECAB: totally endoscopic coronary artery bypass; LAD: left anterior descending artery
with smaller incision to minimize surgical trauma, improve cosmesis, reduce risk of infection and produce least post-operative pain. With MIDCAB and off-pump coronary artery bypass (OPCAB) techniques, the morbidity has reduced compared to the conventional CABG on CPB. With development of femoral Port Access technology for peripheral CPB induction, the skin incision could further be reduced\textsuperscript{10,11} (Fig. 5). It was TECAB using robotic telemanipulators which finally revolutionized the minimally invasive techniques of CABG.\textsuperscript{6,8} If done on the arrested heart, the Port Access technique is mandatory. Our experience with Port Access surgeries which we have been routinely performing for atrial septal defect (ASD) closure and mitral valve surgery was helpful, as was our experience on beating heart surgery which we are now routinely applying for most CABGs. Our CPB time of 64 min and cross clamp time of 44 min is comparable with other centers which are performing TECAB mostly on arrested heart.\textsuperscript{6}

We believe that there should be a low threshold for conversion to open technique in the initial stages of robotic surgeries to reduce the patient’s risk. Although pleural as well as pericardial adhenolysis is very much possible but unless sufficient experience with this technique is gained, it should be avoided.

Adequate port placement was possible in all patients. However, as each patient has a different chest anatomy, proper marking of port sites is of utmost importance to avoid unnecessary struggle due to instrument collision and inability for complete IMA takedown due to left shoulder or subcostal interference. This is more so in patients who have medium-sized chest cavities, or extremely obese males, or females with large breasts. In our view, these are the patients who will benefit from an endoscopic procedure, because risk of wound infection is almost nil with this procedure, as seen in our series. The feasibility and safety of closed chest IMA takedown has been shown by several other groups.\textsuperscript{7,12,13} Although the use of TECAB can be extended to patients with double vessel disease, as done in one of our patients where RIMA was anastomosed to a large diagonal, a suitable anatomy is a must before going ahead. Dogan et al.\textsuperscript{6} reviewed their experience with double vessel disease using both isolated IMAs and as sequential anastomosis.\textsuperscript{9}

Bilateral IMA grafting is feasible but appears to be challenging and time consuming, therefore it has a very limited indication. The use of multidetector computerized tomographic (CT) scanning in determining the exact position of coronary target site and size for anastomosis using TECAB has also been reported.\textsuperscript{6}

Although all our patients were ambulated by the 1st post-operative day and most were fit for discharge by the 2nd post-operative day, as a protocol they were discharged by the 4th post-operative day and came for first follow-up on the 7th post-operative day.

The ultimate success of the Robotic procedure is a combined effort of the surgeon at the console, the assistant surgeon at the slave cart, the anesthesiologist and the perfusionist who all need to work as a team with communication at every stage. From the change of instruments to hemodynamic monitoring, the CO\textsubscript{2} pressures and routine blood gas monitoring all require utmost vigilance at all times to perform this minimally invasive procedure to perfection.

The hemodynamics of single lung ventilation and anesthesiologic management of all patients undergoing robotic surgery is an emerging domain in cardiac anesthesia.\textsuperscript{14} Hypotension, which is secondary to raised intrathoracic pressure due to CO\textsubscript{2} insufflation, needs to be controlled meticulously.

Although most centers continue to perform TECAB on arrested heart, it is yet premature to comment on the quality of anastomosis on beating versus arrested heart. With our experience in beating heart surgery and results of beating heart TECAB, we do believe that TECAB done on beating heart is a safe option which circumvents all the deleterious effects of CPB especially if used as a new procedure. As in all other upcoming technologies, the learning curve is gradual, a word of caution is a must for all beginners.

With passage of time, the present limitations of the system such as additional degree of freedom inside the chest cavity, an additional support of the beating heart and approachability to different target vessels will be overcome.
The addition of the third arm and the next version of robotic to provide vibrotactile sensations while grasping and suturing will be a step ahead in the developing technology.

**Conclusions:** The use of telematic technology is feasible for performing CABG on arrested as well as beating heart with good post-operative results. This can also be extended to achieve complete myocardial revascularization by bilateral robotic IMA takedown and direct anastomosis via small thoracotomy.

**References**

Predictors of Left Atrial Appendage Clot: A Transesophageal Echocardiographic Study of Left Atrial Appendage Function in Patients with Severe Mitral Stenosis

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Department of Cardiology, Cardiothoracic Sciences Centre, All India Institute of Medical Sciences, New Delhi

Background: The purpose of this study was to prospectively evaluate a large group of consecutive, non-anticoagulated patients with severe rheumatic mitral stenosis and to analyze the left atrial appendage function in relation to left atrial appendage clot and spontaneous echo contrast formation.

Methods and Results: We prospectively studied left atrial appendage function in 200 consecutive patients with severe mitral stenosis who underwent transesophageal echocardiography and correlated it with spontaneous echo contrast and left atrial appendage clot. The mean age was 30.2±9.4 years. Fifty-five (27.5%) patients were in atrial fibrillation. Left atrial appendage clot was present in 50 (25%) patients and 113 (56.5%) had spontaneous echo contrast. The older age, increased duration of symptoms, atrial fibrillation, spontaneous echo contrast, larger left atrium, depressed left atrial appendage function and type II and III left atrial appendage flow patterns correlated significantly (p<0.05) with the left atrial appendage clot. Left atrial appendage ejection fraction was significantly less in patients with clot (21.8±12.8% v. 39.1±13.2%, p<0.0001) and in those with spontaneous echo contrast (30.3±16.2 % v. 40.3±11.8%, p<0.001). Left atrial appendage filling (18.0±11.7 v. 27.6±11.8 cm/s, p <0.0001) and emptying velocities (15.4±7.0 v. 21.5±9.6 cm/s, p<0.001) and filling (1.4±1.0 v. 2.5±1.4 cm, p<0.0001) and emptying (1.5±1.2 v. 2.1±1.2 cm, p <0.05) velocity time integrals were also significantly lower in patients with clot as compared to those without clot. On multivariate regression analysis, atrial fibrillation (odds ratio 6.68, 95% CI 1.85-24.19, p=0.003) and left atrial appendage ejection fraction (odds ratio 1.06, 95% CI 1.00 - 1.11, p = 0.04) were the only two independent predictors of clot formation. Incidence of clot was 62.5% in patients with left atrial appendage ejection fraction ≤25% as compared to 10.4% in those having left atrial appendage ejection fraction >25%. Similarly patients with spontaneous echo contrast had lower filling (21.7±11.5 v. 29.4±12.7 cm/s, p <0.0001) and emptying (17.0±8.1 v. 23.9±10.9 cm/s, p <0.0001) velocities, as well as filling (1.9±1.3 v. 2.7±1.3 cm, p<0.01) and emptying (1.7±1.0 v. 2.3±1.4 cm, p<0.01) velocity time integrals as compared to patients without spontaneous echo contrast. In a subgroup of the patients with normal sinus rhythm, the left atrial appendage ejection fraction was significantly less in patients with clot compared to those without clot (31.2±13.2 v. 41.3±11.5 %, p<0.01).

Conclusions: In the patients with severe mitral stenosis, besides atrial fibrillation, a subgroup of patients in normal sinus rhythm with depressed left atrial appendage function (left atrial appendage ejection fraction ≤25%) had a higher risk of clot formation in left atrial appendage and these patients should be routinely anticoagulated for prevention of clot formation. (Indian Heart J 2004; 56: 628-635)

Key Words: Mitral stenosis, Left atrial appendage function, Left atrial clot

The incidence of thromboembolic complications is higher in patients with rheumatic mitral stenosis specially in those with atrial fibrillation (AF) and there is general consensus that prophylactic anticoagulation is needed in this subset of patients. Left atrial appendage (LAA) is the most common site of clot formation. During the last decade, the focus was on the presence of left atrial
spontaneous echo contrast in patients with rheumatic valvular disease and non-rheumatic AF and many studies have shown it as an independent marker of thrombus formation and thromboembolic episodes.4,6,9-16 LAA had been the site of great interest because of its predilection for spontaneous echo contrast and clot formation. Several studies have evaluated its mechanical and flow dynamics and correlated with the clot formation, spontaneous echo contrast and thromboembolic risk in patients with rheumatic valvular diseases,16-19 non-rheumatic AF,20-23 and various cardiomyopathies.24 However, previous studies evaluating patients with mitral stenosis were either too small or included a heterogenous group of mitral valve disease patients consisting of the whole spectrum of mitral stenosis severity, patients with associated mitral regurgitation and patients who were on anticoagulation.18,19,25 The purpose of this study was to evaluate prospectively a large group of consecutive, non-anticoagulated patients with severe rheumatic mitral stenosis and to analyze the LAA function in relation to LAA clot and spontaneous echo contrast formation.

Methods

Study patients: Two hundred consecutive patients with severe mitral stenosis (mitral valve area ≤ 1 cm²) being evaluated for percutaneous transvenous mitral commissurotomy (PTMC), were studied in our institute, a tertiary-care referral centre in north India. All clinical and echocardiographic data were collected prospectively. Patients with associated > 2/4 mitral regurgitation, significant aortic valve disease, previous closed mitral valvotomy and those on anticoagulation or antiplatelet therapy were excluded. Twenty age-matched patients with cerebrovascular accidents who underwent transesophageal echocardiographic study and who were free of heart disease, hypertension and diabetes, were taken as controls.

Transthoracic echocardiography (TTE): The transthoracic studies were done by standard techniques using a Hewlett Packard Sonos 1500 machine with 3.5 MHz transducer. Left atrial diameter was taken in the parasternal long axis view in M-mode at end-systole. Left atrial end-systolic area on 2D echocardiography was taken in two views (parasternal long axis and apical 4-chamber views) and these two values were averaged.

Transesophageal echocardiography (TEE): TEE was performed after TTE on the same day in all cases as described by us earlier.8 A 5 MHz transducer with capacity for pulsed Doppler (Hewlett Packard omniplane probe) was used. In patients with normal sinus rhythm, the maximum area of LAA (LAAmax) was measured just before the P wave and minimum area of LAA (LAAmin) was measured at just after the QRS complex at the end of LAA systole, by planimetry. The perimeter extended from the tip of the limbus between the upper left pulmonary vein along a straight line drawn to the aorta at its shortest point at the base of LAA. The LAA area was calculated from the computer-assisted table of the echocardiographic machine.

The LAA blood flow velocities were obtained by placing the pulsed Doppler sample volume into the outlet of the appendage ≥ 1 cm away from the LA cavity. Three different types of LAA flow patterns were analyzed. Type I flow was characterized by a biphasic flow of clearly defined waves (Figs 1 and 2). Type II flow was characterized by saw tooth morphology (Fig. 3), whereas in type III flow (Fig. 4) there were no identifiable flow waves (i.e., absolutely no flow recorded despite minimal velocity scale and minimal wall filter, or a minor flow with velocity <10 cm or spontaneous echo contrast).

LAA clot was diagnosed by the presence of clearly defined echogenic intracavitary mass with an echo texture different from that of the underlying endocardium and not due to the pectinate muscle as described by us earlier.8

\[
\text{LAA ejection fraction} = \frac{\text{LAA}_{\text{max}} - \text{LAA}_{\text{min}}}{\text{LAA}_{\text{max}}}
\]

The LAA blood flow velocities were obtained by placing the pulsed Doppler sample volume into the outlet of the appendage ≥ 1 cm away from the LA cavity. Three different types of LAA flow patterns were analyzed. Type I flow was characterized by a biphasic flow of clearly defined waves (Figs 1 and 2). Type II flow was characterized by saw tooth morphology (Fig. 3), whereas in type III flow (Fig. 4) there were no identifiable flow waves (i.e., absolutely no flow recorded despite minimal velocity scale and minimal wall filter, or a minor flow with velocity <10 cm or spontaneous echo contrast).

LAA clot was diagnosed by the presence of clearly defined echogenic intracavitary mass with an echo texture different from that of the underlying endocardium and not due to the pectinate muscle as described by us earlier.8

Fig. 1. Pulse Doppler transesophageal recording of the type I flow pattern at the outlet of left atrial appendage in a normal control.
Spontaneous echo contrast was diagnosed by the presence of dynamic smoke-like echoes in the LAA with a characteristic swirling motion distinct from white noise artefact after properly adjusting the gain settings. All studies were reviewed independently by two experienced observers and any discrepancy was resolved by consensus.

**Statistical analysis:** Data are presented as mean ± SD. For comparison, unpaired student's t test was used for continuous variables and Chi-square test for categorical variables and values were considered significant when p value was <0.05. Univariate, multivariate logistic regression analysis and discriminant function analysis were done for all the variables to determine the factors that independently predict the presence of clot and spontaneous echo contrast.

**Results**

The mean age of the patients was 30.2 ± 9.4 years (range 13-60 years); 97 (48.5%) patients were males. Mean duration of symptoms was 32.0 ± 27.6 months (range 1-180 months). One hundred and eighteen (59%) patients were in New York Heart Association (NYHA) class II, 75 (37.5%) in class III, and 7 (3.5%) in class IV. The baseline patient characteristics and its comparison with controls are shown in Table 1. The LA size and LAA area were significantly more and the LAA ejection fraction, emptying and filling velocities and their respective velocity time integrals (VTIs) were significantly less in patients with mitral stenosis as compared to controls.

**Clinical and echocardiographic variables in relation to LAA clot (Tables 1 and 2):** The age, duration of symptoms and LA size (both area and diameter) were significantly more in patients with clot. The mitral valve area and mean diastolic gradient were not significantly different in the two groups. The incidences of AF and spontaneous echo contrast were significantly higher in patients with clot (p<0.0001 for both). The LAA\textsubscript{max} was significantly more (p<0.0001) and ejection fraction was significantly less (p<0.0001) in patients with clot as compared to those without clot. The LAA peak emptying (p<0.001) and filling (p<0.0001) velocities and emptying (p<0.05) and filling (p<0.0001) VTIs were significantly lower in patients with clot as compared to those without clot. Patients with type II and type III flow patterns had higher incidence of LAA clot (58.3% and 71.4%, respectively) as compared to patients with type I flow pattern (9.8%, p <0.0001).

After including all clinical and LAA function variables
in multivariate logistic regression analysis, AF [odds ratio (OR) 6.68, 95% CI 1.85 - 24.19, p=0.003] and LAA ejection fraction (OR 1.06, 95% CI 1.00 - 1.11, p = 0.04) were found to be independently related to the presence of clot in LAA and when LAA ejection fraction of 25% was arbitrarily taken as a cut off point, 62.5% (35/56) patients with LAA ejection fraction ≤ 25% had clot (6 times more) as compared to 10.4% (15/144) patients with LAA ejection fraction > 25% (p<0.0001).

On discriminant function analysis two variables i.e. AF and LAA ejection fraction, turned out to be the most important variables to discriminate the two groups. The
derived discriminate equation is:

\[ D = 0.392 + (-0.027 \times \text{LAA ejection fraction }\%) + \\
(2.134 \times 1 \text{ if AF is present and 0 if AF is absent}) \]

Where if \( D \) is > 0, the predictive group was with clot and if < 0 then the predicted group was without clot with an accuracy of 80.5%.

In the subgroup of patients with NSR (Table 3), larger LA size and lower LAA ejection fraction were significantly associated with LAA clot. In this subgroup, when LAA ejection fraction of 25% was arbitrarily taken as a cut off point, 50% (8/16) patients with LAA ejection fraction \( \leq 25\% \) had clot (8 times more) as compared to 6.2% (8/129) patients with LAA ejection fraction > 25%. Though maximum LA size was larger and peak filling and emptying velocities and their respective VTIs were lesser in patients with clot, but they did not reach statistical significance.

**LAA Doppler flow patterns and LAA function:** Type I flow was present in 143 (71.5%) patients and all were in NSR. Type II flow was present in 36 (18%) cases and all were in AF. Type III flow was observed in 21 (10.5%) cases, NSR was noted in 2 (both were having large LAA clot occupying whole of the LAA) and rest were in AF. LAA function with respect to LAA ejection fraction, peak filling and emptying velocities and VTIs were significantly different between type I, type II and type III flow patterns. Type III flow pattern had the lowest LAA ejection fraction and peak velocities as compared to type I and type II. The LAA clot and spontaneous echo contrast were significantly more in patients with type II and type III flow patterns as compared to type I (Table 2).

**LAA function in relation to the presence of spontaneous echo contrast (Table 4):** Spontaneous echo contrast was present in 113 patients. LAA area was significantly more and LAA ejection fraction was significantly less in the patients with spontaneous echo contrast as compared to patients without spontaneous echo contrast. The LAA peak emptying and filling velocities and LAA emptying and filling VTIs were also significantly lower in patients with spontaneous echo contrast as compared to

<table>
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<tr>
<th>Parameters</th>
<th>Patient with clot (n=16)</th>
<th>Patient without clot (n=129)</th>
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<td>LA area (cm²)</td>
<td>33.9±10.6</td>
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<tr>
<td>LAA maximum area (cm²)</td>
<td>6.4±2.8</td>
<td>5.4±1.9</td>
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<tr>
<td>LAA ejection fraction (%)</td>
<td>31.2±13.2</td>
<td>41.3±11.5</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>LAA emptying velocity (cm/s)</td>
<td>22.2±12.7</td>
<td>22.3±9.5</td>
<td>NS</td>
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<tr>
<td>LAA filling velocity (cm/s)</td>
<td>25.9±14.9</td>
<td>28.7±11.5</td>
<td>NS</td>
</tr>
<tr>
<td>LAA emptying VTI (cm)</td>
<td>1.8±1.1</td>
<td>2.1±1.2</td>
<td>NS</td>
</tr>
<tr>
<td>LAA filling VTI (cm)</td>
<td>1.8±1.3</td>
<td>2.6±1.3</td>
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LAA: left atrial appendage; LA: left atrium; NSR: normal sinus rhythm; VTI: velocity time integral; NS: not significant

<table>
<thead>
<tr>
<th>Parameters</th>
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<td>52.2±8.1</td>
<td>45.9±6.5</td>
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<td>LA area (cm²)</td>
<td>35.5±10.8</td>
<td>27.6±6.9</td>
<td>&lt;0.0001</td>
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<tr>
<td>LAA maximum area (cm²)</td>
<td>6.5±2.7</td>
<td>5.5±1.9</td>
<td>&lt;0.05</td>
</tr>
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<td>LAA ejection fraction (%)</td>
<td>30.3±16.2</td>
<td>40.3±11.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LAA emptying velocity (cm/s)</td>
<td>17.0±8.1</td>
<td>23.9±10.9</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LAA filling velocity (cm/s)</td>
<td>21.7±11.5</td>
<td>29.4±12.7</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LAA emptying VTI (cm)</td>
<td>1.7±1.0</td>
<td>2.3±1.4</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>LAA filling VTI (cm)</td>
<td>1.9±1.3</td>
<td>2.7±1.3</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

LA: left atrium; LAA: left atrial appendage; VTI: velocity time integral; SEC: spontaneous echo contrast
patients without spontaneous echo contrast. After multivariate logistic regression analysis, AF (OR 5.33, 95% CI 1.64-17.34, p=0.005) and LAA emptying velocity (OR 1.06, 95% CI 1.00 - 1.11, p = 0.02) were found to be independently related to the presence of spontaneous echo contrast in LAA.

In the subgroup of patients with NSR, peak filling (25.9±11.6 v. 30.7±12.2 cm/s, p <0.005) and emptying (19.3±7.8 v. 24.9±10.7 cm/s, p <0.05) velocities were found significantly less in patients with spontaneous echo contrast as compared to patients without spontaneous echo contrast. Although LAA area (5.6±2.2 v. 5.4±1.9 cm²) was larger and LAA ejection fraction (38.7±14.0 v. 41.2±11.3 %) was lower in patients with spontaneous echo contrast, it did not reach statistical significance.

**Discussion**

Various studies have shown that LAA is the major site of clot formation, especially in patients with mitral stenosis. It is assumed that the larger size and poor contraction of LAA in mitral stenosis, which is reflected by a decrease in ejection fraction, and reduced filling and emptying velocities, leads to stasis of blood, which helps in formation of clot. After the introduction of TEE, which enables the cardiac chambers to be examined in more detail than with TTE, the interest to evaluate the role of LAA contractile function has increased and many reports on various heart diseases have shown its correlation with presence of clot and spontaneous echo contrast formation in LA or LAA. Among all the cardiovascular diseases, mitral stenosis had the highest incidence of clot formation in LAA. However, there are not enough studies properly evaluating LAA function in a large number of patients with severe mitral stenosis. In the present study we prospectively evaluated LAA function in 200 consecutive patients with severe mitral stenosis and compared them with controls. The values of LAA ejection fraction and LAA flow velocities in the controls were in agreement with previously published reports.

The incidence of rheumatic heart disease is still high in the developing countries and the majority of the patients who need anticoagulation were not receiving it because of the delay in diagnosis, poor drug compliance and lack of facilities to monitor the prothrombin time in the remote areas. So we were able to collect a large number of patients with severe mitral stenosis who were not on any anti-coagulation despite being in AF and having past history of embolic episodes.

**Type of LAA flow pattern and its correlation with LAA function and clot formation:** In our study we consistently found that LAA emptying velocity was significantly less than LAA filling velocity in all the three types of flow patterns, which was not reported in the previous studies. In our control subset, both filling and emptying velocities were identical. Previous studies had either evaluated the emptying velocity or found both filling and emptying velocities to be similar. This difference in velocities in our study may be because of the fact that in patients with severe mitral stenosis the elevated LA pressure favors the filling waves while opposing the emptying waves thus increasing the velocity of filling waves and decreasing the velocity of emptying waves, which may not be true in patients with non-rheumatic AF and other diseases with normal LA pressure.

When patients were grouped according to the type of LAA flow pattern, type II and type III had higher incidence of clot and spontaneous echo contrast formation as compared to type I. We consistently found that patients with type II and type III flows had significantly larger LA and LAA sizes, lower LAA ejection fraction, lower filling and emptying velocities and VTIs as compared to those with type I flow. There were few reports which studied patients with mitral stenosis. These studies had smaller number of patients and did not evaluate all LAA function parameters and flow patterns with respect to clot and spontaneous echo contrast formation. Garcia-Fernandez et al. studied 27 patients with rheumatic valvular heart disease (not isolated mitral stenosis) and found that patients with type III flow had highest incidence of LAA clot and spontaneous echo contrast as compared to those with type I and type II flows; however, they did not correlate the type of flow pattern with other LAA function parameters. Porte et al. reported that patients with mitral stenosis having type II and type III flow patterns (n=37), had larger LA and LAA sizes, lower LAA ejection fractions, lower filling and emptying velocities as compared to those with type I flow pattern, but they did not correlate the LAA flow patterns with LAA clot and spontaneous echo contrast. In a different subset of patients (various cardiovascular diseases, not isolated mitral stenosis), Li et al. reported that patients with type II and type III flow patterns had significantly lower LAA ejection fraction, lower peak emptying velocity and higher chance of spontaneous echo contrast and clot formation as compared to those having type I flow.

**LAA function and LAA clot:** In the patients with severe
mitral stenosis we found significantly larger LAA size, lower LAA ejection fraction and lower filling and emptying velocities and VTIs as compared to controls. In the present study LAA size was significantly more and ejection fraction was significantly less in patients with clot in LAA. The LAA emptying and filling velocities were also significantly less in the patients with clot. Even in the subgroup of patients with NSR, LAA ejection fraction was independently correlated with clot formation in LAA. The higher incidence of clot in patients with larger and poorly functioning LAA with decreased ejection fraction, decreased filling and emptying velocities favors the hypothesis of stasis of blood in this chamber leading to increased incidence of clot formation. After multivariate logistic regression analysis, LAA ejection fraction along with AF was found to be independently correlated with presence of clot. Pollick et al. were the first to assess the LAA flow patterns and the effect of LAA function on clot formation in a different subgroup of patients (for evaluation of prosthetic valve, stroke and endocarditis). They found that patients with sinus rhythm and LAA clot had increased LAA size as compared to patients without clot. The LAA ejection fraction and LAA velocities were also significantly less in patients with clot as compared to patients without clot. Patients with AF and clot or spontaneous echo contrast had larger LAA area as compared to patients with AF but without clot or spontaneous echo contrast.

**LAA function and spontaneous echo contrast:** The presence of spontaneous echo contrast in LA has been found to be strongly correlated with the development of the clot and thromboembolization. The spontaneous echo contrast may be confined to the LAA alone and when distributed throughout the left atrium, it is usually more dense in LAA thus lending credence to the hypothesis that LAA function may be a useful indicator of the propensity of spontaneous echo contrast. Many factors like AF, large size of LA and poor LAA ejection fraction, type of flow pattern and lower flow velocities were found to be predictors for the development of spontaneous echo contrast in patients with non-rheumatic and rheumatic heart diseases. In our study, LAA was larger, LAA ejection fraction and LAA emptying and filling velocities were lower in patients with spontaneous echo contrast as compared to patients without spontaneous echo contrast. Patients with type II and type III flow patterns had significantly higher prevalence of spontaneous echo contrast as compared to type I. The presence of AF and lower LAA emptying velocity were found to be the most important variables for the development of spontaneous echo contrast.

on multivariate logistic regression analysis. Even in patients with NSR, LAA emptying velocity was found to be the only predictor of spontaneous echo contrast formation. The lower emptying velocity in patients with spontaneous echo contrast further strengthens the role of blood stasis in the formation of spontaneous echo contrast.

**Study limitations:** The possibility of intermittent AF in the patients with normal sinus rhythm could not be ruled out, thus not strictly isolating the patients with true normal sinus rhythm. This study only highlights the patients with severe mitral stenosis; the patients with mild to moderate mitral stenosis need to be further examined.

**Conclusions:** In the patients with severe mitral stenosis, AF and LAA ejection fraction appear to be independent predictors of clot and spontaneous echo contrast formation in LAA. In a subgroup of patients with NSR, patients with lower LAA ejection fraction (≤25%) had a higher risk of LAA clot formation. In patients with mitral stenosis the emptying velocity was consistently lower than filling velocity and lower emptying velocity was the only independent predictor for spontaneous echo contrast formation in LAA. We suggest that these patients should be anticoagulated for prevention of clot formation.

**References**


Background: This study sought to find out QT dispersion in healthy individuals and patients of acute myocardial infarction and to find correlation, if any, between QT dispersion and the incidence of ventricular arrhythmias in acute myocardial infarction.

Methods and Results: QT dispersion was calculated from a 12-lead electrocardiogram in 100 patients of acute myocardial infarction admitted in intensive coronary care unit and 100 age- and sex-matched healthy individuals. In patients of acute myocardial infarction, QT dispersion was calculated on admission, 24 hours after admission and at the time of discharge from intensive coronary care unit. Average QT dispersion in acute myocardial infarction was found to be significantly higher on admission (76.4±18.3 ms), 24 hours after admission (62.8±17.52 ms) and at the time of discharge from intensive coronary care unit (51.79±16.79 ms) than in healthy individuals (29.76±6.06 ms; p<0.05). QT dispersion was found to be significantly increased in patients of acute myocardial infarction with ventricular arrhythmias (82.06±16.86 ms) than in those without (66.75±16.28 ms; p<0.01). Patients of acute myocardial infarction with ventricular tachycardia or ventricular fibrillation had significantly increased QT dispersion (96.25±15.97 ms) than those who had only ventricular premature beats (80±15.04 ms; p<0.01). QT dispersion was found to be significantly greater in patients with anterior wall acute myocardial infarction (79.80±18.19 ms) than in those with inferior wall acute myocardial infarction (71.9±17.48 ms; p<0.05). At the time of discharge from intensive coronary care unit no statistically significant difference was found in QT dispersion in those who received thrombolysis (51.58±16.05 ms) and those who did not (48.18±14.68 ms; p>0.05). QT dispersion was found to be significantly higher in those who died (88.66±15.97 ms) than in those who survived (74.23±17.91 ms; p<0.05). QT dispersion was significantly higher in ventricular arrhythmic deaths (97.14±17.04 ms) than those who had non-arrhythmic deaths (81.25±11.25 ms; p<0.05).

Conclusions: Interlead QT variation and its measure as QT dispersion challenges our current approach to the electrocardiographic assessment of arrhythmic risk. QT dispersion may provide a potentially simple, cheap, non-invasive method of measuring underlying dispersion of ventricular excitability. (Indian Heart J 2004; 56: 636-641)

Key Words: QT dispersion, Acute myocardial infarction, Arrhythmia
simple non-invasive and low cost procedure such as QT dispersion, so that they could receive appropriate treatment.

Methods

One hundred patients of AMI admitted to intensive coronary care unit (ICCU) and 100 age- and sex-matched healthy individuals were included in the study. AMI was diagnosed on the basis of history of typical chest pain lasting for \( \geq 30 \) min and unresponsive to nitrates and the presence of ST segment elevation in the electrocardiogram of 0.1 mv in \( \geq 2 \) limb leads or 0.2 mv in \( \geq 2 \) precordial leads.4 Simultaneous 12-lead electrocardiogram was recorded on Schiller CS-200 diagnostic work station, at a paper speed of 25 mm/s. QT dispersion was calculated in all the patients of AMI as described by Van de Loo et al.4 on admission and in those who survived, 24 hours after admission and at the time of discharge from ICCU. QT dispersion was defined as the difference between the maximum and minimum QT interval measurements among all the measured 12 leads on the standard electrocardiogram8 (QTd = QT\(_{max} - QT_{min}\)). For analysis of QT dispersion, RR and QT intervals were measured in as many of the 12 leads as possible. Each measurement was taken as the mean value of 2 to 3 consecutive RR and QT intervals. Patients were excluded from the study when the admission electrocardiogram exhibited technical limitations for analysis of QT dispersion (<8 evaluable leads) or patients were in atrial fibrillation (AF) or flutter or had left or right bundle branch block. Patients receiving long-term medications with drugs influencing QT duration were also not considered for the present study. Ventricular arrhythmias were analyzed and its relationship to QT dispersion was observed.

Statistical analysis: Continuous variables were expressed as mean±SD. Standard error of difference between two means was used for comparing the differences. A value of \( p<0.05 \) was considered statistically significant.

Results

Baseline characteristics: The present study consisted of 100 patients of AMI and an equal number of age- and sex-matched healthy individuals. The age of the healthy individuals ranged from 25 to 90 years with a mean of 56.02±12.65 years. The age of patients with AMI ranged from 25 to 91 years with a mean of 55.66±12.97 years. There were 81 males and 19 females in each group. Out of 100 patients of AMI, 58 were having anterior wall AMI and 42 had inferior wall AMI.

QT dispersion among AMI: QT dispersion in AMI was found to be significantly higher (76.4±18.30 ms) than in normal individuals (29.76±6.06 ms, \( p<0.001 \)). QT dispersion in patients of AMI was found to be higher on admission (76.4±18.30 ms) and was found to decrease later in the course of disease (62.88±17.52 ms), 24 hours after admission and at the time of discharge from ICCU after an average stay of 4 days (51.79±16.79 ms). The difference observed was statistically significant (\( p<0.05 \)). The value at the time of discharge (51.79±16.79 ms) was still higher than normal (29.76±6.06 ms) and the difference was statistically significant (\( p<0.05 \)). QT dispersion was significantly greater in patients with anterior wall AMI (79.80±18.19 ms) than in those with inferior wall AMI (71.9±17.48 ms; \( p<0.05 \)).

QT dispersion and arrhythmias: QT dispersion was significantly higher (82.06±16.86 ms) in 63 patients with ventricular arrhythmias than 37 patients without ventricular arrhythmias (66.75±16.28 ms; \( p<0.01 \)). Fifty-five patients had ventricular premature beats (VPBs), 2 had ventricular tachycardia (VT) and 6 had ventricular fibrillation (VF). QT dispersion was significantly higher in patients with VT/VF (96.25±15.97 ms) than those who had only VPBs (80.15±15.04, \( p<0.01 \)).

QT dispersion and thrombolytic therapy: Out of 100 patients of AMI, 70 were thrombolyzed with streptokinase and 30 were not. No statistically significant difference was observed in QT dispersion in the two groups (51.58±16.05 ms vs 48.18±14.68 ms; \( p>0.05 \)) at the time of discharge from ICCU.

QT dispersion and prognosis: QT dispersion was found to be significantly higher in those who died (88.66±15.97 ms) than in those who survived (74.23±17.91 ms; \( p<0.05 \)). QT dispersion was significantly higher in arrhythmic deaths (97.14±17.04 ms) than in those who had non-arrhythmic deaths (81.25±11.25 ms; \( p<0.05 \)).

Discussion

The present prospectively designed study aimed to examine QT dispersion in 100 patients of AMI and an equal number of age- and sex-matched healthy individuals.

QT dispersion in normal individuals: In normal individuals a low QT dispersion was observed (29.76±6.06 ms). Similar values of QT dispersion have been reported earlier.4,6,9,11 Somewhat higher values have been reported in few other studies.12-16 The results obtained by non-invasive assessment of QT dispersion from the surface...
electrocardiogram are further substantiated by data obtained from endocardial or epicardial catheter mapping. Using this method, several studies have demonstrated regional differences in ventricular repolarization times of 40 to 55 ms. Extensive body surface mapping has also been used to assess disparities in ventricular repolarization in healthy persons and has revealed difference in QT duration of up to 60 ms. Taken together these findings suggest that a range of QT dispersion between 30 and 50 ms appears to represent the normal limits of this parameter.

**QT dispersion in AMI:** QT dispersion in patients of AMI ranged from 40 ms to 120 ms with an average of 76.4±18.3 ms which was significantly higher (p<0.001) than in normal healthy individuals (29.76±6.06 ms). Our results are similar to that reported in other studies. Patients with MI may have an inhomogenous ventricular repolarization process. In the setting of AMI, the interplay between ischemic living tissue and relatively depolarized dying tissue would create a complex transition period affecting QT interval dispersion. In early stage of AMI, increase in QT dispersion would be primarily due to local shortening of action potential. However, within few hours prolongation of QT interval could become the dominant feature governing QT dispersion.

In AMI, QT dispersion was highest at the time of admission (76.4±18.3 ms) and was found to decrease in the course of time, 62.88±17.52 ms at 24 hours after admission and 51.79±16.79 ms at the time of discharge. The difference observed was statistically significant (p<0.05). Similar observations have been made earlier. Glancy et al. measured QTc dispersion on days 1, 2, 3 and 6 in 17 patients with AMI. They found the maximal QTc dispersion assessed at admission or after 2 and 3 days.

In the present study QT dispersion was significantly greater in anterior wall AMI (79.80±18.19 ms) than in inferior wall AMI (71.9±17.48 ms; p <0.05). Similar observations have been made earlier. However, Cowan et al. did not observe any significant difference in QT dispersion with different territory MI.

**QT dispersion and site of infarct:** QT dispersion was significantly greater in anterior wall AMI (79.80±18.19 ms) than in inferior wall AMI (71.9±17.48 ms; p <0.05). Similar observations have been made earlier. However, Cowan et al. did not observe any significant difference in QT dispersion with different territory MI.

**QT dispersion and reperfusion therapy:** In essence, the determinants of increased QT dispersion during AMI are: speed of reperfusion, patency of the infarct-related artery (IRA) and location of AMI. Quick restoration of blood in the IRA post-MI decreases QT dispersion. Studies have shown that post-infarction patients with open arteries have a lower mortality rate than patients with closed arteries. Mortality rates as low as 2.5% have been reported in patients with patent arteries compared with 15% in patients with closed arteries. Mechanisms proposed to account for the beneficial effects of early and late reperfusion on mortality have been reviewed by Gersh and Anderson.

In the present study no statistically significant difference was noted in QT dispersion at the time of discharge from ICCU in those who received thrombolytic therapy (51.58±16.05 ms) and those who did not (48.18±14.68 ms, p>0.05). Some previous studies also showed significant reduction in QT dispersion while others reported no change in QT dispersion after thrombolytic therapy.

Moreno et al. studied 244 patients of AMI in whom they assessed reperfusion and the IRA by coronary angiography obtained 2.4±1 hours after start of thrombolysis. The degree of QT dispersion significantly related to reperfusion status. QT dispersion averaged 96±31 ms in patients with permanently occluded IRA (TIMI grade 0), 88±25 ms in patients with TIMI grade 1 reperfusion, 60±22 ms and 52±19 ms in patients with TIMI grade 2 or 3 reperfusion, respectively (p=0.0001). Difference in QT dispersion post-thrombolysis perhaps became clearer after a week or 10 days of AMI as observed by Ciolli et al. and Parale et al. Endoh et al. determined QT dispersion during the acute phase (2.0±0.9 days) and during recovery period (14±6 days) after AMI. They showed a significant reduction in the amount of QT dispersion in patients with successful reperfusion therapy whereas changes in QT dispersion were insignificant in patients who did not undergo recanalization of the IRA. Yunus et al. observed that mechanical relief of ischemia by percutaneous transluminal coronary angioplasty (PTCA) decreased QT dispersion (from 60±9 ms pre-PTCA to 29±18 ms post-PTCA) which returned back to pre-PTCA levels with restenosis. Studies involving larger number and patients with comparable QT dispersion values between the two groups are needed to confirm the results.

**QT dispersion, ventricular arrhythmias and mortality in AMI:** In experimental investigations, electrodes placed several millimeters apart with a small field of view have measured regional disparities in repolarization. Variation in ventricular recovery time is an important factor in experimental tachyarrhythmias. The usual site of abnormal dispersion from which arrhythmias occur is at border zone of the infarcted area.

In the present study QT dispersion was significantly higher (p<0.01) in patients of AMI with ventricular
arrhythmias (82.06±16.86 ms) than those without (66.75±16.28 ms). QT dispersion was significantly higher (p<0.01) in those with VT/VF (96.25±15.97 ms) than in those with VPBs (80±15.04 ms) (Fig. 1). Similar observations have been reported earlier.4,9,13-16,30-32 It simply illustrates the gradual increase in the heterogeneity of ventricular recovery from normal subjects to patients with uncomplicated MI to those with serious ventricular arrhythmias. A graded relationship has been found between the Lown grade (modified) of ventricular arrhythmia on 24 hours monitoring and QT dispersion 88±17 ms in VT, 60±14 ms in monomorphic VPB and 43±8 ms in controls.33 These data therefore suggest that QT dispersion increase in post-MI may relate to arrhythmias, and is decreased by measures that relieve ischemia or decrease arrhythmia incidence. This suggests that QT dispersion should relate to prognosis in post-AMI patients, and indeed that has been found in one major post-MI study (AIREX study) wherein those with AMI who had complicating heart failure, QT dispersion (measured on day 5) was found to be an independent (albeit rather weak) predictor of death.34 The study may not be applicable to all post-MI patients as it looked at only those with heart failure complicating AMI.

However, study by Leich et al.35 did not reveal any significant difference in QT dispersion in both the groups. Tomassoni et al.36 assessed QT dispersion in 543 consecutive patients enrolled in the TAM1-9 or the GUSTO-1 study: 43 of these patients suffered from VF. QT dispersion was repeatedly measured in the electrocardiograms taken at 2, 24 and 48 hours after the infarct. At all three time intervals there were no significant differences in QT dispersion between patients with and without primary VF. Methodological problems in assessing QT dispersion may at least in part be responsible for the observed discrepancy between the various studies addressing this question.

The major negative study suggesting that in unselected post-MI patients there is no relation between QTc dispersion and prognosis is provided by LIMIT II.37 QTc dispersion was measured 2–3 days post-AMI (>2000 subjects followed for 1 day/5 years) and comparison of QTc dispersion made between those 163 patients who died (112.1±44.4 ms) and who survived (109.9±42.7 ms). No difference was found. The authors concluded that QTc dispersion measured at hospital discharge was not helpful in predicting mortality, though perhaps a criticism of the study is the end point, being over-all mortality rather than sudden cardiac death. This study found that over time QTc dispersion did however decrease more in those who survived than in those who died (by 34 ms and 9 ms, respectively) (p=0.016), suggesting that in long-term post-MI, a failure to shorten the QTc dispersion might be associated with a poorer prognosis. The failure of QT dispersion post-MI to predict arrhythmic or total mortality has been confirmed recently by Zabel et al.38 in a prospective study of 280 patients. According to Davey39 also, it seems unlikely that there is a powerful relationship between QT dispersion post-MI and subsequent outlook. In the present study, QT dispersion at admission was high in patients with AMI who died than those who survived (88.66±15.97 v. 74.23±17.91 ms, p<0.05). QT dispersion at admission was higher in patients with AMI with arrhythmic death (97.14±17.04 ms) than those who had non-arrhythmic death (81.25±11.25 ms, p<0.05). Sredniawa et al.21 have made similar observation.

From the numerous studies conducted over last 5 to 8 years it is obvious that AMI is associated with changes in the electrophysiological properties of the heart. By means of assessing QT dispersion from the surface electrocardiogram there is convincing evidence that in AMI, inhomogeneity in ventricular repolarization is augmented. Some clinical observations also indicate that this increased disparity in repolarization is directly accompanied by the occurrence of ventricular arrhythmias and may help identify patients at high risk of sudden death. QT dispersion challenges our current approaches to the electrocar-
diagnostic assessment of arrhythmic risk. It provides a potentially simple, cheap, non-invasive method of measuring underlying dispersion of recovery of ventricular excitability. One should keep in mind, however, various problems inherent in the current technology used to determine QT dispersion from the surface electrocardiogram. It remains to be seen whether future refinements in technology will enable clinicians to use non-invasive assessment of disparity of ventricular repolarization as any adjunctive means for improving the care of patients with this common disease. The prognostic importance of abnormalities in QT-heart rate relation awaits the results, of large and long-term studies.

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Association of Common Carotid Intima-Media Thickness and Lipoprotein(a) with Coronary Artery Disease

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**Background:** Carotid artery intimal medial thickness is a simple, non-invasive and reproducible clinical tool to evaluate atherosclerosis and predict coronary artery disease. Lipoprotein(a) levels are related to both atherogenesis and thrombogenesis and may be a key link between lipid and coronary artery disease. This study evaluated the association of carotid intimal medial thickness and lipoprotein(a) with coronary artery disease.

**Methods and Results:** We studied 185 randomly selected patients hospitalized for coronary angiogram in our institute. There were 110 angiographically proven patients of coronary artery disease with mean age of 55.8±9 years (range 34-72 years) and 75 subjects with normal coronary artery anatomy with mean age of 54.8±8 years (range 34-68 years). The mean carotid intimal medial thickness of subjects with coronary artery disease was significantly higher than in subjects without coronary artery disease (0.84±0.16 mm vs. 0.65±0.15 mm, p<0.001). The mean carotid intimal medial thicknesses in patients with triple vessel, double vessel and single vessel disease were 0.96±0.12 mm, 0.84±0.11 mm and 0.78±0.13 mm, respectively (p=0.05). The mean lipoprotein(a) of subjects with coronary artery disease was significantly higher than in subjects without coronary artery disease (35.9±22.3 mg/dl vs. 19.1±21.2 mg/dl, p<0.001). Mean lipoprotein(a) levels in subjects with carotid intimal medial thickness <0.80 was 26.4±24.2 mg/dl and in subjects with carotid intimal medial thickness ≥0.80 was 32.1±22.1 mg/dl (p=0.05).

**Conclusions:** There is a strong correlation between carotid and coronary atherosclerosis and carotid intimal medial thickness is a good predictor of presence and extent of coronary artery disease. Lipoprotein(a) level is a powerful independent risk factor for atherosclerosis. Carotid intimal medial thickness and lipoprotein(a) in conjoint can predict coronary artery disease reliably. (Indian Heart J 2004; 56: 642–645)

**Key Words:** Carotid intimal medial thickness, Lipoprotein(a), Coronary artery disease

Atherosclerosis is a multifactorial and dynamic process. One of its feature is the presence of fatty streaks along the vessel wall leading to build-up of plaques on the wall of arteries, which leads to reduction in caliber of vessels. Coronary artery disease (CAD) in India is reaching alarming and epidemic proportions.1,2

Lipoprotein(a) [Lp(a)] was first described 40 years ago and adequate prospective data on its role in CAD have been recently published. Numerous studies have shown that Lp(a) is one of the major risk factors for CAD.3-6 Lp(a) acts by two mechanisms. Firstly, Lp(a) inhibits the binding of plasminogen to endothelial cells, fibrin and platelets by the competitive inhibition and secondly, it regulates the synthesis of plasminogen activator-1 by the endothelium. Lp(a) levels may be related to both atherogenesis and thrombogenesis and may be a key link between lipids and thrombosis. Lp(a) is 10 times more atherogenic than low-density lipoprotein cholesterol (LDL-c). The levels of Lp(a) have been found to be three times higher in Asian Indians. Studies on Indians showed increased Lp(a) levels in patients with atherosclerotic vascular disease as compared to controls.7 A striking feature was that elevated Lp(a) leads to CAD more prematurely and severely. Thus Lp(a) may be a powerful risk factor for the development of premature CAD in Indians.

The effects of Lp(a) get multiplied by abnormal lipid profile. Lp(a) excess increases the risk of premature CAD 3- to 100-fold, depending on the presence or absence of concomitant risk factors.
Developments in technology have now made it possible to assess the early sub-clinical changes of atherosclerosis, which include endothelial dysfunction and gradual thickening of intima. Pignoli et al. further developed the technique of intimal medial thickness (IMT) measurements. Today, progression of carotid IMT is considered as one of the best indices of future CAD risk. As atherosclerosis predominantly affects the intimal layer of the artery, technique, which facilitates the study of intima of the artery, is the principle behind the IMT assessment. Carotid IMT technique of intimal medial thickness (IMT) measurements. Today, progression of carotid IMT is considered as one of the best indices of future CAD risk. As atherosclerosis predominantly affects the intimal layer of the artery, technique, which facilitates the study of intima of the artery, is the principle behind the IMT assessment. Carotid IMT assessed non-invasively by B-mode ultrasound has been recently shown to be the physiological marker for atherosclerosis. It is well known that there are marked ethnic differences in the prevalence of CAD. Similarly, carotid IMT also differs in different populations studied. Individuals from countries with high prevalence rates of CAD tend to have greater mean IMT. This prompted us to take up a study on IMT as Indians have high rates of CAD. Carotid IMT has been shown to be correlated with CAD in Indian subjects in previous studies.

Methods

Selection of patients: A total of 185 randomly selected patients hospitalized for coronary angiogram in our institution were studied. Patients without any angiographic abnormality of coronary arteries were designated as control subjects. CAD was defined as >50% diameter stenosis in one or more arteries; 75 controls and 110 angiographically proven CAD patients were included in the study.

Study design: Baseline biochemistry included lipid profile and liver function tests to rule out any other systemic illness or a secondary cause of dyslipidemia. Blood samples were taken after a fasting period of 12 hours in all subjects. Total cholesterol (TC), triglycerides (TG), high-density lipoproteins (HDL), low-density lipoprotein (LDL) and very low density lipoprotein (VLDL) were analyzed using enzymatic methods. Lp(a) was measured by enzyme immunoassay (ELISA) technique and the kit was manufactured by Biopool International, USA. The assay utilizes affinity-purified polyclonal antibodies raised against Lp(a). Carotid IMT measurement was done in all the patients prior to angiogram. Measurement of carotid IMT was done on B-mode using 7.5 MHz probe (HP 5000). Six well-defined arterial wall segments were measured in each (right and left) carotid system: the near wall and far wall of the proximal 1 cm of the internal carotid artery, the near wall and far wall of the carotid bifurcation, beginning at the tip of the flow divider, and extending 1 cm below this point and near and far wall of the arterial segment, extending 1 cm below the tip of the flow divider into common carotid artery, recorded in videotape and two independent observers measured carotid IMT. B-mode examination was performed twice by 2 sonographers on 2 different days, with at least a 2-week interval between the first and the second scan. Each operator selected and processed 10 images from each scan performed by himself. Intraoperator and interoperator percent errors in the evaluation of mean IMT were 2.5% (range: 0-0.54%) and 5.9% (range: 0 - 8.31%), respectively. Coronary angiography was performed by the percutaneous Judkins technique and conventional views were taken to assess the severity of the CAD.

Statistical analysis: Data were presented as mean±SD. The statistical analyses were performed with the SPSS statistical software package. Clinical parameters in patients with and without CAD were compared by univariate analysis using Student's t test for continuous variables and Chi-square test for categorical variables. The variables that were significantly different between CAD and non-CAD patients in multiple univariate analysis were subjected to multivariate analysis using a stepwise logistic regression. For all analysis, a p value less than 0.05 was considered significant.

Results

Coronary artery disease was documented in 110 patients while 75 subjects had normal coronary anatomy. The mean age (55.8±9 years v. 54.8±8 years) and gender distribution were similar in the two groups as shown in Table 1. Smoking, hypertension and diabetes mellitus were significantly more common among those with CAD. Patients with CAD also had significantly higher TC, TG, LDL and lower HDL levels. Patients with CAD had higher mean carotid IMT (0.84±0.16 mm v. 0.65±0.15 mm, p<0.001) and mean Lp(a) levels (35.9±22.3 v. 19.1±21.2 mg/dl, p < 0.001). CAD and carotid IMT were highly correlated with correlation coefficient of 0.51 (p<0.01) (Fig. 1). The mean carotid IMT of triple vessel, double vessel and single vessel diseases was 0.96±0.12 mm v. 0.84±0.11 mm v. 0.78±0.13 mm, respectively (p=0.05 for all three groups among themselves) (Table 2).

Of 185 subjects studied, 77 (41%) had Lp(a) > 30 mg/dl while 108 (59%) had Lp(a) ≤ 30 mg/dl as shown in Table 3. Of the 77 subjects with Lp(a) > 30 mg/dl, 59 (77%) had CAD and of the 108 subjects with Lp(a) ≤ 30 mg/dl, 51 (47%) had CAD. In subjects with CAD, 54% (n=59) had Lp(a) >30 mg/dl as compared to subjects with normal
coronary artery anatomy, where only 24% (n=18) had Lp(a) >30 mg/dl (p<0.001). A significantly higher proportion of subjects having Lp(a)> 30 mg/dl had carotid IMT>0.80 mm than patients having Lp(a)≤ 30 mg/dl (56% v. 40%, p<0.001) (Fig. 2). Mean Lp(a) levels of subjects with triple vessel, double vessel and single vessel diseases were 39.2±19.5 mg/dl, 33.5±17.8 mg/dl and 31.8±16.8 mg/dl, respectively (p=0.05) while with normal coronary anatomy, subjects had mean Lp(a) of 16.6 mg/dl. Taking CAD as the dependent variable, on univariate analysis, diabetes, smoking, TG, TC, LDL-c, HDL-cholesterol (HDL-c), TC to HDL-c ratio, Lp(a) and carotid IMT were found to have significant correlation with CAD. On multivariate analysis we found that diabetes [odds ratio (OR) = 1.08, 95% CI=0.47-2.51, p<0.01], HDL-c (OR=0.87, 95% CI=0.83-0.92, p<0.01) and carotid IMT (OR=1.068, 95% CI=1.043-1.095) showed strong correlation with CAD as shown in Table 4. These 3 predictors had overall predictive power of 80% to predict disease, with 85% correct prediction of patients with CAD and 72% correct prediction of controls.

Table 1. Baseline characteristics of the study group

<table>
<thead>
<tr>
<th>Parameters</th>
<th>CAD (n=110)</th>
<th>Non-CAD (n=75)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>55.8±9</td>
<td>54.8±8.4</td>
<td>0.47</td>
</tr>
<tr>
<td>Male</td>
<td>73 (66)</td>
<td>45 (60)</td>
<td>0.37</td>
</tr>
<tr>
<td>Female</td>
<td>37 (34)</td>
<td>30 (40)</td>
<td>0.37</td>
</tr>
<tr>
<td>Smoking</td>
<td>39 (35)</td>
<td>15 (20)</td>
<td>0.02</td>
</tr>
<tr>
<td>Hypertension</td>
<td>31 (28)</td>
<td>11 (15)</td>
<td>0.03</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>48 (43)</td>
<td>18 (24)</td>
<td>0.006</td>
</tr>
<tr>
<td>Family history of CAD</td>
<td>20 (18)</td>
<td>8 (11)</td>
<td>0.16</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>25.6±3.2</td>
<td>24.8±3.1</td>
<td>0.39</td>
</tr>
<tr>
<td>Total cholesterol (mg/dl)</td>
<td>210±43</td>
<td>159±42</td>
<td>0.001</td>
</tr>
<tr>
<td>Triglycerides (mg/dl)</td>
<td>176±59</td>
<td>132±46</td>
<td>0.001</td>
</tr>
<tr>
<td>LDL-cholesterol (mg/dl)</td>
<td>137±43</td>
<td>93±40</td>
<td>0.001</td>
</tr>
<tr>
<td>HDL-cholesterol (mg/dl)</td>
<td>29±7</td>
<td>37±8</td>
<td>0.001</td>
</tr>
<tr>
<td>Total cholesterol/HDL</td>
<td>7.6±2.5</td>
<td>4.4±3.4</td>
<td>0.001</td>
</tr>
<tr>
<td>Lp(a) (mg/dl)</td>
<td>35.9±22.3</td>
<td>19.1±21.2</td>
<td>0.001</td>
</tr>
<tr>
<td>Carotid IMT (mm)</td>
<td>0.84±0.16</td>
<td>0.65±0.15</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Values in parentheses are percentages.
IMT: intimal medial thickness; CAD: coronary artery disease; Lp(a): lipoprotein(a); LDL: low-density lipoprotein; HDL: high-density lipoprotein

Table 2. Severity of disease in different groups of carotid IMT patients

<table>
<thead>
<tr>
<th>Age in years (mean)</th>
<th>Carotid IMT (mm)</th>
<th>SVD (n=28)</th>
<th>DVD (n=47)</th>
<th>TVD (n=35)</th>
</tr>
</thead>
<tbody>
<tr>
<td>52.79</td>
<td>≤0.59</td>
<td>8</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>54.87</td>
<td>0.60-0.79</td>
<td>12</td>
<td>15</td>
<td>2</td>
</tr>
<tr>
<td>56.58</td>
<td>0.80-0.99</td>
<td>6</td>
<td>25</td>
<td>17</td>
</tr>
<tr>
<td>57.74</td>
<td>≥1.00</td>
<td>2</td>
<td>3</td>
<td>14</td>
</tr>
</tbody>
</table>

Values in parentheses are percentages, p value<0.01.
IMT: intimal medial thickness; SVD: single vessel disease; DVD: double vessel disease; TVD: triple vessel disease

Table 3. Distribution of patients in each group of Lp(a) on the basis of carotid IMT

<table>
<thead>
<tr>
<th>Carotid IMT (mm)</th>
<th>Lp(a) ≤30 (n=108)</th>
<th>Lp(a) &gt;30 (n=77)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAD (n=51)</td>
<td>Non-CAD (n=57)</td>
<td>CAD (n=59)</td>
</tr>
<tr>
<td>≤0.59</td>
<td>8 (16)</td>
<td>29 (51)</td>
</tr>
<tr>
<td>0.60-0.79</td>
<td>14 (27)</td>
<td>14 (24)</td>
</tr>
<tr>
<td>0.80-0.99</td>
<td>23 (45)</td>
<td>13 (23)</td>
</tr>
<tr>
<td>≥1.00</td>
<td>6 (12)</td>
<td>1 (2)</td>
</tr>
</tbody>
</table>

Values in parentheses are percentages.
IMT: intimal medial thickness; CAD: coronary artery disease; Lp(a): lipoprotein(a)

Table 4. Multivariate predictors of coronary artery disease

<table>
<thead>
<tr>
<th>Predictors</th>
<th>Odds ratio</th>
<th>95% confidence interval</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes mellitus</td>
<td>1.08</td>
<td>0.47-2.51</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>HDL-cholesterol</td>
<td>0.87</td>
<td>0.83-0.92</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Carotid IMT</td>
<td>1.068</td>
<td>1.043-1.095</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

CAD: coronary artery disease; HDL: high-density lipoprotein; IMT: intimal medial thickness

Fig. 1. Percentage of patients in CAD and non-CAD group on the basis of carotid IMT.
CAD: coronary artery disease; IMT: intimal medial thickness

Fig. 2. Percentage of patients in Lp(a) group on the basis of carotid IMT.
Lp(a): lipoprotein(a); IMT: intimal medial thickness
Discussion

Carotid artery IMT is a simple, non-invasive and reproducible clinical tool to evaluate atherosclerosis and predict CAD in humans. In our study, 61% of CAD patients had carotid IMT > 0.8 mm while only 25% patients with normal coronary had carotid IMT > 0.80 mm, suggesting that the patients with carotid IMT >0.80 mm had higher chances of having CAD. The cardiovascular health study collaborative research group\(^1\) showed that in 4476 subjects without clinical cardiovascular disease, who were followed up for 6 years, the relative risk for myocardial infarction or stroke for the quintile with highest IMT, as compared with the lowest, was 3.87.

Carotid IMT showed a positive association with traditional risk factors like male sex, age, obesity, hypertension, serum cholesterol, smoking and diabetes. In the Chennai urban population study,\(^4\) the mean IMT among diabetic subjects was higher (0.95±0.31 mm) than non-diabetic subjects (0.074±0.14 mm) (p<0.001).

In our study, mean Lp(a) levels were higher in CAD patients in comparison to those with normal coronaries. In this study, patients with increased carotid IMT had significantly higher level of Lp(a). Budde et al.\(^6\) showed that Lp(a) levels correlate with number, severity and length -extension of coronary lesions in patients undergoing coronary angiography for clinically suspected coronary atherosclerosis. In our study, patients with triple vessel disease had highest level of Lp(a), while patients with single vessel disease had least Lp(a) levels among CAD patients. We found that Lp(a) had an association with CAD in univariate analysis but not as an independent risk factor in multivariate regression analysis.

Limitations: The limitation of our study was that it was not a prospective study but a cross sectional observational study. Our subjects with CAD belong to a high risk subset with more prevalence of conventional risk factors and dyslipidemia.

Conclusions: Carotid IMT is a simple, non-invasive and reproducible clinical tool to evaluate atherosclerosis. There was a strong correlation between carotid atherosclerosis and coronary atherosclerosis and carotid IMT is a good predictor of presence and extent of CAD, hence it can be used as a marker in the prediction of pre-clinical atherosclerosis and CAD. Measurements of carotid IMT and Lp(a) can help identify high risk individuals for CAD.

References

High Prevalence of Multiple Coronary Risk Factors in Punjabi Bhatia Community: Jaipur Heart Watch-3

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Background: Studies among emigrant Indian populations have shown a high prevalence of obesity and many coronary risk factors in Bhatia community. To determine the prevalence of risk factors in this community within India we performed an epidemiological study.

Methods and Results: An ethnic-group sample survey to determine prevalence of cardiovascular risk factors was performed using community registers for enrollment. Methodology used was similar to Jaipur Heart Watch studies performed in 1995 and 2002. We invited 600 randomly selected subjects listed in Punjabi Bhatia community registers and could examine 458 (76.7%) persons (men 226, women 232). Evaluation for coronary risk factors, anthropometric measurements, blood pressure, electrocardiogram, fasting blood glucose and serum lipids was performed using standard definitions. Mean age was 43.2 ± 14.6 years in men and 44.7 ± 15.3 years in women. In both men and women there was a high prevalence of family history of coronary heart disease in 45 (19.9%) and 50 (21.6%), family history of diabetes in 96 (42.5%) and 77 (33.2%), sedentary habits in 82 (36.3%) and 73 (31.5%), smoking or tobacco use in 59 (26.1%) and 4 (1.7%), overweight or obesity (body mass index ≥ 25 kg/m²) in 123 (54.0%) and 161 (69.4%), severe obesity (body mass index > 30 kg/m²) in 47 (20.8%) and 75 (32.3%), truncal obesity (waist-hip ratio: men > 0.9, women > 0.8) in 175 (77.4%) and 186 (80.2%), increased waist (waist size: men > 102 cm, women > 88 cm) in 78 (34.5%) and 129 (55.6%), hypertension (blood pressure ≥ 140/90 mmHg) in 116 (51.3%) and 120 (51.3%), diabetes in 40 (17.7%) and 33 (14.2%), hypercholesterolemia (total cholesterol ≥ 200 mg/dl) in 75 (33.2%) and 67 (28.9%), high triglycerides in 55 (24.3%) and 34 (14.7%), low high-density lipoprotein cholesterol in 169 (74.8%) and 155 (66.8%), and the metabolic syndrome (defined by American National Cholesterol Education Program) in 84 (36.2%) and 111 (47.8%) respectively. Body mass index correlated significantly with (age-adjusted r² value - men, women) waist diameter (0.52, 0.12), waist-hip ratio (0.21, 0.10), truncal obesity (0.54, 0.60), systolic blood pressure (0.19, 0.16), diastolic blood pressure (0.12, 0.16), hypertension (0.19, 0.31), and metabolic syndrome (0.28, 0.44) (p < 0.05). There was a significant linear relationship of body mass index with the prevalence of hypertension, hypercholesterolemia, diabetes (women), and the metabolic syndrome (χ² for trend p < 0.05). Prevalence of these risk factors was the lowest in subjects with body mass index < 20 kg/m². A multivariate ordinal logistic regression analysis revealed that obesity was independently associated with multiple risk factors characterized by metabolic syndrome after adjustment for age, hypertension, and diabetes in both men (odds ratio 2.45, 95% confidence intervals 1.69, 3.57) as well as in women (odds ratio 2.93, 95% confidence intervals 1.86, 4.61) (p < 0.01).

Conclusions: There is a high prevalence of obesity, abdominal obesity, hypertension, diabetes, lipid abnormalities and the metabolic syndrome in this community that is significantly greater than reported studies in Jaipur and urban populations elsewhere in India. Obesity correlates strongly with multiple coronary risk factors of which it is an important determinant. (Indian Heart J 2004; 56: 646-652)

Key Words: Obesity, Coronary risk factors, Epidemiology

Various studies have reported that there is difference in prevalence of coronary risk factors and coronary heart disease (CHD) among emigrant Indian sub-communities.
Ramaiya et al.\textsuperscript{1,2} reported that coronary risk factors were more prevalent in Patel (Gujarati) and Bhatia (Punjabi) communities living in Tanzania. Bhopal et al.\textsuperscript{3} reported a greater prevalence of risk factors amongBangladeshi emigrants as compared to Pakistani and Indian subjects in UK. In India it has been reported that Gujaratis living in Delhi have a greater coronary risk factor profile as compared to local communities and there was no difference in risk factors among Hindu and Muslim communities.\textsuperscript{4,5} Gupta et al.\textsuperscript{6} did not report any significant differences in coronary risk factors in Hindu and Muslim communities in Jaipur. A higher prevalence of hypertension in Parsi community in Mumbai has been reported.\textsuperscript{7} Studies on migrants have found a greater prevalence of coronary risk factors among the North Indian Bhatia community in Tanzania and Britain.\textsuperscript{1,2} The city of Jaipur has a large numbers of subjects of this community. Therefore to evaluate the prevalence of various coronary risk factors in randomly selected sample of Bhatia community in Jaipur and using the methodology of previous Jaipur Heart Watch (JHW) studies,\textsuperscript{8,9} we performed an epidemiological study, the Jaipur Heart Watch-3.

**Methods**

The study was approved by the institution ethics committee. A proforma was prepared that incorporated information regarding demographic, anthropometric and clinical parameters.\textsuperscript{8,9} This included the family history of hypertension and CHD, details of major cardiovascular risk factors such as smoking, amount of physical activity, diabetes and hypertension. Physical examination was undertaken for measurement of height, weight, waist-hip ratio (WHR) and blood pressure (BP). Height was measured in centimetres and weight in kilograms using calibrated spring-balance. Standing waist girth was measured at the level of umbilicus with person breathing quietly and standing. The hip girth was measured at inter-trochanteric level according to the World Health Organization (WHO) guidelines.\textsuperscript{10} Sitting blood pressure was measured using standard mercury manometer. At least two readings at 5 min intervals as per WHO guidelines were recorded.\textsuperscript{11} If a high blood pressure (\(\geq 140/90\)) was noted, a third reading was taken after 30 min. The lowest of the three readings was taken as blood pressure. Fasting blood sample was obtained from all the individuals for estimation of glucose, total cholesterol (TC), high-density lipoprotein cholesterol (HDL-c), low-density lipoprotein (LDL) cholesterol (LDL-c) and triglycerides (TG) using the previously standardized techniques.\textsuperscript{12}

This study was designed to investigate the people of a single community in Jaipur (JHW-3) unlike the previously reported population-based JHW-1 in 1995\textsuperscript{9} and JHW-2 in 2002.\textsuperscript{9} We studied Bhatia populations in colonies of Jawahar Nagar, Janta Colony and Adarsh Nagar. Details of the Bhatia subjects in these locations were available from the Bhatia community register maintained at Bhatia Bhawan, Jaipur. The target subjects were adults \(\geq 20\) years and from the register we randomly selected 600 subjects (300 men, 300 women). The study was preceded by meetings with local leaders who cooperated in identifying and ensuring participation of selected subjects.

**Diagnostic criteria:** Smokers in India consume tobacco in various forms - rolled tobacco leaves (bidi), Indian pipe (chillum, hookah), cigarettes and tobacco-chewing, and more than one form is used by many making it difficult to accurately measure the amount of tobacco consumed. Therefore, users of all types of tobacco products and present and past smokers have been included in smoker category. The diagnostic criteria for tobacco use as well as other coronary risk factors adopted were in accordance with American College of Cardiology clinical data standards.\textsuperscript{13} Physical activity was measured by asking about both work-related and leisure-time activities as used in the previous study.\textsuperscript{4} Hypertension was diagnosed when systolic BP was \(\geq 140\) mmHg and diastolic BP was \(\geq 90\) mmHg or a person was a known hypertensive. Body mass index (BMI) was calculated as weight in kg divided by square of height in metres and overweight and obesity defined as BMI \(\geq 25\) kg/m\(^2\). Truncal obesity was diagnosed when waist-hip ratio (WHR) was \(>0.9\) in males and \(>0.8\) in females while abdominal obesity was diagnosed when waist size was \(>102\) cm in men and \(>88\) cm in women as per the US National Cholesterol Education Program (NCEP) guidelines.\textsuperscript{14} Dyslipidemia was defined by the presence of high TC (\(\geq 200\) mg/dl), high LDL-c (\(\geq 130\) mg/dl), low HDL-c (\(<40\) mg/dl) or high TG (\(\geq 150\) mg/dl) according to NCEP guidelines.\textsuperscript{14} Metabolic syndrome was also diagnosed according to NCEP guidelines when any three of the five identifying risk factors [abdominal obesity, fasting glucose \(>110\) mg/dl or diabetes, BP \(\geq 130/90\) mmHg, low HDL-c (men \(<40\) mg/dl, women \(<50\) mg/dl) or high TG (\(\geq 150\) mg/dl)] were present.\textsuperscript{14}

**Statistical analysis:** Continuous variables are reported as mean \(\pm 1\) SD. The prevalence rates are given in percentage. Age-related trends have been examined by Mantel-Haenzel \(\chi^2\) for trend. To determine correlation of BMI with multiple coronary risk factors a Pearson correlation analysis was first performed and as age is an important determinant of
BMI, partial correlation coefficients ($r^2$) were calculated after age-adjustment. Continuous variables have been compared using t test and categorical variables by $\chi^2$ test. BMI levels were divided into different groups with BMI $<20$, 20.0 to 22.9, 23.0 to 24.9, 25.0 to 29.9 and $\geq 30$ kg/m$^2$ according to WHO guidelines.10

Prevalence of coronary risk factors in different BMI groups was determined and trends examined using Mantel-Haenzel $\chi^2$ for trend and least-squares regression method. To determine influence of obesity on prevalence of multiple metabolic abnormalities in men and women we performed a conditional multivariable logistic regression analysis using a commercially available statistical programme (SPSS Version 10.0, SPSS Inc, Chicago, USA). The dependent variable was presence or absence of metabolic syndrome and independent variables were obesity, age, diabetes, hypertension and truncal obesity. Age was included as a continuous variable while other variables were dichotomized. $p$ values <0.05 were considered significant. Direct method of age-adjustment was used to compare prevalence rates of various risk factors in the present study with the previous Jaipur Heart Watch studies.

Results

We could evaluate 458 subjects (226 men and 232 women) out of the targeted 600 (response rate 76.7%). The mean age of men was 43.2±14.6 and in women it was 44.7±15.3 years (p= NS). Prevalence of risk factors in the study group is described in Table 1. There was a high prevalence of family history of CHD and diabetes in the study subjects. A high prevalence of obesity, abdominal obesity, hypertension, diabetes, lipid abnormalities and multiple metabolic abnormalities (the metabolic syndrome) was also seen in both men and women.

Age-specific prevalence of risk factors is outlined in Table 2. In men, increasing age was associated with a significantly increasing trend in prevalence of severe obesity (BMI $\geq 30$ kg/m$^2$), truncal obesity, waist (abdominal) obesity, hypertension, diabetes, metabolic syndrome and high cholesterol levels. In women, with increasing age there was a significant increase of obesity, severe obesity, increased waist circumference, hypertension, diabetes, metabolic syndrome and lipid abnormalities (Mantel-Haenzel $\chi^2$ for trend, $p<0.05$).

In men the BMI in age groups 20-29, 30-39, 40-49, 50-59 and $\geq 60$ years was 25.6±11.1, 26.6±5.6, 27.2±4.3, 27.8±4.5 and 24.1±4.6 kg/m$^2$, respectively (ANOVA F= 2.29, $r^2=0.03$, eta$^2=0.04$, $p=0.061$). In women it was 23.5±4.7, 26.9±4.9, 28.7±4.9, 29.9±6.2 and 30.1±6.1 kg/m$^2$ respectively (ANOVA F=10.46, $r^2=0.14$, eta$^2=0.18$, $p<0.0001$). BMI correlated ($r$ value - men, women) significantly with waist diameter (0.67, 0.14), systolic BP (0.26, 0.26), diastolic BP (0.20, 0.19), fasting glucose (0.12, 0.15), TC (0.13, 0.27) and TG (0.14, 0.15) ($p<0.05$). As age was a major confounding factor, we calculated partial correlation coefficients ($r^2$) for BMI with various factors after adjustment for age. A significant correlation of BMI was observed in men and women with waist diameter (0.54, 0.12), WHR (0.21, 0.10), truncal obesity (0.54, 0.60), systolic BP (0.19, 0.16), diastolic BP (0.12, 0.16), prevalence of hypertension (0.19, 0.31), and metabolic syndrome (0.28, 0.44) ($p<0.05$).

Trend analysis ($\chi^2$ for trend, Table 3) demonstrated that there was a significant linear relationship of BMI with the presence of hypertension ($p<0.0001$), hypercholesterolemia ($p=0.039$), hypertriglyceridemia ($p=0.003$) and the metabolic syndrome ($p<0.0001$) in men. In women a significant correlation was observed with hypertension ($p<0.0001$), diabetes ($p=0.006$), hypercholesterolemia ($p=0.01$), low HDL-c ($p=0.07$) and the metabolic syndrome ($p<0.0001$). The lowest prevalence of these risk factors is observed at BMI $<20$ kg/m$^2$ and a marked increase is seen at BMI $\geq 25$ kg/m$^2$ (Fig. 1). Multivariate ordinal logistic regression analysis confirmed that obesity was an independent determinant of multiple metabolic abnormalities as shown by metabolic syndrome. Results of conditional logistic regression with metabolic syndrome as dependent variable and successive addition of independent variables of obesity, age, hypertension,
Table 2. Age-specific prevalence of coronary risk factors

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Age 20-29</th>
<th>Age 30-39</th>
<th>Age 40-49</th>
<th>Age 50-59</th>
<th>Age ≥60</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Men (n=226)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number</td>
<td>42</td>
<td>45</td>
<td>58</td>
<td>34</td>
<td>47</td>
<td>226</td>
</tr>
<tr>
<td>Smoking/tobacco</td>
<td>8 (19.0)</td>
<td>15 (33.3)</td>
<td>17 (29.3)</td>
<td>10 (29.4)</td>
<td>9 (19.1)</td>
<td>59 (26.1)</td>
</tr>
<tr>
<td>Physical inactivity</td>
<td>20 (47.6)</td>
<td>18 (40.0)</td>
<td>22 (37.9)</td>
<td>10 (29.4)</td>
<td>12 (25.5)</td>
<td>82 (36.3)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>9 (21.4)</td>
<td>19 (42.2)</td>
<td>28 (48.3)</td>
<td>27 (79.4)</td>
<td>33 (70.2)</td>
<td>116 (51.3)*</td>
</tr>
<tr>
<td>Obesity (BMI ≥25 kg/m²)</td>
<td>14 (33.3)</td>
<td>24 (53.3)</td>
<td>38 (65.5)</td>
<td>28 (82.3)</td>
<td>19 (40.4)</td>
<td>123 (54.0)*</td>
</tr>
<tr>
<td>Severe obesity (BMI ≥30 kg/m²)</td>
<td>5 (11.9)</td>
<td>11 (24.4)</td>
<td>18 (31.0)</td>
<td>11 (32.4)</td>
<td>3 (6.4)</td>
<td>47 (20.8)*</td>
</tr>
<tr>
<td>Truncal obesity (WHR &gt;0.9)</td>
<td>24 (57.1)</td>
<td>34 (75.5)</td>
<td>49 (84.5)</td>
<td>29 (85.3)</td>
<td>39 (82.9)</td>
<td>175 (77.4)*</td>
</tr>
<tr>
<td>Abdominal obesity &gt;102 cm</td>
<td>4 (9.5)</td>
<td>13 (28.9)</td>
<td>25 (48.1)</td>
<td>21 (61.8)</td>
<td>15 (31.9)</td>
<td>78 (34.5)*</td>
</tr>
<tr>
<td>Diabetes (history or FBG ≥126 mg/dl)</td>
<td>1 (2.3)</td>
<td>1 (2.2)</td>
<td>9 (15.5)</td>
<td>12 (35.3)</td>
<td>17 (36.2)</td>
<td>40 (17.7)*</td>
</tr>
<tr>
<td>High cholesterol (≥200 mg/dl)</td>
<td>6 (14.3)</td>
<td>15 (33.3)</td>
<td>24 (41.4)</td>
<td>16 (47.1)</td>
<td>14 (29.8)</td>
<td>75 (33.2)*</td>
</tr>
<tr>
<td>High LDL (≥130 mg/dl)</td>
<td>8 (19.0)</td>
<td>20 (44.4)</td>
<td>24 (41.4)</td>
<td>18 (52.9)</td>
<td>16 (34.0)</td>
<td>86 (38.1)</td>
</tr>
<tr>
<td>Low HDL (&lt;40 mg/dl)</td>
<td>28 (66.7)</td>
<td>35 (77.7)</td>
<td>45 (77.6)</td>
<td>27 (79.4)</td>
<td>34 (72.0)</td>
<td>169 (74.8)</td>
</tr>
<tr>
<td>High TG (≥150 mg/dl)</td>
<td>7 (16.7)</td>
<td>11 (24.4)</td>
<td>14 (24.1)</td>
<td>15 (55.1)</td>
<td>8 (17.0)</td>
<td>55 (24.3)</td>
</tr>
<tr>
<td>Metabolic syndrome</td>
<td>7 (16.7)</td>
<td>12 (26.7)</td>
<td>21 (36.2)</td>
<td>23 (67.6)</td>
<td>21 (44.7)</td>
<td>84 (37.2)*</td>
</tr>
<tr>
<td><strong>Women (n=232)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Number</td>
<td>40</td>
<td>62</td>
<td>49</td>
<td>44</td>
<td>37</td>
<td>232</td>
</tr>
<tr>
<td>Smoking/tobacco</td>
<td>-</td>
<td>2 (3.2)</td>
<td>1 (2.0)</td>
<td>1 (2.3)</td>
<td>-</td>
<td>4 (1.7)</td>
</tr>
<tr>
<td>Physical inactivity</td>
<td>16 (40.0)</td>
<td>20 (32.2)</td>
<td>14 (28.6)</td>
<td>12 (27.3)</td>
<td>11 (29.7)</td>
<td>73 (31.5)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>3 (7.5)</td>
<td>18 (29.0)</td>
<td>33 (67.3)</td>
<td>32 (72.7)</td>
<td>34 (91.9)</td>
<td>120 (51.3)*</td>
</tr>
<tr>
<td>Obesity (BMI ≥25 kg/m²)</td>
<td>14 (35.0)</td>
<td>46 (74.2)</td>
<td>39 (79.6)</td>
<td>34 (77.3)</td>
<td>29 (78.4)</td>
<td>161 (69.4)*</td>
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<tr>
<td>Severe obesity (BMI ≥30 kg/m²)</td>
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<td>18 (40.9)</td>
<td>19 (51.4)</td>
<td>75 (32.3)*</td>
</tr>
<tr>
<td>Truncal obesity (WHR &gt;0.8)</td>
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<td>52 (83.9)</td>
<td>42 (85.7)</td>
<td>37 (84.1)</td>
<td>27 (72.9)</td>
<td>186 (80.2)</td>
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<tr>
<td>Abdominal obesity &gt;88 cm</td>
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<td>33 (53.2)</td>
<td>29 (59.2)</td>
<td>32 (72.7)</td>
<td>24 (64.9)</td>
<td>129 (55.6)*</td>
</tr>
<tr>
<td>Diabetes (history or FBG ≥126 mg/dl)</td>
<td>-</td>
<td>1 (1.6)</td>
<td>6 (12.2)</td>
<td>12 (27.3)</td>
<td>14 (37.8)</td>
<td>33 (14.2)*</td>
</tr>
<tr>
<td>High cholesterol (≥200 mg/dl)</td>
<td>5 (12.5)</td>
<td>14 (22.6)</td>
<td>17 (34.7)</td>
<td>15 (34.1)</td>
<td>16 (42.2)</td>
<td>67 (28.9)*</td>
</tr>
<tr>
<td>High LDL (≥130 mg/dl)</td>
<td>6 (15.0)</td>
<td>20 (32.2)</td>
<td>18 (36.7)</td>
<td>18 (40.9)</td>
<td>19 (51.4)</td>
<td>81 (34.9)*</td>
</tr>
<tr>
<td>Low HDL (&lt;40 mg/dl)</td>
<td>18 (45.0)</td>
<td>42 (67.7)</td>
<td>35 (71.4)</td>
<td>30 (68.2)</td>
<td>30 (81.1)</td>
<td>155 (66.8)*</td>
</tr>
<tr>
<td>High TG (≥150 mg/dl)</td>
<td>4 (10.0)</td>
<td>6 (9.7)</td>
<td>9 (18.4)</td>
<td>7 (15.9)</td>
<td>8 (17.0)</td>
<td>34 (14.7)*</td>
</tr>
<tr>
<td>Metabolic syndrome</td>
<td>4 (10.0)</td>
<td>19 (42.2)</td>
<td>29 (50.0)</td>
<td>30 (88.2)</td>
<td>29 (61.7)</td>
<td>111 (47.8)*</td>
</tr>
</tbody>
</table>

Values in parentheses are percentage. BMI: body mass index; BP: blood pressure; FBG: fasting blood glucose; LDL: low-density lipoprotein; HDL: high-density lipoprotein; TG: triglycerides; *χ² for trend p<0.05

Discussion

The present study shows that there is a high prevalence of obesity, abdominal obesity, hypertension, diabetes, lipid abnormalities and the metabolic syndrome in the North Indian Punjabi Bhatia community. The prevalence of these risk factors is significantly greater than reported in studies from Jaipur and urban populations elsewhere in India. BMI and obesity correlate strongly with multiple coronary risk factors, and are major determinants of these risk factors.

Ramiya et al. studied emigrant Indian populations in Tanzania for prevalence of cardiovascular risk factors. They reported that obesity, hypertension, glucose intolerance and diabetes and lipid abnormalities were significantly greater in Bhatia and Patel Hindu communities as compared to other South Asian groups. Age-adjusted prevalence of impaired glucose tolerance (27.2%), diabetes (14.3%), stage
II hypertension (19.4%), overweight (22.7%) and mild hypercholesterolemia (26.8%) were the highest in Bhatia community as compared to six other groups. In a study comparing cardiovascular risk factors and diabetes in Bhatia community living in Tanzania and in the UK it was reported that prevalence of known diabetes, hypertriglyceridemia, hypertension and obesity were not different in Tanzanian and UK Bhatias but the prevalence of impaired glucose tolerance, diabetes, hypercholesterolemia and smoking was significantly higher and sedentary lifestyle more common in subjects in Africa. Williams et al. reported on non-biochemical cardiovascular risk factors in different South Asian groups in Glasgow, UK. South Asians, especially the British Punjabi subjects had a lower prevalence of smoking but there was a greater prevalence of sedentary habits, higher diastolic blood pressure, higher BMI, insulin resistance, stress, and socioeconomic deprivation. Cappuccio et al. reported prevalence of cardiovascular risk factors in different ethnic groups in South London. As compared to subjects of Caucasian and African descent, South Asians had a two-to-three fold excess of hypertension and diabetes and an inferior control of hypertension. It was concluded that the excess of CHD mortality among South Asians may be due to the higher prevalence of non-metabolic as well as metabolic risk factors. Greater prevalence of coronary risk factors in the Punjabi Bhatia community in Jaipur, when compared to the previous studies, is in agreement with these observations.

In India there have been only a few community-specific studies of risk factors. Chopra and Chopra studied prevalence of high blood pressure among different groups in India in early 1940s. They reported higher mean systolic blood pressure in North Indians, especially those living in Punjab, as compared to the South Indian subjects. Malhotra studied railway workers for cardiovascular risk factors in mid 1960s and found that there was a difference in prevalence of CHD as well as risk factors in different parts of India. He reported a higher prevalence of risk factors in North Indian workers as compared to the South Indians. Gopinath et al. reported prevalence of risk factors in multiple ethnic groups in Delhi. The prevalence rates of CHD were the highest in Sikhs, lowest in Muslims and identical in Hindus and Christians. Sikhs also had the highest prevalence of obesity, hypertension and diabetes. The present study also shows that the Punjabi Bhatia community has a very high prevalence of obesity and multiple coronary risk factors as compared to Jaipur general population. This is similar to the Delhi study. All these studies have been performed using different tools by different persons. However, the role of methodological differences in producing biased results cannot be overlooked. The present study, using methodology of JHW-1 and JHW-2 shows that the prevalence of coronary risk factors is significantly greater in the Bhatia community as compared to previous studies in Jaipur (Table 5).

Studies of obesity in Asian subjects show that generalized obesity is the major determinant of cardiovascular risk in the Chinese and East Asian subjects while central obesity is associated with greater cardio-

<table>
<thead>
<tr>
<th>BMI groups (kg/m²)</th>
<th>Numbers</th>
<th>Hypertension</th>
<th>Diabetes</th>
<th>High TC (≥200 mg/dl)</th>
<th>High triglycerides (≥150 mg/dl)</th>
<th>Low HDL cholesterol (&lt;40 mg/dl)</th>
<th>Metabolic syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 20.0</td>
<td>27</td>
<td>8 (29.6)</td>
<td>3 (11.1)</td>
<td>3 (11.1)</td>
<td>1 (3.7)</td>
<td>21 (77.8)</td>
<td>3 (11.1)</td>
</tr>
<tr>
<td>20.0-22.9</td>
<td>25</td>
<td>4 (16.0)</td>
<td>8 (32.0)</td>
<td>9 (36.0)</td>
<td>2 (8.0)</td>
<td>17 (68.0)</td>
<td>4 (16.0)</td>
</tr>
<tr>
<td>23.0-24.9</td>
<td>51</td>
<td>23 (45.1)</td>
<td>5 (9.8)</td>
<td>17 (33.3)</td>
<td>12 (23.5)</td>
<td>41 (80.4)</td>
<td>8 (15.7)</td>
</tr>
<tr>
<td>25.0-29.9</td>
<td>75</td>
<td>50 (66.7)</td>
<td>18 (24.0)</td>
<td>28 (37.3)</td>
<td>29 (38.7)</td>
<td>55 (73.3)</td>
<td>39 (52.0)</td>
</tr>
<tr>
<td>≥ 30.0</td>
<td>48</td>
<td>17 (35.4)</td>
<td>6 (12.5)</td>
<td>18 (37.5)</td>
<td>11 (22.9)</td>
<td>35 (72.9)</td>
<td>30 (62.5)</td>
</tr>
</tbody>
</table>

χ² trend (p value) : 22.04, <0.0001

<table>
<thead>
<tr>
<th>BMI groups (kg/m²)</th>
<th>Numbers</th>
<th>Hypertension</th>
<th>Diabetes</th>
<th>High TC (≥200 mg/dl)</th>
<th>High triglycerides (≥150 mg/dl)</th>
<th>Low HDL cholesterol (&lt;40 mg/dl)</th>
<th>Metabolic syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 20.0</td>
<td>16</td>
<td>1 (6.3)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>20.0-22.9</td>
<td>31</td>
<td>9 (29.3)</td>
<td>3 (9.7)</td>
<td>5 (16.1)</td>
<td>6 (19.4)</td>
<td>13 (41.9)</td>
<td>4 (12.9)</td>
</tr>
<tr>
<td>23.0-24.9</td>
<td>23</td>
<td>9 (39.1)</td>
<td>3 (13.0)</td>
<td>7 (30.4)</td>
<td>3 (13.0)</td>
<td>16 (69.6)</td>
<td>7 (30.4)</td>
</tr>
<tr>
<td>25.0-29.9</td>
<td>86</td>
<td>44 (51.2)</td>
<td>8 (9.3)</td>
<td>26 (30.2)</td>
<td>12 (13.9)</td>
<td>62 (72.1)</td>
<td>42 (48.8)</td>
</tr>
<tr>
<td>≥ 30.0</td>
<td>76</td>
<td>57 (75.0)</td>
<td>19 (25.0)</td>
<td>29 (38.2)</td>
<td>12 (30.3)</td>
<td>55 (72.4)</td>
<td>58 (76.3)</td>
</tr>
</tbody>
</table>

χ² trend (p value) : 36.04, <0.0001

Values in parentheses are percentage. TC: total cholesterol; HDL: high-density lipoprotein; BMI: body mass index.
Table 4. Conditional logistic regression analysis for determining independent significance of obesity in metabolic syndrome (odds ratios and 95% confidence intervals)

<table>
<thead>
<tr>
<th>Variables</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obesity</td>
<td>2.25 (1.68, 3.00)*</td>
<td>2.96 (2.13, 4.12)*</td>
</tr>
<tr>
<td>Obesity + age</td>
<td>2.39 (1.77, 3.23)*</td>
<td>2.93 (2.03, 4.23)*</td>
</tr>
<tr>
<td>Obesity + age + hypertension</td>
<td>2.05 (1.48, 2.83)*</td>
<td>2.73 (1.81, 4.12)*</td>
</tr>
<tr>
<td>Obesity + age + hypertension +</td>
<td>2.45 (1.69, 3.57)*</td>
<td>2.93 (1.86, 4.61)*</td>
</tr>
<tr>
<td>diabetes</td>
<td>1.08 (0.68, 1.71)</td>
<td>1.09 (0.56, 2.11)</td>
</tr>
</tbody>
</table>

*p < 0.001

Table 5. Age-adjusted coronary risk factor prevalence in JHW-1, 1995, JHW-2, 2002 and JHW-3

<table>
<thead>
<tr>
<th></th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoking/tobacco</td>
<td>JHW-1 (n=1415)</td>
<td>JHW-2 (n=550)</td>
</tr>
<tr>
<td>Smoking/tobacco</td>
<td>548/1415</td>
<td>196/550</td>
</tr>
<tr>
<td>Sedentary habits</td>
<td>(38.7)</td>
<td>(35.6)</td>
</tr>
<tr>
<td>History of diabetes</td>
<td>15/1415</td>
<td>42/550</td>
</tr>
<tr>
<td>Obesity (BMI ≥27 kg/m²)</td>
<td>158/1415</td>
<td>123/550</td>
</tr>
<tr>
<td>Truncal obesity: Males &gt;0.9, Females &gt;0.8</td>
<td>128/250</td>
<td>280/550</td>
</tr>
<tr>
<td>Hypertension (≥140/90)</td>
<td>417/1415</td>
<td>165/550</td>
</tr>
<tr>
<td>Diabetes (history or fasting glucose ≥126 mg/dl)</td>
<td>72/550</td>
<td>27/226</td>
</tr>
<tr>
<td>High total cholesterol</td>
<td>49/199</td>
<td>183/532</td>
</tr>
<tr>
<td>(≥200 mg/dl)</td>
<td>(24.6)</td>
<td>(34.4)</td>
</tr>
<tr>
<td>High LDL cholesterol</td>
<td>44/199</td>
<td>182/532</td>
</tr>
<tr>
<td>(&gt;130 mg/dl)</td>
<td>(22.1)</td>
<td>(34.2)</td>
</tr>
<tr>
<td>Low HDL cholesterol</td>
<td>86/199</td>
<td>284/532</td>
</tr>
<tr>
<td>(&gt;40 mg/dl)</td>
<td>(43.2)</td>
<td>(53.4)</td>
</tr>
<tr>
<td>High triglycerides</td>
<td>53/199</td>
<td>163/532</td>
</tr>
<tr>
<td>(&gt;150 mg/dl)</td>
<td>(26.6)</td>
<td>(30.6)</td>
</tr>
<tr>
<td>Metabolic syndrome</td>
<td>-</td>
<td>98/532</td>
</tr>
</tbody>
</table>

Values in parentheses are percentage. JHW-1: Jaipur Heart Watch-1 study; JHW-2: Jaipur Heart Watch-2 study; JHW-3: Jaipur Heart Watch-3 study; BMI: body mass index; LDL: low-density lipoprotein; HDL: high-density lipoprotein; * p < 0.05, ** p < 0.01, *** p < 0.001

Fig. 1. Body mass index (BMI) is directly correlated with prevalence of metabolic syndrome indicating that obesity is associated with multiple metabolic abnormalities in Punjabi Bhatia men and women (χ² for trend p < 0.0001).

vascular risk in South Asians. Deurenberg-Yap et al. determined body fat percentages (BF%) in Singaporean Chinese, Malays and Indians and concluded that when the BF% prediction equation based on BMI in Caucasian populations was applied to these three ethnic groups in Singapore, there was a gross underestimation of actual BF%. The mean bias in prediction ranged from 2.7 to 5.6% BF. They noted that for the same BMI values, Chinese have the lowest BF% while Indians have the highest. The present study shows that majority of cardiovascular risk factors in Bhatia men and women increase at BMI of ≥25 kg/m² and therefore this cutoff, instead of BMI ≥30 kg/m², should be used to determine obesity in South Asians. Similar recommendations have been made by other Indian investigators as well as those from China and other Asian countries. The present study also shows that BMI levels accurately predict hypertension, diabetes and metabolic syndrome in this community. BMI was not an accurate predictor of lipid abnormalities. In the JHW-2
study, we reported that BMI accurately predicts non-biochemical coronary risk factors more accurately than WHR, while the latter is more reliable in predicting the biochemical risk factors of hyperglycemia and lipid abnormalities.

**Conclusions:** Punjabi Bhatia community has a high prevalence of obesity which is an important determinant of cardiovascular risk factors. Although a lower BMI cutoff to diagnose obesity (≥25 kg/m²) is suggested by this study, it needs to be confirmed by larger prospective epidemiological studies. The INTERHEART case-control study of coronary risk factors in acute myocardial infarction has recently reported that obesity, especially central obesity, is an important coronary risk factor in most of the developing countries of Asia, Europe, Africa and South America. Community-wide preventive measures that focus on obesity reduction are imperative.

**Acknowledgements**

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**References**

19. Deurenberg P, Deurenberg-Yap M, Guricci S. Asians are different from Caucasians and from each other in their body mass index/body fat percent relationship. Obesity Rev 2002; 3: 141–146
Plasma Endothelin-1, Homocysteine and Serum Nitric Oxide Values in Patients with Left-to-Right Shunt

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Departments of Clinical Microbiology, Pediatrics, Biochemistry, Cardiovascular Surgery and Biostatistics, Faculty of Medicine, Inonu University, Malatya, Turkey

Background: This study aimed to evaluate the effect of pulmonary blood flow and pulmonary hypertension on plasma endothelin-1, homocysteine and serum nitric oxide levels in patients with left-to-right shunt lesions with pulmonary hypertension and also with normal pulmonary arterial pressure.

Methods and Results: Plasma endothelin-1, homocysteine and nitric oxide levels were measured in 44 patients (Group 1) with left-to-right shunt and normal pulmonary arterial pressure (Qp/Qs: 2.1), 65 patients (Group 2) with left-to-right shunt and pulmonary hypertension (Qp/Qs: 2.4), 20 healthy control subjects (Group 3), and 17 post-operative patients (Group 4). Plasma endothelin-1 and serum nitric oxide levels were significantly higher in Group 2 than in groups 1, 3, and 4 (p<0.001). Plasma homocysteine levels were significantly higher in Group 2 than in Groups 1 and 4 (p<0.001 and p<0.01, respectively).

Conclusions: The increase in serum nitric oxide levels in patients with left-to-right shunt and pulmonary hypertension may be attributed to the compensatory mechanism. However, this increase does not improve pulmonary hypertension because of increased endothelin-1 and homocysteine levels. In the light of present study, we conclude that vascular changes caused by increased homocysteine and endothelin-1 may provoke pulmonary hypertension in patients with left-to-right shunt. (Indian Heart J 2004; 56: 653–657)

Key Words: Congenital heart disease, Nitric oxide, Left-to-right shunt

Under physiologic conditions, the vascular endothelium produces some factors that maintain normal vascular tonus and homeostasis. Under pathologic conditions, two of the most important factors produced by the vascular endothelium are an endothelial-derived relaxing factor, nitric oxide (NO) and an endothelial-derived vasoconstrictor peptide, endothelin-1 (ET-1). ET-1 has potent physiologic activities including vasoconstriction, cell proliferation, edema, and possibly inflammation. Several studies have demonstrated the interaction between NO and ET-1 in the vascular endothelium. Endothelium-derived NO is known as most potent endogenous vasodilator. Some studies indicate that NO plays a major homeostatic role in modulating vascular resistance. Blood vessels dilate in response to increases in blood flow. It has been shown that elevated plasma NO synthase (NOS) could explain the increased basal release of endothelial NO due to high pulmonary blood flow. Total plasma homocysteine (Hcy) is now established as a clinical risk factor for coronary artery disease (CAD), as well as other arterial and venous occlusive diseases in adults. It is postulated that Hcy may damage endothelial cells or act as a direct causal factor in the thromboembolic process. Hcy potentiates vascular tension in human umbilical artery possibly by suppressing bioavailable NO and by the oxidative stress from Hcy autooxidation. The prevalence of hyperhomocysteinemia ranges from 20 - 40% in different populations with CAD. It can contribute to the pathogenesis of pulmonary hypertension (PH) in patients with congenital heart disease.

In the present study, we investigated the level of plasma ET-1, Hcy and serum NO levels in children having left-to-right (L-R) shunt with or without PH and children with surgically closed shunt.

Methods
We studied the children having L-R shunt older than 6 month of age. Patients with complex congenital heart disease, metabolic disorders, renal disease, infection, systemic hypertension and anemia were excluded.

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The study was performed on four groups. Group 1 consisted of 44 patients with L-R shunt and normal pulmonary artery pressure (NPAP); Group 2 had 65 patients having L-R shunt with PH; Group 3 included 20 normal control subjects; and Group 4 had 17 patients who underwent L-R shunt closure surgery. Fourty-four patients without PH were diagnosed as - 37 ventricular septal defect (VSD), 5 atrial septal defect (ASD), and 2 ASD plus VSD; 65 children with PH were diagnosed as 36 VSD, 17 VSD plus ASD, 5 VSD plus patent ductus arteriosus (PDA), and 7 atrioventricular (AV) canal defects. Post-operative patients consisted of 11 VSD, 3 ASD and 3 AV canal defect. None of the post-operative cases had PH on 6th month echocardiographic evaluation.

All patients were catheterized after midazolam or ketamine sedation. Pressures of different chambers and pulmonary artery mean pressure (P AMP) were recorded by a fluid-filled and catheter-connected pressure transducer. Pulmonary and systemic flows were calculated by Fick method.

Blood samples of the patients were obtained from the pulmonary artery during cardiac catheterization. Control group consisted of normal healthy children and blood samples were withdrawn from peripheral veins. The parents of all participants were duly informed before blood collection and consent was obtained from the parents of patients and controls. In post-operative group, blood samples were taken from peripheral veins at least 6 months after surgery. ET-1 was measured by an enzyme immunoassay (ELISA) kit (Endothelin-1 Enzyme Immunoassay Kit, Cayman Chem, Ann Arbor, MI, USA) and Hcy was analyzed by Axys Homocysteine ELISA kit (Homocysteine Enzyme Immunoassay Kit, Bio-Rad Lab, Oslo, Norway). Because NO is converted to nitrite and nitrate just after production in vivo, serum nitrite and nitrate levels was taken as an index of serum NO. By coloring with Griess reagent after cadmium reduction, total nitrite (nitrite + nitrate) was determined by spectrophotometric method using a visible spectrophotometer (LKB Biochrom Spectrophotometer, Cambridge, UK).

Statistical analysis: All data was reported as mean ± standard deviation (SD). All parameters were tested with Kolmogorov-Smirnov test. If its distribution was not normal (p>0.05), Mann-Whitney U test was used as dual comparison.

Results

Endothelin-1, total homocysteine and NO levels in serum of patients with L-R shunt both having PH and NPAP, normal healthy persons, and a group of patients operated for shunt were studied. Some characteristics of participants and the values of ET-1, NO, and Hcy in different groups are summarized in Table 1 and Figs 1, 2 and 3.

ET-1 and Hcy levels were higher in patients having PH. NO levels were higher in patients with or without PH when compared to the other groups. In post-operative patients, ET-1, NO and Hcy levels were lower than those of pre-operative patients having PH. Endothelin-1 levels in patients with L-R shunt and NPAP were significantly lower than those of other groups (p<0.001) except post-operative patients. Patients with L-R shunt and NPAP and post-operative patients had significantly lower plasma ET-1 levels than those of control subjects (p<0.001 in both). Similarly, NO levels in patients with L-R shunt with PH were higher compared to other groups (p<0.01). The serum NO levels in L-R shunt patients with PH and post-operative patients were higher compared to healthy persons (p<0.01 in both). Plasma total Hcy levels in patients with L-R shunt with PH were significantly higher compared to the patients with L-R shunt with NPAP and post-operative patients (p<0.001, p<0.01, respectively). There was a statistically significant lower Hcy levels in patients with L-R shunt and NPAP compared to healthy controls (p<0.01).

Discussion

Pulmonary hypertension seen in the patients with L-R shunt may be partially related to increased pulmonary blood flow. There are many other causes of PH, some of

Table 1. Characteristics of the patients and control groups and the results of parameters studied

<table>
<thead>
<tr>
<th>Groups</th>
<th>No.</th>
<th>Age (years)</th>
<th>ET-1 (pg/ml)</th>
<th>NO (µmol/L)</th>
<th>Hcy (µmol/L)</th>
<th>P AMP (mmHg)</th>
<th>Qp/Qs</th>
</tr>
</thead>
<tbody>
<tr>
<td>L-R shunt+NPAP</td>
<td>44</td>
<td>5.3±5.2</td>
<td>1.1±0.5</td>
<td>22.3±19.6</td>
<td>8.2±2.1</td>
<td>16.6±3.3</td>
<td>2.1±0.7</td>
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<tr>
<td>L-R shunt+PH</td>
<td>65</td>
<td>4.4±4.9</td>
<td>26.7±7.1</td>
<td>30.5±44.9</td>
<td>12.8±4.8</td>
<td>42.1±17.5</td>
<td>2.4±1.1</td>
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<tr>
<td>Healthy controls</td>
<td>20</td>
<td>3.9±4.1</td>
<td>11.8±5.1</td>
<td>7.2±4.5</td>
<td>10.7±4.4</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Post-Op</td>
<td>17</td>
<td>5.5±4.8</td>
<td>1.0±0.5</td>
<td>12.7±9.4</td>
<td>8.6±2.9</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

ET-1: endothelin-1; NO: nitric oxide; Hcy: homocysteine; P AMP: pulmonary artery mean pressure; L-R: left-to-right; NPAP: normal pulmonary artery pressure; PH: pulmonary hypertension; Post-Op: post-operation
them are still unknown. The normal endothelium elaborates a panoply of proteins, prostanoids, and other paracrine substances to maintain a delicate balance between vasoconstriction and vasodilation, coagulation and blood fluidity, as well as inhibition and promotion of vascular growth.7

The endothelium responds to hemodynamic forces. Blood vessels dilate in response to increased blood flow. The integrity of endothelium is essential for this flow-mediated vasodilation.11-13 Flow-mediated vasodilation is largely due to the release of NO,7 which is known to modulate smooth muscle growth, too. On the other hand, ET-1 produced by vascular endothelial cells has potent vasoconstrictor and mitogenic activities on vascular smooth muscle cells.14-16 ET-1 contracts isolated pulmonary vessels17 and increases pulmonary vascular resistance (PVR).18 Endothelial injury appears to be an important mechanism of enhanced release of ET-1 in animal models.19,20

In our study, NO levels in L-R shunt patients with or without PH were significantly higher than that of controls. After surgical closure, NO values decreased. Although there was no significant difference in Qp/Qs ratio between groups 1 and 2. The plasma ET-1 levels were significantly higher in patients with PH than those without PH (p<0.001). There was also a decrease of ET-1 level in post-operative patients. Several studies have shown that plasma ET-1 levels are increased in patients with primary or secondary PH.21-25 Yoshibayashi et al.25 reported an absolute increase in ET-1 levels across the pulmonary circulation in patients with congenital heart disease and PH compared with those of non-PH group. Ishikawa et al.26 demonstrated that successful surgery decreased the elevated plasma ET-1 levels from 3.96 to 1.98 pg/ml in young patients with PH caused
by congenital heart disease indicating that the elevation of ET-1 in these patients was reversible. Increased ET-1 level associated with PH was found to be correlated with the severity of disease. In our three patients with PH, ET-1 levels were very high and decreased after surgery. Some investigators could not establish a direct positive correlation between increased blood flow and increased ET-1 levels. We also could not find such a correlation.

Increased plasma ET-1 levels can result from either an increase in the production of ET-1 or a decrease of its clearance. Dupuis et al. have shown that the metabolic capacity of the lung to remove ET-1 from circulation greatly reduces in PH. As a result of decreased clearance, the quantity of ET-1 that survives passage through the lungs increases in patients with PH. On the other hand, it has been demonstrated that expression of ET-1 increases in the pulmonary vascular endothelial cells of patients with PH. It may aggravate the pulmonary hemodynamics through its potent and long-lasting vasoconstrictive as well as proliferative actions on pulmonary arteries. Goreño et al. reported that plasma ET-1 did not significantly differ among patients with ASD, VSD and PDA. Hence, we did not divide the patients into subgroups.

Several studies have demonstrated the interaction between NO and ET-1 in the vascular endothelium. Some investigators have reported an increased ET-1 and a decreased NO production in patients with PH and in experimental PH models. In our study, we found that both ET-1 and NO levels were high in patients with PH. The activation of a vasoconstrictor such as ET-1 on the endothelium induces the release of NO. Flow-mediated vasodilation is mostly related to NO release. It has been also shown that elevated plasma NOS could explain the increased basal release of endothelial NO due to high pulmonary blood flow.

A rise in Hcy plasma level is considered an independent risk factor for the development of vascular damage. Two major hypotheses have been proposed to explain how Hcy induces its harmful effects. It can damage endothelial cells lining the vasculature allowing plaque formation. Simultaneously, it interferes with the vasodilatory effect of NO. Hcy has also been found to promote vascular smooth muscle cell hypertrophy. Both of these processes induce vessel occlusion. A few studies have investigated Hcy levels in children. De Laet et al. studied the reference range of Hcy in Belgian pediatric population. In their study, total Hcy concentrations were lowest in younger children, and increased with age. In 5-9 year-old age group, Hcy geometric means were 6.2 μmol/L (our mean values were 10.7 μmol/L in control group and 8.2 μmol/L in Group 1, respectively). In our study, Hcy levels in PH group were significantly higher than post-operative patients and patients without PH (p<0.01 and p<0.001, respectively). We could not find a significant difference between post-operative group and controls. Most of the operated patients were from the group without PH. It is supposed that hyperhomocysteinemia damages endothelial cells and causes thromboembolic process, and these factors could contribute to PH.

Increased pulmonary blood flow alone is not effective in the development of PH. Vasoactive substances such as NO and ET-1 and endothelial damaging agents such as Hcy have important roles in the pathogenesis of PH. The reason for increased ET-1 levels in PH, whether because of its over-production or decreased clearance is not known precisely.

On the other hand, ET-1 has vasoconstrictive and proliferation-stimulating effects and may cause PH. NO levels increase in patients with high pulmonary blood flow with or without PH. In the rats injected Hcy, endothelial NOS increased 2-fold and inducible NOS 3-fold in aortic endothelium. It is observed that although high levels of Hcy and NO in PH were detected, Hcy has not only endothelial damaging and thromboembolic effects, but it also decreases the bioavailability of NO. Hence, NO level is higher but less effective in PH.

Conclusions: Vascular changes caused by hyperhomocysteinemia may provoke PH in patients with L-R shunt. Hyperhomocysteinemia which is seen in 9-15% in general population should be investigated in these patients and treated with folate and vitamin B12.

References
Thromboembolism after percutaneous transseptal mitral commissurotomy (PTMC) is a recognized but dreadful complication. This most commonly happens to cerebral vessels. Till lately, conservative treatment was the only available option in this condition. However, in recent years thrombolytic therapy and percutaneous transluminal angioplasty (PTA) are being increasingly utilized to reperfuse these vessels. There is increasing tendency to resort to PTA. We report a case of middle cerebral embolic occlusion following PTMC treated with PTA.

Case Report
A 20-year-old female had history of acute rheumatic fever in 1994 and she developed rheumatic mitral stenosis in 1996 for which she underwent PTMC. She presented again with progressive breathlessness of 6 months duration due to severe mitral restenosis. On echocardiography, mitral valve area was found to be 1.0 cm² without any mitral regurgitation. There was severe tricuspid regurgitation and severe pulmonary artery hypertension with normal sinus rhythm. Valve was considered suitable for PTMC. There was no left atrial or left atrial appendage thrombus on transesophageal echocardiography (TEE).

She (height 160 cm) was taken up for PTMC, which was successfully performed with Inoue technique with single dilation with balloon of 25 size under cover of 5000 units of heparin. The end-diastolic gradient reduced to 2 mmHg with no mitral regurgitation. The procedure went uneventfully and she was shifted to the recovery room. She developed right-sided hemiplegia with aphasia nearly 10 min after completion of the PTMC. She was diagnosed to have embolic occlusion of middle cerebral artery (MCA). The cause was thought to be thrombus formation during PTMC. She was wheeled back into the cardiac catheterization laboratory and four-vessel angiogram was performed. There was no abnormality on bilateral vertebral and right carotid angiograms. Left cerebral artery angiogram showed complete occlusion of the M₁ segment of the middle cerebral artery with no distal flow (Fig. 1). We considered local delivery of thrombolytic therapy versus immediate balloon angioplasty. She was taken up for PTA after consent and discussion with the relatives.
Left carotid artery was hooked with JR 3.5 6 F guide catheter. Balanced middle weight coronary guidewire (Guidant Corporation, Santa Clara, USA) was passed across the occlusion (Fig. 2). Marked tortuosity of the vessels and absence of any flow distally made it difficult to wire. A 1.5 × 10 mm balloon followed by 2.5 × 15 mm balloon (Medtronic AVE, Minneapolis, USA) was positioned in MCA and dilated at multiple sites at 2-4 atm pressure for 15-20 s each (Figs 3 and 4). Thus, normal flow was restored (Fig. 5). There was no residual lesion or distal embolization. The procedure time was 65 min and fluoroscopy time, 22 min following which she made rapid but incomplete recovery.
right on the table, which subsequently progressed to complete recovery within 24 hours.

**Discussion**

Thromboembolism after PTMC to cerebral vessels is known complication. Until lately, conservative treatment was the only choice. Recently thrombolytic therapy and PTA are increasingly being utilized to reperfuse these vessels. However, there are only few centers where such measures are employed. We recently embarked on direct PTA to revascularize one such patient with due consent of her relatives. The outcome was very rewarding.

Development of excellent hardware has made it possible to reach intracranial vessels and perform PTA. Several studies have shown feasibility and safety of PTA in intracranial vessels though complication rates still remain high. Complications include rupture of the vessel with sub-arachnoid hemorrhage, spasm, distal embolization, dissection and stent thrombosis if stents are used.

Angioplasty of intracranial vessels is distinctly different from coronary angioplasty. Intracranial vessels float freely in sub-arachnoid space without any connective tissue support. This makes them prone to rupture and therefore they have to be dilated at low pressures ranging from 2-8 atm only. Intracranial vessels give rise to lenticulostriate branches, which are difficult to visualize on angiograms, and protect during angioplasty. Occlusion of these branches may cause procedure-related neurological deficit. Leptomeningeal collaterals are poorly developed in acute occlusions; therefore these vessels do not tolerate prolonged dilations during angioplasty, which have to be short i.e. 10-20 s. Cerebral vessels are prone to spasm and pose technical difficulties due to tortuosity.

Thrombolytic therapy in MCA occlusions has been used successfully but has distinct disadvantages. Thrombolytic therapy leads to delayed and incomplete resolution of thrombus. Nakano et al. compared 36 patients given thrombolytic therapy with 34 patients undergoing PTA. Recanalization was achieved in 63% cases following thrombolysis as opposed to 91.2% cases with PTA. If thrombolytic therapy is instituted late after endothelial damage has already taken place, there is possibility of hemorrhagic transformation and neurological deterioration despite arterial recanalization. Re-occlusion after thrombolytic therapy is also common. As opposed to this, PTA has advantage that it can expediently treat embolic and also atherosclerotic disease, if present, without enhancing chances of hemorrhagic transformation. Operator may also choose to stent the stenotic area in order to reduce chances of re-occlusion. Safety of stenting of intracerebral vessels has been shown by recent trials.

We decided to resort to PTA because the patient was still in cardiac catheterization laboratory with arterial sheath in place. Her stroke was clearly embolic with no suspicion of any atherosclerotic disease. We expected a fast recanalization of the artery if performed early. However, relative inexperience, and complete occlusion of MCA with difficulty in wiring an occluded tortuous vessel with no distal collaterals were major challenges. We were rewarded with complete recovery of neurological deficit in an iatrogenic stroke.

**Conclusions:** Embolic stroke is common and can happen during interventional procedures. While thrombolytic therapy has been a standard therapy, there are several reports of successful treatment with PTA. Larger studies will be required to better define the method of choice but at present limited reports suggest that PTA is feasible, safe and effective means of revascularization in middle cerebral artery occlusion.

**References**

Transcatheter Guidewire Perforation of the Pulmonary Valve as a Palliative Procedure in Pulmonary Atresia with Intact Interventricular Septum

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Glenmark Cardiac Centre, Mumbai

We report two cases of pulmonary atresia with intact interventricular septum in whom we successfully perforated and performed balloon dilation of the atretic pulmonary valve using a simple guidewire technique. The technical challenges of performing this procedure in small infants are highlighted. (Indian Heart J 2004; 56: 661-663)

Key Words: Congenital heart disease, Pulmonary atresia, Balloon dilation

Pulmonary atresia (PA) with intact interventricular septum (IVS) is a complex congenital heart disease that has a wide morphological spectrum with variable prognosis. In those with a better prognosis, initial palliation is by right ventricular decompression. Over the last few years, transcatheter perforation of the pulmonary valve has been increasingly used in the favorable forms of PA with intact IVS having only a moderate right ventricular (RV) hypoplasia and a patent infundibulum. The procedure can be performed with the use of a simple guidewire, radio-frequency wire or laser. We report our experience with two children who underwent successful perforation using simple guidewire technique.

Case Reports

Case 1: A two-month-old boy weighing 3.4 kg presented with increasing cyanosis and shortness of breath. The oxygen saturation was 42%. Two-dimensional echocardiography and color Doppler examination revealed PA with intact IVS. The pulmonary circulation was duct-dependent and there was no right ventricle-dependent coronary circulation. The tricuspid valve (TV) annulus measured 6.5 mm and the pulmonary annulus measured 5.0 mm. There was only a moderate degree of RV hypoplasia. The patient underwent transcatheter perforation of the pulmonary valve under general anesthesia. Vascular access was via the right femoral vein and left femoral artery. Initial diagnostic angiography was performed in lateral view with a 5 F NIH catheter positioned in the right ventricle (Fig. 1A). After pinpointing the exact position of the atretic pulmonary valve, the angiographic catheter was exchanged for a 4 F, 3.5 curve right Judkin’s (JR 3.5) catheter which was positioned just below the pulmonary valve. The proximal hub of the catheter was connected to a Tohey-Borst adaptor to enable scout angiograms throughout the procedure. Through the JR catheter the hard end of a 0.018” coronary angioplasty guidewire was passed which tended to straighten the right coronary catheter. It therefore had to be given a gentle curve so that the JR catheter pointed posteriorly and a little superiorly. After confirming the catheter position, a jab was made with the wire pointing in such direction as to enter the lumen of the main pulmonary artery (MPA) (Fig. 1B). Repeat scout injections were performed to confirm whether the wire had perforated the pulmonary valve and entered the lumen of the MPA. Once this was confirmed, the hard end of the wire was removed and the floppy end maneuvered through this tiny hole and positioned in the distal right pulmonary artery. A 1.5 mm coronary angioplasty balloon (Maverick, Boston Scientific) was then passed over this wire and attempts made to cross the pulmonary valve. This was unsuccessful, hence the balloon was withdrawn and a right coronary angioplasty Judkin’s guide catheter was introduced. With the support of the guide catheter the balloon easily crossed the valve and an initial inflation-deflation cycle was performed till the balloon waist disappeared (Fig. 1C). Thereafter, sequential balloon...
dilations were performed with increasing sizes of coronary angioplasty balloon catheters up to 3.5 mm. Then, over the same wire, a 6 mm and then an 8 mm valvuloplasty balloon were used (Tyshak-II, Boston Scientific) till the waist disappeared completely (Fig. 1D). The hemodynamics before and after the procedure are summarized in Table 1. Repeat angiography revealed excellent antegrade flow in the MPA with a complete opening of the pulmonary valve (Fig. 1E). At 6 months follow-up, he was asymptomatic with a saturation of 92% and a transpulmonic gradient of 26 mmHg and grade 2/3 pulmonary regurgitation.

Subsequently patient improved but presented again at 3 months of age. Repeat two-dimensional echocardiography and color Doppler examination confirmed the presence of PA with intact IVS. In addition, there was a fistula formed by the attempted perforation of the valve, which resulted in a tract across the posterior aspect of the pulmonary valve through the IVS into the RV body. There was a gradient of 136 mmHg across the tract with pulmonary regurgitation. The patient was taken up for perforation of the pulmonary valve. This time initially itself the right Judkin’s guide catheter (6F) and angioplasty assembly were used. Great care was taken to avoid entering the pulmonary artery through the fistula. The procedure was performed identical to the one performed in the first case. Final pulmonary valve dilation was performed using an 8 mm balloon. The hemodynamic results are summarized in Table 1. Angiographic findings before and after the procedure are shown in Fig. 2 (A to D). At follow-up, echo-Doppler evaluation revealed a gradient of 15 mmHg across the pulmonary valve and the flow through the fistula had become insignificant.

### Table 1. Hemodynamics pre- and post-balloon dilation

<table>
<thead>
<tr>
<th></th>
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<th>Case 2</th>
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<tr>
<td>Saturation (pre)</td>
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<td>62%</td>
</tr>
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<td>Saturation (post)</td>
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RV: right ventricular; PV: pulmonary valve; LV left ventricular

### Case 2:
A 3-month-old baby weighing 4.0 kg was diagnosed as a case of PA with intact IVS at birth and underwent a left classical Blalock-Taussig (BT) shunt at day 7 of life. At the time of surgery, an attempt was made to perforate the pulmonary valve in a retrograde fashion. Subsequently patient improved but presented again at 3 months of age. Repeat two-dimensional echocardiography and color Doppler examination confirmed the presence of PA with intact IVS. In addition, there was a fistula formed by the attempted perforation of the valve, which resulted in a tract across the posterior aspect of the pulmonary valve through the IVS into the RV body. There was a gradient of 136 mmHg across the tract with pulmonary regurgitation. The patient was taken up for perforation of the pulmonary valve. This time initially itself the right Judkin’s guide catheter (6F) and angioplasty assembly were used. Great care was taken to avoid entering the pulmonary artery through the fistula. The procedure was performed identical to the one performed in the first case. Final pulmonary valve dilation was performed using an 8 mm balloon. The hemodynamic results are summarized in Table 1. Angiographic findings before and after the procedure are shown in Fig. 2 (A to D). At follow-up, echo-Doppler evaluation revealed a gradient of 15 mmHg across the pulmonary valve and the flow through the fistula had become insignificant.

![Fig. 1 A: Right ventricular angiography showing atretic pulmonary valve with no antegrade flow. Arrow points to atretic pulmonary valve. B: Arrow points to guidewire which has successfully perforated the atretic pulmonary valve to enter the main pulmonary artery. C: 1.5 mm coronary angioplasty balloon inflated across the pulmonary valve. D: Final dilation of the pulmonary valve using an 8 mm valvuloplasty balloon. E: Final right ventricular angiography in lateral view showing widely open pulmonary valve with good antegrade flow into the pulmonary arteries.](image1)

![Fig. 2 A: Balloon angiography of the right ventricle. Arrow points to fistulous connection between the right ventricular outflow and the main pulmonary artery. B: Right ventricular angiography in lateral view. Arrow points to the atretic pulmonary valve. C: Balloon inflated across the pulmonary valve. D: Final right ventricular angiography reveals a widely open pulmonary valve with excellent antegrade flow into the pulmonary artery. Arrow shows marked reduction of flow through the fistulous tract.](image2)


Discussion

Transcatheter perforation of pulmonary valve as a palliative procedure in PA with intact IVS was introduced for the first time by Qureshi et al. in 1991.\(^6\) It has subsequently been validated by numerous investigators.\(^2\)\(^3\)\(^4\) Choosing only those with favorable forms (as in our 2 cases) decreases procedure-related morbidity and mortality. Both our cases were more than 3 kg and had a patent infundibulum. A recent study\(^7\) found a success rate of 85% with a procedural mortality of 5% and morbidity of 12%. The patient population in this series consisted of almost all sick neonates in contrast to the relatively older age of our 2 patients.\(^7\) Procedural success was dependent on adequate visualization of the RV outflow tract and this was best profiled in the lateral view. Due to limitations imposed by the weight of the neonates and small infants, contrast quantity was of primary importance. We therefore used up to a maximum of 6-7 ml/kg of the contrast and diluted this further so as to allow a large number of contrast injections to be made. This helped in accurate evaluation of the pulmonary valve with respect to guide catheter and the perforating guidewire. Our preference for perforation was the hard end of a 0.018" coronary angioplasty guidewire rather than the regular wire. The smaller wire was used in the hope that if the RV outflow myocardium was perforated inadvertently, it would not result in a major pericardial effusion or tamponade. Reshaping the guidewire helped to a great extent in ensuring that the guide catheter pointed in the direction of the MPA. One of the operators should keep the guide catheter very steady before jabbing the hard end of the guidewire. Inadvertent movement of the catheter at this critical juncture can result in perforation of the RV outflow tract at wrong place. Once the perforation was successful, it is impossible to maneuver the hard end of the wire into the distal branch pulmonary artery or duct. Our strategy was to remove the wire at this juncture and then attempt to pass the floppy end of the same wire through the hole that has been made, and place it in the distal right or left pulmonary artery. Due to the extreme severity of the obstruction, the first balloon passed was a very low profile coronary angioplasty balloon (1.5 mm, Maverick, Boston Scientific). The poor support provided by the monorail system made it mandatory to take coronary angioplasty guide catheter support for the balloon to track across the pulmonary valve. The balloon size was gradually increased, finally ending with the regular balloon valvuloplasty catheters equal to 120% to 140% of the annulus size. In various series, up to 75% of neonates undergoing this procedure may still need a BT shunt or RV outflow patch because the impaired RV compliance prevents maintenance of adequate systemic saturations.\(^7\) In this situation, ductal stenting has also been performed as an alternative palliative procedure with satisfactory results.\(^8\) The favorable anatomy and the relatively older age in both our patients, and the prior BT shunt in Case 2, probably obviated the need for any additional surgery. Although radiofrequency perforation is the procedure of choice in most centers the world over, it is not available in the majority of centers in India. This report of two cases shows that guidewire perforation of the pulmonary valve using easily available accessories is a feasible option in infants with pulmonary atresia and intact IVS with favorable anatomy (normal-sized RV). This pre-selection may allow biventricular correction in the majority of such patients with a lower mortality and morbidity.

References

Left Ventricular Hydatid Cyst with Myocardial Infarction in a Patient with Severe Rheumatic Mitral Stenosis

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Brief Report

Cardiac echinococcosis is rare, and the most serious of all hydatid infestations. We report a case of 30-year-old female who had a hydatid cyst, myocardial infarction and severe rheumatic mitral stenosis. Following mitral valvotomy, the hydatid cyst and the left ventricular aneurysm were totally excised under cardiopulmonary bypass. The patient was discharged on the post-operative day 15 with the advice to continue albendazole for 5 years. (Indian Heart J 2004; 56: 664–667)

Key Words: Hydatid cyst, Echocardiography, Mitral stenosis

Echinococcosis is a tissue infestation perpetuated by the larvae of echinococcus granulosus, where man is the accidental host, sheep the intermediate host and dog the definitive host. Infestation occurs by intestinal and airborne routes. Larvae reach the myocardium through the coronary circulation and the distribution of the cyst in the heart varies according to the blood supply. The left ventricle (LV), having the most abundant supply, is most frequently involved (55%-60%). The other sites include the right ventricle (15%), the interventricular septum (IVS) (5-9%), left atrium (LA) (8%), pericardium (8%), pulmonary artery (7%) and the right atrium (RA) (3-4%). When the scolices reach the myocardium, they start cyst formation; the cysts enlarge and protrude toward epicardium or endocardium. Surgical resection is the only remedy. Cystectomy has a high rate of complete recovery. Irrigation of the cyst with scolicidal agents prior to excision is essential to avoid anaphylactic reactions. Supplemental therapy with broad spectrum antihelminthics is warranted to prevent recurrences.

Case Report

A 30-year-old female presented with shortness of breath of 2 years duration. She gave no history of handling dogs or of having reared sheep. Clinical examination revealed an accentuated first heart sound, a loud pulmonary component of second heart sound and rumbling mid diastolic murmur at the cardiac apex. With the clinical diagnosis of rheumatic mitral stenosis, the patient was further evaluated. Electrocardiogram (ECG) showed sinus rhythm with left atrial enlargement and non-progression of R waves in the anterior chest leads. We did not think of myocardial infarction (MI), as cardiac space occupying lesions also can produce ECG changes mimicking MI. Echocardiogram revealed severe mitral stenosis (orifice area 0.7 cm²), mild aortic regurgitation and a large cyst in the left ventricle (Figs 1a and 1b). The cyst measured 6 cm in diameter and was multiloculated. Serology by immunoelectrophoresis was positive for echinococcus. Computerized tomographic (CT) scan and magnetic resonance imaging (MRI) of the thorax revealed a well defined, non-enhancing, globular hypodense lesion (7.5 x 5 cm) with multiple septations and a volume of 170 - 180 ml (Figs 2a and 2b). The cyst appeared to be situated in the lower IVS on the LV side and was seen compromising the LV cavity. No pre-operative coronary angiogram was done as we did not suspect MI in this young lady who had no symptoms of coronary artery disease (CAD). Abdominal ultrasonogram did not reveal similar cysts in the liver or elsewhere. The patient was put on albendazole 15 mg/kg body weight in 2 divided doses for a period of 4 weeks before she was submitted for surgery.

Under cardiopulmonary bypass, the LA was opened and mitral valvotomy was performed. Two pieces of thrombi in the LA were removed. As the cyst was not visualized through the mitral orifice, left ventriculotomy was done and the cyst exposed (Fig. 3). Although the pre-operative CT scan and MRI showed the cyst to arise from the lower IVS at surgery, the origin of the cyst was from the apicoanterior wall of the LV. The lower 2/3rd of the IVS was found to be
thinned out and the LV apex was aneurysmal, probably due to MI. The left anterior descending coronary artery (LAD) was obliterated in its middle and distal third. The cyst was irrigated with 20% hypertonic saline and its wall was opened. Multiple cysts, 10 to 20 in number, were totally evacuated taking care to avoid spilling of its contents (Fig. 4). The cyst wall was completely excised and the LV was washed with hypertonic saline and iodine solutions. After the cyst was totally excised, the apical LV aneurysm was partially excised. A large defect surrounded by thinned and scarred tissue was left behind in the apicoanterior wall of the LV. This scarred tissue was used to strengthen the suturing with Teflon pledges while reconstructing the defect in the apicoanterior wall. The post-operative period was uneventful. Echocardiogram done on the post-operative day 10 revealed redundant myocardial edges where the cyst was excised. There was no evidence of remains of the cyst or its wall. The lower 2/3rd of the IVS and the LV anterior wall were hypokinetic, the LV apex was dyskinetic and there was moderate LV systolic dysfunction. The LV apex was still dyskinetic because the LV aneurysm
was only partially excised and a portion of the fibrous wall of the aneurysm was left behind to aid in the proper reconstruction of the defect in the apicoanterior wall. She was discharged on the post-operative day 15, with the advice to continue albendazole for 5 years. Two months later, on the first post-operative review, echocardiogram revealed improvement in the global LV systolic function. Selective coronary angiography was done. Although we initially interpreted it as normal, after further evaluation it was concluded that the LAD was abruptly cut off in its middle third (Figs 5 and 6). The other coronary arteries were normal.

**Discussion**

Cardiac echinococcosis, serious as it is, can sometimes be totally asymptomatic till the cyst has grown to large dimensions. The effects of cysts are usually due to pressure, arrhythmias, angina, valvular dysfunction, pericardial reaction, pulmonary or systemic embolism and anaphylactic reactions.\(^2\)\(^-\)\(^4\) In our patient, the symptoms were attributed to the mitral stenosis and the cyst was noted only during routine echocardiography. Cysts in the IVS and the apicoanterior wall, as with our case, have been reported,
but are relatively rare. Cysts once diagnosed have to be removed. The recent trend is for off-pump procedures for cysts which are purely intramyocardial and for those enlarging toward the epicardium.\(^3\) Cysts in the IVS and those protruding into the LV cavity have to be excised only under cardiopulmonary bypass as was done in our patient. At surgery, irrigation with scolicidal agents is mandatory to prevent anaphylaxis.\(^3\) We used 20% hypertonic saline which is the safest. Compression of the right and the left ventricular outflow tracts and conduction system producing conduction disturbances have been reported in literature but this is the first time a hydatid cyst associated with MI is being reported. The MI was probably due to compression and obliteration of the LAD by the cyst. Generally, compression of a vessel by a cyst results in angina rather than MI, but exceptions can occur. Further, the slowly occluding lumen of the vessel could have been totally occluded by an embolus from the clot in the left atrial appendage. The diagnosis of MI was entertained only at the time of surgery. The chance occurrence of rheumatic heart disease with the cardiac hydatid cyst has also not been reported in literature. We followed the recommended dose of albendazole. Cyst in the heart should alert one to look for cysts elsewhere and our patient did not have any extracardiac cyst.

**Conclusions:** Once thought to be a formidable disease, cardiac echinococcosis can now be effectively managed by excellent non-invasive diagnostic imaging procedures and equally effective surgical expertise and techniques. Cardiac hydatidosis, a disease of varied presentations is, exemplified in our case where a cardiac hydatid cyst was associated with MI and severe rheumatic mitral stenosis. To our knowledge, this combination is the first report in literature. Further medical treatment is mandatory not only pre-operatively but also post-operatively to prevent cyst recurrence.

**References**

Syncope in a Middle Aged Male due to Acute Rheumatic Fever

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Rheumatic fever is a multi system disease which occurs following infection with group A beta hemolytic streptococcus. It is commonest in the age group of 5-15 years but can occur in adults also. First degree atrioventricular block is a common manifestation of acute rheumatic fever and is included in the Jones criteria but Wenckebacks phenomena and complete heart block are relatively rare manifestations of rheumatic fever. Syncope occurring in acute rheumatic fever is also infrequently reported. We report the case of a 38-year-old male with rheumatic carditis who had advanced atrioventricular block which resulted in syncope and required a temporary pacemaker insertion. (Indian Heart J 2004; 56: 668-669)

Key Words: Rheumatic carditis, Syncope, Complete heart block

Case Report

A 38-year-old male, truck driver by profession, was admitted in our hospital with fever of 10 days duration. There was no previous history of any cardiorespiratory complaints or joint pains. There was no history of intake of any drugs. His examination revealed a blood pressure (BP) of 130/90 mmHg, pulse of 100 beats per min (bpm) and fever of 101°F. General physical examination did not reveal any erythema marginatum or subcutaneous nodules. Cardiovascular examination revealed a high pitched, blowing pansystolic murmur (Grade 3), best heard at the apex and radiating to the axilla. An S3 gallop rhythm could also be appreciated. The investigations revealed leukocytosis with erythrocytesedimentation rate (ESR) of 120 mm/hour. The anti-streptolysin-O (ASO) titre was 405 Todd units/ml and C-reactive protein (CRP) was positive by latex method. Routine biochemical investigations were normal. Three blood cultures taken at specific intervals were sterile. Viral markers and HIV status were negative. Chest X-ray showed mild cardiomegaly. The electrocardiogram (ECG) at time of admission showed first degree AV block with PR interval of 0.24 s (Fig. 1a). Two-dimensional echocardiography (2D echo) revealed moderate mitral regurgitation (MR) with trivial aortic regurgitation (AR) and left ventricular ejection fraction (EF) of 60%. There was no regional wall motion abnormality (RWMA). Transesophageal echocardiogram (TEE) confirmed the above findings and also confirmed the absence of vegetation on any of the valves. As patient had definite evidence of rheumatic carditis, he was started on injectable penicillin and hydrocortisone. Two days after admission, the patient complained of a sinking sensation. ECG done at this time showed presence of Wenckebacks phenomenon (Fig. 1b). Few hours later, the patient had a syncopal attack and ECG revealed a complete heart block (Fig. 1c). In view of a syncopal attack and presence of complete heart block, a temporary pacemaker was inserted.

The AV block lasted for about 5 days and then regressed in a stepwise fashion to first degree AV block. He improved, and was discharged on day 10 of hospital stay with an
Indian Heart J 2004; 56: 668–669

Mohindra et al. Syncope in Rheumatic Fever

advice to get prophylactic injection benzathine intra-
muscular penicillin every 3 weeks. His ECG done on
outpatient follow-up 10 days later was normal (Fig. 2).

Fig. 1. Electrocardiogram showing (a) Normal sinus rhythm with prolonged
PR interval of 0.24 s (b) Wenckebach phenomenon (c) Complete heart block.

Discussion

Incidence of acute rheumatic fever in older age group is
significantly lower as compared to younger age group. The
peak age of occurrence of rheumatic fever is 5-15 years6
but initial attacks of rheumatic fever occurring in 4th
decade have also been reported.7 Our patient fulfilled one
major and 3 minor Jones criteria and echocardiography
confirmed the evidence of valvular involvement. This
patient also had syncope which occurred secondary to
complete heart block. There was no history of intake of
drugs which could have slowed the AV conduction nor was
there any evidence of ischemic heart disease (IHD) as
revealed by absence of RWMA on 2D echo. Thus it was
safely assumed that this 38-year-old male had acute
rheumatic fever which caused a complete heart block
resulting in syncope.

Advanced AV conduction defects are uncommon in
acute rheumatic fever as shown by Zalzstein et al.4 They
studied 65 children with acute rheumatic fever and showed
the presence of advanced AV block in 6% cases.5 A similar
prevalence of advanced AV block was also shown by Veasy
et al.3 in their study of 232 patients with rheumatic fever.

Advanced AV block in acute rheumatic fever is usually
temporary as shown by Veasy et al.5 Our patient required a
temporary pacemaker but his advanced AV block reverted
to first degree AV block in about 5 days. The genesis of
advanced AV block in rheumatic fever is thought to be
secondary to inflammation of the conducting tissue but
an underlying disease of the conducting tissue has to be
ruled out in an older patient.

Thus, diagnosis of acute rheumatic fever should be
considered in any young adult or middle aged patient
presenting with fever and advanced AV block of
undetermined etiology and an aggressive management
plan should be sought as this can significantly reduce the
morbidity and mortality among the young patients.

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Several innovative approaches have been described to achieve endocardial pacing in patients with operated complex congenital heart diseases. We report herein a case of Ebstein’s anomaly who underwent a Hardy’s repair with a bidirectional Glenn shunt, tricuspid valve annuloplasty and atrial septal defect closure following which she developed complete heart block. The chest was reopened through the previous mid sternotomy and a screw-in lead implanted transatrially that resulted in optimal pacing thresholds. This technique offers a viable alternative for endocardial pacing in peri-operative patients requiring permanent pacing. (Indian Heart J 2004; 56: 670–672)

Key Words: Pacemaker, Glenn shunt, Congenital heart disease

A 33-year-old lady was diagnosed to be having Ebstein’s anomaly with class III exertional dyspnea. Chest X-ray showed a cardiothoracic ratio of 65% and significant right atrial enlargement. Pre-operative electrocardiogram (ECG) revealed normal sinus rhythm with right bundle branch block and right atrial (RA) enlargement. Echocardiogram showed situs solitus with atroventricular and ventriculoarterial concordance, a 22 mm displacement of the septal leaflet of the tricuspid valve (TV). There was severe low pressure tricuspid regurgitation. Right ventricular (RV) size was adequate with a mildly reduced RV function.

Cardiac catheterization and angiography were performed as per standard protocols through the right femoral route. Hemodynamic data of the patient is summarized in Table 1. RV angiogram revealed severe tricuspid regurgitation with a grossly enlarged RA. The pulmonary arteries were confluent and good sized. The patient underwent a Hardy’s repair with a bidirectional Glenn shunt, TV annuloplasty and atrial septal defect (ASD) closure. Post-operatively the patient was in complete heart block (CHB) that did not recover over a week. The underlying escape rhythm was slow and a decision was made to implant a screw-in transatrial lead that resulted in optimal pacing thresholds.

Table 1. Hemodynamic data

<table>
<thead>
<tr>
<th>Pressure Location</th>
<th>Pressure Range</th>
<th>Oximetry</th>
</tr>
</thead>
<tbody>
<tr>
<td>SVC</td>
<td>50.1</td>
<td></td>
</tr>
<tr>
<td>RA</td>
<td>a 40–46 μmHg</td>
<td>5.9</td>
</tr>
<tr>
<td>RV</td>
<td>18–20/8–9 mmHg</td>
<td>63.8</td>
</tr>
<tr>
<td>PA</td>
<td>18/10 mHg</td>
<td>59.6</td>
</tr>
<tr>
<td>PCW</td>
<td>a 10–12 μmHg</td>
<td>-</td>
</tr>
<tr>
<td>LV</td>
<td>100/8–10 mmHg</td>
<td>-</td>
</tr>
<tr>
<td>Ao</td>
<td>125/75–90 mmHg</td>
<td>96.4</td>
</tr>
</tbody>
</table>

PVRI : 4.1 U/m²

SVC: superior vena cava; RA: right atrium; RV: right ventricle; PA: pulmonary artery; PCW: pulmonary capillary wedge; LV: left ventricle; Ao: aorta; PVRI: pulmonary vascular resistance index; m: mean
taken for an early permanent pacemaker implantation instead of the usual waiting period of 2 weeks.

Several options—standard epicardial (steroid-eluting button electrode), transhepatic or transfemoral/transiliac approach were considered for implanting the permanent pacemaker. Transhepatic approach was considered unsafe in view of patient’s RV dysfunction and congestive heart failure. Transfemoral and transiliac procedures were not done because of lack of experience and the fear of lead damage because of repeated squatting that is a common posture amongst Indians. It was decided to go transatrially as this was an early post-operative period and the sternum could be easily reopened.

The sternum was opened and a direct needle puncture made into the low anterior right atrium and a 9 F peel away sheath inserted into the RA. A screw in lead (4068, Medtronic Inc.) was inserted into the right atrium under fluoroscopic guidance but could not be manipulated into the RV. The sheath was removed and this incision was closed. The same sheath was then inserted higher into the RA, at the SVC-RA junction avoiding the sinoatrial nodal area. Manipulation into the RV was easy from this site and the lead was placed in the right ventricular outflow tract (RVOT)/mid interventricular septum (Fig. 1). The lead was screwed in connected to a VVIR (Medtronic Sigma 203) pacemaker. The implant parameters were found satisfactory (amplitude threshold at 0.5 ms was 0.9 V, impedance 730 ohms and an R wave of 15.5 mV). As a back-up, a steroid-eluting button electrode (Medtronic, 4965) was also sutured over the RV anterior wall (implant parameters: amplitude threshold 2 V at 0.5 ms, impedance 540 ohms and R wave of 6.8 mV). The pacemaker was put in an abdominal subrectal pocket. Post-operative course was uneventful. Interrogation 3 months post-implant revealed an amplitude threshold <0.5 V at 0.4 ms pulse width and a pulse width threshold of <0.18 ms at 2.5 V. The pacemaker was programed to 3 V × 0.4 ms, 60-120 beats per minute (bpm). The epicardial wire could obviously not be interrogated at this stage.

**Discussion**

Permanent pacemaker implantation in neonates and infants and in patients with complex congenital heart diseases wherein access to the atrium has been lost from the SVC has traditionally been done epicardially. Earlier, epicardial systems were fraught with high thresholds at implantation and exit blocks along with early battery depletion and occasional deaths. The steroid-eluting button electrode seems to have obviated many of the problems and thresholds nearly as good as endocardial pacing have been reported. However, implant requires a limited sternotomy and low thresholds may be difficult to get on a scarred atrium or ventricle and the initial low impedance may be a source of significant current drain. Our own experience with the epicardial electrodes has been similar with a significant number of early failures/revisions with the screw-in/fish type electrode, but better early outcomes with the button electrode. The transfemoral/transiliac route was not favored in our patient, in view of her right ventricular dysfunction and elevated RA pressures that could have resulted in deep vein thrombosis with its antecedent complications. Temporary femoral venous pacing has been shown to have up to a 30% incidence of venous thrombosis.

Transhepatic pacing was another option but was not considered in this patient due to lack of previous experience with this procedure. Elevated RA pressures may theoretically pose a higher risk but this approach has been safely performed in patients with previous Fontan surgery, and therefore, is not contraindicated. We, therefore, decided to proceed with an approach that, though rarely used, seemed logical and better.

![Fig. 1. Chest X-ray, PA view showing a dilated heart with an enlarged right atrium. A pacemaker lead can be seen entering the right atrium directly (notice, there is no lead in SVC) and screwed into the high septal RV wall. A button electrode (arrow) is also seen that has been left in the subrectus pocket. SVC: superior vena cava; RV: right ventricular](image-url)
Technically, direct right atrial entry was straightforward. The risk of air embolism is likely to be the same as the subclavian/axillary approach. Puncture should probably be done high in the atrium, as it may be more difficult to manipulate from below in a big atrium. Furthermore, a high puncture makes one manipulate in the same way as in a routine endocardial placement that is familiar to most cardiologists. It may be preferable to use a long sheath (like a coronary sinus sheath) that reaches the RV apex/outflow and push the lead through it, as it is difficult to manipulate the lead in this situation. Long-term thresholds have been similar to any other endocardial lead.

To conclude, the suggested alternative route for endocardial pacing is specially suited for peri-operative patients requiring permanent pacing.

References
Systemic to pulmonary artery shunt is an established palliative treatment to increase pulmonary blood flow in cyanotic congenital heart diseases. The incidence of acute and subacute blockage of a modified Blalock-Taussig (BT) shunt is reported to be around 3%. The important causes of shunt blockage include thrombosis in a polycythemic child due to reduced intravascular volume, subsequent to fever and dehydration, or distortion of the pulmonary arteries leading to stenosis at the pulmonary artery end. Previously, surgical revision of the shunt was the only option available but in the last decade, transcatheter recanalization of the blocked shunt is developing as an important modality of management in such patients. We hereby report a case of successful transcatheter dilation and thrombolysis of a blocked right modified Blalock-Taussig shunt (RMBTS) due to thrombosis.

Case Report

A four-month-old male infant weighing 5.5 kg, was referred to our institute with history of cyanotic spells since 20 days of age. Cardiac examination revealed a single second heart sound and ejection systolic murmur in the left second intercostal space. The child had systemic oxygen saturation of 65-70% in room air. Transthoracic echocardiography (TTE) with color flow imaging revealed dextrocardia, corrected transposition of the great arteries, subaortic ventricular septal defect (VSD), pulmonary atresia with hypoplastic confluent pulmonary arteries measuring 4 mm each [Z score: right pulmonary artery (RPA) = -1.9 and left pulmonary artery (LPA) = -1.62] and restrictive patent ductus arteriosus (PDA). The infant underwent RMBTS using 4 mm polytetrafluoroethylene tube. The surgery was uneventful but the child required prolonged post-operative ventilatory support due to culture-positive respiratory infection, hyperreactive airways and diaphragmatic paresis and he was extubated after 3 weeks once the above mentioned factors were appropriately dealt with. TTE with color flow imaging immediately after extubation revealed a functioning RMBTS with an adequate shunt flow seen in the pulmonary arteries. Subsequently the child was clinically stable with oxygen (O2) saturation of 70% and was continued on aspirin 4 mg/kg/day, along with rest of the supportive management. After 4 days, the child had a sudden episode of desaturation (O2 saturation: 40% on 4 L/min O2), with tachypnea and mild alteration of sensorium. A TTE with color flow imaging revealed a non-functioning RMBTS. A transcatheter balloon angioplasty was planned, and the infant was taken for cardiac catheterization under general anesthesia. Right femoral vein (5 F) and artery (4 F) were cannulated. Heparin bolus was given at a dose of 50 units/kg body weight. Right subclavian artery angiography revealed a completely occluded RMBTS with a small proximal stump (Fig. 1). The RMBTS was probed with a 0.025" Terumo wire (Terumo Corporation, Tokyo, Japan) over which a Judkin’s right diagnostic catheter (JR 3.5) was advanced into the proximal stump of the shunt and then into the left pulmonary artery, and the wire was replaced with a straight 0.018"/300 cm exchange wire, which was advanced across
the shunt and its tip positioned in the distal LPA. A Symmetry balloon (4 mm × 20 mm) (Fig. 2) was positioned across the occluded shunt and inflated thrice along the blocked shunt with 1st inflation at 7 atm and 2nd and 3rd inflations distally at 3 atm.

A repeat angiography in BT shunt revealed good antegrade flow across the RMBTS, with evidence of a thrombus in the distal shunt extending into the RPA (Fig. 3). In view of the extensive thrombosis of the shunt, local thrombolysis was administered. Urokinase (4400 units/kg) was injected in the RMBTS locally, over 10 minutes; it was continued as a systemic infusion at 4400 units/kg/hour for the next 24 hours. Post-procedure, systemic oxygen saturation was 70%. A check angiography after 24 hours of thrombolysis (Fig. 4) revealed a patent RMBTS with a good flow into the RPA and a competitive flow into the LPA through the PDA, with mild narrowing of the proximal RPA. Heparin infusion at 10 units/kg/hour replaced urokinase after 24 hours and was continued for 72 hours, with APTT monitoring. The child was also simultaneously started on warfarin 0.1 mg/kg/day, which was continued, along with aspirin for 3 months. The infant was clinically stable with O₂ saturations >70% at room air and TTE with color flow imaging after 48 hours revealed functioning RMBTS.

On follow-up after 3 months, the child was asymptomatic with O₂ saturation of 75% at room air and had a significant weight gain. TTE with color flow imaging on follow-up revealed functioning RMBTS, and good-sized branch pulmonary arteries.

**Discussion**

Transcatheter recanalization of a compromised systemic to pulmonary artery shunt provides a feasible and effective way to restore or increase the pulmonary blood flow.
Fischer et al. reported the first successful balloon dilation of an obstructed BT shunt in 1985, in a case of complex cyanotic heart disease. In 1988, Marx et al. reported a series of 6 BT shunt dilations with suboptimal results, with clear success obtained in only 2 patients. The investigators suggested that the suboptimal results might be due to part to the strict limitations placed on maximum balloon diameter. In 1989, Qureshi et al. reported three successful balloon dilations of stenotic BT shunts. There are several other reports of dilation of BT shunts. Thrombolysis after BT shunt dilation was used by Marasini et al.

Transcatheter dilation and local thrombolysis was first reported by Robinson et al. in two cases with RMBTS, aged 5 months and 10 years respectively, with significant improvement in saturation and complete restoration of shunt patency. Ries et al. in 1994 reported thrombolysis with recombinant tissue plasminogen activator in a modified BT shunt in a 10-day-old infant, 4 days after surgery for complete shunt thrombosis. It resulted in complete clot dissolution and reperfusion without hemorrhagic complication. In this case, thrombolysis was considered safe even 4 days after surgery.

Balloon dilation along with local thrombolysis of a thrombosed occluded shunt results in mechanical thrombus disruption and an increase in the surface area of thrombus susceptible to pharmacological thrombolysis, thus increasing the efficacy of the thrombolytics administered as an infusion over the next 48-72 hours. There is always an issue as to how early the thrombolysis can be administered in case of occlusion of RMBTS immediately after surgery. According to the standard guidelines, thrombolytic agents can be administered safely after 10 days of any surgical procedure. The management of thrombosed systemic to pulmonary artery shunts, with balloon dilation and thrombolysis, holds considerable promise, as it avoids a repeat surgical procedure with its inherent morbidity and mortality. Complications associated with thrombolytic therapy for thrombosed BT shunts in early post-operative period include serious bleeding requiring transfusion and also possibility of excessive bleeding during reoperation if thrombolytic therapy fails.

In our patient, the distal anastomotic site of the RMBTS was stenosed which could have led to the alteration of the laminar blood flow in the shunt and subsequent thrombosis. Following administration of urokinase infusion for 24 hours, the thrombus was significantly reduced which was confirmed on check angiography done after 24 hours. As the flow observed in RMBTS subsequent to balloon angioplasty and thrombolysis was satisfactory, stent deployment was not considered in this case.

Stent implantation is an attractive alternative therapy for shunt stenosis or occlusion due to thrombosis, particularly in the immediate post-operative period, when fibrinolytic therapy may be hazardous. There are many reports of stent placement in blocked BT shunt for restoration of its patency. Zahn et al. reported in 1997, an emergency stent deployment for acute BT shunt obstruction after stage I Norwood surgery in a neonate at 8 days of life with immediate clinical improvement and shunt patency maintained on 5-month follow-up. Lee et al. reported a series of 13 patients who underwent stent implantation for restoration of aortopulmonary shunt patency. All patients had improved saturations subsequent to stent implantation.

Peuster et al. reported successful transcatheter recanalization and subsequent stent implantation in 2 infants with post-operative thrombosis of modified BT shunts. Both patients had shunt thromboses in the immediate post-operative period, with significant improvement in saturation and complete shunt patency which was maintained on 3 months follow-up. Bader et al. reported the use of balloon-expandable stents in stenosed BT shunts in 3 patients aged 23 to 32 years with mixed results. One patient had a procedural failure due to stent migration. A recent study by Sivakumar et al. reported stent implantation to restore the patency of acutely thrombosed modified BT shunt in 2 cases with residual stenosis following transcatheter balloon dilations. One patient developed acute stent thrombosis, which was managed successfully with local thrombolysis. At 6 and 12 months follow-up, both the stented patients maintained patent shunts with adequate oxygen saturation. Stent implantation helps avoid the complications associated with fibrinolytic therapy as well as reoperation with its associated morbidity and mortality. Balloon angioplasty and stent implantation reduce scar formation, and therefore, improve the outcome of the patient at subsequent corrective operative therapy. Angioplasty and stent deployment should be performed very carefully, with adequate sized balloons, since overexpansion may lead to rupture of the sutures.

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Is It Possible to Prevent Rheumatic Fever?

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Rheumatic fever (RF) and rheumatic heart disease (RHD) continue to be serious health hazards in most developing countries including India. RHD has always been considered to be a preventable disease. The purpose of the present review is to assess whether RF and RHD can be prevented. The three strategies for prevention consist of (i) primordial prevention, (ii) primary prevention, and (iii) secondary prevention.

Primordial Prevention
Primordial prevention requires, preventing the development of ‘risk factors’ in the community to prevent the disease in the population and thus protect individuals. Measures for primordial prevention in relation to RF and RHD consist of: (i) Improvement in socio-economic status, (ii) Prevention of overcrowding, (iii) Prevention of under-nutrition and malnutrition, (iv) Availability of prompt medical care, and (v) Public education regarding the risk of RF from sore throat specially below the age of 15 years. The last one, that is, public education is the most important component for primordial prevention. Unless parents know that a sore throat can cause RF and RHD, it is most unlikely to be seen by a physician and treated. It is necessary to point out that the recent resurgence of RF in United States of America (USA) occurred in well off families, without any overcrowding and with good quality medical facilities being readily available.1 As such, improvement in socio-economic status and preventing overcrowding cannot be relied upon to reduce the burden of RHD. Improvement in socio-economic status is also not under medical control and it is not possible to wait for it to happen.

Primary Prevention
Primary prevention of RF is theoretically feasible but practically almost impossible to achieve at the community level. However, it can be practised on an individual basis. Primary prevention requires identification of group-A beta hemolytic streptococcal (GABHS) sore throat and use of penicillin to eradicate the streptococci. Measures for primary prevention consist of: (i) Public awareness regarding danger of RF from sore throat, (ii) Identification of sore throat as being streptococcal, and (iii) Use of injectable penicillin to cure the streptococcal infection. It is important to know that oral penicillin may not be effective in preventing RF. RF occurred in 15% to 48% children given oral penicillin for 10 days in the recent epidemic in USA.2,4 It is, therefore, essential that injectable penicillin is used in order to prevent RF. The recommended dose of penicillin is 400,000 units of procaine penicillin twice daily for 10 days. Although recommended, one injection of 1.2 mega units of benzathine penicillin may not be enough to eradicate GABHS infection.5 The inability to utilize primary prevention at the community level is due to the large number of sore throats required to be treated to prevent RF. Community level management requires a sledge hammer approach, that is, treating each sore throat. Bacteriological facilities required to diagnose streptococcal sore throat at the community level for the whole country, at present, do not exist and are not likely in the near future. Hence, each sore throat will need to be treated. This is logistically not feasible for the whole country. Anywhere from 3% to 20% of sore throats can be streptococcal, the rest being viral infections which do not require treatment. About 0.3% of streptococcal sore throats result in RF. Recent data suggests that almost 90% of those who get RF develop RHD.6 Hence if 10,000 sore throats are treated by the sledge hammer approach, anywhere between 300 to 2000 streptococcal sore throats would be required to be treated (assuming that 3-20% of these are streptococcal). This would result in preventing RF in 1 to 6 children (0.3% streptococcal sore throats cause RF), and RHD in 5 or 6 children (Fig. 1). Thus community level primary prevention is not feasible although it may be possible for select individual patients.

Another problem with sledge hammer approach is the identification of sore throat and its treatment. The data related to resurgence of RF in USA indicates that up to 78% of streptococcal sore throats may be asymptomatic. The 10-day oral penicillin treatment was not followed even by well educated families and up to 48% of those given oral...
penicillin still developed RF.\textsuperscript{2,4} Unless a sore throat is symptomatic, it would not be treated and can result in RF.\textsuperscript{4} This makes primary prevention, based on the diagnosis of streptococcal sore throat and use of oral penicillin, inadequate to reduce the burden of RHD in the country.\textsuperscript{7}

As of today there are no markers which can be utilized to identify susceptibility to RF.\textsuperscript{7} Susceptibility to RF in the form of studies of HLA and the B-lymphocyte antigen, D8/17 have not given results which can be utilized to identify the susceptible people in the population to practice primary prevention.\textsuperscript{7}

However, primary prevention is feasible if an anti-streptococcal vaccine becomes available.

Secondary Prevention

Secondary prevention requires identification of those who have had RF or have RHD. Once identified, the patient needs injections of benzathine penicillin, given once in two to three weeks, depending on age, body size and muscle mass. Benzathine penicillin is painful, and may result in fever and very rarely (one in a million injections in children) in anaphylactic reactions. Most physicians are very reluctant to give benzathine penicillin injections. Penicillin prophylaxis is considered necessary because RF has a tendency of recurrence in those who have had RF in the past. Each new attack causes further damage to the valvular tissue making the disease worse than before.\textsuperscript{6} Secondary prevention can reduce the chance of recurrence but cannot prevent the initial damage. While it is ethically mandatory to prevent recurrences, secondary prevention cannot reduce the burden of RHD.

Anti-Streptococcal Vaccine

Availability of an anti-streptococcal vaccine which could prevent streptococcal infection is essential for primary prevention of RF. It is at present not available.

Several GABHS protein components and the polysaccharide have been considered for utilization in developing a vaccine.\textsuperscript{8} Most work has been done in relation with the M-protein, considered to be the virulence factor of the GABHS. M-protein has been found to be strain-specific, that is, each strain has its specific characteristics and will protect against only that particular strain. Since more than hundred different strains have been identified it becomes essential that the vaccine must be polyvalent, that is, it should incorporate all those strains which are present in the community. The problem associated with M-protein is that the GABHS has a strong tendency for mutation which can occur rapidly.\textsuperscript{9} A vaccine made from the locally dominant strains of GABHS may not be effective if the infection is due to a mutant organism. M-protein has a conserved C-region component which is common to most strains and variable A and B regions which differ from strain to strain. Attempts to use the preserved C-region component of M-protein have not succeeded as yet.

More recently GABHS has been found not to express M-protein.\textsuperscript{10} If fatal infection can occur from GABHS which does not have M-protein, it is difficult to accept that M-protein is the main virulence factor of GABHS. Vaccine based on M-protein is unlikely to succeed because: (i) M-protein cross-reacts with myocardium and may not be safe, (ii) M-protein is strain-specific, hence the anti-GABHS vaccine has to include all the strains in the community, (iii) since GABHS strains vary from place to place, in a large country like India, vaccine based on M-protein made in Delhi may not be effective in Chandigarh, Chennai or Mumbai, (iv) GABHS mutation alters the emm gene sequence of the M-protein. Mutation can occur in a few weeks, making the vaccine ineffective even in a very short time\textsuperscript{9} and, (v) virulent GABHS is now known not to express M-protein. Hence, M-protein cannot be the chief virulence factor of GABHS.\textsuperscript{10}

Other components of GABHS which are being tried for preparing a vaccine are GABHS C5a peptidase, a major surface virulence factor; fibronectin binding protein sfb1, and the chimeric peptide J8 from the conserved region of the M-protein.\textsuperscript{11}

Streptococcus pneumoniae (pneumococcus) is another variety of streptococcus species causing disease in humans. A vaccine against pneumococcal infection is already available and is being used though it is, as yet, not as...
effective as one would like it to be. The vaccine has been prepared using the polysaccharide conjugated with proteins to make it stable and have a longer duration of effectiveness. The GABHS polysaccharide has been shown to be immunologically active and reactive with cardiac valvular tissue. Since the polysaccharide component of GABHS is uniformly identical, it is surprising that it is not being utilized to prepare an anti-GABHS vaccine as has been done for the anti-pneumococcal vaccine.

We are fortunate in our country that the health of the child generally remains a priority and responsibility of the parents even when the child becomes an adult. Hence, prevention of RF and RHD is possible to a large extent if we can provide the message, in local languages, to the population (parents) that sore throats should not be neglected; that sore throats should be shown to a doctor for treatment to prevent RF and RHD. All India Radio and Doordarshan are the only means available for reaching each and every corner of the country and should be utilized for this purpose. If education can be made compulsory till the age of 15 years, school health care facilities can be utilized to control RF.

The answer to the question, “Is it possible to prevent rheumatic fever?” has to be “No” for primary prevention at the community level. Primary prevention will have to wait till a safe and effective GABHS vaccine becomes available.

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References

Iatrogenic Aortocoronary Arteriovenous Fistula

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Fig. 1. Angiogram showing left internal mammary artery (LIMA,↑↑) anastomosed to a cardiac vein, which is draining into the coronary sinus (CS,↓).

A 60-year-old male patient having undergone coronary artery bypass surgery (CABG) three months back in another hospital, presented to us for evaluation of his persistent symptoms of exertional angina (NYHA class II). As per the operative records, revascularization had been performed in all the three major coronary arteries with a left internal mammary artery (LIMA) bypass to the left anterior descending artery (LAD) and aortocoronary saphenous venous grafts to the right coronary artery (RCA) and the left circumflex artery (LCx). The patient was taken up for coronary angiography, which showed total occlusion of proximal LAD, 99% stenosis of LCx continuing as major obtuse marginal and 90% stenosis of mid RCA with LAD filling retrogradely from the right system. Angiogram of the graft vessels showed patent saphenous venous grafts to LCx and RCA, while angiogram of the LIMA showed that it was anastomosed distally to a cardiac vein instead of LAD, which in turn was draining via the coronary sinus into the right atrium (Fig. 1). A right heart pressure study along with a full oxygen saturation run was done. Though the pressures in the right heart chambers and the pulmonary artery were normal, there was significant step up in oxygen saturation in the coronary sinus (84%, normal being < 50%) and from right atrium (72%) to pulmonary artery (80%) with calculated Qp-Qs ratio of 1.5:1. In view of the patient’s persistent symptoms and a significant left-to-right shunt, closure of the fistula was decided. He was taken up for percutaneous revascularization of LAD to be followed by coil occlusion of the LIMA. However, we failed to cross the totally occluded LAD, hence the patient was referred for surgical correction.

Aortocoronary venous fistula caused by inadvertent grafting of a coronary vein is a rare complication of coronary artery bypass graft surgery (CABG). The occasional intramyocardial course and the overlying epicardial fat of target coronary arteries cause difficulty in identifying the target coronary arteries resulting in an inadvertent aortocoronary vein fistula. The natural history of inadvertent aorto-coronary arterial to coronary vein fistulas is unknown but bacterial endocarditis, fistula rupture, myocardial ischemia, and development of significant left-to-right shunts with possible congestive heart failure have been suggested as possible complications similar to that seen in congenital arteriovenous coronary fistulas. Potentiation of myocardial ischemia is a significant concern in this patient population, as arterialization of the coronary venous system without ligation of the vein proximally has not been shown to result in retrograde perfusion of the myocardium. Further, fistulas of this type also produce myocardial ischemia by the coronary steal phenomenon. While the traditional therapeutic approach has been surgical closure, a growing experience has been reported with transcatheter embolization of the fistula combined with revascularization of the originally intended target vessel.

References

Role of Cardiac Magnetic Resonance Imaging in Identification of Amyloid Cardiomyopathy

We congratulate the authors on their recent comprehensive article on cardiac amyloid. The role of echocardiography in making the diagnosis was discussed in some detail and it is likely to remain the principal imaging modality for most patients. In a few cases, however, a limited acoustic window with poor myocardial visualization necessitates further investigation. We suggest that there is a role for cross-sectional techniques such as cardiac computed tomography (CT) and magnetic resonance imaging (MRI) in this situation.

Frequently, the principal differential diagnosis other than amyloid in a patient with features of restrictive myocardial disease is that of hypertrophic cardiomyopathy. As the authors point out, the distinction can be difficult on echocardiography where diffuse myocardial hypertrophy is the rule in both conditions. Cardiac MRI can enable differentiation between these pathologies to be made on the basis of both morphological appearances and signal intensity characteristics.

The literature on this topic is sparse but several recent reports indicate that increase in right or left atrial wall thickness, or thickening of the interatrial septum in the setting of biventricular hypertrophy and depressed contractility is highly suggestive of cardiac amyloidosis. Experience at our centre confirms these findings. In the last few years we have seen several cases of biopsy-proven cardiac amyloid. In each case the diagnosis was suggested at MRI on the basis of diffuse left ventricular hypertrophy (LVH) in association with right atrial wall thickening and/or nodularity (Fig. 1). Similar findings may also be observed...
on CT of the thorax which can be a useful investigation where facilities for MRI are not available (Fig. 2). Finally, pyrophosphate scanning should also be considered as cardiac amyloid often demonstrates diffuse myocardial uptake with this technique (Fig. 3).4

We thus urge your readers to consider the contribution that all forms of non-invasive imaging may make, when pursuing this often-difficult clinical diagnosis.

References

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Transhepatic Balloon Dilation of the Interatrial Septum

Balloon atrial septostomy is a life-saving procedure in patients with d-transposition of great arteries who have inadequate mixing between the systemic and pulmonary circulations. When the septum is thick, a blade septostomy1 or static balloon dilation of the interatrial septum2 may be done. These procedures are commonly done through the femoral venous access. However, in case the femoral venous access is not available, transhepatic route may be considered.3,4 A nine-week-old (2.5 kg) infant was referred to the emergency department with cyanosis since birth with acute worsening of three days duration. Initial assessment in the emergency department revealed a deeply cyanotic infant in shock. Blood gas analysis showed arterial oxygen saturation of 26% and a pH of 7.24 with a bicarbonate of 15.5 meq/L. The patient was managed with bolus infusion of intravenous (IV) fluids, inotropes and antibiotics. Echocardiographic assessment showed d-transposition of great arteries, small ventricular septal defect, and restrictive atrial septal defect. The atrial septum was found to be thick, not amenable to balloon atrial septostomy. He was taken up for static balloon atrial dilation. It was impossible to obtain the venous access from the femoral route probably because of earlier bilateral saphenous venous cut down done in another center prior to referral to our institution. We did a percutaneous cannulation of the right hepatic vein to obtain access for the procedure. Under general anesthesia, percutaneous puncture of right hepatic vein was done using a 20 gauge needle introduced in the right subcostal margin at the midclavicular line, and the hepatic vein was cannulated using ultrasound guidance. A 0.025" hydrophilic guidewire (Terumo Corp, Tokyo, Japan) was introduced into the right hepatic vein to the inferior vena cava and right atrium (Fig. 1). The needle was exchanged for a 5 F sheath. The atrial septum was crossed using a Cournand catheter and a 0.018" exchange guidewire was placed in the left upper pulmonary vein through this. The atrial septum was dilated by a 12 mm × 3 cm Tyshak II balloon (NUMED Canada Inc.) tracked over the wire (Fig. 2). Echocardiography following the procedure showed a 5 mm bidirectionally shunting atrial septum defect. Oxygen saturation improved to 68% following the procedure. At the end of the procedure the sheath was removed from the

Fig. 1. Anteroposterior view showing the guidewire (white arrow) in the right atrium introduced transhepatically via the 20 gauge needle (black arrow).
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hepatic vein and gelfoam embolization of the liver parenchyma was done for hemostasis. Ultrasound examination of the abdomen done subsequently did not show any perihepatic blood collection or ascites. However, the patient succumbed to sepsis and multiorgan failure before definitive repair could be done.

Transhepatic access in children is being increasingly reported for various diagnostic and interventional procedures. The access is obtained by a 22 gauge Cheba needle or by using conventional 20 gauge needle. The failure rates for percutaneous hepatic vein cannulation reported by these series were 5.5% and 17%. Fatalities have been reported from intraperitoneal bleed, thus it is not a procedure of choice. To the best of our knowledge, balloon dilation of the atrial septum has not been previously reported using this access. In conclusion, balloon dilation of the atrial septum through transhepatic route is feasible in infants and should be appropriately utilized in the absence of other venous access.

Lipid Levels and Coronary Heart Disease: Need for Region-Specific Guidelines

The recent recommendations for the National Cholesterol Education Program Adult Treatment Panel (NCEP ATP) III guidelines by Grundy et al. do not differ significantly from the previous version of ATP III. Although evidence has been mounting on lowering low-density lipoprotein cholesterol (LDL-c) even in apparently normal individuals, the ATP III guidelines still stratify LDL-c goals based on presence of risk factors. It is now known that screening for conventional risk factors fails to identify more than 50% of the individuals who will present with acute coronary syndromes. In this context I presume that the LDL-c goals set by the ATP III may not be able to cover many patients who may be at risk of coronary heart disease. The normal range of LDL-c in a newborn is a median value of 100 mg/dl. There is no physiological reason why an adult should have an acceptable LDL-c of more than 100 mg/dl irrespective of the presence or absence of risk factors. A simple goal of keeping LDL-c levels below 100 mg/dl in all patients will enable more patients to reduce the risk of coronary artery disease.

In most diseases we tend to follow Western guidelines due to a lack of such guidelines in developing countries. South Asia has a vast talent of medical and epidemiological personnel and is well equipped to form guidelines and practice recommendations on its own. Moreover the dietary habits and lipid profile of south Asians differ from that of Western population. Guidelines can be implemented by forming a task force among all SAARC countries which will also augment better regional co-operation.

References


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Late Stent Thrombosis Following Antiplatelet Withdrawal While Fasting During Holy Months

Serious clinical implications of discontinuing antiplatelet therapy even many months after drug-eluting stent implantation have been reported. We report the case of a patient who presented with acute myocardial infarction and angiographic late thrombosis 135 days following bare metal stent implantation. The patient had discontinued all medications including dual antiplatelets one week prior to presentation while observing a religious fast.

A 53-year-old Hindu gentleman admitted to the hospital in June 2004 had a significant lesion in the left anterior descending artery. He underwent percutaneous intervention the same week with 2 bare metal stents (3 ×15 mm; Driver™, Medtronic Galway, Ireland, and 2.5 × 23 mm Prolink™, Vascular Concepts Ltd Crawley, UK; both deployed at 16 atm) being placed in the left anterior descending artery. He had no further symptoms. He stopped all medications in October 2004. One week later (135 days after stenting), he presented with anterior myocardial infarction. Angiography showed stent occlusion and extensive thrombus after guidewire passage. Percutaneous intervention restored vessel patency.

Discontinuation of medications (mainly antiplatelets) is particularly relevant in Asian countries with large Hindu and Muslim populations. People of both these faiths observe several weeks of religious fasting during the holy months of Navratras and Ramjan respectively. This patient had discontinued all medications for one week during the Navratras (nine nights of worship for the Mother Goddess Durga during the moonlit fortnight).

This report illustrates that discontinuation of antiplatelets is relevant to bare metal stents as well. This complication has been studied extensively with brachytherapy and stenting. It is clear that endothelialization is delayed by brachytherapy and possibly by drug-eluting stents; however it is still not clear when and whether endothelialization is absolutely complete with bare metal stents. Therefore, until such time we have definite data, we believe that all patients receiving either drug-eluting or bare metal stents should continue aspirin lifelong which should not be withheld for prolonged periods. It remains to be decided how long we continue dual antiplatelet therapy. In this context, there is also the possibility of a greater rebound increase in platelet activity on withdrawal of both antiplatelet drugs. Stenting should be avoided in patients who are likely to be non-compliant, scheduled for major surgery and those at high risk for late thrombosis. The absolute need for prolonged and uninterrupted aspirin therapy for stented patients should be emphasized to patients, physicians and health care workers across all religions and societies.

References

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Angina Pectoris Presenting as Headache

Angina pain has been known to radiate from the chest to the shoulders, extremities, neck, jaws and teeth. Anginal equivalents above the mandible and below the umbilicus are quite rare. We report a case of ischemic heart disease who presented with global headache without chest pain.
A 66-year-old woman, who was a known hypertensive and diabetic, came to our emergency department with complaint of severe episodic headache with uneasiness. Her pulse rate was 86 beats per min (bpm) and blood pressure was 130/90 mmHg. She was admitted in medical ward for observation where her electrocardiogram revealed 1-2 mm ST segment depression in anterior leads. She underwent coronary arteriography which revealed 75% stenosis in proximal left anterior descending artery (LAD). She underwent percutaneous transluminal coronary angioplasty (PTCA) with stenting to proximal LAD, following which she was completely asymptomic.

Headache is a rare symptom of myocardial ischemia. When present, it is often associated with typical angina. In our patient headache was the only symptom of myocardial ischemia. The association of cardiac headache with coronary artery disease (CAD) has been previously reported. Anatomic convergence of cardiac nerve fibers on central pathway receiving somatic afferent from the head is likely to be responsible for the perception of cardiac ischemic pain as headache. It would be worth following up similar cases to seek a possible explanation for headache associated with angina, or consider headache as an anginal equivalent.

References

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Prophylactic Use of an Implantable Cardioverter Defibrillator after Acute Myocardial Infarction


Summary

Recent trials have shown that prophylactic use of implantable cardioverter defibrillator (ICD) therapy in high risk patients of ischemic heart disease (IHD), reduced overall mortality specially in those with compromised myocardial contractility. These studies dramatically increased implantation of ICDs worldwide. This is an expensive form of therapy and raises the question of cost effectiveness specially if all patients with a prior MI and significant LV dysfunction are candidates for receiving such therapy. The Defibrillator IN Acute Myocardial Infarction Trial (DINAMIT) investigators conducted this randomized, open label trial in 674 patients who had suffered an MI 6-40 days prior to randomization (332 patients given ICD compared with 342 patients receiving optimal medical therapy). Patients were eligible for enrollment if following a recent MI, they had a reduced LVEF of $\leq 35\%$ and impaired cardiac autonomic function in the form of depressed heart rate variability (a standard deviation of normal-to-normal RR intervals of $\leq 70$ ms) or an increased average 24-hour heart rate $[\geq 80$ beats per min (bpm)] on Holter monitoring. Criteria for exclusion included congestive heart failure, revascularization or accepted indications for ICD such as sustained VT/VF >48 hours after MI. The primary outcome in this trial was death from any cause. Deaths due to cardiac arrhythmia were the secondary outcome. During the mean follow-up of 30±13 months, 120 patients died, 62 in the ICD group and 52 in the medical therapy group. Deaths due to cardiac arrhythmia were less in the ICD group compared with the controls ($n=29$). The annual rate of arrhythmic deaths was 1.5% in ICD group compared with 3.5% in controls. This statistically significant decrease in arrhythmic deaths in the ICD group was however countered by more deaths from non-arrhythmic causes: 6.1% per year ($n=50$) in ICD group versus 3.5% per year ($n=29$) in the medical therapy group. Of the 50 non-arrhythmic deaths in the ICD group the majority (78%) were cardiovascular in nature. Similarly 79% of deaths in the medical therapy group were also cardiovascular in nature.

Comments

DINAMIT investigators found that prophylactic ICD implantation, in a high risk subset of patients with recent MI, did not improve overall survival. However, the ICD group had a significant reduction in the number of arrhythmic deaths. In the secondary prophylaxis trials meta-analysis of the three trials – CID, AVID and CASH found that ICDs reduced the total mortality rate by 25% compared to amiodarone ($p<0.05$). Defining patient population at a sufficiently high risk for sudden cardiac death (SCD) and justifying a prophylactic ICD implantation, has been the focus of many trials. The MADIT-I and II and MUSTT all favored prophylactic ICD implantation in the high risk patients of IHD. However, this study has thrown up results in direct contrast to the previous studies. The authors have reasoned out the increase in non-arrhythmic deaths. There was no increase in the complication rate associated with the implantation procedure. However, the patients in the DINAMIT study were enrolled early (within 6-40 days) after MI. In comparison the MUSTT and MADIT trials recruited majority of patients >1 year after the index MI. In MADIT-II a retrospective analysis revealed that patients with remote MI (at least 18 months previously) benefited whereas those with a more recent MI did not benefit from ICD therapy. This is possibly so because with the ACE inhibitors and beta blockers, the adverse ventricular remodeling following MI is prevented or at least delayed. As the ventricular remodeling that contributes to electrophysiological disturbances is delayed, it appears reasonable to expect that the benefits of ICD in preventing SCD may also be delayed following MI. The other reason may be that the presence of autonomic dysfunction identifies patients who have progressive heart failure. So when the ICD treats the ventricular tachyarrhythmias, the progressive heart failure continues to notch up mortalities, thus diluting the ICD advantage. The decrease in SCD is being offset by an increase in the deaths due to heart failure. Do the ICD delivered shocks stun the ventricle into overt failure? In fact, whether cardiac resynchronization therapy would have improved the outcome is at present not known. In conclusion, this trial has proved that routine implantation of ICD in all patients with LV dysfunction following recent MI cannot be recommended.
Prevention of Lesion Recurrence in Chronic Total Coronary Occlusions by Paclitaxel Eluting Stents

Werner GS et al. J Am Coll Cardiol 2004; 44:2301-2306

Summary
This study was undertaken with the aim to assess the safety and efficacy of paclitaxel eluting stents in chronic total coronary occlusion (CTO). Polymer-based paclitaxel eluting stents (Taxus, Boston Scientific Corp., Massachusetts) were implanted in 48 consecutive patients with a CTO of > 2 weeks duration (median duration 6.3 months). These 48 patients given Taxus stents were compared with a similar number of patients who received bare metal stents (BMS). The two groups were matched evenly including history of diabetes, prior myocardial infarction (MI), lesion site, left ventricular (LV) function, size of stent and number of stents deployed. Exclusion criteria was LV aneurysm and TIMI flow grade <3 after stenting. All patients were followed up clinically for 12 months and angiography was performed at 6 months. The primary end point was the one-year incidence of major adverse cardiac events (MACE) that included MI, death and target lesion revascularization (TLR). Secondary end points were the rate of restenosis [minimal luminal diameter (MLD) <50% of reference diameter] and incidence of reocclusion. The angioplasty procedure was performed with the goal of < 20% residual stenosis within the stent. The strategy was to cover the occlusion as well as adjacent dissections with one or more overlapping stents. The mean number of stents were 1.7±0.9 with a mean length of 40±19 mm in Taxus group. The occlusion length was 17±13 mm whereas the total length of stent was more than double. This was matching in the BMS group. The one-year MACE was 12.5% in the Taxus group and 47.9% in the BMS group (p<0.001), which was driven by a reduced need for repeat percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) (3 v. 21 patients). On angiography at 6 months, there was 8.3% restenosis in the Taxus group versus 51.1% in the BMS group (p <0.001). Moreover the restenosis in the Taxus stents was focal and successfully treated with repeat PCI with an additional Taxus stent. The late re-occlusion was seen in 2.1% in Taxus and 23.4% in BMS group, a reduction of 91%.

Comments
Chronic total occlusions are encountered in about a third of the patients undergoing angiography. Percutaneous intervention of CTOs accounts for 10-15% of all angioplasties but the efficacy of BMS is limited with a significant rate of restenosis (30-50%) and reocclusion (8-12%). Drug eluting stents (DES) have been proven to be superior to BMS in the type A lesions. However, there is little data on the benefit of in the treatment of CTOs. The study included all patients irrespective of angiographic characteristics, lesion length, reference vessel diameter etc. Since long lesions and small vessels (<2.5 mm) were not excluded and one-third of the patients were diabetic; this study encompasses what we can call a “real world” type of experience. This explains the high rate of target vessel failure (TVF) in BMS group. Despite tackling lesions at highest risk for failure, the Taxus group showed a reduction in late loss by 84% as compared with BMS. The TVF in the Taxus group was unrelated to stent length whereas in the BMS group, TVF reflected on the length of stent used (38% in single stent and 71% with ≥2 stents). Similarly, diabetics had a TVF rate of 64.3% versus 35.3% in the non-diabetics in BMS group whereas in the Taxus group there was no significant influence of diabetes on TVF (6.3% v. 9.4%). The safety profile of Taxus stent was very satisfactory with no periprocedural MI or subacute stent thrombosis. At the follow-up angiography, no coronary artery aneurysms was seen, which has been an area of concern with DES. A recent study on sirolimus eluting stents (SES) in CTOs by Hoye et al. showed that the cumulative survival free of MACE was 96.4% in the SES versus 82.8% in the BMS group (p<0.05) at one year. Restenosis rate at 6 months was 9.1% and one case of re-occlusion was seen. The results match those of the present study. The present study has some limitations including small number of cases. This was not a double blind randomized trial but a comparison with matched controls. The positive results of this study makes it clear that DES are safe and efficacious in the treatment of CTOs. The use of DES in CTOs is associated with a reduction in MACE and restenosis rate compared with BMS.
Amiodarone or Implantable Cardioverter Defibrillator for Congestive Heart Failure


Summary

Patients with left ventricular (LV) dysfunction are at a high risk for sudden death. Implantable cardioverter defibrillators (ICDs) have improved survival in patients with coronary artery disease (CAD) and LV dysfunction as seen in recent trials. The present trial was conducted to test the efficacy of treatment with amiodarone versus ICD in high risk patients who have LV systolic dysfunction secondary to either ischemic (52%) or non-ischemic causes. The Sudden Cardiac Death in Heart Failure Trial (SCD HeFT) investigators randomized 2521 patients with LV ejection fraction (LVEF) of < 36%, in NYHA class II or III, to either of the three arms – placebo, amiodarone or ICD therapy. The placebo and amiodarone were administered in a double blind fashion. The ICD used was a single chamber ICD programmed to shock only mode (Medtronic). The primary end point was death from any cause. No dual chamber or biventricular devices were used and the ICD was programed to treat sustained ventricular tachyarrhythmias. The three groups were comparable at baseline as regards the clinical and demographic characteristics. The median LVEF was 25% with 30% of the patients studied being in NYHA class III and 70% in class II. The median follow-up was 45.5 months and all surviving patients were being followed for at least 2 years. Amiodarone was discontinued in 32% patients and placebo was discontinued in 22%. The adverse effects associated with amiodarone were chiefly hypothyroidism (6%) and tremor (4%). ICD implantation was unsuccessful in 1 patient and 5% of implantations were associated with complications, defined as clinical events requiring hospitalization, surgical correction, and unanticipated drug therapy. An additional 9% of patients had ICD-related complications later in the course of the trial; 11% of patients (188) in the drug group received an ICD subsequently. On follow-up, of the 829 patients in the ICD group, 259 (31%) had received a shock from the device with 68% of those shocked having received it for rapid ventricular tachycardia or fibrillation. The average annual rate of ICD shocks was 7.5%. There were 244 (29%) deaths in the placebo group, 240 (28%) in the amiodarone group and 182 (22%) in the ICD group. There was no difference in the risk of death in the placebo and amiodarone groups [hazard ratio (HR) p=0.53], whereas ICD therapy was associated with a decreased risk of death of 23% (HR: 0.77; p=0.007). The absolute decrease in mortality was 7.2% points after 5 years in the overall population. In the pre-specified subgroups, NYHA class III patients had no reduction in the risk of deaths with ICD therapy, while there was 46% reduction in NYHA class II patients.

Comments

This trial has convincingly shown that amiodarone therapy does not confer a mortality benefit in patients with LV systolic dysfunction and heart failure. ICD therapy significantly decreased the relative risk of death by 23% compared with the conservatively managed patients (placebo or amiodarone group). This reduction of death was irrespective of the cause of congestive heart failure (CHF). It is important to remember that the SCD HeFT investigators programed the ICDs conservatively with detection above 187 beats per minute (bpm) and ‘shock only’ therapy. In this trial, anti-tachycardia pacing was not programed and the back up bradycardia pacing was kept at the lowest value of 34 bpm. There has been a concern that anti-tachycardia pacing may do more harm than good because of the potential for acceleration of the tachycardia rate which may degenerate into a more dangerous rate or rhythm. Another concern has been that anti-bradycardia pacing tends to worsen CHF, therefore the lowest rate was kept so that pacing was done minimally. By the same reasoning, rate response pacing was also not allowed. In this study 68% of shocks were deemed appropriate. There was a high complication rate of 5% acutely and 9% on follow-up. Despite this, the benefit is pronounced. Another important point to emphasize is that all patients with LV dysfunction irrespective of etiology, benefited from ICD therapy; 30% of the patients were in NYHA class III and it is surprising that this trial did not show the same benefit of ICD therapy in this group as seen for NYHA class II patients. Whether in this more symptomatic patient subgroup, resynchronization therapy in those with broad QRS and mechanical dissynchrony be beneficial is for future trials to explore. There was no benefit with amiodarone therapy over placebo in NYHA class II patients and 44% decreased survival in NYHA class III patients. In conclusion, this trial has shown the benefit of ICD in reducing mortality in patients with mild to moderate CHF, irrespective of etiology. This trial has also shown amiodarone to be ineffective in improving survival, despite optimal conservative therapy.
Calendar of Conferences/CSI Executive Committee

February 18-20, 2005, International Summit on CAD and Cardiovascular Interventions, Mumbai
Contact: Dr Satyavan Sharma
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February 24-27, 2005, 2nd World Congress of Interventional Cardiology, Mumbai
Contact: Dr Lekha Adik Pathak
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April 1-4, 2005, 2nd International Conference on Interventional Cardiology, New Delhi
Contact: Dr M Khalilullah, Organizing Secretary
Suite 310, The Heart Centre
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