Severe Spasm of a Large Patent Ductus Arteriosus

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An eight-month-old boy weighing 5.7 kg was found to have large patent ductus arteriosus (PDA) and was taken up for transcatheter occlusion. A check angiogram by hand in the lateral view with a 4F Judkin’s right coronary catheter showed 5.2 mm, unrestrictive tubular ductus (Fig. 1A). With the same catheter, ductus was crossed to enter the pulmonary trunk. The pulmonary artery pressure was found to be two-third of the systemic pressure. This catheter was replaced with a 4F pigtail catheter and an aortogram was performed, which showed the PDA to be severely constricted in the middle with only minimal flow across it (Fig. 1B). At this juncture, the aortic pressure increased from 85/30 mmHg to 110/62 mmHg. A repeat angiogram performed via a 7 F Balkin’s contralateral sheath (Cook Inc) introduced from the venous side showed no ductal constriction suggesting complete “relief” of the spasm (Fig 1C). Coil occlusion of this duct was then performed. Three coils (two 0.038” thick, 8 mm in diameter and one 0.052” thick, 6 mm in diameter; Cook Inc) were simultaneously delivered via this sheath using a 5.2 F bioptome (Cook Inc). The coils were released 10 min later when a repeat angiogram showed minimal residual flow and stable coil position (Fig. 2A). A hand injection into the pulmonary arterial end of the duct showed persistence of the constriction in the middle (Fig. 2B). Echocardiography done 20 hours later showed no residual flow with laminar color Doppler flows in branch pulmonary arteries and descending aorta.

Successful coil closure of PDA depends on accurate assessment of the size and morphology of the ductus. Pulmonary artery end of the PDA has smooth muscles and can constrict in response to various pharmacological stimuli.1 Spontaneous intermittent closure of PDA has been documented hemodynamically earlier.2 Catheter-induced spasm is also well known, and results in underestimation of the size of the ductus. This leads to improper coil selection and inadvertent embolization of coils.3 In addition to errors related to calibration, one has to remember the possibility of ductal constriction when assessing the size of PDA angiographically. It is therefore necessary to accurately assess duct size and morphology through echocardiography as well. In our institution transcatheter PDA closure is guided by the largest recorded diameter by either technique rather than by angiography alone.

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References
Classification of Transmitral Doppler Patterns

There are several confusing terms, measures and indices to study transmitral left ventricular Doppler filling patterns (LV-DFPs). However, a systematic but simplified approach will make eye ball pattern recognition and analysis easy.

The use of the term LV-DFP assumes that the valves are normal. LV-DFPs are commonly used to study diastolic function. However, these patterns should be considered as a ‘tool’ which just happen to occur in diastole. Then we can extend the use of this ‘tool’ to study systolic function too.

When the systolic function is normal, LV-DFP can be used to study the chamber properties. Here, two patterns, are discernible, (i) Relaxation abnormality or ‘R pattern’, and (ii) Compliance abnormality or ‘C pattern’. Many indices are used for chamber properties. However, the commonly used index of E wave deceleration time has practical problems in estimation. A simpler and more accurate method would be determination of the early filling time (EFT). This is the duration of the E wave from the beginning of the E wave to the end. As a general rule, a prolonged EFT could point to relaxation abnormality (R pattern) while a shortened EFT could point to a compliance abnormality (C pattern). In some cases where the E and A waves merge, the EFT cannot be measured. Such patterns should be termed ‘indeterminate’.

LV-DFP concurrently provides hemodynamic information (Fig. 1). LV-DFP is dependent on left atrial pressure (LAP). Variations in LAP can be studied by the behavior of the E and A wave relative velocities. The five main patterns are termed –1, 0, 1, 2, 3. Using the current terminology, pattern 0 is ‘normal’, pattern 1 is ‘E/A reversal’, pattern 2 is the ‘pseudo-normal’, and pattern 3 is the ‘restrictive’. Pattern –1 is also E/A reversal but due to decreased pre-load, as seen in dehydration. We can describe any pattern with this numerical system. Increasing pre-load (LAP) shifts a pattern to the right and conversely, decreasing pre-load shifts a pattern to the left. A shift to the left could be possible with physiological maneuvers or drug challenge. When LAP is markedly elevated, the pattern is ‘irreversible’ and should be termed 3+.

In cases with impaired systolic function, LV-DFP can be used to assess the severity of hemodynamic impairment and prognosis. This is because LAP indicates LV end-diastolic pressure, which in turn reflects the systolic function. In impaired systolic function we would also include cases with wall motion abnormalities and apparently normal overall LV contractility. Pattern 1 indicates mild hemodynamic impairment, pattern 2 indicates moderate impairment and pattern 3 is severe hemodynamic impairment. In cases of systolic dysfunction, LV-DFP is a continuous variable reflecting the increasing LAP. The increasing LAP could be confirmed by the pulmonary venous flow abnormalities. As a corollary, in cases with resting or stress-induced wall motion abnormalities and apparently normal ejection fraction, a pattern to the right of 0 could indicate a systolic dysfunction. In serial studies, a shift to the right will indicate worsening systolic function while a shift to the left will indicate improvement.

Any pattern can be accurately described with this classification and terminology. The classification is based on currently available information. A deductive reasoning and logical extrapolation were used to arrive at the conclusion. Doppler patterns reflect the cardiac physiology at particular instant and display significant variability. There are some gray areas too. Having recognized these limitations, we can derive an algorithm to analyze LV-DFP.
When confronted with an abnormal LV-DFP, the following steps may be taken for proper analysis:

i. Is it technically proper.

ii. If yes, is it physiological or pathological.

iii. If physiological find the cause – age, rate, hydration.

iv. If pathological, what is the LV systolic function? If the LV systolic function is good then it has some diagnostic role; in that case, is it an R pattern (hypertension, ischemia, diabetes or hypertrophy) or a C pattern (restrictive cardiomyopathy or pericardial disease).

v. If the systolic function is not satisfactory, then one can assess the severity and prognosticate using the LV-DFP as mentioned above. Remember, LV-DFP can only be interpreted in the context of systolic function.

vi. In a complex situation, it is possible to identify the problem by recognizing the predominant hemodynamic pattern and factoring in the complicating chamber property.

vii. The accuracy of interpretation of LV-DFP is best in the young (<50 years) where age-related R pattern is eliminated. This algorithm uses pattern recognition with minimal measurements. The only measurement of EFT can also be done away with once the operator is used to the display sweep settings.

Detection of R pattern should make the clinician search for causes like hypertension, diabetes, ischemic heart disease and cardiomyopathy in the young (< 50 years of age). Similarly, detection of pattern 1 in a young individual could also indicate systolic dysfunction and should make the clinician search diligently for the wall motion abnormalities.

Although a gross simplification of a complex phenomenon, this systematic analysis could give useful diagnostic information and therapeutic options. The precise terms will improve communication and standardize research.

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Single Chamber versus Dual Chamber Pacing for High-grade Atrioventricular Block


Summary
The appropriate pacing mode in patients with high-grade atrioventricular (AV) block remains an unsettled issue. In the past, many non-randomized studies have suggested the superiority of dual chamber pacing over single chamber pacing, with a reported lower incidence of atrial fibrillation (AF), stroke and heart failure (HF). The United Kingdom Pacing and Cardiovascular Events (UKPACE) trial was a randomized multicenter, parallel-group trial conducted in 46 centers in the United Kingdom that compared the clinical benefits of single (ventricular) chamber and dual chamber pacing in 2021 elderly patients (≥70 years) who were undergoing their first pacemaker implant for a high grade AV block. The primary end point was death from all causes. Secondary end points included AF, HF and a composite of stroke, transient ischemic attack (TIA) or other episodes of thromboembolism. Patients were followed for a minimum of 3 years at regular intervals. Of the enrolled patients, 1009 randomly received single chamber pacing and 1012 received dual chamber pacing. Of those enrolled for single chamber pacing, 504 received fixed rate pacing and 505 were assigned to rate adaptive pacing. At the end of the study, 92% of patients assigned to dual chamber mode were receiving this mode of pacing and 3.1% of patients had crossed over from single chamber to dual chamber pacing because of intolerance of the pacing mode. The mean annual rate of death from all causes was 7.2% in the single chamber groups and 7.4% in the dual chamber groups (p=0.56). The annual rate of death due to cardiovascular causes was 3.9% in single chamber groups and 4.5% in the dual chamber groups (p=0.07). There was no significant difference in the mean annual event rate for HF and the combined outcome of stroke, TIA or thromboembolism. There was no significant difference in the incidence of AF in the two groups (p=0.74).

Comments
In this UKPACE trial, Toff and colleagues report no mortality benefit of dual chamber pacing over single chamber pacing in an elderly population with high degree AV block. Previously published trials have demonstrated the advantage of AV synchrony in improving stroke volume and reducing pulmonary capillary wedge pressure. It was expected that the hemodynamic benefit of dual chamber pacing would translate into a reduction in cardiac mortality, a reduced risk of HF and a better quality of life. In the PAcemaker selection in the Elderly (PASE) study, more than 400 patients aged ≥65 years were randomly assigned to receive single chamber ventricular or dual chamber pacing. After one and half years of follow-up there was no survival benefit in the dual chamber pacing group. Similarly in the Canadian Trial Of Physiologic Pacing (CTOPP), no significant difference in the rate of death was seen in the 2568 patients who randomly received either of the two pacing modes. However, there was 20% reduction in relative risk of AF with dual chamber pacing. In the UKPACE study there was no difference in the incidence of AF. Thus the difference in the two studies may be because of the longer follow-up and perhaps a younger population in the CTOPP study.

An important aspect of dual chamber pacing that the UKPACE trial has not demonstrated is the quality of life improvement with dual chamber pacing. In a previously published randomized crossover trial by Sulke and colleagues, the effects of different pacing modes were compared and it emerged that a majority (86%) of those studied opted for dual chamber pacing as the preferred mode. The authors have endeavored to explain why counter intuitively, dual chamber mode has not proved to be clinically beneficial over the single chamber pacing mode. They suggest that the interventricular dissynchrony resulting from right ventricular (RV) apical pacing may counter the benefit that might have emerged from AV synchrony. It is well accepted that there is deterioration in left ventricular (LV) function over long-term due to AV apical pacing. To conclude, this trial has demonstrated that in elderly patients with a high grade AV block, the pacing mode does not influence long-term mortality or the incidence of adverse cardiovascular events. The single chamber pacing mode is not objectively worse off when compared to the physiological dual chamber pacing. However, further trials with different algorithm and different pacing sites are currently underway to enable us to answer the question of the ‘best’ pacing mode.
Sirolimus-Eluting Stents versus Paclitaxel-Eluting Stents in Patients with Coronary Artery Disease

Kastrati et al., JAMA 2005; 294: 819-825

Summary
In numerous studies, drug-eluting stents (DESs) have been shown to be superior to bare metal stents in preventing restenosis. At present only two DESs, namely the sirolimus-eluting stents (SES) and the paclitaxel-eluting stents (PES) have been approved by the US Food and Drug Administration (FDA). There is comparatively little data on the relative efficacy of these two types of DESs. Recently few randomized studies comparing the DES and PES have been presented. This meta-analysis by Kastrati and colleagues evaluated the data from these recent randomized trials and tried to answer whether one type of stent is better and safer than the other. The primary outcome of interest was target lesion revascularization (TLR). Other clinical outcomes evaluated were stent thrombosis, myocardial infarction (MI), death and the composite of death and MI. Restenosis, defined as at least 50% diameter stenosis at follow-up, was measured by quantitative angiography. The clinical and/or angiographic follow-up in the selected trials was for at least 6 months. The data from 6 randomized trials that compared the efficacy and safety of SES with PES in patients of coronary artery disease (CAD) with symptoms or objective evidence of ischemia was studied. Angiographic restenosis was the primary end point in three trials (CORPAL, ISAR-DESIRE and REALITY) while combined incidence of death, MI and TLR was the primary end point in SIRTAX and TAXI trials. In the ISAR-DIABETES trial, angiographic late lumen loss on follow-up was compared. A total of 3669 patients were included in this meta-analysis. Baseline demographic and angiographic characteristics were similar in the two groups. On follow-up, TLR was performed in 95 out of 1845 (5.1%) patients assigned to the SES group and in 142 of 1824 (7.8%) patients in whom PES were deployed [odds ratio (OR): 0.64, 95% confidence interval (CI): 0.49-0.84; p=0.001]. The incidence of angiographic restenosis was 9.3% (151/1616 lesions) in the SES group versus 13.1% (211/1613) in the PES group (OR: 0.68; 95% CI: 0.55-0.86, p=0.001). Stent thrombosis rates were similar in the two groups (1.1% in SES and 0.9% in the SES group, p=0.62). There were 25 (1.4%) deaths in SES group and 29 (1.6%) deaths in PES group. The composite end point of death and MI was also similar in the two groups (p=0.23).

Comments
This meta-analysis involving 3669 patients has demonstrated that there is no significant difference between SES and the PES with respect to MI, death or their composite end point. However there is a 36% reduction in the odds of TLR in patients receiving SES compared to PES group. Although both drugs act by inhibiting new intimal hyperplasia, there are differences in the mechanism of action of paclitaxel and sirolimus. There are also differences in the drug delivery system in the two stent types. Sirolimus is an immunosuppressive anti-inflammatory, cytostatic agent that produces cell cycle arrest in the G1/S phase. Paclitaxel is essentially an anti-cancer drug that is cytotoxic and produces cell arrest in the G2/M phase. There is also difference in the drug delivery system including coating material used. In the sirolimus stent, the polymer used allows all the drug to be locally released within 30 days whereas the polymer used for the paclitaxel-coated stent allows only 10% release in 2 months with the rest of the drug remaining in the coating of the stent indefinitely. Moreover, the SES has a closed cell design as opposed to the open cell design of the PES, which may provide a more uniform drug distribution. The authors attribute the observed differences in this meta-analysis to these inherent differences. There was a reduction in late lumen loss with SES which was responsible for the lower restenosis rate observed in SES group compared to PES group. However, this lower restenosis rate did not translate into a clinical benefit as far the rate of death, MI or their composite end point was concerned. It is probable that a longer follow-up period would further clarify the lack of difference between the two stent types.

There was no difference in incidence of stent thrombosis in patients who received either of two drug-eluting stents. Therefore, safety profile of the two stents is comparable. In the context of a developing country like ours the cost of the individual stent also needs to be considered. If there is no significant difference in the safety and clinical efficacy of the two stents, then the cost factor should also be taken into account when decision regarding the type of stent to be used is taken. However, it seems that the rate of restenosis is lower with the SES resulting in lower rate of target vessel revascularization as compared to PES.
Sudden Death in Patients with Myocardial Infarction and Left Ventricular Dysfunction, Heart Failure or Both


Summary
The VALIANT (Valsartan in acute myocardial infarction trial) study was a randomized trial of treatment with valsartan, captopril or both in 14703 patients with acute myocardial infarction (AMI) complicated by left ventricular (LV) dysfunction with ejection fraction (EF) of ≤40%, heart failure (HF) or both. In the present sub-study, Solomon and colleagues have tried to analyze the factors that influence the risk of sudden death following myocardial infarction (MI). The median duration of follow-up was 24.7 months. Deaths due to cardiovascular or non-cardiovascular causes, sudden death and resuscitated cardiac arrest were noted. The incidence and timing of sudden death and their relation to the three subgroups of patients with EF < 30%, between 30% and 40% and > 40% was analyzed. Of the 14,609 patients enrolled, 1067 (7%) had an event. There was sudden death in 903 patients and 164 were resuscitated after cardiac arrest. Nineteen percent of all patients had an event in the first month after MI (126 deaths and 72 resuscitated cardiac arrest), an event rate of 1.4% [95% confidence interval (CI): 1.2-1.6%]. After the first 30 days, the rate of death or cardiac arrest with resuscitation decreased significantly, declining to 0.14% per month (95% CI: 0.11-0.18) after 2 years. The patients with EF < 30% were at the highest risk with an event rate of 2.3% per month (95% CI: 1.8-2.8). Ten percent of all patients with EF < 30% died suddenly or had cardiac arrest, 21% (85/399) had the event in the first month. In comparison, 21 of the 119 patients with EF >40% (18%) had the event in the first month. When the LV EF fraction was considered as a continuous variable, each decrease of 5% in the EF was associated with a 21% increase in the risk of death or resuscitated cardiac arrest, in the first 30 days after MI.

Comments
This study has shown that the risk of death or resuscitated cardiac arrest is the greatest in the first 30 days following AMI. It has also shown that the risk is greatest for those with more severe LV dysfunction (EF <30%). However, in the first 30 days, even patients with a relatively preserved LV function are at a high risk. This discriminatory effect of LV function loses its value after 6 months and at the end of the first year, the rate of sudden death was almost similar in the three subgroups, though the relative risk remains higher in those with lowest EF.

Among patients who died, there were no demonstrable characteristics to separate those who died suddenly and those who had a non-sudden (likely non-arrhythmic) death. It is important to separate patients with compromised LV function who are at a higher risk for arrhythmic sudden death because identifying such a subgroup would make therapy with implantable cardioverter-defibrillators (ICD) more cost effective. At present no such test, apart from electrophysiologic study, is available to the clinician. The high risk that the patient experiences in the early post-MI setting makes the case for considering a prolonged hospitalization or early ICD implantation. Based on previous studies (MUSTT and MADIT-II) the current guidelines do not recommend implantation of an ICD in the first month after the MI. The result of the recent DINAMIT study that included patients in the early post-MI setting, did not show any benefit of treating patients with LV dysfunction with an ICD. This is contrary to this VALIANT sub-study results that have shown enhanced risk of dying suddenly in the first 30 days. The authors have tried to explain this discrepancy by pointing out that the average time to recruit in DINAMIT was 18 days which was 13 days later than the average enrolment time in VALIANT. So it is possible that the selected patients were already at a lower risk. Also the DINAMIT was probably underpowered to detect a clinically important difference between the two groups. In addition, the VALIANT study data clearly shows that even in patients with EF > 40% there is a high risk of sudden death in the first month after MI, suggesting that even these patients require at least a short-term prevention strategy.

To summarize, the VALIANT substudy by Solomon and colleagues has analyzed the natural history of patients following MI and has clearly demonstrated that the risk of sudden death is the highest in the first month following MI in patients with LV dysfunction, heart failure or both. It therefore makes a case for evolving a cost effective strategy to prevent sudden death in selected patients earlier than at presently recommended.
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Glycoprotein IIb/IIIa Receptor Antagonists: Are we Ignoring the Evidence

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The armamentarium of cardiologists has strengthened tremendously in recent years with the introduction of glycoprotein (Gp) IIb/IIIa receptor antagonists. Large-scale trials have established their broader applicability, heightened clinical benefits and acceptable safety profile in various sub-groups of coronary artery disease (CAD). Three intravenous Gp IIb/IIIa receptor antagonists are available for clinical use: abciximab (human-murine chimeric monoclonal Fab antibody), eptifibatide (cyclic heptapeptide), and tirofiban (tyrosine derivative non-peptide mimetic inhibitor). This editorial will highlight the recent advances in the use of Gp IIb/IIIa receptor antagonists in elective percutaneous coronary intervention (PCI), unstable angina (UA) or non-ST segment elevation myocardial infarction (NSTEMI), and ST segment elevation myocardial infarction (STEMI).

Role in Elective Percutaneous Coronary Intervention

The role of Gp IIb/IIIa receptor antagonist, abciximab during PCI was first addressed in three large-scale randomized trials - Evaluation of 7E3 for the Prevention of Ischemic Complications (EPIC), Evaluation in PTCA to Improve Long-term Outcome with abciximab Gp IIb/IIIa blockade (EPILOG), and Evaluation of Platelet IIb/IIIa Inhibitor for STENTing (EPISTENT) enrolling more than 7000 patients.1-3 The results of these trials provided a concrete evidence of profound efficacy of abciximab in reducing the composite end points of death, myocardial infarction (MI), or urgent repeat revascularization associated with PCI at 30 days. These benefits appear to extend to all patients treated, regardless of their underlying demographic or clinical characteristics. The pooled analysis of these trials revealed that the percentage risk reduction in the primary composite end points at 30 days was 57%, 58%, and 44% in low, moderate, and high-risk patients, respectively.4 In addition, the use of abciximab was associated with long-term survival benefit. There was 22% relative (1.3% absolute) reduction in mortality with abciximab therapy at 3 years of follow-up. The benefit appeared to increase over time and was maximal in high-risk category patients as predicted by the clinical risk score.4

Although the treatment effect was present in both high- and low-risk angiographic subgroups, patients with complex coronary lesions (long lesion, calcified arteries, presence of thrombus, ostial and bifurcation lesions etc.) derived more benefit. Abciximab reduced the one-year composite end points of death or MI by 50% in the complex lesion group (absolute reduction of 7.3%, p<0.001) and by 35% in the simple lesion group (absolute reduction 3.5%, p<0.001).5

In comparison to abciximab, these benefits were less marked with the use of small-molecule Gp IIb/IIIa receptor antagonists as revealed in the Integrilin to Minimise Platelet Aggregation and Coronary Thrombosis-II (IMPACT-II) and Randomized Efficacy Study of Tirofiban for Outcomes and REstenosis (RESTORE) trials using eptifibatide and tirofiban, respectively.6,7 This could partly be explained by the lower doses used in these trials resulting in insufficient blockade of Gp IIb/IIIa receptors. Subsequently, modification of doses led to substantially better treatment effects with eptifibatide and tirofiban in the Enhanced Suppression of the Platelet IIb/IIIa Receptor with Integrilin Therapy (ESPRIT) and The Additive Value of Tirofiban Administered with the High Dose Bolus in the Prevention of Ischemic Complications During High-Risk Coronary Artery Angioplasty (ADVANCE) trials, respectively.8,9

Despite limitations of inter-trial analysis of these agents with respect to patient selection and heterogeneity of data, abciximab therapy appears to have superior clinical efficacy. At 30 days, the reduction in composite end point was 50-60% with abciximab whereas only modest risk reduction of 15%-35% was seen with the use of eptifibatide and tirofiban. In addition, as compared to abciximab, significant reduction in the long-term mortality by the small molecule Gp IIb/IIIa receptor antagonists has not been demonstrated. Only a non-significant trend toward mortality reduction at one year was seen in the ESPRIT trial.10 These differential benefits may relate to variability in the pharmacodynamics...
of receptor binding of these agents, and non-specific blockade of vitronectin and leukocyte Mac-1 receptors in addition to Gp IIb/IIIa receptors provided with abciximab.11,13

Use of thienopyridines: Dual antiplatelet therapy with aspirin and thienopyridines has improved the efficacy and the safety of coronary artery stenting. It has been shown that the inhibition of platelet aggregation by thienopyridines is dependent not only on their concentration but also on the duration of treatment.14 The protocol specified use of thienopyridines in various trials that varied in accordance with evolution of antiplatelet regimens for coronary stenting. Therefore, the role of Gp IIb/IIIa receptor antagonists in patients who are adequately pre-treated with dual antiplatelet therapy needs to be re-addressed. Recently published data from the Intracoronary Stenting and Antithrombotic Regimen—Rapid Early Action for Coronary Treatment (ISAR-REACT) trial highlights this issue. This trial enrolled more than 2000 patients with stable CAD to receive either abciximab or placebo during low- to intermediate-risk PCI. All patients were pre-treated with a 600 mg dose of clopidogrel at least two hours before the procedure. Administration of abciximab failed to provide any additional clinical benefit at 30 days with respect to the composite of death, MI, and urgent target vessel revascularization (TVR).15 Even at a follow-up of one year, no trend toward clinical benefit was observed with abciximab.16 Interestingly, the event rate in the placebo arm of this trial was lower than in low-risk subgroups of similar controlled trials of Gp IIb/IIIa antagonists, thereby indirectly suggesting a favorable effect with pre-treatment regimen of clopidogrel. Thus, at present, as per the data available from the ISAR-REACT trial, elective low- to intermediate-risk PCI can be managed with adequate pre-treatment with aspirin and clopidogrel. Whether this benefit of pre-loading with high dose of clopidogrel can be translated to a high-risk population of acute coronary syndrome (ACS) or acute MI is being addressed in ISAR-REACT-2 and Bavarian Reperfusion Alternatives Evaluation (BRAVE)-3 trials, respectively.

Elective percutaneous coronary intervention in diabetic patients: Given the greater prevalence and complexities of atherosclerosis among diabetics, these patients who constitute a significant proportion in various trials need to be evaluated separately. It has been shown that the results of PCI in diabetic patients are poorer as compared to non-diabetics.17 This is perhaps due to enhanced platelet activation, adhesiveness, and aggregability and greater expression of platelet Gp IIb/IIIa receptors in diabetic patients.18-19 In the pooled analysis of EPIC, EPILOG, and EPISTENT trials, abciximab decreased the mortality of diabetic patients to the level of placebo-treated non-diabetic patients (diabetics: 4.5%-2.5%, non-diabetics: 2.6%-1.9%) at one year. These benefits were more pronounced if diabetes was associated with hypertension or obesity, or with multi-vessel intervention.20 However, no such differential benefit was seen in low-risk diabetic patients using eptifibatide in ESPRIT trial.21 This is further supported by the results of the recently published ISAR-SWEET (Is Abciximab a Superior Way to Eliminate Elevated Thrombotic risk in diabetics) trial which evaluated the role of abciximab in diabetic patients undergoing elective coronary stenting after pre-treatment with a 600 mg loading dose of clopidogrel. Patients with MI and ACS were excluded in this trial. There was no reduction in the cumulative risk of death or MI during the year after the intervention with the use of abciximab.22 These results may partly be due to the effective pharmacological pre-treatment with dual antiplatelet therapy. Thus, the contention whether all diabetics undergoing elective PCI should receive Gp IIb/IIIa receptor antagonists in the present era when dual antiplatelet pre-treatment is a norm, is not yet proved and will require inputs from future studies.

Role in Unstable Angina or Non-ST Segment Elevation Myocardial Infarction

While the benefits of Gp IIb/IIIa receptor antagonists are evident across all groups, patients with ACS derive enhanced benefits. Several trials have defined the role of Gp IIb/IIIa receptor antagonists in patients with ACS managed either with routine early invasive strategy or with initial conservative strategy.

Early invasive strategy: Gp IIb/IIIa receptor antagonists have been shown to be beneficial in patients with ACS undergoing PCI. Use of these agents has been associated with a reduction in death or MI by approximately 50% across various studies.23 The use of abciximab in patients undergoing PCI for more severe and refractory UA was evaluated in 1997 in the Chimeric 7E3 AntiPlatelet Therapy in Unstable angina R Efactory to standard treatment (CAPTURE) trial. The 30-day composite end point of death, MI, or urgent intervention for ischemia was significantly reduced in favor of abciximab therapy (15.9% placebo, 11.3% abciximab, p=0.012).24 Whether the small molecule tirofiban also provides the same benefits was studied in the Do Tirofiban and ReoPro Give Similar Efficacy Trial (TARGET) which directly compared tirofiban with
abciximab in patients undergoing PCI. Approximately 60% patients in both the groups were having ACS. The findings demonstrated that abciximab was superior to tirofiban in reducing composite end points of death, MI, or urgent TVR at 30 days in the sub-group of patients with ACS (6.3% v. 9.3%, p=0.002). The differential benefits between these two agents may be related to the dose of tirofiban used in this trial that could have resulted in insufficient Gp IIb/IIIa receptor blockade as compared to abciximab. Either dose modification (high bolus dose) or starting tirofiban before PCI (as compared to use in the catheterization laboratory) might prove to be more beneficial. Two recent studies [Treat Angina with Aggrastat and Determine Cost of Therapy with an Invasive or Conservative Strategy (TACTICS - TIMI 18) and ISAR-COOL] have provided indirect evidence for its efficacy as upstream therapy followed by continued use during PCI. Both these studies analyzed the benefit of an invasive strategy along with aggressive antiplatelet therapy including upstream tirofiban in patients with ACS. The role of Gp IIb/IIIa receptor antagonists in such a strategy becomes more evident by comparing these data with earlier randomized trials addressing invasive strategy without the use of Gp IIb/IIIa receptor antagonists.

In the earlier trials such as FRagmin and fast revascularization during InStability in Coronary artery disease (FRISC)-II, the rate of cardiac events especially MI tended to be higher during the first several weeks following routine early PCI. In contrast, there was a significantly lower rate of MI during this period with the additional use of tirofiban, an effect attributable to the well-documented protection afforded by Gp IIb/IIIa receptor inhibition during PCI.

**Early conservative strategy**

Clinical efficacy of Gp IIb/IIIa receptor antagonists in patients with UA who are not routinely scheduled to undergo early revascularization is less obvious. Six major randomized trials: Platelet Receptor Inhibition in Ischemic Syndrome Management (PRISM), Platelet Receptor Inhibition in Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms (PRISM-PLUS), Platelet IIb/IIIa Antagonism for the Reduction of Acute coronary syndrome events in a Global Organization Network (PARAGON-A), Platelet glycoprotein IIb/IIIa in Unstable angina: Receptor Suppression Using Integrilin Therapy (PURSUIT), PARAGON-B, and the Global Utilization of Strategies To Open Occluded coronary arteries (GUSTO)-IV ACS enrolling more than 30,000 patients have addressed this issue. Gp IIb/IIIa receptor antagonists did reduce cardiac end points in majority of these trials. In the trials with a positive trend, the event reduction was often lower than expected, and statistical significance was not always achieved. Meta-analysis of these trials revealed that Gp IIb/IIIa receptor antagonists were associated with a 9% relative and 1% absolute reduction in 30 days rate of death or MI as compared with control therapy (10.8% v. 11.8%, p=0.015) in patients managed with initial conservative strategy.

Indeed, as compared to other trials, divergent findings were seen with GUSTO-IV ACS trial which deserves special mention. This trial randomized patients to abciximab bolus plus 48-hour infusion, abciximab bolus plus 24-hour infusion, or placebo. At 30 days, the composite end point of death or MI was not statistically different amongst the study groups. Reasons for these results are not clear but may be due to pro-inflammatory features of abciximab during extended infusion and raise a question regarding toxicity of intravenous Gp IIb/IIIa receptor antagonists somewhat similar to the administration of long-term oral Gp IIb/IIIa receptor antagonists.

The overall benefit of early Gp IIb/IIIa receptor antagonists in UA/NSTEMI is dramatically enhanced when viewed according to risk stratification (troponin level, TIMI risk score, ST-segment changes, presence of diabetes etc). Use of Gp IIb/IIIa receptor antagonists was associated with 15% relative risk reduction in the 30 days end points in troponin positive patients (10.3% v. 12.0%). In comparison, in patients with negative troponins, no risk reduction was seen (7.0% v. 6.2%). This differential treatment advantage with respect to troponin was significant (p=0.045). Similarly, significant interaction between the use of Gp IIb/IIIa receptor antagonists and the diabetic status has been observed. Meta-analysis of diabetic patients in these six large-scale trials revealed a 26% mortality reduction associated with the use of these agents at 30 days compared with placebo. This translates to one life saved for every 63 patients treated. The most marked survival advantage conferred by platelet Gp IIb/IIIa inhibitors was observed in diabetic patients undergoing PCI during index hospitalization translating to one life saved for every 36 patients treated. Thus, the data are compelling enough to suggest that the administration of Gp IIb/IIIa inhibitors should be considered the standard of care in high-risk patients (troponin-positive or presence of diabetes) with UA/NSTEMI.

**Comparative analysis and recommendations**

Roffi et al. analyzed a cohort of approximately 30,000 patients of ACS to assess the relative efficacy of Gp IIb/IIIa receptor inhibition based on the revascularization strategy. There
was a clear gradient of benefit with a 26% reduction in death or MI at 30 days in patients undergoing PCI while on a Gp IIb/IIIa receptor antagonists (p=0.02), a 13% reduction if PCI was performed after discontinuation of the drug (p=0.17), and a 5% reduction in those treated medically. Although caution must be exercised in the interpretation of results obtained from such non-randomized subgroups, ACC/AHA Guideline Committee recommended the use of Gp IIb/IIIa antagonists in patients with UA/NSTEMI who are likely to undergo PCI. Any of the three available Gp IIb/IIIa antagonists (preferably abciximab) may be started immediately before or in the course of the PCI. The two small molecule Gp IIb/IIIa receptor antagonists (epifibatide and tirofiban) can also be started “upstream,” i.e., 24-48 hour before, and continued during PCI, however, the data is more robust for abciximab. There are no convincing data to support switching small molecule Gp IIb/IIIa receptor antagonists, if started prior to PCI, to abciximab at the time of procedure. None of the Gp IIb/IIIa antagonists appear to be indicated in the routine management of low-risk, troponin-negative patients in whom early invasive strategy is not planned. However, the administration of small molecule Gp IIb/IIIa inhibitors i.e. epifibatide or tirofiban should be considered standard of care in high-risk patients (elevated troponin, continuing ischemia, high TIMI risk score etc.) with UA/NSTEMI managed conservatively. In accordance with the findings of GUSTO-IV ACS trial, abciximab is not indicated in patients with ACS in whom early PCI is not planned. It would be useful to evaluate prospectively “upstream” early treatment with a small-molecular Gp IIb/IIIa antagonist in patients with UA/NSTEMI with the commencement of therapy just before PCI. The results of the Early glycoprotein IIb/IIIa inhibition in non-ST segment elevation Acute Coronary Syndrome (EARLY ACS) trial which is designed to investigate utility of early initiation of epifibatide in high risk patients with ACS (NSTEMI) in whom an invasive strategy is planned no sooner than the next day, will substantiate the utility of this strategy.16

Role in ST Segment Elevation Myocardial Infarction

Despite successful mechanical revascularization of the epicardial coronary artery either by thrombolytic therapy or by primary PCI, sub-optimal microvascular perfusion may persist resulting in unfavorable clinical outcome. This primarily results from the distal embolization of platelet aggregates and plugging of distal microvasculature, thereby necessitating the need of potent platelet antagonists. The role of adjunctive Gp IIb/IIIa receptor antagonists has been evaluated both in the setting of primary PCI and as a combination therapy with thrombolytic treatment.

Primary percutaneous coronary intervention: Several studies have highlighted the efficacy of Gp IIb/IIIa receptor antagonists for better tissue perfusion and preservation of left ventricular contractile function in this clinical setting.40-42 Among the three agents, only abciximab has been extensively studied in form of large-scale randomized trials. Six major randomized trials - ReoPro and Primary PTCA Organization and Randomized Trial (RAPPORT), ISAR-2, Abciximab before Direct Angioplasty and Stenting in myocardial Infarction Regarding Acute and Long-Term Follow-up (ADIMRAL), Petronio et al.41, Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications (CADILLAC), and Abciximab and Carbostent Evaluation (ACE), evaluated the role of abciximab in primary PCI.43-48 Individually, these studies revealed a significant reduction in the composite end points of death, MI, and urgent revascularization with the use of abciximab. These benefits were largely driven by the reduction in rates of urgent TVR. A recently published meta-analysis of these patients highlighted the mortality benefits with the use of abciximab. There was a significant reduction in short-term (30-day) mortality in patients undergoing primary angioplasty as compared to controls (2.4% v. 3.4% respectively, p=0.047). There was also a significant reduction in 30-day reinfarction rate (1.0% v. 1.9% respectively, p=0.031).49 Therefore, there is enough evidence to recommend routine use of abciximab in patients under-going primary PCI.

Role of Gp IIb/IIIa receptor antagonists in two subgroups of patients of acute MI deserves special mention. Only limited data is available regarding use of Gp IIb/IIIa receptor antagonists in patients undergoing rescue PCI after failed thrombolysis for acute MI. The fear of increased risk of bleeding if Gp IIb/IIIa receptor antagonists are used after full-dose thrombolytics, has limited their widespread application in this setting.46,50 Petronio et al.46 randomized 89 such consecutive patients to abciximab treatment or placebo. At 30 days follow-up, the echocardiographic left ventricular wall motion score index showed a significantly higher improvement in the abciximab group (p < 0.001). At 6 months follow-up, the incidence of major adverse cardiac events of death, reinfarction, congestive heart failure, target lesion revascularization, or recurrent ischemia was 11% in the abciximab group versus 38% in the placebo group (p =0.004). Thus, the available data.
although limited, suggest that abciximab can be used in patients with acute MI and failed thrombolysis, with an acceptable increased risk of bleeding. Similarly, the role of adjunctive abciximab and PCI for cardiogenic shock has not been clearly established. Recent observational studies have highlighted the impact of use of abciximab along with coronary stenting. Thus, high-risk patients presenting with cardiogenic shock following acute MI, the composite event rate of death, MI and TVR at 30 days was better with the use of abciximab (31% with abciximab v. 63% without abciximab; p = 0.002). The best results were seen with the use of abciximab and stents. The combination was synergistic and resulted in improvement of all components of the composite end point beyond that seen with each therapy alone. The long-term benefits of this synergism are further supported by Chan et al., who prospectively analyzed the data of 96 consecutive patients undergoing emergent PCI for cardiogenic shock. Patients were classified as receiving stent plus abciximab, stent alone, percutaneous transluminal coronary angioplasty (PTCA) plus abciximab, or PTCA alone. Achievement of post-procedural TIMI-3 flow was higher with stent plus abciximab than with the other interventions (85% v. 65%, p = 0.048). During 2.5 years of follow-up, the mortality rates for stent plus abciximab, stent only, PTCA plus abciximab, and PTCA alone were 33%, 43%, 61%, and 68%, respectively (p = 0.028). Thus, high-risk patients presenting with cardiogenic shock should receive stents with abciximab, when subjected to primary PCI.

**Timing of administration:** As is the case with thrombolytic agents, the timing of administration of abciximab is an important issue. In most of the trials, abciximab was administered just prior to PCI in the catheterization laboratory. Only limited literature is available regarding the early use of Gp IIb/IIIa receptor antagonists during the organization phase of PCI (in emergency room) as compared to immediately before PCI (catheterization laboratory). In the ADMIRAL trial, 26% of patients received the upstream use of abciximab. Upstream use of abciximab during the organization phase of PCI resulted in early recanalization of infarct-related artery and subsequent better myocardial tissue perfusion. These patients have less complicated in-hospital course and better survival. However, pre-hospital administration of tirofiban in the ONGoING Tirofiban In Myocardial infarction Evaluation (ON-TIME) trial failed to show an impact on clinical outcome after PCI. Thus, at present, no definite conclusions can be drawn from the data available. Further studies are required to prove whether early administration of Gp IIb/IIIa receptor antagonists in the emergency department or even earlier - pre-hospital administration rather than in the catheterization suite, provides additional benefits in clinical outcome and myocardial salvage.

**Combination therapy (Gp IIb / IIIa antagonists and thrombolysis) for STEMI:** Even if epicardial coronary arteries are opened, the myocardial perfusion may not improve following reperfusion therapy. This could partly be due to paradoxical platelet activation leading to microvascular dysfunction and propensity for re-infarction. Thus, there is rationale for combining thrombolytic therapy with Gp IIb/IIIa receptor antagonists. Initial results were encouraging in several pilot studies using this combination therapy in STEMI. The initial trials testing a combination of streptokinase with either abciximab or eptifibatide were discontinued due to higher incidence of bleeding. Two 6-phase clinical trials: TIMI-14, Strategies for Patency Enhancement in the Emergency Department (SPEED), Integrilin and Low-dose Thrombolysis in Acute Myocardial Infarction (INTRO-AMI), Integrilin and Tenecteplase in Acute Myocardial Infarction (INTEGRITY) TIMI 20, Enoxaparin and TNK-tPA with or without Gp IIb/IIIa Inhibitor as REperfusion strategy in ST elevation MI-Thrombolysis In Myocardial Infarction (ENTIRE) TIMI-23, and Fibrinolytics and Aggrastat with STElevation Resolution (EASTER) TIMI-24, tested optimal combination of reduced dose (50% - 75%) of thrombolytic agents (t-PA, r-PA, TNK) and Gp IIb/IIIa receptor antagonists (abciximab, eptifibatide or tirofiban) as compared to full dose of thrombolytic therapy. Early and enhanced myocardial perfusion as judged by TIMI grade 3 flow, ST segment resolution or myocardial blush score was seen with combination therapy in these trials. In addition, clinical impact of combination therapy was tested in two large-scale, randomized trials. In GUSTO V trial, patients with AMI were assigned to receive either full dose reteplase or a combination of abciximab and half-dose reteplase. At 30 days follow-up, there was no difference in the mortality between the two groups. However, there was significant reduction in the rates of non-fatal ischemic complications with the use of combination therapy. Nevertheless, these benefits failed to translate into mortality benefits at one-year follow-up. In contrast, combination therapy was associated with more bleeding complications, specially in the elderly population. The Assessment of the Safety and Efficacy of a New Thrombolytic Regimen (ASSENT) - 3 randomized the patients to receive either full dose TNK and enoxaparin (enoxaparin arm), half-dose...
TNK with low-dose unfractionated heparin (UFH) and abciximab (abciXimab arm) or full-dose TNK with UFH (heparin arm). There was no significant mortality difference in the three groups. However, there were fewer efficacy end points (composite of 30-day mortality, inhospital reinfarction, or in-hospital refractory ischemia), and efficacy plus safety end points (in-hospital intracranial hemorrhage, or in-hospital major bleeding complications) in the enoxaparin and abciximab groups than in the UFH group.

Thus, combination therapy, while providing key reduction in secondary end points, is not associated with mortality benefits over standard thrombolytic therapy, and carries the additional risk of bleeding complications, specially in the elderly population. Given the failure of secondary end point reduction to translate into survival benefits at one year, and the tendency of increased bleeding complications, at present, this combination therapy cannot be recommended for routine incorporation into clinical practice.

Facilitated percutaneous coronary intervention: Strategy of planned early PCI after pharmacological reperfusion with thrombolytic agents and platelet Gp IIb/IIIa inhibitors (alone or in combination) fuses the best aspects of reperfusion strategies of acute MI. The evidence of this facilitation was first seen in the subgroup of patients in the ADMIRAL trial that received early administration of abciximab. This resulted in better TIMI flow at the time of PCI and accounted for better 30-day and 6-month clinical outcomes. A sub-study from the TIMI-14 trial revealed that adjunctive PCI significantly improved myocardial perfusion as assessed by ST segment resolution in patients who had been treated with combination therapy (abciximab and a reduced-dose thrombolytic agent) as compared to those who received full-dose thrombolytic agent. Subgroup analysis of SPEED (GUSTO-4 Pilot) trial in which patients received either reteplase or the combination of abciximab and half dose of reteplase also addressed this issue. A cohort of 323 patients who underwent immediate PCI had a significantly lesser ischemic events at 30 days as compared to patients not undergoing revascularization. These results do support the concept of "union in reperfusion", the use of pharmacological agents to quickly open both the artery and the microvasculature and the use of adjunctive interventions to further improve flow and keep arteries open. Further studies are required for definite conclusions. The ADESSing the Value of facilitated Angioplasty after Combination therapy or Epftibatide monotherapy in acute Myocardial Infarction (ADVANCE MI) trial was intended to evaluate efficacy of eptifibatide and half-dose tenceteplase before PCI. However, the trial was terminated prematurely due to slow recruitment. Two large-scale, randomized, prospective clinical trials: Combined Abciximab REteplase Stent Study in acute myocardial infarction (CARESS) and Facilitated Intervention with Enhanced reperfusion Speed to Stop Events (FINESSE) are ongoing to address this issue.

Conclusions

The last decade witnessed an explosion of evidence that has defined the role of Gp IIb/IIIa receptor antagonists in the entire spectrum of CAD. Their use is recommended in high-risk PCI, however, low- to intermediate-risk elective PCI in stable CAD patients can be done with proper pre-treatment with dual antiplatelet agents. Patients with ACS who are undergoing early PCI tremendously benefit from their use. Similarly, these agents are of proven benefit in high-risk (elevated troponins, high TIMI risk score) patients presenting as ACS and can be managed conservatively. The available data support their use as an adjuvant in primary PCI. Whether these agents will be useful as pre-hospital treatment of acute MI before PCI needs to be proved in large-scale randomized studies.

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Echocardiography continues to be the primary non-invasive imaging modality for the assessment of cardiac structure and function. The advances in imaging modalities in the modern ultrasound systems in tandem with the development of newer agents have made contrast imaging more effective and applicable to daily clinical practice. Myocardial contrast echocardiography (MCE) utilizes acoustically active gas-filled microspheres (microbubbles) which have a rheology similar to that of red blood cells. Detection of myocardial perfusion during echocardiographic examination permits simultaneous assessment of global and regional myocardial structure, function, and perfusion, enabling optimal non-invasive assessment of coronary artery disease (CAD). In future, its use will not be limited solely to diagnostic assessment. MCE has the potential for therapeutic delivery of growth factors, genes and aiding thrombolysis. MCE has evolved from the experimental laboratory to daily clinical practice for the bedside evaluation of ischemic heart disease.

Microbubble Contrast Agents

Contrast agents are typically of 2 to 4 microns in size (Table 1), consisting of gaseous material encapsulated by a stabilizing outer shell. To ensure successful negotiation of the pulmonary microvasculature and adequate visualization of the myocardium, microbubbles have undergone a number of modifications over recent years. The prolonged survival of microbubbles has been achieved primarily through the use of more stable outer shells and the substitution of air with a high density, high molecular weight gas both of which confer improved stability.

The significant acoustic difference created between microbubbles and blood allows for their easy detection using specific ultrasound imaging techniques. Importantly, microbubbles oscillate at a rate of several million times per second in response to ultrasound waves, the same frequency as used for echocardiography. Thus, microbubbles not only act as passive reflectors but also as strong sources of sound. Oscillations generated thereby, have characteristics in received waves which are not present in transmitted waves. These signal characteristics are critical for effective separation of microbubble signals from tissue signals.

Microbubbles are hemodynamically inert and remain entirely within the intravascular space. These two properties differentiate it from tracers used in other forms of cardiac imaging i.e. positron emission tomography (PET), single photon emission-computed tomography (SPECT), cardiovascular magnetic resonance (CMR) and computed tomography (CT).

Myocardial Contrast Echocardiography

The volume of blood present in the entire coronary circulation (arteries, arterioles, capillaries, venules, and veins) is approximately 12 ml/100 g of cardiac muscle. Approximately one-third of this volume is present within the myocardium itself and is termed as myocardial blood volume (MBV). The predominant (90%) component of MBV resides within the capillaries. The myocardial signal assessed visually as contrast intensity reflects the concentration of microbubbles within the myocardium. Therefore, when the entire myocardium is fully saturated during a continuous infusion of microbubbles, the signal intensity denotes the capillary blood volume. Any alteration in signal in such a situation must, therefore, occur predominantly from a change in capillary blood volume. Furthermore, it has been shown that following destruction of microbubbles in the myocardium during high power imaging, replenishment of the myocardium can be observed. The capillary blood velocity is 1 mm/s. With an ultrasound beam elevation of 5 mm, it will take approximately 5 seconds for complete replenishment of the myocardium. Any decrease in myocardial blood flow (MBF) prolongs replenishment time proportionate to the reduction in MBF. Myocardial perfusion is defined as tissue blood flow at the capillary level. The two components of tissue blood
flow are capillary blood volume and microbubble velocity (i.e., rate of microbubble replenishment following destruction of microbubbles). The product of these two components denotes MBF at the tissue level. Thus, MCE can detect capillary blood volume and, by virtue of its temporal resolution, can also assess MBF. This imaging technique requires delivery of a series of high energy ultrasound pulses to destroy microbubbles in the myocardium (Fig. 1). Ultrasound imaging is then continued either intermittently (during high-power imaging) or continuously (during low-power imaging) to observe contrast intensity and microbubble velocity.

**MCE in Acute ST Elevation Myocardial Infarction (STEMI)**

The extent of myocardial necrosis after acute myocardial infarction (AMI) is directly related to: (i) total duration of coronary occlusion; (ii) the extent of myocardium subtended by the occluded artery; and (iii) the quality of collateral circulation.

**Assessment of infarct-related artery (IRA) patency:** Following AMI, the progression of myocardial necrosis may be halted if the IRA opens either spontaneously, after reperfusion therapy, or if there is sufficient collateral circulation supplying the jeopardized region despite an occluded epicardial artery. IRA patency may not be achieved in approximately 30% of patients following thrombolytic therapy. Clinical predictors (i.e., resolution of chest pain, resolution of ST elevation, and degree of cardiac enzyme release) for detecting IRA patency immediately following thrombolysis have been shown to have limited accuracy. However, IRA patency can be reliably determined with MCE. During acute total coronary occlusion, in the absence of collateral flow, a transmural contrast perfusion defect occurs. Following reperfusion the defect will no longer be transmural. Thus, if MCE is performed before and after reperfusion therapy, the IRA patency can be determined by comparing the transmural extent of the defects in each image. If IRA patency is not achieved following thrombolysis, the patient can be referred for urgent rescue percutaneous coronary intervention (PCI), thus allowing appropriate early triage of patients most likely to benefit from rescue PCI.

**Detection of low-reflow/no-reflow phenomenon:** Recent studies have revealed that in STEMI, restoration of epicardial coronary artery patency is not equivalent to restoration of tissue perfusion. An early visualization of a perfusion defect after AMI can be due to either persistent occlusion of the epicardial coronary artery or due to the lack of tissue perfusion, despite establishment of epicardial coronary flow by revascularization. Functional and structural microvascular disturbance, i.e.

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**Table 1. General characteristics of various microbubble contrast agents**

<table>
<thead>
<tr>
<th>Agent</th>
<th>Mean bubble size (micron)</th>
<th>Gas</th>
<th>Shell composition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albunex</td>
<td>4.5</td>
<td>Air</td>
<td>Albumin</td>
</tr>
<tr>
<td>Levovist</td>
<td>2-3</td>
<td>Air</td>
<td>None – bubbles adhere to galactose microparticles</td>
</tr>
<tr>
<td>EchoGen</td>
<td>2-5</td>
<td>Perfluoropentane</td>
<td>Stabilized surfactant</td>
</tr>
<tr>
<td>Sonogen</td>
<td>2-5</td>
<td>Perfluoropentane</td>
<td>Anionically charged surfactant</td>
</tr>
<tr>
<td>Optison</td>
<td>4.7</td>
<td>Perfluoropropane</td>
<td>Albumin</td>
</tr>
<tr>
<td>Definity</td>
<td>1.5</td>
<td>Perfluoropropane</td>
<td>Phospholipid</td>
</tr>
<tr>
<td>Imagent</td>
<td>5.0</td>
<td>Perfluoroxane nitrogen</td>
<td>Stabilized surfactant</td>
</tr>
<tr>
<td>Sonovue</td>
<td>2.5</td>
<td>Sulphur hexafluoride</td>
<td>Phospholipid</td>
</tr>
<tr>
<td>Cardiosphere</td>
<td>4.0</td>
<td>Nitrogen</td>
<td>Biodegradable polymer bilayer</td>
</tr>
<tr>
<td>NC100100</td>
<td>3.4</td>
<td>Unspecified perfluorocarbon</td>
<td>Unknown</td>
</tr>
<tr>
<td>AI-700</td>
<td>2.0</td>
<td>Perfluorocarbon</td>
<td>Synthetic polymer</td>
</tr>
</tbody>
</table>

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**Fig. 1.** Frame (i) is immediately following a high power ultrasound flash which destroys the microbubbles within the myocardium. Frames (ii)-(iv) show replenishment of microbubbles in the septum and lateral walls within 2 heart beats. A clear apical perfusion defect (A) is demonstrated which persists.
low- or no-reflow phenomenon, despite patency of IRA, represents important pathphysiologic phenomenon in the setting of reperfused STEMI. Prolonged ischemia may result with the failure to establish microvascular reperfusion despite restoration of epicardial coronary patency. No-reflow is a marker of myocyte necrosis and hence, residual myocardial viability. However, in the immediate reperfusion period coronary hyperemia may occur and this may result in underestimation of myocardial necrosis by any technique that uses intravascular tracers like MCE.

MCE performed shortly before and after reperfusion by therapeutic intervention can be used to assess success of the intervention. In a study performed by Greaves et al., MCE performed 24 hours after restoration of IRA patency with PCI was found to be superior to clinical and angiographic predictors of myocardial perfusion. Restoration of epicardial coronary flow in the infarct-related region after AMI may result in coronary hyperemia that lasts for 3 to 6 hours. This reactive hyperemia disappears about 3 to 6 hours after primary coronary intervention. Sakuma et al. have shown that the most appropriate time for performing MCE, for predicting early ventricular functional recovery, is 48 hours after the reperfusion. Increased contrast enhancement in an infarcted area after reperfusion following passage of the reactive hyperemic period reflects preserved microvascular integrity. Delayed opacification in the infarcted area with triggered imaging has been shown to be a marker of regional recovery of function irrespective of the severity of residual stenosis of the IRA. An important role of MCE in delineating the functional area at risk in this patient population has been established by a number of studies demonstrating prognostic power after AMI. Ito et al. suggested that in reperfused anterior AMI, the presence of no-reflow correlates with the occurrence of adverse left ventricular (LV) remodeling.

Assessment of myocardial viability: The correct differentiation between stunned and necrotic myocardium early after infarction helps in risk stratification and identifies patients at increased risk of complications such as congestive heart failure, ventricular tachycardia and death. The early re-establishment of epicardial coronary artery patency, either pharmacologically using thrombolitics, or mechanically by angioplasty, is the key factor for curbing infarct size. The microvascular integrity in the infarcted area is a prerequisite for the salvage of the myocardium and it depends not only on the duration of the ischemic episode but also on the residual flow in the region subtended by the collateral vessels. As MCE interrogates the whole intra-myocardial microvasculature, it is ideal for assessing microvascular reflow after acute infarct and recanalization. Studies using intracoronary, and later with intravenous injection of contrast agents have demonstrated that this technique is useful in assessing reperfusion in the area at risk. The presence of adequate contrast enhancement (patchy or full opacification) has been shown to be a reliable marker of viable myocardium. Patients with adequate contrast opacification in the infarcted region represent a group with a better clinical outcome in comparison to patients with a perfusion defect.

In STEMI, the accuracy of MCE in predicting recovery of function after reperfusion is excellent. We have shown that the extent and severity of contrast defects after AMI correlates with recovery of global function at 3 months after revascularization. Absence of contrast opacification after 15 cycles using low-power continuous imaging essentially excluded subsequent recovery of function. MCE compares favorably with dobutamine stress echocardiography (DSE) for predicting regional LV dysfunction after AMI. Indeed, a recent study showed that presence of contrast opacification in dysfunctional myocardium, where dobutamine-induced contractile reserve is absent, may show recovery of function. Hence MCE may provide incremental information to that obtained from DSE. Many investigators believe that the gold standard for defining viability should be myocardial functional recovery after revascularization. This infers that minimal islands of viable myocardium should have no prognostic value. There is extensive evidence that functional recovery is dependent on the degree of myocyte loss and the extent to which they are replaced by fibrous tissue. However, independent of regional myocardial resting function recovery, partial viability may still be beneficial for contractile reserve, exercise tolerance, favorable remodeling and survival. Recently demonstrated the favorable effect of myocardial perfusion detected by MCE on LV remodeling.

Assessment of collateral blood flow in the presence of persistently occluded IRA: Adequate collateral blood flow at rest can sustain myocardial viability despite persistent occlusion of the IRA in AMI. We used qualitative and quantitative MCE to analyze myocardial perfusion in the akinetic segments in 20 patients with AMI and an occluded IRA who subsequently underwent revascularization. Contractile reserve, which is a marker of myocardial viability, was assessed with low-dose dobutamine 12 weeks after mechanical revascularization. Of the 102 akinetic segments, 37 (36%) showed contractile...
reserve. Contractile reserve was present in 24 of the 29 segments (83%) with homogenous contrast opacification and absent in 60 of the 73 segments (82%) with reduced/absent opacification. Quantitative peak contrast intensity, microbubble velocity, and MBF were significantly higher (p < 0.0001) in the segments with contractile reserve than in those without contractile reserve. MCE may thus be used as a reliable bedside technique for the accurate evaluation of collateral blood flow in the presence of an occluded IRA after AMI.

Detection of residual stenosis of the IRA and multivessel disease early after AMI: Detection of residual IRA stenosis subtending significant viable myocardium and the identification of multivessel disease (MVD) may help to triage patients who may benefit from mechanical revascularization after AMI and thrombolysis. In our study of patients post-AMI with low-power MCE at rest and after dipyridamole stress during SonoVue® infusion, the sensitivities to detect >50% IRA stenosis and MVD were 88% and 72%, respectively. The accuracy of detecting significant coronary stenosis in the anterior (left anterior descending coronary artery) versus inferoposterior (right coronary artery/left circumflex artery) circulation was similar for both IRA (85% v. 91%) and remote territories (91% v. 81%). Quantitative parameters had incremental value in the detection of stenosis.

Detection of infarct transmurality and contractile reserve: Both MCE and CMR can identify myocardial necrosis after AMI. We performed MCE and CMR in 42 patients with AMI 7-10 days after thrombolysis. Contractile reserve with low-dose dobutamine was evaluated 12 weeks after revascularization. Both qualitative and quantitative MCE parameters showed a significant (p < 0.0001) inverse relationship with increasing infarct transmurality. However, microbubble velocity was the single best predictor of infarct transmurality (p = 0.002). Both qualitative and quantitative MCE parameters predicted contractile reserve similar to CMR.

MCE in Acute Non-ST Elevation Myocardial Infarction (NSTEMI)

Despite all the advances in clinical, electrocardiographic (ECG) and serologic assessment of AMI, the diagnosis of non-STEMI remains problematic in patients presenting to the emergency services with chest pain. ST-segment elevation is seen only in about one-third of patients with AMI. Other patients with non-STEMI have either normal ECGs or exhibit non-specific ST-T changes that are associated with other concomitant cardiac conditions including hypertension, congestive heart failure, and digitalis use, making the diagnosis of AMI difficult. Although serological markers such as CK-MB, troponin and myoglobin ultimately become abnormal in these patients, it takes several hours before results become available. A recent multi-center study has demonstrated that imaging of regional myocardial function and perfusion has incremental value, both for diagnosis as well as for short-term prognosis when compared with routine demographic, clinical and electrocardiographic findings in patients presenting to the emergency with chest pain, without ST-segment elevation. Concordance between MCE and SPECT was 77% for all territories, with a higher concordance for the anterior wall (84%). This information can be used to triage patients for admission or discharge.

MCE in Detection of Chronic Coronary Artery Disease

Resting epicardial coronary blood flow (CBF) remains normal even in the presence of a severe luminal stenosis. Resting CBF does not decrease until more than 85% to 90% of the luminal diameter is encroached by a stenosis. Although resting flow remains unchanged with non-critical stenosis, flow during maximal hyperemia is reduced when the luminal diameter stenosis severity exceeds 50%. Capillaries offer the most resistance to CBF during hyperemia and limit the maximal increase in hyperemic CBF. It has been shown that the MBV fraction decreases during hyperemia in the presence of a stenosis, and this decrease is proportional to stenosis severity. Decrease in MBV in the stenosed myocardial bed during hyperemia and the degree of this decrease which is proportional to stenosis severity, is the basis of a perfusion defect detected by MCE.

Experimental and clinical studies have confirmed the ability of MCE to evaluate the presence and severity of CAD during pharmacological or exercise stress. Initial clinical studies have demonstrated excellent concordance between MCE and nuclear imaging techniques. Shimoni et al. have shown that real time MCE can be used to evaluate myocardial perfusion during exercise echocardiography. The combination of exercise echocardiography and MCE offers the best balance between sensitivity and the specificity in detecting CAD (86% and 88%, respectively) with the highest accuracy (86%) compared to exercise echocardiography alone or with nuclear techniques.
Myocardial perfusion abnormalities detected using real time pulse inversion Doppler imaging during DSE in patients without known CAD proved to be superior to the wall motion analysis for the detection of significant coronary artery stenosis. Senior et al. have demonstrated that MCE is superior to SPECT during dipyridamole stress for the diagnosis of CAD in patients with a medium pre-test probability of CAD. (Fig. 2).

MCE in Detection of Hibernating Myocardium in Chronic CAD

It is well known that the patients with chronic CAD have impairment of contractile function. This is regarded as a protective mechanism in which the heart spontaneously downregulates its function, minimizes its energy requirements and prevents irreversible tissue damage. Patients with hibernating myocardium appear to be at increased risk for future cardiac events, but restoration of coronary flow allows recovery of lost ventricular contractile function. Detection of viable myocardium in ischemic cardiomyopathy patients is of paramount importance. de Filippi et al. and Nagueh et al. studied effectiveness of intracoronary MCE in detecting hibernating myocardium. Nagueh et al. reported high sensitivity (89%), but low specificity (43%) for MCE to predict recovery of myocardial function after reperfusion in patients with LV ischemic dysfunction. Predictive accuracy of MCE was found to be similar to that of thallium scintigraphy. Shimoni et al. have demonstrated that when a quantitative method of myocardial perfusion was used, the diagnostic accuracy of MCE increased, with high sensitivity of 90% but moderate specificity of 61%. Large-scale clinical studies are required to evaluate the incremental value of MCE to currently available echocardiographic methods for evaluation of myocardial viability in chronic CAD.

Limitations

Like any other technique, MCE has some limitations. Attenuation of basal segments of the LV may occur, thus hampering detection of perfusion defects localized to these segments. During flash echocardiography, the refilling curve is influenced by several variables such as depth, angle, instrument settings and adequacy of microbubble destruction. These factors may affect accurate evaluation of myocardial blood flow.

Future Directions

Functional ultrasound imaging of tissue using targeted microbubbles represents a new approach that departs from the concept that microbubbles passively transit the microcirculation like red blood cells. In this technique, microbubbles are designed to adhere to molecular epitopes on the surface of abnormal endothelium, and subsequently targeted contrast imaging could provide capabilities for in vivo ultrasonic detection of features of endothelium that predate clinical disease or are otherwise not detectable.
using the currently available technologies. The field of targeted ultrasound imaging is still in its infancy and much remains to be done to develop this area into a clinically mature entity.

Finally, targeted microbubbles may ultimately have utility beyond their diagnostic attributes. Ultrasonic distribution of microbubbles seems to enhance delivery of genes and drug and the lysis of clots. The ability to target therapeutics by designing the delivery agent (microbubble) to the site of interest i.e. clot, atherosclerotic plaque, tumor, apoptic cells, or disease microvasculature - may ultimately prove to be another compelling and powerful clinical application of this exciting technology.

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Two-Year Outcomes in Patients Admitted with Non-ST Elevation Acute Coronary Syndrome: Results of the OASIS Registry 1 and 2


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Background: Acute coronary syndrome continues to have significant long-term morbidity and mortality. This study sought to compare baseline characteristics, practice patterns and clinical outcomes for patients with non-ST elevation acute coronary syndrome from a broad range of low-, middle- and high-income countries.

Methods and Results: We compared the data from a prospective registry of patients with non-ST elevation acute coronary syndrome involving 4615 patients from 65 centers in 8 low and middle income countries (OASIS registry 2) with those obtained from 7987 patients from 95 centers in 6 middle and high income countries (OASIS registry 1). Patients in the OASIS registry 2 were younger, were more often males and smokers, presented later to the hospital after symptom onset and had a lower prevalence of diabetes at admission [with the exception of India, which had the highest age-adjusted prevalence (39.1%)]. There were marked variations in the angiography and intervention rates during the hospital stay, but the uses of proven pharmacological therapies were comparable. The two-year mortality rates adjusted for baseline covariates ranged from 6.9% to 15%. Patients from China had the lowest two-year mortality rate (6.9%) and patients from India had the highest rate (15%). Combining the two registries, the covariate-adjusted rate of death or myocardial infarction did not differ across countries with in-hospital angiographic rates of ≥50% (17.1%), 25-49% (16.7%) or <25% (16.5%). However, the covariate-adjusted rates for subsequent myocardial infarction (7.6%, 9.2% and 10.8% respectively, p<0.0001), refractory angina (21.3%, 27.7% and 35.4% respectively, p<0.0001) and the composite of death, myocardial infarction or refractory angina (34.9%, 40.7% and 46.8% respectively, p<0.0001) differed depending on the angiographic rates.

Conclusions: Among the participating countries there was a marked heterogeneity in patient characteristics, coronary interventions, resulting in differences in the two-year composite rates of death, myocardial infarction and refractory angina among patients admitted with non-ST elevation acute coronary syndrome. (Indian Heart J 2005; 57: 217–225)

Key Words: Coronary artery disease, Acute coronary syndrome, Unstable angina
types of centers and countries that participate. International registries have mainly focused on developed countries, and have reported heterogeneity in individual patient risks, practice patterns and outcomes in those with NSTEMI ACS, associated with large regional variations in outcomes. Moreover in most registries, because of the challenges of long-term follow-up, the reporting of outcomes is mainly confined to in-hospital events, or events occurring within six months of the index episode. We have previously reported a 6-month combined cardiovascular death and myocardial infarction (MI) rate to be substantially higher than the in-hospital event rate (11% vs. 4.7%) in a large registry of 7987 patients with ACS conducted in high and middle income countries. In this report we provide data from an additional 4615 patients recruited mainly from developing countries with differing income ranges representing low (Bangladesh, India and Maldives) and middle income countries (China, Lithuania, the Russian Federation and Ukraine). Patients from both registries were followed up for two years. Data collection, definitions and follow-up were similar in the two registries. Thus, this report compares the patient’s risk, practice patterns, and clinical outcomes for patients with ACS from a large range of countries (developing countries with low and middle income such as Bangladesh, Brazil, Hungary, China, India, Lithuania, Maldives, Poland, Russia and Ukraine and developed and high income countries such as Australia, Canada, Slovenia and USA).

The aims of this report are: (i) to describe patient characteristics, presentation, treatment patterns, and in-hospital outcomes in these countries; (ii) to document the risk of death and MI after two years of follow-up, and analyze whether these rates differ substantially across regions; and (iii) to explore the reasons for observed variations in outcomes, in relation to differing management strategies.

Methods
The methods and patient population recruited in the first registry have been published previously. The OASIS registry 1 enrolled 7987 patients from 95 centers in 6 countries (Australia, Brazil, Canada, Hungary, Poland and United States). The second registry enrolled 4615 patients from 68 centers in 8 countries (Bangladesh, China, India, Lithuania, Russia, Maldives, Slovenia, and Ukraine). In each registry, participating hospitals enrolled consecutive eligible patients. The first registry enrolled patients in the years 1995 and 1996 and the second registry between 1999 and 2000. The number of patients recruited from Bangladesh, Maldives, Slovenia and Russia were less than 100 per country. We combined the data of Bangladesh with India (similar ethnicity), Russia with Ukraine (part of the former Soviet bloc) and Slovenia with Lithuania (nearest national income category). For a comparison of outcomes between countries based on their income and level of development we further grouped the countries into developed and high income countries (Australia, Canada, Slovenia and USA) and developing and low (Bangladesh, India and Maldives) and middle income countries (Brazil, China, Hungary, Lithuania, Poland and Russia) based on the classification provided by the World Bank group.

Detailed descriptions of patients and methods have been published elsewhere. Briefly the OASIS registries included patients with acute ischemic chest pain within 48 hours of onset and patients with suspected unstable angina or acute MI without initial ST elevation. Patients who presented with ischemic symptoms at admission required either supportive electrocardiographic (ECG) evidence of ischemia (> 1 mm ST depression in 2 contiguous leads or T wave inversion or positive troponin T test) or should have had a prior cardiac event such as past MI, or proven coronary artery disease (CAD) by coronary angiography.

Data on clinical variables, procedures and events were collected prospectively through the use of standardized forms during hospitalization. If patients were transferred from one hospital to another for a procedure, these data were also recorded. Data were collected on interim procedures, occurrence of a new MI, re-hospitalization for unstable angina and death at 7 days or discharge, 6 months, 1 year and 2 years after the index episode. All data were transmitted and analyzed centrally. Extensive quality control efforts were made to ensure complete accuracy of data. To ensure similar approaches to diagnosing outcomes, standardized definitions were used in both the registries. The definitions have been published elsewhere. The protocol was approved by each hospital’s ethics committee and informed consent was obtained from each patient.

Statistical analysis: Baseline historical data, clinical characteristics, in-hospital management, in-hospital outcomes, 6 month and 2-year outcomes were summarized. Continuous data were compared by analysis of variance (ANOVA) and categorical data with a Mantel-Haenzel Chi square statistic or a logistic regression analysis. Univariate and multivariate relative hazards and 95% confidence intervals (CI) for mortality, MI, refractory angina, stroke, the composite rates of death, MI and death, MI, stroke and refractory angina at 2 years were calculated using log rank test, the Cox proportional hazards model and Kaplan-Meier estimates. For the multivariate analysis our
model included the following factors: age, sex, duration from onset of symptoms to presentation in the hospital, abnormal ECG at presentation, presence of congestive heart failure (CHF), serum creatinine, use of aspirin, heparin, β-blockers, angiographic procedure, prior percutaneous coronary intervention (PCI), prior coronary artery bypass grafting (CABG), MI following admission, diabetes and individual risks such as prior MI and CHF as all these were significant univariate predictors. For the baseline characteristics and in-hospital outcomes we used the data from all the centers and all recruited patients. Kaplan-Meier estimate was used for outcome of 6 months and 2 years. For calculating the risks of 2-year outcome events we used the Cox proportional hazards model. Because there were substantial loss to follow-up at 2 years especially among some Indian centers, we carried out a sensitivity analysis (with adjustment for the country) by comparing the baseline characteristics and outcomes from all the participating centers with those centers that had >80% follow-up at the end of 2 years. All statistical analysis was done with the use of SAS version 8.0.

Results

Baseline characteristics: The baseline characteristics (at admission to the hospital) of all patients (n=12602) are reported in Table 1.

Variations in demographic characteristics at baseline: Inter-country variations among the countries that participated in the OASIS registry 1 have been published previously.1 We now present the overall rates from the registry 1 and compare them with the individual rates from the countries participating in registry 2 (Table 1). In general, patients from countries participating in the OASIS registry 2 were younger, more likely to be male and smokers and presented later to the hospital after onset of symptoms. This general pattern is typified by patients from India, who were almost 9 years younger at presentation (mean age: 56 years) as compared to patients from countries of the registry 1 (mean age: 65 years). Similarly the proportion of Indian patients younger than 65 years of age was 77.0% as compared to 51.1% in registry 1. The age-adjusted rates of diabetes were lower among the countries participating in registry 2, except among Indians.

Table 1. Hospital, patient and treatment characteristics

<table>
<thead>
<tr>
<th>Countries of OASIS registry 1</th>
<th>China</th>
<th>India</th>
<th>Lithuania and Slovenia</th>
<th>Ukraine and Russia</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hospitals</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number participating</td>
<td>95</td>
<td>37</td>
<td>12</td>
<td>6</td>
<td>13</td>
</tr>
<tr>
<td>Number with CCU</td>
<td>84 (88.4%)</td>
<td>32 (86.4%)</td>
<td>12 (100%)</td>
<td>5 (81.3%)</td>
<td>8 (61.5%)</td>
</tr>
<tr>
<td>Number with angiographic facilities</td>
<td>54 (56.8 %)</td>
<td>12 (33.3%)</td>
<td>6 (50.0%)</td>
<td>3 (50.0%)</td>
<td>2 (15.4%)</td>
</tr>
<tr>
<td><strong>Patients</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Numbers enrolled</td>
<td>7987</td>
<td>2295</td>
<td>1028</td>
<td>200</td>
<td>1092</td>
</tr>
<tr>
<td>Numbers with 6-month status known</td>
<td>7891</td>
<td>2234</td>
<td>808</td>
<td>199</td>
<td>1073</td>
</tr>
<tr>
<td>Numbers with 2-year status known</td>
<td>7386</td>
<td>2173</td>
<td>442</td>
<td>161</td>
<td>1041</td>
</tr>
<tr>
<td>Mean age (years)</td>
<td>64.9</td>
<td>62.3</td>
<td>57.3</td>
<td>64.1</td>
<td>60.7</td>
</tr>
<tr>
<td>&lt; 65 years (%)</td>
<td>51.1</td>
<td>57.1</td>
<td>77.0</td>
<td>54.5</td>
<td>65.8</td>
</tr>
<tr>
<td>Female (%)</td>
<td>39.2</td>
<td>37.6</td>
<td>27.8</td>
<td>39.0</td>
<td>32.7</td>
</tr>
<tr>
<td>Current smokers (%)</td>
<td>22.1</td>
<td>23.7</td>
<td>26.3</td>
<td>13.0</td>
<td>26.3</td>
</tr>
<tr>
<td>Hours to presentation</td>
<td>8.2</td>
<td>11.5</td>
<td>11.8</td>
<td>12.2</td>
<td>13.7</td>
</tr>
<tr>
<td>Diabetes* (%)</td>
<td>21.4</td>
<td>19.3</td>
<td>19.1</td>
<td>16.0</td>
<td>15.1</td>
</tr>
<tr>
<td>Abnormal ECG* (%)</td>
<td>86.0</td>
<td>90.0</td>
<td>93.0</td>
<td>88.8</td>
<td>95.0</td>
</tr>
<tr>
<td>Previous MI* (%)</td>
<td>42.1</td>
<td>25.4</td>
<td>41.7</td>
<td>37.9</td>
<td>40.9</td>
</tr>
<tr>
<td>Heart failure (%)</td>
<td>11.5</td>
<td>7.5</td>
<td>7.2</td>
<td>11.5</td>
<td>19.2</td>
</tr>
</tbody>
</table>

**In-hospital treatment/ procedure**

| IV heparin (%)                | 7.12  | 15.9  | 50.9                   | 42.0               | 20.1    | <0.001  |
| Subcutaneous heparin (%)      | 26.3  | 13.9  | 20.6                   | 18.0               | 57.4    | <0.001  |
| Aspirin (%)                   | 91.9  | 94.2  | 98.2                   | 95.5               | 93.9    | <0.001  |
| Beta-blockers (%)             | 61.3  | 67.5  | 72.1                   | 74.5               | 65.3    | <0.001  |
| Calcium antagonists (%)       | 51.3  | 57.3  | 47.4                   | 22.2               | 17.4    | <0.001  |
| IV nitrates (%)               | 51.4  | 81.4  | 73.3                   | 42.5               | 76.0    | <0.001  |
| Angiography rates by day 7 (%)| 39.0  | 14.4  | 31.0                   | 47.4               | 9.5     | <0.001  |

*Age-adjusted rates  ** Kaplan-Meier age-adjusted percentages

CCU: Coronary care unit; ECG: electrocardiography; MI: myocardial infarction; IV: intravenous
which was the highest at 39.1%. The prevalence of heart failure was variable but relatively low in patients from Brazil, China and Lithuania. Minor variations were noted in other baseline characteristics such as the proportion having abnormal ECGs and the proportion with a previous infarction.

**Differences in the baseline management and treatment strategies (Table 2):** Some variations were noted in the use of antiplatelet, antithrombotic, β-blocker and other anti-anginals. Notably the use of heparin was infrequent among countries from the OASIS registry 2. However, the use of aspirin was over 90% in all the countries with use of β-blockers ranging between 63% to 75%.

During the hospital stay the angiography rates were higher among patients from Brazil, Lithuania and USA (57.3%, 52.1% and 68.7%, respectively) with lowest angiographic rates from Poland (3.1%). Other countries had intermediate rates. Similarly the rates of PCI were variable with USA and Brazil having a higher frequency as compared to Ukraine, Poland and Hungary. The rates of CABG were low in Poland, Ukraine, Hungary and China. Thus the highest proportion of total revascularization was highest in USA and Brazil as compared to the East European countries, and both revascularization procedure rates paralleled the angiography rate across countries.

We also carried out a comparison of patient characteristics and in-hospital treatments between developed and developing countries (Table 2). Patients from developing countries were younger, had a lower proportion of females and presented much later to the hospital as compared to patients from developed countries. There were minor differences in other baseline characteristics. With regard to in-hospital treatments, patients from developing countries were more likely to receive intravenous (IV) heparin and calcium channel blockers and undergo angiography much more frequently than patients from developing countries. Patients from developing countries were more likely to receive IV nitrates, β-blockers and antiplatelet drugs.

**Event rates at 7 days, 6 months and 2 years:** Table 3 shows the rate of death, MI, stroke and refractory angina of all the patients considered for this analysis. The rates for all these events were substantial at the end of 2 years as compared to the rates at 7 days and 6 months indicating the continued high risk of these patients after the acute phase (Fig. 1). For example the mortality at the end of 2 years was 10% as compared to a 7-day rate of 0.8% and a 6-month rate of 4.9% and the composite of death and MI rate was 16.0% at 2 years as compared to a 7-day rate of 4.1% and a 6-month rate of 9.8%. We further evaluated inter-country variations in these outcomes at 2 years (Table 4, Figs 2 and 3). The rates for total mortality and the composite of death and MI were comparable in all the countries except China. Patients from China had low rates for all the events except stroke. Patients from India had a low stroke and refractory angina rates. Similarly, a comparison by the economic status of countries revealed comparable rates of death and MI between developing and developed countries. However, there was a higher rate of stroke and refractory angina among patients from developing countries resulting in higher rates for the composites of death, MI, stroke and refractory angina (Table 5).
Two-year hazards for adverse outcomes in relation to the management strategy: The rates of death or MI did not differ significantly when countries were categorized by their rates of angiography. To explore this further we classified the participating countries into three groups based on their in-hospital angiography rates. The countries with low angiography rates (angiography in <25% of hospitalized patients) included Poland, Hungary, Russia and Ukraine and countries with high angiography rates were USA, Brazil, and Lithuania (>50% of hospitalized patients). Australia, Canada, China, India and Slovenia had intermediate rates. When compared to countries with low angiography rates, patients from countries with high angiography rates during the hospital stay appeared to have a significantly higher risk for 2-year mortality, but the risk for the composite outcome of death and MI did not differ significantly (Table 6). However, for the composite of all outcomes (death, MI, stroke and refractory angina) countries with high angiographic rates had significantly lower rates and lower hazard as compared to countries with low angiographic rates (2-year rate of 34.9% vs. 46.8% and a hazard ratio 0.7). This benefit resulted largely from a reduction in refractory angina and MI rates. Because both India and China appeared to be outliers with considerably high and low mortality rates as compared to other countries and as there was a high rate of dropouts among Indian patients (71% available at 6 months and with only a third of patients available at 2-year follow-up), we carried out the same analysis after exclusion of patients from India and China. However, despite the exclusion of patients from India and China the rates for death and MI did not differ significantly among countries with high, intermediate and low angiographic rates (data not shown). Likewise the rates

### Table 3. Kaplan-Meier age-adjusted outcome at 7 days, 6 months and 2 years, in all patients (95% CI)

<table>
<thead>
<tr>
<th>Event</th>
<th>7 days (%)</th>
<th>6 months (%)</th>
<th>2 years (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total death</td>
<td>0.8 (0.7-1.0)</td>
<td>2.4 (2.1-2.8)</td>
<td>4.7 (4.3-5.1)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>5.7 (5.4-6.0)</td>
<td>8.2 (7.6-8.7)</td>
<td>10.0 (9.4-10.5)</td>
</tr>
<tr>
<td>Refractory angina</td>
<td>4.7 (4.4-5.1)</td>
<td>7.6 (7.0-8.2)</td>
<td>10.4 (9.8-11.0)</td>
</tr>
<tr>
<td>Stroke</td>
<td>0.2 (0.1-0.3)</td>
<td>0.7 (0.6-0.8)</td>
<td>1.2 (1.1-1.3)</td>
</tr>
</tbody>
</table>

Composite outcomes:
- Death and MI: 4.1 (3.8-4.4) 10.2 (9.7-10.8) 17.5 (16.8-18.2)
- Death and stroke: 4.4 (4.0-4.7) 11.2 (10.7-11.8) 19.5 (18.8-20.2)
- Death and MI and refractory angina: 8.4 (7.8-8.9) 25.3 (24.3-25.9) 41.3 (40.3-42.0)

Composite outcomes:
- Death, MI, stroke and refractory angina: 8.6 (8.0-9.0) 25.9 (25.2-26.6) 42.6 (41.7-43.5)

Values in parentheses show the range

### Table 4. Kaplan-Meier age-adjusted outcomes at 2 years among participating countries (95% CI)

<table>
<thead>
<tr>
<th>Countries of OASIS registry 1</th>
<th>Death (%)</th>
<th>MI (%)</th>
<th>Stroke (%)</th>
<th>Refractory angina (%)</th>
<th>Death/MI (%)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>China</td>
<td>6.9</td>
<td>7.9</td>
<td>1.8</td>
<td>28.2-30.3</td>
<td>16.8-18.6</td>
<td>43.8</td>
</tr>
<tr>
<td>India</td>
<td>15.0</td>
<td>9.9</td>
<td>0.7</td>
<td>23.9</td>
<td>21.3</td>
<td>18.5</td>
</tr>
<tr>
<td>Lithuania and Slovenia</td>
<td>12.4</td>
<td>8.2</td>
<td>2.1</td>
<td>19.7</td>
<td>19.7</td>
<td>49.2</td>
</tr>
<tr>
<td>Ukraine and Russia</td>
<td>11.3</td>
<td>13.7</td>
<td>4.8</td>
<td>17.7</td>
<td>22.1</td>
<td>51.1</td>
</tr>
</tbody>
</table>

Values in parentheses show the range

### Table 5. Kaplan-Meier age-adjusted outcomes at 2 years comparing developed and developing countries (95% CI)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Developed countries (%)</th>
<th>Developing countries (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total death</td>
<td>10.2 (9.5-10.9)</td>
<td>9.5 (8.5-10.3)</td>
</tr>
<tr>
<td>MI</td>
<td>10.0 (9.4-10.7)</td>
<td>9.9 (8.9-10.8)</td>
</tr>
<tr>
<td>Stroke</td>
<td>2.9 (2.6-3.4)</td>
<td>3.6 (3.1-4.3)</td>
</tr>
<tr>
<td>Refractory angina (%)</td>
<td>29.5 (28.4-30.5)</td>
<td>32.2 (30.7-33.7)</td>
</tr>
</tbody>
</table>

* Grouping based on the classification provided by the World Bank group.12

Developed countries include countries with high income (Australia, Canada, Slovenia and USA) and developing countries include countries with low and middle income (Bangladesh, Brazil, Hungary, China, India, Lithuania, Maldives, Poland and Russia).

Values in parentheses show the range

### Table 5. Kaplan-Meier age-adjusted outcomes at 2 years comparing developed and developing countries (95% CI)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Developed countries (%)</th>
<th>Developing countries (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total death</td>
<td>10.2 (9.5-10.9)</td>
<td>9.5 (8.5-10.3)</td>
</tr>
<tr>
<td>MI</td>
<td>10.0 (9.4-10.7)</td>
<td>9.9 (8.9-10.8)</td>
</tr>
<tr>
<td>Stroke</td>
<td>2.9 (2.6-3.4)</td>
<td>3.6 (3.1-4.3)</td>
</tr>
<tr>
<td>Refractory angina (%)</td>
<td>29.5 (28.4-30.5)</td>
<td>32.2 (30.7-33.7)</td>
</tr>
</tbody>
</table>

* Grouping based on the classification provided by the World Bank group.12

Developed countries include countries with high income (Australia, Canada, Slovenia and USA) and developing countries include countries with low and middle income (Bangladesh, Brazil, Hungary, China, India, Lithuania, Maldives, Poland and Russia).

Values in parentheses show the range

Cl: confidence interval; MI: myocardial infarction
Table 6. Outcomes at 2 years among participating countries based on angiographic rates (adjusted for baseline co-variates) (95% CI)

| Event at 2 years          | Countries with low angiography rates (%) | Countries with intermediate angiography rates (%) | Countries with high angiography rates (%) | Hazard ratio
|---------------------------|------------------------------------------|---------------------------------------------------|------------------------------------------|----------------
|                           | (n=5483)                                 | (n=10518)                                         | (n=2593)                                 | CI: confidence interval;
|                          |                                           |                                                   |                                          | MI: myocardial infarction;
|                          |                                           |                                                   |                                          | ECG: electrocardiography;
|                          |                                           |                                                   |                                          | CHF: congestive heart failure;
| Death                     | 8.2                                      | 9.1                                               | 10.9                                     | 1.4
| (7.3-8.9)                 | (8.1-10.0)                               | (9.6-12.3)                                        | (1.2-1.7)                               |
| MI                       | 10.8                                     | 9.2                                               | 7.6                                      | 0.8
| (9.9-11.8)                | (8.3-10.2)                               | (6.5-8.7)                                        | (0.6-0.9)                               |
| Stroke                    | 3.8                                      | 2.6                                               | 1.1                                      | 0.9
| (3.2-4.4)                 | (2.0-3.2)                                | (2.1-1.8)                                        | (0.6-1.3)                               |
| Refractory angina         | 15.4                                     | 27.7                                              | 21.3                                     | 0.6
| (13.8-16.9)               | (26.2-29.3)                              | (19.6-23.1)                                      | (0.5-0.6)                               |
| Composite outcomes        |Death and MI                              |                                                   |                                          | 1.1
|                           | 16.5                                     | 16.7                                              | 17.1                                     | (1.0-1.3)
|                           | (15.4-17.6)                              | (15.5-17.9)                                      | (15.4-17.9)                             |
| Death, MI                 | 46.8                                     | 40.7                                              | 44.9                                     | 0.7
| (45.2-48.4)               | (39.0-42.4)                              | (32.8-47.3)                                      | (0.6-0.8)                               |
| Refractory angina         |                                         |                                                   |                                          | 1.4
| Adjusted for age († for every increase by 10 years); female sex; presence of diabetes; abnormal ECG; presence of CHF; serum creatinine >1.6 mg/dL; presence of prior MI during hospital admission; angiography by day 7; and aspirin, beta-blocker and heparin use during the hospital stay.

(i) Low angiography rates: defined as < 25% in-hospital angiography rate
(ii) Intermediate angiography rates: defined as 25-49% in-hospital angiography rate
(iii) High angiography rates: defined as > 50% in-hospital angiography rate

Values in parentheses show the range

Discussion

We have compared the baseline characteristics, in-hospital and long-term outcomes of patients between OASIS registries 1 and 2. The major findings of this study are (i) younger ages at presentation and delayed presentation to hospital after symptom onset among patients from OASIS registry 2 (low and middle income countries), (ii) similarity of β-blockers and aspirin use, but marked variations in the use of other drugs, angiography and intervention rates, (iii) a continuing high risk for all outcomes such as mortality, MI, stroke and refractory angina and related composite outcomes at 2 years, and (iv) a comparable mortality, MI and stroke rates among a wide range of high and middle income countries, but lower refractory angina in countries with higher intervention rates.

Variations in patient characteristics and treatments among patients with ACS are well known and have been reported, earlier by us and others.11,13,14 However, to the best of our knowledge, this is the first report on patient characteristics and treatment among patients of NSTEMI from a wide range of low and middle income developing countries. Despite these variations, the morbidity and mortality rates, among the participating countries were comparable. Among all the participating countries, the event rates after 2 years of follow-up were high indicating the continuing risk for long-term mortality, subsequent MI, refractory angina and stroke after admission in a hospital for NSTEMI emphasizing the need for therapies that lower long-term risk. We noted two differences between countries. First, both the adjusted and unadjusted event rates among the Chinese patients were low (except for stroke) as compared to patients from other countries. While the total death rate (adjusted for baseline covariates mentioned in Table 4) at 2 years in the Chinese population was 6.9% versus 11.3% to 15.0% among patients from other countries, the rate for stroke was 3.8% versus 0.9% to 3.0% among patients from other countries, with the exception of Ukraine and Russia which had a higher age-adjusted rate for stroke. For reasons ill understood, the reported rates of coronary heart disease (CHD) as well as mortality due to CHD are low among the Chinese population, while the reported rates for stroke deaths are higher.14 In general the high stroke rates have been attributed to hypertension and high salt intake among the Chinese population.15,16 Thus while the 2-year event rates among the Chinese patients in our study can be partially attributed to their ethnicity, we believe the lower risk of Chinese patients at admission could also have played a major role as indicated by the lower prevalence of diabetes, congestive heart failure and prior MI at admission (Table 4). The second notable difference was the low risk of stroke among Indian patients, probably due to their being younger as compared to patients from other participating countries (mean age of 57.3 years v. mean ages ranging from 60.7-64.1 years.)

We explored the relationship of in-hospital angiography with long-term outcomes by grouping patients from countries into various categories with different angiographic rates during the first 7 days after admission. There was no statistically significant difference in the rates of death and MI across countries with varying rates of angiography. However, the rates of refractory angina and the composite of death, MI and refractory angina was inversely related to the rates of angiography, with higher rates among countries with the lowest angiographic rates. Our results are consistent with a pooled analysis of all the large trials, which indicates only a modest reduction in the composite of death and MI (RR=0.88; 95% CI=0.78-0.99) but a more marked reduction in refractory angina with an invasive strategy compared to a more conservative strategy in patients with NSTEMI ACS.18 Three recent trials reported their primary outcomes as composites of death and MI with either rehospitalization or refractory
angina\textsuperscript{18-22}. Of these three trials only the FRISC 2 trial has reported independent mortality benefit of invasive strategy at 1 year.\textsuperscript{21} In all the three trials refractory angina or rehospitalization for unstable angina was the outcome that showed the greatest reductions. This benefit of reduction in refractory angina was consistent across all these trials despite the heterogeneity with respect to the risk of death and MI and differing rates of use of co-therapies such as glycoprotein (Gp) IIb/IIIa inhibitors. Though the use of Gp IIb/IIIa inhibitors was likely to be lower in our registries as compared to clinical trials, a remarkable similarity was observed in the direction of outcomes in our registry compared to clinical trials, among patients undergoing in-hospital angiography. Also, in both the FRISC 2 and the TACTICS trial the definitions of MI utilized different thresholds between the invasive and conservative arms, which could artifically decrease the rates of MI in the conservative arm.\textsuperscript{18} Finally the patients, physicians (operator skills) and settings in clinical trials may be 'different' in many respects from real world situation. For example, subgroup analysis suggests that the benefits seen in clinical trials from an invasive strategy are confined to high-risk patients. In contrast, previous analysis from our registry indicated that interventions are mainly used among low risk patients.\textsuperscript{3} While only experienced operators participate in trials generally, in a registry, no effort is made to select operators who are experienced. In this respect the registry is a better indicator of routine practice in a range of participating hospitals. Despite these potential differences, the overall consistency of the findings from our registry, as compared with other trials is reassuring. The high long-term event rates emphasize the need for novel approaches and risk factor modification to reduce long-term risk.

**Limitations:** There are a few limitations to our study, which are common to most registries. First, the hospitals chosen were not necessarily the random samples of all hospitals in a given country. The hospitals chosen were mainly located in large urban centers and volunteered to participate in the study. It is possible that if smaller hospitals and rural centers had been included in countries such as India (which will include more patients with lower socioeconomic status) there might have been an even higher mortality and morbidity rates. However, given the much higher prevalence of CHD in urban settings compared to rural areas, this may be less important on a countrywide basis. Secondly, the multivariate adjustments that we have carried out in our analysis may not account for all the baseline differences among individual patients. However, we did collect several key baseline data that are predictive of outcomes. Third, the loss to follow-up was high especially among several centers from India. Therefore we carried out a sensitivity analysis (with adjustment by country) comparing the baseline characteristics and outcomes between patients from all participating centers and patients from those centers that had more than 80% follow-up at 2 years. This analysis did not reveal any differences between the two groups both for the baseline variables and outcomes, thereby suggesting that loss to follow-up are unlikely to affect our conclusions. Further, analysis of the overall data after excluding patients from India did not alter the overall conclusions. Fourth, the data of the two registries were collected 4 years apart, during which period, the practice patterns have changed with increasing use of Gp IIb/IIIa inhibitors and clopidogrel in many countries. Gp IIb/IIIa inhibitors have a modest long-term effect (i.e. 9% RRR at 30 days for death),\textsuperscript{23} whereas clopidogrel produces a moderate effect (i.e. 20% RRR at 1 year for the composite of death, MI and stroke).\textsuperscript{24} Even taking this into account, the 2-year event rates are likely to be still high in patients with ACS. This emphasizes the need for strategies targeted at reducing long-term risk in patients with NSTEMI ACS.

**Conclusions:** Despite differences in patient characteristics, varying economic circumstances, practice patterns and rates of interventions, between a large number of countries, both short- and long-term mortality risks (with the exception of India and China) among patients hospitalized for NSTEMI ACS were similar. The chief differences in outcomes between these countries were the lower rates of refractory angina, with no major differences in death and MI. The high 2-year event rate even in patients undergoing invasive strategies emphasizes the need for risk factor modification\textsuperscript{13} and developing new approaches to lower this risk.

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**Contributors:** Dorairaj Prabhakaran developed the concept of this paper and was primarily responsible for writing the paper. Salim Yusuf initiated both the registries, supervised their overall conduct and contributed in writing and revising the paper. All other authors facilitated and supervised the study in their own country and commented on the drafts of the protocol and the paper.

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References


Non-Invasive Assessment of Arterial Stiffness by Pulse-Wave Velocity Correlates with Endothelial Dysfunction

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Background: Pulse-wave velocity is the speed of the blood pressure wave to travel a given distance between two sites of the arterial system and is determined by the elasticity, wall thickness and blood density. Pulse-wave velocity correlates well with arterial distensibility and stiffness and is a useful non-invasive index to assess arteriosclerosis. Arterial endothelial dysfunction is one of the key early events in atherogenesis, preceding structural atherosclerotic changes. This study sought to establish the correlation of non-invasive estimation of arterial wall stiffness by pulse-wave velocity and its association with endothelial dysfunction in subjects at higher risk for arteriosclerosis.

Methods and Results: A total of 102 subjects (60 males and 42 females, mean age 51 years), including those with hypertension (n=39), type 2 diabetes mellitus (n=26), concomitant type 2 diabetes mellitus and hypertension (n=29) and primary dyslipidemia without diabetes mellitus and hypertension (n=8). Pulse-wave velocity was measured by the Vascular Profiler 1000 (VP-1000) waveform analysis and vascular evaluation system, an automated, non-invasive, screening device. Endothelial function was assessed by flow-mediated dilation of the brachial artery. The brachial-artery diameter was measured on B-mode ultrasound images, with the use of a 7.0 MHz linear-array transducer. Mean brachial artery pulse-wave velocity on the right extremity was 1699 cm/s and on the left 1694 cm/s. Mean flow-mediated dilation in the study subjects was 3.6±8.4%. Mean brachial artery pulse-wave velocity in the right and left extremities and the higher value of brachial artery pulse-wave velocity of the two extremities showed a negative and significant correlation with flow-mediated dilation of the brachial artery (correlation coefficient r = -0.32, p = 0.001; r = -0.40 p < 0.0001; r = -0.37, p = 0.001, respectively). Mean heart-brachial pulse-wave velocity also showed a negative and significant correlation with flow-mediated dilation of the brachial artery (r=-0.23, p = 0.022). Mean arterial stiffness was 36.2 ± 22%. Arterial stiffness in the right extremity and the higher value of the two extremities showed a negative and significant correlation with flow-mediated dilation of the brachial artery (correlation coefficient r = -0.31, p = 0.002; r = -0.32, p = 0.001, respectively).

Conclusions: Increased values of pulse-wave velocity reflecting upon arterial stiffness show an excellent correlation with reduced values of brachial artery flow-mediated dilation. We propose that the non-invasive modalities of estimation of the pulse-wave velocity and endothelial function estimation by flow-mediated dilation of brachial artery be used in clinical practice in assessment of pre-clinical atherosclerosis. (Indian Heart J 2005; 57: 226–232)

Key Words: Endothelial dysfunction, Flow-mediated dilation, Pulse-wave velocity

Arterial stiffness measurement could serve as an important tool in identifying patients at risk of cardiovascular disease, and the ability to identify these patients would lead to better risk stratification and earlier and more effective preventive therapy. Pulse-wave velocity (PWV) is the speed of the blood pressure wave to travel a given distance between two sites of the arterial system. PWV is determined by the elasticity and other properties of the artery (i.e. wall thickness and blood density). PWV correlates well with arterial distensibility and stiffness and is a useful non-invasive index to assess arteriosclerosis. High velocity corresponds to higher arterial stiffness and lower distensibility.

Arterial endothelial dysfunction is one of the key early events in atherogenesis, preceding structural atheros-
cerebrovascular changes. It is also important in the late stages of obstructive atherosclerosis, predisposing to constriction and/or thrombosis. Endothelial function can be measured in coronary arteries and in the periphery by measuring vasomotor function after intra-arterial infusion of pharmacological substances, which enhance the release of endothelial nitric oxide. The disadvantage of this method is its invasive nature, which generally makes it unsuitable for studies involving asymptomatic subjects. For this reason, non-invasive tests of endothelial function have been developed. In the most widely used of these, an ultrasound-based method described by Celermajer et al., arterial diameter is measured in response to shear stress, which causes endothelium-dependent dilation.

The present study aims at the non-invasive estimation of arterial wall stiffness by PWV and its correlation with endothelial dysfunction in high-risk subsets in a western India population.

Methods

A total of 102 outpatients belonging to the category of increased atherosclerosis risk were included in the study. Informed consent was obtained from the study subjects. Subjects included those with hypertension (n=39), type 2 diabetes mellitus (n=26), concomitant type 2 diabetes mellitus and hypertension (n=29) and primary dyslipidemia without diabetes mellitus and hypertension (n=8). Coronary artery disease (CAD) was diagnosed along with clinical presentation with electrocardiography, symptom-limited exercise stress test, Doppler echocardiography, and coronary angiography documentation in 12 subjects.

PWV velocity was measured by the Vascular Profiler 1000 (VP-1000) waveform analysis and vascular evaluation system, an automated, non-invasive, screening device for early detection and quantification of atherosclerosis (Colin Corporation, Japan; marketed by Wipro GE Medical Systems Pvt Ltd).

The VP-1000 Vascular Profiler recorded electrocardiogram (ECG), phonocardiogram (PCG) and pulse volume recording (PVR) simultaneously and calculated time delay of the pulse to obtain pulse-wave transmit time (PTT). Distance of each segment was automatically calculated based on the patient’s height by the Vascular Profiler and was derived from statistical studies.

Brachial artery pulse-wave velocity (baPWV) was calculated as the time delay from ascending point of right brachial PVR to ascending point of each ankle PVR. PWV was calculated using the following formula:

$$PWV = \frac{\text{Distance between 2 sites}}{\text{Pulse-wave transmit time (PTT)}}$$

Many modalities, both invasive and non-invasive, have been applied to the assessment of arterial distensibility in vivo. Non-invasive modalities fall into three groups: (i) measuring PWV, (ii) relating change in diameter of an artery to distending pressure, and (iii) assessing arterial pressure waveforms. PWV increases with stiffness and is measured by the Moens-Korteweg equation:

$$PWV^2 = \frac{Eh}{2pr^2}$$

where h = arterial thickness, R = internal radius and p= blood density.

Arterial stiffness can be readily calculated by the Vascular Profiler, based on the percentage of variation in the value of the baPWV from the expected age-matched value. Values ≤ 12% (1SD) are normal and > 36% (2SD) are considered in the higher risk zone. Heart-brachial pulse-wave velocity (hbPWV) values < 600 cm/s and heart-ankle pulse wave velocity (haPWV) values < 900 cm/s are considered normal. Mean arterial pressure (% MAP) values ≤ 50% are normal and > 50% indicative of brachial-artery arteriosclerosis. Normal range of upstroke time (UT) is between 120-160 ms. UT < 120 ms is indicative of arterial sclerosis and > 160 ms of arterial stenosis. Ankle-brachial index (ABI) range between 0.9 and 1.3 indicates normal compliant arteries. There is a high correlation between baPWV and PWV from aorta. Aortic PWV of 900 cm/s is defined as a threshold value for high risk of cardiovascular disease in clinical studies, and has excellent correlation with baPWV value of 1400 cm/s as validated further by an in-house study by Colin Corporation.

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

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

Flow-mediated dilations were calculated, and the average results of the two observations were recorded. Inter-observer variability was 0.003 cm and intra-observer variability was 0.004 cm. This method is accurate and reproducible for measuring small changes in arterial diameter with low rates of inter-observer error in measuring FMD. Flow-mediated dilations were calculated, and the average results of the two observations were recorded. Inter-observer variability was 0.003 cm and intra-observer variability was 0.004 cm. This method is accurate and reproducible for measuring small changes in arterial diameter with low rates of inter-observer error in measuring FMD. FMD was analysed as the percent change from baseline to hyperemia. Operator for the brachial artery FMD to assess endothelial function was unaware of the results of PWV throughout the entire study.

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

**Statistical analysis:** Data collected was managed on Excel spreadsheet. One-way ANOVA or students t test was used as appropriate to compare the mean of the continuous variables. Chi-square test was used for comparison. Pearson’s correlation coefficient was used to look for association amongst the baPWV, arterial stiffness and brachial artery FMD. All analyses were performed with the SPSS Version 10 and p values <0.05 were considered significant.

**Results**

Baseline characteristics of the subjects and the lipid profile are shown in Table 1. Mean age was 51 years. Mean duration of diabetes was 3 years and of hypertension 4.6 years. Subjects included 60 males and 42 females. Mean baPWV in the right extremity was 1699 cm/s and in the left 1694 cm/s, as the study involved a population at a higher risk with type 2 diabetes mellitus, hypertension and dyslipidemia. In an earlier pilot study, baPWV value in normal, healthy individuals was < 1300 cm/s in either extremity. On lipid estimation, mean LDL-c value was 126±37 mg/dl, HDL-c 44±12 mg/dl, total cholesterol; HDL-c ratio 5.1±3.2 and triglycerides 139±71 mg/dl. Mean systolic and diastolic blood pressure of the study group was 133±19 mmHg and 80±10 mmHg, respectively. Mean pulse pressure was 54±13 mmHg.

**Table 1. Baseline characteristics of the study group**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Mean</th>
<th>Median</th>
<th>Standard deviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>51.1</td>
<td>49.0</td>
<td>10.1</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>67.4</td>
<td>65.5</td>
<td>11.3</td>
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<tr>
<td>Height (cm)</td>
<td>160.3</td>
<td>160.0</td>
<td>8.6</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>26.0</td>
<td>25.3</td>
<td>4.5</td>
</tr>
<tr>
<td>FBS (mg/dl)</td>
<td>127</td>
<td>117</td>
<td>50</td>
</tr>
<tr>
<td>PPBS (mg/dl)</td>
<td>180</td>
<td>177</td>
<td>64</td>
</tr>
<tr>
<td>Cholesterol (mg/dl)</td>
<td>197</td>
<td>193</td>
<td>41</td>
</tr>
<tr>
<td>LDL-c (mg/dl)</td>
<td>126</td>
<td>126</td>
<td>37</td>
</tr>
<tr>
<td>HDL-c (mg/dl)</td>
<td>44</td>
<td>42</td>
<td>12</td>
</tr>
<tr>
<td>TC:HDL ratio</td>
<td>5.1</td>
<td>4.7</td>
<td>3.2</td>
</tr>
<tr>
<td>TG (mg/dl)</td>
<td>139</td>
<td>121</td>
<td>72</td>
</tr>
<tr>
<td>VLDL (mg/dl)</td>
<td>33</td>
<td>29</td>
<td>16</td>
</tr>
</tbody>
</table>

BMI: body mass index; FBS: fasting blood sugar; PPBS: post-prandial blood sugar; LDL-c: low-density lipoprotein cholesterol; HDL-c: high-density lipoprotein-cholesterol; TC: total cholesterol; TG: triglycerides; VLDL: very low-density lipoprotein.
Descriptive statistics of the comprehensive vascular profile data is shown in Table 2. The mean baPWV values in the right and left extremity were 1699 mm/s and 1694 mm/s respectively. Arterial stiffness values were similar in the right and left extremity (36.2±22%). Baseline mean value of brachial artery diameter was 4.5± 0.7 mm and during the phase of hyperemia 4.67±0.7 mm. The mean FMD in the study subjects was 3.6±8.4%. The mean FMD

Table 2. Vascular profile readings of the study group

<table>
<thead>
<tr>
<th></th>
<th>Mean</th>
<th>SD</th>
<th>Interquartile range</th>
<th>25th Percentile</th>
<th>50th Percentile</th>
<th>75th Percentile</th>
</tr>
</thead>
<tbody>
<tr>
<td>FMD-Pre(mm)</td>
<td>4.52</td>
<td>0.7</td>
<td>1.17</td>
<td>3.98</td>
<td>4.39</td>
<td>5.15</td>
</tr>
<tr>
<td>FMD-Post(mm)</td>
<td>4.67</td>
<td>0.7</td>
<td>0.98</td>
<td>4.22</td>
<td>4.66</td>
<td>5.20</td>
</tr>
<tr>
<td>rb MAP(%)</td>
<td>52.5</td>
<td>2.8</td>
<td>5</td>
<td>50</td>
<td>53</td>
<td>55</td>
</tr>
<tr>
<td>raMAP(%)</td>
<td>38.5</td>
<td>3.7</td>
<td>5</td>
<td>36</td>
<td>38.5</td>
<td>41</td>
</tr>
<tr>
<td>rbUTMS (ms)</td>
<td>146</td>
<td>18</td>
<td>15</td>
<td>135</td>
<td>144</td>
<td>150</td>
</tr>
<tr>
<td>laMAP (%)</td>
<td>37.9</td>
<td>3.6</td>
<td>4</td>
<td>36</td>
<td>38</td>
<td>40</td>
</tr>
<tr>
<td>lbUTMS (ms)</td>
<td>144.4</td>
<td>16.9</td>
<td>16</td>
<td>134</td>
<td>141</td>
<td>150</td>
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<td>ABIR</td>
<td>1.1</td>
<td>0.1</td>
<td>0.13</td>
<td>1.0</td>
<td>1.1</td>
<td>1.11</td>
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<tr>
<td>ABIL</td>
<td>1.1</td>
<td>0.1</td>
<td>0.11</td>
<td>1.0</td>
<td>1.1</td>
<td>1.11</td>
</tr>
<tr>
<td>hbPWV (cm/s)</td>
<td>354</td>
<td>71</td>
<td>80</td>
<td>315</td>
<td>344</td>
<td>395</td>
</tr>
<tr>
<td>halPWVR (cm/s)</td>
<td>899</td>
<td>152</td>
<td>198</td>
<td>789</td>
<td>880</td>
<td>987</td>
</tr>
<tr>
<td>halPWVL (cm/s)</td>
<td>884</td>
<td>193</td>
<td>201</td>
<td>788</td>
<td>872</td>
<td>989</td>
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<tr>
<td>baPWVR (cm/s)</td>
<td>1699</td>
<td>355</td>
<td>477</td>
<td>1430</td>
<td>1682</td>
<td>1907</td>
</tr>
<tr>
<td>baPWVL (cm/s)</td>
<td>1694</td>
<td>398</td>
<td>466</td>
<td>1422</td>
<td>1699</td>
<td>1888</td>
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<tr>
<td>SBP(mmHg)</td>
<td>133</td>
<td>19</td>
<td>21</td>
<td>119</td>
<td>132</td>
<td>140</td>
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<tr>
<td>MBP(mmHg)</td>
<td>100</td>
<td>14</td>
<td>17</td>
<td>91</td>
<td>98</td>
<td>108</td>
</tr>
<tr>
<td>DBP(mmHg)</td>
<td>80</td>
<td>10</td>
<td>13</td>
<td>72</td>
<td>78</td>
<td>85</td>
</tr>
<tr>
<td>AS-R (%)</td>
<td>36.2</td>
<td>22</td>
<td>33</td>
<td>17</td>
<td>35</td>
<td>50</td>
</tr>
<tr>
<td>AS-L (%)</td>
<td>36.2</td>
<td>22</td>
<td>30.3</td>
<td>20</td>
<td>34.5</td>
<td>50.3</td>
</tr>
<tr>
<td>FMD-Cha (%)</td>
<td>3.7</td>
<td>8.4</td>
<td>9.7</td>
<td>-1.55</td>
<td>3.5</td>
<td>8.2</td>
</tr>
</tbody>
</table>

FMD-Pre: flow-mediated dilation–pre-brachial artery diameter; FMD-Post: flow-mediated dilation–post-brachial artery diameter; rbMAP: right brachial mean arterial pressure; raMAP: right ankle mean arterial pressure; rbUTMS: left brachial artery upstroke time in milliseconds; laMAP: left ankle mean arterial pressure; lbUTMS: left ankle mean arterial pressure; ABIR: ankle brachial index–right; ABIL: ankle brachial index–left; hbPWV: heart-brachial pulse-wave velocity; halPWVR: heart-ankle pulse-wave velocity–right; halPWVL: heart-ankle pulse-wave velocity–left; baPWVR: brachial-ankle pulse-wave velocity–right; baPWVL: brachial-ankle pulse-wave velocity–left; SBP: systolic blood pressure; MBP: mean blood pressure; DBP: diastolic blood pressure; AS-R: arterial stiffness—right; AS-L: arterial stiffness—left; FMD-Cha: flow-mediated diameter-change in arterial diameter from pre to post.

Fig. 1. Correlation of the baPWV in right extremity with FMD of the brachial artery (r = -0.32, p = 0.001).

baPWV: brachial-ankle pulse-wave velocity; FMD: flow-mediated dilation

Fig. 2. Correlation of baPWV in the extremity with higher value and FMD of the brachial artery (r = -0.37 p = 0.001).

baPWV: brachial-ankle pulse-wave velocity; FMD: flow-mediated dilation
value of healthy volunteers enrolled for the prior reproducibility study was 12.6%.

Mean baPWV in the right and left extremities and the higher value of baPWV of the two extremities showed a negative and significant correlation with FMD of the brachial artery (correlation coefficient $r = -0.31$, $p = 0.002$; $r = -0.32$, $p = 0.001$, respectively) as shown in Figs 4 and 5. Mean hbPWV also showed a negative and significant correlation with FMD of the brachial artery ($r = -0.23$, $p = 0.022$) as shown in Fig. 3. Arterial stiffness in the right extremity and the higher value of the two extremities showed a negative and significant correlation with FMD of the brachial artery (correlation coefficient $r = -0.31$, $p = 0.002$; $r = -0.32$, $p = 0.001$, respectively) as shown in Figs 4 and 5. Correlation of pulse pressure (PP) with FMD was not statistically significant despite a positive trend as shown in Fig. 6.

**Discussion**

Brachial-ankle pulse wave velocity is a non-invasive and simple method of measuring arterial stiffness and an independent predictor of cardiovascular mortality in some lifestyle-related diseases. The validity and reproducibility...
of baPWV measurements are considerably high, and this method seems to be an acceptable marker reflecting vascular damages.\textsuperscript{13}

Flow-mediated dilation of the brachial artery and PWV has been shown to be good surrogate marker of clinical atherosclerosis.\textsuperscript{14} We determined the interrelation between these measurements in the present study. There was a statistically significant correlation between PWV and FMD. Increased values of PWV indicate an increased arterial stiffness in subjects with risk factors, coexisting with endothelial dysfunction. These results reveal vascular dysfunction and potentially increased risk for development of atherosclerosis. In a study of 135 subjects to determine the inter-relationship between FMD, carotid intimal medial thickness (IMT) and PWV, each of the worst tertiles was associated with a higher prevalence of atherosclerotic disease and carotid plaques compared to the other tertiles. Subjects with the worst tertiles of all three measurements had a markedly higher prevalence of atherosclerotic disease and carotid plaques.\textsuperscript{14} The clinical application of baPWV in patients with CAD has been recently evaluated. High baPWV was shown to be a good independent predictor for the presence of CAD.\textsuperscript{15}

Pulse wave velocity, determined by brachial ankle arterial pressure wave measurements correlates well with carotid femoral PWV as shown in a recent study \( r = 0.755, p < 0.00001 \).\textsuperscript{16} Age, systolic blood pressure, and the stage of hypertensive organ damage are the major determinants of baPWV. baPWV values beyond 1400 mm/s are considered abnormal.

Ultrasonography is a reliable and accurate technique to determine FMD dilation in the superficial arteries. Reproducibility of the FMD determination is best in the brachial artery in healthy subjects and in patients with progressed atherosclerosis. B-mode ultrasound scan including brachial artery FMD may be of clinical value in the screening of patients with CAD.\textsuperscript{17,18} An important inference from the current study in the absence of previous information from India was the close correlation of an automated technique of PWV measurement with a non-automated technique of endothelial function estimation of brachial artery by FMD. This has implications for wider application of the technique in assessment of pre-clinical atherosclerosis.

\textbf{Conclusions:} Pulse wave velocity measured by this simple, non-invasive method is suitable for screening vascular damages in a large population. Increased values of PWV reflecting upon arterial stiffness show an excellent correlation with reduced values of brachial artery FMD, a surrogate clinical marker of endothelial dysfunction. We propose that the non-invasive modalities of estimation of PWV and endothelial function estimation of brachial artery by FMD be used in clinical practice in assessment of pre-clinical atherosclerosis.

\textbf{Acknowledgements}

We thank A Karthik and DP Singh for statistical analysis.

\textbf{References}

intima-media thickness and pulse wave velocity. Atherosclerosis 2004; 173: 13–18
Effect of Mechanical Coronary Reperfusion on QT Dispersion in Acute Coronary Syndrome

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MS Ramaiah Medical College, Bangalore, and Department of Psychiatry and Behavioral Neurosciences, Wayne State University School of Medicine, Detroit, USA

Background: The time for cardiac repolarization and homogeneity of repolarization on surface electrocardiogram is denoted by QT interval and QT dispersion, respectively. Numerous studies suggest an association between an increased dispersion of the QT interval obtained from the 12-lead electrocardiogram and increased risk for serious cardiac events.

Methods and Results: We evaluated the effect of thrombolysis and percutaneous transluminal coronary angioplasty on QT dispersion in acute coronary syndrome in 45 patients (age: 55±6 years). QT dispersion was calculated on admission and immediately after the procedure (thrombolysis and percutaneous transluminal coronary angioplasty). There was a significant decrease in QT dispersion after percutaneous transluminal coronary angioplasty (75±21 ms to 38±20 ms, p<0.0001). In a subset of these patients with acute myocardial infarction (n=29) who underwent thrombolysis, QT dispersion decreased only marginally (78±19 ms to 67±22 ms, p<0.05). Even in this subgroup, there was a significant decrease in QT dispersion after percutaneous transluminal coronary angioplasty (to 37±22 ms, p<0.0001). In patients with unstable angina (n=16), there were similar significant changes after percutaneous transluminal coronary angioplasty (p<0.0001).

Conclusions: These results suggest a highly significant decrease in QT dispersion after percutaneous transluminal coronary angioplasty compared to a less significant decrease after thrombolysis, which may have clinical implications. (Indian Heart J 2005; 57: 233–236)

Key Words: Thrombolysis, Percutaneous transluminal coronary angioplasty, QT dispersion

The QT interval on the surface electrocardiogram (ECG) reflects the time for ventricular repolarization. There is substantial evidence suggesting an increase in QT dispersion in some cardiac diseases, especially in association with serious arrhythmias.1,2 QT dispersion is defined as the difference between the maximum and minimum QT interval obtained from the 12-lead ECG.3 QT dispersion reflects the homogeneity of ventricular repolarization. Since a significant number of patients die suddenly following myocardial infarction (MI), measuring QT dispersion appears to be one of the simplest non-invasive ways to predict a significant risk for sudden death among these patients. Some studies4-8 have shown that coronary angioplasty decreases QT dispersion. In this study, we investigated the effect of thrombolytic therapy and percutaneous transluminal coronary angioplasty (PTCA) on QT dispersion in patients with acute coronary syndrome (ACS), with clinical conditions ranging from unstable angina to acute MI.

Methods

This study was performed over a period of two years. The study population included 45 patients (38 males, 7 females) with a diagnosis of ACS (mean age: 55±6 years). They were all in sinus rhythm on admission. Patients with arrhythmias and on antiarrhythmic medication that affect the QT interval were excluded from the study. All the patients were interviewed; a detailed history was taken and physical examination was performed to rule out any other medical problems. A 12-lead ECG was obtained on admission and one hour after the procedure. About 25% of patients with unstable angina (UA) had ST-T changes on admission prior to the procedure. A 12-lead ECG was obtained after thrombolytic therapy in acute MI patients and another ECG was also obtained following PTCA.
Our study cohort (n = 45) had dyslipidemia in 60% of the patients, hypertension in 57.7%, diabetes mellitus in 51.1%, physical inactivity in 49%, smoking in 40%, obesity in 31% and a family history of coronary artery disease (CAD) in 27%. All the women were post-menopausal and had diabetes. Among these 45 patients, 62.2% presented with ST elevation myocardial infarction (STEMI), 35.6% with UA, and 2.2% with non-STEMI (NSTEMI). In patients with acute MI (n = 29), 59% presented with anterior wall myocardial infarction (AWMI), 21% with inferior wall myocardial infarction (IWMI), 17% with IWMI+right ventricular myocardial infarction (RVMI), and 3% with IWMI+anterior wall MI.

Sixty-three percent of the patients presenting with ACS had no complications, whereas 24% had recurrent angina, 7% hypotension, 4% left ventricular failure (LVF) and 2% had recurrent angina and LVF.

Coronary angiography revealed single vessel disease in 77.8%, double-vessel disease in 13.3%, and triple vessel disease in 8.9%. The commonest artery involved was left anterior descending (LAD) (in 49%).

Among the patients who underwent PTCA, there was single vessel involvement in 94%; [LAD: 49%, left circumflex (LCx): 27%, right coronary artery (RCA): 18%] and multivessel involvement in 6%. Forty-three patients underwent balloon angioplasty with stenting and two patients, plain balloon angioplasty. Eighty percent of the patients were on beta-blockers and 60% on angiotensin-converting enzyme (ACE) inhibitors. All patients also received antiplatelet medication (aspirin and clopidogrel). Fourteen patients received heparin and glycoprotein (Gp) IIb/IIIa inhibitors (abciximab) as adjunctive therapy and 31 patients only heparin. All the patients with STEMI received thrombolysis within 10-15 min of admission. Once, the patients became stable, they were taken up for PTCA 3±2 days (range 1-6 days) after the acute MI. The patients who had UA underwent PTCA within 1-3 days. Table 1 shows the results of QT dispersion for all subjects before and after thrombolysis and/or PTCA.

Overall, there was a significant decrease in QT dispersion, which was seen in 87% of those patients who underwent PTCA compared to 52% of the patients after thrombolysis. One patient had recurrent angina after the procedure due to acute coronary thrombosis, for which a reangioplasty was performed. This patient had QT dispersion values of 40, 20, 70 and 30 ms before the first PTCA, after the procedure, after recurrent angina and after the repeat PTCA, respectively. Reangioplasty significantly improved the patient’s condition. These data also illustrate the changes in QT dispersion associated with this patient’s condition at different time points. Changes in QT dispersion were seen in patients with normal ECG/echocardiographic findings as well as in those with abnormalities in ECG and echocardiogram.

**Responders versus non-responders to thrombolysis:**

The values of QTc dispersion before thrombolysis were 90±30 ms and 89±33 ms for the responders and non-responders, respectively. After thrombolysis, these values were 80±27 and 78±33 ms, respectively for these two groups. The pre-/post-thrombolysis comparisons showed a trend toward significance (p<0.05) for either group.

**Complications:** The major complication in the study was in-stent thrombosis in one patient. The minor complications included small hematoma and allergic drug reaction in one patient each.

### Table 1. Measures of QTc dispersion (ms) before and after PTCA and thrombolysis

<table>
<thead>
<tr>
<th></th>
<th>Pre-thrombolysis/Post-PTCA</th>
<th>Pre-PTCA</th>
<th>Post-thrombolysis</th>
<th>Post-PTCA</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>75±21</td>
<td>67±22</td>
<td>87±18</td>
<td>38±20</td>
<td>p&lt;0.05</td>
</tr>
<tr>
<td>Unstable angina</td>
<td>66±18</td>
<td>57±14</td>
<td>78±19</td>
<td>57±22</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>AMI (n=29)</td>
<td>78±19</td>
<td>67±22</td>
<td>95±17</td>
<td>57±16</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>IWMI (n=6)</td>
<td>93±18</td>
<td>37±14</td>
<td>109±17</td>
<td>39±13</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>RVMI (n=5)</td>
<td>109±17</td>
<td>36±7</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Comparisons relate to pre-PTCA to post-PTCA conditions:

- x p<0.05; x p<0.001; pre- and post-PTCA for sub-classification:
  x p<0.001; AMI: acute myocardial infarction; PTCA: percutaneous transluminal coronary angioplasty; AWMI: anterior wall myocardial infarction; IWMI: interior wall myocardial infarction; RVMI: right ventricular myocardial infarction.
Discussion

This study clearly demonstrates a significant decrease in QT dispersion after PTCA in patients with ACS. The most significant decrease in QT dispersion occurred mainly after PTCA but not after thrombolysis. This is important in the context of the fact that PTCA is generally associated with better clinical outcomes compared to thrombolytic therapy. To our knowledge, this is a new finding that has not been reported in an Indian cohort and is specially relevant since morbidity and mortality associated with ACS is higher in Asians compared to other races. Though the number of subjects is small in each subgroup of patients, in our study most significant change after PTCA was seen in IWMl and IWMl+RVMl patients (Fig. 1).

Franz and Zabel\(^9\) have discussed the issue of QT dispersion in detail and differentiated between the spatial difference in action potential duration mirrored in the various QT intervals and the variation in surface ECG measurements with different projections of a common ‘Q’ wave vector. They further suggested that new markers such as advanced ‘T’ wave loop variables may best reflect the abnormal repolarization on the surface ECG. The recent measures of temporal variability in QT variability in each lead might also yield valuable information along with the spatial variability of the QT intervals.\(^10\)

Future directions: It will be very important to determine whether pathology in different regions of the myocardium affects QT dispersion differentially and whether different treatment modalities will have different clinical outcome. It would also be desirable to include other measures such as QTc and temporal QT variability in different leads to examine these results more comprehensively. In this context, the role played by different kinds of anti-hypertensive drugs will also be of clinical significance.

Conclusions: Our findings suggest that QT dispersion is a reversible electrophysiological abnormality in a substantial number of patients with ACS and this abnormality decreases after reperfusion therapy. Also, PTCA decreases QT dispersion much more significantly than thrombolysis alone. However, large longitudinal studies will be required to show that this decrease in QT dispersion in the acute phase following reperfusion will translate into long-term favorable clinical outcome if the difference persists between thrombolysis and PTCA.

References


Fig. 1. Changes in QT dispersion in one patient before (a) and after (b) percutaneous transluminal coronary angioplasty.


Background: Longitudinal studies have revealed significant correlation between exaggerated blood pressure response to exercise and higher incidence of developing resting hypertension in future. Normotensive persons at high risk of developing systemic hypertension have greater cardiovascular reactivity to exercise.

Methods and Results: Our study compared the blood pressure response to treadmill exercise in normotensive offspring of the hypertensive parents (age 22±1.7 years, n=50; study group) with those of the normotensive parents (age 22±1.4 years, n=50; control group). The morphometric characteristics, resting, exercise (treadmill exercise with Bruce protocol) and recovery blood pressure values of all the subjects were recorded. The analysis showed that the difference in mean peak systolic blood pressure during exercise was the only statistically significant parameter in the study and control groups (188.52±25.16 mmHg and 178.56±14.96 mmHg, respectively, p<0.05). The number of hyperreactors (defined as peak systolic blood pressure > 200 mmHg during exercise) was significantly more in study group compared to control group (10 and 3 respectively). The mean resting systolic blood pressure of hyperreactors (126.46 + 8.49 mmHg) falls in the pre-hypertension category as designated by JNC VII. Also, their resting diastolic blood pressure, recovery blood pressure and body mass index were significantly higher as compared to normoreactors.

Conclusions: Our study showed that this response pattern could represent impairment in cardiovascular adjustment to exercise indicating a greater risk for development of resting hypertension in the future. Therefore there is a need for early lifestyle modifications to postpone/prevent development of hypertension. (Indian Heart J 2005; 57: 237–240)

Key Words: Treadmill testing, Prevention, Hypertension

Hypertension is an established major risk factor for coronary artery disease (CAD). Therefore, it seems prudent to identify the population at risk and to initiate lifestyle modification at an early stage for delaying or preventing the development of hypertension.

Persons with a parental history of hypertension are at a higher risk of development of this disorder. Elevated resting pressures within normal range (pre-hypertension) are also predictive of future hypertension. But the assessment of exercise blood pressure is more predictive. In our study, we compared resting, exercise and recovery blood pressure (BP) in young normotensive males with and without history of parental hypertension. We also attempted to study the difference in morphological characteristics between normoreactors and those with an exaggerated blood pressure response (peak systolic BP ≥ 200 mmHg) to exercise. This delineation should improve our understanding of the enhanced neurogenic drive thought to occur in the early stages of hypertension.

Methods

One hundred apparently healthy, normotensive males in the age group 19 to 25 years were randomly selected amongst the medical graduates of our Medical College, at Wardha. Those with hypertension, history of cardiac, pulmonary or renovascular disease, those on cardioactive drugs and having abnormal cardiac examination were excluded from the study. They were divided into study group and control group. The study group, consisting of 50 subjects, had a parental history of hypertension in either or both the parents. The control group, also consisting of 50 subjects, had normotensive parents. A written consent was taken from all the subjects after explaining the nature of test to them.
Medical history, physical examination and morphometric measurements of each subject was recorded. They were prepared for the treadmill test (TMT) in a standard recommended protocol. Detailed history was recorded in pre-decided proforma, covering baseline characteristic of all subjects like age, weight, height. Body mass index (BMI) was derived from weight and height.

All the subjects had a treadmill exercise test under the supervision of an experienced physician. TMT was performed on a motor-driven computerized treadmill. The inclination and speed of treadmill was calibrated according to Standard Bruce Protocol. While on TMT, peak exercise was defined as a point when the subject attained predetermined heart rate (220 - age in years) or symptoms, whichever was earlier.

**Blood pressure recording:** Blood pressure was recorded by a mercury sphygmomanometer in left arm at the level of heart by auscultatory method at rest, during standing, during the last minute of each stage of exercise, at peak exercise and during the third minute of recovery with the help of an assistant. The first and fifth Korotkoff's sounds were taken as systolic blood pressure and diastolic blood pressure, respectively.

**Statistical analysis:** Statistical analysis was performed on computer by (i) Student’s t test for comparing different variables in two groups, and (ii) Chi - square test for the same, (iii) One-way analysis of variance (ANOVA) for comparing variables in three groups, and (iv) Regression analysis, using Pearson's coefficient and multiple linear regression, to test the relationship between different independent variables and dependent variable. A p value < 0.05 was considered as significant.

**Results**

Subjects in our study were all males between age of 19-25 years. The mean height, weight and BMI in the two groups were comparable (p>0.5). Resting blood pressure, both systolic and diastolic in two groups were also comparable. (118.54 ±10.23 mmHg v. 119.16±8.75 mmHg, p>0.70 and 71.92± v. 7.79 mmHg v. 73.4±5.98 mmHg, p> 0.30, respectively) (Tables 1 and 2).

Blood pressure at rest and during exercise did not differ significantly in study group with either or both parents being hypertensive. Mean peak systolic blood pressure during exercise was significantly higher in study group (188.52±25.16 mmHg and 178.56±14.96 mmHg, p>0.01). However diastolic blood pressure during exercise was comparable in two groups (81.64±29.05 mmHg and 79.88±6.90 mmHg, p> 0.27) (Tables 3 and 4, Fig. 1).

### Table 1. Morphometric measurements and resting blood pressure in the two groups

<table>
<thead>
<tr>
<th>Variable</th>
<th>Study group (Parents hypertensive) (n=50)</th>
<th>Control group (Parents normotensive) (n=50)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>22±1.7</td>
<td>22±1.4</td>
<td>0.8981</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>170±8.6</td>
<td>168±8.4</td>
<td>0.3309</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>66.0±9.4</td>
<td>63.0±10.0</td>
<td>0.2518</td>
</tr>
<tr>
<td>Mean BMI (kg/m²)</td>
<td>22.4±3.46</td>
<td>22.60±2.98</td>
<td>0.2158</td>
</tr>
<tr>
<td>Resting systolic BP (mmHg)</td>
<td>118.54±10.23</td>
<td>119.16±8.74</td>
<td>0.7060</td>
</tr>
<tr>
<td>Resting diastolic BP (mmHg)</td>
<td>71.92±7.79</td>
<td>73.4±5.98</td>
<td>0.3026</td>
</tr>
</tbody>
</table>

BP: blood pressure; BMI: body mass index

### Table 2. Resting and exercise blood pressure (mmHg) according to parental hypertension

<table>
<thead>
<tr>
<th>Parental hypertension</th>
<th>Resting SBP</th>
<th>Resting DBP</th>
<th>Peak SBP</th>
<th>Peak DBP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parent hypertensive</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mother hypertensive</td>
<td>119.52±12.60</td>
<td>72.88±9.36</td>
<td>193.00±31.70</td>
<td>79.8±10.06</td>
</tr>
<tr>
<td>Father hypertensive</td>
<td>116.84±4.90</td>
<td>71.84±7.52</td>
<td>181.51±24.10</td>
<td>76.84±8.23</td>
</tr>
<tr>
<td>Both hypertensive</td>
<td>112.00±6.38</td>
<td>69.33±1.63</td>
<td>188.30±22.20</td>
<td>72.30±4.63</td>
</tr>
<tr>
<td>p value</td>
<td>0.4615</td>
<td>0.6318</td>
<td>0.3802</td>
<td>0.1707</td>
</tr>
</tbody>
</table>

SBP: systolic blood pressure; DBP: diastolic blood pressure

### Table 3. Blood pressure recordings (mmHg) during Treadmill exercise in two groups

<table>
<thead>
<tr>
<th>Blood pressure (mmHg)</th>
<th>Study group</th>
<th>Control group</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>G-1 Exercise SBP</td>
<td>157.00±19.80</td>
<td>147.00±14.83</td>
<td>0.3065</td>
</tr>
<tr>
<td>Peak SBP</td>
<td>188.52±25.16</td>
<td>178.56±14.96</td>
<td>0.0180</td>
</tr>
<tr>
<td>Peak DBP</td>
<td>81.64±9.05</td>
<td>79.88±6.90</td>
<td>0.2704</td>
</tr>
<tr>
<td>SBP during recovery</td>
<td>141.88±18.97</td>
<td>141.88±10.20</td>
<td>0.5130</td>
</tr>
<tr>
<td>DBP during recovery</td>
<td>74.00±8.84</td>
<td>74.56±5.58</td>
<td>0.0607</td>
</tr>
</tbody>
</table>

SBP: systolic blood pressure; DBP: diastolic blood pressure

### Table 4. Different variables in normo- and hyperreactors

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hypertensive response (n=11)</th>
<th>Normotensive response (n=87)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>22±2.11</td>
<td>21.87±4.42</td>
<td>0.0751</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>171.6±8.09</td>
<td>166.1±9.14</td>
<td>0.220</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>77.3±13.79</td>
<td>62.17±9.29</td>
<td>&lt;0.0003</td>
</tr>
<tr>
<td>BMI</td>
<td>26.70±4.5</td>
<td>22.49±4.61</td>
<td>&lt;0.0003</td>
</tr>
<tr>
<td>Resting SBP (mmHg)</td>
<td>126.4±28.49</td>
<td>117.65±29.11</td>
<td>0.004</td>
</tr>
<tr>
<td>Resting DBP (mmHg)</td>
<td>77.21±6.74</td>
<td>71.95±6.86</td>
<td>0.0099</td>
</tr>
<tr>
<td>BP during G-1 exercise (mmHg)</td>
<td>164.6±21.83</td>
<td>146.4±16.82</td>
<td>0.0003</td>
</tr>
<tr>
<td>Peak SBP (mmHg)</td>
<td>221.00±31.18</td>
<td>176.7±21.52</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>BP during recovery (mmHg)</td>
<td>86.00±7.25</td>
<td>74.48±6.41</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure

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**Fig. 1.** Distribution of mean blood pressure recordings in the two groups. BP: blood pressure; SBP: systolic blood pressure; DBP: diastolic blood pressure.
Mean maximum systolic pressure response [peak systolic blood pressure (SBP)-resting SBP] was significantly higher in study group compared to the control group (62.72±21.94 mmHg and 58.4±12.87 mmHg, p< 0.05).

During recovery phase, blood pressure in the two groups did not differ significantly (p>0.5). Hypertensive response was seen in a total of 13 patients, 10 in study group and 3 in control group (p<0.01). Weight and BMI were very significantly increased in hyperreactors than in normoreactors. This group also had significantly higher resting systolic and diastolic pressure (p< 0.001).

The difference in mean peak systolic blood pressure during exercise was the only parameter found to be significantly different in the two groups in our study (p<0.05). We tried to find out the relationship between peak systolic blood pressure (PSBP) and different subject variables by using Pearson's Moment correlation coefficient (r). In this univariate analysis it was observed that age in both the groups did not have significant correlation with PSBP (r=0.22, p<0.1 and r = - 0.1, p>0.1 in study and control groups respectively). This could be because the subjects in the study group were younger (19-25 years). However, BMI had a highly significant correlation with PSBP in both study and control groups (r= 0.41, p<0.01 and r=0.34, p<0.05, respectively).

Similarly, resting blood pressure (both systolic and diastolic) correlates significantly in both the study and control groups with PSBP (for resting SBP, r=0.53, p< 0.001, and r= 0.56, p <0.001, respectively and for resting DBP, r=0.54, p<0.001 and r=0.49, p< 0.001, respectively).

Multivariate analysis in all the 100 subjects was performed using multiple linear regression equation. The combined effect of age, BMI, and resting systolic and diastolic blood pressure was assessed on changes in PSBP during exercise. It was observed that among the four independent variables, increase in age could explain only 1.16% change in PSBP, while increase in BMI explained 15.91%, resting SBP 26.12% and DBP explained 23.17% changes in PSBP, respectively.

**Discussion**

Prevention of hypertension remains elusive, and efforts must be continued to make its primary prevention a realistic public health goal. Studies suggest that exaggerated blood pressure response to exercise in high-risk population correlates well with development of subsequent hypertension on long-term follow-up. In an attempt to identify forerunners of hypertension, we compared the blood pressure response to treadmill exercise in normotensive children of hypertensive and normotensive parents.

Our most important finding is that those with a family history of hypertension had a persistent elevation of blood pressure across several stages of treadmill exercise. Mean PSBP was found to be significantly high in study group (p< 0.05). Other studies have also come up with similar observations. Likewise, mean maximum SBP response (peak SBP-resting SBP) was also significantly higher in study group (p<0.05). Our observations match with other studies of similar design. However, Neutel et al. had opposite results, possibly due to older study population (55 years) in their study with likely left ventricular (LV) dysfunction. Various theories have been proposed for the exaggerated systolic blood pressure response to exercise in subjects with parental hypertension. Julius et al. suggested that those who have a positive family history of hypertension frequently exhibit hyperactive sympathetic nervous system (SNS). The consequences of SNS stimulation are peripheral vasoconstriction, an increase in heart rate, and a resultant increase in peripheral vascular resistance with rise in systemic blood pressure. Mehta et al. suggested that independent of the blood pressure levels, the subjects with parental hypertension have a reduced proximal and distal arterial compliance. The lower arterial compliance could have resulted in an exaggerated blood pressure response during exercise.

During recovery, mean blood pressure values did not differ significantly in two groups. These are consistent with the findings of other studies. However, some researchers found higher diastolic pressure during recovery in their study subjects. Hypertensive response defined as SBP > 200 mmHg during exercise was found in a total of 13 subjects. Out of these, 10 subjects were from study group while only 3 from control group (p< 0.01).

Defining hypertension has been, and still continues to be an evolving process. Recently, JNC VII suggested normal blood pressure as <120/80 mmHg. SBP between 120-139 mmHg and DBP between 80-89 mmHg has been classified as pre-hypertension. The mean SBP of hyperreactors (126.46±8.49 mmHg) in our study falls in pre-hypertension category. This recommendation will have impact on early identification of subjects at risk for lifestyle modifications. These subjects were also found to have significantly higher mean weight, BMI, and resting and recovery blood pressure values as compared to normoreactors. Thus, exaggerated blood pressure response to exercise could better reflect increase in the overall burden in the subjects genetically predisposed to develop hyper-
tension in the future.

This response pattern in high-risk group could represent a generally stable characteristic consisting of an impaired cardiovascular adjustment to exercise, which is not apparent at rest and maybe unmasked only during exercise. This may indicate a greater risk for development of hypertension in such subjects. Frequently, regular hemodynamic stress in high-risk subjects with exaggerated blood pressure response during exercise could constitute an additional risk factor for the development of LV hypertrophy and accelerated target organ damage. Thus, the concept of pre-hypertension may have an important impact on interpretation of resting blood pressure in high-risk group. Among the high-risk group, pre-hypertensives may be recommended to undergo exercise testing to assess their likelihood of exaggerated blood pressure response. On multivariate analysis resting blood pressure, DBP and BMI correlate well with PSBP on exercise. Age alone contributes very little to this blood pressure response. These findings in our studies are consistent with other studies.3,6,17

Conclusions: In our study, normotensive young adults of hypertensive parents showed significantly increased tendency for abnormal blood response to TMT. In addition to resting blood pressure recording, blood pressure response to TMT can be a good tool to stratify them further for future monitoring. Further, blood pressure in pre-hypertensive range at rest and high BMI are more likely to predict hypertensive response to TMT in these subjects. As for abnormal blood pressure response translating into future hypertension, long-term follow-up studies may provide the answer.

References
Predictors of Arrhythmic Events during Second Day Monitoring in Patients with Normal First Day Holter Recordings

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Department of Pacemaker and Electrophysiology, Rajaie Cardiovascular Medical and Research Center, and Iran University of Medical Sciences, Tehran, Iran

Background: The diagnostic yield of Holter monitoring in patients with syncope is variably reported to be between 6%-20%. This study was done to define predictors of arrhythmic events during the second day of Holter monitoring in patients whose first day Holter recording was normal.

Methods and Results: Two serial 24-hour Holter recordings were obtained in a consecutive series of 100 patients (49 patients with unexplained syncope and/or pre-syncope and 51 patients with palpitation). The age of patients was 53.4 ± 16.9 years and 51 were men. Seventy-six patients had underlying heart disease. Main electrocardiographic findings were found in 40 (40%) patients including non-sustained ventricular tachycardia in 19, sinus pause in 13, symptomatic bradycardia in 5, paroxysmal atrial fibrillation in 4, sustained supraventricular tachycardia in 2, and Mobitz type II second-degree atrioventricular block in 3 patients. Twenty-seven (27%) patients had 33 main electrocardiographic findings during the first day and 13 out of the remaining 73 patients (17.8%) had it during the second day of Holter recording. Presenting symptom (syncope/pre-syncope), age > 65 years, and male gender were significantly associated with increased likelihood of main electrocardiographic findings during the second day of Holter monitoring (p=006, 0.023, and 0.024, respectively). The risk of main electrocardiographic findings ranged from 5% in patients with one or no predictor to 35% in those with ≥2 predictors (OR=9.95, 95% CI=2.01-49.2, p=0.002).

Conclusions: Presenting symptom (syncope/pre-syncope), age > 65 years, and male gender increased the likelihood of main electrocardiographic findings during the second day of Holter monitoring. (Indian Heart J 2005; 57: 241–244)

Key Words: Syncope, Arrhythmia, Holter monitoring

Ambulatory electrocardiographic (Holter) monitoring is a widely used, non-invasive test for evaluation of patients with a wide variety of symptoms including syncope, pre-syncope and palpitation. The diagnostic yield of Holter monitoring in patients with syncope is variably reported to be between 6%-20%. In a study of Holter monitoring, symptoms correlated with arrhythmias in 4% of patients (leading to a diagnosis of arrhythmic syncope), and symptoms occurred without arrhythmias in 17%. In 79% of patients, either brief arrhythmias or no arrhythmias were found. However, arrhythmic syncpe cannot be excluded in these patients, because arrhythmias may be episodic. In these cases, other more invasive costly and time consuming procedures may be necessary to reach the diagnosis.

Increasing the duration of monitoring to 48 hours may not increase the yield for symptomatic arrhythmias. However, others have found the opposite. The present study was done to compare the diagnostic yield of 48-hour Holter monitoring with 24-hour Holter monitoring in patients with and without syncope and/or pre-syncope and define predictors of arrhythmic events during the second day of Holter monitoring in patients whose first day Holter recordings were normal.

Methods

Study population: Patients selected from those referred
to our arrhythmia clinic for investigation of syncpe, pre-syncope and/or palpitation constituted the study population. Patients were included if they had recurrent unexplained syncpe, one episode of syncpe associated with injury, pre-syncope or palpitation and gave written informed consent for two consecutive 24-hour Holter recordings. Before enrolment, detailed history was recorded and patients underwent clinical assessment, including postural blood pressure measurement, 12-lead electrocardiogram (ECG) and transthoracic echocardiography (TTE). The study was approved by our institution’s ethics committee.

**Holter recording:** Each patient underwent two serial 24-hours Holter recording (VISTA®, Novacor, France). During Holter recording, patients were asked to note the timing if any symptom occurred. To check for all possible arrhythmias, we used a full-disclosure method that allowed review of all 48 hours of ECG recording. A cardiologist, blinded to presenting symptom read the reports and ECG printouts of arrhythmias during symptomatic and asymptomatic episodes.

**End points:** The end point was a clinically significant main electrocardiographic findings (MEF) defined as non-sustained ventricular tachycardia (NSVT) ≥ 3 beats, sinus pause > 3 s, symptomatic bradycardia (heart rate < 30/min), paroxysmal atrial fibrillation, sustained supraventricular (heart rate > 150/min) or ventricular (heart rate > 100/min) tachycardia, Mobitz type II second or third degree atrioventricular block.

**Statistical analysis:** Variables are expressed as mean ± SD, and percentage. Differences in frequency of characteristics were assessed by unpaired *t* test for continuous variables and chi-square statistics (or Fisher’s exact test if necessary) for discrete variables. We used Mantel-Haenszel test to generate p value for the reported odds ratios. A two-tailed p value <0.05 was considered statistically significant. We used SPSS® 11.0 (SPSS Inc., USA) for data analysis.

**Results**

**Baseline characteristics:** One hundred consecutive patients with recurrent unexplained syncpe, one episode of syncpe associated with injury, pre-syncope (group 1, n=49) or palpitation (group 2, n=51) were included in the study. The mean age of patients was 53.4 ± 16.9 years and 51 were men. Table 1 shows the baseline characteristics of these patients.

**Table 1. Baseline characteristics of patients**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Group 1 (Syncope/Pre-syncope)</th>
<th>Group 2 (Palpitation)</th>
<th>p value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>54.6 ± 16.8</td>
<td>52.2 ± 17.0</td>
<td>0.48</td>
</tr>
<tr>
<td>Sex (male/female)</td>
<td>28/21</td>
<td>23/28</td>
<td>0.24</td>
</tr>
<tr>
<td>Underlying heart disease</td>
<td>35</td>
<td>41</td>
<td>–</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>19</td>
<td>18</td>
<td>–</td>
</tr>
<tr>
<td>Hypertensive heart disease</td>
<td>4</td>
<td>9</td>
<td>0.46</td>
</tr>
<tr>
<td>Valvular heart disease</td>
<td>4</td>
<td>9</td>
<td>–</td>
</tr>
<tr>
<td>Congenital heart disease</td>
<td>5</td>
<td>4</td>
<td>–</td>
</tr>
<tr>
<td>Dilated cardiomyopathy</td>
<td>1</td>
<td>1</td>
<td>–</td>
</tr>
<tr>
<td>Hypertrophic cardiomyopathy</td>
<td>2</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

*Two-tailed p value

**Symptoms during Holter recording:** Among 40 patients with 46 MEF, 9 (22.5%) had symptom correlation with index arrhythmia during Holter monitoring. Among these, pre-syncope, syncpe and palpitation happened in 3, 1 and 5 patients, respectively. Four (44%) of these episodes (2 NSVT, 1 each sinus pause and sinus bradycardia) happened on the first day and 5 (56%) on the second day (3 NSVT, 1 each sinus pause and sinus bradycardia) of Holter monitoring.

**Table 2. Major electrocardiographic findings during Holter monitoring**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Group 1 (n=49)</th>
<th>Group 2 (n=51)</th>
<th>p value*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(Syncope/Pre-syncope)</td>
<td>(Palpitation)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Day 1</td>
<td>Day 2</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-sustained ventricular tachycardia</td>
<td>5</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Sinus pause &gt; 3 s</td>
<td>3</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Symptomatic sinus bradycardia</td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Mobitz II atrioventricular block</td>
<td>2</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Paroxysmal atrial fibrillation</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Sustained supraventricular tachycardia</td>
<td>-</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>11</td>
<td>23</td>
</tr>
</tbody>
</table>

*Two-tailed p value, for comparison of second day results between group 1 and 2.
ECG findings: Forty-six MEFs were observed in 40 patients during 48-hour Holter recording. Table 2 summarizes MEF in these patients. The second day of Holter monitoring revealed additional 13 MEFs (17.8%) in 73 patients whose first day Holter monitoring was normal. The incremental diagnostic yield of the second day of Holter monitoring was largely confined to patients with syncope and/or pre-syncope (15%) compared to those with palpitation (2.8%) (p=0.002).

Underlying heart disease (UHD) was present in 23 of 27 (85%) patients whose first day Holter monitoring showed an MEF, and was comparable with those whose second day Holter revealed an MEF (11 of 13, 84.6%). Among 60 patients whose 48-hour Holter showed no MEF, 43 (72%) had UHD. Although there was a trend toward a higher incidence of UHD among patients with MEF, it failed to reach statistical significance (p=0.34).

Predictors of MEF during second day Holter: Table 3 shows the predictors of MEF during the second day of Holter recording. Presence of UHD did not predict MEF during the second day of Holter recording [odds ratio (OR): 2.02, 95% confidence interval (CI): 0.4 - 10.2, p = 0.34]. Presenting symptom (syncope and/or pre-syncope) was an important predictor of MEF during the second day of Holter recording (OR: 8.5, 95% CI: 1.2 – 62, p=0.006). Five out of 50 (10%) patients with age < 65 years and 8 out of 23 (34.8%) patients with age ≥ 65 years had an MEF during the second day of Holter recording (OR: 4.5, 95% CI: 1.23 – 16.4, p=0.023). Eleven out of 13 (85%) patients whose second day Holter showed an MEF, were male and two (15%) were female (OR:6.3, 95% CI:1.3 – 31.5, p=0.024).

The risk of arrhythmic events during the second day of Holter monitoring was correlated with the number of predictors (Table 4). The risk of MEF ranged from 5% in patients with one or no predictor to 35% in those with two or three predictors (OR: 9.95, 95% CI:2.01 - 49.2, p=0.002).

Discussion

The present study demonstrated that 48-hour Holter recording reveals more MEF compared to 24-hour Holter monitoring. This additional diagnostic yield was largely confined to those patients whose presenting symptom was syncope and/or pre-syncope. Male sex and age ≥ 65 years were additional predictors of MEF during the second day of Holter recording (Table 3). In addition, the risk of MEF during the second day of Holter monitoring was correlated with the number of predictors (Table 4).

Recently, Sarasin et al.8 created a risk score for predicting arrhythmia in patients with unexplained syncope. They developed a risk score in a cohort of 175 patients with unexplained syncope and validated it in another group of 269 patients with unexplained syncope. They found that abnormal 12-lead ECG on presentation, history of heart failure and age > 65 years predict arrhythmia in these patients. The risk of arrhythmia ranged from 6% in patients with one risk factor to 41% and 60% in those with two and three risk factors, respectively.

In our study, presence of UHD was not associated with MEF during the second day of Holter recording. To the contrary, Bass et al.5 have suggested that presence of UHD is a predictor of MEF during Holter recording longer than 24 hours (OR: 2.2). The difference could be explained by different patient populations. While they studied patients with syncope we also included a control group of patients with palpitation without syncope but with the same prevalence of UHD (Table 1). On the other hand, although we reached to a comparable unadjusted OR (2.02), the confidence interval was wide and included the range below 1 with p value of 0.34. Adjustment for age and sex further attenuated the effect of UHD (adjusted OR:1.2, 95% CI : 0.45 - 3.2, p=0.71).

The overall diagnostic yield of 48-hour Holter monitoring for MEF in our cohort reached 41% (42.8% in group 1 and 49% in group 2). Although the reported diagnostic yield of Holter monitoring varies widely (6%-20%),1 studies with comparable patient population gave similar results.9 Finally, our data confirmed findings of Kinlay et al.10 and showed that contrary to patients whose presenting symptom was syncope and/or pre-

<p>| Table 3. Predictors of electrocardiographic finding on second day Holter recording |
|-----------------|-----------------|-----------------|-----------------|</p>
<table>
<thead>
<tr>
<th>Variables</th>
<th>Odds ratio</th>
<th>Confidence interval</th>
<th>p value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presenting symptom (Syncope/Pre-syncope)</td>
<td>8.5</td>
<td>1.2 – 62</td>
<td>0.006</td>
</tr>
<tr>
<td>Age ≥ 65 years</td>
<td>4.5</td>
<td>1.23 – 16.4</td>
<td>0.023</td>
</tr>
<tr>
<td>Male sex</td>
<td>6.3</td>
<td>1.3 – 31.5</td>
<td>0.024</td>
</tr>
</tbody>
</table>

* p value (two-tailed) < 0.05 is considered significant

<p>| Table 4. Effect of number of the predictors on second day Holter results |
|-----------------|-----------------|-----------------|-----------------|</p>
<table>
<thead>
<tr>
<th>Number of predictors</th>
<th>Second day Holter results</th>
<th>p value</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>Negative</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-----------------</td>
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<td>-----------------</td>
<td>-----------------</td>
</tr>
<tr>
<td>0</td>
<td></td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td></td>
<td>2 (8%)</td>
<td>23</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>7 (28%)</td>
<td>18</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>4 (50%)</td>
<td>4</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>13</td>
<td>60</td>
</tr>
<tr>
<td>-----------------</td>
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<td>-----------------</td>
<td>-----------------</td>
</tr>
</tbody>
</table>

IHJ-867-05(OA).p65 9/19/2005, 11:36 AM
syncope, extending the Holter recording duration in patients with palpitation might not be as useful as in the former group.\textsuperscript{10}

\textbf{Study limitation:} We did not assess the effect of history or symptoms of heart failure and left ventricular function on outcome of second day Holter monitoring. However, as mentioned above Sarasin et al.\textsuperscript{8} have demonstrated that history or symptoms of heart failure is a predictor of arrhythmic cause of syncope.

Secondly, our study was not large enough to find the predictors of the symptomatic episodes of MEF which could have had greater clinical significance although all the episodes of clinically significant arrhythmias are not necessarily associated with the symptoms.\textsuperscript{6,7} Further large scale studies are warranted to validate our findings and evaluate the predictors of symptomatic MEF during long-term ambulatory electrocardiographic monitoring.

\textbf{Conclusions:} Forty-eight hours Holter monitoring, compared to standard 24-hour Holter recording identifies more symptomatic and asymptomatic MEF. Syncope and/or pre-syncpe as the presenting symptom, age $\geq 65$ years and male sex but not concomitant UHD were predictors of MEF during the second day of Holter.

\textbf{Acknowledgements}

The authors thank the Holter clinic team: Simin Abedi, Mahboobeh Zeyghami, Forouzan Asgari, Shahrbanoor Azari, Azita Ahmadzadeh, and Parisa Sabaghiyeh.

\textbf{References}

4. McClenn S, Zimetbaum PJ, Ho KK, Goldberger AL. Holter monitoring: are two days better than one? \textit{Am J Cardiol} 2000; 85: 562–564
Screening for Pre-Clinical Hypertrophic Cardiomyopathy by Tissue Doppler Imaging

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Background: Hypertrophic cardiomyopathy is an autosomal dominant inherited disorder. On a routine clinical basis, genetic analysis is both time consuming and impractical at present. Thus, use of tissue Doppler imaging as a surrogate for genetic screening is an attractive option.

Methods and Results: Fifty-five first-degree relatives of 15 patients with hypertrophic cardiomyopathy were screened. Of them, two were found to have hypertrophic cardiomyopathy and were included in Group 1, which hence had 17 patients with overt hypertrophic cardiomyopathy. Group 2 had 53 family members who did not manifest any overt echocardiographic abnormality. Twenty healthy volunteers comprised Group 3. Doppler tissue myocardial longitudinal velocities were measured in systole and early diastole and with atrial contraction at the medial mitral annulus, lateral mitral annulus, mid lateral wall and mid interventricular septum. The tissue Doppler characteristics were analyzed for the presence of abnormalities suggestive of subclinical myocardial involvement. Myocardial velocities were highest in the normal control group and lowest in the hypertrophic cardiomyopathy group. The velocities of the relatives without overt hypertrophy were intermediate in range. Of the 53 relatives screened, nine (17%) subjects showed tissue Doppler abnormality in the systolic and early diastolic velocities at the medial and lateral mitral annulus suggestive of a possibility of pre-clinical hypertrophic cardiomyopathy and a carrier state for a hypertrophic cardiomyopathy. Twenty-two of the 53 screened members had a mean early diastolic velocity less than 13.5 cm/s, among this group 9 had an ejection fraction more than 68%. These findings suggest that at least 16.7% of the screened population may carry beta-myosin heavy chain mutation.

Conclusions: Screening for hypertrophic cardiomyopathy is feasible and tissue Doppler imaging is a sensitive and easy means to detect subclinical myocardial involvement in apparently normal family members without overt hypertrophy. (Indian Heart J 2005; 57: 245–250)

Key Words: Hypertrophic cardiomyopathy, Echocardiography, Tissue Doppler imaging

Hypertrophic cardiomyopathy (HCM) is an autosomal dominant inherited disorder, characterized by unexplained left ventricular hypertrophy (LVH). The estimated prevalence of HCM in the general population is approximately 0.1 to 2.0 per 1000 population.\(^1\)\(^-\)\(^3\) One particular challenge in the clinical management of HCM is the screening of family members. In 1989, it was first discovered that mutations in the genes coding for the proteins of cardiac sarcomere were associated with familial HCM.\(^4\) Since then more than 200 mutations in 10 different genes coding for cardiac sarcomeric proteins and 2 genes coding for cardiac mitochondria have been associated with clinical HCM.\(^5\)\(^-\)\(^9\) However, each family seems to harbor a unique, family-specific mutation, and the clinical expression of mutations is highly variable, even within individual families. On a routine clinical basis this molecular diversity renders systematic screening for these mutations by genetic analysis both time consuming and impractical at present.\(^7\)

The tissue Doppler velocities of the mitral annulus have been shown to correlate with invasive measures of global systolic and diastolic left ventricular (LV) performance\(^10\)\(^-\)\(^12\). Two clinical studies have used tissue Doppler velocities of mitral annulus for the detection of individuals with HCM-causing mutations, in the absence of LVH with 100% sensitivity and >90% specificity.\(^13\)\(^-\)\(^14\) Familial HCM is inherited in an autosomal-dominant pattern, thus
predicting a 50% pre-test probability of disease in first-degree relatives. Thus, the use of tissue Doppler imaging (TDI) as a surrogate for genetic screening is an attractive option. The significance of a pre-clinical diagnosis is further emphasized by the recent placebo-controlled studies with losartan and simvastatin that showed a marked reduction in the phenotype of fibrosis and hypertrophy and improved ventricular function in genetic animal models of human familial HCM. Hence this study was conducted with the objective to assess subclinical myocardial involvement in apparently normal first-degree relatives of HCM patients by TDI.

Methods

Study population: Our study population consisted of three groups of patients. Group 1 consisted of patients with overt HCM with typical clinical and echocardiographic features. The index cases and the patient's relatives, who were found to have overt abnormality on screening, were included in this group. Group 2 consisted of all the apparently normal first-degree relatives of these patients, who consented for the screening procedure. Group 3 consisted of healthy volunteers. Individuals were excluded if they were found to have coexistent conditions that may contribute to the development of LVH or diastolic dysfunction (systemic hypertension, valvular heart disease and coronary artery disease).

The 55 first-degree relatives of 15 HCM patients were screened. Of them, two were found to have HCM and were included in Group 1, which thus had 17 overt HCM patients. Group 2 had 53 family members of patients with HCM, who did not manifest any overt echocardiographic abnormality. Twenty healthy volunteers comprised Group 3.

Echocardiographic protocol: Echocardiographic studies were performed with an HP Sonos 5500 ultrasound system. Standard 2-dimensional imaging, M-mode, spectral and color Doppler and pulse Doppler tissue interrogation were performed. LV septal and posterior wall thickness, cavity dimensions and volumes were determined from 2-dimensional images according to established criteria. LV ejection fraction (EF) was calculated from LV volumes using the modified Simpson's method. Peak early (E) and late (A) transmitral velocities, E/A ratio, E wave deceleration time and isovolumetric relaxation time (IVRT) were measured from spectral Doppler displays. TDI was done online using pulse tissue Doppler. The setting used was Power -17.7 db, gain setting 0%, Gute length smallest possible, wall filter 50-199 Hz, spectral baseline middle, spectral scale 15-20 cm/s above and below baseline, compress 1, reject 8, temporal smoothing 1 and velocity smoothing at 1. Sample volumes were placed at the lateral aspect of mitral valve annulus, septal side of mitral valve annulus, mid-lateral wall, and mid-septum. Peak early diastolic velocity (Ee), late diastolic velocity (Ae), systolic velocity (Ss) and deceleration time for E wave (Edt) were recorded for 3 different cycles in all patients and the mean value was taken. The color tissue Doppler images were acquired at 150 frames per second. The Doppler examinations were recorded on high fidelity VCD and/or magnetic optical discs for future reference. All echocardiographic recordings were done by a single operator (SS) and analyzed online during the patient study. The intra-observer coefficient of variability for measurement of the E velocity at the lateral annulus was 5.2% for that observer (SS) which is within acceptable limits. Doppler tissue myocardial velocities were measured in systole (Sa) (2nd peak measured after the isovolumetric contraction) and early diastole (Ee) and with atrial contraction (Aa) at the medial mitral annulus, lateral mitral annulus, mid lateral wall and mid interventricular septum. The velocities were measured in the apical 4-chamber and 2-chamber views. Three values were taken for each site and then averaged.

Statistical analysis: Statistical analysis was used was SPSS statistical software (version 10.0). Multiple group comparisons of echocardiographic parameters among the 3 study groups were made using one-way ANOVA followed by post hoc testing with Bonferroni correction. A p value <0.05 was considered statistically significant. All data are expressed as mean ± 1 standard deviation.

Results

Clinical characteristics: The clinical and baseline echocardiographic characteristics of the study subjects are shown in Table 1. The HCM patients were slightly older than their relatives and the controls (38.4 years v. 31 years v. 25 years, respectively) but we do not expect much variation in tissue Doppler velocities in this age range of 25 to 40 years, though the tissue Doppler velocities do decrease with increasing age in the elderly. The patients of HCM had a significantly higher LV EF as compared to that of the controls and family members. Traditional measures of diastolic function, including E/A ratio, E wave deceleration time and IVRT, were not significantly different among the 3 groups.

Doppler tissue imaging: Compared with normal control subjects, the patients with HCM and also the relatives of these patients without overt hypertrophy had evidence of
abnormal diastolic function by TDI (Fig. 1). This was manifested as significantly lower diastolic velocities at each of the sites interrogated, namely the medial mitral annulus, lateral mitral annulus and the mid interventricular septum and lateral wall (Table 2). Myocardial velocities were highest in the normal control group and lowest in the HCM group. The velocities of the relatives without overt hypertrophy were intermediate (Fig. 2). The myocardial velocities were lowest in the interventricular septum compared to the other areas in the HCM group and in the apparently uninvolved relatives. It is interesting to note that the most significant difference in the mean myocardial velocities between controls and the relatives of HCM patients was observed at the interventricular septum, probably reflecting early involvement of the interventricular septum in them.

### Prediction of affected family members
Criteria for picking up genetic mutations have been suggested by both Nagueh et al.\(^1\) and Ho et al.\(^2\) Nagueh et al.\(^1\) suggested that a lateral Sa <13 cm/s had a sensitivity of 100% and a specificity of 93% for differentiating the mutation positives without LVH from the controls. Similarly, a lateral Ea <14 cm/s had 100% sensitivity and 90% specificity. Septal Sa <12 cm/s and Ea <13 cm/s both had 100% sensitivity and 90% specificity. When we applied these criteria in our patients, we observed that 13 of the 53 relatives (24.5%) satisfied all four criteria. An additional 10 (18.9%) satisfied three of the four criteria (the lateral annulus Ea in them

### Table 1. Clinical and echocardiographic characteristics of the study groups

<table>
<thead>
<tr>
<th></th>
<th>HCM patients</th>
<th>Relatives</th>
<th>Normal controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>38±16</td>
<td>31±19</td>
<td>24±7</td>
</tr>
<tr>
<td>Females/males</td>
<td>2/17</td>
<td>20/51</td>
<td>7/20</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>82±10</td>
<td>85±7</td>
<td>79±8</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>124±1.5</td>
<td>124±1.5</td>
<td>114±4.2</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>8±1.8</td>
<td>78±4.5</td>
<td>81±5.1</td>
</tr>
<tr>
<td>LV end-diastolic diam. cm</td>
<td>1.7±0.8</td>
<td>4.18±0.8</td>
<td>4.92±0.6</td>
</tr>
<tr>
<td>LV end-systolic diam. cm</td>
<td>2.4±0.8</td>
<td>3.4±0.9</td>
<td>3.40±7</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>73±1.11</td>
<td>60±16.1</td>
<td>60±14.8</td>
</tr>
<tr>
<td>Septal thickness, mm</td>
<td>2.11±0.7</td>
<td>0.7740.11</td>
<td>0.7240.31</td>
</tr>
<tr>
<td>Posterior wall thickness, mm</td>
<td>1.52±0.7</td>
<td>0.85±0.12</td>
<td>0.77±0.2</td>
</tr>
<tr>
<td>Peak E wave velocity, cm/s</td>
<td>83±2.24</td>
<td>90±2.32</td>
<td>83±2.204</td>
</tr>
<tr>
<td>Peak A wave velocity, cm/s</td>
<td>65±2.24</td>
<td>54±1.16</td>
<td>50±1.77</td>
</tr>
<tr>
<td>E/A ratio</td>
<td>1.34±0.2</td>
<td>1.44±0.3</td>
<td>1.72±0.6</td>
</tr>
<tr>
<td>E deceleration time, ms</td>
<td>192±5.67</td>
<td>165±29.2</td>
<td>166±28.4</td>
</tr>
<tr>
<td>IVRT, ms</td>
<td>114±1.82</td>
<td>101±1.35</td>
<td>102±1.14</td>
</tr>
</tbody>
</table>

HCM: hypertrophic cardiomyopathy; bpm: beats per minute; BP: blood pressure; LV: left ventricular; LVEF: left ventricular ejection fraction; IVRT: isovolumic relaxation time

### Table 2. Myocardial tissue doppler velocities in the study groups

<table>
<thead>
<tr>
<th></th>
<th>HCM patients</th>
<th>Relatives</th>
<th>Normal controls</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Medial annulus</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sa</td>
<td>8.00±1.65(^*)</td>
<td>9.56±1.44(^*)</td>
<td>11.44±1.80</td>
</tr>
<tr>
<td>Ea</td>
<td>7.67±1.89(^*)</td>
<td>13.89±3.18 (^*)</td>
<td>15.52±2.00</td>
</tr>
<tr>
<td>Aa</td>
<td>7.81±1.72(^*)</td>
<td>8.96±2.05(^*)</td>
<td>12.69±3.89</td>
</tr>
<tr>
<td><strong>Interventricular septum</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sa</td>
<td>6.44±1.56(^*)</td>
<td>7.47±2.07(^*)</td>
<td>11.14±1.86</td>
</tr>
<tr>
<td>Ea</td>
<td>6.94±1.43(^*)</td>
<td>11.95±1.12(^*)</td>
<td>14.91±3.86</td>
</tr>
<tr>
<td>Aa</td>
<td>7.34±1.87(^*)</td>
<td>7.96±2.41(^*)</td>
<td>12.14±3.14</td>
</tr>
<tr>
<td><strong>Lateral annulus</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sa</td>
<td>8.30±2.23(^*)</td>
<td>10.17±2.69(^*)</td>
<td>12.47±2.16</td>
</tr>
<tr>
<td>Ea</td>
<td>9.31±2.87(^*)</td>
<td>16.64±4.51(^*)</td>
<td>16.73±2.31</td>
</tr>
<tr>
<td>Aa</td>
<td>8.04±2.62(^*)</td>
<td>9.69±2.05(^*)</td>
<td>11.32±1.66</td>
</tr>
<tr>
<td><strong>Lateral wall</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sa</td>
<td>8.18±1.91(^*)</td>
<td>10.07±2.57(^*)</td>
<td>11.56±2.76</td>
</tr>
<tr>
<td>Ea</td>
<td>7.85±2.07(^*)</td>
<td>12.17±2.14(^*)</td>
<td>14.78±3.15</td>
</tr>
<tr>
<td>Aa</td>
<td>6.64±1.47(^*)</td>
<td>8.34±1.84(^*)</td>
<td>13.78±2.11</td>
</tr>
<tr>
<td><strong>Average</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sa</td>
<td>7.70±1.90(^*)</td>
<td>9.30±2.50(^*)</td>
<td>11.60±2.00</td>
</tr>
<tr>
<td>Ea</td>
<td>7.90±2.30(^*)</td>
<td>14.30±4.60(^*)</td>
<td>15.70±2.30</td>
</tr>
<tr>
<td>Aa</td>
<td>7.50±2.00(^*)</td>
<td>8.70±2.20(^*)</td>
<td>12.60±2.60</td>
</tr>
</tbody>
</table>

\(^*\) p < 0.05 compared to normal controls    \(^\#\) p < 0.05 compared to HCM patients
\(^\#\) p < 0.0001 compared to normal controls   \(^\text{c}\) p < 0.0001 compared to HCM patients

HCM: hypertrophic cardiomyopathy; Sa: systole; Ea: early diastole; Aa: atrial contraction

### Fig. 1. Tissue Doppler traces from [A] a normal control, [B] a patient with HCM and [C] a relative of an HCM patient with reduced tissue velocities. Sa represents peak systolic velocity, Ea represents peak early diastolic filling and Aa represents peak late diastolic filling. HCM: hypertrophic cardiomyopathy
In the screened relatives, we found 22 out of 53 (41.5%) to have a mean $E_a < 13.5$ cm/s. Among this group, 9 had an EF > 68%. These findings suggest that at least 16.7% of the screened population may carry a $\beta$-MHC mutation. Interestingly, 6 of the 9 possible carriers of $\beta$-MHC mutation also satisfied all 4 of Nagueh’s criteria and an additional two satisfied 3 of the 4 criteria.

**Discussion**

Hypertrophic cardiomyopathy is a disease of cardiac muscle. It is the final common manifestation of at least 200 mutations occurring in 10 different genes. Overt hypertrophy occurs at a later stage of the disease process. How the mutations in the genes encoding myocardial structural proteins translate into functional abnormality and ultimately into overt structural hypertrophy is not well understood. But clearly, functional abnormality precedes clinical hypertrophy, and is therefore an earlier manifestation of the disease process. Picking up this early functional derangement in patients who harbor a mutation but still have not developed hypertrophy is feasible. Studies done in animals and humans in this direction have convincingly shown that patients who carry HCM disease-causing mutations but without myocardial hypertrophy can be identified by TDI. In this study, we screened the first-degree relatives of 15 HCM patients. Of a total of 55 relatives screened two were identified to have overt hypertrophy. The remaining 53 relatives who did not manifest overt hypertrophy were assessed for the presence of abnormal myocardial velocities by TDI.

The mean age of the HCM patients was 12 years more than that of the controls and that of the family members was > 14 cm/s). Of these 23 subjects showing abnormality, 8 were females. The mean age was 44.9 ± 19 years. The youngest was 10 years and there were 3 subjects below 18 years of age. Three families had three members involved, including one with overt hypertrophy. Five families had at least two members involved, including one with overt hypertrophy picked up during screening. We derived cut-off values (using mean minus 2 times the standard error for the control group, rounded to the nearest integer) for normal tissue Doppler in our Indian patients in order to adapt Nagueh’s criteria for Indian patients, and used these to see how many of the HCM relatives were abnormal. The values for normal tissue Doppler that we used were $S$ (medial annulus) < 10 cm/s, $E$ (medial annulus) < 13 cm/s, $S$ (lateral annulus) < 10 cm/s and $E$ (lateral annulus) < 14 cm/s. The cut-off values derived from our controls were similar for the $E$ velocities but lower for the $S$ velocities as compared to the data by Nagueh et al.11 When we applied these criteria in our patients, we observed that 9 of the 53 (17%) relatives satisfied all four criteria. An additional eight (15.1%) satisfied 3 of the 4 criteria.

Ho et al.14 suggested a cut-off value for averaged $E_a$ velocity of $\leq 13.5$ cm/s to predict $\beta$-myosin heavy chain (MHC) mutation HCM in family members (sensitivity of 75% and specificity of 86%). The combination of EF > 68% and $E_a$ velocity < 15 cm/s had the maximum specificity in predicting genetic status. This combination yielded a sensitivity of 44% and specificity of 100% in predicting affected genotype. Looking at our own control values, we found that the averaged $E$ velocities were 15.7 ± 2.3 cm/s. Using values of mean ± 1 standard deviation, we also got a value of 13.4 suggesting that our control population also had similar $E$ velocities as those of Ho et al. Using these criteria, in the screened relatives we found 22 out of 53 (41.5%) to have a mean $E_a < 13.5$ cm/s. Among this group, 9 had an EF > 68%. These findings suggest that at least 16.7% of the screened population may carry a $\beta$-MHC mutation. Interestingly, 6 of the 9 possible carriers of $\beta$-MHC mutation also satisfied all 4 of Nagueh’s criteria and an additional two satisfied 3 of the 4 criteria.
screened was 7 years younger than the controls. The difference in tissue velocities cannot be explained by age alone as the tissue velocities within a narrow range of 20–40 years are unlikely to be very different though the velocities are known to decrease in the elderly.20

We measured the myocardial velocities at the medial annulus, lateral annulus, and mid interventricular septum and mid lateral wall. Nagueh et al.13 measured the tissue Doppler velocities in the medial and lateral annulus, whereas Ho et al.14 chose medial, lateral, and anterior annulus. However, in a study by Severino et al.21 regional myocardial dysfunction has been demonstrated at the level of the interventricular septum. Hence we chose to analyze the myocardial velocities in the mid-interventricular septum and mid lateral wall also. Expectedly we were able to demonstrate lowest myocardial contraction velocities in the interventricular septum in the HCM patients and their family members.

As documented in the previous studies by Nagueh et al.13 and Ho et al.14, the tissue Doppler velocities were the lowest in the HCM patients. The relatives screened in our study are likely to comprise both subjects harboring the mutation and those without these mutations. This will explain the wide distribution of the tissue Doppler velocity parameters observed by us in this group (Fig. 2).

These two studies have been done to predict subclinical involvement by TDI in HCM genotype positive patients without overt hypertrophy. Nagueh et al.13 studied 13 patients with mutations in β-MHC (n=4), cardiac troponin T (n=1), and myosin-binding protein C (n=7). None of the 13 mutation-positive individuals had LVH on electrocardiogram or echocardiography. They found that systolic and early diastolic tissue Doppler velocities were significantly lower in mutation-positives without LVH than in controls. Reduced tissue Doppler velocities had an overall sensitivity of 100% and a specificity of 93%. When we applied their criteria in the first degree relatives of our patients without apparent LVH, it was observed that 23 of the 53 (41.5%) patients screened showed abnormality. As HCM is an autosomal dominant disease, 50% of the offspring of the affected patients will be at risk of inheriting the gene and developing the disease. Our study demonstrated an abnormality in 32% (17% with 4 criteria and 15.1% with 3 abnormal criteria) of the screened relatives. This could be due to the fact that 14 of the 53 subjects were the parents of the affected individuals and some of them may not be carrying any disease-causing mutation (the mutations in their offspring could be sporadic).

Previous echocardiographic data indicate that 55% of the cases of HCM are familial and the remainder are sporadic.22,23

Ho et al. studied a genotyped HCM population with β-MHC mutations. Individuals with LVH (n=18) and without LVH (n=18) were compared with normal control subjects (n=36). LVEF was significantly higher in the group with β-MHC mutation irrespective of presence of LVH (75±5% and 71±6%, respectively, v. 64±5% in control subjects; p<0.0001). Mean early diastolic myocardial velocities (Ea) were significantly lower irrespective of LVH (p<0.02) in patients carrying the mutation. The combination of EF ≥ 68% and Ea velocity <15 cm/s was 100% specific and 44% sensitive in predicting affected genotype. Interestingly, when we applied these criteria in the first-degree relatives of our patients without apparent LVH we observed that 9 of the 53 (17%) patients satisfied these criteria. Moreover, 6 of these 9 patients also satisfied Nagueh’s criteria for carrying any HCM mutation, implying that among the HCM causing mutations in our population studied β-MHC may account for 34.3%. This is in accordance with the available data from the EUROGENE Heart Failure Project5 where 197 unselected HCM patients were screened and 124 the disease-causing mutation was identified. Of these 124 patients, mutations in the myosin binding protein C were identified in 42% and β-MHC mutations were identified in 40% subjects.24

HCM screening by conventional echocardiography in pre-adolescent children < 13 years of age is not productive because substantial LV remodeling with spontaneous appearance of hypertrophy occurs with accelerated body growth during adolescence.24 In our study we were able to demonstrate tissue Doppler abnormality in 3 patients < 18 years of age; however, none of the 9 relatives below the age of 10 years manifested any abnormality. It is not known whether the tissue Doppler velocities are sensitive enough to pick early changes in this age group of patients.

HCM is the most common heritable cardiovascular disease. Yet it is important to note that there are at least 200 different mutations in 10 different genes that can lead to this phenotypic expression. Systematic screening for these mutations by genetic analysis on a routine clinical basis is both time consuming and has a low sensitivity, as seen in the EUROGENE project5 where, in only 63% of patients with overt hypertrophy screened, a disease-causing mutation could be identified. This study proves the feasibility of screening family members with a simple echocardiographic technique, which may be more sensitive than presently available genetic screening technique. The prospect of such an approach is more exciting when we consider the treatment options with simvastatin and losartan16,17 in subjects without LVH with a view to preventing progression of the disease to the stage of overt hypertrophy.
Study limitations: Tissue Doppler velocities are likely to vary from population to population and therefore we need Indian data to derive normal limits. We derived cut off values based on our 20 controls but a larger control population with representation of all age groups might have given better values. Tissue Doppler values can also vary between different machines and standard values need to be established for different machines. Our data is based on using online pulse tissue Doppler with an HP machine. Values obtained by offline analysis of stored color tissue Doppler data give different peak velocities and this fact has to be kept in mind when using this data. Our cut off values are based on mean±2 standard error in order to get an approximation of the population mean but this is based only on 20 controls and perhaps a larger study may provide more reliable values.

Conclusions: Screening for hypertrophic cardiomyopathy is feasible and tissue Doppler imaging is a sensitive and easy means to detect subclinical myocardial involvement in apparently normal family members without overt hypertrophy.

References
Closure of Two Atrial Septal Defects using Two Separate Amplatzer ASD Devices

Robin J Pinto, Bharat Dalvi
Glenmark Cardiac Centre, Mumbai

The majority of patients with atrial septal defect require a single device for closure but a small proportion have more than one defect in the atrial septum. We report a patient who had two moderate-sized atrial septal defects in whom transcatheter closure of both the defects using two Amplatzer septal occluders was performed successfully. *(Indian Heart J 2005; 57: 251–254)*

**Key Words:** Congenital heart disease, Atrial septal defects, Amplatzer device

Transcatheter closure of atrial septal defects (ASDs) using a percutaneous approach is now commonly performed. With the Amplatzer septal occluder, even large defects can be closed safely. However, a small proportion of ASDs may have multiple fenestrations and these are often considered unsuitable for device closure. We report a case having a fenestrated ASD with two separate moderate-sized secundum ASDs which were successfully closed using two Amplatzer septal occluders.

**Case Report**

A 32-year-old gentleman was detected to have ASD during a routine check-up. He was asymptomatic. The electrocardiogram (ECG) revealed an incomplete right bundle branch block (RBBB) with right axis deviation. Chest X-ray showed mild cardiomegaly with increased pulmonary vascular markings and a prominent pulmonary conus. A transthoracic two-dimensional color Doppler echocardiography revealed features of right ventricular volume overload, dilated pulmonary arteries and a drop-out in the atrial septum with a left-to-right shunt. Due to a suboptimum echocardiographic window and inadequate delineation of the anatomic details of the ASD, a transesophageal echocardiography (TEE) was performed. The latter revealed the presence of two separate ASDs (Fig. 1A). The superior one was situated in the superior part of the interatrial septum with a margin of about 10 mm separating it from the entrance of the superior vena cava.

It measured 14 mm on echocardiography. Below this, in a more posterior plane was another moderate-sized ASD measuring about 16 mm, separated from the higher ASD by septal tissue measuring 12 mm in length. The inferior rim was marginally deficient and measured 5 mm. The flow through both the defects was significant, laminar and left-to-right. The patient opted for the transcatheter closure of the defects.

The procedure was performed under general anesthesia and endotracheal intubation. A TEE was repeated under anesthesia and the findings were confirmed. Both femoral veins and the left femoral artery were used for vascular access. The patient was given heparin 100 IU/kg intravenously on obtaining vascular access. The right superior pulmonary vein was entered using a 6 F NIH catheter and angiography was performed. The location and size of both the ASDs was confirmed and so were their relation to each other and to the superior and inferior rims. The superior ASD was first crossed using a 6F right Judkin’s coronary catheter which was exchanged for a superstiff Amplatzer wire (AGA, Golden Valley, MN). Balloon sizing of this ASD was then performed and the stretched balloon diameter came to be 22 mm. It was decided to close this ASD using a 24 mm device. The wire was then exchanged for a 10 F sheath through which the device was advanced, screwed to the tip of the delivery cable. Under fluoroscopic and echocardiographic guidance the left disk was deployed in the left atrium, the whole assembly was pulled back gently against the septum and then the right atrial disc was deployed (Fig. 1B). At this point the device was not released (Fig. 2A). TEE revealed it to be properly positioned with the anterior limbs straddling the aorta. Repeat assessment of
the second ASD showed it to be significant in size with left-to-right shunt. We then proceeded to perform the same procedure for the lower ASD. Balloon sizing of this defect revealed it to be 24 mm in size (Fig. 2A). We decided to use a 26 mm device to close this defect. The same procedure was followed as for deploying the first device. There was a mild superimposition of the second device over the first one (Fig. 1C, 2B). With both devices in place, but not released, the TEE was reviewed. It was confirmed that the devices were not interfering with the mitral and tricuspid valves. The “Minnesota wiggle” was performed on both the devices after which they were released sequentially (Fig. 2C), the superior one followed by the inferior one. Repeat TEE revealed excellent position of the devices with no residual left-to-right shunt through any of the defects (Fig. 1D, 2D). The patient was discharged 24 hours after the procedure and administered aspirin and clopidogrel daily for six months. Aspirin was continued thereafter.

Discussion

There is considerable variation in the morphology of secundum-type ASDs. In the study of Podnar et al., only 24% patients had centrally placed defects while 7.3% of patients had multiple septal defects. Experience of closing these multiple ASDs using more than one Amplatzer septal occluder is limited. In the worldwide registry report of use of the Amplatzer septal occluder, 3460 patients received a single device while only 45 patients received two devices for multiple ASDs. Cao et al. reported a series of 22 patients who had two septal occluders implanted simultaneously for multiple ASDs. The strategy for closure
of multiple defects depends upon the size, location and separation between the defects. In closely positioned defects, the septal occluder should be implanted in the largest defect aiming to cover any smaller defects. Using such a strategy, Szkutnik et al. achieved an acute success rate of complete closure of both the ASDs in 61% of the 39 patients in whom this was attempted. This increased to 95% at two years. Alternatively, consolidation of multiple defects in a fenestrated fossa ovalis into a single large defect by simple balloon atrial septostomy followed by implantation of a single large device has been reported to effectively close all the defects. However, when the defects are widely separated more than one device is required. When the defects are small in size, overlapping of the devices may not be an issue and putting two separate devices appears rational and befitting. Also, the procedure is technically straightforward. Echocardiographic studies have suggested that patients should have a rim of tissue measuring at least 7 mm between the defects to allow the deployment of two septal occluders. In our case, however, the ASDs were moderate in size (balloon stretched diameter of 22 and 24 mm, respectively) and although the intervening septal length

Fig. (2A). Balloon sizing of the lower ASD after the superior one has been closed with a 24 mm Amplatzer device. (2B) Both the ASDs occluded with the Amplatzer devices; the occluders have not been released and are still attached to the delivery cables. (2C) Release of the superior ASD device with the inferior one still attached to the delivery cable. (2D) Final picture with both the ASD devices released and properly deployed. Note the minimal overlap of the two devices.

ASD: atrial septal defect
was adequate (12 mm), overlapping of the devices during deployment was unavoidable.

The primary concern, when using two or more devices which overlap, is the friction of metal from both the devices which can theoretically affect the stability of the devices after deployment and lead to embolization. In addition, the septal length should be adequate to accommodate both the devices without significant interference with each other, and also avoid encroaching surrounding structures especially the atrioventricular valves. Technically the procedure followed was the same as is usually practiced but there are a few important procedural details to be adhered to. Since the highly thrombogenic sheaths remained in the left atrium for a longer period of time, repeated boluses of heparin were administered to ensure the activated clotting time of > 200 s. Once the first device was deployed, its stability was confirmed before proceeding to deploy the second device. This was assessed by TEE and by performing the “Minnesota wiggle”. Also, deployment of the second device was performed gently with the left atrial disc of the second device partly overlapping the first one. The second device was oversized by 2 mm since there was a concern about device embolization due to the deficient inferior rim. The adequate intervening septal length between the two devices allowed us this leeway. There was a concern about the possibility of increased thrombogenicity of the increased amount of metal associated with use of the two devices. For this purpose clopidogrel was added to his antiplatelet regimen and aspirin was continued beyond 6 months. There was also a concern whether the friction between the two devices would interfere with adequate endothelialization. However, we feel that since the profile of the devices appeared flat, this may not be a problem. More widespread use of intracardiac and three-dimensional echocardiography may allow for a faster procedure time by allowing comprehensive assessment of multiple ASD anatomy and particularly allowing clear visualization of the inferior atrial septum. 

References
Congenital Atresia of Left Main Coronary Artery

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We report a rare case of congenital atresia of left main coronary artery in an elderly male presenting with angina and positive stress thallium test. Coronary angiogram showed absence of left main coronary artery in the left aortic sinus. Collaterals from right coronary artery supplied left anterior descending artery and left circumflex artery territories. Despite collaterals, the left anterior descending and left circumflex arteries were rudimentary. Poor size of left-sided arteries precluded any surgical revascularization which is the treatment of choice in this rare entity. *(Indian Heart J 2005; 57: 255–257)*

**Key Words:** Congenital heart disease, Single coronary artery, Coronary artery disease

Coronary artery anomalies are rare and form only 1.33% of all congenital heart diseases and single coronary artery forms a mere 4% of all coronary artery anomalies. Congenital atresia of left main coronary artery (LMCA) is an extremely rare condition akin to, but distinct from, single right coronary artery (RCA). In single coronary artery there is only one coronary ostium which gives rise to two vessels which run in their usual positions after crossing over from the opposite side. This results in a centrifugal flow of blood from proximal to distal vessels and capillaries. On the other hand, in congenital atresia of LMCA, the single RCA fills the left-sided coronaries by collaterals so that significant quantity of blood flows in centripetal direction from capillaries to central vessels. We present an extremely rare case of congenital atresia of LMCA.

**Case Report**

A 55-year-old hypertensive male patient was admitted to our hospital with class II angina of effort. Examination revealed well controlled blood pressure, and normal cardiovascular system. Electrocardiogram (ECG) was normal without any features of left ventricular (LV) hypertrophy. Echocardiography revealed no LV hypertrophy, and ejection fraction of 65%. Stress thallium examination revealed reversible perfusion defect in left anterior descending (LAD) coronary artery territory. He was subjected to coronary angiogram.

The angiogram revealed that the RCA was grossly enlarged to about 7-8 mm in size, had a normal course and was free of any stenosis (Figs 1 and 2). There was complete absence of the LMCA from the left aortic sinus or from any other site in the aorta as shown by aortic root angiogram (Fig. 3). Conal artery from RCA was supplying collaterals to LAD region. Posterior descending artery (PDA) and...
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Fig. 2. Late frames from the same angiogram as in Fig. 1, showing leach of vessels supplying LAD artery territory with reformation of the stump of LMCA (arrow) near the left aortic sinus without any identifiable LAD or LCx in this view.
LAD: left anterior descending artery; LMCA: left main coronary artery; LCx: left circumflex artery

Fig. 3. Injection into left coronary sinus showing absence of any left coronary artery filling.
posterior left ventricular (PLV) branches were supplying collaterals to left circumflex (LCx) artery territory. However, the LAD or the LCx were only rudimentary at their usual sites. During late frames of RCA angiogram LMCA filled up and formed a small dot near its expected origin from the aorta (Fig. 4). In such situations LMCA has been known to arise from pulmonary artery, subclavian artery, carotid artery, descending aorta etc. In our case, we looked for LMCA in abnormal positions in the ascending aorta and its branches but it could not be found. Since all the territories of left ventricle were perfused from collaterals with no bare area and the LMCA remnants were visualized in the late frames, there was no suspicion of abnormal origin of LMCA. Diagnosis of left main atresia was confirmed.

Fig. 4. Late frames of lateral view of the RCA angiogram showing diminutive LAD artery (small arrow) and diminutive LCx artery (long arrow) and stump of LMCA (double line arrow).
RCA: right coronary artery; LAD: left anterior descending artery; LCx: left circumflex artery; LMCA: left main coronary artery

Discussion
Congenital coronary artery anomalies are rare and account for 1.33% of all congenital heart diseases. Single coronary artery as congenital heart disease is even rarer (0.04%). Single coronary artery has been classified differently by many authors. Smith classified it as Type 1 if one coronary artery supplied the whole heart and the other coronary artery was absent, as in our case. Type 2 are those in which single coronary artery is divided into two arteries which have normal distribution in their respective territories. Type 3 were classified as any other combination.
Congenital Heart Surgery Nomenclature and Database have classified coronary artery anomalies based on unique hierarchy-based system. The present case would be classified as "Coronary anomaly; Congenital absence of left main coronary artery". Musiani et al. reviewed this entity in 1997 and found only 28 reported cases including two of their own. Congenital atresia of LMCA is classified as a distinct entity separate from single coronary artery. Single coronary artery is said to be present when both the coronary arteries arise from a single ostium from the aorta, which subsequently divides into two or three vessels. These vessels reach their target areas and supply blood to the myocardium in centrifugal direction (main vessel to capillaries). Congenital atresia of LMCA is diagnosed when single RCA supplies collaterals to the LAD or LCx or both in such a manner that the filling occurs in retrograde direction (collaterals to the main vessel). The LMCA has no connection with the aorta. In adults, it may be difficult to distinguish it from atherosclerotic occlusion of LMCA. However, certain features are helpful. In congenital atresia of LMCA the RCA is usually of large size, reformed LAD or LCx is very diminutive, other atherosclerotic lesions are uncommon. In our case also the whole of RCA was very large (nearly 7-8 mm), atherosclerotic lesions were absent and LAD as well as LCx were diminutive, which is diagnostic of congenital atresia of LMCA.

Congenital atresia of LMCA presents during infancy with syncope, tachyarrhythmias, and failure to thrive. Adults usually present with angina. Asymptomatic patients are very rare as they might go undetected. Cause of angina in congenital atresia of LMCA is multifactorial and occurs in the absence of atherosclerosis. Inadequate caliber, kinking, angulation and compression of collaterals have been implicated. Long time delay in delivery of blood to the LV via collaterals could result in blood reaching during systole rather than diastole resulting in ischemia. In all 28 cases of congenital atresia of LMCA, as compiled by Musiani et al., either LAD or LCx or both were well visualized after filling from the collaterals. As a result, 16 of these cases could undergo coronary artery bypass grafting (CABG) with grafts to LAD, LCx or both to relieve ischemia. In the present case as well, there was poor filling of main body of LAD and LCx and that of diminutive stump of LMCA, although their territories were perfused by leash of small collateral vessels. This resulted in nearly complete centrifetal flow of blood. It is also noteworthy that this form will be difficult to treat with bypass grafting as was possible in most cases of Musiani’s compilation. Creation of an aortic baffle to reconstruct the LMCA ostium has also been attempted and was possible in our case. Since our case stabilized on medical treatment we did not consider this kind of surgical intervention. Musiani et al. reviewed this condition extensively and have recommended bypass grafting in all cases, including pediatric ones, to relieve ischemia. Without revascularization the outlook is grim with high mortality. Immediate surgical results are good but there are no reports of long-term outcome.

To conclude, we report an extremely rare case of congenital atresia of left coronary artery where both LAD and LCx were rudimentary and not amenable to bypass grafting.

References

Aneurysm of the muscular interventricular septum, most of which are congenital, have been uncommonly reported. Usually the site afflicted is mid-portion of the trabecular interventricular septum. Aneurysms of the basal interventricular septum are rare. A detailed search of the literature has yielded two case reports only. This report describes a 32-year old young man who underwent mitral valve replacement with a tilting disc prosthesis in 1995 and was incidentally found to have aneurysmal deformity of the basal interventricular septum on follow-up after thrombolysis of the obstructed mitral prosthesis. Putative mechanisms of this phenomenon are discussed.

Case Report

A 31-year male patient presented with acute pulmonary edema 7 days after stopping oral anticoagulant therapy for suspected peptic ulcer in 2004. He had undergone mitral valve replacement with Omnicience 27 mitral prosthetic valve 1995 and was asymptomatic on regular follow-up and anticoagulant therapy till the day of index event. Following successful thrombolysis with streptokinase using standard regimen and echocardiographic evidence of apparently normal disc motion and residual mean transprosthetic mitral gradient of 9 mmHg (but peak velocity of 2.5 m/s), he was discharged. Pre-discharge echocardiographic examination showed aneurysmal deformity of the basal interventricular septum persisting throughout the cardiac cycle. The operative notes and pre-operative echocardiographic data showed severe non-calcific mitral stenosis with moderate mitral regurgitation and pulmonary systolic pressure of 54 mmHg. No mention of this deformity was recorded. This deformity was carefully examined by regular cross-sectional echocardiography, but did not show any change at 2 months post-thrombolysis. The most recent examination showed a thin-built average young man without any distress. Physical examination revealed supine blood pressure of 110/80 mm Hg, regular heart rate of 71 beats per minute (bpm) and no evidence of heart failure. First and second heart sounds were normal and prosthetic clicks were sharp and loud. No definite murmur was heard. A 12-lead electrocardiogram showed sinus rhythm and non-specific ST-T changes. Plain chest skiagram showed mild cardiomegaly with left atrial enlargement. Internationalized normal ratio (INR) for anticoagulation was 2.49. Selective coronary angiogram showed no abnormality.

Detailed cross-sectional echocardiographic study showed enlarged left atrium (52 mm) and the left ventricle (LVIDd: 54 mm) with estimated ejection fraction (EF) of 45%. Mitral disc motion was normal in range but the prosthetic orifices were directed towards interventricular septum. There was an outward bulge of the basal and mid-interventricular septum both in systole and diastole (curvature 4.5 cm, area of bulge 13 cm²) with preserved wall thickness (Fig. 1). This deformity was not seen in the parasternal long axis view and did not involve membranous septum. Color flow examination showed two trans-prosthetic forward flow jets impinging upon the basal
interventricular septum before being redirected apically. Peak and mean gradients across the mitral prosthesis were 13 mmHg and 6 mmHg, respectively (Fig. 2). The patient has maintained asymptomatic status on follow-up.

Fig. 1. Cross-sectional echocardiographic 4-chamber view in diastole showing mitral prosthesis in open position and aneurysmal deformity of the basal septum (arrow, left panel). Right panel shows eccentric double jets impinging upon the septum.

Fig. 2. Left panel shows aneurysmal deformity of basal septum in the 4-chamber view and the right panel shows transmitral flow velocities with a gradient of 6 mmHg.
Discussion

Aneurysms involving basal muscular interventricular septum are extremely rare. Surprisingly there are no reports of this entity associated with ischemic heart disease, possibly because of bilayered structure more pronounced in the basal portion and splinting effect of right ventricular chamber pressure. One adult patient with recurrent ventricular tachycardia was shown to have this deformity and in the absence of any definite etiology, was labeled as idiopathic. Another case had scarring of the basal septum following viral myocarditis resulting into a well-defined aneurysm.

Pseudoaneurysms burrowing into the basal septum have been reported and so also the dissections involving this part of the interventricular septum. However, these anomalies have distinct echocardiographic features and are unlikely to be confused with true aneurysms of the septum. Although true aneurysms of the muscular septum of congenital etiology have been reported either in isolation or with other congenital deformities, basal portion is usually spared. Our patient had well-defined but contractile deformity of the basal interventricular septum with no involvement of the membranous septum.

It is difficult to speculate about the exact mechanism of development of this aneurysmal deformity. In all probability, it may be idiopathic or congenital in origin, although previous echocardiographic examination of this patient does not mention about its presence or absence. It is possible that turbulent and eccentric antegrade transprosthetic flow jets might have been constantly hammering this area resulting into a permanent deformity. It is to be noted that localized aneurysms and deformities of the pulmonary trunk and aorta in patients with pulmonary and aortic valve stenosis have been reported in the past. However, its pre-existence causing eccentric seating of the mitral prosthesis also cannot be ruled out although the detailed operative data do not mention this fact.

To conclude, this report describes a rare case of aneurysm of the basal muscular interventricular septum in a patient with tilting disc mitral prosthesis with speculations about its genesis.

References

Acute Myocardial Ischemia Following Accidental Intravenous Administration of Epinephrine in High Concentration

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Inadvertent and accidental epinephrine overdose might result in potentially lethal complications. We present a case of acute epinephrine toxicity resulting in acute myocardial ischemia in a young boy with combined variable immunodeficiency syndrome who developed severe allergic reaction to intravenous immunoglobulin, and was subsequently given epinephrine by mistake intravenously rather than subcutaneously. He developed significant ischemic changes in standard 12-lead electrocardiogram, transiently raised cardiac enzymes, reduced left ventricular systolic function, pulmonary edema and pulmonary hemorrhage. It is suggested that special precautionary measures should be taken regarding the dose and the route while administering epinephrine to avoid mishaps. (Indian Heart J 2005; 57: 261–264)

Key Words: Epinephrine, Myocardial ischemia, Toxicity

Catecholamines are naturally occurring hormones in the body. Synthetic catecholamines are an important part of conjoint management of medical emergencies like severe allergies, cardiac resuscitation and anaphylaxis. It is well known that overdose of epinephrine results in tachycardia, hypertension and chest pain. This happens due to the positive ionotropic and chronotropic effects which result in increased myocardial oxygen consumption. We describe a case of acute myocardial ischemia in a 14-year old boy who received concentrated epinephrine (1:1000) at a dose of 0.01 ml/kg intravenously (IV) by mistake rather than subcutaneously.

Case Report

A 14-year-old boy, weighting 32 kg, and born of consanguineous marriage had been diagnosed as a case of combined variable immunodeficiency (CVID) syndrome since the age of two years. As a treatment for his condition he was placed on monthly intravenous immunoglobulin (IVIG) infusions. He was admitted in day procedure unit for his routine monthly dose of IVIG. His vital signs were within normal limits. heart rate: 79/min, respiratory rate: 20/min, oxygen saturation: 99% and blood pressure 100/65 mmHg (Figs 1 and 2, point A).

At the end of the immunoglobulin infusion he developed hives over his back and chest in addition to pruritus. He had mild sweating, cold extremities and mild drop in blood pressure down to 85/53 mmHg (Fig. 2, point B). A written order was given to give 25 mg of diphenhydramine IV infusion over 10 min in addition to 0.3 ml of epinephrine (1:1000) to be given subcutaneously. Both a nurse and clinical pharmacist present at bedside verified dosage and concentration. Epinephrine was given by mistake as an IV push, and not subcutaneously. Within a few minutes, the patient started to develop tightness of chest, shortness of breath, palpitation and subsequently hemoptysis. His heart rate increased to 140/min and the blood pressure increased up to 140/110 mmHg. He developed significant tachypnea at a rate of 60/min and the oxygen saturation dropped to 90% (Figs 1 and 2, point C). Chest auscultation revealed crackles all over, suggestive of acute pulmonary edema. The heart examination revealed third heart sound in addition to tachycardia. The patient was immediately transferred to intensive care unit. A chest X-ray showed severe pulmonary venous congestion and mild cardiomegaly. An echo-cardiogram showed global hypokinesia and depressed left ventricular systolic function with an ejection fraction (EF) of 30%. He was given 40 mg of furosemide intravenously and non-invasive mechanical ventilation was initiated using BIPAP because of
persistent respiratory distress (Fig. 1, solid arrow). The patient started to improve gradually. The hemoptysis stopped within few hours and the chest pain disappeared. His chest gradually became clear to auscultation; a repeat chest X-ray also showed resolved pulmonary edema. Oxygen inhalation was discontinued the next day (Fig. 1, interrupted arrow), which was well tolerated. An echocardiogram obtained 48 hours after the episode revealed markedly improved systolic function with normal EF. He was discharged 48 hours after the episode in stable condition. Follow-up after two weeks showed him asymptomatic with completely normal cardiac function on echocardiography.

**Electrocardiographic findings:** Twelve-lead electrocardiogram (EKG) done immediately after the event (Fig. 3) showed ST segment depression of more than 3 mm in leads II, III, aVF and in the chest leads V5 and V6. In addition, ST segment elevation of about 2 mm was noted in leads aVR and aVL, indicating inferolateral ischemia. A second EKG, completed 15 min after the IV epinephrine showed significant improvement in ST segment changes (Fig. 4). A third EKG taken 30 min after the event showed normalization of ST-T changes (Fig. 5).

**Cardiac enzyme:** Creatine phosphokinase (CK) levels are shown in Fig. 6. It showed a sudden rise in CK levels from 90 (immediately after the event) to 160 U/L nine hours later (normal: 24–195 U/L). CK-MB mass at that point rose to 11.8 µg/L. Next morning CK dropped to 144 U/L and at
discharge to 54 U/L. At this point CK-MB mass also returned to normal level.

**Troponin-T levels** (Fig. 7): First set of values was obtained 9 hours after the event. Troponin was high, 0.7 µg/L (normal=0.01 µg/L); 18 hours later troponin level dropped to 0.17 µg/L, and at 42 hours after the event to < 0.1 µg/L.

**Fig. 6.** Creatine phosphokinase levels; solid arrow depicts the time of significantly raised CK-MB mass to 11.8 µg/L (normal level is < 5 µg/L).

**Fig. 7.** Serum troponin levels during the whole length of stay showing significant raise about 9 hours after the administration of epinephrine, which returned back to normal 42 hours later.

**Discussion**

Catecholamines are naturally occurring hormones in the body and play a major role in the physiological hemodynamic regulatory mechanisms especially in stress and strain situations when their levels are increased.¹ High levels for a long period of time can cause myocardial cell damage and fibrosis.² These effects result from a reduction in intracellular glutathione levels with accumulation of reactive oxygen radicals.³ Behonick et al.⁴ found that auto-oxidation of catecholamines to aminochromes results in cardiotoxic effects on cultured human cardiac muscle. Rump et al.⁵ tested the effect of three different concentrations of nor-adrenaline on rabbit myocardial cells and found that low concentrations of $10^{-7}$ mmol/L can cause myocardial infarction and the effect can be blocked by propranolol while the effect caused by higher concentrations, in the range of $10^{-6}$ to $10^{-5}$ mmol/L, can only be blocked by superoxide dismutase.

There are quite few reports in the literature addressing the toxic effect of catecholamines in vivo. Davis and Wax⁶ reported a case of a 5-year-old boy who received 10 times the recommended dose of epinephrine subcutaneously for allergic reaction. He developed myocardial ischemia and supraventricular tachycardia. Another recent report by Akashi et al.⁷ describes an 80-year-old lady who developed ST segment elevation in the inferior and lateral leads as a result of catecholamine toxicity. In that case, angiography revealed normal coronaries while left ventriculography revealed significant regional wall motion abnormalities with depressed systolic function. Plasma catecholamine levels were significantly elevated which explained the myocardial dysfunction.

In our case, the concentrated form of epinephrine (1:1000), which is used subcutaneously, was administered intravenously by mistake. The dose was correct and had been verified, but was delivered by the incorrect route. The patient developed myocardial ischemia and left ventricular dysfunction. These effects were transient and subsided once the metabolites were cleared from the body. Our case adds to the limited existing reports and highlights the fact that catecholamines are not well tolerated if higher concentration is administered as an IV push. This report is expected to sensitize the readers so that more precautionary measures could be taken to avoid such mishaps.

**Conclusions:** Catecholamine cardiotoxicity is rather uncommon but a serious and potentially lethal complication. It may result not only from overdose but also from the administration of regular subcutaneous dose intravenously.

**References**


Comparison of Target Concentration Intervention Strategy with Conventional Dosing of Digoxin

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Digoxin is a widely used drug in patients with congestive heart failure. The present study compared the quality of life of congestive heart failure patients on one year follow-up period with two different dosing of digoxin (5/7 therapy and 7/7 therapy in whom the target serum digoxin concentration is maintained). Quality of life significantly improved in intervention group thus emphasizing the need for continuous dosing of digoxin based on target concentration. (Indian Heart J 2005; 57: 265–267)

Key Words: Quality of life, Digoxin, Arrhythmia

There is clear evidence of benefit of digoxin use in patients with congestive heart failure (CHF) who are on diuretics and angiotensin-converting enzyme (ACE) inhibitors. However, role of digoxin dosage is the subject of considerable debate in heart failure patients in normal sinus rhythm. Digoxin has been widely used in India for the treatment of heart failure due to systolic dysfunction and as therapy for atrial fibrillation and supraventricular tachyarrhythmias. Therapeutic drug monitoring (TDM) is not routinely practiced in most Indian hospitals due to lack of facilities, high cost involved and lack of awareness. It is a common practice in most Indian hospitals to use ‘5/7 therapy’ of digoxin in order to reduce the incidence of toxicity in the absence of adequate TDM facilities.

The present study compared the conventional 5/7 digoxin dosing (digoxin given for 5 days a week) with 7/7 dosing (daily digoxin) in which the target serum digoxin concentration (SDC) is individualized, on various clinical outcomes.

Brief Report

The open label study was approved by the Institutional Ethics Committee. Written informed consent was obtained from the patients before enrolment. Adult patients with CHF and on sinus rhythm who were taking digoxin for at least 6 months were included in the study. Exclusion criteria included major disorders of the hepatic, pulmonary, gastrointestinal or hemopoietic systems, myocardial infarction in the previous 3 months, unstable angina, history of supraventricular or ventricular arrhythmia, stroke within the previous 12 months and patients with fluctuating or rapidly deteriorating renal function.

Patients in the control group were continued on standard care. Patients in the target concentration intervention (TCI) group were changed to continuous dosing of digoxin titrated to an individualized target concentration and maintained in the range of 0.5 to 0.9 ng/ml. Serum samples of both groups were analyzed for trough level of digoxin (24 hours post-dose) using automated chemiluminescence system (Bayer Diagnostics India Ltd, India). Digoxin dosing in the TCI group was individualized based on TDM report and clinical parameters. All the co-medications the patients were taking for CHF were maintained at the same dosage as far as possible throughout the study period. SDCs were also measured whenever there was significant change in the therapy leading to possible alterations in the serum digoxin levels. Quality of life (QoL) of the patients in both the groups was assessed using the disease-specific Minnesota Living with Heart Failure Questionnaire. Statistical comparisons were made with one-way ANOVA followed by post-hoc comparison using Student-Newman Keuls test (q value).

The study included 41 patients: 28 in control group (9 males) and 13 in TCI group (7 males). The baseline
characteristics including body weight, disease severity and concomitant drug usage were similar in two groups.

In the control group, 26 patients were taking 0.25 mg/day of digoxin and 2 patients were taking 0.125 mg/day of digoxin on 5/7 dosing schedule. The duration of digoxin use in these patients ranged from 0.5 year to 15 years with a mean of 3.93±3.1 years. The trough SDCs in these patients ranged from 0.27 ng/ml to 3.8 ng/ml with a mean of 1.12±0.64 ng/ml. Two (7.1%) patients had treatment failure and were switched over to 0.375 mg/day of digoxin on continuous therapy. In the TCI group, all the 13 patients were taking 0.25 mg/day of digoxin on 5/7 dosing schedule. The duration of digoxin use in these patients ranged from 1 to 13 years with a mean of 4.5±3.5 years. The trough SDCs in these patients ranged from 0.22 to 2.86 ng/ml with a mean of 1.12±0.9 ng/ml. All the patients were changed to continuous therapy and had dosage modification based on the initial estimates of SDCs to target SDC as decided by the treating clinician. After dosage modification, 6 (46.2%) patients were on 0.25 mg/day of digoxin. 3 patients were on 0.125 mg/day of digoxin. 2 patients were on 0.0625 mg/day of digoxin. 1 patient was on 0.375 mg/day of digoxin and 1 patient was on 0.5 mg/day of digoxin. After the dosage modifications, these patients had their trough SDCs in the range of 0.36 to 1.13 ng/ml with a mean of 0.8±0.2 ng/ml.

At baseline, control group patients had a QoL score of 47.5±10.8 which did not change significantly (49.7±11.5 at the end of the one year). QoL of both male and female patients of control group remained the same throughout the follow-up period. Male and female patients of the TCI group had significant improvement in their QoL score at one year of follow-up (56.3±13.8 vs. 41.4±8.4 for males and 52.2±11.1 vs. 38.8±3.9 for females).

Patients with preserved renal function [glomerular filtration rate (GFR)>50 ml/min] had a higher QoL score at the baseline than the patients whose renal function was compromised (GFR<50 ml/min) (44.1±7.1 vs. 50.9±12.9 for control group and 51.5±10.9 vs. 70.5±2.1 for TCI group). QoL of patients in the control group remained the same during the follow-up period whereas the QoL of patients in the TCI group showed significant improvement on follow-up. The patients with compromised renal function showed much higher improvement than the patients with preserved renal function (70.5±2.1 vs. 35.5±0.7 for patients with compromised renal function and 51.5±10.9 vs. 41.1±6.8 for patients with preserved renal function, p<0.05).

QoL scores of patients were also assessed based on serum digoxin concentrations.

In the control group, patients with serum digoxin levels<0.5 ng/ml had a QoL score of 45.9±13.4 at baseline and 43.4±8.3 at the end of follow-up, patients with serum digoxin levels between 0.5 and 0.9 ng/ml had a QoL score of 40.4±4.3 at baseline and 41.4±6 at the end of follow-up, patients with serum digoxin level between 0.9 and 1.2 ng/ml had a QoL score of 45.2±4.1 at baseline and 47±6.6 at the end of follow-up, and patients with serum digoxin levels >1.2 ng/ml had a QoL score of 53.6±11 at baseline and 63.3±10.1 at the end of follow-up.

In the TCI group patients with serum digoxin levels < 0.5 ng/ml had a QoL score of 48±1.4 at baseline and 36.5±2.1 at the end of follow-up, patients with serum digoxin levels between 0.5 and 0.9 ng/ml had a QoL score of 50±8.8 at baseline and 43.7±7.5 at the end of follow-up, patients with serum digoxin levels between 0.9 and 1.2 ng/ml had a QoL score of 39 at baseline and 32 at the end of follow-up, and patients with serum digoxin levels>1.2 ng/ml had a QoL score of 68±9.1 at baseline and 39±4.5 at the end of follow-up. Analysis of QoL scores on this basis revealed that the patients with SDCs above 1.2 ng/ml had lower QoL. Significant improvement was seen in this group due to target concentration intervention.

In the control group, 11 patients (39.3%) had adverse drug reactions (ADRs) during the one-year follow-up period. Of these, six (21.4%) patients had 2 ADRs each, two (7.1%) patients had 3 ADRs each and three (10.6%) patients had 4 ADRs each. One (3.5%) patient had serious ADR. There were 31 (mean: 1.1±1.1) unplanned hospital visits/admissions (12 visits and 19 admissions) in this group and of these, 24 (mean: 0.9±0.9) including 7 visits and 17 admissions were related to cardiovascular events and ADRs. In the TCI group, no patient had ADRs during the follow-up and two patients had one hospital admission each which were related to cardiovascular events.

Discussion
In Indian population, data on serum concentration and clinical effect of digoxin is lacking. Dosing of digoxin has been the subject of research for many years. Previous studies have clearly proved that contractility increases progressively with escalating doses of digoxin but a plateau is reached at higher doses and the maximum effect may be achieved at a serum concentration of 1 ng/ml.44 Because digoxin has both sympathoinhibitory and sympathoexcitatory effects that are dose-dependent, it is possible that lower doses attenuate the neurohormonal activation without improving the hemodynamics, whereas higher doses improve hemodynamics without having a modulating effect on neurohormones.7
DIG trial results indicated that higher SDCs (>1.2 ng/ml) were associated with increased crude all-cause mortality rates. Adams et al. also reported that there was no relationship between randomization SDC and any of the study end points and patients in the low SDC performed significantly better (p < 0.05) on all clinical end points compared to those in whom digoxin was discontinued. Based on these studies, the target concentration for our study patients in the TCI group was titrated to < 1 ng/ml.

In our study, 7/7 therapy of digoxin with target concentration intervention strategy significantly improved QoL of patients on digoxin. This trend was seen in all the sub-groups analyzed. Mild CHF, absence of risk factors, preserved renal function (GFR > 50 ml/min) and SDCs < 1 ng/ml were found to be the factors contributing to good QoL at the baseline. QoL of patients in the control group remained the same during the follow-up period whereas the QoL of patients in the TCI group showed statistically significant improvement. TCI group also had better clinical outcomes with respect to hospital visits/admissions and occurrence of ADRs.

In our study, renal function and concomitant drug use were not taken as covariates for analysis since SDC was set, and maintained in the intervention group, irrespective of renal function and concomitant drug use. We also could not observe sex differences influencing patient outcomes due to the small number of patients involved. At the same time, our results indicate that patients with renal failure and those showing clinical features of digoxin toxicity should be subjected to target concentration intervention strategy since these sub-groups gain significantly from the intervention.

In the DIG trial, there was no statistically significant change in the QoL of patients with heart failure in sinus rhythm. In DIG trial all patients had their serum digoxin within the therapeutic range. In our study, patients in the standard therapy did not have significant difference between their baseline and one-year follow-up QoL scores. However, in patients subjected to target concentration intervention, there was a statistically significant improvement in the QoL. Our study differs from the DIG trial in two aspects: (i) all our patients were on digoxin whereas patients in the DIG trial consisted of placebo and treatment groups; and (ii) control group patients in our group had different serum concentrations of digoxin and TCI group patients had SDCs titrated to lower side of therapeutic range whereas patients in the DIG trial had their SDCs titrated within therapeutic range.

Conclusions: Our study has shown that continuous dosing of digoxin with target serum concentrations below 1 ng/ml will improve patient outcomes and QoL and this benefit is highly significant in patients who compromised renal function and in patients in whom clinical features of digoxin toxicity are seen.

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Secundum ASD - Not for Closure

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A 32-year-old man with 17 mm secundum atrial septal defect showed hemodynamic deterioration during temporary balloon occlusion of the defect. The closure was not done. Further investigation led to the diagnosis of primary cardiac amyloidosis. *(Indian Heart J 2005; 57: 268–269)*

**Key Words:** Atrial septal defect, Device closure, Amyloidosis

In view of ASD with biventricular hypertrophy, patient was taken up for cardiac catheterization and possible device closure. Coronary arteries were normal on angiography. Hemodynamic data showed mild pulmonary artery hypertension (45/20 mmHg, mean 26 mmHg), mild pulmonary venous hypertension (a19, v17-19, mean 16 mmHg) with an LV end-diastolic pressure of 24 mmHg. A left-to-right shunt of 2.4:1 was present with pulmonary vascular resistance index of 1.2 units. In view of the presence of biventricular hypertrophy, it was decided to analyze the hemodynamic changes during transient balloon occlusion prior to definitive closure of the defect. The ASD was sized with Meditech balloon catheter. The ASD was temporarily occluded with the same balloon catheter. Pulmonary capillary wedge pressure (PCWP) was measured with Swan-Ganz catheter for 10 min during complete balloon occlusion of the defect (Fig. 1) and immediately after

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**Case Report**

A 32-year-old man was referred to our institution for transcatheter closure of a single secundum ASD. He had symptoms of dyspnoea on routine activity (NYHA class II) of one year duration. His heart rate was 86/min and blood pressure was 120/70 mmHg. Auscultation revealed a wide split and fixed second heart sound with a loud pulmonary component and an ejection systolic murmur of grade 3/6 at the left 2nd intercostal space. There was evidence of increased pulmonary blood flow on chest X-ray and a cardiothoracic ratio of 0.65.

Electrocardiogram (ECG) revealed normal sinus rhythm with right axis deviation and incomplete right bundle branch block (RBBB). A secundum ASD of 17 mm size was seen on transthoracic two-dimensional (2D) echocardiography. Right atrium and right ventricle were dilated. The estimated pulmonary artery systolic pressure was 40 mmHg. In addition, there was biventricular hypertrophy with septal thickness of 16 mm and left ventricular (LV) posterior wall thickness of 17 mm. LV internal dimensions were 33 mm and 17 mm in diastole and systole, respectively.

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In Fig. 1, Pulmonary capillary wedge pressure tracings before (A), and after (B) balloon occlusion of the atrial septal defect. Note the rise in mean PCWP from 16 mmHg to 24 mmHg.

PCWP: pulmonary capillary wedge pressure.
deflation of the balloon. The balloon was not obstructing mitral valve or any pulmonary vein on echocardiography.

During balloon occlusion of the ASD, mean PCWP increased from 16 to 24 mmHg and immediately after deflation of the balloon it decreased to 16 mmHg. Simultaneously, mean pulmonary artery pressure also increased from 26 to 41 mmHg and the systemic arterial pressure decreased by 10 mmHg (from 120/76 to 110/80 mmHg) during balloon occlusion.

In view of significant increase in PCWP on balloon occlusion for 10 min, we decided not to close the ASD. An endomyocardial biopsy was done from the septal surface of right ventricle, which revealed cardiac amyloidosis. Further investigations led to the diagnosis of primary cardiac amyloidosis.

**Discussion**

This case demonstrates that closing an ASD may not always be appropriate, even if it is technically feasible. Presence of recent onset symptoms of dyspnoea on exertion and ventricular hypertrophy on echocardiography alerted us about the possibility of another disease process (cardiac amyloidosis in this case). Balloon occlusion showed that acute hemodynamic worsening would occur with closure of ASD. Similarly, Ewert et al. in a study of 18 elderly patients showed that temporary balloon occlusion of ASD can unmask the LV dysfunction, and acute pulmonary edema can occur if such a patient undergoes ASD closure. Acute LV failure has also been reported after ASD closure in patients with hypertrophic cardiomyopathy (HCM), or coronary artery disease (CAD). Even the closure of foramen ovale that is serving to decompress left ventricle might be deleterious in patients with HCM.

The reasons for deterioration appear simple. A sudden increase in pulmonary venous pressure due to inability of the non-compliant LV to accommodate increased preload leads to pulmonary edema. Further acute increase in LV pre-load leads to increase in myocardial oxygen demand. The acute hemodynamic deterioration may settle down with time in some patients but it may not be possible to reliably identify those cases pre-operatively and fatalities have been reported with surgical closure of ASD in similar circumstances. Thus, patients with ASD and cardiomyopathy may deteriorate following ASD closure and a temporary test occlusion may be useful in selecting patients for device closure in appropriate circumstances.

**References**

Cardiovascular diseases are the leading cause of mortality and morbidity in the developing and the developed countries. Over the past few years, research in cardiovascular diseases has focused on different biochemical variables such as positive family history, lipid levels, smoking, alcoholism etc. However, all these are useful only when the patient is in the advanced stage of the disease. One would definitely like to prevent the occurrence of cardiovascular diseases much earlier than this and in an individualized manner. The advances in the field of genetics and genomics have enabled us to understand the role of genes and its minor variations in the pathogenesis of different diseases. With the “Human Genome Project” completed and the rapid technological advances in the field of biotechnology and molecular biology, new candidate genes are continuously emerging for various aspects of cell biology, for modulating cardiovascular disease. This would help us to understand the pathogenesis of atherosclerosis in a better manner. Also, the human gene sequence would give us a better correlation between genotype-phenotype and may also help us identify individuals at an increased risk of cardiovascular diseases.

One of the major advances from studying various polymorphisms (including SNPs) of multitudes of genes which are involved in the pathogenesis of cardiovascular diseases is the possibility of predicting the development of cardiovascular disease and its probable outcome. This is increasingly being realized through introduction of DNA/cDNA microarray systems and functional genomic and proteomic studies. This review article focuses on the new strategies in the diagnosis, management and treatment of cardiovascular diseases using the advances in the field of genomics and proteomics.

Since the discovery of DNA in 1950s and elucidation of this molecule as the information keeper of the cell, explosive knowledge and development of technologies have taken place in the field of molecular biology. Various techniques like cell transformation, gene transduction, reverse copying of mRNA to cDNA, cutting DNA at desired places using restriction enzymes, ability to join the desired fragments with multitude of DNA and RNA ligating enzymes, discovery of PCR technology etc. have resulted in understanding the detailed mechanism of gene control by environmental factors, the process of cell division, apoptosis, angiogenesis, vasculogenesis and several other cellular events within our body. In order to understand better how different genes interact and how minor differences in various genes ultimately translate into differences in various disease conditions and survival, it is essential to be able to read the whole human genome. These considerations led to “Human Genome Project” in 1990s which has now been completed successfully and we are in a position to look ahead and see how this knowledge can be helpful in understanding and managing cardiovascular diseases.

Genetic Aspects of Cardiovascular Diseases

Despite high contribution of factors such as hypercholesterolemia, systemic hypertension, smoking, and diabetes in development of coronary artery disease (CAD), evidence from family studies show that genetic factors also contribute significantly to the predisposition to CAD. Knowledge of genetic risk factors will help define the mechanisms of the disease and could ultimately assist in the rational design of selective prophylaxis or therapy. Many single genes have been identified as the basis for different cardiovascular diseases. However, unlike other genetic disorders, cardiovascular diseases are not solely due to a single gene mutation/polymorphism. The major genetic causes for cardiovascular diseases are: (i) chromosomal disorders and single gene disorders (8%), (ii) environmental teratogens (2%), and (iii) multifactorial disorders, which means both genetic and environmental factors interact (90%). Hence, it is important to bear in mind that in cardiovascular diseases one has to study multiple genes focusing on different aspects like lipids, blood coagulation, circulation as well as gene-environment interactions.

Long before “Human Genome Project” was even conceived, clinical studies showed that cardiovascular
diseases are associated with strong genetic components with different types of inheritance.2,3 After the completion of “Human Genome Project”, by proper linkage analysis of various families with different kinds of hereditary cardiovascular disorders it is now possible to localize and amplify such genes. If its function is unknown then from gene library of different animals it is possible to find out whether similar genes in animals are known with identified function. Other technical advances in biological sciences and in information technology with powerful software programme allow us to study the precise location of the abnormal gene in the members of the affected family. Once the location of the abnormal gene is known, that gene can be amplified by using information from Genome Project. These oligonucleotides on a PCR reaction can amplify the target area a million times. Apart from possible therapeutic developments, once the abnormalities in the gene leading to disease in the family is identified, it may be possible to assign the risk to the other members of the family who have not yet developed the disease or to offer prenatal diagnosis. A list of different gene polymorphisms in relation to cardiovascular diseases in given in Table 1.

### Cardiovascular Disease in Transgenic and Knock out Animals

Creation of animal model is one of the major tools in biological understanding of disease. By the time the disease is diagnosed in a patient, usually the disease is far advanced. Moreover, in a patient it is not only difficult but is often impossible to control social and environmental influences on disease. Many newly developed drugs can be tested in the animal model for their efficacy, prior to future human trials. Moreover, even when we consider influences of

<table>
<thead>
<tr>
<th>Area</th>
<th>Polymorphism</th>
<th>Phenotype</th>
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<tbody>
<tr>
<td>Lipid metabolism</td>
<td>Apo E Cys 112 Arg</td>
<td>Increased levels of Apo E</td>
</tr>
<tr>
<td></td>
<td>Apo E Arg 158 Cys</td>
<td>Increased levels of Apo E</td>
</tr>
<tr>
<td></td>
<td>LPL Ser 447 Ter</td>
<td>Protective; Increasing HDL- cholesterol and lowering triglyceride levels</td>
</tr>
<tr>
<td></td>
<td>LPL Asn 291 Ser</td>
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<tr>
<td></td>
<td>LPL Asp 9 Asn</td>
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<tr>
<td>Blood coagulation</td>
<td>Fib β4455 G/A</td>
<td>Increased levels</td>
</tr>
<tr>
<td></td>
<td>Fib β4448 Arg/Lys</td>
<td>Increased levels</td>
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<tr>
<td></td>
<td>Fib α3α 312Thr</td>
<td>Altered clot structure</td>
</tr>
<tr>
<td></td>
<td>F VII Arg 353Gln</td>
<td>Increased levels</td>
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<td></td>
<td>F XIII Val34Leu</td>
<td>Protective effect</td>
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<td></td>
<td>FV Leiden</td>
<td>Activated protein C resistance</td>
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<td></td>
<td>PT G20210A</td>
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<tr>
<td></td>
<td>HPA 1α/1b</td>
<td>Altered platelet reactivity</td>
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<tr>
<td></td>
<td>GP Ia VNTR</td>
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<tr>
<td></td>
<td>GP Ib IX Thr 145 Met</td>
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<td>GP Ib IX C3550 T</td>
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<tr>
<td></td>
<td>MTHFR C677T</td>
<td>Increased homocysteine levels</td>
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<td></td>
<td>EPCR 23 bp repeat</td>
<td>Altered expression on cell surface</td>
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<tr>
<td>Circulation</td>
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<td>Unknown</td>
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<td></td>
<td>Thrombomodulin Ala455Thr</td>
<td>Altered expression on cell surface</td>
</tr>
<tr>
<td>Transport channels</td>
<td>ACE intron 16</td>
<td>Increased ACE activity</td>
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<tr>
<td></td>
<td>ACE 286 bp insertion/deletion</td>
<td>Increased ACE activity</td>
</tr>
<tr>
<td></td>
<td>Angiotensin Met235Thr</td>
<td>Increased levels of angiotensin</td>
</tr>
<tr>
<td>Marfan syndrome</td>
<td>Mutation in sodium channel</td>
<td>Repetitive openings of channels</td>
</tr>
<tr>
<td></td>
<td>Mutation in potassium channel</td>
<td>Reduction in functioning of channels</td>
</tr>
<tr>
<td></td>
<td>Mutations in the subunit assembly</td>
<td>Aberrant subunit assembly reducing the functioning of channels by 50%</td>
</tr>
<tr>
<td>Nitric oxide synthase</td>
<td>Glu298Asp</td>
<td>Decreased enzyme activity</td>
</tr>
<tr>
<td></td>
<td>T786C</td>
<td>Decreased promoter activity</td>
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Apo: apolipoprotein; HDL: high-density lipoprotein; ACE: angiotensin-converting enzyme
genetic factors in disease, they can be suitably controlled in transgenic and knock out animals once their pure colony is made. In purely bred animal colonies, several generation of such animals now can be studied from the inception to the clinical expression of disease. “Human Genome Project” will allow us to pick up those genes whose functions are not yet known and allow those whose function is already known as possible candidates of cardiovascular disease by careful pedigree analysis, candidate gene approach and analysis of VNTR mini satellite and micro satellite linkages. The knock out animal will allow us to observe the effects of absence of a particular gene in development of an animal in the context of angiogenesis, vasculogenesis and development of heart. The same animal can also be studied to see if the gene is really involved in accelerating or decelerating degenerative cardiovascular diseases.

Another area where animal models can be useful will be in developing the field of tissue engineering. Tissue engineering can meet the demand for heart valve replacement, cardiac tissue for diseased heart and vessels for coronary and lower limb bypass surgery.

cDNA microarray technology has been used in determining the molecular phenotype in cardiac growth, development and response to injury using rats as the animal model. This may pave way for further studies for understanding the process of cellular recruitment and gene regulation in the myocardium following injury.

**Graft Engineering and Cell Therapy in Managing Cardiovascular Diseases**

Bone marrow transplantation and peripheral stem cell transplantation have become an established mode of treatment for many incurable and hitherto untreatable malignant and non-malignant hematological disorders. This therapy has also given certain insights about how stem cells function, and has enriched our understanding of stem cell biology leading to development of the concept of plasticity of stem cells. This concept simply means that after suitable environmental conditions are created, a hemopoietic stem cell develops the capability to trans-differentiate between nerve cell, muscle cell, etc. This is an extremely powerful and important concept in biology and medicine. Potentially we can use hemopoietic stem cell from bone marrow and use it for repair of certain cellular defects in the heart i.e. lost myocardium in acute myocardial infarction or even in certain form of cardiomyopathy. This therapy is now in its infancy but promises to be a powerful therapeutic tool in future. Bone marrow transplantation was used successfully in a study to treat hyperlipidemia in apolipoprotein (apo) E-deficient mice.

**Pre-natal Diagnosis of Cardiovascular Diseases**

As of today, pre-natal diagnosis of congenital heart diseases is being done by fetal echocardiography. With the advances in biological research nowadays it is possible to give a pre-natal diagnosis for simple gene disorders if the gene causing the disease is known. Many disorders of myocardium may arise from single gene defect, which may control the ion pumps, adhesion molecules, sarcolemmal architectures, actin molecule, myosin molecule or gene defects in mitochondria which affect the bioenergetics and terminal metabolism in the muscle cell. If the abnormal genes for the disease are known, the family can be analyzed for the mutations and carrier status can be assigned to family members and proper counseling can be given. A preliminary study has been carried out in France on the genetic testing of hypertrophic cardiomyopathy (HCM). Advances in embryo culture and implantation technology will, in future, allow for extensive pre-implementation embryo diagnosis and this may be acceptable to various religious groups where abortion is interim acceptable mode of make-up.

**Gene Therapy in Cardiovascular Diseases**

The first human trial in cardiovascular disease started in 1994, treating peripheral vascular disease with vascular endothelial growth factor (VGEF). Since then, many different potential angiogenic growth factors have been tested. Therapeutic angiogenesis using VGEF gene has been in use since 1997 for the treatment of ischemic heart disease. A major drawback of catheter-based coronary interventions like coronary angioplasty is restenosis. VGEF has been shown to improve myocardial perfusion in CAD patients.

Another candidate gene which has received interest since 1990s is nitric oxide synthase (NOS) gene. This gene is responsible for the synthesis of nitric oxide which exerts critical and diverse functions in the cardiovascular system. The three isoforms of NOS gene i.e. endothelial, neuronal and inducible have been used in gene therapy with encouraging results.

Although gene therapy is still in infancy stage, it holds tremendous promise to be used in routine clinical practice as an adjunct to the existing procedures since it can help to overcome the limitations associated with current therapeutic regimen.
Understanding Gene Function through Ethnopharmacology and Medicines

The effect of traditional medicines (like Ayurvedic, Japanese, Chinese etc.) has been studied in relation to atherosclerosis. Abana, an Ayurvedic preparation, when tested in hypercholesterolemic rabbits, was found to arrest the rise of total cholesterol, low-density lipoprotein (LDL) cholesterol and very low-density lipoprotein (VLDL) cholesterol. In addition, Abana was found to raise the levels of high-density lipoprotein (HDL) cholesterol. The antiatherogenetic effect of Chinese medicine Angelica was tested in a rabbit model. It was found to decrease the levels of serum triglycerides. Another such medicine is Commiphora mukul (Guggul); its hypolipidemic and anti-inflammatory properties have been established by various studies. Several preparations of Guggul are used in Ayurvedic medicine for different purposes. Studies need to be done how Guggul alters the patterns of various gene expressions to bring about its salutary effect in lipid profile. Additionally, other herbs like fenugreek (Trigonella foenum-graecum), red yeast rice and artichoke (Cynara scolymus) have shown a reduction in serum cholesterol levels between 10-33%. Hence, many herbal products have a potential for reducing hypercholesterolemia and further research is essential for confirming their efficacy before their use on a regular basis. The biggest advantage of these herbal medicines is their low cost and hence, their easy affordability to everyone which is beneficial for a developing country like India. The area of ethnopharmacology, effect of various ancient drugs on gene expression is a promising area of research and is likely to provide rich dividends in the form of improved therapy for various cardiovascular diseases in future.

Future Prospects

There are several challenges in the prevention and management of atherosclerotic heart disease. The principal challenge is to identify susceptible individuals before they develop the disease. Advances in the field of genomics and proteomics will help us in preventing and treating this multifactorial disease. The mainstays in therapy for occlusive diseases are the revascularization procedures. In this respect, understanding the mechanism of angiogenesis for development of newer therapies will go a long way in overcoming the risk of restenosis associated with these procedures. Stem cell therapy also holds a great promise for future since it can regenerate the lost tissue in myocardial infarction which is not possible with the current therapeutic measures.

Conclusions

In this short overview we have attempted to show how completion of “Human Genome Project” and development of innumerable areas of cell biology and information technology have given us an immense insight and power to develop various molecules to prevent and treat cardiovascular diseases.

References