Management of Coronary Artery Disease in Patients with Diabetes Mellitus

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Diabetes mellitus (DM) is a common medical problem and a major risk factor for the development of atherosclerotic coronary artery disease (CAD). Worldwide, more than 100 million people have DM and this figure is projected to double in the next 20 years. In India alone, it is estimated that there are more than 20 million diabetics. There is no doubt that DM is going to be a major burden on the health care system in the twenty-first century. DM is not only associated with increased incidence and prevalence of CAD, but diabetic patients also have a 2-fold increase in mortality after acute myocardial infarction (AMI). The outcome following coronary angioplasty (PTCA) and coronary bypass grafting (CABG) is also poor. The Framingham Heart Study data showed that patients with DM, particularly women, exhibited an increased risk of cardiovascular events including angina, stroke, claudication, heart failure, myocardial infarction and sudden death. Diabetics have the same degree of cardiovascular risk as non-diabetics who have had a myocardial infarction (MI). A number of pathophysiological mechanisms contribute to the development of both macrovascular and microvascular complications in patients with DM. The presence of associated risk factors for atherosclerosis like obesity, advanced age, dyslipidemia and hypertension, as well as multiple metabolic abnormalities like hyperglycemia, hyperinsulinemia and abnormalities of platelet function and coagulation contribute to the cardiovascular complications.

Control of Risk Factors

In diabetics, coronary risk factors are magnified several times, and these need to be strictly controlled. Smoking is an independent predictor of mortality in diabetics and cessation of smoking should be recommended for all patients. Weight loss and increased physical activity have been shown to improve glycemic control, lipid profile and insulin resistance.

Intense glycemic control is highly effective in preventing and retarding macrovascular and, to some extent, macrovascular complications in both insulin-requiring DM (IRDM) and non-insulin requiring DM (NIRDM).

There is no specific trial addressing the effect of lipid lowering in diabetic patients; however, subgroup analyses from a number of trials with statins have shown the efficacy of this therapy. The Scandinavian Simvastatin Survival Study (4S) trial, which enrolled 202 diabetic patients, indicated that simvastatin reduced five-year mortality by 43% in diabetic patients with hypercholesterolemia and CAD, as compared to 29% reduction in non-diabetic patients. The Cholesterol and Recurrent Events Trial (CARE) enrolled post-MI patients with average cholesterol levels. Treatment with pravastatin showed a greater reduction in major coronary event rate during a five-year follow-up in patients with DM compared to non-diabetics (37% vs. 29%). In the Long-term Intervention with Pravastatin in Ischemic Disease (LIPID) study (which enrolled 811 diabetics), pravastatin therapy showed a 19% reduction in the composite end-point of CAD-related death and MI during 6 years of follow-up in the subgroup of diabetics with past history of MI or unstable angina. The data available from studies on the use of fibrate therapy is limited. The Helsinki Heart Study had suggested a trend towards decreased coronary events in diabetic patients treated with gemfibrozil compared to non-diabetics.

There are a number of studies which have shown that adequate control of blood pressure markedly reduces major cardiovascular events. Most of the available data are from studies using beta-blockers and diuretics and they continue to be recommended as first-line therapy. There are sufficient data to show that they reduce mortality and morbidity in patients with diabetic nephropathy and in NIRDM patients. Strict control of blood pressure to a mean of 144/82 mmHg has been shown to significantly reduce strokes, diabetes-related deaths, heart failure, microvascular complications and visual loss in UKPDS trial. There is a growing amount of data coming up in support of angiotensin-converting enzyme (ACE) inhibitors and calcium channel blockers. The revised guidelines of the Joint National Committee (JNC) on Prevention, Detection, Evaluation and Treatment of High Blood Pressure recommended a level of 130/85 mmHg for diabetic patients.
Issues in Management

Managing CAD patients with DM requires special attention. The majority of data on the management of CAD in DM are based on retrospective subgroup analysis of major clinical trials, which on average included 20%–30% diabetic patients. Patients with DM have a number of adverse clinical, angiographic and metabolic features contributing to poor prognosis. Diabetic patients with CAD are more often female, obese and hypertensive. They usually have severe angina, history of previous MI or CABG and marked left ventricular failure. They have abnormal endothelial function with reduced coronary flow reserve. There is platelet activation with increased thromboxane A2 secretion. The levels of fibrinogen and Factor VII are higher than normal, while antithrombin III and plasma fibrinolytic activity are lower. Angiographically, they have diffuse, extensive involvement of smaller reference vessels, multivessel involvement, higher incidence of left main coronary artery disease, poorer collaterals, lower ejection fraction and more thrombus formation.

Two important issues need to be considered in the management of CAD in patients with DM—management of acute myocardial infarction and coronary revascularization (both surgical and catheter-based).

Management of Acute Myocardial Infarction

Management strategies include the use of thrombolytics, beta-blockers, ACE inhibitors, nitrates and antiplatelet agents.

Thrombolytic therapy: Diabetic patients are less likely to receive thrombolytic therapy as they present late and/or with atypical symptoms, perhaps due to impaired sensation of pain. There is also undue concern regarding the adverse effects of thrombolytic agents, especially ocular complications. The efficacy of thrombolysis may also be reduced in DM due to enhanced platelet activity, elevated procoagulant activity and impaired intrinsic fibrinolysis. Despite achieving similar patency rates (70%) as non-diabetics, the mortality is higher in diabetics (17.3% v. 10.2%), probably because of impaired endothelial function and diminished myocardial flow reserve. Reocclusion with recurrent ischemia was also higher in diabetics (9.2% v. 5.3%) in the Global Use of Strategies To Open Occluded Arteries (GUSTO) study. However, in spite of several factors unfavorable for thrombolysis, they still derive substantial benefit from it. The Fibrinolytic Therapy Trialists (FTT) Collaborative Group in an overview of 58 600 patients including 4529 diabetics, showed that the absolute reduction in the 35-day mortality after thrombolysis in patients with DM was 3.7% compared with 1.5% in non-diabetics. In diabetic patients it fell to 13.6% following thrombolysis as compared to 17.3% in the control group, while in the non-diabetic group, the mortality was reduced to 8.7% versus 10.2% in the control group.8

The fear of increased adverse effects of thrombolytic therapy in diabetics is not borne out by the available data. The data from the FTT Collaborative Group showed no statistically significant increase in hemorrhagic stroke in patients with DM receiving thrombolytic therapy (0.6% v. 0.4%). In the GUSTO study, the incidence of clinically evident ocular complications was only 0.02% and there was no case of intraocular hemorrhage. Stroke rates were comparable in diabetics and non-diabetics (1.9% v. 1.4%). Vitreous hemorrhage in diabetic patients was rare.8

There are some data to show the superiority of an accelerated tissue plasminogen activator (tpa) regimen in patients with DM. In the GUSTO-1 study, diabetics given tpa had a 30-day mortality of 8% compared to 10.2% in the group given streptokinase (STK). The stroke rate was not significantly different in two groups (1.7% in the tpa group and 1.4% in the STK group). Thus, the accelerated tpa regimen appears to be better than STK. However, the cost-effectiveness of this regimen in our country remains questionable.

Post-thrombolysis strategies: Whether to follow a conservative or an invasive approach following thrombolysis in AMI, is a matter of debate. Clinical variables collected for the 3339 patients of the Thrombolysis In Myocardial Infarction (TIMI)-II study were analyzed retrospectively to identify predictors of clinical events at 42 days, so as to identify the subgroups in which an invasive or conservative strategy might be superior. Patients with DM had a higher mortality in the invasive compared to the conservative strategy group (14.8% v. 4.2%, p<0.001). A conservative approach after thrombolysis seems to be a better option in DM, and angioplasty should be recommended only in the presence of post-infarction angina or objective evidence of ischemia.

Primary angioplasty: Primary angioplasty is equally successful in diabetics and non-diabetics and appears to be more effective than thrombolytic therapy. The GUSTO-IIB angioplasty substudy compared the efficacy and relative benefits of primary angioplasty over thrombolytic therapy among diabetics.11 Diabetics had worse baseline clinical and angiographic profiles. Despite more severe stenosis and poorer flow in the culprit artery, procedural success with angioplasty was similar for diabetics (70.4%) and non-
Antiplatelet agents: Diabetics have increased platelet activation and accelerated turnover of platelets. Thus, theoretically, they may need higher doses or higher frequency of aspirin administration, or need additional antiplatelet agents like ticlopidine or clopidogrel. The subset analysis of the Second International Study of Infarct Survival (ISIS-2) found no benefit of 160 mg per day of aspirin in diabetic patients. Since this was a subgroup analysis, it could be a chance finding but it did put a question mark on the efficacy of low-dose aspirin in diabetic patients. However, a meta-analysis of the Anti-Platelet Trialists’ Collaborative Group was done to determine the effect of antiplatelet therapy on vascular events. It showed a significant benefit of aspirin therapy in DM with or without vascular disease, for the combined end-point of stroke, MI or vascular death. In diabetic patients, the vascular event rate with aspirin fell to 18.5% as compared to 22.3% in controls. The magnitude of this benefit was similar in diabetics and non-diabetics. The most widely tested antiplatelet regimen was “medium-dose” (75–325 mg/day) aspirin. Doses throughout this range seemed to have a similar effect. There was no appreciable evidence that either a higher aspirin dose or any other antiplatelet regimen was more effective than medium-dose aspirin in preventing vascular events.

Glycoprotein(Gp) IIb/IIIa inhibitors reduce the early and mid-term incidence of death, MI and recurrent angina in patients with acute coronary syndrome (ACS). They have been found to be useful alone and in combination with thrombolytic agents such as STK and tpa. They are also useful during percutaneous coronary intervention (PCI). The data regarding their efficacy in diabetics are based on subgroup analysis of some of the major trials. In the Platelet Receptor Inhibition for Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms (PRISM-PLUS) study, the reduction in clinical events in the group receiving tirofiban plus heparin compared to heparin alone was significant in both the diabetic and non-diabetic subgroups. The rate of death or MI at 180 days was 11.2% with tirofiban plus heparin versus 19.2% with heparin alone. In the PURSUIT study (10 948 patients including 20% diabetics), reduction in the 30-day mortality with eptifibatide was more in diabetic patients than non-diabetics. A meta-analysis of 10 recent clinical trials also showed that diabetics had twice the absolute reduction in event rates as compared to non-diabetics.

Anticoagulants: The majority of recent trials of low-molecular-weight heparins (LMWH) in ACS have shown their superiority over unfractionated heparin (UFH) in the 30-day incidence of a composite end-point of death, MI or recurrent angina. They have been shown to be especially useful in the high-risk subgroups, i.e. patients with electrocardiographic changes, positive troponin-T and DM. The diabetic patients (n=2175) in the randomized GUSTO-IIB study (n=12142) showed a tendency towards a lower risk of death or reinfarction with hirudin as compared to heparin at 30 days (12.2% v. 13.9%) and 6 months (17.8% v. 20.2%). However, they had a higher incidence of major bleeding and stroke.

Beta-blockers: Clinicians are hesitant to use beta-blockers for diabetic patients because of their concerns regarding impaired glucose metabolism and worsening of dyslipidemia, and the fear that symptoms of hypoglycemia would be masked. These concerns are only of academic interest since the benefits outweigh the theoretical risks. A number of studies evaluating the effect of beta-blockers in AMI have demonstrated a two-fold reduction in the relative risk in terms of mortality benefit after MI in diabetics as compared to non-diabetics. With beta-blockers, the percentage reduction in mortality was higher in diabetics (37%) compared to non-diabetics (13%). There were similar trends for reinfarction rates with a 55% reduction in patients with DM versus 21% reduction in non-diabetics.

From a database of 14 417 patients with chronic CAD who had been screened for participation in the Bezafibrate Infarction Prevention (BIP) study, 19% had NIRD. The total mortality during a 3-year follow-up was 7.8% in those receiving beta-blockers compared with 14.0% in those who were not (44% reduction). Multivariate analysis identified beta-blocker therapy as a significant independent contributor to improved survival. Within the diabetic population, the main benefit associated with beta-blocker therapy was observed in older patients, in those with a history of MI, those with limited functional capacity, and those at lower risk. Thus, therapy with beta-blockers appears to be associated with improved long-term survival in the high-risk subgroup of patients with DM and CAD.

Angiotension-converting enzyme inhibitors: ACE inhibition in AMI improves left ventricular remodelling, the fibrinolytic balance, endothelial function and sympathovagal balance. It delays renal dysfunction and improves glycemic control.

A retrospective analysis of the data of the GISSI-3 study
revealed a decreased 6-week mortality in diabetic patients with lisinopril (8.7% v. 12.4%), an effect that was significantly (p<.025) higher than that observed in non-diabetic patients (5.6% v. 5.9%). An analysis from the MI Collaborative Group comprising the pooled data of Consensus II, CCS-1 and GISSI-3 trials showed a trend towards higher benefit of ACE inhibition in diabetic patients (1.3 lives saved per 1000 diabetics treated v. 3.2 lives saved per 1000 non-diabetics treated). Even in the CONSENSUS-II trial, which showed no overall improvement in mortality by intravenous enalapril, a 22% reduction in mortality was seen at 6 months in the diabetic subgroup. The Survival of Myocardial Infarction Long-Term Evaluation (SMILE) Study revealed 34% cumulative reduction in the risk of death or severe congestive heart failure (CHF) with zofenopril at 6 weeks (risk reduction of 61% in diabetics and 23% in non-diabetics). The Trandolapril Cardiac Evaluation (TRACE) study also showed the benefit of ACE inhibition following AMI in diabetic patients with severe left ventricular dysfunction (ejection fraction <35%). One life was projected to be saved in 26 months by treating only 6 diabetics compared to 17 non-diabetics. Thus, the efficacy of ACE inhibitors in CAD patients with DM is overwhelming.

Glucose–insulin infusion: The long-term results of Diabetes and Insulin–Glucose infusion in the Acute Myocardial Infarction (DIGAMI) study from Sweden showed that the mortality in diabetic patients with AMI can be reduced by 29% with an insulin–glucose infusion followed by multidose insulin therapy. At 1 year, 18.6% patients in the intervention group had died compared to 26.1% in the control group. The mortality reduction was particularly evident in patients who had a low cardiovascular risk profile and no previous insulin treatment. These observed benefits from glucose–insulin infusions may be due to suppression of free oxidation of fatty acids. Free fatty acids potentiate ischemic injury by direct toxicity and by inhibition of glucose oxidation and increased oxygen demand. Some of these innovative treatments may be useful in reducing mortality in patients with DM after AMI.

Revascularization in Diabetic Patients

One-third of patients undergoing coronary revascularization are diabetic and have a poorer prognosis compared to non-diabetics, partly due to the adverse baseline variables. The National Heart, Lung, and Blood Institute (NHLBI) PTCA registry data showed that diabetic patients were older, had more co-morbid baseline conditions and triple-vessel disease.

Balloon angioplasty: PTCA in diabetic patients has a high angiographic success rate (85%–90%) but the risk of inhospital complications is more (MI: 0.4%–7%; mortality: 0.6%–3.2%), the rate of restenosis is higher (35%–41%) and the long-term outcome is not as good as in non-diabetic patients with a long-term mortality of 10%–40% over 5 to 10 years of follow-up. Overall, 5-year survival is less in diabetics undergoing PTCA, especially in those with IRDM (8.2%) compared to NIRDM (91%). The 10-year survival was 59% in diabetic patients and much higher in non-diabetic patients (83%) following PTCA in the LDCMC registry data. Similarly, 9-year incidence of mortality (35.9% v. 17.9%), nonfatal MI (29.0% v. 18.5%), repeat CABG (36.7% v. 27.4%), and repeat PTCA (43.7% v. 36.5%) was significantly higher in diabetics than in non-diabetics in the NHLBI Registry. On multivariate analysis, diabetes remained a significant predictor of decreased 9-year survival.

In an angiographic study by Rozenman et al., in addition to the high restenosis rate (41% v. 35%), a significant finding was the development of new lesions (22% in diabetics compared to 12% in non-diabetics). PTCA in DM has additive risk for the development of new narrowing.

Inability to revascularize all ischemic territories, a high restenosis rate and progression of atherosclerosis leading to repeat revascularization procedures are possible reasons for poor long-term results in CAD patients with DM.

Stents: Coronary stenting has reduced the incidence of in-hospital complications and rates of restenosis after angioplasty. The data on stenting in patients with DM is mainly based on subgroup analysis of major clinical trials. The initial angiographic success is similar (92%–100%) to the results in non-diabetic patients. As compared to plain balloon angioplasty, the restenosis rates are significantly reduced by stenting. However, the restenosis rates are higher in DM (24%–55%), compared to non-diabetic patients (17%–28%). The higher restenosis in diabetes is due to exaggerated intimal hyperplasia. Van Belle et al. found restenosis rates to be almost double in diabetic patients (63% v. 36%) due to greater late loss and a higher rate of late vessel occlusion. In the data reported by Elezi et al., the
The incidence of both restenosis (37.5% vs 28.3%, p<0.001) and stent vessel occlusion (5.3% vs 3.4%, p=0.037) was significantly higher in diabetic patients. One-year event-free survival was significantly lower in patients with DM than in non-diabetic patients. (73.1% vs 78.5%, p<0.001). The follow-up was characterized by a higher incidence of death, myocardial infarction and re-interventions. In the series reported by Abizaid et al., in-hospital mortality was highest (2%) in the IRDM group compared to the NIRDM group (0%) and non-diabetics (0.3%). The need for target vessel revascularization (TVR) was 28% in IRDM, compared to 18% in NIRDM and 16% in non-diabetics. Insulin-requiring diabetics fared worse than non-insulin requiring diabetics (one-year event-free survival 60% in IRDM, 70% in NIRDM and 76% in non-diabetics).

In the study by Lau et al., it was shown that diabetics were more prone to in-stent restenosis, especially in the small vessels. Follow-up angiography at 5 months revealed an in-stent restenosis rate of 40.5% in diabetics and 16.7% in non-diabetic patients. The restenosis rate of 55% was particularly high in diabetics receiving stents <3 mm in diameter compared to 27% in diabetics who received larger stents.

**Role of glycoprotein IIb/IIIa receptor antagonists during PCI:**

The data available on the role of Gp IIb/IIIa receptor antagonists during coronary interventions in diabetic patients are based on subgroup analysis from recent trials. They suggest that the use of these agents is beneficial in stented diabetic patients and there are preliminary data to suggest that they also reduce neointimal proliferation.

The EPIC trial showed a similar reduction (35%) in acute coronary events by abciximab in both diabetic and non-diabetic patients over a period of one month, but on follow-up of three years, diabetic patients had more cardiac events and the initial benefit was lost. In the EPILOG trial, abciximab therapy in diabetics led to a significant reduction in death and MI at 30 days and 6 months, but the TVR at 6 months was not reduced in diabetics.

In the EPISTENT study (n=2399), diabetic patients were a prospectively defined subset with 173 randomized to stent–placebo, 162 to stent–abciximab, and 156 to balloon angioplasty–abciximab. The primary end-point of combined death, MI or TVR at 6 months was significantly reduced in the stent–abciximab group (13%) compared to the stent–placebo (25.2%) and balloon–abciximab (23.9%) groups (p=0.005). The 1-year mortality rate for diabetics was 4.1% for stent–placebo and only 1.2% for stent–abciximab patients (p=0.11).

Pooled data from the EPIC, EPILOG and EPISTENT trials showed that abciximab reduced the 1-year mortality of diabetic patients to that of placebo-treated non-diabetic patients. In the non-diabetics, the placebo group had a one-year mortality of 2.6% which was reduced to 1.9%. In the diabetics, abciximab reduced the mortality to 2.5% compared to 4.5% in placebo group.

**CABG multivessel angioplasty in diabetic patients:**

DM is an important predictor of poor outcome after CABG as well as PTCA. Which strategy is better in patients with multivessel disease is a subject of much debate initiated by the Bypass Angioplasty Revascularization Investigation (BARI) trial results.

In the BARI trial, symptomatic patients with multivessel disease (n=1829) were randomly assigned to CABG or multivessel PTCA. Estimates of 7-year survival for the total population were 84.4% for CABG and 80.9% for PTCA (p=0.043). This difference could be explained by the 353 patients with treated DM for whom estimates of 7-year survival were worse for PTCA compared to CABG (55.7% vs 76.4%). Among the remaining 1476 patients, survival was virtually identical by the assigned treatment (86.4% CABG, 86.8% PTCA, p=0.72). The PTCA group also had substantially higher subsequent revascularization rates than the CABG group (59.7% v 13.1%, p<0.001).

The BARI study included 4039 patients with multivessel CAD; 1829 consented to randomization, and 2010 did not, but were followed up in a registry. In contrast to the randomized trial, the 7-year mortality rate of treated diabetics in the registry was equally high (26%) with PTCA and CABG. Seven-year mortality was higher for patients undergoing PTCA in the randomized trial than in the registry (19.1% v 13.9%, p<0.01) but not for those undergoing CABG (15.6% v 14.2%, p=0.57). This suggested that BARI physicians were able to select patients for multivessel PTCA who underwent revascularization without compromising long-term survival either in the overall population or in treated diabetics.

Similar results were seen in the Coronary Angioplasty versus Bypass Revascularisation Investigation (CABRI). Diabetics randomized to PTCA as well as CABG had higher mortality than respective non-diabetics; however, the association reached significance only in the former (RR 2.41, p=0.002). In the CABRI study, diabetics had twice the long-term mortality compared to non-diabetics; this difference was statistically significant both for the entire population and for those randomized to PTCA, but not for those randomized to CABG.

In contrast, the Emory Angioplasty versus Surgery Trial (EAST) and Randomized Intervention Treatment of Angina (RITA)-1 trials, did not show the same benefit of CABG over multivessel PTCA in diabetic patients. The smaller
single-center EAST had 15% drug-treated diabetic patients. In these patients, the overall 8-year mortality demonstrated no statistically significant difference relative to the first revascularization procedure selected. In the RITA-1 trial, the predefined primary end-point of death or nonfatal MI occurred in 17% of PTCA patients and in 16% of CABG patients (p=0.64). Diabetics did not fare any differently from non-diabetic patients.37

Weintraub et al.29 reported data from the Emory University showing that angiographic and clinical success rates after multivessel angioplasty were similar in diabetics and non-diabetics. In-hospital major complications were infrequent (3%), with a trend towards higher death or MI in those with IRDM. The 10-year survival rate in diabetics after multivessel PTCA was 45% while it was 48% after CABG. The survival in insulin-requiring diabetics was lower (31% after PTCA and 48% after CABG).29

The Northern New England Cardiovascular Disease Study Group has recently reported that patients with DM treated with percutaneous coronary intervention had significantly greater mortality relative to those undergoing CABG (risk-adjusted hazard ratios [HR]=1.49; p=0.037). The risk of mortality tended to increase further among patients with three-vessel disease (HR=2.02; p=0.038) than among patients with two-vessel disease (HR=1.33; p=0.21).48

The St Luke database49 showed that only 42% of diabetic patients could achieve complete revascularization by multivessel PTCA as compared to 79% after CABG. Six-year survival was 63% after PTCA and 70% after CABG. It showed that completeness of revascularization rather than the mode was predictive of late mortality.49 A majority of trials comparing multivessel plain balloon angioplasty with CABG revealed that overall long-term survival is better with CABG and the need for repeat revascularization is less. The Duke university database (1984 to 1990) included patients receiving intracoronary stents. At six years, the cardiovascular mortality was similar with two revascularization strategies (19% after CABG and 20% after PTCA in diabetics, and 10% and 8% in non-diabetics).50 The better results with multivessel PTCA in this database were attributed to the use of stents in some of the cases.

All these trials with multivessel angioplasty were initiated when stents had not really become part of routine coronary interventions. This naturally raises the question whether multivessel stenting would be better than CABG. The Arterial Revascularization Therapies Study (ARTS) group sought to answer this question.51 At one year, there was no significant difference in terms of the rates of death, stroke or MI between the patients undergoing multivessel stenting and CABG, while the rate of event-free survival was better in the latter group (73.8% v 87.8%). However, multivariate Cox regression analysis showed that presence of DM was the key predictor of outcome in the stented group. Therefore, even multivessel stenting may not solve the problems of percutaneous revascularization in diabetic patients.

Conclusions

The management of CAD in diabetic patients poses a challenging problem. The risk factors need to be vigorously controlled with tight management of lipids and blood pressure. Strict control of hyperglycemia should be ensured. The benefit of treating diabetics, especially with thrombolysis and ACE inhibitors, is more in terms of lives saved. Percutaneous interventions in diabetics are associated with higher rates of in-hospital complications and more restenosis as compared to non-diabetics. Long-term results of CABG in diabetics are better than those with multivessel PTCA. The availability of newer techniques of angioplasty, better stents and the use of Gp IIb/IIIa antagonists may improve the prognosis in diabetics. Intracoronary radiation may reduce neointimal proliferation. Stents coated with antiproliferation agents like rapamycin and taxol may be useful. For patients whose vessels are not suitable for any revascularization procedure, gene therapy may provide a solution.

References


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Percutaneous Coronary Intervention in Patients with Unstable Angina

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Acute coronary syndrome refers to a constellation of symptoms that are compatible with acute myocardial ischemia. It encompasses ST segment elevation, ST segment depression myocardial infarction, and unstable angina. Unstable angina and non-ST segment elevation myocardial infarction (UA/NSTEMI) are components of the acute coronary syndrome. UA and NSTEMI share common clinical, pathophysiologic and treatment features, and thus the 2 entities are often considered together for diagnosis and management. Patients with UA/NSTEMI account for more than 1 million hospital admissions annually in the United States, and 6%–8% of patients either die or have nonfatal myocardial infarction within the first year of diagnosis.1

Pathophysiology

The pathophysiology of UA/NSTEMI has some similarity with that of Q wave myocardial infarction. Coronary thrombus after rupture of a vulnerable plaque plays a key role in the pathogenesis. Autopsy studies have demonstrated plaque rupture in approximately 60% of cases and plaque erosion in 30%.2 The process of atherogenesis, lipid accumulation and cellular proliferation in UA/NSTEMI is not linear and is unpredictable. New high-grade lesions appear in previously mildly diseased segments. In a previous study of patients undergoing serial angiography, 66% of patients presenting with myocardial infarction and total occlusion of an artery on coronary angiography had less than 50% stenosis, and 97% of patients had less than 70% stenosis at the time of the initial coronary angiogram predating the infarction.1 This unpredictable and episodic progression is most likely a result of plaque rupture and subsequent intracoronary thrombus. Most plaque ruptures occur at the shoulder region (junction of the plaque cap and the adjacent more normal arterial wall). Several factors contribute to the clinical syndrome of UA/NSTEMI, namely, platelet aggregation, altered vasomotion, thrombus in the setting of plaque erosion (endothelial cell denudation), rupture of a vulnerable plaque (related to the rich lipid core), macrophage activity and metalloproteinases.4–6

Classification

There is no universally accepted definition for UA/NSTEMI. It encompasses a range of different clinical presentations. These clinical variables with different prognostic implications have been grouped under one diagnosis. In a proportion of patients admitted with a diagnosis of UA, the condition evolves into NSTEMI during the hospital stay. This process makes interpretation of published data difficult. The Braunwald classification7 has helped, but it is still not widely used, as ideally should be the case (Table 1). This classification was recently revised.8 Class IIIB (unstable angina with rest pain occurring within the preceding 48 hours without a recent myocardial infarction) was divided into troponin-positive and troponin-negative groups. The risk of cardiac death or myocardial infarction within 1 month was estimated to be 15%–20% in the class IIIB troponin-positive group and less than 2% in the class IIIB troponin-negative group. A second sample of troponin was recommended if the first was negative at admission. The association between increased troponin levels and increased mortality was evident in patients with normal creatine kinase-MB (CK-MB) levels. There was also a significant increase in mortality with increasing levels of troponin. The recent American College of Cardiology/American Heart Association (ACC/AHA) guidelines have stratified patients with UA/NSTEMI into 3 categories: low, intermediate and high risk, according to the clinical information, including history and physical examination, 12-lead electrocardiogram, and cardiac enzymes values (Table 2). This stratification is important not only for prognostic purposes but also for treatment; different treatments may be offered depending on the risk profile of the patient at admission or during hospital stay.

Prognosis of Patients with Unstable Angina

Excellent predictive models are available for patients with UA/NSTEMI. Simple risk scores are available from the Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy (PURSUIT) data, the Thrombolysis in Myocardial Infarction (TIMI) risk score derived from TIMI IIB, and Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q-Wave Coronary Events
(ESSENCE) trials. The risk factors associated with a higher risk for death or myocardial infarction in the PURSUIT trial were older age, faster heart rate, lower blood pressure, signs of heart failure and ST depression. An enrollment diagnosis of myocardial infarction was associated with a 50% increase in 30-day reinfarction. Therefore, most information about cardiac risk can be obtained at admission from patients presenting with UA/NSTEMI. The TIMI score identified that in patients with UA/NSTEMI, the following factors were associated with a higher risk for death, myocardial infarction, refractory ischemia, or urgent revascularization within 30 days. The benefit of abciximab persisted for up to 3 years after the procedure. The Evaluation in PTCA to Improve Long-term Outcome with Abciximab Gp IIb/IIIa blockade (EPLOG) trial tested the benefits of abciximab in patients at lesser risk who were given lower doses of weight-adjusted heparin. In 2972 enrolled patients, those who received abciximab and low-dose heparin had a 57% reduction in the composite end-points at 30 days, compared with patients receiving standard heparin therapy (11.7%). In the Chimeric 7E3 Antiplatelet Therapy in Unstable Angina Refractory to Standard Treatment (CAPTURE) trial, patients were randomized after coronary angiography to either placebo or abciximab. Abciximab therapy was given for 18 to 24 hours before coronary intervention and was continued for 1 hour after the intervention. The CAPTURE trial was prematurely terminated because the abciximab-treated patients had a significant reduction in the composite end-points at 30 days. Also, the progression of myocardial infarction before coronary intervention was significantly reduced (0.6% v. 2.1%; p=0.03).

The 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), and the Randomized Efficacy Study of Tirofiban for Outcomes and Restenosis (RESTORE) trials evaluated tirofiban. Among 1570 patients who had percutaneous coronary intervention (PCI) in PRISM-PLUS, there was a 42%
reduction in the 30-day incidence of death or myocardial
infarction. The RESTORE trial randomized patients to
either percutaneous transluminal coronary angioplasty
(PTCA) or directional atherectomy. In 2139 patients, the
study showed a trend for reduction of the combined end-
points of death or myocardial infarction, emergency
coronary artery bypass grafting, unplanned stent
placement for abrupt closure, and recurrent ischemia
compared with placebo at 6 months (24.1% vs. 27.1%,
\(p = 0.11\)).

In the Integrilin to Manage Platelet Activation to Prevent
Coronary Thrombosis (IMPACT-II) study, analysis of
treated patients showed an 24% reduction in the composite
deadly outcomes of death or myocardial infarction, emergency
coronary artery bypass grafting, unplanned stent
placement for abrupt closure, and recurrent ischemia
compared with placebo at 6 months (24.1% vs. 27.1%,
\(p = 0.11\)).

Abciximab is currently approved for treatment of UA/
NSTEMI as an adjunct to PCI or when the intervention is
planned within 24 hours. The longer half-life of abciximab
makes it less suitable in patients likely to need coronary
artery bypass grafting. In this setting, Gp IIb/IIIa inhibitors
with a shorter half-life (eptifibatide) would be optimal.

Tirofiban used in combination with heparin is approved for
use both for medical management and in conjunction with
PCI. Clinical markers that put the patient in the higher-risk
category may guide patient selection. Patients with ST
segment depression or increased cardiac marker values
derive the maximum benefit from this expensive therapy.

These trials indicate that Gp IIb/IIIa receptor inhibitors
are of benefit in patients with UA/NSTEMI, especially if PCI
is planned. Treatment benefits were observed within hours
after intervention and were sustained in the long term. The
clinical trials revealed a greater magnitude of benefit with
abciximab than with the other 2 agents. The effects of two
Gp IIb/IIIa inhibitors were compared in the recent Do
Tirofiban And Reopro Give Similar Efficacy Outcomes Trial
(TARGET) (presented at the American Heart Association 2000
meeting), in which 4812 patients were randomized to
receive either abciximab (n=2414) or tirofiban (n=2398).

<table>
<thead>
<tr>
<th>Feature</th>
<th>High risk (at least 1 of the following features must be present)</th>
<th>Intermediate risk (no high-risk feature but must have 1 of the following features)</th>
<th>Low risk (no high- or intermediate-risk feature but may have any of the following features)</th>
</tr>
</thead>
<tbody>
<tr>
<td>History</td>
<td>Accelerating tempo of ischemic symptoms in preceding 48 h</td>
<td>Prior MI, peripheral or cerebrovascular disease, or CABG: prior aspirin use</td>
<td></td>
</tr>
<tr>
<td>Character of pain</td>
<td>Prolonged ongoing (&gt;20 min) rest pain</td>
<td>Prolonged (&gt;20 min) rest angina, now resolved, with moderate or high likelihood of CAD</td>
<td>New-onset CCS class III or IV angina in the past 2 weeks with moderate or high likelihood of CAD</td>
</tr>
<tr>
<td>Clinical findings</td>
<td>Pulmonary edema, most likely related to ischemia</td>
<td>Age &gt;70 years</td>
<td>New-onset CCS class III or IV angina in the past 2 weeks with moderate or high likelihood of CAD</td>
</tr>
<tr>
<td>ECG findings</td>
<td>Angina at rest with transient ST segment changes &gt;0.05 mV Bundle branch block, new or presumed new Sustained ventricular tachycardia</td>
<td>T wave inversions &gt;0.2 mV Pathologic Q waves</td>
<td>Normal or unchanged ECG during an episode of chest discomfort</td>
</tr>
<tr>
<td>Cardiac markers</td>
<td>Markedly elevated (e.g. TnT or Tnl &gt;0.1 ng/mL)</td>
<td>Slightly elevated (e.g. TnT &gt;0.01 but &lt;0.1 ng/mL)</td>
<td>Normal</td>
</tr>
</tbody>
</table>

CABG: coronary artery bypass grafting; CAD: coronary artery disease; ECG: electrocardiography; MI: myocardial infarction; NTG: nitroglycerin; TnI: troponin I; TnT: troponin T.

An estimation of the short-term risks of death and nonfatal cardiac ischemic events in unstable angina is a complex multivariable problem that cannot be fully specified in a
table such as this. Therefore, the table is meant to offer general guidance and illustration rather than rigid algorithms.

The 2 groups were matched for the baseline characteristics. Sixty-three percent had acute coronary syndrome (ST segment elevation myocardial infarction and patients with cardiogenic shock were excluded). Ninety-five percent received intracoronary stents. The primary end-point of death, myocardial infarction, or urgent target vessel revascularization was achieved in 7.55% of patients in the tirofiban group and in 6.01% in the abciximab group (RR=1.26, p=0.037).

The greater benefit with abciximab is possibly due to both its longer biological half-life and its effects on non-IIb/IIIa vitronectin receptors. Dosing issues and underestimation of platelet inhibition are possible explanations for the worse outcome with tirofiban than with abciximab. The current ACC/AHA guidelines recommend that Gp IIb/IIIa inhibitors be given to patients with continuing ischemia or with high-risk features and to patients in whom PCI is planned.

**Coronary Angioplasty in Unstable Angina**

**General considerations:** Coronary angioplasty in a setting of unstable angina differs from that in stable angina pectoris and may be associated with increased complications. Angioplasty can aggravate thrombus formation by endothelial denudation and platelet activation. The presence of an intracoronary thrombus is an independent predictor of increased complications with PCI, especially myocardial infarction. The ineffectiveness of Gp IIb/IIIa inhibitors in a setting of thrombus makes this option less attractive. The setting of UA/NSTEMI also may exacerbate the dissection at the site of plaque rupture. Vasoreactivity of the treated vessel can also be a problem because the thrombus generates vasoactive substances. Finally, the risk of distal embolization is increased. These complications are less frequent in a setting of chronic stable angina. Recently, the introduction of intracoronary stents and filter and thrombectomy devices, in addition to improvement in the angioplasty equipment and operator experience, has led to resurgence of the concept of an early revascularization strategy in this high-risk subgroup.

**Combination therapy:** Unfractionated heparin has long been the main antithrombin agent used in the management of acute coronary syndromes. The most important limitation of unfractionated heparin is the variable dose–response relationship in different patients, necessitating frequent monitoring of the anticoagulation status. It can also bind to plasma proteins and endothelial cells and may result in rebound hypercoagulability, induce thrombocytopenia, and facilitate platelet aggregation.

Low-molecular-weight heparins (LMWHs) have been developed to address some of these limitations. These agents can be administered subcutaneously, and no monitoring is required. The efficacy of LMWH has been addressed in the ESSENCE and TIMI IIB trials. In the ESSENCE trial, 3171 patients with UA/NSTEMI were randomized to either subcutaneous enoxaparin or unfractionated heparin. Therapy was administered for a median of 2.6 days. The primary end-point of death, myocardial infarction, or recurrent angina occurred within 14 days of enrollment in 16.6% of patients receiving enoxaparin and in 19.8% of patients receiving unfractionated heparin (p=0.02). Similar results were reported in the TIMI IIB trial comparing enoxaparin and unfractionated heparin. The other trials with LMWH have not demonstrated their superiority over unfractionated heparin. In the Fast Revascularization During Instability in Coronary Artery Disease (FRISC II) trial, dalteparin was given to all patients for a minimum of 5 days. Subsequently, the patients were randomized to receive placebo or dalteparin for up to 90 days. There was a significant reduction in the incidence of death or myocardial infarction at 30 days but not at 3 months (6.7% v 8.0%).

The benefits of dalteparin were limited to patients with increased troponin T levels and those managed medically. Recently, the National Investigators Collaborating on Enoxaparin (NICE) 4, in an open-labeled study, compared the safety and efficacy of enoxaparin used in place of unfractionated heparin in the setting of acute coronary syndrome. The preliminary data compared favorably with the previously published results. Clinical Revascularization Using Integrilin Simultaneously with Enoxaparin (CRUISE) is an ongoing randomized trial to address this issue. The current ACC/AHA guidelines recommend treatment with either unfractionated heparin or with LMWH to be added to antiplatelet therapy.

**Early invasive versus conservative strategy in unstable angina (Tables 3 and 4):** The 2 strategies for the treatment of patients with UA/NSTEMI are widely debated. In the early conservative arm, PCI is reserved for patients who have recurrent ischemia at rest or minimal activity or who have a strongly positive stress test despite maximal medical therapy. The advantage of the early conservative treatment is that it limits the risks and costs of the invasive procedure in all patients presenting with UA/NSTEMI.

In contrast, early revascularization has several potential advantages that can partially offset the increased hazard of an early invasive strategy. It defines the coronary anatomy in patients with UA/NSTEMI. Typically, less than 10% have significant left main coronary artery disease, multivessel disease is present in 40% to 50%, single-vessel disease is present in a third, and 10% to 20% have no
The treatment strategy can be decided on the basis of the clinical profile and the coronary anatomy. Patients without significant coronary artery disease can be expeditiously dismissed. The revascularization strategy is determined by considering several factors: the patient’s clinical risk, coronary anatomy, ventricular function, severity of symptoms, co-morbidities and life expectancy. The decision for early invasive or conservative treatment strategies is based on the trials and registries described below.

### Table 3. Recent studies on unstable angina: features

<table>
<thead>
<tr>
<th></th>
<th></th>
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<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>1473</td>
<td>920</td>
<td>7987</td>
<td>7632</td>
<td>2433</td>
</tr>
<tr>
<td>Study design</td>
<td>2×2 factorial design</td>
<td>Randomized trial of non-Q wave MI</td>
<td>Prospective registry, studied the relationship between rates of cardiac procedures and outcomes</td>
<td>Early invasive strategy in recent years was compared with that in earlier years</td>
<td>Randomized trial Early invasive vs early conservative strategy</td>
</tr>
<tr>
<td>Primary endpoint</td>
<td>Death, nonfatal MI, positive ETT</td>
<td>Death or nonfatal MI</td>
<td>–</td>
<td>–</td>
<td>Death or nonfatal MI</td>
</tr>
<tr>
<td>Time from randomization-revascularization</td>
<td>18–72 hours</td>
<td>8 days (median)</td>
<td>–</td>
<td>–</td>
<td>2–7 days</td>
</tr>
<tr>
<td>Catheterization in the conservative group</td>
<td>64%</td>
<td>48%</td>
<td>48% v. 8.5% (7 d) in hospitals with and without cardiac cath lab, respectively</td>
<td>–</td>
<td>48% within 6 months</td>
</tr>
<tr>
<td>Limitations</td>
<td>Old study excluded post-MI patients</td>
<td>Predominantly male patients</td>
<td>–</td>
<td>Retrospective, single-institution experience</td>
<td>Older patients and patients with prior CABG excluded</td>
</tr>
<tr>
<td>Three-vessel disease</td>
<td>&lt;20%</td>
<td>50% with 3-vessel or left main coronary artery disease</td>
<td>–</td>
<td>30%</td>
<td>–</td>
</tr>
</tbody>
</table>

CABG: coronary artery bypass grafting; cath lab: catheterization laboratory; ETT: exercise tolerance test; MI: myocardial infarction; PTCA: percutaneous transluminal coronary angioplasty; TP A: tissue plasminogen activator

### Table 4. Recent studies on unstable angina: results

<table>
<thead>
<tr>
<th>Result</th>
<th>TIMI IIIB</th>
<th>VANQWISH</th>
<th>OASIS</th>
<th>Mayo Clinic</th>
<th>FRISC II</th>
</tr>
</thead>
<tbody>
<tr>
<td>In-hospital death</td>
<td>Inv (15)</td>
<td>Cons (2)</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>MI</td>
<td>18 (2.4)</td>
<td>18 (2.5)</td>
<td>21</td>
<td>6*</td>
<td>–</td>
</tr>
<tr>
<td>Death/MI</td>
<td>38 (5.1)</td>
<td>42 (5.7)</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Death/MI on F-U</td>
<td>7.5</td>
<td>8.2</td>
<td>7.7</td>
<td>3.3*</td>
<td>5.0</td>
</tr>
<tr>
<td>Death/MI on F-U</td>
<td>120 (16.2)</td>
<td>133 (18.1)</td>
<td>111</td>
<td>85*</td>
<td>11.0</td>
</tr>
<tr>
<td>Refractory angina, readmissions for unstable angina</td>
<td>55 (7.8)</td>
<td>100 (14.1)*</td>
<td>–</td>
<td>16.1</td>
<td>19.3</td>
</tr>
</tbody>
</table>

Cons: conservative; F-U: follow-up; Inv: invasive; MI: myocardial infarction; C lab: catheterization laboratory

*Significant difference Figures in parentheses are percentages of the cases
arm. Additionally, 64% of patients assigned to the early conservative arm underwent coronary angiography and almost half underwent revascularization within 6 weeks of presentation.

The DANAMI (DANish Trial in Acute Myocardial Infarction) study\textsuperscript{26} compared an early invasive strategy of PTCA or coronary artery bypass grafting with a conservative strategy in patients with inducible myocardial ischemia who received thrombolytic therapy for first myocardial infarction. In 503 patients randomized to an early invasive strategy, PTCA was performed in 266 (53%) and coronary artery bypass grafting in 147 (29.2%). In the conservative arm, only 1.6% of patients were revascularized 2 months after acute myocardial infarction. At a 2.4-year follow-up, there was no significant difference in mortality between the invasive and the conservative groups (3.6% v. 4.4%). Patients assigned to an early invasive strategy had a significant reduction in the incidence of acute myocardial infarction (5.6% v. 10.5%; \(p=0.0038\)) and a lower incidence of admission for unstable angina (17.9% v. 29.5%; \(p<0.00001\)). There was a significant reduction in the primary end-points of death, myocardial infarction, or admission for unstable angina in the early invasive arm (23.5% v. 36.6% at 2 years; \(p=0.00001\)).

The Veterans Affairs Non-Q-Wave Infarction Strategies In Hospital (VANQWISH) trial\textsuperscript{27} was a randomized trial also comparing the two strategies of early invasive and early conservative treatment in 920 patients admitted to the Veterans Administration hospitals. This trial showed that patients assigned to early invasive treatment had worse clinical outcomes during an average follow-up of 23 months. The number of patients with a primary end-point (death or nonfatal myocardial infarction) at hospital dismissal was significantly higher in the early invasive group than in the early conservative group (36 v. 15 patients; \(p=0.004\)) and also at 1 year (111 v. 85; \(p=0.05\)). Mortality was 11.3% in patients who underwent early coronary artery bypass grafting. In comparison, there was no mortality in patients who had early angioplasty. The reason for this difference is unexplained. It did, however, contribute to the overall conclusions of the trial.

The Organisation to Assess Strategies for Ischaemic Syndrome (OASIS) registry\textsuperscript{28} studied the relationship to the overall conclusions of the trial. For this difference is unexplained. It did, however, contribute to the overall conclusions of the trial. The reason for this difference is unexplained. It did, however, contribute to the overall conclusions of the trial. This was a prospective registry-based study in 6 different countries with different approaches to intervention. This study found no significant difference in the rates of cardiovascular death or myocardial infarction at 7 days and 6 months in countries with the highest rates of invasive procedures, but the rates of refractory angina and readmission for unstable angina were significantly lower. Moreover, death and myocardial infarction rates in 2 countries with high rates of early angiography and interventions (United States and Brazil) were different. The incidence of death and myocardial infarction in the United States was lower. This finding means that differences in procedural practice alone may be insufficient to explain the difference in the outcome between different countries.

A study from Mayo Clinic\textsuperscript{29} analyzed the in-hospital and intermediate-term outcomes of 7632 patients with unstable angina who underwent coronary interventions in the previous 20 years. The 3 study groups were determined by the year of intervention. The most recent group represented the years 1994 to 1998, an era with more experienced operators, use of effective antiplatelet strategy, and moderate use of intracoronary stents. The clinical success (as defined by residual stenosis less than 50% without in-hospital death, Q wave myocardial infarction, or coronary artery bypass grafting) was significantly higher in the recent period, as was reduction in the in-hospital complications, including 40% reduction in mortality, 60% decline in Q wave myocardial infarction, and 85% decrease in the need for emergency coronary artery bypass grafting (Fig. 1). This study documented that the results of coronary interventions had improved in the previous 4 years.

The most recent trial is the Fast Revascularisation during In Stability in Coronary artery disease (FRISC II).\textsuperscript{24} This is a multicenter randomized study (\(n=3048\)) from Europe of early invasive versus conservative strategy. All patients were treated with dalteparin, an LMWH, for 5–7 days. There were 1219 patients with unstable angina or non-Q wave...
myocardial infarction who were randomized to the early invasive group and 1214 patients in the noninvasive group. Patients older than 75 years or with previous coronary artery bypass grafting were excluded. The primary outcome of death or myocardial infarction at 6 months was 9.5% in the invasive group and 12% in the noninvasive group (p=0.045). The differences were more pronounced in men. There was a significant reduction in angina and hospital admissions in patients with unstable angina. The mortality at 1 year favored the early invasive strategy (2.2% v. 3.9%).

The main drawback of the FRISC II study was a delay of 6 days in achieving revascularization. Second, the highest-risk groups (older patients and patients who had coronary artery bypass grafting) were excluded. In the recently presented Treat Angina with Aggrastat+Determine Cost of Therapy with an Invasive or Conservative Strategy TIMI 18 (TACTICS-TIMI 18) study, 2220 patients with UA/NSTEMI from 9 countries were randomized to routine early catheterization (4–48 hours) or an early conservative strategy. The primary end-point of death, myocardial infarction, or early rehospitalization for acute coronary syndrome at 6 months was 15.9% in the early invasive arm and 19.4% in the conservative group (p=0.025). Older patients and patients with prior bypass grafting were not excluded. This trial extends the benefit of the early invasive group to early randomization and revascularization and also to the high-risk groups excluded in the FRISC II trial.

Currently, the ACC/AHA guidelines recommend that early invasive treatment be considered for patients with the following findings:

1. Recurrent angina or ischemia at rest or with low-level activities despite maximal anti-ischemic therapy
2. Recurrent angina or ischemia with symptoms of congestive heart failure
3. High-risk findings on noninvasive stress testing
4. Depressed left ventricular function (ejection fraction <0.40)
5. Hemodynamic instability
6. Sustained ventricular tachycardia
7. PCI within 6 months
8. Prior coronary artery bypass grafting
9. Repeated presentations with acute coronary syndrome despite therapy and without evidence for ongoing ischemia or high risk
10. Age older than 65 years, presentation with ST segment depression, and presentation with increased levels of cardiac markers without contraindications to revascularization.

The results of some of the early trials comparing invasive and conservative strategy have been mixed and controversial because of different study designs, the technology used, and the end-points tested. The results of the Mayo Clinic, FRISC II and TACTICS-TIMI 18 studies showed that the outcome of coronary interventions significantly improved in the late 1990s. Management strategies in these high-risk patients need to be re-examined.

**Approach to a patient with UA/NSTEMI:** The recent improved results of coronary interventions, as shown by the Mayo Clinic experience,29 the FRISC II study,24 and the TACTICS-TIMI18 studies, indicate that our strategy for the management of patients with unstable angina needs reorganization. Early coronary angiography allows better definition of coronary anatomy, including recognition of the culprit lesion, identification of patients with 3-vessel disease or left main coronary artery disease, and exclusion
of patients with normal coronary arteries and early hospital dismissal.

Medical management has improved, and the results of early PCI are encouraging. Once a patient is admitted with a diagnosis of UA/NSTEMI, risk stratification by clinical, electrocardiographic, or biochemical criteria is of paramount importance. Patients with a low or intermediate risk can be channeled to early dismissal, or kept under observation in the chest pain unit. The acute ischemia pathway outlined by the ACC/AHA guidelines helps triage a patient to early coronary angiography with or without percutaneous or surgical revascularization (Fig. 2). In any decision-making, factors to be considered are the risks for an acute adverse cardiac event, life expectancy, other comorbid diseases, the experience of the operator and the institution in doing PCI in the setting of UA/NSTEMI, the patient’s and hospital resources, and the country’s policies.

References

25. Effects of tissue plasminogen activator and a comparison of early invasive and conservative strategies in unstable angina and non-Q-wave myocardial infarction. Results of the TIMI IIb Trial. Circulation 1994; 89: 1545–1556
Failed Thrombolysis: A Continuing Problem

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Batra Heart Centre, Batra Hospital and Medical Research Centre, New Delhi

Trials of thrombolysis and primary angioplasty have shown that coronary artery patency and flow characteristics following thrombolytic therapy are independent prognostic predictors of outcome in acute myocardial infarction (AMI). A number of studies suggest that patency rates with TIMI-3 flow cannot be achieved in more than 54% of patients even with the best thrombolytic regimen. The timely detection of this failed reperfusion is very important for the further rational management of patients with AMI. The need is to diagnose it accurately and cost-effectively, preferably using noninvasive techniques (Table 1). This has to be followed by prompt and efficient attempts to reperfuse the blocked vessels by pharmacological, catheter-based or combined strategies.

Table 1. Failed thrombolysis—noninvasive diagnosis

1. Nonresolution of chest pain
2. Nonresolution of ST segment elevation on ECG (<25%–50% resolution at 90–180 min post-thrombolysis)
3. Enzyme kinetics
   - Troponin-T or creatinine kinase-MB or myoglobin ratio post-/pre-thrombolysis
   - <0.5 at 60 min
   - <1 at 90 min
4. Myocardial contrast echocardiography

Diagnosis of Failed Reperfusion

Cessation of chest pain has been regarded as a clinically predictive sign of reperfusion though its quantification for clinical trials is difficult. Only complete resolution of chest pain is a good predictor and this sign has been reported in only 29% of patients with patent arteries. Analgesia, which is an important part of the management of AMI, can mask this sign. It is, therefore, necessary to have more objectively defined markers of reperfusion besides resolution of chest pain.

Reperfusion arrhythmias: Although observed frequently after thrombolysis and primary percutaneous transluminal coronary angioplasty (PTCA), none of the observed arrhythmias (such as accelerated idioventricular rhythm) have been shown to add independently to the predictive value of diagnosing reperfusion.

Electrocardiography: Nonresolution of ST segment changes after thrombolysis has been shown to be a predictor of worse long-term outcome compared with a cohort with good resolution. However, this analysis is a better predictor of successful perfusion than of failed reperfusion. Studies have shown a variety of electrocardiographic (ECG) indices for reperfusion failure or success. These include 25% reduction in ST segment elevation, identified in the “worst lead” on the 60–180 min post-thrombolytic ECG; and a post- to pre-thrombolysis maximal ST segment elevation ratio or sum of post- to pre-thrombolysis ST segment elevation ratio equal to or less than 0.5. All these indices have been described as having reasonable sensitivity and specificity, irrespective of the infarct site. Continuous ST segment monitoring has also been shown to have a good predictive value for nonreperfusion in the GUSTO-I study, especially when the initial ST segment elevation is more than 4 mm.

Biochemical markers: Of the numerous markers, creatine kinase isoenzymes, troponin-T or I and myoglobin measurements have been used extensively for the early diagnosis of AMI. The rapid peaking of myoglobin seems to be the earliest marker of a successful recanalization, whilst the rate of rise of troponin-T post-thrombolysis over 3 hours has revealed very high (94%) sensitivity as well as specificity. There is, however, limited evidence that any of these markers can predict failure to achieve TIMI-3 flow at 60–90 min with any degree of similar accuracy.

At present, these assays are mostly reserved for post hoc confirmation rather than direct decision-making so they are of no help in the triage for patients with failed reperfusion. Early peaking of levels of these markers, while suggesting restoration of flow, does not necessarily mean achievement of reperfusion at tissue level (restoration of microvascular reperfusion). The lack of accuracy and interpretation makes their reliable use difficult in the setting of failed reperfusion, especially in the absence of concomitant ST segment resolution.
There is some evidence to suggest that patients who fail to achieve detectable fibrinogenolysis following thrombolysis could benefit from additional thrombolysis. In one small study, benefit was confined to those patients whose fibrinogen remained at greater than 1 g/L following therapy with streptokinase. Although fibrinogen assay is not routinely used, this measurement is potentially advantageous for distinguishing patients in whom nonreperfusion is primarily due to nonfibrinogenolysis rather than due to no reflow. In such cases, further thrombolysis and/or intensified antiplatelet therapy is more likely to be beneficial rather than interventional treatment.

**Emerging diagnostic strategies:** Even though sestamibi is accurate in assessing patency after systemic thrombolysis, the need to obtain prethrombolytic scans precludes this method from wide clinical application. The acute assessment of microvascular perfusion by myocardial contrast echocardiography may be the most promising strategy. Contrast agents are currently being tested in preclinical trials and are likely to become available for clinical trial assessment shortly.

**Management of Patients in Whom Thrombolysis has Apparently Failed**

**Repeat thrombolysis and additional antiplatelet therapy:** Readministering the thrombolytic agent is a frequently used strategy although the evidence supporting its utility is limited. Lack of attempts to prove the benefit of this therapy are surprising, considering the potentially large impact it could have in most hospitals. White et al. and Verheugt et al. showed the advantages of opening the infarct related artery with systemic or intracoronary tissue plasminogen activator (tPA) following failure with systemic streptokinase. Their investigations were, however, made as nonrandomized trials. In a small group of patients, stratified on the basis of 25% nonresolution of the ECG, Mounsey et al. also showed the benefit of additional intravenous alteplase in terms of improvement in the left ventricular ejection fraction at 6 weeks.

Pathophysiological studies, however, fail to support the theoretical benefit of repeat thrombolysis. Moreover, there seems to be little benefit from repeating thrombolysis later (more than 6 hours) rather than sooner, as the limited positive impact of late recanalization on reperfusion can be offset by the small but possibly deleterious effect of increased risk of bleeding. The issue of the efficacy of repeat thrombolysis can be sorted out only by a large dedicated trial but, in view of more recent advances in targeted antiplatelet therapy, the role of repeat thrombolysis may need to be redefined.

The safety of antiplatelet therapy combined with thrombolytic therapy will be assessed in GUSTO IV. The TIMI 4 trial has shown that a combination of abciximab and a half dose of tPA is efficacious and gives the best TIMI-3 flow (72%). However, the same was not true for the combination with streptokinase, which led to higher bleeding problems, including cerebral bleeds. Data on combining thrombolytics and antithrombins continue to suggest that the therapeutic window is narrow. So far, however, there are no data on the combination of thrombolytics with glycoprotein IIb/IIIa inhibitors in a setting of "rescue therapy", i.e. when thrombolysis has failed. For routine use, we will also need information about its safety, especially with the potential risk of increased bleeding.

**Role of percutaneous coronary intervention (PCI):** It is clear that something needs to be done in patients with clinical signs of failed reperfusion. However, little is known regarding the true value of the more costly rescue PCI from the data of trials that have already been carried out. In the TIMI IV subgroup analysis, no significant benefit was seen in the intervention group compared to conservative management. On the other hand, observational studies by Juliard et al. and Kaul et al. have shown that rescue PCI results compare well with the primary PCI in the same hospital. However, in their reported series, Kaul et al. have used abciximab in all the patients taken up for rescue PCI. Analysis of the intervention subgroup of the GUSTO I substudy has shown a trend towards improved left ventricular function and 30-day mortality in the PCI group compared to conservative strategy. The outcome of these patients was, however, less favorable than that of patients in whom initial thrombolysis was successful. Failed rescue PCI in the setting of failed thrombolysis was a significant predictor of high mortality (30%).

Analysis of the TAMI 5 study subgroup of patients with an occluded artery post-thrombolysis showed no benefit in patients who underwent early rather than predischarge PCI. The RESCUE trial compared patients with late signs (>8 hours) of occlusion of the left anterior descending artery post-thrombolysis and the results suggested improvement in the left ventricular function and composite endpoints. The relative benefits in these trials, however, have been quite modest. The benefits could possibly be significant if catheter-based interventions are combined with the use of glycoprotein IIb/IIIa inhibitors as has been done in the study reported by Kaul et al.

Although primary PCI has been shown to be superior to
thrombolysis in patients who can be taken up for the procedure without delay, it has had very little impact on AMI treatment in a community setting, mainly because of logistic reasons.

Referring only patients with failed reperfusion to a cardiac centre with interventional facilities could probably be both a good and realistic trade-off between additional expenses and resources and a significant contribution to cardiac care in the community. Whether the active research for signs of failed reperfusion in the early stage of AMI is superior to the strategy of initial conservative treatment with predischarge risk stratification and selection for late intervention remains to be seen. The use of intra-aortic balloon counterpulsation in a setting of failed thrombolysis can be useful, especially in hemodynamically unstable and high-risk patients who need transfer for catheter-based intervention. Data from a few trials do suggest the utility of this supportive procedure. A dedicated study funded by the British Heart Foundation, the REACT study (REscue Angioplasty versus Conservative management of Thrombolysis), has been planned to answer this important question.

Newer strategies, which include intracoronary therapeutic ultrasound or thrombectomy, could be useful in achieving lysis of an intra coronary thrombus as well as promoting microvascular reperfusion. There is a good theoretical basis for these which, if proven in clinical trials, could add to the present armamentarium as adjunctive procedures combined with PCI.

Therapeutic options used in failed thrombolysis are listed in Table 2.

**Table 2. Therapeutic options in failed thrombolysis**

1. Repeat thrombolysis (newer agents)
2. Glycoprotein IIb/IIIa inhibitors (abciximab, eptifibatide, tirofiban)
3. Intra-aortic balloon counterpulsation (IABP)
4. Rescue PTCA
5. Combination of glycoprotein IIb/IIIa blocker and PCI

**Emerging/Combined Strategies**

With the advent of new, potent, targeted antiplatelet agents (abciximab, eptifibatide, etc.) there are some promising data suggesting that they could be very useful not only as bail out measures both prior to and during intracoronary interventions but also as a primary adjunctive treatment. In the TIMI 14 study, thrombolysis was facilitated with a combination of reduced doses of alteplase and abciximab. Data from the GRAPE study suggests that abciximab used in anticipation of further intervention could rechannelize up to 40% of the occluded vessels. It is, therefore, likely that a combination of all reperfusion methods (thrombolysis, antiplatelet agents, intracoronary interventions) could offer the best reperfusion strategy in AMI. To this end, data from the SPEED trial advances these efforts by demonstrating that it is safe and efficacious to perform PCI after either thrombolytic monotherapy or combination therapy (rPA and abciximab). The study, however, suffers from the limitation that it is a nonrandomized comparison.

**Conclusions**

Failed thrombolysis continues to be a significant clinical problem in the management of patients with AMI. There is no proven strategy which is clearly superior and can be recommended as the treatment of choice. In the absence of sound clinical data, however, it seems logical to recommend a careful, frequent assessment of the patient’s clinical status after instituting systemic thrombolysis. This should include frequent 12-lead ECG control. A 90–120 min recording is very important since it could form a basis for consideration of further management, which could be PCI after administering Gp IIb/IIIa blockers if the option is easily achievable.

It is likely that patients with failed thrombolysis comprise a heterogeneous group with different levels of failed lysis, microvascular no reflow or different degrees of critical narrowing in the target or infarct related vessel. Careful evaluation of these factors in individual patients will result in a more tailored and step-wise approach.

**References**

9. Purcell IP, Newall N, Farrer M. Change in ST segment elevation 60 minutes after thrombolytic initiation predicts clinical outcome as accurately as later electrocardiographic changes. Heart 1997; 78: 465–471
A Randomized Study of the Safety and Efficacy of Reused Angioplasty Balloon Catheters

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Background: To lower costs, many centers around the world utilize previously used, resterilized balloon catheters to perform coronary angioplasty. There are no controlled trials regarding their safety and efficacy.

Methods and Results: We performed the first randomized, double-blind, controlled, single-center clinical trial comparing the safety (clinical success) and efficacy (angiographic success) of reused versus new coronary angioplasty balloon catheters. A total of 377 procedures were included, 178 in the reused catheter arm and 199 in the new catheter arm. There were no significant differences in clinical or lesion characteristics among the two arms. The incidence of first balloon failure in the reused catheter arm was similar to that of the new catheter arm (12 cases [7%] v. 10 cases [5%], respectively). The angiographic success rate was also similar—176 cases (98.9%) in the reused catheter arm and 196 cases (98.5%) in the new catheter arm. The number of balloon catheters used per lesion, amount of contrast, and procedural and fluoroscopy time were similar in the two arms. At 30 days, the incidence of major adverse cardiac events was similar in both arms, 8 cases (4.5%) in the reused catheter arm and 10 cases (5%) in the new catheter arm. The incidence of fever was also similar.

Conclusions: When performing coronary angioplasty, reused catheters are as effective (similar angiographic success) and safe (similar clinical success) as new catheters. (Indian Heart J 2001; 53: 167–171)

Key Words: Angioplasty, Reused balloons, Coronary disease

It is estimated that coronary angioplasty (PTCA) is performed in more than one million cases worldwide annually. As the cost of equipment is substantial, several centers utilize previously used and resterilized balloon catheters to perform these procedures. In the field of cardiology, ablation catheters and pacemakers are also often reused. Although reuse of expensive materials is a standard practice in the operating room, according to the manufacturers these balloon catheters are intended for single use only.

Observational studies have differed in their assessment of the safety and efficacy of reused balloon catheters. According to one observational study, the potential for cost saving is great; however, much of the costs saved in the reuse strategy are lost in treating complications. Therefore, if there were no increase in complications, cost savings would be substantial.

There are no randomized controlled studies looking at the safety and efficacy of reused balloon catheters. We performed the first such study with the aim of demonstrating the safety (as judged by clinical success) and efficacy (as judged by angiographic success) of reused balloon catheters (RC) versus new balloon catheters (NC). We also measured other relevant factors including volume of contrast, number of balloons used and fluoroscopy time.

Methods

From February 1999 to February 2000, all patients undergoing coronary angioplasty at our institute were considered for enrollment in the study. Exclusion criteria included total occlusion (Thrombolysis In Myocardial Infarction, TIMI-0 flow) of unknown duration or longer than one month, and the presence of cardiogenic shock. Informed verbal consent was obtained from all patients. To qualify for enrollment in the trial, the lesion had to be crossed with a guidewire and the appropriate-size balloon had to be available (Fig. 1). Once these conditions were met, the patients were randomized to the reused balloon strategy or new balloon strategy in a ratio of 1:1. The operator was blinded to the choice of balloon catheter. If the “first”
balloon failed to cross the lesion, then a “second” smaller diameter balloon of the same randomization type (i.e. new or used) was utilized. If this second balloon catheter failed to cross, then a crossover to the other randomization arm was allowed. When crossover occurred, a balloon catheter similar in size was used. When multivessel PTCA was performed, only one vessel was enrolled in the study, and when there was more than one lesion in a vessel, only one lesion was enrolled.

Definitions: Lesion assessment was carried out visually, and they were classified according to the American College of Cardiology/American Heart Association lesion classification as modified by Ellis et al.\textsuperscript{7} Angiographic success was defined as a lesion residual stenosis of $<50\%$ by visual estimation. Clinical success was defined as angiographic success without in-hospital major adverse cardiac events (MACE), a composite of myocardial infarction (MI), death, emergency PTCA or coronary bypass surgery (CABG). A diseased vessel is defined as one that has a $\geq 50\%$ diameter stenosis and is a major epicardial coronary vessel or surgically bypassable branch thereof. Procedure time was always calculated beginning from the time of use of the guide catheter, and contrast volume was calculated as the total volume used after cannulation with the guide catheter. A buccal temperature of $>38\,^\circ C$ indicated fever.

Catheter preparation for reuse: Immediately after completion of the angioplasty procedure, the balloon catheter was inspected for any deformities. If the catheter had no defects, the shaft and the distal end of the catheter were cleaned with tap water to remove the blood and contrast medium, if any. The contrast from the balloon was sucked out by applying repeated negative pressure with a 10 ml luer lock syringe and the balloon was cleaned several times with distilled water. The monorail lumen was also flushed repeatedly and then checked with a guidewire for patency. The balloon port was left exposed to the air and the catheter left to dry for 24–48 hours. When the balloon was dry, a small stylet with a cover for the balloon was inserted and it was packed in its original cover. The balloon catheter was then sterilized with ethylene oxide.

Statistics: Data are expressed as mean $\pm$SD. Comparisons were performed using two-sided Student’s $t$ test for continuous variables. The tests of proportions were carried out when associated variables were categorical. A statistical probability of $<0.05$ was considered to be significant.

Results

A total of 433 patients underwent 452 PTCA procedures during the study period. Of these, 359 patients (377 lesions) were enrolled in the study (83% enrollment rate). The baseline clinical and angiographic characteristics (Tables 1 and 2) indicate that both groups were comparable. Unstable angina was present in 56% of the study population. The incidence of diabetes was high in both groups.

The procedural characteristics (Table 3) showed a high and similar success rate for crossing the lesion with the first chosen balloon (93\% for reused balloons and 95\% for new balloons). If the first balloon failed, the success of crossing the lesion with the second chosen balloon was also similar (4\% for both types of balloons). However, the crossover rate (failure to cross the lesion with the initial chosen strategy) was higher in the reused arm (3\% compared with 0.5\% in the new arm, $p=0.04$). The angiographic success rate in both arms (98.9\% for reused and 98.5\% for new balloons.)
and the number of balloon catheters used per lesion were similar. Contrast volume used and procedure and fluoroscopy time were also similar in both arms, and success or failure of the first balloon in crossing the lesion did not affect the success of the procedure or clinical outcome (Tables 4 and 5) in any of the strategies.

The performance of balloon catheters in certain lesion

<table>
<thead>
<tr>
<th>Table 1. Clinical characteristics of the patients</th>
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<tbody>
<tr>
<td><strong>Used balloon, n=178</strong></td>
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<tr>
<td><strong>New balloon, n=199</strong></td>
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<tr>
<td><strong>n (%)</strong></td>
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<tr>
<td><strong>n (%)</strong></td>
</tr>
<tr>
<td>Number of lesions</td>
</tr>
<tr>
<td>Age (years)</td>
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<tr>
<td>Age range (years)</td>
</tr>
<tr>
<td>Sex (males)</td>
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<tr>
<td>Clinical presentation</td>
</tr>
<tr>
<td>Stable angina</td>
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<tr>
<td>Unstable angina</td>
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<tr>
<td>Acute myocardial infarction</td>
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<tr>
<td>Asymptomatic</td>
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<tr>
<td>Previous myocardial infarction</td>
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<tr>
<td>≤30 days</td>
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<tr>
<td>&gt;30 days</td>
</tr>
<tr>
<td>Diabetes</td>
</tr>
<tr>
<td>Extent of CAD</td>
</tr>
<tr>
<td>1 vessel</td>
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<tr>
<td>2 vessel</td>
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<tr>
<td>3 vessel</td>
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Values are mean±SD. All values are statistically not significant

<table>
<thead>
<tr>
<th>Table 2. Angiographic characteristics</th>
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<tr>
<td><strong>Used balloon, n=178</strong></td>
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<tr>
<td><strong>New balloon, n=199</strong></td>
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<td><strong>n (%)</strong></td>
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<tr>
<td><strong>n (%)</strong></td>
</tr>
<tr>
<td>Target vessel</td>
</tr>
<tr>
<td>Left anterior descending</td>
</tr>
<tr>
<td>Diagonal—ramus</td>
</tr>
<tr>
<td>Circumflex—marginal</td>
</tr>
<tr>
<td>Right coronary artery</td>
</tr>
<tr>
<td>Graft (Saphenous vein)</td>
</tr>
<tr>
<td>PTCA procedure</td>
</tr>
<tr>
<td>Multivessel</td>
</tr>
<tr>
<td>Single vessel</td>
</tr>
<tr>
<td>Single lesion</td>
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<tr>
<td>Multilest</td>
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<tr>
<td>Electro PTCA</td>
</tr>
<tr>
<td>Ad hoc PTCA</td>
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<tr>
<td>Lesion type</td>
</tr>
<tr>
<td>De novo</td>
</tr>
<tr>
<td>Restenosis</td>
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<tr>
<td>Stent restenosis</td>
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<tr>
<td>Modified ACC/AHA lesion class</td>
</tr>
<tr>
<td>A</td>
</tr>
<tr>
<td>B1</td>
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<tr>
<td>B2</td>
</tr>
<tr>
<td>C</td>
</tr>
<tr>
<td>Thrombus</td>
</tr>
<tr>
<td>Calcification (moderate or greater)</td>
</tr>
<tr>
<td>Tortuosity</td>
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<tr>
<td>% diameter stenosis</td>
</tr>
<tr>
<td>Before PTCA</td>
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<tr>
<td>Final result</td>
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<td>Left ventricular ejection fraction</td>
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All values are statistically not significant

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<th>Table 3. Procedural characteristics</th>
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<tr>
<td><strong>Used balloon</strong></td>
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<td><strong>New balloon</strong></td>
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<tr>
<td><strong>n (%)</strong></td>
</tr>
<tr>
<td><strong>n (%)</strong></td>
</tr>
<tr>
<td>Number of lesions</td>
</tr>
<tr>
<td>Lesions crossed with first balloon</td>
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<tr>
<td>Lesions crossed with second balloon</td>
</tr>
<tr>
<td>Lesions crossed over to other strategy</td>
</tr>
<tr>
<td>Failure to pass any balloon</td>
</tr>
<tr>
<td>Lesions stented</td>
</tr>
<tr>
<td>Angiographic success</td>
</tr>
<tr>
<td>Balloon catheters/lesion</td>
</tr>
<tr>
<td>Guiding catheters/lesion</td>
</tr>
<tr>
<td>Guide wires/lesion</td>
</tr>
<tr>
<td>Contrast volume (ml)/per patient</td>
</tr>
<tr>
<td>Procedure time (min)</td>
</tr>
<tr>
<td>Fluoroscopy time to cross lesion</td>
</tr>
<tr>
<td>with wire (min)</td>
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<tr>
<td>Fluoroscopy time after lesion crossed with wire (min)</td>
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Values are mean±SD. All values are statistically not significant

<table>
<thead>
<tr>
<th>Table 4. Influence of first balloon success on results</th>
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<tr>
<td><strong>Used balloon</strong></td>
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<tr>
<td><strong>New balloon</strong></td>
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<tr>
<td><strong>n (%)</strong></td>
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<tr>
<td><strong>n (%)</strong></td>
</tr>
<tr>
<td>Number of lesions</td>
</tr>
<tr>
<td>Angiographic success</td>
</tr>
<tr>
<td>Number of balloon catheters/lesion</td>
</tr>
<tr>
<td>Contrast volume (ml)</td>
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<tr>
<td>Procedure time (min)</td>
</tr>
<tr>
<td>Fluoroscopy time to cross lesion with wire (min)</td>
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<tr>
<td>Fluoroscopy time after lesion crossed with wire (min)</td>
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<tr>
<td>MACE</td>
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Values are mean±SD. All values are statistically not significant

<table>
<thead>
<tr>
<th>Table 5. Influence of first balloon failure on results</th>
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<tr>
<td><strong>Used balloon</strong></td>
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<tr>
<td><strong>New balloon</strong></td>
</tr>
<tr>
<td><strong>n (%)</strong></td>
</tr>
<tr>
<td><strong>n (%)</strong></td>
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<tr>
<td>Number of lesions</td>
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<tr>
<td>Angiographic success</td>
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<tr>
<td>Number of balloon catheters/lesion</td>
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<tr>
<td>Contrast volume (ml)</td>
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<tr>
<td>Procedure time (min)</td>
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<tr>
<td>Fluoroscopy time to cross lesion with wire (min)</td>
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<tr>
<td>Fluoroscopy time after lesion crossed with wire (min)</td>
</tr>
<tr>
<td>MACE</td>
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</tbody>
</table>

Values are mean±SD. †p=0.05, ‡p=0.004

MACE: major adverse cardiac events.
subsets was examined (Table 6). In lesions that had ≥90% stenosis there were significantly more crossovers, more balloon catheters were utilized per lesion, and a longer fluoroscopy time was required in the used balloon arm as compared to the new balloon arm. In tortuous lesions, crossing with the first balloon occurred less frequently with used balloons than with new balloons; 75% v. 97%, respectively.

The incidence of MACE was similar—4.5% for reused and 5% for new balloon catheters (Table 7). At 30 days of follow-up, fever was noted in 1% of those in the RC arm and in 2% of those in the NC arm.

### Table 6. Performance of used v. new balloons in different lesion subsets

<table>
<thead>
<tr>
<th></th>
<th>Modified ACC/AHA class B2</th>
<th>Calcification</th>
<th>Tortuosity</th>
<th>Stenosis ≥90%</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Used n=53 New n=50</td>
<td>Used n=10 New n=11</td>
<td>Used n=32 New n=35</td>
<td>Used n=118 New n=149</td>
</tr>
<tr>
<td>Lesions crossed with first balloon</td>
<td>49 (92) 50 (100)†</td>
<td>9 (90) 11 (100)</td>
<td>24 (75) 33 (97)†</td>
<td>107 (91) 140 (94)</td>
</tr>
<tr>
<td>Lesions crossed with second balloon</td>
<td>1 (2) 0</td>
<td>1 (10) 0</td>
<td>5 (16) 2 (6)</td>
<td>5 (4) 9 (6)</td>
</tr>
<tr>
<td>Lesions crossed over to other strategy</td>
<td>3 (6) 0</td>
<td>0 0</td>
<td>3 (9) 0</td>
<td>6 (5) 0‡</td>
</tr>
<tr>
<td>Angiographic success</td>
<td>52 (98) 50 (100)</td>
<td>9 (90) 11 (100)</td>
<td>32 (100) 35 (100)</td>
<td>117 (99) 147 (99)</td>
</tr>
<tr>
<td>Balloon catheters/lesion</td>
<td>1.3±0.4 1.2±0.4</td>
<td>1.1±0.3 1.3±0.5</td>
<td>1.6±0.6 1.3±0.4†</td>
<td>1.3±0.4 1.2±0.4†</td>
</tr>
<tr>
<td>Fluoroscopy time after lesion crossed with wire (min)</td>
<td>5.2±2.1 4.8±2.4</td>
<td>6.4±3.6 6.1±4.0</td>
<td>7.1±4.0 5.7±2.4</td>
<td>6.6±4.6 5.0±3.1‡</td>
</tr>
</tbody>
</table>

†p value <0.05  
‡p value <0.01

### Table 7. In-hospital major adverse cardiac events and hospital stay

<table>
<thead>
<tr>
<th></th>
<th>Used balloon, n=178</th>
<th>New balloon, n=199</th>
</tr>
</thead>
<tbody>
<tr>
<td>Follow-up at 30 days</td>
<td>174 (98)</td>
<td>194 (98)</td>
</tr>
<tr>
<td>Fever</td>
<td>2 (1)</td>
<td>4 (2)</td>
</tr>
<tr>
<td>MACE</td>
<td>8 (4.5)</td>
<td>10 (5)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>7 (3.9)</td>
<td>8 (4)</td>
</tr>
<tr>
<td>Q wave</td>
<td>2 (1.1)</td>
<td>5 (2.5)</td>
</tr>
<tr>
<td>Non-Q wave</td>
<td>5 (2.8)</td>
<td>3 (1.5)</td>
</tr>
<tr>
<td>Emergency PTCA</td>
<td>1 (0.6)</td>
<td>3 (1.5)</td>
</tr>
<tr>
<td>Emergency CABG</td>
<td>2 (1.1)</td>
<td>1 (0.5)</td>
</tr>
<tr>
<td>Death</td>
<td>1 (0.6)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Hospital stay (days)</td>
<td>2.4±4</td>
<td>2.3±2.4</td>
</tr>
</tbody>
</table>

Values are mean±SD. All values are statistically not significant  
MACE: major adverse cardiac events

The concerns relating to balloon reuse include the risk of bacterial and viral infections, the risk of pyrogenic reaction, ethical and medicolegal concerns, and the argument that any cost saving would be offset by a possible increase in complications. With proper cleaning and sterilization, and ensuring the patency of the catheter lumen, the risk of bacterial infections from reused catheters does not appear to increase. There is no strong basis for concerns of possible transmission of viral diseases such as hepatitis B, C and HIV, or Creutzfeldt–Jakob disease. In one report, HIV was not detected by tissue culture technique after 1 to 3 days of drying. In addition, there have not been any cases reported worldwide of the transmission of viral diseases due to the reuse of catheters several times over.

To our knowledge, no randomized clinical trial has been published comparing catheter reuse strategy with single-use strategy. Data from observational studies have shown conflicting results regarding the safety and efficacy of reused balloons. Our study sample was representative of a busy catheterization laboratory as we had a high enrollment rate (83%). As compared to the published literature, there was a particularly high prevalence of diabetes in our series. The safety of PTCA in both strategies was the same, as judged by a similar rate of MACE and fever. The efficacy of both strategies was also the same, as reflected in the use of balloon catheters and fluoroscopy time.
We did not perform a cost analysis, Mak et al. have demonstrated that in a wide variety of patients, the results of reused balloon catheters are similar to those of new catheters. The potential for cost saving is high.

The rate of crossing the lesion with the first balloon was high and similar in the two strategies. This could be due to the advancements in balloon technology leading to the creation of small-profile catheters that maintain their low profile after initial use. However, when the first balloon fails to cross the lesion, it seems logical that one should switch to a new balloon of a smaller size. This is supported by our finding that a second smaller reused balloon failed to cross the lesion in 6 out of 12 lesions, while a second smaller new balloon crossed the lesion in 8 out of 9 lesions. Our study also demonstrated that, regardless of the initial balloon type, failure to cross with the first balloon will lead to prolonged procedure and fluoroscopy time and additional contrast. We examined the performance of used balloons in lesions with adverse characteristics, e.g. modified ACC/AHA class B2 lesions, tortuous lesions and lesions with ≥90% stenosis. The numbers, however, were small in these subgroups. Although used balloons did not perform as well as new balloons in these lesion subsets, the angiographic success rate remained high and was similar in both balloon types.

This study has demonstrated that there is no evidence of increased risk with reused balloon catheters. Although we did not perform a cost analysis, Mak et al. have suggested that in the absence of increased complications, the potential for cost savings are tremendous. The ethical and medicolegal concerns of the patient relate to the benefits, risks and cost of the procedure. We have demonstrated that the patient is not subjected to any procedural risks with reused balloons and there are no increased complications. Added to this is the fact that surgical equipment is resterilized and reused widely without raising any ethical concerns regarding their use.

Conclusions: This study is the first randomized study to demonstrate that in a wide variety of patients, the results of reused balloon catheters are similar to those of new catheters. The potential for cost saving is high.

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Lipid-Lowering Effect of Simvastatin in Patients of Type 2 Diabetes Mellitus

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Department of Medicine JLN Medical College & AG Hospitals, Ajmer

The incidence of macrovascular disease is increased two- to five-fold in diabetics as compared to nondiabetic patients. This is attributed mainly to diabetic dyslipidemia. In type 2 diabetes mellitus, dyslipidemia is usually present in the form of increased serum triglyceride (TG) levels, decreased high-density lipoprotein cholesterol (HDL-c) levels, normal or slightly higher low-density lipoprotein cholesterol (LDL-c) levels as compared to nondiabetics. However, the qualitative abnormalities of LDL-c (denser, smaller, glycosylated and oxidised particles) increase their affinity towards the endothelium, making them more atherogenic. Thus, an elevated level of LDL-c is the primary

Background: Dyslipidemia is an important factor in causation of macrovascular disease in type 2 diabetics. The role of simvastatin in the management of dyslipidemia in patients with type 2 diabetes mellitus is not very well elucidated, particularly in the context of the recent American Diabetes Association criteria 2001. The American Diabetes Association suggests that aggressive therapy of diabetic dyslipidemia will reduce the risk of coronary heart disease in diabetics and that optimal levels are serum low-density lipoprotein cholesterol <2.60 mmol/L (<100mg/dl), high-density lipoprotein cholesterol >1.15 mmol/L (>45 mg/dl) and triglycerides <2.30 mmol/L (<200mg/dl). This study was planned to compare the effect of simvastatin together with behavioral modification and behavioral modification alone, in age, sex and body mass index matched patients with type 2 diabetes mellitus with dyslipidemia, in reaching the target levels of various lipids as suggested by the American Diabetes Association criteria 2001.

Methods and Results: An open-label, prospective study was conducted on 80 patients with type 2 diabetes mellitus, who had fair to moderate glycemic control with a total glycated hemoglobin <10%. The patients in the control group (n=40) were treated with only behavioral modifications like calorie control and daily walking for 30 minutes, and no lipid-lowering agent was given. The lipid profile was re-evaluated after 6 and 12 weeks. The patients in the test group (n=40) were advised behavioral modification and given simvastatin. The starting dose was 10 mg at bed time. After 6 weeks of simvastatin therapy, a lipid profile was done. If the goal of low-density lipoprotein cholesterol <100 mg/dl and/or triglycerides <200 mg/dl and/or high-density lipoprotein cholesterol >45 mg/dl was not achieved, the dose of simvastatin was increased to 20 mg at bedtime for another 6 weeks. It was observed that low-density lipoprotein dyslipidemia was most prevalent. In the control group, a favorable alteration in lipid levels was brought about but none was statistically significant and the American Diabetes Association goals were not achieved in any of the patients. In the test group, there was a significant and favorable alteration in all lipid moieties, and the target levels were achieved in 80% of patients after 12 weeks. There was no significant alteration in glycemic control and liver functions. Myopathy and epigastric pain were seen in 1 patient in each group.

Conclusions: In our study, behavioral modification alone did not achieve the target levels of various lipids in diabetic dyslipidemia as per the American Diabetes Association guidelines. Hence, pharmacological therapy with statins should be resorted to in patients with type 2 diabetes mellitus who carry a high risk of coronary heart disease. Simvastatin is a safe and efficacious lipid-lowering drug. (Indian Heart J 2001; 53: 172–176)

Key Words: Lipids, Statins, Diabetes mellitus
risk and prognostic factor for coronary heart disease (CHD) in patients with type 2 diabetes mellitus.\textsuperscript{1} Aggressive lipid optimizing therapy, particularly for LDL-c, reduces cardiac morbidity and mortality, as well as total mortality.\textsuperscript{4}

The various statins (lovastatin, pravastatin, simvastatin, fluvastatin, atorvastatin and cerivastatin) not only lower the lipid levels but also stabilize vulnerable plaque, restore endothelial function, and have an antithrombotic, antiplatelet, anti-inflammatory, and antioxidant action.\textsuperscript{5} The reduction in LDL-c levels achieved by statins is approximately 30\%–60\%, a dimension never previously seen with diet control or any other treatment.\textsuperscript{6}

Simvastatin has been shown to reduce the total serum cholesterol and LDL-c by a mean of 22\%–32\% and 28\%–41\%, respectively, and to increase HDL-c by a mean of 8\%–13\%.\textsuperscript{7} The role of simvastatin in the management of dyslipidemia in patients with type 2 diabetes mellitus is not very well elucidated, particularly in the context of the recent American Diabetes Association (ADA) criteria 2001.\textsuperscript{8}

The ADA suggests that aggressive therapy of diabetic dyslipidemia will reduce the risk of CHD in diabetics in whom the optimal levels are a serum LDL-c level of <2.60 mmol/L (<100 mg/dl), a HDL-c level of >1.15 mmol/L (>45 mg/dl) and a TG level of <2.30 mmol/L (<200 mg/dl) (Table 1). The primary therapy should be directed mainly at lowering LDL-c levels. These recommendations are based not only on the high incidence of CHD in patients with diabetes but also on the case fatality rate of diabetics with CHD. Since a large proportion of diabetic patients die before they reach the hospital, a preventive strategy based solely on secondary prevention, would not be able to save a large number of these patients.

**Table 1. Category of CHD risk based on various lipid parameters in adult type 2 diabetics (ADA, 2001)**

<table>
<thead>
<tr>
<th>Risk</th>
<th>LDL-c</th>
<th>HDL-c</th>
<th>Triglyceride</th>
</tr>
</thead>
<tbody>
<tr>
<td>Optimal</td>
<td>&lt;100</td>
<td>&gt;45</td>
<td>&lt;200</td>
</tr>
<tr>
<td>Borderline</td>
<td>100–129</td>
<td>35–45</td>
<td>200–399</td>
</tr>
<tr>
<td>Higher</td>
<td>≥130</td>
<td>&lt;35</td>
<td>≥400</td>
</tr>
</tbody>
</table>

Data are given in mg/dl

LDL-c: low-density lipoprotein cholesterol; HDL-c: high-density lipoprotein cholesterol

This study was, therefore, planned to compare the effect of simvastatin and behavioral modification together with the effect of behavioral modification alone, in age, sex and body mass index (BMI) matched patients with type 2 diabetes mellitus and dyslipidemia, in reaching target levels of various lipids as suggested by ADA (2001).

**Methods**

An open-label, prospective study was carried out on 80 patients with type 2 diabetes mellitus. The criteria for diagnosis of diabetes mellitus and dyslipidemia were based on those laid down by ADA (2001).\textsuperscript{3,8} Patients with type 2 diabetes mellitus with a serum level of LDL-c >100 mg/dl and/or HDL-c <45 mg/dl and/or TG >200 mg/dl were recruited for this study.

All patients with type 2 diabetes mellitus had been under a fair or moderate glycemic control with a total glycated hemoglobin (HbA1) <10\%. Blood pressure was maintained at less than 140/90 mmHg and controlled with only calcium channel blockers or ACE inhibitors; thiazide diuretics and β-blockers were avoided and the patients were not given any lipid-lowering drugs. They were asked to avoid alcohol, smoking and oral contraceptive pills during the study. Diabetic patients suffering from hypothyroidism, renal disease, including diabetic nephropathy, and cirrhosis of liver were not included in the present study.

A detailed history was taken and a thorough physical examination, including calculation of anthropometric measurements, carried out in each patient.\textsuperscript{10} Total cholesterol, TG and HDL-c levels were measured enzymatically.\textsuperscript{11,12} Low-density lipoprotein cholesterol values were calculated using the Friedewald equation.\textsuperscript{13} Two baseline lipid values separated by an interval of 2 weeks were taken and their mean calculated. For those subjects in whom the values differed more than 30 mg\%, a third value was taken after 2 weeks and the average calculated.\textsuperscript{14} Statistical evaluation was done by determining the p value which was obtained after calculating the “t” value by the student’s t test. The 0.05 level was used for statistical evaluation. Data were expressed as mean±standard deviation. The patients were asked to avoid various drugs like phenytoin, corticosteroids, amiodarone, vitamin C, vitamin A, erythromycin, isoniazid, tetracycline, α-blockers, etc. which could affect cholesterol and TG levels during the estimation.\textsuperscript{15}

Patients in the control group (n=40) were treated with only behavioral modifications like calorie control and a daily walk for 30 minutes and no lipid-lowering agent was given. The lipid profile was re-evaluated after 12 weeks. The desirable body weight was estimated using a height–weight nomogram.\textsuperscript{10} The diabetic subjects were labeled as underweight (20\% below ideal body weight) or obese (20\% above ideal body weight), and the rest as having an ideal body weight. The recommended daily caloric intake per kg body weight was 20 kcal/kg for obese patients, 30 kcal/kg for patients with an ideal body weight and 40 kcal/kg for underweight patients. The subjects were asked to avoid a
high fat diet, such as, butter, ghee, cheese, chocolate, cream, ice-cream, fried foods, cakes, pastries, etc., and to take only 2 tablespoonsfuls of whichever oil (except coconut oil) they consumed. A diet rich in refined carbohydrates like bread, cake, honey, sugar, sweets, dried fruits, carbonated beverages, alcoholic and sweetened drinks was also to be avoided and they were advised to consume green leafy vegetables and fruits (except the very sweet and very ripe ones) in plenty. An individualised diet chart of the estimated caloric intake was given to each subject.

After assessing the risk of exercise, each subject was encouraged to take a brisk walk (with good footwear) for 30–45 minutes everyday and was advised to eat a snack after exercising to prevent hypoglycemia. The subjects were interviewed every week regarding their behavioral modification, and necessary corrections made wherever required. A close watch was kept on the glycemic control after exercising to prevent hypoglycemia. The subjects were encouraged to take a brisk walk (with good footwear) for 30–45 minutes everyday and was advised to eat a snack after exercising to prevent hypoglycemia.

Patients in the test group (n=40) were advised behavioral modification and given simvastatin in an initial dose of 10 mg at bedtime. After 6 weeks of simvastatin therapy, the lipid profile levels were tested. If the goal of serum levels of LDL-c <100 mg/dl and/or TG <200 mg/dl and/or HDL-c >45 mg/dl was not achieved, the dose of simvastatin was increased to 20 mg at bedtime for another 6 weeks. The patients were asked to report any side-effects at every visit. The creatine phosphokinase (CPK) level was estimated if the patient had symptoms of myopathy, and if it was more than 10 times normal, simvastatin therapy was discontinued. The SGOT and SGPT levels were estimated initially and after every 6 weeks, and the simvastatin therapy discontinued if there was a three-fold rise above the normal levels.

**Results**

Patients with type 2 diabetes mellitus matched in both the groups with respect to age, sex, waist–hip ratio, BMI, systemic blood pressure and various biochemical parameters, particularly the lipid levels (Table 2).

The CHD risk stratification depending on lipid levels in diabetic patients with dyslipidemia was evaluated. It was observed that LDL dyslipidemia was most prevalent and the majority of these patients, i.e. 76 (95%) were at a higher risk of developing CHD. Most of the patients (60%) with TG dyslipidemia were in the lower risk category, whereas those with HDL dyslipidemia (57.5%) were at moderate risk of developing CHD (Table 3).

<table>
<thead>
<tr>
<th>Table 2. Various parameters at the baseline of both the groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>Variable</td>
</tr>
<tr>
<td>Age (years)</td>
</tr>
<tr>
<td>Sex (M:F)</td>
</tr>
<tr>
<td>Weight (kg)</td>
</tr>
<tr>
<td>Waist–hip ratio</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
</tr>
<tr>
<td>Plasma glucose (F)(mg%)</td>
</tr>
<tr>
<td>HbAl (%)</td>
</tr>
<tr>
<td>SGOT (IU/ml)</td>
</tr>
<tr>
<td>SGPT (IU/ml)</td>
</tr>
<tr>
<td>BUN (mg%)</td>
</tr>
<tr>
<td>Serum creatinine (mg%)</td>
</tr>
<tr>
<td>Serum cholesterol (mg%)</td>
</tr>
<tr>
<td>Triglycerides (mg%)</td>
</tr>
<tr>
<td>LDL-cholesterol (mg%)</td>
</tr>
<tr>
<td>HDL-cholesterol (mg%)</td>
</tr>
</tbody>
</table>

Table 3. Baseline lipid levels in patients with diabetic dyslipidemia and their stratification based on CHD risk

<table>
<thead>
<tr>
<th>Table 3. Baseline lipid levels in patients with diabetic dyslipidemia and their stratification based on CHD risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Variable</td>
</tr>
<tr>
<td>Range (mg/dl)</td>
</tr>
<tr>
<td>Mean±SD (mg/dl)</td>
</tr>
<tr>
<td>Lower risk n (%)</td>
</tr>
<tr>
<td>Moderate risk n (%)</td>
</tr>
<tr>
<td>Higher risk n (%)</td>
</tr>
<tr>
<td>Range (mg/dl)</td>
</tr>
<tr>
<td>Mean±SD (mg/dl)</td>
</tr>
<tr>
<td>Lower risk n (%)</td>
</tr>
<tr>
<td>Moderate risk n (%)</td>
</tr>
<tr>
<td>Higher risk n (%)</td>
</tr>
</tbody>
</table>

In the control group (n=40), after 12 weeks of only behavioral modification, the weight reduced by 2.1 kg and 3.5 kg after 6 and 12 weeks, respectively. There were favorable alterations in the lipid levels but none were statistically significant, and the ADA goals were not
achieved in any of the patients (Table 4). In the test group, after simvastatin therapy (10 mg per day at bedtime for 6 weeks) along with behavioral modification, the weight reduced by 1.06 kg and 2.15 kg after 6 and 12 weeks, respectively. A significant and favorable alteration in all lipid moieties was achieved; but the target levels were achieved in only 30% (n=12) of the patients. The remaining 70% (n=28), received a higher dose of simvastatin (20 mg per day at bedtime) in continuation for another 6 weeks. A significant percentage alteration was obtained in lipid moieties as compared to baseline levels. However, target levels were not achieved in 8 patients (20%) even after this higher dosage (20 mg/day) of simvastatin (Table 5).

After 12 weeks of simvastatin therapy, HbA1 decreased from a mean of 8.80±0.72 g% to 8.43±0.74 g% (p>0.05); thus, there was no significant alteration in glycemic control after the therapy. Similarly, fasting plasma glucose decreased from 146.54±7.20 to 141.82±6.40 mg/dl. The SGOT and SGPT levels increased from a mean of 22.1±6.27 IU/ml to 32.85±8.33 IU/ml (p<0.001) and 22.85±6.49 IU/ml to 31.56±9.18 (p<0.001), respectively after 6 weeks, and values returned to near normal values of 23.24±4.82 and 24.20±5.60 IU/ml, respectively after 12 weeks. Jaundice or other symptoms of deranged liver functions were not observed in any patient treated with simvastatin. Only one patient developed epigastric pain after a dose of 20 mg/day of simvastatin but a dose of 10 mg/day was well tolerated. In one patient, who developed bilateral proximal upper limb weakness with CPK values of 1200 IU, simvastatin therapy was discontinued and the CPK values returned to normal with complete recovery of paresis within 10 days. Other side-effects like constipation, flatulence, nausea, dyspepsia, headache, asthenia, sleep disturbances, fatigue, dizziness, skin rash or myoglobinuria were not observed in any of the patients.

Discussion

The present study revealed that LDL dyslipidemia was the most prevalent while TG dyslipidemia was the least prevalent form of dyslipidemia when the ADA (2001) guidelines for diabetic dyslipidemia and CHD risk were applied. This is at variance with the common belief that TG dyslipidemia is the most prevalent in Indian diabetics.

In the present study, the content of the diet prescribed and exercise chosen was one which is practical for Indian diabetics, taking into consideration the regional food habits, lifestyle, and lack of availability of fitness programmes and

| Table 4. Effect of behavioral modification alone in diabetic dyslipidemia (Control Group) |
|-----------------------------------|------------------|------------------|------------------|
| **Parameters**                    | **Baseline**     | **After 6 weeks (n=40)** | **After 12 weeks (n=40)** |
|                                  | Mean ± SD        | Mean ± SD        | Mean ± SD        |
|                                  |                  | Change(%)*       |                  |
| Total Cholesterol                | 242.12±36.19     | 230.22±32.40     | 218.30±37.20     |
| Triglyceride                     | 163.45±49.55     | 140.20±46.54     | 144.90±45.30     |
| LDL-cholesterol                  | 170.28±34.93     | 151.82±32.45     | 148.82±34.90     |
| HDL-cholesterol                  | 39.21±6.20       | 41.48±5.55       | 42.10±4.96       |
| Weight (kg)                      | 61.20±12.74      | 61.20±10.26      | 59.80±10.10      |

The values of lipids are given in mg/dl
*Changes from baseline were not clinically significant (p>0.05)

| Table 5. Effect of simvastatin therapy plus behavioral modification in diabetic dyslipidemia (Test Group) |
|-----------------------------------|------------------|------------------|------------------|
| **Parameters**                    | **Baseline**     | **After 6 weeks (n=40)** | **After 12 weeks (n=28)** |
|                                  | Mean ± SD        | Mean ± SD        | Mean ± SD        |
|                                  |                  | Change(%)*       |                  |
| Total Cholesterol                | 252.84±38.22     | 188.75±29.19     | 178.75±23.97     |
| Triglyceride                     | 180.76±50.18     | 146.86±32.42     | 136.69±30.03     |
| LDL-cholesterol                  | 177.36±40.59     | 117.26±29.41     | 107.25±22.80     |
| HDL-cholesterol                  | 37.96±5.75       | 44.99±5.75       | 45.46±4.19       |
| Weight (kg)                      | 68.30±9.68       | 67.24±8.32       | 66.15±7.28       |

The values of lipids are given in mg/dl
*Simvastatin therapy in dosage of 10 mg/day for the initial 6 weeks
*Simvastatin therapy in dosage of 20 mg/day for the next 6 weeks in 28 patients who did not achieve target levels with 10 mg/day
*All changes from baseline were clinically significant (p<0.001) except for the change in weight (p>0.05)
equipment to calculate a patient’s oxygen uptake. Behavioral modification alone did not achieve the target levels for lipids. However, TG levels were lowered by 18.5%, similar to the levels obtained by a simvastatin therapy of 10mg for 6 weeks. Regular exercise has been shown to be consistently effective in lowering TG levels. Low-density lipoprotein was lowered by only 12.6%, a finding that implies that even with strict dietary control and rigorous exercise, which may not be possible for diabetics, LDL-c is lowered only by 15–25mg/dl. The HDL-c was increased by 7.37%, a finding similar to the ADA’s observation that most studies have failed to demonstrate a significant improvement in HDL-c levels.

Simvastatin (10–20mg per day) along with behavioral modification significantly reduced the levels of total cholesterol (29.3%), LDL-c (41.2%) and TG (24.3%), and increased the levels of HDL-c (19.80%) with target levels being achieved in 80% of patients with type 2 diabetes.

Simvastatin did not affect glycemic control in diabetics, as assessed by fasting plasma glucose and HbA1c, like most of the other studies except that of Daubresse et al. (1994). Furthermore, it was well-tolerated by most patients except for one who developed myopathy and another who developed gastrointestinal intolerance with a dose of 20mg but tolerated 10mg well. The incidence of myopathy is <0.2% and gastrointestinal intolerance about 2% in various studies. Thus, simvastatin is an effective lipid-lowering drug in achieving the goal for lipids, especially LDL-c, as compared to behavioral modification alone in patients with type 2 diabetes mellitus with dyslipidemia. It has no adverse effect on glycemic control.

In the present study, it was found that in diabetic dyslipidemia, behavioral modification alone does not achieve lipid levels low enough to reach the target levels as per the ADA guidelines. Hence, pharmacological therapy with statins should be resorted to in patients with type 2 diabetes mellitus who carry a high risk of CHD.

The limitations of the present study include a short-term follow-up and a small number of subjects. Also, there was no diet and exercise run-in period of 4 weeks prior to starting simvastatin. The absence of the above-mentioned run-in period could affect the comparison of lipid levels lowered by behavioral modification versus simvastatin; but it does not affect the comparison between the effect of behavioral modification alone and in conjunction with simvastatin in achieving the target levels for lipids as per the ADA (2001).

Since the dysmetabolic syndrome with its serious effects on mortality and morbidity through macrovascular disease is prevalent in Indians, aggressive lowering of lipid levels should be tried. However, long-term randomized follow-up studies are required to evaluate the efficacy of simvastatin or other lipid-lowering drugs in Indians with type 2 diabetes with dyslipidemia.

References

Relationship of Xba1 and EcoR1 Polymorphisms of Apolipoprotein-B Gene to Dyslipidemia and Obesity in Asian Indians in North India

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Department of Medicine and Biostatistics, All India Institute of Medical Sciences, New Delhi and Division of Biochemistry and Biotechnology, National Institute of Communicable Diseases, New Delhi

Background: Genetic investigation of dyslipidemia and obesity prevalent in the Indian population form the basis of this study.

Methods and Results: The frequency of restriction fragment length polymorphisms (Xba1 and EcoR1) of the apolipoprotein-B gene was investigated in a case–control study of 30 hyperlipidemic and 40 normolipidemic subjects. By univariate analysis, old age, higher body mass index, waist–hip ratio and sum of four skinfolds were found to be significantly associated with hyperlipidemia. The frequencies of X- and E+ alleles of the apolipoprotein-B gene were significantly higher in North Indians in the state of New Delhi (0.83 and 0.91, respectively) as compared to the observations made in Caucasians in previous studies, but was similar to the frequency reported in Indians settled in Singapore and the UK. There were no significant differences in the allele or genotype frequencies of either Xba1 or EcoR1 polymorphisms between the hyperlipidemic and normolipidemic groups. On multiple logistic regression analysis considering body mass index, waist–hip ratio, percentage body fat and genotypes as independent variables, no association was observed between the apolipoprotein-B genotypes and serum lipid components. Further, there were no associations between apolipoprotein-B polymorphisms and generalized obesity (as assessed by body mass index, sum of four skinfolds, and percentage total body fat) and abdominal obesity (as measured by waist circumference and waist–hip ratio).

Conclusions: We conclude that apolipoprotein-B (Xba1 and EcoR1) polymorphisms do not appear to influence serum lipid levels and parameters of generalized and regional obesity in the study sample. (Indian Heart J 2001; 53: 177–183)

Key Words: Genetics, Obesity, Hyperlipoproteinemia

A polipoprotein-B (apo-B) is involved in the assembly and secretion of chylomicrons from the small intestine and very low-density lipoprotein cholesterol (VLDL-c) from the liver.1 Apolipoprotein-B 100, virtually the only protein component of low-density lipoprotein cholesterol (LDL-c), functions as a ligand for the LDL-receptor and mediates the cellular uptake of cholesterol.2 Variants of the apo-B gene may, therefore, be involved in the pathogenesis of atherosclerosis. The apo-B gene is located on the short arm of chromosome 2 (2p23-24).3 Several restriction fragment length polymorphisms (RFLPs) of the apo-B gene have been described, including Xba1,4 EcoR1,5 and insertion/deletion (ins/del) polymorphism of the signal peptide region.6

Epidemiological studies have shown an association between the apo-B gene polymorphisms and an increase in various lipoprotein subfractions (total cholesterol [TC]. LDL-c and triglycerides [TG]) and atherosclerosis,7-19 though most of these studies have been carried out on Caucasian subjects. Further, a few studies have also shown a good correlation between apo-B polymorphisms and generalized obesity.13,15,17 Asian Indians are prone to develop dyslipidemia and accelerated atherosclerosis.20-24 Genetic investigations of the Asian Indian populations settled in other countries show a correlation of apo-B gene polymorphisms with hyperlipidemia.15,17 The subjects recruited in these studies, however, were either Indians from the southern states of India (primarily Tamil Nadu),17 or from the state of Punjab.15 No study has been carried out on the Asian
population in north India, which may be genetically different. Environmental and dietary influence, which are important for the development of a phenotypic profile, may also be distinctive in this population. Moreover, the correlation of general and regional obesity with apo-B gene polymorphisms has never been done on the population of north India.

We have, therefore, attempted to correlate apo-B gene polymorphisms (XbaI and EcoR1) with the lipid profile and body composition, particularly the percentage body fat (%BF) of hyperlipidemic and normolipidemic subjects in a tertiary medical care hospital in north India.

Methods
The study was carried out at the All India Institute of Medical Sciences, New Delhi, which draws patients from the northern, central and north-eastern regions of India. Particular care was taken to select patients residing in the city or its suburbs. The study was carried out from September 1997 to March 1999. One hundred consecutive patients (age range: 20–60 years), attending the medicine outpatient department and lipid research clinic, and healthy volunteers (recruited by a local advertisement) were screened for the study. Of these, 74 non-diabetic subjects were categorized into Group I (entry criteria: hyperlipidemics—TC >240 mg/dl and/or TG >250 mg/dl) and Group II (entry criteria: normolipidemics—both TC and TG <200 mg/dl). Patients with secondary hyperlipidemia (e.g. diabetes mellitus, hypothyroidism), definitive familial hyperlipidemia (e.g. familial hypercholesterolemia), and those with overt coronary heart disease (CHD) were excluded from the study. The study population constituted 30 in Group I and 40 in Group II.

Anthropometric measurements: The body mass index (BMI) was calculated using the formula, BMI=weight/height². Weight was measured to the nearest kilogram and height to the nearest centimeter. Waist circumference was measured midway between the iliac crest and the lowermost margin of the ribs and the hip circumference at the maximum circumference of the buttocks; all measurements were taken with the subject standing with feet placed together. A mean of three readings was taken for the calculation of waist–hip ratio (W–HR). Biceps, triceps, subscapular and suprailliac skinfolds were measured using Lange skinfold calipers. For the biceps skinfold, with the right arm pendulant, the biceps fat pad was measured at the level of the nipple line and for the triceps skinfold, the fat pad was measured midway between the acromion process of the scapula and the olecranon process. Fat pads at the inferior angle of the scapula, and superiorly on the iliac crest directly in the mid-axillary line were measured for the subscapular and suprailliac skinfolds. All skinfolds were measured to the nearest millimeter. A mean of three readings was recorded at each site. The equation of Durnin and Womersley was used for the calculation of body fat (BF) from skinfold thickness.

Metabolic measurements: All subjects underwent a 75 g oral glucose tolerance test performed according to standard WHO guidelines. Blood for lipid analysis was collected after a 12-hour overnight fast. Total cholesterol was estimated using the ferric chloride method. The method described by Gottfried and Rosenberg was used for the determination of TG. After precipitation of VLDL-c and LDL-c from the serum by phosphotungstic acid and magnesium chloride, high-density lipoprotein-cholesterol (HDL-c) was measured from the supernatant using the method described for TC. The value of LDL-c was calculated using the Freidwald's formula. LDL-c=TC – (HDL-c + TG/5).

DNA analysis: A modification of the procedure employed by Renges et al. was used. A venous blood sample of 2 ml was collected in an EDTA vial for genetic analysis. Genomic DNA was isolated using a QIA Amp Blood kit (QIAGEN, Germany) by following the standard protocol. The polymorphism detected by XbaI is due to a neutral substitution at codon 2488 (Thr2488) of the apo-B gene and that detected with EcoR1 is due to glutamate/lysine substitution at codon 4154 (Glu/Lys4154). The genotypes at XbaI and EcoR1 polymorphic sites of the apo-B gene were determined by polymerase chain reaction using restriction site-specific primers, synthesized on the ABI 392 DNA/RNA Synthesizer (Perkin-Elmer, Connecticut, USA). The following primers were used:

For XbaI site
Forward primer (F) 5’ – GGA GAC TAT TCA GAA GCT AA – 3’
Reverse primer (R) 5’ – GGA GAG CCT GAA GAC TGA CT – 3’

For EcoR1 site
Forward primer (F) 5’ – CTG AGA GAA GTG TCT CGG AAG – 3’
Reverse primer (R) 5’ – CTC GAA AAG TGG TAT AAC CAC – 3’

For PCR, the Gene Amp PCR reagent kit (Perkin-Elmer, Connecticut, USA) was used and the reaction set up according to the manufacturer’s protocol for a final volume of 50 µL. The reaction contents were mixed thoroughly, centrifuged briefly and placed on a Gene Amp PCR System 2400 (Perkin-Elmer, Connecticut, USA) using a thermal profile of 94°C for 5 s (denaturation), 58°C for 10 s (annealing) and 72°C for 30 s (extension) for 50 cycles.
Overnight restriction enzyme (RE) digestion of the PCR products was done separately at room temperature with 10 U of Xba1 and 20 U of EcoR1 for a 20 μL reaction volume. Electrophoresis of the reaction mixture of RE digestion was done on 1.2% agarose gel in a TBE buffer at a constant voltage of 100 V for 45 minutes. The DNA bands thus separated on agarose gel were visualized under an ultraviolet transilluminator (Biometra, GmbH, Germany). For the Xba1 site, a 710 bp fragment was amplified, which was digested with Xba1 into two fragments of 433 bp and 277 bp in the presence of the cutting site (X+) allele. For the EcoR1 site, a fragment of 480 bp was amplified, which was digested with EcoR1 into two fragments of 253 bp and 227 bp in the presence of the cutting site (E+).

Statistical analysis: The data were recorded on a pre-designed proforma and managed with Excel software. Data entry was double-checked for any human error. The allele frequencies of DNA polymorphism of the apo-B gene were estimated by gene counting. After confirming the normality aspect of the quantitative variable, descriptive statistics were computed using mean and standard deviation (SD). Proportions summarized qualitative variables. As age was statistically different among hyperlipidemias and normolipemias, analysis of covariance (ANCOVA) was applied to compare the mean±SD of anthropometric measurement, adjusting for age. The Student’s t test was used to compare the mean values of quantitative parameters among hyperlipidemic and normolipidemic groups. Association between hyperlipidemia and other categorical variables was assessed by the Chi-square test.

At the next stage of analysis, the associations were quantified by unadjusted odds ratio (OR) and 95% confidence interval (CI). Stepwise binary logistic regression analysis was applied to determine a parsimonious model from candidate variables identified in the second stage. The criteria used to decide the candidate variables to be included in the stepwise multivariate logistic regression analysis were based on statistical and clinical significance as follows: (i) all variables showing a statistically significant association with hyperlipidemia at p≤0.2 (age, BMI, W–HR and %BF); and (ii) Xba1 and EcoR1 genotype, though statistically not significant, were included in the model due to their clinical importance. Further, hyperlipidemic and normolipidemic groups were divided according to Xba1 and EcoR1 genotypes. The mean values of BMI, W–HR and %BF in the different genotypes were calculated and compared using the Student’s t test. Any association having p<0.05 was considered statistically significant. Statistical analysis was done using the Intercooled STATA version 6.0 (STATA Corp, Houston, Texas, USA) software package.

Results
We studied a total of 70 subjects of which 30 (25 males and 5 females) had hyperlipidemia (Group 1) and 40 (34 males and 6 females) were normolipidemic (Group 2). Group 1 consisted of 11 (37%) and 13 (43%) subjects having hypercholesterolemia and hypertriglyceridemia alone, and 6 subjects (20%) with both raised TC and TG. While subjects in both the groups were young, the subjects in Group 1 were significantly older than the subjects in Group 2 (37 years v. 30.6 years, P<0.009). The mean BMI in subjects in Group 1 was significantly higher than that in Group 2 subjects (Table 1). Subjects with a BMI ≥25 had 5 times higher odds of being hyperlipidemic than subjects with a BMI ≤25 (OR 5.35; 95% CI: 1.64–17.47). Abdominal obesity, as defined by W–HR, was present in 23 subjects in Group 1 (83%) as compared to 12 subjects in Group 2 (34%) (P<0.001). Subjects in Group 1 had a higher mean W–HR as compared to Group 2 subjects (Table 1). The odds of being hyperlipidemic were 7 times higher for a subject with abdominal obesity (OR 7.12; 95% CI: 2.4–21.13). Sum of the skinfold thickness at four sites (triceps, biceps, subscapular and suprailiac), termed as total skinfold thickness (TSFT) and mean %BF, as calculated from TSFT, were significantly higher in subjects in Group 1 as compared to Group 2 (Table 1). Subjects with %BF more than 20% had nearly 3 times higher odds for being hyperlipidemic as compared to those with lower body fat (OR 2.96; 95% CI: 1.03–8.53).

Table 1. Demographic and anthropometric profile

<table>
<thead>
<tr>
<th>Variables</th>
<th>Hyperlipidemic subjects</th>
<th>Normolipidemic subjects</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>37 (11.5)</td>
<td>30.6 (8.5)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Sex (M:F)</td>
<td>25:5</td>
<td>34:6</td>
<td>ns</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>24.92 (3.7)</td>
<td>20.8 (3.27)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>W–HR</td>
<td>0.93 (0.07)</td>
<td>0.875 (0.06)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>TSFT (mm)</td>
<td>75.2 (25.05)</td>
<td>52.51 (26.98)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>%BF</td>
<td>25.85 (6.9)</td>
<td>20.65 (8.14)</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

BMI: body mass index; W–HR: waist–hip ratio; TSFT: sum of four skinfolds; %BF: percentage body fat; ns: statistically not significant

Xba1 polymorphism was analyzed in 29 and 39 subjects in Groups 1 and 2, respectively; details are given in Table 2. The difference in genotype frequencies was not statistically significant in the two groups. The odds of a person with X2 genotype (X+X+ or X+X-) being hyperlipidemic was 0.58 (95% CI: 0.21–1.6) as compared to a person with X1 genotype (X–X–). EcoR1 polymorphisms, analyzed in 28 subjects in Group 1 and 40 subject in Group 2 are given in Table 2.
There was no statistically significant difference between EcoR1 genotype frequencies of the two groups. The odds of an E2 genotype being hyperlipidemic was 0.81 (95% CI: 0.22–2.98) as compared to the E1 genotype. The frequency of the more common alleles of each polymorphism (X– allele in case of XbaI and E+ allele in case of EcoR1) was calculated by gene counting. The frequencies of X– and E+ in all the subjects were 0.79 and 0.92, respectively. The corresponding values in subjects in Group 1 were 0.81 and 0.91 and in subjects in Group 2 were 0.78 and 0.92. There was no difference in allele frequencies between subjects in the two groups (Table 2).

### Table 2. Allele frequencies and genotypes in the hyperlipidemic and normolipidemic subjects

<table>
<thead>
<tr>
<th>Variables</th>
<th>Hyperlipidemic subjects (n=30)</th>
<th>Normolipidemic subjects (n=40)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allele frequency</td>
<td>X– 0.81</td>
<td>0.78</td>
</tr>
<tr>
<td>XbaI genotype*</td>
<td>X–X– (%) 20 (69)</td>
<td>22 (56)</td>
</tr>
<tr>
<td></td>
<td>X–X+ (%) 7 (24)</td>
<td>17 (43)</td>
</tr>
<tr>
<td></td>
<td>X+X+ (%) 2 (7)</td>
<td>0</td>
</tr>
<tr>
<td>EcoR1 genotype**</td>
<td>E+E– (%) 5 (18)</td>
<td>6 (15)</td>
</tr>
<tr>
<td></td>
<td>E+E+ (%) 23 (82)</td>
<td>34 (85)</td>
</tr>
</tbody>
</table>

* Analyzed in 29 hyperlipidemic and 39 normolipidemic subjects
** Analyzed in 28 hyperlipidemic and all normolipidemic subjects

Stepwise logistic regression analysis yielded BMI and W–HR as the two significant predictors of hyperlipidemia. After adjusting for other covariates, it was found that obese individuals (BMI>25) had 7 times higher odds of being hyperlipidemic than nonobese individuals (adjusted OR 7.39; 95% CI:1.49–36.69). Subjects with abdominal obesity (W–HR>0.9) were 12 times more likely to be hyperlipidemic than those without abdominal obesity (adjusted OR 12.82; 95% CI: 2.99–54.98) (Table 3).

Out of a total of 29 subjects in Group 1 in whom XbaI polymorphism results were available, 20 had X1 genotype and 9 had X2 genotype (X–X–7, X+X+=2). There was no statistically significant difference in the body composition of these two subgroups as measured by BMI (25.2 v. 24.6), W–HR (0.92 v. 0.95) or %BF (26.23 v. 25.67). EcoR1 analysis of 28 subjects in Group 1 was carried out. Of these, 5 had E1 genotype and 23 had E2 genotype. There was no statistically significant difference in BMI (26.3 v. 24.7), W–HR (0.94 v. 0.92) or %BF (27.20 v. 25.63) between these two subgroups.

In Group 2, XbaI results were available in 39 subjects. Twenty-two subjects had X1 genotype and 17 had X2. Body composition did not differ between the two groups as measured by BMI (20.93 v. 20.21), W–HR (0.86 v. 0.88), or %BF (21.23 v. 19.53). Six subjects in Group 2 had E1 genotype and 34 had E2 genotype. There was no statistically significant difference in BMI (20.10 v. 20.90), W–HR (0.86 v. 0.88) or %BF (18.3 v. 21.08) between E1 and E2 groups in subjects in Group 2.

### Discussion

Allele frequency of Apo-B gene polymorphisms (Table 4): The overall allele frequencies, and those of hyperlipidemic and normolipidemic subjects in the present study were similar to those in studies carried out on Indians settled in other countries. Saha et al.\(^{17}\) recorded a frequency of 0.83 for the X– allele of XbaI polymorphism and 0.9 for the E+ allele of EcoR1 polymorphism in their studies on Indians

### Table 3. Unadjusted and adjusted OR (95% CI) for various parameters using univariate and multivariate stepwise binary logistic regression

<table>
<thead>
<tr>
<th>Variables</th>
<th>Hyperlipidemic subjects</th>
<th>Normolipidemic subjects</th>
<th>Unadjusted OR (95%CI)</th>
<th>Adjusted OR (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>≤30 10 24 1.0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt;30 20 16 1.12–8.06 1.0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>≤25 17 35 1.0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt;25 13 5 5.35 (1.64–17.47) 7.39 (1.49–36.69)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>W–HR</td>
<td>≤0.9 7 28 1.0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt;0.9 23 12 7.12 (2.4–21.13) 12.82 (2.99–54.98)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TSFT (mm)*</td>
<td>≤50 6 18 1.0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt;50 24 21 3.43 (1.15–10.24)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>%BF*</td>
<td>≤20 7 18 1.0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt;20 23 21 2.96 (1.03–8.53)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>XbaI*</td>
<td>X1 20 22 1.72 (0.62–4.76) 1.56 (0.47–5.26)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>X2 9 17 1.0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EcoR1</td>
<td>E1 5 6 1.23 (0.33–4.54) 2.94 (0.46–20)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>E2 23 34 1.0</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

BMI: body mass index; W–HR: waist–hip ratio; TSFT: sum of four skinfolds; %BF: percentage body fat; X1: X–X–; X2: X+X+; or X+X–; E1: E+E–; E2: E+E+; E3: E+E+;
*Observation incomplete in one subject.

or %BF (21.23 v. 19.53). Six subjects in Group 2 had E1 genotype and 34 had E2 genotype. There was no statistically significant difference in BMI (20.10 v. 20.90), W–HR (0.86 v. 0.88) or %BF (18.3 v. 21.08) between E1 and E2 groups in subjects in Group 2.

### Table 4. Relative allele frequencies of X– and E+ alleles in different ethnic groups

<table>
<thead>
<tr>
<th>Ethnic groups</th>
<th>n</th>
<th>X–</th>
<th>p value</th>
<th>E+</th>
<th>p value</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Native North Indians</td>
<td>70</td>
<td>0.79</td>
<td>0.92</td>
<td>0.92</td>
<td>Present study</td>
<td></td>
</tr>
<tr>
<td>Caucasians (Norway)</td>
<td>56</td>
<td>0.48</td>
<td>&lt;0.001</td>
<td>$</td>
<td>$</td>
<td>Berg et al.7</td>
</tr>
<tr>
<td>Caucasians (Sweden)</td>
<td>91</td>
<td>0.44</td>
<td>&lt;0.001</td>
<td>0.81</td>
<td>&lt;0.01</td>
<td>Peacock et al.12</td>
</tr>
<tr>
<td>Asian Indians (UK)</td>
<td>107</td>
<td>0.71</td>
<td>ns</td>
<td>0.89</td>
<td>ns</td>
<td>Renges et al.15</td>
</tr>
<tr>
<td>Chinese (Singapore)</td>
<td>221</td>
<td>0.91</td>
<td>&lt;0.001</td>
<td>0.92</td>
<td>ns</td>
<td>Saha et al.16</td>
</tr>
<tr>
<td>Asian Indians (Singapore)</td>
<td>181</td>
<td>0.83</td>
<td>ns</td>
<td>0.90</td>
<td>ns</td>
<td>Saha et al.17</td>
</tr>
<tr>
<td>Caucasians (UK)</td>
<td>62</td>
<td>0.50</td>
<td>&lt;0.001</td>
<td>0.82</td>
<td>&lt;0.01</td>
<td>Talimud et al.19</td>
</tr>
<tr>
<td>Sri Lankans</td>
<td>190</td>
<td>0.80</td>
<td>ns</td>
<td>$</td>
<td>*</td>
<td>Mendis et al.13</td>
</tr>
</tbody>
</table>

$: not done; *not available; p value: significance of difference from present study; ns: statistically not significant from present study
settled in Singapore. According to Renges et al., a frequency of 0.71 and 0.89, respectively, was observed in a South Asian population consisting predominantly of people from the state of Punjab. The allele frequencies in our study were also similar to those reported in a population of Sri Lankans. In the Chinese population, however, the frequency of X− allele was higher but that of E+ allele was similar to that of our study group. A distinct difference is observed when the allele frequencies in the Caucasian population (largely European) are compared to those in Asian populations. Several of these studies reveal that frequencies of X− and E+ were lower in Caucasian subjects. However, besides ethnic and geographic differences, age and sex distribution, and the composition of the population studied by various authors are different.

Saha et al. studied a population comparable to the present study in the age group of 17–70 years, with a female preponderance. Of significance were the allele frequencies reported by Saha et al. and Berg et al. from a sample of the general population while other investigators excluded CHD patients. The frequency reported by Talmud et al. was of normolipidemic individuals.

**Association of Apo-B gene and hyperlipidemia:**

Table 5 shows that there was no significant difference in the genotype and allele frequencies of XbaI and EcoR1 polymorphisms between hyperlipidemic and normolipidemic subjects. The findings are similar to the observations made in a Caucasian population in USA; however, the authors used Southern blot to study the genetic polymorphisms and followed a system for the nomenclature of alleles different from that used currently. Although the apo-B gene polymorphism did not have any influence on the lipid levels, there was an association of X1 and R1 alleles with CHD. Association of the X+ allele and TC, TG, and LDL-c levels in Caucasian populations has been demonstrated repeatedly. Similar findings were also demonstrated in Asian Indians settled in Singapore, where the X+ allele was significantly associated with higher levels of serum TC, TG and low HDL-c. Renges et al. showed that in Asian Indians in the UK, X+ allele was associated with a low HDL-c level.

There may be several reasons for the differences observed in the various studies. A simple explanation could be that the populations studied by Saha et al. and Renges et al. were genetically distinctive, consisting of Indians from the southern states of India and from the state of Punjab, respectively. Moreover, gene–environment interplay may also account for the differential data since there may be substantial differences in the diet and lifestyle of Indians settled in other countries when compared to the north Indian population studied by us. Further, the sample size of the current study being small, a larger study would answer the questions in a more definitive manner. The RFLP detected with XbaI is due to substitution in the third wobble position of a codon, which does not alter the amino acid sequence of the apo-B. The effect of the substitution on the lipid levels is probably due to a linkage disequilibrium with ins/del polymorphism, which causes an amino acid change in the signal peptide of the apo-B gene. Many other researchers, including Saha et al., simultaneously studied ins/del polymorphism and showed the existence of a strong disequilibrium between it and the XbaI site polymorphism.

Absence of an association between EcoR1 polymorphism of apo-B and serum lipid levels is, however, similar to the observations made by Saha et al. and Renges et al. The RFLP detected with EcoR1 is due to a single base pair change in the coding region of the gene, which is known to cause an amino acid change in the apo-B by itself. This phenomenon may explain the general concurrence of our findings with other workers regarding correlation between EcoR1 polymorphism and serum lipids, while correlation with XbaI polymorphism was not observed. Indeed, association of serum lipid levels with the E− allele has been rarely described, except in a study of Canadian population.

**Association of the apo-B gene and body fat:** There was no association of generalized obesity (as measured by BMI

### Table 5. Apolipoprotein-B gene–lipid association studies

<table>
<thead>
<tr>
<th>Population</th>
<th>n</th>
<th>XbaI</th>
<th>EcoR1</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caucasians (Norway)</td>
<td>56*</td>
<td>X+→low HDL-c</td>
<td></td>
<td>Berg1</td>
</tr>
<tr>
<td>Caucasians (Italy)</td>
<td>119</td>
<td>X+→low HDL-c</td>
<td>None</td>
<td>Corbo et al.</td>
</tr>
<tr>
<td>Israelis</td>
<td>516</td>
<td>X+→low HDL-c</td>
<td></td>
<td>Friedlander et al.</td>
</tr>
<tr>
<td>Caucasians (USA)</td>
<td>84*</td>
<td>None</td>
<td>None</td>
<td>Hegge et al.</td>
</tr>
<tr>
<td>Caucasians (Sweden)</td>
<td>87*</td>
<td>X+→low HDL-c</td>
<td>None</td>
<td>Peacock et al.</td>
</tr>
<tr>
<td>Caucasians (Canada)</td>
<td>91*</td>
<td>X+→low HDL-c</td>
<td></td>
<td>Pouliot et al.</td>
</tr>
<tr>
<td>Asians Indians</td>
<td>46*</td>
<td>X+→low HDL-c</td>
<td>None</td>
<td>Saha et al.</td>
</tr>
<tr>
<td>(Singapore)</td>
<td>221</td>
<td>X+→low HDL-c</td>
<td>None</td>
<td>Saha et al.</td>
</tr>
<tr>
<td>Asians Indians</td>
<td>181</td>
<td>X+→low HDL-c</td>
<td>None</td>
<td>Saha et al.</td>
</tr>
<tr>
<td>(Singapore)</td>
<td>195</td>
<td>X+→low HDL-c</td>
<td>None</td>
<td>Talmud et al.</td>
</tr>
<tr>
<td>Sri Lankans (Sri Lanka)</td>
<td>95*</td>
<td>X+→low HDL-c</td>
<td>S</td>
<td>Mendis et al.</td>
</tr>
<tr>
<td>Sri Lankans (USA)</td>
<td>111</td>
<td>None</td>
<td>None</td>
<td>Genest et al.</td>
</tr>
<tr>
<td>Native North Indians</td>
<td>70 #</td>
<td>None</td>
<td>None</td>
<td>Present study</td>
</tr>
</tbody>
</table>

*Patients with coronary heart disease; *normal healthy population; #: selected hyperlipidemic and normolipidemic subjects; $: Not done; TC: total serum cholesterol; TG: serum triglycerides; HDL-c: high-density lipoprotein cholesterol; LDL-c: low-density lipoprotein cholesterol.
and %BF), and abdominal obesity (as measured by W–HR) with the genetic polymorphisms in the current study. Again, these findings are in variance with those of other workers and no firm conclusions can be drawn. Renges et al.13 observed an association of X+X+ genotype with low BMI and W–HR, whereas Saha et al.17 in their study found that the X+ allele was associated with a higher BMI. Pouliot et al.13 observed an association between the E– allele and lower body and abdominal fat.

In summary, the frequencies of apo-B gene polymorphisms, as determined with XbaI and EcoR1 in a sample of north Indian subjects studied by us were similar to those reported by previous authors regarding Asian Indians settled in other countries but were significantly different from those reported in the Caucasian population. There was no evidence of association of apo-B polymorphisms (XbaI and EcoR1) with serum lipid levels or generalized and abdominal obesity. In view of the strong associations reported in some studies, including those on immigrant Indians, studies are needed with a larger sample size to study ins/del polymorphisms and its linkage with XbaI polymorphism. In addition, association studies should be performed for other genetic loci, e.g. apolipoprotein-E, using gene sequencing.

Acknowledgments

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The Isoprenoid Pathway in Lone Atrial Fibrillation with Embolic Stroke

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Department of Biochemistry, University of Kerala, Trivandrum

Background: The isoprenoid pathway was assessed and compared in patients of lone atrial fibrillation with embolic stroke as well as in patients with right hemispheric, left hemispheric and bihemispheric dominance to determine the role of hemispheric dominance in its pathogenesis.

Methods and Results: The activities of hydroxyl methyl glutaryl-CoA reductase and RBC sodium–potassium ATPase as well as serum levels of plasma magnesium, digoxin, dolichol and ubiquinone were measured. The tyrosine/tryptophan catabolic patterns, glycoconjugate metabolism, free radical metabolism and RBC membrane composition were also assessed. In patients with lone atrial fibrillation with embolic stroke, there was elevated digoxin synthesis, increased dolichol and glycoconjugate levels, and low ubiquinone and elevated free radical levels. There was also an increase in tryptophan catabolites and a reduction in tyrosine catabolites; and an increase in the cholesterol: phospholipid ratio with a reduction in the glycoconjugate levels of the RBC membrane. The same biochemical patterns were obtained in individuals with right hemispheric dominance whereas the patterns were reversed in patients with left hemispheric dominance.

Conclusions: Lone atrial fibrillation with embolic stroke is associated with an upregulated isoprenoid pathway and elevated digoxin secretion from the hypothalamus. This occurs in right hemisphere-dominant individuals.

Key Words: Atrial fibrillation, Ions, Isoprenoid pathway

Original Article

Lone atrial fibrillation (AF) is considered to represent the tachycardia phase of the tachycardia bradycardia syndrome. Specific disease states associated with lone AF include obstruction of the sinus node artery and infiltration of the atrial myocardium in amyloidosis. Lone AF is the most important cause of embolic stroke in the elderly. The presumed stroke mechanism is thrombus formation in the fibrillating atrium or atrial appendage and its subsequent embolization. Cardiac toxicity of digoxin includes sinus arrhythmia, sinus bradycardia and all degrees of atrioventricular block, while premature ventricular contraction, ventricular bigeminy, ventricular tachycardia and ventricular fibrillation can also occur. The combination of supraventricular tachyarrhythmias is highly suggestive of digoxin toxicity. The human hypothalamus is reported to produce an endogenous membrane sodium–potassium ATPase (Na⁺–K⁺ ATPase) inhibition digoxin. Digoxin, being a steroidal glycoside, is produced by the isoprenoid pathway, and it was, therefore, considered pertinent to study this pathway and endogenous digoxin synthesis in patients with lone AF. Hemispheric dominance may play a role in the predisposition to cardiac arrhythmias. As hypothalamic digoxin can modulate the synaptic transmission of multiple neurotransmitter systems, the isoprenoid pathway was also assessed in individuals with differing hemispheric dominance to determine the role of hemispheric dominance in the pathogenesis of lone AF. The results are presented in this paper.

Methods

Three sets of patient populations were chosen for the study.
1. Fifteen cases of lone AF with embolic stroke—left middle cerebral artery territory and capsular infarct.
2. Fifteen cases of age- and sex-matched bihemisphere-dominant controls.
3. Fifteen cases each of right hemisphere, left hemisphere and bihemisphere-dominant individuals diagnosed by the dichotic listening test.

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The age range of the patients as well as the controls was 50–70 years. None of the subjects studied was under medication at the time their blood was tested and those included in the study were nonsmokers (active or passive). Informed consent was obtained from the subjects and the study was approved by the ethics committee of the institute. Fasting blood samples were collected in citrate tubes from each of the patients. Red blood cells (RBC) were separated within one hour of collection of the blood for the estimation of membrane Na⁺–K⁺ ATPase. The plasma was used for the analysis of various parameters. All the biochemicals used in this study were obtained from M/s Sigma Chemicals, USA. The activity of hydroxyl methyl glutaryl-CoA (HMG-CoA) reductase of the plasma was estimated by the method used by Rao and Ramakrishnan which determines the ratio of HMG-CoA to mevalonate. For the determination of the RBC Na⁺–K⁺ ATPase activity of the erythrocyte membrane, the procedure described by Wallach and Kamath was used. Digoxin in the plasma was determined by the procedure described by Arun et al. while for the estimation of ubiquinone and dolichol in the plasma, the procedures described by Palmer et al. were used. Magnesium in the plasma was estimated by atomic absorption spectrophotometry, and tryptophan, tyrosine, serotonin and catecholamines were estimated by the procedures mentioned in Methods of Biochemical Analysis. The quinolinic acid content of the plasma was estimated by HPLC (C₁₈, column micro Bondapak™, 4.6×150 mm), solvent system 0.01 M acetate buffer (pH 3.0) and methanol (6:4), flow rate 1.0 ml/min and detection UV (250 nm). Morphine, strychnine and nicotine were estimated by the methods described by Arun et al. Details of the procedures used for the estimation of total and individual glycosaminoglycan (GAG), carbohydrate components of glycoproteins, the activity of enzymes involved in the degradation of GAG and the activity of glycolipidases have been described earlier. Serum glycolipids were estimated as given in Methods in Enzymology. Superoxide dismutase (SOD) was assayed by the method used by Nishikimi et al. and modified by Kakkar et al. Catalase, glutathione peroxidase and glutathione reductase were estimated by the procedures described in Methods of Enzymatic Analysis. Malondialdehyde (MDA), conjugated dienes and hydroperoxides and reduced glutathione as well as membrane cholesterol and phospholipids were estimated by the procedures given in Methods of Biochemical Analysis. Nitric oxide (NO) in the plasma was estimated by the method used by Gabor and Allon. Statistical analysis was done by the Student’s t test.

Results

The results showed that HMG CoA reductase activity, serum digoxin and dolichol were higher in patients with lone AF and embolic stroke, indicating upregulation of the isoprenoid pathway but serum ubiquinone, RBC membrane Na⁺–K⁺ ATPase activity and serum magnesium were lower compared to the control group (Table 1).

### Table 1. Concentration of serum digoxin, dolichol, magnesium and ubiquinone, and RBC membrane Na⁺–K⁺ ATPase activity in lone AF with embolic stroke

<table>
<thead>
<tr>
<th>Groups</th>
<th>HMG-CoA reductase/ (µg/dl)</th>
<th>Digoxin (µg/dl)</th>
<th>Dolichol (µg/dl)</th>
<th>Ubiquinone (µg/dl)</th>
<th>Na⁺–K⁺ ATPase (µg/p/mg protein)</th>
<th>Magnesium (µg/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control (1)</td>
<td>(±0.12)</td>
<td>(±1.09)</td>
<td>(±2.16)</td>
<td>(±8.65)</td>
<td>(±0.22)</td>
<td>(±0.24)</td>
</tr>
<tr>
<td>Lone AF (2)</td>
<td>(±0.06)</td>
<td>(±1.47)</td>
<td>(±4.19)</td>
<td>(±8.13)</td>
<td>(±0.18)</td>
<td>(±0.22)</td>
</tr>
</tbody>
</table>

Mean of the values from 15 samples ± SD

Group 2 has been compared with Group 1

*p<0.01

The concentration of tryptophan, quinolinic acid, serotonin, strychnine and nicotine was found to be higher in the plasma of patients with lone AF and embolic stroke while that of tyrosine, dopamine, norepinephrine and morphine was lower (Table 2).

There was an increase in the concentration of serum total GAG, individual GAG fraction, glycolipids and carbohydrate components of glycoproteins in patients with lone AF and embolic stroke. The carbohydrate components—total hexose, fucose and sialic acid—did not increase to the same extent in all cases, suggesting a qualitative change in glycoprotein structure. The activity of GAG degrading enzymes and that of glycohydrolases showed a significant increase in the serum of patients with lone AF and embolic stroke (Table 3).

The cholesterol:phospholipid ratio of the RBC membrane was higher in patients with lone AF and embolic stroke. The concentration of total GAG, hexose and fucose content of glycoprotein decreased in the RBC membrane and increased in the serum of patients with lone AF and embolic stroke (Table 3).

There was an increase in lipid peroxidation, as evidenced by the increase in the concentration of MDA, conjugated dienes, hydroperoxides and NO, with decreased antioxidant protection as indicated by a decrease in ubiquinone and reduced glutathione in patients with lone AF and embolic stroke. The activity of the enzymes involved in free radical...
scavenging, like superoxide dismutase, catalase, glutathione peroxidase and glutathione reductase, is decreased in patients with lone AF and embolic stroke, suggesting reduced free radical scavenging (Table 4).

Table 2. Tyrosine and tryptophan catabolic patterns in lone AF with embolic stroke

<table>
<thead>
<tr>
<th>Group</th>
<th>Tryptophan (mg/dl)</th>
<th>Tyrosine (mg/dl)</th>
<th>5HT (µg/dl)</th>
<th>Dopamine (ng/dl)</th>
<th>Norepinephrine (µg/dl)</th>
<th>Quinolinic acid (µg/dl)</th>
<th>Morphine (µg/dl)</th>
<th>Strychnine (µg/dl)</th>
<th>Nicotine (µg/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control(1)</td>
<td>1.11±0.08</td>
<td>1.14±0.09</td>
<td>20.9±1.9</td>
<td>12.89±0.67</td>
<td>45.15±2.15</td>
<td>370.60±21.07</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>Lone AF(2)</td>
<td>2.95±0.07</td>
<td>0.81±0.07</td>
<td>48.9±3.9</td>
<td>8.43±0.44</td>
<td>30.54±1.78</td>
<td>655.73±48.88</td>
<td>ND</td>
<td>ND</td>
<td>3.54±0.37</td>
</tr>
</tbody>
</table>

Mean of the values from 15 samples ± SD
Group 2 has been compared with Group1
*p<0.01

Table 3. Concentration of plasma glycoconjugates, lysosomal enzymes and RBC membrane composition in lone AF with embolic stroke

| Groups | Total glycosaminoglycans (mg uronic acid/dl plasma) | Hyaluronic acid (mg uronic acid/dl plasma) | Heparan sulphate (mg uronic acid/dl plasma) | Heparin (mg uronic acid/dl plasma) | Dermatan sulphate (mg uronic acid/dl plasma) | Chondroitin sulphate (mg uronic acid/dl plasma) | Hexose (mg/g protein) | Fucose (mg/g protein) | Sialic acid (mg/g protein) | Ganglioside (µg/dl) | Glycosyl diglyceride (µg/dl) | Cerebrosides (µg/dl) | Sulphatides (µg/dl) | Beta glucuronidase (µg p-nitrophenol/hr/g protein) | Beta N-acetyl hexosaminidase (µg p-nitrophenol/hr/g protein) | Hyalurondiase (µg N-acetyl glucosamine/hr/g protein) | Cathepsin D (µg tyrosine/hr/g protein) | Beta galactosidase (µg of p-nitrophenol/hr/mg protein) | Beta fucosidase (µg of p-nitrophenol/hr/mg protein) | Beta glucosidase (µg of p-nitrophenol/hr/mg protein) | Glycosaminoglycan (µg/mg protein) | Hexose (µg/mg protein) | Fucose (µg/mg protein) | Cholesterol (nmol/mg protein) | Cholesterol:Phospholipid |
|--------|-----------------------------------------------|----------------------------------------|-----------------------------------------|---------------------------------|---------------------------------------------|---------------------------------------------|----------------|-------------------|-----------------------------------------|----------------|-------------------------------|----------------|----------------|---------------------------------|---------------------------------|--------------------------|-------------------------|---------------------------------|---------------------------------|-----------------|-------------------|----------------|----------------|---------------------|
| Control (1) | 4.57±0.41                                    | 0.55±0.41                             | 0.12±0.02                               | 0.28±0.02                      | 2.83±0.23                                   | 0.59±0.04                                   | 13.55±1.26 | 1.65±0.15         | 8.55±0.62                               | 26.5±1.2       | 12.5±0.72                            | 16.25±1.10       | 5.25±0.61 | 59.52±5.26                          | 227.3±78.6                               | 62.9±4.1                                 | 23.63±1.65                          | 27.36±2.46                          | 6.62±0.71                              | 145.09±11.8                     | 63.33±4.60                      | 704.33±63.09                  | 4.0±4±0.48                       | 2.0±2.04±0.37 | 5.0±5.0±0.37 | 5.0±5.0±0.37 | 5.0±5.0±0.37 | 5.0±5.0±0.37 |
| Lone AF (2) | 10.83±0.43                                     | 253.60±10.18                          | 142.2±3.19                              | 3.49±0.12                      | 3.70±0.60                                    | 3.54±0.37                                   | 10.38±0.73 | 2.51±0.21         | 10.27±0.82                              | 36.58±2.1      | 20.22±1.66                           | 22.52±1.4        | 7.94±0.63 | 114.29±2.2                           | 329.4±79.5                               | 224±6.8                                | 44.6±1.32                           | 43.42±1.71                           | 4.03±0.48                               | 52.65±24.38                      | 38.0±2.17                        | 824±47±3.06                  | 43.42±1.45                       | 2.12±1.20                       | 42.20±1.32       |

Mean of the values from 15 patients in each group ± SD
Group 2 has been compared with Group1
*p<0.01; t between 0.05–0.01

Table 4. Free radical metabolism in lone AF with embolic stroke

<table>
<thead>
<tr>
<th></th>
<th>Control (1)</th>
<th>Lone AF (2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MDA (µm/ml RBC)</td>
<td>10.83±0.43</td>
<td>12.63±0.29</td>
</tr>
<tr>
<td>Hydroperoxide (µm/ml RBC)</td>
<td>253.60±10.18</td>
<td>289.84±8.21</td>
</tr>
<tr>
<td>Conjugated dienes (µm/ml RBC)</td>
<td>49.3±2.53</td>
<td>66.9±4.81</td>
</tr>
<tr>
<td>Nitric oxide (µm/g protein)</td>
<td>2.84±0.21</td>
<td>3.42±0.16</td>
</tr>
<tr>
<td>Glatuthionine (µg/ml RBC)</td>
<td>256.60±10.96</td>
<td>142.2±3.19</td>
</tr>
<tr>
<td>Superoxide dismutase (units/mg protein)</td>
<td>43.14±1.94</td>
<td>32.43±1.45</td>
</tr>
<tr>
<td>Catalase (×10^{-2} units/mg protein)</td>
<td>3.49±0.12</td>
<td>2.12±0.99</td>
</tr>
<tr>
<td>GSH peroxide (units/mg protein)</td>
<td>48.1±2.64</td>
<td>42.20±1.32</td>
</tr>
<tr>
<td>GSH reductase (units/mg protein)</td>
<td>8.37±0.87</td>
<td>6.65±0.32</td>
</tr>
</tbody>
</table>

Mean of the values from 15 patients in each group ± SD
Group 2 has been compared with Group1
*p<0.01

The increased synthesis of endogenous digoxin, a potent inhibitor of membrane Na""±""K"" ATPase, can decrease the enzyme activity in patients with lone AF with embolic stroke.4,5 The inhibition of membrane Na""±""K"" ATPase by digoxin is known to cause an increase in intracellular Ca""++, resulting from an increased Na""±""Ca""++ exchange.1 This increase in intracellular Ca""++, by displacing Mg""++, from its binding site, causes a decrease in the functional availability of Mg""++, which can cause decreased mitochondrial ATP formation which, along with low Mg""++, can result in further inhibition of membrane Na""±""K"" ATPase, since the ATP--Mg""++ complex is the actual substrate for this reaction. There

Discussion

The results showed that HMG-CoA reductase activity, serum digoxin and dolichol were increased and ubiquinone reduced in left-handed/right hemisphere-dominant individuals, but the converse was true for right-handed/left hemisphere-dominant individuals. The concentration of tryptophan, quinolinic acid, serotonin, strychnine and nicotine was found to be higher in the plasma of left-handed/right hemisphere-dominant individuals while that of tyrosine, dopamine, morphine and norepinephrine was lower. The results were reversed in the plasma of right-handed/left hemisphere-dominant individuals (Tables 5 and 6).

The increased synthesis of endogenous digoxin, a potent inhibitor of membrane Na""±""K"" ATPase, can decrease the enzyme activity in patients with lone AF with embolic stroke.4,5 The inhibition of membrane Na""±""K"" ATPase by digoxin is known to cause an increase in intracellular Ca""++", resulting from an increased Na""±""Ca""++ exchange.1 This increase in intracellular Ca""++, by displacing Mg""++, from its binding site, causes a decrease in the functional availability of Mg""++, which can cause decreased mitochondrial ATP formation which, along with low Mg""++, can result in further inhibition of membrane Na""±""K"" ATPase, since the ATP--Mg""++ complex is the actual substrate for this reaction. There
is, thus, a progressive inhibition of membrane Na\textsuperscript{+}–K\textsuperscript{+} ATPase activity, first triggered by digoxin.\textsuperscript{17} Membrane Na\textsuperscript{+}–K\textsuperscript{+} ATPase inhibition thus leads to an increase in intracellular Ca\textsuperscript{++} and a decrease in intracellular Mg\textsuperscript{++} stores. Increased digoxin levels and consequent hypomagnesemia can affect the atrial conduction, leading to atrial fibrillation.\textsuperscript{3} Increase in intracellular Ca\textsuperscript{++} can activate the G protein, coupled thrombin receptor and platelet activating factor, producing the left atrial thrombus observed in patients with lone AF and embolic stroke.\textsuperscript{18}

There is an increase in tryptophan and its catabolites and a reduction in tyrosine and its catabolites in the serum of patients with lone AF and embolic stroke. This could be due to the fact that digoxin can regulate the neutral amino acid transport system with preferential promotion of tryptophan transport over tyrosine.\textsuperscript{19} The decrease in membrane Na\textsuperscript{+}–K\textsuperscript{+} ATPase activity in lone AF with embolic stroke could be due to the fact that the hyperpolarizing neurotransmitters (dopamine, morphine and noradrenaline) are reduced and the depolarizing neuroactive compounds (serotonin, glutamate, strychnine, nicotine and quinolinic acid) are increased.

The elevation in the level of dolichol and Mg\textsuperscript{++} deficiency can increase the synthesis of structurally abnormal glycoconjugates.\textsuperscript{20} Structurally abnormal glycoproteins and proteoglycans interact between themselves and resist catabolism by lysosomal enzymes leading to their accumulation and amyloid formation in the conducting tissue. The cholesterol:phospholipid ratio of the RBC membrane was increased in patients with lone AF with embolic stroke, consequent to Mg\textsuperscript{++} deficiency inhibiting phospholipid synthesis and an upregulated isoprenoid pathway increasing cholesterol synthesis. The incorporation of the glycoconjugates into the membranes was reduced due to inhibition of membrane trafficking GTPases and lipid kinases by Mg\textsuperscript{++} deficiency. The change in membrane structure can lead to further membrane Na\textsuperscript{+}–K\textsuperscript{+} ATPase inhibition. Alteration in the membrane of the conducting tissue can also lead to atrial fibrillation, while alteration in the left atrial endocardial membrane can produce platelet adhesion and aggregation, contributing to the formation of an LA thrombus; and alteration of the lysosomal membranes can result in defective lysosomal stability with increased release of lysosomal enzymes, contributing to the rupture of the thrombus and embolisation.

In lone AF with embolic stroke, there is mitochondrial dysfunction and increased generation of free radicals consequent to: (i) digoxin-induced decreased tyrosine availability, which leads to inhibition of ubiquinone synthesis; (ii) increased intracellular Ca\textsuperscript{++}, which induces NO synthase and liberates NO. There is also reduced free

### Table 5. Concentration of serum digoxin, dolichol, magnesium ubiquinone and RBC membrane Na\textsuperscript{+}–K\textsuperscript{+} ATPase activity/hemispheric dominance

<table>
<thead>
<tr>
<th>Groups</th>
<th>HMG-CoA reductase/ HMG-CoA mavalonate</th>
<th>Digoxin (ng/dl)</th>
<th>Dolichol (µg/dl)</th>
<th>Ubiquinone (µg/dl)</th>
<th>Na\textsuperscript{+}–K\textsuperscript{+} ATPase (µg/p/mg protein)</th>
<th>Magnesium (mg/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LH Dom (1)</td>
<td>1.13±0.12\textsuperscript{a}</td>
<td>7.80±0.06\textsuperscript{a}</td>
<td>36.1±2.36\textsuperscript{a}</td>
<td>142.1±8.65\textsuperscript{a}</td>
<td>5.02±0.22\textsuperscript{a}</td>
<td>2.90±0.24\textsuperscript{a}</td>
</tr>
<tr>
<td>Bihem Dom (2)</td>
<td>0.82±0.07</td>
<td>14.80±1.01</td>
<td>63.8±2.96</td>
<td>86.4±5.91</td>
<td>3.01±0.18</td>
<td>1.72±0.13</td>
</tr>
<tr>
<td>RH Dom (3)</td>
<td>0.46±0.07\textsuperscript{a}</td>
<td>30.95±2.19\textsuperscript{a}</td>
<td>90.2±3.63\textsuperscript{a}</td>
<td>42.8±2.12\textsuperscript{a}</td>
<td>1.01±0.12\textsuperscript{a}</td>
<td>1.06±0.11\textsuperscript{a}</td>
</tr>
</tbody>
</table>

Dom: dominance
Mean of the values from 15 samples ± SD
Group 1 and 3 have been compared with Group 2
*p<0.01; \textsuperscript{a}p between 0.01–0.05

### Table 6. Tyrosine and tryptophan catabolic patterns/hemispheric dominance

<table>
<thead>
<tr>
<th>Group</th>
<th>Tryptophan (mg/dl)</th>
<th>Tyrosine (mg/dl)</th>
<th>Serotonin (µg/dl)</th>
<th>Dopamine (ng/dl)</th>
<th>Norepinephrine (ng/dl)</th>
<th>Quinolinic acid (ng/dl)</th>
<th>Morphine (µg/dl)</th>
<th>Strychnine (µg/dl)</th>
<th>Nicotine (µg/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bihem Dom (1)</td>
<td>2.02±0.05</td>
<td>0.84±0.06</td>
<td>43.9±1.9</td>
<td>8.72±0.42</td>
<td>30.56±1.32</td>
<td>632.52±49.42</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>LH Dom (2)</td>
<td>1.13±0.09\textsuperscript{a}</td>
<td>1.15±0.08\textsuperscript{a}</td>
<td>17.9±1.8\textsuperscript{a}</td>
<td>11.7±0.62\textsuperscript{a}</td>
<td>42.10±2.30\textsuperscript{a}</td>
<td>362.28±51.63\textsuperscript{a}</td>
<td>7.56±0.56\textsuperscript{a}</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>RH Dom (3)</td>
<td>2.96±0.08\textsuperscript{a}</td>
<td>0.14±0.06\textsuperscript{a}</td>
<td>52.7±2.2\textsuperscript{a}</td>
<td>4.92±0.42\textsuperscript{a}</td>
<td>21.19±1.32\textsuperscript{a}</td>
<td>690.28±41.32\textsuperscript{a}</td>
<td>ND</td>
<td>0.92±0.02\textsuperscript{a}</td>
<td>6.28±0.24\textsuperscript{a}</td>
</tr>
</tbody>
</table>

Dom: dominance
Mean of the values from 15 samples ± SD.
Groups 2 and 3 have been compared with Group 1
*p<0.01
radical scavenging owing to: (i) dysfunction of glutathione synthetase and glutathione reductase induced by Mg

++
deficiency; (ii) superoxide dismutase leakage due to opening of the mitochondrial PT pore by increased intracellular Ca

++;21 and (iii) catalase dysfunction due to a membrane peroxisomal defect. Increased generation and reduced destruction of free radicals, like the superoxide ion and hydroxyl radical, can produce lipid peroxidation and cell membrane damage, which can further inactivate Na–K ATPase, triggering the cycle of free radical generation once again. This can lead to membrane Na–K ATPase inhibition of the conducting tissue and AF.

The patterns obtained in right hemispheric dominance correlated with those obtained in patients with lone AF with embolic stroke. Right hemisphere-dominant individuals showed increased digoxin and dolichol levels with reduced ubiquinone levels. The tryptophan catabolites were increased and tyrosine catabolites were lowered. In left hemisphere-dominant individuals, there was a hypodigoxinemic state and the biochemical patterns were reversed. Right hemispheric dominance may thus control the risk for developing lone AF with embolic stroke.

References

Prevalence of Coronary Artery Disease in Patients with Symptomatic Peripheral Vascular Disease

Rajeev Bhardwaj, Neeraj Ganju, Manish Sharma, Sandeep Sud, Sanjeev Asotra
Department of Cardiology, Indira Gandhi Medical College, Shimla

Atherosclerosis is a systemic disease with the potential to affect multiple vascular beds. The specific association of coronary artery disease (CAD) and peripheral vascular disease (PVD) is well established. The impact of co-morbid CAD in patients with PVD is two-fold. First, the prognosis for perioperative morbidity and mortality in patients undergoing vascular reconstructive surgery is primarily determined by the presence and extent of the associated CAD. The specific perioperative events include myocardial infarction (MI), congestive cardiac failure (CCF) and arrhythmias. Cardiac etiology accounts for 40%–60% of early deaths in patients undergoing vascular reconstructive surgery. Late mortality is the second impact of coronary disease on patients with PVD. It is well established that in patients who undergo vascular surgery, there is a decrease in survival if there is presence of coronary disease. Crawford et al. collected extensive long-term survival data on patients who underwent aortic surgery for either aneurysms or occlusive disease. Actual survival rates at 5 years were 84%–89% for patients without clinical CAD and only 54% in patients with CAD. Hence, determination of the extent and severity of CAD is important in the management of patients with PVD.

Methods
During the last 2 years, 53 patients presenting with symptoms of PVD were subjected to peripheral angiography. Patients with lower limb ischemia presented with claudication and/or nonhealing ulcer/gangrene. Easy fatigability was the presenting symptom in patients with upper limb ischemia and transient ischemic attacks/syncope in cases with carotid/vertebral artery involvement. Patients who showed evidence of weakness/absence of at least one major vessel were subjected to peripheral angiography. Patients with more than 50% diameter stenosis were labeled as having PVD and were also subjected to coronary arteriography (CART). Patients with more than 50% stenosis in one or more coronary arteries were labeled as having CAD. None of these patients had clinical or historical evidence of CAD. A right femoral arterial puncture was used for catheterization, but when the right femoral artery was not palpable, the left femoral approach was used. When both femoral pulses were absent, angiography was done through a left brachial artery puncture.

Background: Prevalence of coronary artery disease has been reported to be quite high in patients with peripheral vascular disease in western literature. Therefore, it is important to study the coronary anatomy in patients with symptomatic peripheral vascular disease.

Methods and Results: Fifty-three patients presenting with symptoms of peripheral vascular disease underwent peripheral angiography in our institute during the last 2 years. The total number of vessels involved in these patients was 117. Fifteen patients had involvement of the upper limb vessels. 46 patients had involvement of the lower limb vessels and 6 patients had involvement of the carotid/vertebral arteries. Coronary arteriography was done in all the patients. Only 8 (15%) patients were found to have coronary artery disease with involvement of 11 arteries. Eighty-four (72%) peripheral vessels out of the 117 vessels involved showed total occlusion, whereas only 2 (18%) coronary arteries out of 11 vessels involved showed total occlusion.

Conclusions: This study shows that the majority of patients with symptomatic peripheral vascular disease have normal coronaries, the extent of their involvement being low despite severe peripheral vascular disease.

Key Words: Peripheral vascular disease, Coronary disease, Angiography
Exclusion criteria: These were: (1) patients with age <40 years; (2) patients with acute arterial embolic occlusion; and (3) patients fulfilling the criteria for aortoarteritis and collagen disorders.

Results
Fifty-three patients with symptomatic PVD were subjected to peripheral and coronary angiography. Six patients had evidence of gangrene or a nonhealing ulcer on the foot. Patient characteristics are given in Table 1.

Overall, 15 patients had involvement of the upper limb arteries, with or without involvement of other regions; 46 had involvement of the lower limb vessels; and 6 had involvement of the vertebral/carbon arteries, with or without involvement of other regions. Details of the vessels involved are given in Table 2.

Coronary arteriography was done in all 53 patients, out of which 8 patients (15%) showed CAD. Table 2 shows the details of involvement of CAD in these patients.

Table 1. Patient characteristics

<table>
<thead>
<tr>
<th>Category</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number</td>
<td>53</td>
</tr>
<tr>
<td>Males</td>
<td>44</td>
</tr>
<tr>
<td>Mean age (years)</td>
<td>54±11</td>
</tr>
<tr>
<td>Smokers</td>
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</tr>
<tr>
<td>Hypertension</td>
<td>9</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>2</td>
</tr>
<tr>
<td>Family history of CAD</td>
<td>1</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>8</td>
</tr>
<tr>
<td>Males</td>
<td>6</td>
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<tr>
<td>Single vessel disease</td>
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<td>Double vessel disease</td>
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<td>Regions involved in PVD</td>
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<tr>
<td>Upper limb arteries</td>
<td>7</td>
</tr>
<tr>
<td>Lower limb arteries</td>
<td>40</td>
</tr>
<tr>
<td>Carotid/vertebral arteries</td>
<td>0</td>
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<tr>
<td>Upper/lower limb arteries</td>
<td>2</td>
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<tr>
<td>Upper limb/carotids/vertebral arteries</td>
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<tr>
<td>Upper &amp; lower limb/carotids/vertebral arteries</td>
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</tr>
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</table>

Table 2. Details of vessels involved

<table>
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<tr>
<th>Region involved</th>
<th>Total patients</th>
<th>Arteries involved</th>
<th>Extent of vessel involvement</th>
<th>Vessels involved</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Total occlusion</td>
<td>70%-99%</td>
</tr>
<tr>
<td>Upper Limb</td>
<td>15</td>
<td>20</td>
<td>15 (75%)</td>
<td>5 (25%)</td>
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<tr>
<td>Lower Limb</td>
<td>46</td>
<td>87</td>
<td>68 (78%)</td>
<td>16 (18%)</td>
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<tr>
<td>Carotid and vertebral</td>
<td>6</td>
<td>10</td>
<td>1 (10%)</td>
<td>8 (80%)</td>
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<td></td>
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</tr>
<tr>
<td>CAD</td>
<td>8</td>
<td>11</td>
<td>2 (18%)</td>
<td>8 (72%)</td>
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</tr>
<tr>
<td>PVD in CAD patients</td>
<td>8</td>
<td>19</td>
<td>13 (68%)</td>
<td>6 (31%)</td>
</tr>
<tr>
<td>PVD in patients without CAD</td>
<td>45</td>
<td>98</td>
<td>71 (72%)</td>
<td>23 (23%)</td>
</tr>
</tbody>
</table>

Scl: subclavian; Br: brachial; Il: iliac; Eexternal: I: internal; Femoral: Pop: popliteal; Tibial: A: anterior; P: posterior; Innom: innominate; Car: carotid; C: common; Vert: vertebral; Rt: right; Lt: left; CAD: coronary artery disease; LAD: left anterior descending; LCX: left circumflex; RCA: right coronary artery; PVD: peripheral vascular disease
If we analyze CAD in relation to the site of involvement in PVD, 7 out of the 8 patients with CAD had involvement of only the lower limb vessels, and 1 patient who had single vessel disease showed involvement of the upper limb vessel. None of the patients with involvement of two or all three regions had CAD. The only patient with a three vessel disease had involvement of the lower limb vessels, type 2 diabetes mellitus and hypertension. Table 3 shows the risk profile of CAD patients.

<table>
<thead>
<tr>
<th>Table 3. Risk profile of CAD patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total no. of patients</td>
</tr>
<tr>
<td>Patients with CAD</td>
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<tr>
<td>Mean age (years)</td>
</tr>
<tr>
<td>Males</td>
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<tr>
<td>Smokers</td>
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<tr>
<td>Diabetes mellitus</td>
</tr>
<tr>
<td>Hypertension</td>
</tr>
<tr>
<td>Family history of CAD</td>
</tr>
<tr>
<td>Dyslipidemia</td>
</tr>
</tbody>
</table>

CAD: coronary artery disease

When we compared patients with and without CAD in relation to the extent of PVD, 19 peripheral vessels were found to be involved in 8 patients with CAD as compared to 98 vessels in 45 patients without CAD. Thirteen vessels (68%) were totally occluded out of the 19 vessels in patients with CAD, whereas 71 (72%) vessels out of 98 involved showed total occlusion in patients without CAD (Table 2).

Discussion

Coronary artery disease and PVD are both common diseases but the symptoms of one usually predominate. The patient may be incapacitated due to exertional angina so the symptoms of PVD may not be evident till revascularization for CAD is done and vice versa. Peripheral vascular disease usually presents with intermittent claudication. Criqui et al. reported the prevalence of PVD (2.2% for men and 1.7% for women) using historical data and noninvasive measurements of blood flow. A general survey of 5738 men and 5224 women between the ages of 30 and 59 years was conducted in Finland. The prevalence of intermittent claudication increased with age and was similar in men (2.1%) and women (1.8%). Smoking and an increased serum cholesterol level were related to increased prevalence, but high blood pressure and serum triglyceride levels were not.

The prevalence of CAD has been reported to be quite high in patients with PVD. Hertzer performed elective coronary angiography in 1000 consecutive patients considered for elective peripheral vascular reconstruction. Coronary artery disease was found in 56% of patients with lower extremity ischemia (LEI). Only 10% of those with LEI had normal coronary vessels while 38% had two or three vessel CAD and 34% had indication of ventricular dysfunction. In contrast, our study shows the presence of asymptomatic CAD in only 15% patients. Our patients had severe PVD which is evident from the fact that 75% of upper limb vessels, 78% of lower limb vessels and 10% of neck vessels had total occlusion. A total of 117 peripheral vessels were involved in 53 patients. In contrast, only 11 coronary arteries were involved in 8 patients found to have CAD, and only 2 (18%) of the arteries showed total occlusion.

Thus, in spite of extensive involvement of PVD in our patients, CAD is not as common as has been reported in western studies. In another study from South India, a low incidence of CAD was found in patients with PVD. Our data suggest that some patients with atherosclerosis are prone to peripheral vessel involvement while others are more prone to coronary vessel involvement. There may be some as yet unknown factors that determine the preferential involvement of a particular vessel.

References

Background: Percutaneous transseptal mitral commissurotomy has been successfully performed in selected pregnant patients with severe symptomatic mitral stenosis. Its safety and efficacy needs to be evaluated in a large number of cases.

Methods and Results: Percutaneous transseptal mitral commissurotomy was performed in 85 severely symptomatic (New York Heart Association functional class III or IV) pregnant women aged 22.7±4.1 years (range 18–39 years) with critical mitral stenosis at 24.8±4.7 weeks (range 20–34 weeks) of gestation. Percutaneous valvotomy was performed using a flow-guided Inoue balloon in all the patients. The procedure was considered successful in 80 (94%) patients. The hemodynamic mean end-diastolic gradient decreased from 26.7±6.8 mm Hg (range 16–35 mmHg) to 4.5±3.8 mmHg (range 0–14 mmHg) (p<0.001). The mean diastolic gradient decreased from 29.1±9.1 mmHg (range 18–38 mmHg) to 7.2±4.1 mmHg (range 4.1–18 mmHg) (p<0.001). The mean mitral valve area assessed by echocardiography increased from 0.75±0.5 cm² (range 0.4–1.0 cm²) to 2.0±0.5 (range 1.0–2.7 cm²) (p<0.001). The mean fluoroscopy time was 3.6±3.2 minutes. The results of the mitral valvotomy were considered suboptimal in 4 patients. Mitral regurgitation increased by 1 grade in 16 patients and more than 2 grades in 2 patients. One patient developed pericardial tamponade during the procedure and was managed by catheter drainage. Percutaneous mitral valve dilatation was then successfully performed in this patient. No fetal abortion occurred after the procedure.

Conclusions: The results of this study indicate that percutaneous transseptal mitral commissurotomy is a safe and effective procedure for severe symptomatic mitral stenosis in pregnancy. (Indian Heart J 2001; 53: 192–196)

Key Words: Valvuloplasty, Mitral stenosis, Pregnancy

Rheumatic mitral valve disease continues to be the most prevalent organic valve disease encountered in pregnant women in South Asia.¹ Normal pregnancy is associated with a hyperdynamic circulatory state characterized by an increase in blood volume, heart rate and stroke volume, and a decrease in systemic vascular resistance.²-⁵ This increase in cardiac output (usually about 50%) may lead to the unmasking of a previously asymptomatic valve lesion and worsening of already symptomatic lesions. In patients with mitral stenosis (MS), increased blood volume and tachycardia impair left atrial emptying and can lead to a significant rise in the venocapillary pulmonary pressure. This hemodynamic stress, along with other factors like anemia, atrial fibrillation and thromboembolism, may precipitate acute pulmonary edema and cardiogenic shock with unacceptable maternal and fetal mortality.⁶-⁷ Thus, pregnancy with mitral stenosis presents a complex therapeutic problem. Closed or open surgical commissurotomy can be performed but the procedure still carries a significant morbidity and mortality.⁸-¹²

Over the last few years, percutaneous transseptal mitral commissurotomy (PTMC) has been performed during pregnancy with excellent short-term results in selected patients with mitral stenosis.¹³-²⁶ Long-term follow-up studies have also shown a low risk of complications in the fetus and a good outcome of these pregnancies.²⁴,²⁵,²⁷ Concerns regarding the risk of radiation exposure still persist even though some reports have found no harmful

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effects on long-term follow up. We report our experience of PTMC in pregnant women with severe symptomatic rheumatic MS.

Methods

PTMC was performed in 85 pregnant patients with severely symptomatic critical MS (New York Heart Association [NYHA] functional class III or IV) at our center. Clinical characteristics of these patients are shown in Table 1. All the patients were NYHA functional class III or IV symptomatic despite receiving high doses of diuretic therapy, digoxin and β-blockers. Patients were accepted for PTMC if they fulfilled the following clinical and echocardiographic critiera: (i) presence of critical MS (absolute mitral valve area [MVA] <1.0 cm²); (ii) NYHA functional class III or IV; (iii) absence of more than mild mitral regurgitation; (iv) absence of left atrial/left atrial appendage thrombus; and (v) duration of pregnancy greater than 20 weeks. Twenty patients were in atrial fibrillation with a controlled ventricular rate. Five patients had mitral restenosis (3 of these had earlier undergone closed mitral commissurotomy while 2 were post-balloon valvotomy patients). In 55 patients, a diagnosis of MS had been made prior to the current pregnancy while in 30 the diagnosis of MS was made for the first time during the same pregnancy. Twenty-five patients were primigravidae.

| Table 1. Clinical characteristics of pregnant patients who underwent PTMC (n=85) |
|---------------------------------|-----------------|
| Age                     | 22.7±4.1 years (18–39 years) |
| Duration of pregnancy at the time of PTMC | 24.8±4.7 weeks (20–34 weeks) |
| Gravida | Primi 25 (29.4%), Multi 60 (70.6%) |
| Functional class | NYHA class III 46 (54.1%), NYHA class IV 39 (45.9%), Atrial fibrillation 20(23.5%) |

PTMC : percutaneous transseptal mitral commissurotomy
NYHA : New York Heart Association

Echocardiographic evaluation: Two-dimensional (2-D) echocardiographic and color Doppler studies were performed using standard techniques on Hewlett-Packard Sonos 1500 and 2500 machines before and after PTMC. The severity of MS and the morphology of the mitral valve were carefully assessed and transmitral gradients were measured. Planimetry of the mitral valve area was done. Pulmonary artery systolic pressure was estimated using tricuspid regurgitation Doppler signal velocity.

Cardiac catheterization and PTMC: Informed consent was obtained from all the patients and the risks associated with the procedure were explained, including potential harm to the fetus. To limit radiation exposure during the procedure, the patient’s abdomen was circumferentially wrapped from the subcostal margin to the symphysis pubis with a lead apron. Fluoroscopy was used only when absolutely essential. Complete right heart study was avoided. A 6 F pigtail catheter was placed at the root of the aorta. Left ventriculography was not done in any patient.

PTMC was performed using the conventional Inoue balloon technique. A transseptal puncture of the left atrium was done using a Brockenbrough needle inserted via the right femoral vein. Heparin was administered (50 U/kg intravenously) after positioning the Inoue balloon in the left atrium. The mitral valve mean and end-diastolic gradients were recorded before and immediately after the valve dilatation. The step-wise dilatations were done till the transmitral end-diastolic gradient decreased to less than 5 mmHg, unless a prominent V wave, suggesting significant mitral regurgitation, appeared on the hemodynamic trace. The valve area and mitral regurgitation were assessed by 2-D and color-flow Doppler echocardiography after the procedure. The procedure was considered successful if MVA was increased by >50% as compared to the baseline and the final absolute mitral valve area was >1.5 cm² in the absence of significant mitral regurgitation.

Antenatal evaluation: All patients underwent a detailed obstetric evaluation and follow-up, including ultrasound (USG) examination, both before and after the procedure. After PTMC, patients were carefully followed up (including repeated USG evaluations) for fetal growth and well-being. Spontaneous labor was awaited in all the patients unless there was an obstetric reason for induction of labor or performing cesarean section.

Statistical analysis: All data are expressed as mean±SD. Comparison of data before and after PTMC was performed using the paired t test. A p value <0.05 was considered significant.

Results

PTMC was successful in 80 of the 85 (94.1%) patients studied. All the patients showed an improvement in the functional class by at least 1 grade when assessed 24 to 48 hours after the procedure. Seventy-six patients were in NYHA functional class I (89.4%) and 8 were in class II (9.4%) one month after the procedure. The MVA increased from 0.75±0.5 cm² to 2.0±0.5 cm² (p<0.005) and there
was a significant decrease in the transmitral end-diastolic pressure gradient from 29.1±9.1 mmHg to 7.2±4.1 mmHg. The mean left atrial pressure fell from 34.6±8.6 mmHg to 14.8±3.8 mmHg (Table 2). Mean fluoroscopy time was 3.6±3.2 minutes. The results of the PTMC were considered suboptimal in 4 patients. Mitral regurgitation increased by 1 grade in 16 patients (18.8%) and by more than 2 grades in 2 patients (2.3%). One patient with severe mitral regurgitation (MR) following suboptimal PTMC was managed medically till term. Elective cesarean section was performed and the patient underwent a mitral valve replacement one month later. Another patient, who developed moderate MR following PTMC, was stabilized on medical management and continued on medical follow-up after delivery. One patient developed pericardial tamponade during PTMC, which was managed successfully by catheter drainage. Percutaneous mitral dilatation was performed successfully in this patient. None of the patients developed any embolic episode or groin complication and there was no death.

No fetal abortion occurred after the procedure. Although balloon inflation caused transient maternal hypotension and a transient decrease in heart rate, these phenomena were generally well tolerated and both parameters returned to baseline within a few seconds of balloon deflation.

Table 2. Hemodynamic and echocardiographic data of pregnant patients undergoing PTMC

<table>
<thead>
<tr>
<th></th>
<th>Pre-PTMC [Mean±SD (range)]</th>
<th>Post-PTMC [Mean±SD (range)]</th>
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<tbody>
<tr>
<td>MVA (cm²)*</td>
<td>0.75±0.5 (0.4–1.0)</td>
<td>2.0±0.5 (1–2.7)*</td>
</tr>
<tr>
<td>EDG (mmHg)**</td>
<td>26.7±6.8 (16–35)</td>
<td>4.5±3.8 (0–14)*</td>
</tr>
<tr>
<td>MDG (mmHg)**</td>
<td>29.1±9.1 (18–58)</td>
<td>7.2±4.1 (4.1–18)*</td>
</tr>
<tr>
<td>LA mean (mmHg)**</td>
<td>34.6±8.6 (22–42)</td>
<td>14.8±3.8 (8–22)*</td>
</tr>
</tbody>
</table>

MVA: mitral valve area; EDG: end-diastolic gradient; MDG: mean diastolic gradient; LA: left atrium; PTMC: percutaneous transseptal mitral commissurotomy

*p<0.005
# Calculated from echocardiographic 2D-planimetry
## Measured during hemodynamic study

## Discussion

Rheumatic valvular involvement remains the commonest type of heart disease in pregnant patients in many countries, and up to 75% of these patients have dominant MS. The presence of MS may impair a pregnant woman’s ability to generate an increased cardiac output despite an increase in blood volume, heart rate and decreased systemic vascular resistance, leading not only to low systemic perfusion but also pulmonary congestion. Deterioration may occur in as many as 25% of patients. The maternal death rate is nearly 1% and varies directly with the NYHA functional class (0.4% for women in class I or II; 6.8% for those in class III or IV). It can reach as high as 17% in those with atrial fibrillation. The highest risk is during labour and the delivery period. Ideally, if severe MS is diagnosed in a nonpregnant woman desiring pregnancy, it should be treated by PTMC or surgical intervention before the patient conceives. However, because of several reasons, this is not always possible. Gupta et al. have also reported that more than half the patients in the group they studied had been diagnosed before pregnancy but no intervention had been carried out. After pregnancy, however, severe MS presents a challenging problem if managed only medically because of unacceptable fetal and maternal complications. Thus, in severely symptomatic patients, there is a need to increase the MVA by some intervention. Surgical commissurotomy of the mitral valve was first performed in pregnant patients in 1952. However, open heart surgery during pregnancy is attendant with a 1.5%–3.3% risk of fetal mortality. The mortality is associated with the establishment of extracorporeal circulation (with the use of high doses of heparin and hypotension) and induced hypothermia. With closed mitral commissurotomy, the risk of fetal morbidity and mortality is lower, although a 5%–15% risk of fetal death is still present. Open mitral valvotomy is also associated with a high maternal mortality.

In this context, PTMC offers an alternative to the surgical approach. The Inoue technique seems to be particularly attractive in this setting. A comparison of PTMC with closed mitral valvotomy (CMV) has shown an equivalent efficacy of these approaches. Thus, PTMC seems a practical approach to these surgically high-risk pregnant patients. It is a relatively safe procedure which has been performed widely over the last decade. In the last few years, some large volume centers (Table 3) have offered PTMC to pregnant women with severe MS. No fetal death occurred after the procedure. Only one fetal death has been reported in about 400 cases of PTMC performed during pregnancy. No untoward effects of radiation have been reported. Long-term studies have confirmed the normal growth of these children.

Our data show that acceptable valve areas can be achieved with the Inoue single-balloon catheter technique. This technique is associated with lower complication rates because of the unique balloon design, flow directed catheter with blunt tip, adjustable balloon diameter, low inflation–deflation time and less fluoroscopy and procedure time.

Although the procedure is efficacious, long-term effects of radiation to the fetus need to be studied. Potentially,
radiation exposure during fluoroscopy may pose a hazard to the unborn child. The fetus receives most of the radiation dose from scatter and this has been estimated to be approximately 0.2 rad during balloon mitral commissurotomy. Therapeutic abortion is recommended when the fetus is exposed to 10 rad or more. Although we did not measure the actual dose received by the fetus in each patient, with our short fluoroscopy time the radiation exposure over the pelvic region should be minimal. Also, patient, with our short fluoroscopy time the radiation did not measure the actual dose received by the fetus in each when the fetus is exposed to 10 rad or more. Although we choice.

Critical rheumatic MS. The procedure produces consistent management of pregnant patients with symptomatic, commissurotomy is a safe and effective method for the pregnant women who had undergone PTMC during pregnancy showed normal growth and development without any clinical abnormalities.

Conclusions: Percutaneous transseptal mitral commissurotomy is a safe and effective method for the management of pregnant patients with symptomatic, critical rheumatic MS. The procedure produces consistent symptomatic and hemodynamic improvement in these critically ill patients. In experienced hands, this procedure is quick and safe and should be considered the treatment of choice.

References


A Meta-analysis of Controlled Clinical Trials Comparing Low-Molecular Weight Heparins with Unfractionated Heparin in Unstable Angina

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Background: Unfractionated heparin has been used extensively for the treatment of unstable angina/non-Q wave myocardial infarction but it has several disadvantages. Low-molecular weight heparins are now recommended although they are 3–5 times costlier than unfractionated heparin since they are convenient to administer and do not require activated thromboplastin time monitoring. Whereas enoxaparin, a low-molecular weight heparin, has been demonstrated to be superior to unfractionated heparin, the results of other low-molecular weight heparins have not been so convincing.

Method and Results: Through manual, MEDLINE and EMBASE search, we identified five randomized trials (excluding enoxaparin trials) that compared low-molecular weight heparins with unfractionated heparin in unstable angina. The prespecified efficacy end point of interest included a composite of death, myocardial infarction, recurrent angina and urgent revascularization. The safety end point was taken as a composite of major hemorrhage, minor hemorrhage, thrombocytopenia, allergic reaction and any other adverse event. We calculated odds ratio (95% confidence interval) for each trial for the composite end point, and the pooled odds ratio (95% confidence interval) was calculated using two established methods of meta-analysis, the Mantel–Haenszel–Peto method and the DerSimonian–Laird method. Both the methods yielded similar odds ratio (95% confidence interval). Separate odds ratio were calculated for efficacy and safety end points. There was a nonsignificant reduction in the incidence of the composite efficacy end point; the odds ratio (95% confidence interval) was 0.83 (0.70–0.99; p=0.08). The odds ratio (95% confidence interval) for the safety data was 0.78 (0.69–1.26; p=0.33).

Conclusions: No statistically significant difference was observed when the efficacy and safety of low-molecular weight heparins were compared with those of unfractionated heparin. A cost-effectiveness analysis of low-molecular weight heparins versus unfractionated heparin must be done urgently to establish more firmly the place of low-molecular weight heparins in the management of unstable angina. (Indian Heart J 2001; 53: 197–202)

Key Words: Angina, Heparins, Meta-analysis

The role of thrombosis in the pathophysiology of unstable angina is well established. In 1982, the idea of the administration of intravenous unfractionated heparin (UFH) for treatment in the acute phase of unstable angina was introduced. Subsequently, several trials proved its efficacy and safety alone as well as in combination with aspirin, and treatment guidelines recommended its use in the routine management of patients with unstable angina/non-Q wave myocardial infarction.

Despite its extensive use in clinical practice, UFH has several disadvantages. These include an unpredictable anticoagulant effect, low and variable bioavailability after subcutaneous administration, a rebound increase in thrombotic events after cessation of treatment and the risk of thrombocytopenia and thrombosis. Low-molecular weight heparins (LMWHs), however, offer the advantage of a stable and predictable anticoagulant response to a given dose, eliminating the need for hematologic monitoring, and the much simpler subcutaneous administration route.

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Two Phase III trials of enoxaparin, a LMWH, demonstrated that it was superior to UFH in reducing the incidence of a composite end point of death and serious cardiac ischemic events in patients with unstable angina/ non-Q wave myocardial infarction. A meta-analysis of these two trials showed that the incidence of individual end point was also significantly less with enoxaparin as compared to UFH. The data from the trials comparing other LMWHs with UFH are less convincing. In a randomized trial carried out in 1995, nadroparin, a LMWH, was shown to be significantly better in reducing the incidence of primary end points than UFH during the acute phase. However, a recent larger trial FRAX.I.S. (FRAxiparin in Ischemic Syndrome), which enrolled 3468 patients, did not demonstrate a statistically significant difference with respect to the primary outcome (cardiac death, myocardial infarction, refractory angina or recurrence of angina). Dalteparin, another LMWH, was compared with UFH in the FRIC (Fragmin In Unstable Coronary artery disease) trial. The combined outcome of death, myocardial infarction or recurrence of angina was observed in 7.6% and 9.3% of patients treated with UFH and dalteparin, respectively (p=0.33). In an Indian study by Suvarna et al., which compared a LMWH, tinzaparin, with UFH, total events (recurrent angina, acute myocardial infarction, urgent revascularization) were seen in 45% of patients treated with UFH and 25% of those treated with tinzaparin. Mattioli et al. compared another LMWH with UFH in patients hospitalized with unstable angina. The primary end points of death, acute myocardial infarction, urgent revascularization and recurrence of angina were seen in 42% and 23% of patients treated with UFH and LMWH, respectively.

The last two trials mentioned above were not adequately powered and the evidence from other larger trials was inconclusive. Keeping this in mind, we decided to conduct a meta-analysis of five randomized, controlled trials (excluding enoxaparin trials) of LMWHs in unstable angina patients, with the objective of detecting a statistically significant difference between UFH and LMWHs.

Methods

Computerized and manual literature searches are the recommended methods to gather relevant information from published studies. We searched the literature, MEDLINE and the EMBASE thoroughly with the key words: LMWHs, unstable angina, randomized clinical trial. The search was also carried out by dropping the word “clinical” from “randomized clinical trial” and replacing “unstable angina” with “unstable coronary”. Only those trials which compared LMWHs with UFH were included in the meta-analysis. The prespecified efficacy end point of interest included a composite of death, myocardial infarction, recurrent angina and urgent revascularization. The safety end point was taken as a composite of major hemorrhage, minor hemorrhage, thrombocytopenia, allergic reaction and any other adverse event.

Statistical Analysis: For each individual trial and for the combination of 5 trials, the odds ratio (OR) for LMWH versus UFH was estimated along with 95% confidence interval (CI) for the composite end point between days 6 and 14 (time of ascertainment of the effects of treatment in the trials). Since it is recommended that two methods be used for assessment of the internal consistency of the observations on the effect of one treatment versus another, we used the fixed-effects Mantel–Haenszel–Peto model and the random-effects DerSimonian–Laird model. The meta-analysis is presented as OR along with 95% CI (Figs. 1 and 2). The OR is depicted as a dot, the size of which is proportional to the quality of the trial, with larger sized dots indicating large, double-blind, randomized studies and smaller dots indicating smaller, single-blind or open studies. The 95% CI are depicted as lines on both sides of the OR. For each of the 2 methods evaluating the treatment effect of LMWH, heterogeneity testing was performed to screen for any important differences between the trials. A p value <0.05 was considered to be statistically significant.

Results

All the trials were similar in that they included patients with unstable angina/non-Q wave myocardial infarction and excluded those who presented with ST-segment-elevation myocardial infarction. The trials were similar in design but differed in the number of patients enrolled (Table 1). In all the trials, intravenous UFH was adjusted to a similar target activated thromboplastin time (APTT). The anti-Factor Xa (antiXa) dose of LMWHs was also similar in all the trials (Table 1). Aspirin and other conventional therapies were given to all the patients in all the trials.

The OR (95% CI) for the pooled data on the efficacy end point and for the individual trials are given in Fig. 1. The incidence of the composite end point of efficacy was lower with LMWHs as compared to UFH, but the difference was not statistically significant. The two methods employed to calculate the pooled OR yielded similar OR (95% CI): by the Mantel–Haenszel–Peto method, the OR (95% CI) was 0.81 (0.68–0.96; p=0.07) and by the DerSimonian–Laird
There was also no difference in the safety end point during the acute phase of treatment with LMWH or UFH (OR 0.78; 95% CI: 0.69–1.26; p=0.33, by the Mantel–Haenszel–Peto method; and OR 0.82; 95% CI: 0.55–1.26; p=0.33, by the DerSimonian–Laird method) as shown in Fig. 2. In both the methods, the heterogeneity was not significant.

**Discussion**

Meta-analysis of randomized, controlled trials is an important method in clinical research.22 Defined as the quantitative synthesis of data from multiple clinical experiences, meta-analysis has matured as a scientific discipline with well developed standards and methods.21,26,27 Several LMWHs are currently available in India and a recent survey of prescriptions carried out by us on
hospitalized unstable angina patients showed that the utilization of LMWHs and UFH is approximately 70% and 30%, respectively (unpublished data). The recent guidelines published in March 2000 recommend that LMWH should replace UFH as the antithrombin of choice.\textsuperscript{6} However, different LMWHs have different anti-Factor Xa: anti-Factor II ratios, different molecular weights and variable efficacy in unstable angina\textsuperscript{12} and, therefore, they may not be considered equivalent.\textsuperscript{28} Enoxaparin is the only LMWH demonstrated to be superior to UFH.\textsuperscript{12,14,15}

The results of our meta-analysis show that the LMWHs (other than enoxaparin) are equivalent to UFH in efficacy and safety in patients with unstable angina/non-Q wave myocardial infarction. Although a trend towards better efficacy of LMWHs was noticed, this failed to reach statistical significance. Our meta-analysis had enough power to detect a difference of 5% between the two treatments. It is possible that if the number of patients was increased, the results would have shown a statistical significance. On the other hand, the possibility of a publication bias cannot be ruled out since negative trials are more difficult to publish, but this would not have altered the findings of our meta-analysis. Since a meta-analysis of two trials of enoxaparin has already been done, we did not include these studies in our meta-analysis. Moreover, as the other LMWHs have not been shown to be unequivocally

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**Fig. 1.** Meta-analysis of the five trials comparing LMWH with UFH in unstable angina for the combined efficacy end points. The larger dots depict the OR of large, double-blind, randomized studies and the smaller ones those of smaller, single-blind or open studies.

**Fig. 2.** Meta-analysis of the three trials comparing LMWH with UFH in unstable angina for the combined safety end points. The larger dots depict the OR of large, double-blind, randomized studies and the smaller ones those of smaller, single-blind or open studies.
superior to UFH in this setting, the results of our meta-analysis are clinically relevant, especially in developing countries like India.

The cost of LMWHs is three to five times higher than that of UFH. However, treatment with UFH requires additional costs of infusion sets, syringes, nursing time and the cost of APTT monitoring. A cost-effectiveness analysis of only enoxaparin has been done, and shown it to be more cost-effective than UFH,\(^1\) but this data has been reported from developed countries. Similar studies from India and other developing countries have not been done. However, our analysis of a recently conducted trial in our hospital (unpublished data) has shown enoxaparin and UFH to be equally cost-effective. No such data are available for the other LMWHs. Only a properly conducted cost-effectiveness analysis can demonstrate whether the three to five times more expensive LMWHs can replace UFH in India and other developing countries. Therefore, there is an urgent need to carry out this analysis for LMWH and UFH in the Indian setting.

Till further evidence is available regarding other LMWHs, it seems appropriate to prescribe enoxaparin to patients with unstable angina/non-Q wave myocardial infarction.\(^4\) However, if patients are unable to afford enoxaparin (the costliest LMWH in India), should they be put on another less expensive LMWH or UFH? The decision has to be made by the treating physician, but no guidelines are available at present. The picture in India, where the patient often pays from his pocket, is different from that in western countries (whose guidelines we follow) where medical treatment is covered by insurance companies.

The results of the heterogeneity test, significant for the efficacy end point, merit further scrutiny. It is established that a positive heterogeneity test makes a meta-analysis difficult to interpret; hence, the results must be interpreted cautiously.\(^10\) All the trials were similar in design, inclusion—exclusion criteria and dosages of drugs, and they all used the same efficacy end points. However, they differed in their results, with two of the trials showing the superiority of LMWH over UFH and three not detecting a statistically significant difference. Even when the same LMWH (nadroparin) was used in two studies,\(^16,17\) it was found to be superior only in one.\(^18\) Regardless of which LMWH is used, 90% of the unstable coronary artery disease patients clinically stabilize after a few days of treatment;\(^12\) therefore, combining the results from trials carried out for different LMWHs seems appropriate.

The analysis of the safety end point was conducted from the data of only three of the trials\(^16-18\) as no adverse events were reported in the other two. A statistically significant increase in the incidence of minor hemorrhage and a nonsignificant increase in major hemorrhage has been seen with enoxaparin.\(^2\) Our results have not demonstrated any difference in the adverse effects of LMWH and UFH.

Meta-analysis has the potential to eliminate idiosyncrasy from the evaluation of medical issues, but it is unrealistic to imagine that it will produce simple statistical answers to complex clinical problems. A meta-analysis may provide conclusions about the effect of treatment that could not be drawn from individual trials because of the small numbers. Its results are, therefore, directly relevant to the formulation of medical policies. Meta-analysis cannot tell clinicians how to treat an individual patient but it can provide information that can help in decision making.

In conclusion, treatment with LMWHs other than enoxaparin is as effective as UFH with all the advantages that LMWHs possess. However, cost-effectiveness analyses need to be carried out for LMWHs to establish their place more firmly in the management of unstable angina.

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Brugada Syndrome with Monomorphic Ventricular Tachycardia in a One-Year-Old Child

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A one-year-old child with a structurally normal heart presented with monomorphic ventricular tachycardia. Electrocardiogram in sinus rhythm showed right bundle branch block with ST segment elevation suggesting a diagnosis of Brugada syndrome. At a later date, when the ST segment was isoelectric, intravenous procainamide caused ST elevation typical of Brugada syndrome. (Indian Heart J 2001; 53: 203–205)

Key Words: Tachyarrhythmias, Syncope, Brugada syndrome

Case Report

Baby N, a one-year-old female child born of a nonconsanguineous marriage is the youngest of three siblings. While the first child is healthy, the second died of sudden cardiac arrest during a febrile illness. Our patient had a mild nonspecific febrile illness of one day’s duration for which she was given paracetamol. On the second day, the child suddenly developed multiple syncopal episodes and was brought to the hospital.

The 12-lead electrocardiogram (ECG) showed VT (Fig. 1) that degenerated intermittently into spontaneously terminating ventricular fibrillation (VF). Her blood chemistry, including magnesium levels, was normal. Her echocardiogram was unremarkable with good left ventricular (LV) and right ventricular (RV) function and no abnormality in wall motion. There was no response to intravenous lidocaine, magnesium and amiodarone. After a few hours, she regained sinus rhythm, but the ECG during sinus rhythm showed right bundle branch block (RBBB) with ST segment elevation in leads V_1–V_2 (Fig. 2). Over the next few days, she did not have any further episodes of VT and the ST segment in the right precordial leads became isoelectric (Fig. 3). After a few days, when the ST segment was still isoelectric, she was given intravenous procainamide which led to a prompt and marked elevation of the ST segment (Fig. 4). She was diagnosed to be suffering from Brugada syndrome. Interestingly, her father, who is asymptomatic, also has RBBB with an isoelectric ST segment. He did not give his consent for an intravenous procainamide challenge.

Discussion

Differential diagnosis of VT in children includes long QT syndrome, ventricular pre-excitation, fascicular VT, myocarditis and arrhythmogenic right ventricular dysplasia (ARVD). The first three conditions can be safely excluded after taking into account the ECG tracings. Good ventricular function and the type of serial ECG changes seen make the diagnosis of myocarditis unlikely. ST segment elevation in early repolarization syndrome is usually localized to leads V_2–V_4 and has an upward concavity with positive T wave polarity accompanied by a notched J point, and is seldom associated with VT. ST segment elevation in Brugada syndrome is limited to the right precordial leads, slowly down sloping and followed by negative T waves. It is often associated with conduction delay in the RV, thereby producing varying degrees of RBBB.

The differentiation between Brugada syndrome and ARVD is controversial. Brugada syndrome may represent a functional abnormality of the electrical activity of the heart, i.e. a primary electrical disease, whereas ARVD is characterized by myocardial atrophy with adipose tissue or fibro-fatty infiltration of the dilated RV, often involving the conducting tissue. Though identified genetic loci and the

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inheritance pattern seem to be different, it is premature to draw definitive conclusions about the existence or lack of relationship between the two conditions.5 A definitive diagnosis of ARVD is based on the histological demonstration of transmural fibro-fatty displacement of the RV myocardium at either necropsy or surgery.6 However, this was not possible in our patient. The Task Force of the Working Group of Myocardial and Pericardial Disease of the European Society of Cardiology suggested certain criteria to diagnose ARVD7 but our patient does not fulfill these criteria.

Brugada syndrome is classically associated with polymorphic VT or VF. Monomorphic VT is distinctly uncommon. However, as in our patient, there are case reports where monomorphic VT, which could be induced, is well documented.8–11 This further raises the question as to whether Brugada syndrome is indeed a part of the spectrum of ARVD.

The mean age of affected individuals is in the mid to late-thirties, but ranges from 4 to 70 years. Our patient seems to be the youngest among those reported so far to have this syndrome.3

Electrical heterogeneity within the RV epicardium leads to phase 2 re-entry and thence to VT and VF.12 Because the ECG changes can be transient and sodium channel blockers can shorten phase 2 of the action potential, their use has been suggested to unmask the ECG changes of Brugada syndrome.13 This is amply demonstrated in our patient (Fig. 4). In addition to procainamide, ajmaline and flecainide can also be used. Conversely, antiarrhythmic agents that selectively block transient outward current (I_to) could prove effective in Brugada syndrome. The incidence of arrhythmic events appears to be the same in patients receiving implantable cardioverter-defibrillator (ICD), amiodarone and β-blockers. However, only patients on ICD are protected from sudden death.

Our patient was empirically started on amiodarone and is now doing well, nearly 18 months later. A repeat evaluation did not show any change in her clinical condition.

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Valvuloplasty Balloon Detaching From the Stem of a Catheter

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A 12-year-old boy underwent pulmonary balloon valvotomy for isolated critical pulmonary stenosis. Following valvotomy, blood was found to be drawn into the syringe during deflation of the balloon, so a provisional diagnosis of a burst balloon was made. However, when the balloon catheter was withdrawn, the balloon got detached from the stem of the catheter at the level of the right atrium and was trapped over the exchange guidewire. The balloon, when retrieved without a snare, was found to be intact. The balloon may have been partially detached at the junction of the proximal end of the balloon and the catheter; hence, blood was drawn from the catheter during deflation. In our institution balloons are reused following sterilization with ethylene oxide gas. We conclude that any balloon presumed to have burst inside the heart must be removed with great caution. In a third world country like India, where cost is an important factor, balloons can be reused, but with caution, keeping in mind complications such as in this case. (Indian Heart J 2001; 53: 206–207)

Key Words: Valvuloplasty, Balloon, Pulmonary stenosis

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Pulmonary balloon valvotomy (PBV) is one of the simplest interventional procedures, producing very good results with rare occurrence of complications.1,2 We report a case of PBV in which the valvuloplasty balloon was detached from the stem of the catheter and trapped at the level of the right atrium, after the balloon was presumed to have burst.

Case Report

A 12-year-old boy presented with dyspnoea on moderate exertion and one episode of exertional giddiness. He was clinically diagnosed as a case of pulmonary stenosis. Echocardiography using a Vingmed CFM 725 machine revealed right ventricular free wall hypertrophy, severe valvar pulmonary stenosis with a peak systolic gradient of 200 mmHg and a pulmonary annulus size of 16 mm with no other associated anomalies.

The case was taken up for elective PBV. Right heart catheterization, using the right femoral vein approach, showed a peak systolic gradient of 264 mmHg across the pulmonary valve. An angiogram of the right ventricle revealed doming of the pulmonary valve, with a thin central jet from the valve during systole, but no significant tricuspid regurgitation.

A 0.032 inch guidewire was anchored through the left inferior pulmonary artery in a good wedge position and a 23 mm × 4 cm pulmonary valvuloplasty balloon was positioned across the pulmonary valve and inflated—there was disappearance of the waist at the level of the pulmonary valve. A second inflation did not show any waist but blood was drawn into the syringe on deflation—and a provisional diagnosis of a burst balloon was made.

The balloon catheter was then withdrawn from the pulmonary position. At the level of the right atrium, the balloon encountered mild resistance and the catheter suddenly seemed to move freely. Fluoroscopy revealed that both the proximal and distal markers of the balloon were at the level of the right atrium but as the stem of the catheter was separate from the balloon (Fig. 1), the guidewire was left in situ and the stem of the catheter removed. A snare was passed over the wire and the balloon was pulled over the wire. It was then retrieved to the level of the right femoral vein, which was exposed and the balloon extricated (Fig. 2). Examination of the balloon following retrieval revealed that the balloon was intact.

On post-procedure echocardiography residual gradient across the pulmonary valve was 20 mmHg. The tricuspid valve was intact—there was no evidence of tricuspid valve tear or regurgitation.
Discussion

Pulmonary balloon valvotomy is a relatively safe procedure. Apart from rare cases of embolic manifestations, pulmonary regurgitation and valve tear, no other complications are reported following PBV. Infective endocarditis following PBV is also rare. MEDLINE search did not reveal any instance of a balloon getting entrapped at the level of the right atrium.

The present case was peculiar in many ways: while it is rare for a balloon to be detached from the stem of a catheter, balloon entrapment at the right atrium is not reported in the literature; an entrapped balloon being retrieved with a snare percutaneously and a presumably ruptured balloon found intact following retrieval are rarer still. Balloons are not reused outside developing nations and, hence, there is a paucity of literature on the topic.

Normally, the balloon and the catheter stem are attached firmly at the proximal and distal points. The central portion is free and expands during inflation. In the present case, the balloon may have detached partially from the catheter during inflation at the junction of the proximal end of the balloon and the catheter; hence, blood was drawn from the catheter during deflation. When the catheter was in the right atrium, the balloon and catheter were totally detached—both at the proximal and distal attachments. Since the entire procedure was done over the wire, the balloon stayed in position and was successfully retrieved with a snare.

Our institution provides free health care to patients and balloons are reused following sterilization with ethylene oxide gas. In a developing country like India, where cost is a major constraint for providing health care, reuse of balloons has been found to be very economical.

During reuse of balloons, two questions arise, namely, the precautions to be taken and the use of a larger sheath to prevent an arteriotomy. As a precautionary measure, we propose that the balloon must be inflated before the procedure and the proximal and distal ends carefully inspected for any signs of leakage. Normally, air is not drawn into the syringe on deflation of the balloon; however, if air is drawn into the syringe, it could provide a clue to partial detachment. A bigger percutaneous sheath to prevent an arteriotomy was not successful because the balloon collapsed and folded on itself as seen in Fig. 1, wherein both the proximal and distal markers are seen close to each other. It is important to note that a burst balloon may or may not necessarily detach from the catheter. The possibility of a manufacturing defect being the cause of detachment is unlikely since balloons are intended for single use.

We conclude that any balloon presumed to have burst inside the heart should be removed with extreme caution. Herein, a provisional diagnosis of partial detachment of the balloon from the catheter should be considered. It is important to have a guidewire in position to facilitate retrieval of such a balloon. In a developing country like India, where cost is an important factor, balloons can be re-used, but with extreme caution.

References

Adenosine-Induced Ventricular Fibrillation

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The use of adenosine has been suggested as a diagnostic tool in the evaluation of wide QRS complex tachycardia. However, adenosine shortens the antegrade refractoriness of accessory atrioventricular connections and may cause acceleration of the ventricular rate during atrial fibrillation. We observed ventricular fibrillation in 2 patients who presented to the emergency department with pre-excited atrial fibrillation and were given 12 mg of adenosine. (Indian Heart J 2001; 53: 208–210)

Key Words: Adenosine, Ventricular fibrillation, Tachyarrhythmias

Sudden arrhythmic death in patients with the Wolff–Parkinson–White (WPW) syndrome usually occurs as a result of atrial fibrillation (AF) with an extremely rapid ventricular response.1,2 In these patients, AF generally presents as an irregular wide QRS complex tachycardia (WQRST). This, in general, represents a diagnostic challenge and adenosine has been advocated by ACC/AHA guidelines in 1992 as an ideal pharmacological agent to distinguish WQRSTs of ventricular origin from those of supraventricular origin with bundle branch block aberrancy.3 In addition, because of its presumed safety, adenosine is used widely in emergency departments. Adenosine, however, has been associated with pro-arrhythmic effects in several patient populations,4–6 can precipitate AF in some patients,7 and has been associated with ventricular fibrillation (VF) in patients with pre-excited AF.8 We report two cases of adenosine-induced VF and discuss strategies to prevent this lethal outcome.

Case Report

Case 1: A 24-year-old man, with a long-standing history of palpitations, presented to the emergency department for the first time. His past history was unremarkable and he was not on any medication. Physical examination revealed a heart rate of 200 beats/min with an irregularly irregular pulse. Blood pressure was 100/68 mmHg and electrocardiogram (ECG) on presentation (Fig. 1) showed an irregular WQRST with the shortest R–R interval of 160 ms. Supraventricular tachycardia (SVT) with aberrancy was suspected and the patient was administered 12 mg of adenosine intravenously followed by a saline bolus. Within 5 seconds, he developed VF (Fig. 2). Electrical defibrillation was performed to convert his heart beat to sinus rhythm. The ECG now showed pre-excitation suggestive of left posteroseptal accessory pathway (AP), which was subsequently ablated using radiofrequency energy.

Case 2: A 35-year-old man with a long-standing history of paroxysmal palpitations, diagnosed as WPW syndrome, presented with palpitations of sudden onset to the emergency department. He had been treated with digoxin and β-blockers in the past, but had not been on any

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Fig. 1. Fast broad irregular QRS complexes suggestive of pre-excited atrial fibrillation. The shortest R–R interval is 160 ms.
medication for a few months. On examination, his blood pressure was 100/72 mmHg and heart rate was 204 beats/min. The ECG was interpreted as SVT with aberrancy in a case of WPW syndrome and the patient was administered 12 mg of adenosine intravenously. Immediately following this bolus dose, the patient developed VF. Sinus rhythm was restored subsequently by electrical defibrillation. An electrophysiological study demonstrated a left lateral AP, which was successfully ablated using radiofrequency energy.

Discussion

The most common arrhythmia in patients with WPW syndrome is orthodromic paroxysmal supraventricular tachycardia (PSVT) which may present either as a narrow QRS complex tachycardia or WQRST (SVT with aberrancy). Antidromic tachycardia is considerably less common and may resemble a regular ventricular tachycardia because of the wide QRS complexes resulting from ventricular activation via the AP.2 Prognostically, the most dangerous arrhythmia in a patient with WPW syndrome is AF with rapid ventricular response as a result of conduction proceeding over the AP. Atrial fibrillation may precipitate VF if the AP allows sufficiently rapid conduction. Atrial fibrillation with an extremely rapid ventricular response is usually the cause of sudden death due to arrhythmia in patients with the WPW syndrome.1,2

Adenosine is short-lived.10 Adenosine, however, has been associated with pro-arrhythmic effects in several distinct patient populations and has been implicated in precipitating AF.4 Pause-dependent ventricular tachycardia has also been described in women with a normal heart.5 It has been associated with the induction of pause-dependent polymorphic ventricular tachycardia in patients with a structurally normal heart and a normal QT interval.6

The patients described above presented to the emergency department with an irregular WQRST. A fast, broad and irregular tachycardia must bring to mind the strong possibility of AF with the WPW syndrome.11 The type of tachycardia was AF as evidenced by the irregularly irregular QRS complexes as well as occasional conduction via the AV node, resulting in narrow QRS complexes. The wide QRS complexes were due to ventricular activation through the AP rather than the AV node. Thus, the AV node was not involved in the development or maintenance of the tachycardia. Since predominant pharmacological effect of adenosine is at the AV node, it predictably would not terminate these tachycardias. Atrial fibrillation also produces marked vasodilatation and a rebound sympathetic surge.

The mechanism of development of VF following adenosine administration in these patients may be multifactorial.

(i) First, adenosine could favor conduction through the AP by slowing conduction over the AV node and decreasing the concealed retrograde conduction into the AP by normally conducted beats.2 However, it is unlikely that slowing of AV conduction is an important factor in patients who have a rapid ventricular response during AF with most complexes conducted through the AP.

(ii) Second, adenosine may shorten the AP effective refractory period (APERP) directly, leading to an increased ventricular rate.

(iii) Third, adenosine may shorten the APERP as a result of a reflex increase in adrenergic tone brought about by its peripheral vasodilatory effect.12 This observation is supported by the uniform observation of a decrease in systolic blood pressure after administration of adenosine.

(iv) Finally, ventricles are more arrhythmogenic under catecholamine stimulation.

We conclude that adenosine may cause VF when administered during pre-excited AF. This phenomenon is seen in patients with rapidly conducting APs with short effective refractory periods. Adenosine may be safely used as a diagnostic aid for regular WQRST but should be avoided for irregular WQRST.
References

Isolated Congenital Left Ventricular Diverticulum in Adults

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Isolated congenital ventricular diverticulum or aneurysm is rare and usually arises from the left ventricle. The presentation of this condition is diverse. We report three cases of isolated congenital left ventricular diverticula. The age range was 17–30 years. Chest X-ray provided the earliest clinical suspicion in these three cases of a cardiac anomaly which was diagnosed by echocardiography and confirmed by angiocardiography. The location of the congenital left ventricular diverticulum was the left ventricular apex in two cases and basal in the other.

We conclude that congenital left ventricular diverticulum is a disease of protean presentations. A high index of suspicion is necessary while interpreting chest X-rays and echocardiographs to diagnose congenital left ventricular diverticulum. A contractile accessory chamber of the left ventricle with a narrow neck with or without midline defects and an electrocardiogram without Q waves is consistent with the diagnosis of congenital left ventricular diverticulum. (Indian Heart J 2001; 53: 211–213)

Key Words: Echocardiography, Aneurysm, Congenital heart defects

Case Reports

Case 1: A 30-year-old female patient presented with features of cardiac failure which had progressed over the last six months. A 12-lead ECG showed complete right bundle branch block (RBBB) while chest X-ray PA view revealed an abnormal apical shadow and evidence of grade II pulmonary venous hypertension. Echocardiography showed an accessory chamber communicating with the apex of the left ventricle (LV) through a narrow neck, with systolic flow from the diverticulum to the LV (Fig. 1). In addition, there was rheumatic mitral stenosis with a mitral valve orifice of 1.8 cm² by planimetry. Selective coronary angiography was normal. Left ventricular angiography confirmed the location of the accessory chamber at the apex and its contraction during systole (Fig. 2). At surgery, external morbid anatomy revealed a large contracting outpouch with a connection to the apex of the LV. Longitudinal opening of the outpouch showed a narrow neck connected to the LV cavity. The outpouch was excised and the narrow neck defect was closed with a synthetic patch adopting the Dor procedure.

Case 2: A 17-year-old male patient presented with an episode of palpitation of sudden onset. Clinical examination was unremarkable except for tachycardia. A 12-lead ECG showed regular wide QRS tachycardia with a rate of 200 per minute, and the patient was hemodynamically stable. Attempts at pharmacological conversion were unsuccessful and electrical cardioversion was performed, following which the 12-lead ECG was within normal limits and clinical examination revealed mild mitral regurgitation. Chest X-ray PA view was normal and echocardiography showed an accessory chamber communicating with the basal part of the LV with a narrow neck, with systolic flow from the...
accessory chamber to the LV on color flow mapping and mild mitral regurgitation. Selective coronary angiography was normal. Left ventricular angiocardiography confirmed the presence and location of the LV accessory chamber at the posterobasal segment of the LV (Fig. 3).

**Case 3:** A 25-year-old male patient presented with a nonanginal type of chest pain. Clinical examination was unremarkable. A 12-lead ECG showed ST depression in leads V5 and V6. Chest X-ray PA view showed an abnormal shadow along the left border of the heart above the apex. Echocardiography revealed an accessory chamber communicating with the LV apex through a narrow neck, and systolic flow was documented from the accessory chamber to the LV by color flow mapping. Selective coronary angiography was normal. Left ventricular angiography showed the LV accessory chamber with three sacs in continuity with each other arising from the LV apex and extending upward along the left border of the heart (Fig. 4). At surgery, a large contracting outpouch communicating with the LV apex was excised and the defect closed with a synthetic patch adopting the Dor procedure.

**Discussion**

Several authors have attempted to classify and differentiate a congenital aneurysm from a diverticulum. An aneurysm may be defined as a localized enlargement or dilatation involving all the tissue layers of the wall secondary to a mechanical weakness caused by a developmental defect or an acquired abnormality. A ventricular aneurysm is classified as congenital in origin when no known causes of acquired aneurysm are found. A diverticulum, on the other hand, is usually defined as a
pouch or sac created by herniation of an internal layer of a tubular organ through a defect in the muscular coat.  

Diverticula of the LV are extremely rare among all forms of diagnosed congenital heart diseases. The age of our patients ranged from 17 to 30 years. Cardiac failure and tachyarrhythmia are the usual modes of presentation as seen in cases 1 and 2. Chest pain can occur as it did in case 3, but the cause-effect relationship is not conclusively proved. Several nonspecific ECG findings have been described, of which Q waves are considered to favor aneurysm but none of our patients showed Q waves in their ECG.  

Right bundle branch block (seen in case 1), ventricular tachycardia (seen in case 2) and ST depression in leads V5–V6 (seen in case 3) have also been documented by other authors. Routine X-ray chest PA view may show an abnormal cardiac silhouette which provides the earliest clue for diagnosis. In a series of 9 patients with diverticulum studied by Baltaxe et al., all had normal chest X-ray as seen in case 2. On echocardiogram, the diverticulum is seen as a small, circular, echo-free space communicating with the LV cavity via a short neck which is akin to the appearance in pseudoaneurysm. The neck is defined as narrow if its diameter is less than 40% of the maximal diameter of the aneurysm. This has been well described in pseudoaneurysms but its application in the case of a diverticulum is unclear. However, Doppler flow mapping in the diverticulum shows systolic flow from the diverticulum to the LV while in a pseudoaneurysm it is in the reverse direction. All the cases reported here follow the systolic flow pattern described for diverticulum. Our cases had an accessory chamber communicating with the LV through a narrow neck, and the sites were apical in two patients and basal in one.

Three general types of LV diverticula have been recognized in the literature. The first type, described by Cantrell et al. in 1958, comprises CLVD which are large, muscular, commonly located at the apex and are part of a syndrome of cardiac anomalies and midline defects. In the second type, the LV diverticula are usually subvalvular and basal, and intimately related to the mitral and aortic valves producing regurgitation, but are occasionally apical. The second type has been described as congenital fibrous diverticulum of the LV and, since the walls of these diverticula are fibrous, they are usually classified as aneurysms. First described by Hoeffel et al., an isolated muscular diverticulum has been designated as the third type and about 13 cases have been reported in the literature.

To differentiate between congenital muscular diverticulum and aneurysm of the LV, the connection to the LV cavity and thoracoabdominal defects are considered. If the connection to the LV cavity is narrow with associated thoracoabdominal defects, the lesion is thought to be a congenital muscular diverticulum. In aneurysm of the LV, the point of connection is wide and there are no midline defects. During LV angiography, diverticula contract during systole and are best seen during diastole, in contrast to aneurysms which are hypokinetic or dyskinetic during systole. However, there is disagreement over this. Singh et al. characterized diverticula as being noncontractile and congenital aneurysms as contractile. In our series, the accessory chamber in all the patients contracted in systole and had a narrow connection to the LV; hence, we classified them as diverticula. As there are no midline defects in any of our patients, we believe they belong to the isolated type of diverticula first described by Hoeffel et al. We operated on 2 patients and the presence of a narrow neck was confirmed. Histologically, they showed features consistent with muscular diverticulum.

We conclude that CLVD is a disease of protean manifestations and, for diagnosis, a high index of suspicion is required during interpretation of chest X-ray and echocardiography. A contractile accessory chamber of the LV with a narrow neck, with or without midline defects, and an ECG without Q waves is consistent with the diagnosis of CLVD.

References

Stenting for SVC Obstruction in an Infant Operated for Total Anomalous Pulmonary Venous Return

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Superior vena cava obstruction following corrective repair of total anomalous pulmonary venous return has rarely been described in the literature. A one-month-old boy who underwent corrective surgery for obstructive supracardiac total anomalous pulmonary venous return with consequent symptomatic superior vena cava obstruction in the immediate postoperative period, is reported. This was treated by balloon dilatation followed by stenting of the superior vena cava. The immediate postoperative result was satisfactory and the infant continued to remain asymptomatic at six months follow up. We suggest that this intervention could prove to be a viable alternative to a repeat surgical procedure for such complex cases. *(Indian Heart J 2001; 53: 214–217)*

**Key Words:** Angioplasty, Superior vena cava syndrome, Stents

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**Case Report**

A one-month-old boy weighing 5 kg presented with a history of shortness of breath and dusky appearance of the lips and nails. Clinical examination revealed mild cyanosis, a respiratory rate of 60 per minute, with subcostal and intercostal retraction. Cardiac examination revealed an active precordium, with a short systolic murmur located in the pulmonary area. Both the components of the second heart sound were well heard and did not vary with respiration. There was a mid-diastolic murmur in the tricuspid area. Chest X-ray revealed cardiomegaly (cardiothoracic ratio 70%) with increased pulmonary vascularity. The electrocardiogram (ECG) showed normal sinus rhythm with a monophasic R in lead V₁. A two-dimensional (2-D) echo and color Doppler evaluation showed nonobstructive supracardiac type of TAPVR with the pulmonary veins draining into the left vertical vein, and then via the left innominate vein and the right SVC into the right atrium. The peak systolic pulmonary artery pressure was 40 mmHg. There was a large ostium secundum atrial septal defect (ASD) with an obligatory right-to-left shunt. There was no other intracardiac defect or extracardiac shunt seen. The child was subjected to intracardiac repair under cardiopulmonary bypass, during which the right SVC was cannulated with a 12 F Pacifico cannula. The left vertical vein was ligated and the common confluence incorporated into the left atrium. The ASD was closed with a pericardial patch in such a way that the pulmonary veins
were re-routed into the left atrium. The child withstood the procedure well. He was discharged after an uneventful post-operative course. He was asymptomatic for six weeks after which the parents noticed puffiness of the face and upper half of the body, including the upper limbs. The puffiness increased progressively and breathlessness set in a fortnight after the onset of edema. The weight of the child was 6 kg at this time. A chest X-ray was done which showed a right-sided pleural effusion. A pleural tap revealed a chylothorax on the right side. The child was treated conservatively for a week but the effusion recurred and the intercostal tube continued to drain 120–150 ml of chyle every 24 hours. A repeat 2-D echo and color Doppler evaluation revealed severe obstruction to the SVC flow with a peak gradient of 15 mmHg and a mean gradient of 7 mmHg. The weight of the child was 6 kg at this time. A chest X-ray was done which showed a right-sided pleural effusion. A pleural tap revealed a chylothorax on the right side. The child was treated conservatively for a week but the effusion recurred and the intercostal tube continued to drain 120–150 ml of chyle every 24 hours. A repeat 2-D echo and color Doppler evaluation revealed severe obstruction to the SVC flow with a peak gradient of 15 mmHg and a mean gradient of 7 mmHg. The child was taken up for cardiac catheterization with a view to dilate and stent the SVC. The procedure was performed under general anesthesia. Under sterile conditions, the right femoral artery and vein were accessed percutaneously. A 6 F and a 4 F Hemaquit were placed in the right femoral vein and artery, respectively and 100 U/kg of heparin was administered. A JR 3 catheter was placed in the right atrium and a 0.032" Crosswire™ guidewire (Terumo Inc., Japan) was used to cross the obstruction. The mean pressures recorded in the right atrium and SVC above the obstruction were 5 mmHg and 12 mmHg, respectively. The JR 3 catheter was exchanged for a 6 F cut pigtail catheter. A jugular and superior vena cava gram were performed, which revealed a tight stenosis of the SVC at the SVC–RA junction (Fig. 1). There were well-developed collaterals which drained into the azygos system. A 0.035” exchange wire was introduced through the pigtail catheter and positioned in the right jugular system. The pigtail catheter was exchanged for a 10×3 mm Tyshak balloon catheter (NuMed, Cornwall, Ontario, Canada). The balloon was inflated three times, till the waist disappeared (Fig. 2). Although the waist disappeared during the first balloon inflation, it reappeared during subsequent inflations, indicating recoil. Hence, it was decided to stent the SVC to obtain satisfactory hemodynamic results. A 8–12 mm long Palmaz stent (Cordis, Warren, NJ) was crimped on a 10×3 mm Tyshak balloon and, after changing the femoral sheath to a 7 F long Hemaquit, the balloon-mounted stent was positioned at the site of maximum stenosis which was confirmed by a test angiogram. The stent was deployed by inflating the balloon (Fig. 3). The post-stent angiogram revealed excellent flow through the SVC with no evidence of any narrowing, no pressure gradient across the stenosis, and the disappearance of collaterals (Fig. 4). A central venous catheter was inserted through the right internal jugular vein for a period of three
days in the postoperative period. There was no evidence of blockage of this catheter at any time and, on removal, there was no clot at the catheter tip. The child was put on oral aspirin 5 mg/kg/day. At follow-up after six months, the child weighs 9 kg and is asymptomatic. On examination, his development is normal with no evident cardiovascular abnormality. A 2-D echo showed the stent in position at the right atrium–SVC junction with a part protruding into the right atrium. On color Doppler evaluation, the peak and mean gradients across the stented portion were 4.2 mmHg and 1.5 mmHg, respectively. The flow was biphasic with evidence of respiratory pressure variations.

**Discussion**

Balloon dilatation and stenting for venous obstruction has been well documented in the literature. Superior vena cava baffle obstruction following the repair of transposition of great arteries (TGA) using the Mustard and Senning procedures has been described. The incidence of the SVC syndrome is 4%–40% following the Mustard procedure, and 10% following the Senning procedure. Superior vena cava obstruction following intracardiac repair of TAPVR has rarely been described in the literature. The patient described in the case above required relief of the SVC obstruction in view of the persistent drainage of chyle from the right pleural cavity and worsening edema, in spite of medical management. The exact cause of SVC narrowing in this patient is not certain; it could be related to the cannulation of the SVC during cardiopulmonary bypass or to the placement of the central line through the right internal jugular vein in the postoperative period; the former seems to be the more likely explanation. Percutaneous venous angioplasty with or without stenting provides an effective nonsurgical treatment for the SVC syndrome following repair of TGA. By avoiding the extensive operative dissection associated with traditional surgical techniques, angioplasty with or without stent placement significantly reduces morbidity and mortality in these often complicated cases. In our patient, simple angioplasty did not result in a drop in the gradients. Moreover, reappearance of the waist with every dilatation was an indicator of recoil. In view of this, it was decided to implant a stent. Placement of stents, which is frequently used in conjunction with angioplasty to treat the SVC syndrome in adults, is not recommended in children as SVC growth could lead to stent migration and would necessitate a repeat dilatation of the stent. However, in our case, we were left with very little choice, in view of the suboptimal results with angioplasty alone. Angioplasty may suffice and can be repeated, if necessary, to maintain
SVC patency until the patient reaches maturity, at which time stent placement may be advisable. Angioplasty may also be used as a “bridge” to definitive surgical repair. By relieving the SVC obstruction, the collaterals get decompressed, thereby reducing the size and number of vessels that bypass the obstructed SVC, thus providing for a greater safety margin during the operative dissection for surgical relief of the SVC syndrome. Whether as a “bridge” or as an independent treatment modality, angioplasty of the SVC in pediatric patients with congenital heart disease is safe and effective and should be considered an important part of the existing treatment modalities in these patients.

References
Pulmonary Embolism with Isolated Right Ventricular Infarction

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The importance of right ventricular (RV) infarction in patients with pulmonary embolism is not widely appreciated, and there are few case reports in the literature. We report a case of sub-massive pulmonary embolism with isolated infarction of the RV anterior wall who presented with sustained ventricular tachycardia (VT).

Case Report

A 52-year-old male was admitted with complaints of sudden onset of palpitation and breathlessness ten days prior to admission. There was no previous history of chronic lung disease. Clinical examination revealed orthopnea, a pulse rate of 200/min (regular), blood pressure of 100/70 mmHg and raised jugular venous pressure with irregularly occurring cannon waves. The electrocardiogram (ECG) (Fig. 1) revealed a broad QRS tachycardia with atrioventricular (AV) dissociation. The mean frontal plane QRS axis was $+105$ with monomorphic negative QRS complexes in the precordial leads (left bundle branch block morphology). The patient did not respond to intravenous lignocaine but the VT reverted to sinus rhythm with a synchronized DC shock of 50 Joules. The ECG in sinus rhythm revealed T wave inversion in leads V$_1$ to V$_6$ without loss of R wave in these leads. There was no right bundle branch block (RBBB) or any other remarkable abnormality.

An X-ray of the chest revealed bilateral mild-to-moderate pleural effusion. Computerized axial tomography of the chest revealed pulmonary embolism in the posterobasal parts of both lungs (Fig. 2), together with consolidation and loss of volume in the lower portion.

On echocardiographic evaluation, all walls of the left ventricle, including the interventricular septum, showed normal thickness and mobility. The RV was dilated with a thin and akinetic anterior wall (Fig. 3). The inferior wall showed normal thickness and movement in a subcostal four-chamber view. MB isoenzyme of creatinine kinase (MB-CK) was 19 IU, and a Doppler evaluation of the lower limb veins did not reveal any thrombus.

The patient was treated with intravenous heparin, intravenous dobutamine, oral warfarin, amiodarone and a small dose of frusemide. He gradually improved and was asymptomatic at the time of discharge. The patient did not agree to undergo any invasive evaluation.

Discussion

Sub-massive pulmonary embolism results in an acute increase in RV afterload. Right ventricular oxygen demand is further increased if there is RV failure with dilatation. Both these factors, along with hypoxia, can contribute to isolated RV infarction. This can happen even if there is no significant coronary artery disease. In some cases, RV infarction could be a primary event, and pulmonary embolism could be secondary to a thrombus dislodged from the RV or congested systemic veins.
Ventricular tachycardia in our patient could be secondary to concomitant RV infarction. Negative QRS deflections in the precordial leads suggest a focus in the RV anterior wall with the dominant vector directed posteriorly. Right axis deviation suggests that the origin of VT was probably close to the RV outflow tract.

Clinical diagnosis of concomitant RV infarction in a case of pulmonary embolism can be difficult because pulmonary embolism by itself can produce gross RV failure and hypotension.

Pulmonary embolism produces ST segment elevation and T wave inversion in the right-sided chest leads and leads V2–V4.4,5 Infarction of the RV anterior wall also produces similar changes in these leads.6 Therefore, an ECG is not helpful in diagnosing additional RV infarction in a case of pulmonary embolism but elevation of MB-CK in a case of pulmonary embolism could be suggestive of the above.7 Serum levels of MB-CK start rising after six hours of infarction and return to baseline within three days. Estimation of this isoenzyme, therefore, may not be helpful in patients presenting very early or those presenting after three days. This could be the reason for normal values of MB-CK in our patient. Echocardiography can reveal RV enlargement with diffuse hypokinesia in patients with massive or sub-massive pulmonary embolism.8 Regional wall motion abnormality without diffuse hypokinesia can help in diagnosing additional RV infarction.3

Concomitant occurrence of pulmonary embolism and RV infarction has some therapeutic implications. Thrombolytic therapy is useful in pulmonary embolism irrespective of whether or not there is concomitant RV infarction. Dobutamine infusion is helpful in patients presenting with hypotension and/or right-sided failure. Nitrates should, however, be used cautiously. These drugs can produce severe hypotension by reducing the filling pressure of the infarcted RV which is already subject to increased afterload due to pulmonary embolism. Fluid infusion is usually recommended for patients of RV infarction with hypotension, though it may not be helpful in cases with concomitant RV infarction and pulmonary embolism. Unlike patients with RV infarction without pulmonary embolism, fluid infusion may not translate into an increased RV output due to a significant increase in afterload. On the contrary, volume overload of an already pressure overloaded and failing RV may cause a further shift of the interventricular septum to the left. This will result in further elevation of left ventricular filling pressure and decrease in its output. Diuretics, when used cautiously, may be helpful in patients with raised jugular venous pressure.
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Secondary Lymphoma of the Heart Presenting as Recurrent Syncope

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The most common secondary tumors in pediatric patients are non-Hodgkin’s lymphoma, leukemia and neuroblastoma.1 Cardiac involvement from non-Hodgkin’s lymphoma can present with pericardial effusion, arrhythmia and congestive heart failure.2 Ventricular tachycardia (VT) as a presentation is rare.3,4 We describe a case of metastatic non-Hodgkin’s lymphoma presenting with syncope due to recurrent VT.

Case Report
GS, a 12-year-old boy was admitted to the medical emergency department with recurrent syncope. He had four episodes of syncope in the past month. During the present admission, his pulse was not recordable and the electrocardiogram (ECG) showed VT with a heart rate of 280/minute (Fig. 1). He was successfully resuscitated with a DC shock and started on amiodarone. On examination after resuscitation, his pulse rate was 100/minute and his supine blood pressure in the right upper limb 106/64 mmHg. Cardiac examination revealed the apical impulse in the left fifth intercostal space within the midclavicular line. Heart sounds were normal and there was a grade II/IV ejection systolic murmur in the second left intercostal space. His left mandibular region was swollen and the left cervical region revealed multiple lymph nodes. Abdominal examination showed hepatomegaly.

Standard ECG revealed sinus rhythm with a QTc interval of 0.36 seconds. The chest X-ray showed normal heart size and configuration, and normal lung fields. Blood investigations revealed a hemoglobin level of 10.1 g/dl, total leucocyte count of 3000/cmm with a normal differential count, and a platelet count of 21000/cmm. Peripheral smear did not reveal any blast cells. Computed tomogram (CT) showed mild hepatomegaly with a focal hypodense area in the right lobe of the liver, small multiple lymph nodes in the retroperitoneal area with normal spleen and kidneys.

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Key Words: Non-Hodgkin’s lymphoma, Ventricular tachycardia, Syncope

Fig. 1. 12-lead ECG showing ventricular tachycardia.
CT scan of the head revealed a mass in the left mandibular region (Fig. 2). Echocardiography showed a homogeneous mass in the right ventricular (RV) cavity with extension into the outflow region (Fig. 3a). On Holter analysis, multiple episodes of ill-sustained polymorphic VT were noted which correlated with the diary event of syncope. Aspiration cytology from the left cervical lymph node showed a monomorphic population of lymphoid cells with a few mature lymphocytes and many lymphoglandular bodies. A lymph node biopsy confirmed the findings, and immunostaining for alpha-fetoprotein and chromogranin were negative. Metastatic non-Hodgkin’s lymphoma was diagnosed.

The patient was started on systemic chemotherapy (CHOP—cyclophosphamide, adriamycin, vincristine and prednisolone). He completed six cycles of chemotherapy and showed complete disappearance of the tumor mass from the RV, as shown in Fig. 3b. For VT, he was initially started on amiodarone in addition to chemotherapy. After disappearance of the tumor from the RV, amiodarone was discontinued as the patient was asymptomatic.

**Discussion**

Primary cardiac lymphoma is rare, but secondary involvement of the heart by a lymphoma is not uncommon. Huh et al. have described three cases of lymphoma in a series of 8 cases of secondary cardiac tumors in children. Patients may present with pericardial involvement in the form of an effusion and cardiac tamponade, while myocardial involvement may result in heart failure or arrhythmia. Ventricular tachycardia due to a lymphoma is uncommon. Miyashita et al. from Japan reported the case of a 70-year-old woman with sustained VT in a primary cardiac lymphoma. In their patient, the lymphoma was localized to the RV outflow tract and there was no evidence of extracardiac involvement. Ventricular tachycardia was successfully terminated with intravenous disopyramide.

In our case, we used electrical cardioversion followed by amiodarone for the treatment of VT. Amiodarone has been successfully used for the control of VT secondary to cardiac
metastasis as reported by Leak.\textsuperscript{9} Danbauch et al.\textsuperscript{4} reported VT in a 19-year-old student with metastatic non-Hodgkin’s lymphoma. Agarwala et al.\textsuperscript{10} reported the case of a 5-year-old child with non-Hodgkin’s lymphoma localized to the right and left atria, whose ECG showed paroxysmal supraventricular tachycardia. Unlike our patient, in their case the tumor was in both atria, and there was no episode of VT. The tumor resolved with chemotherapy alone.

References

Does Moderate Alcohol Intake Protect Against Coronary Heart Disease?

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There is abundant epidemiological and clinical evidence to show that light-to-moderate drinking is associated with a reduced risk of coronary heart disease (CHD), total and ischemic stroke, and total mortality in middle-aged and elderly men and women. The evidence suggests a J- or U-shaped relationship between alcohol and CHD. Alcohol reduces the risk of coronary heart disease both by inhibiting the formation of atheroma and by decreasing the rate of blood coagulation. It appears that for most conditions, other than cardiovascular diseases and cholelithiasis, moderate alcohol consumption has either none or only an intermediate type of risk as compared with the risk of either abstinence or excessive drinking. It is now fully recognized and accepted that drinking alcohol regularly for years is toxic to almost every tissue of the body. However, most people who choose to drink alcohol have little or no problem limiting their consumption to amounts that do not generally cause serious health or social consequences. Moreover, a given dose of alcohol may affect different people differently. It is, therefore, imperative that a critical evaluation, based on the observations made hitherto, be done of both the harmful and the protective effects of alcohol consumption on various organs/systems of the body. This article reviews epidemiological evidence for the protective effects of alcohol on the cardiovascular system and discusses how alcohol might lower the risk of CHD.

Health Risks of Alcohol Consumption

Many of the toxic effects of alcohol are due to disturbances of a wide variety of metabolic functions and organ damage.1-3 Alcohol is a depressant that is absorbed into the bloodstream and transmitted to all the systems in the body. Light-to-moderate doses can reduce physical coordination and mental alertness, making activities such as sports and driving dangerous. Even moderate doses of alcohol can cause staggering, slurred speech, double vision, mood swings and unconsciousness. Persistent impotence and loss of libido as well as hepatitis, esophagitis and pancreatitis may occur with “heavy” alcohol use. Long-term alcohol use increases the risk of liver disease, heart disease, peptic ulcer, certain types of cancer, complicated pregnancies, birth defects, and brain damage. Heavy or binge drinking may even result in respiratory depression and death. Use of alcohol can also cause mood changes and loss of inhibition as well as violent or self-destructive behavior. Alcohol tends to produce a strong psychological dependence and can create physiological addictions. It is also a potent contributing factor to many accidents and tragedies. Alcohol-related effects on organs and tissues based on data published on the health risks and benefits of alcohol consumption are summarized in Table 1. While alcohol in

Table 1. Health effects related to alcohol drinking

<table>
<thead>
<tr>
<th>Effect</th>
<th>Type of drinking</th>
<th>Protective effect</th>
<th>Risk/damage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neurological</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heavy</td>
<td>No</td>
<td>Yes1</td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>*</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Light</td>
<td>Yes2</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal (stomach, oesophagus, pancreas, liver, colon, rectum)</td>
<td>Heavy</td>
<td>No</td>
<td>Yes3</td>
</tr>
<tr>
<td>Fetal</td>
<td>Heavy</td>
<td>No</td>
<td>Yes4</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>Heavy</td>
<td>No</td>
<td>Yes5</td>
</tr>
<tr>
<td>Moderate</td>
<td>*</td>
<td>Yes</td>
<td></td>
</tr>
</tbody>
</table>

Heavy: >80g/day; Moderate: 30–80 g/day; Light: <30 g/day
* Indicates either no effect or that it has not been studied in detail
1 Examples of cognitive deficits: dementia, Wernicke–Korsakoff syndrome, cerebral degeneration
2 Decreases the risk for ischemic stroke by reducing atherothrombotic phenomenon
3 Examples: alcoholic liver cirrhosis, pancreatitis, cancers of the colon and the rectum
4 Alcohol-related birth defects: include craniofacial abnormalities and growth deficiency and deficits in intellectual functioning, leading to difficulties in learning, memory, problem-solving and attention
5 Causes damage to heart muscle, increases risk of congestive heart failure and/or sudden death

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light and moderate doses does not exert any significant risk or benefit on most organs, it certainly has a protective effect on the cardiovascular system.

**What is Moderate Drinking?**

It is difficult to specify “moderate” intake quantitatively as alcohol intake is frequently expressed in “drinks” or “units” that vary with the beverage type, culture and era. “Heavier drinking” usually indicates a daily intake of 3 or more standard-sized drinks per day of wine, liquor or beer; “moderate drinking” usually indicates an intake of 3 or fewer drinks per day. Low-to-moderate alcohol intake is usually defined as an average consumption of 1 to 2 drinks a day. Thus, based upon recent publications, alcohol drinking maybe divided into “heavy”, “moderate” and “light” categories depending upon the amount of alcohol consumed in terms of pure ethanol per day. Generally, daily consumption of 80 g and more of pure alcohol is considered as heavy drinking. Amounts of pure alcohol consumed ranging between 30 to 80 g per day are accepted as moderate drinking and that of below 30 g per day are taken as light drinking.

**Alcohol and the Cardiovascular System**

Disparities in the relationship between alcohol consumption and various cardiovascular disorders are now evident, with complex interrelationships between the conditions. It is best to consider the relationship of alcohol consumption with various disorders separately:

1. Evidence continues to mount that susceptible persons may suffer heart muscle damage following the intake of large amounts of alcohol, leading to alcoholic cardiomyopathy.
2. Consistent epidemiological data support a close relationship between heavy drinking and hypertension; intervention studies show a pressor effect of alcohol which appears and regresses within several days, but the mechanism has not yet been established;
3. Heavy, and possibly moderate, drinking is related to a higher risk of hemorrhagic stroke, but moderate drinking is associated with a lower risk of ischemic stroke, particularly among women;
4. Heavier drinking, especially binge drinking, is related to cardiac rhythm disturbances;
5. A 20% to 40% lower incidence of CHD has been reported among drinkers compared to nondrinkers. This inverse relationship of moderate alcohol use to CHD is supported by a number of epidemiological studies.

**Protective Effects of Alcohol Intake**

Several epidemiological investigations have shown that a low-to-moderate level of alcohol intake has a definitive, protective role against CHD and stroke. Such conclusions have been based upon epidemiological studies on the risks for heart disease, coronary artery disease and death in individuals with low or moderate alcohol intake when compared with the corresponding risks in persons who do not consume alcohol at all. The dose–response curve is usually found to be U- or J-shaped, i.e., the risk is higher when alcohol consumption is high, lower when alcohol consumption is low or moderate and tends to go up again in individuals who do not consume any alcohol.

As compared to people who do not drink alcohol, the risk of CHD in persons who take low or moderate amounts of alcohol seems to be reduced (between a third and a fifth). The level of alcohol consumption that has been associated with a lower risk for CHD ranges widely—from 1 drink to about 3 drinks per day. Studies have found that individuals who consume 1 alcoholic drink every 1 to 2 days have a lower risk of a first acute myocardial infarction (AMI) than abstainers or heavy drinkers but the effect of prior drinking on mortality after AMI is uncertain.

When all cohort data of the above mentioned studies are combined, there appears to be a decline in the risk for myocardial infarction at doses up to 1 drink a day, with little further change in the risk associated with increased alcohol intake. Berger et al. showed that light-to-moderate alcohol consumption reduced the risk of an ischemic stroke in men. The benefit was apparent with as little as 1 drink per week. Greater consumption, up to 1 drink per day, did not increase the observed benefit. Rimm et al. reported that an intake of 30 g of alcohol a day is causally related to a lower risk of CHD through changes in lipids and lipoproteins. At this dose, an increase in high-density lipoprotein (HDL) by 3 mg/dl, apolipoprotein AI by 8.82 mg/dl, triglycerides by 5.69 mg/dl and a modest increase in the hemostatic factor related to the thrombolytic profile was observed.

**Putative Mechanisms Underlying the Protective Effects of Alcohol**

One of the most obvious possibilities could be that the effect of alcohol is associated with other confounding factors affecting the risk of cardiovascular diseases such as age,
sex, high serum cholesterol and triglyceride levels, smoking, a sedentary life style, and an over-enthusiastic approach to day-to-day living. Most of the prospective cohort studies, taking these factors into consideration, have consistently shown that moderate alcohol intake has a protective effect on CHD.14–16,20–22 Several factors have been proposed as explanation for the beneficial effects of moderate alcohol consumption on the development of CHD and atherosclerosis.24,25 These include the effects of alcohol on high-density lipoprotein cholesterol (HDL-c), low-density lipoprotein cholesterol (LDL-c), prostaglandin release and synthesis, platelet aggregability, blood fibrinolytic activity and estrogen levels25–39 (Table 2).

Increase in HDL mediating the protective effect of alcohol: It is amply and unequivocally accepted that alcohol intake is linked to high levels of HDL-c and apolipoproteins AI and AII.25–29 When HDL-c levels were taken into account in a multivariate analysis, the protective alcohol–CHD relationship was quite apparent, supporting the contention that the effect was mediated through HDL.16,25–27 As, it is well accepted that HDL-c is inversely related to CHD and, hence, it has been justifiably proclaimed that the effect of alcohol is mediated through HDL.25–27 However, in a large prospective cohort study, only part of the effect of alcohol was mediated through HDL and other lipid factors.16 Experimental studies have shown that alcohol intake inhibits the transfer of cholesterol esters from HDL to other lipoproteins. The transfer of cholesterol esters between lipoproteins is facilitated by cholesteryl ester transfer protein. A low transfer rate may reduce the reverse transport of cholesterol since much of the HDL-c is taken up by the liver in the form of LDL.

In fact, plaque regression has been demonstrated angiographically in those persons who received drugs that lower cholesterol and increase HDL, indicating that reverse cholesterol transport can be enhanced by raising HDL levels and thereby overcoming the inhibitory effects of oxidized LDL upon the atherogenic process.40 While it was thought earlier that alcohol increased only HDL-3 and not HDL-2, recent observations have shown that both classes contribute equally and additively to the overall efficiency of the reverse transport.41 In addition, an increase in paraoxonase activity was strongly correlated with concomitant increase in the concentration of HDL-c and apolipoprotein AI.23,41 Hence, alcohol intake may raise plasma HDL levels either by altering the synthesis or clearance of HDL or by an effect on the enzymes and proteins influencing HDL metabolism.43

Antioxidative effects of alcohol: Antioxidative effects of alcohol, especially wine, have been frequently proposed as the mode of action of alcohol. It is known that wine contains antioxidants which could slow down the oxidation of unsaturated fatty acids to saturated fatty acids.44 In fact, the antioxidative effect of alcohol is, in all probability, exerted by affecting the oxidation of LDL, thereby hampering the atherosclerotic plaque formation.45 Indeed, polyphenolic antioxidants present in red wine have been shown to inhibit the oxidation of human LDL.46–48 It has been shown recently that distilled alcohol on wood ageing does acquire a significant amount of antioxidants which could be different from those present in red wine.49 These findings indicate that there might not be a large difference between the capabilities of wine (red wine especially) and distilled alcohol in the protection and/or lowering the risk of heart disease.50

Antioxidant effects of alcohol on LDL: Many observational studies have established that dense LDL-c is a major risk factor for CHD. Oxidation of LDL-c is supposed to play a major role in the generation of atherosclerotic lesions.48 The atherogenic potential of LDL in the majority of individuals arises from an increase in the number of small dense LDL particles and not from its cholesterol content per se. Studies have shown that a diet high in saturated fatty acids (SFAs) and cholesterol and low in polyunsaturated fatty acids (PUFAs) and monounsaturated fatty acids (MUFSAs) increases LDL-c.44

| Table 2. Possible biological mechanisms by which alcohol may protect against CHD |
|---------------------------------|------------------|
| **Effect of alcohol**           | **Reference**    |
| Alcohol improves blood lipid profile |                  |
| Increases protective HDL         | 25–27            |
| Inhibits oxidation of harmful LDL| 26–29            |
| Alcohol decreases thrombosis    |                  |
| Reduces platelet aggregation     | 30,31            |
| Reduces fibrinogen               | 32,33            |
| Increases fibrinolysis           | 34               |
| Other positive effects of alcohol drinking |            |
| Increases coronary blood flow    | 35               |
| Reduces blood pressure (<1–2 drinks per day) | 36 |
| Increases blood insulin sensitivity | 37          |
| Increases estrogen levels        | 38               |
| Reduces stress                   | 39               |

Role of paraoxonase in LDL peroxidation: The human serum HDL-linked paraoxonase enzyme limits LDL peroxidation by preventing the transformation of LDL into biologically active atherogenic particles. Paraoxonase serum activity varies among individuals due to a Glu/Arg polymorphism with low (A phenotype) and high
(B phenotype) activity. Recent studies have implicated paraoxonase in providing protection against LDL oxidation, thus affecting the risk of CHD in the general population. Van der Gaag et al.\(^4\) examined the effects of moderate consumption of red wine, beer and spirits in comparison with mineral water on paraoxonase activity in serum. Fasting paraoxonase activity was higher after intake of wine, beer and spirits than after consumption of water but did not differ significantly between the three alcoholic beverages. Similar effects were observed pre- and postprandially. These findings, and those from other recent studies,\(^5\) suggest that increased serum paraoxonase may be one of the biological mechanisms underlying the reduced risk of CHD in moderate alcohol consumers.

**Increased production and altered clearance of apolipoproteins:** Apolipoprotein AI is distributed within HDL between different types of particles, one containing both apolipoprotein AI and apolipoprotein AII (LpAI:AII), the other containing no apolipoprotein AII (LpAI). Branchi et al.\(^5\) demonstrated a significant increase in plasma concentrations of apolipoprotein AI and apolipoprotein AII in men drinking more than 30 g of alcohol a day as compared to nondrinkers. Gottrand et al.\(^5\) found that increase in the plasma concentration of apolipoprotein AII was due to the reduced plasma clearance of apolipoprotein AII as well as an increase in its production. Hence, alcohol drinking increased the plasma concentrations of apolipoprotein AI and apolipoprotein AII, the main components of HDL particles. Based upon epidemiological data, it has been estimated that an average individual consuming 30 g of alcohol per day would show an 8 mg/dl increase in the plasma apolipoprotein AI concentration, primarily due to its increased synthesis in the liver.\(^6\)

**The effect of alcohol on Lp(a):** The protein component of this lipoprotein consists of apolipoprotein-B covalently linked to a series of kringles homologous with those comprising plasminogen. Recent observational studies confirm and extend previous evidence that Lp(a) plays a significant role in atherosclerosis and is one of the major risk factors for cardiovascular diseases.\(^5\),\(^5\) Epidemiologically, Lp(a) is a strong positive risk factor for CHD, the presumed mechanism being the inhibition of fibrinolysis by reduced plasminogen levels due to elevated Lp(a) levels.\(^5\) These levels have been found to be significantly higher in ischemic stroke patients and in those with carotid plaques than in controls.\(^5\) A number of intervention studies in human subjects support the notion that alcohol consumption reduces plasma Lp(a) concentrations.\(^8\),\(^9\) Most convincing are the finding of Kervinen et al.\(^6\) in which the cessation or reduction in beverage alcohol was accompanied by a significant increase in plasma Lp(a). Our group was amongst the first to demonstrate that coronary artery disease patients had higher levels of Lp(a) and those who were alcohol drinkers showed significantly low Lp(a) levels.\(^6\) Further, Paassilta et al.\(^6\) have shown that social drinking, i.e. <39 g alcohol/week is associated with low Lp(a) lipoprotein concentration in middle-aged men and thus concluded that low Lp(a) lipoprotein concentration maybe one factor explaining low mortality and retarded progression of coronary artery disease in social drinkers. However, a number of studies have yielded conflicting results, some apparently demonstrating a negative association between Lp(a) and alcohol consumption\(^8\),\(^9\) while others failed to find any such relationship.\(^6\),\(^8\)

**Additional Factors Contributing to the Protective Effect of Alcohol**

**Platelet aggregation and blood clotting:** Recent studies have shown HDL-c levels can account for only 50% of the protective effect of alcoholic beverages.\(^1\) The other 50% may be partly related to decreased platelet activity.\(^3\),\(^4\) The antplatelet activity of wine is explained not only by ethanol but also by the polyphenolic components with which red wines are richly endowed. It has been suggested that wine phenolics could reduce platelet activity mediated by nitric oxide. Moreover, wine phenolics increase vitamin E levels while decreasing the oxidation of platelets subjected to oxidative stress. However, a rebound phenomenon of hyperaggregability is observed after acute alcohol consumption but not after the consumption of wine. This protection afforded by wine has been duplicated in animals with grape phenolics added to alcohol. It appears that wine, and wine phenolics in particular, could significantly inhibit platelet aggregation and that this could explain, at least in part, the protective effect of red wine against atherosclerosis and CHD.

Excessive alcohol consumption clearly affects platelet function. Moderate alcohol consumption may affect several hemostatic factors, including fibrinogen concentration, platelet aggregability and the fibrinolytic factors — tissue-type plasminogen activator and plasminogen activator inhibitor. Plasma fibrinogen concentrations are decreased by moderate alcohol consumption.\(^1\),\(^2\) Hence, alcohol has been shown to reduce coagulation of blood.\(^3\),\(^4\)

**Role of homocysteine:** Recent studies suggest that high plasma homocysteine concentrations are an independent risk factor for coronary, cerebral and peripheral arterial occlusive diseases.\(^5\),\(^6\) Its effect appears to depend upon its
direct toxicity for endothelial cells. Endothelial dysfunction is associated with atherogenesis and oxidative stress in humans. Serum homocysteine increases after moderate consumption of red wine and spirits, but not after moderate consumption of beer. These authors argue that vitamin B₉ in beer prevents the alcohol-induced rise in serum homocysteine. One of several routes for metabolism of homocysteine involves methylation using betaine as the methyl donor. Betaine is often added to less expensive wine when beet sugar is used to increase alcohol content. In France, a diet high in saturated fat and cholesterol is associated with low coronary artery disease mortality and drinking wine is commonly believed to be protective against ischemic heart disease. Recently, Mar and Zeisel found that many commercial wines contain betaine—an average glass of wine contains approximately 3 mg of betaine. This small amount is less than the dose used to lower the homocysteine level in patients with genetic forms of hyperhomocysteinemia. However, whether humans with modest elevations of homocysteine would be influenced by this dose is not known.

Conclusions

As reviewed in detail in this article, alcohol may directly increase the hepatic production and secretion of apolipoproteins and lipoprotein particles, increase triglyceride lipase concentrations, and decrease the removal of circulating HDL-c. Lipolysis of triglyceride-rich particles increases the flow of cholesterol to HDL particles from the circulating very low density lipoprotein remnants and raises the overall HDL concentration. Although speculative, alcohol may also interfere with the activity of cholesteryl ester transfer protein and reduce the transfer of cholesteryl esters in HDL particles to more atherogenic particles. The effect of alcohol on the thrombolytic and coagulation processes are not well understood. The mechanism by which alcohol decreases fibrinogen concentration is not known, although the effect has been documented in several large cross-sectional studies as well as the small experimental studies described. Alcohol inhibits induced platelet aggregation in several in vitro systems.

Taken together, results from many observational studies provide strong evidence that moderate alcohol intake lowers the risk of CHD. This has given rise to what is now popularly termed the “French paradox”. This relationship has been observed in both men and women and in different age, ethnic and geographic groups. It is independent of dietary and other known risk factors for heart disease, such as smoking and obesity. Moreover, short-term trials of alcohol intake show significant changes in concentrations of lipids and clotting factors. The evidence that moderate alcohol consumption is healthful is ample and consistent. Should physicians, therefore, recommend such consumption to their patients? Looking at the benefits of moderate consumption of alcohol to the cardiovascular system, especially atherosclerosis, it may be worthwhile to accept moderate drinking. While there is no consensus among physicians on whether to inform their patients of the beneficial effects of moderate alcohol consumption, most concur with the notion “A little is good, but a lot is not better”.

Acknowledgments

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Polygraph, introduced towards the end of the last century, was probably the first cardiac investigation to become popular. This instrument recorded heart rate, rhythm, arterial pulse, venous pulse and respiration. Later, other investigations like chest X-rays, electrocardiogram, vectorcardiogram, ballistocardiogram, etc. were introduced. During the early part of the latter half of this century, cardiac catheterization and angiography became the last word in cardiac investigations and cine film was the standard format in which angiograms were recorded and stored. With the introduction of echo and Doppler techniques, video recording became popular and high-quality Super VHS was the best format available. Nuclear cardiology was probably the first discipline to introduce total digital technology for imaging, image processing and archiving. As coronary angiography and angioplasty became popular, cardiologists wanted cine pictures to be re-run immediately after the procedure. Cine fluoroscopy pictures were recorded and replayed from videotapes. However, permanent video archiving with adequate image quality in a cost-effective manner posed a problem! Hence, cine film continued to be used as the only medium of storage for angiograms.

During the 1980s, equipment vendors developed digital imaging techniques for the cath lab which provided superior image quality over standard video fluoroscopy. Even though video fluoroscopy became popular, image acquisition and archiving was on videotapes and cine films, the analog format dominating the field. Analog imaging is a method of representing data using continuously varying information. Video/analog images displayed on a television monitor consist of 625 lines where every line of video is a continuous wave form representing the brightness of the image. Digital imaging is a method of representing information or data using discrete or sample (noncontinuous) information. Images are represented by discrete picture elements called pixels. Each pixel represents the brightness of the image sample in quantum steps. For example, the brightness of a pixel can range from 0 to 255 levels of intensity. A value of 0 corresponds to black and 255 represents white.

Limitations of Analog Imaging

Analog imaging systems are expensive to maintain and often require custom adjustment and calibration. Quantitative analysis or postprocessing of recorded images is not possible and exact duplication of these images is virtually impossible. Recorded images lose their quality significantly. Image quality is extremely difficult to control and maintain over a period of time.

Advantages of Digital Imaging

Digital imaging enables image quality to be measured and quantified using software tools. These systems are less expensive to maintain. Recorded images could be used for off-line measurement and quantification using software tools. Digital X-ray angiographic images enable the user to measure the diameter of the coronary artery or the cardiac chambers in actual millimeters/centimeters. This format facilitates exact image reproduction without losing any information or clarity. Image quality can be altered by postprocessing and, as the quality is quantifiable, data management is software dependent and precise.

Digital Angiography

Normally, an angiographic image is created by a complex process involving at least 5 phases. The X-ray tube emits the incident beam which after passing through the patient falls on the the image intensifier, which then converts it into a visible light signal. An optical system consisting of two very fast, highly corrected lenses projects this image onto the pick-up tube of a television camera and, finally, the television signal is displayed on a television monitor. Video fluoroscopic images are also connected to the digital image processor for digitalization and necessary image manipulation. Computer techniques offer superior image quality over standard video fluoroscopy. Optimal image quality depends on the proper integration of the X-ray generator, the image intensifier system, optical coupling, video image detectors, monitors and the configuration of the whole system. In the new totally digital imaging system, the entire analog image intensifier-based imaging chain is replaced by a flat panel, amorphous silicon detector.
In most digital systems, image processing is done in a sequential manner. Images are acquired and then processed by an image processor commonly called the “digital pipeline”. Multiple simultaneous operations can be applied to the image. For medical imaging, the most commonly used digital processing elements in the digital pipeline are as follows.

(i) **Anti-blooming** (Extended Dynamic Range) enhancement is a technique for equalizing the brightness of an image.

(ii) **Subtraction** processing removes unwanted data and increases the contrast of anatomical objects of interest. The difference between two images is calculated pixel by pixel for removing extraneous structures such as bones and soft tissues.

(iii) **Edge enhancement/filtering** improves the sharpness and contrast on any structure containing distinct edges, like coronary arteries.

(iv) **Zoom and pan** technique is used to expand areas of interest and to bring such images to the center of the monitor.

(v) **Upscan interpolation** improves the perceived resolution of an image. It is another form of the zoom filter.

(vi) **Brightness and contrast enhancement** modifies the brightness and/or contrast of images.

### Image Archiving

Cardiac cine-angiographic study generates a large volume of digital data so that special care is required to select only the desired data for archiving. Angiograms use a matrix of at least $512 \times 512$ pixels with 8 bits/pixel providing 256 grey levels. One frame of $512 \times 512 \times 8$ bits consists of 256 000 bytes (0.25 MB). One second of digital angiogram consists of 7.5 MB of digital data and each angiogram lasts for 6 to 8 seconds. A patient study consisting of 9 to 10 injections requires 450 to 500 MB of storage space. At the conventional angiogram speed of 30 frames/s for coronary angiography, transfer rates of at least 7.5 MB/s will be required. We should remember that if we decide to buy an equipment with a 1024×1024 matrix, the transfer rate of data has to be 4 times faster. Archiving of such a large volume of data can be done cost effectively on a compact disk (CD). However, we will need standard formats for data compression and storage which are acceptable to all equipment vendors and users.

### Digital Echocardiography

Echo Doppler study enables one to view dynamic pictures of cardiac anatomy, physiology and hemodynamic parameters. Some rudimentary digital image storage and retrieval systems were in place in some echo labs as early as 1970. These systems allowed a “snapshot” of a video field from a videotape and the resultant storage on a floppy disk. With the advent of stress echocardiography, the ability to digitize loops of videotapes was achieved. Now, with the new generation echo Doppler equipment, digital acquisition, storage, retrieval and transmission are a reality.

Echocardiography is in transition today; changing from a modality in which most images are stored in analog fashion on videotape into one where most data are stored digitally. This transformation was helped by three factors.

1. Widespread recognition of the value of digital storage of echocardiograms, allowing random review of current and prior studies on split screen on the same monitor, easier quantification and remote transmission without image degradation.

2. Ongoing revolution in the computer industry, doubling the price–performance ratio of computers every 18 months, makes all-digital storage of echocardiograms both feasible and affordable.


### Digital file format

The echocardiographic image has to be broken down into discrete bits of information that can be recorded in a binary code on floppy disk, optical disk, CD or computer tape. A single full-screen of the video image in color may take close to 1 MB of storage space. Concurrent storage of calibration data will allow linear and area measurements as well as direct quantification from spectral and color Doppler studies. Video recordings allow 5 to 10 cardiac cycles for each imaging plane to be recorded and stored. However, this is not possible with the digital format. One beat loop for each imaging plane has to be stored and grabbing these “best cardiac cycles” needs some practice. During the learning curve, this may increase the scanning time by 50%. But this will be more than compensated by saving time for queuing up tapes, searching for old studies, filing tapes, etc.

### Digital Storage of Medical Images

From 1983, the American College of Radiology and the National Electrical Manufacturers Association (ACR/NEMA) were trying to develop common standards for exchange of digital medical images. DICOM was originally developed for black and white still images in radiology. The current version DICOM 3.0 permits color and moving images with encoding specified for cardiac cine-
angiography, diagnostic ultrasonography, nuclear medicine and numerous other investigations. For the first time, DICOM 3.0 specifies a file format for actual storage of images rather than simply exchange protocols for data over a network, and part of this specifically sanctions the use of a data compression scheme in disk storage. In 1996, Thomas and Nissen from Cleveland Clinic reported that approximately one quadrillion bytes (or one million gigabytes, also called "one pedabyte") had to be stored in one year from the echo Doppler and angiographic laboratories of that center.

The resolution of a digital image is determined by the number of pixels, typically ranging from 256×256 (64,000 pixels) to 1024×1024 (1 million pixels). For grey scale images (angiography), 8 bits per pixel (256 levels) whereas for color imaging up to 24-bits per pixel (16.7 million hues) are required. For moving images, the storage requirement, naturally, is enormous. Echocardiography typically requires a 512×512 pixel matrix with 24-bit color at 30 frames/s, i.e. 24 MB/s, while angiography requires only 7.5 MB/s. A recordable 5.25 inch CD was found to be the ideal device for storing angiographic images. This CD, commonly used for multimedia applications, has a capacity of 680 MB. This format for recording angiograms was accepted at the annual session of the 1995 American College of Cardiology and the European Society of Cardiology, and adopted by all leading equipment vendors. The CD-R storage capacity of 680 MB permits a recording of nearly 2400 frames per disk. This will be insufficient to archive all cardiovascular examinations on a single disk. An average echocardiographic study, lasting 10 minutes, would exceed 14 GB of storage, which is completely impractical in clinical practice at present. Most hospital networks use the ethernet standard, allowing data transmission at about 10 megabits/s, which is too slow to allow real-time transmission and viewing of echocardiographic images over the network. Data transmission at a speed of 189 megabits/s is required for transmission of moving color echo Doppler pictures.

Digital data compression will allow us to store a large amount of digital information in less space. The techniques available are either lossless or lossy compression algorithms. Lossless compression is fully reversible or bit preserving and allows 3:1 data compression by techniques like run-length encoding. Large areas of homogeneous pixel intensity like the black screen surrounding the echocardiographic sector are compressed to two bytes, one giving the number of encoded pixels and the other giving the grey value for those pixels. The images are identical, pixel for pixel when reconstructed, to the original. Lossy compression enables significant space saving without much degradation of image quality. This technique, as recommended by the Joint Photographic Expert Group (JPEG), is being accepted internationally. It is simple to implement for coding (compressing) and decompression. With a compression ratio of up to 20:1 there is no image degradation. Image degradation becomes significant with compression ratios higher than 25:1. Increase of compression ratio results in an increase in the scatter in pixel intensity and a decrease in the signal to noise ratio. The image quality of Super VHS video replay produces an image degradation equivalent to 26:1 digital compression.

We should remember that degradation of endocardial borders and myocardial texture is far worse in videocassette replay images. When a digitally compressed image is decoded for display and then manipulated—cropped, edge enhanced, etc.—and then re-encoded through JPEG compression, progressive degradation of the image may occur. Hence, digital compression must be used only once and all image processing should be done before archiving.

The clinician can conserve archiving space by: always using single loops and four images in quad screens; reducing playback speed from 30 to 15 frames/s; storing in 256×256 matrix rather than 512×512 and recording with fewer grey levels, from the current 256 to 64. An 8 cell loop may be used instead of a 32 cell loop. By these measures, an original 1 second loop requiring 7.86 MB could be stored in 0.18 MB. Such a compromised archival technique may not be the ideal solution but it facilitates storage of studies on floppy disks (1.44 MB) and ordinary PC stations may be used for storage and viewing. While recording stress echo pictures, one should store the data as a pair of quad screen loops with 256×256 rasterization and save only the systolic frames. This will allow storage of each patient's data without compression in a single floppy disk, as the space required will be only 1 MB.

The Ad Hoc Standards committee suggested digital data compression to increase the storage capacity of the CD-R so that complete patient files could be stored in a single disk. Archiving and storage in a CD jukebox will facilitate random access to data as well as access from any workstation in a hospital network. However, one should ensure a data transmission speed of at least 189 megabits/s through fiberoptic cabling within the hospital building. It is also advisable that workstation monitors should have a very high image resolution. Once proper archiving and hospital networks are established, it is easy to expand the utility of this facility by establishing hospital to hospital data transmission as well as tele-medicine consultations with remote centers.
DICOM Standard for Nuclear Cardiology

Nuclear cardiology evolved with a totally digital imaging format. However, it is often difficult or impossible to transfer nuclear cardiology images from one computer system to that with a different configuration. All companies write data using proprietary software and media. Most of the equipment vendors have now accepted that their system will provide the capability to format and exchange data according to the DICOM 3.0 standard. Necessary software will be provided to record nuclear cardiology studies (images, regions of interest, time activity curves, etc.) on a CD-R. The same CD could have echo or angio images on it and could be replayed on stand-alone stations or even on home PCs.

Strategy for the Next Millennium

The percentage of medical specialists using electronic patient records is still low but many general practitioners and pharmacists have moved over to the electronic era in the last few years. Many hospitals have automated patients registration and appointments, pharmacies, laboratories as well as hospital finances and administration. Laboratory results are also processed, reported and stored using computer systems. Institutions are developing internet sites with public information on local health services and there are attempts to develop building blocks for a virtually distributed electronic patient record. This will facilitate data storage in a central location although it has been collected from different places such as doctors’ offices, hospitals, laboratories and pharmacies. Delivery of integrated data will be the facilitator of improved health care delivery. Patient histories, clinical reports, medical records, physiological waveforms and various imaging data are now available in digital format. All this information could be integrated, displayed, shared, archived and transmitted to any part of the world. In the future, a patient’s records could be stored in a card that may be kept in a pocket, information could be accessible through a secure internet connection at the doctor’s home, office or even by a portable computer. However, to achieve this goal, we have to overcome many obstacles. Once these problems are solved, paperless offices, laboratories and hospitals will be the order of the day.

References

4. Thomas JD, Nissen SE. Digital storage and transmission of cardiovascular images: what are the costs, benefits and timetable for conversion? Heart 1996; 76: 13–17
A 36-year-old male presented with dyspnoea which had progressively increased in the last six months. He had one episode of significant hemoptysis (200 ml of fresh blood) just prior to admission. His general physical examination was unremarkable. Chest X-ray revealed an oval-shaped 2×3 cm retrocardiac shadow in the right lower zone. Echocardiography revealed no gross intracardiac abnormality. However, the pulmonary venous drainage was...
not clearly visualized because of the suboptimal parasternal window. Computerized tomography (CT) of the chest revealed a dilated tortuous vascular structure in the posterior segment of the right lower lobe abutting on the inferior vena cava but draining into the left atrium (Fig. 1). It had smooth, well-defined margins with no evidence of extravasation of blood. There was soft tissue thickening in the perivascular space in the left hilar region (Fig. 2) with a suggestion of narrowing of the left pulmonary vein at its opening into the left atrium, probably of inflammatory etiology. Cardiac catheterization revealed severe pulmonary arterial hypertension (65/30 mmHg). An unexpected finding was the high pulmonary artery wedge pressure—36 mmHg on the left side and 22 mmHg on the right. Since the mitral valve and left atrium were normal on echocardiography and the left ventricular end-diastolic pressure was 6 mmHg, the pulmonary vascular resistance was located between the pulmonary capillary bed and the left atrium. Selective right pulmonary artery angiography in the venous phase showed a large globular tortuous opacity in the right lower zone (Fig. 3), sluggishly emptying into the left atrium (Fig. 4). Selective left pulmonary artery angiogram showed markedly delayed filling of the pulmonary veins on the left side. A diagnosis of right lower zone pulmonary varix with bilateral pulmonary venous obstruction was made.

The hemoptysis could have been due to rupture of bronchopulmonary collaterals secondary to pulmonary venous hypertension, as seen in patients with mitral stenosis. As the patient’s problem seemed to be due to an obstruction of the pulmonary veins, for which surgical correction would be difficult, it was decided to keep him on close medical follow-up. The patient remained stable during hospitalization with no recurrence of hemoptysis. At follow-up after six months, he is doing well with no recurrence of hemoptysis.

A pulmonary vein varix is an innocuous lesion, usually picked up on routine chest X-ray as a coin lesion or a mediastinal mass. It may be congenital or acquired. The former is usually asymptomatic while the latter presents with symptoms of the associated disease. Acquired pulmonary vein varix is the result of sustained pulmonary venous hypertension and is usually reported with mitral valve disease. These varices sometimes regress after mitral valve replacement or balloon valvuloplasty. Its association with pulmonary venous stenosis, which itself is a rare disorder, has not been reported. Pulmonary venous stenosis may be congenital or secondary to pulmonary veno-occlusive disease, thrombosis, constrictive pericarditis, mediastinal fibrosis and mediastinal tumour. We speculate that the slow progression of stenosis by a chronic inflammatory disorder (mediastinal fibrosis) led to the development of the varix. Usually, patients of pulmonary varix are managed conservatively. Surgical resection is advised if the size of the lesion increases significantly or if there is recurrent hemoptysis.

References
**Effects of Atorvastatin on Early Recurrent Ischemic Events in Acute Coronary Syndromes. The MIRACL Study**

**Summary**

Myocardial Ischemia Reduction with Aggressive-Cholesterol Lowering (MIRACL) was a multicentric, randomized, double-blind trial that compared the effect of atorvastatin 80 mg/day, initiated 24 to 96 hours after acute coronary syndrome (ACS), with a placebo and followed up these patients for 16 weeks. A total of 3086 adults aged 18 years or older with unstable angina or non-Q wave acute myocardial infarction (AMI) were enrolled in the study. The primary end-point events were death, nonfatal myocardial infarction (MI), cardiac arrest with resuscitation, or recurrent symptomatic myocardial ischemia with objective evidence and requiring emergency rehospitalization. The primary end-point event occurred in 228 patients (14.8%) in the atorvastatin group and 269 patients (17.4%) in the placebo group (relative risk [RR], 0.84; 95% confidence interval [CI]: 0.70–1.00; p=0.048). However, despite significantly lower rates of readmission (6.2% v. 8.4%; RR 0.74; 95% CI: 0.57–0.95; p=0.02), reduction in mortality (4.0% v. 4.4%) and nonfatal MI (6.6% v. 7.3%) was not significant. Reduction of primary ischemic events by atorvastatin did not appear to depend on the baseline level of LDL cholesterol. There was no significant difference in the incidence of secondary outcomes of coronary revascularization procedures, worsening heart failure or worsening angina, although there were fewer strokes in the atorvastatin group (12 v. 24 events; p=0.045). Elevation of liver transaminases (>3 times the upper limit of normal) were more common in the atorvastatin group (2.5% v. 0.66%; p<0.001).

**Comments**

Numerous trials have demonstrated the efficacy of lipid lowering in both primary prevention (Helsinki Heart Study and WOSCOPS Study) and secondary prevention (Post CABG, 4S, LIPID and CARE) of coronary artery disease (CAD). Lowering of lipids leads to reduction of nonfatal MI and reduces cardiovascular and overall mortality. Statins are the most effective lipid-lowering agents. Conventionally, they have been used for secondary prevention only in patients with stable CAD. The studies excluded patients who had an ACS within 3–6 months of enrollment. These patients were excluded because it was believed that determination of total cholesterol levels during the acute phase may be fallacious and factors which are important during the acute phase like left ventricular dysfunction, ventricular arrhythmias, and mechanical complications were unlikely to be affected by lowering the lipid levels. Furthermore, as per lipid-lowering studies in stable CAD, it took at least 1–2 years before a significant reduction in cardiovascular events occurred and therefore lipid lowering was not considered to be of immediate importance. As the highest risk of death and recurrent ischemic events is within the first few weeks of ACS, any therapeutic strategy during this period is likely to provide more benefit. The nonlipid-lowering effects of statins like plaque stabilization, improvement in endothelial function, antithrombotic and anti-inflammatory activities are well known. However, whether these effects are operative in an acute coronary syndrome setting and lead to an additional reduction in cardiovascular events have not been addressed by a large prospective randomized study. In an observational study by the Swedish Registry of Cardiac Intensive Care, the use of statins at or before discharge after AMI was associated with 25% reduction in relative risk for mortality at 1 year. The MIRACL study is the first prospective randomized study which shows that potent lipid-lowering therapy (atorvastatin 80 mg) started within 96 hours of ACS could reduce event rate as early as 16 weeks after initiation of therapy even in patients with nearly normal baseline cholesterol levels (mean LDL cholesterol 124 mg/dl). However, the MIRACL study was not empowered to detect small differences in mortality. The reduction in stroke rate in the MIRACL study appears to be an additional benefit of statin therapy. However, data from the MIRACL study requires careful interpretation. The positive findings in this trial are not very definitive. The p value of 0.048 is marginally significant. The MIRACL study lost 11 patients to follow-up, 8 of them from the atorvastatin group. If these patients were lost to follow-up because of death or severe stroke, the result would no longer be statistically significant. Thus, the possibility of a type I statistical error cannot be ruled out. Secondly, a fixed dose of atorvastatin 80 mg/day was used. This high dose may not be necessary because the beneficial effects may be due to effects other than lipid lowering. However, limitations notwithstanding, the results of the MIRACL study are optimistic and, given the potential for short-term benefit, the definite longer-term benefit and absence of harm, it may be prudent as of now to include statins as an integral part of therapy in ACS. Several other trials including A to Z, PRINCESS and PACT are also evaluating the role of statins in acute coronary syndromes.
Unprotected Left Main Coronary Artery Stenting: Immediate and Medium-Term Outcomes of 140 Elective Procedures


Summary
This study evaluated immediate and medium-term outcomes after stenting in 140 consecutive unsel ected patients with unprotected left main coronary artery (LMCA) disease. Patients were divided into two groups. Group I included 47 patients categorized as poor surgical candidates because of a contraindication to cardiopulmonary bypass by one or more surgeons or the presence of any of the following factors: age more than 75 years, history of heart surgery, left ventricular ejection fraction lower than 35%, renal failure, inadequate coronary distal run-off or severe respiratory failure. Group II included 93 patients with no such contraindication (low-CABG-risk patients). Nearly half the cases (49%) presented with unstable angina whereas 11% patients had silent ischemia. Besides the LMCA, the right coronary artery was occluded in 14% of patients and another 33% showed significant stenosis. Overall, 47% of patients had triple-vessel disease. The site of the LMCA lesion was the ostium in 10%, midportion of the artery in 38% and the distal portion in 52%. The mean number of lesions treated per patient was 1.8 and complete revascularization was achieved in 70% of cases. Procedural success was obtained in 100% of cases with a very low local complication rate (0.7%). One-month mortality was 9% in Group I and 0% in Group II. Among the 4 deaths that occurred in Group I patients, 2 were due to subacute thrombosis, 1 due to terminal left ventricular failure and 1 due to aortic prosthetic thrombosis. No stent thrombosis was observed in Group II. A follow-up angiography was obtained in 82% of cases, and target lesion revascularization (TLR) was required in 17.4% (10.5% in Group I and 21% in Group II). Medium-term results showed a restenosis rate of 23%. One-year actuarial survival was 89% in Group I patients and 97.5% in Group II patients. The authors attribute the excellent immediate results to the absence of acute thrombosis, probably because of the large size of the LMCA, optimal deployment of stents (with kissing balloon inflation for bifurcation) and perfect compliance with ticlopidine therapy. The problem of distal LMCA dilatation could be overcome to a great extent after the introduction of a simultaneous double balloon dilation of the LAD and circumflex arteries at the end of the procedure. This probably brought down the overall restenosis rate (similar to that seen after stenting at other coronary sites). The low rate of complications could be ascribed to the use of ticlopidine and 6 F or 7 F guiding catheters. Stenting reduces the need for hemodynamic assistance (IABP, circulatory support), which is a well known source of local morbidity.

Comments
Conventionally, CABG has been considered to be the treatment of choice in patients with LMCA disease. Results of medical stabilization have been disappointing. Plain balloon angioplasty was associated with several problems. There was a substantial perioperative mortality, restenosis rates were high, and long-term survival rates were unsatisfactory. In patients in whom the LMCA was “unprotected”—that is, lacking a patent graft to either the left anterior descending or circumflex artery—the one-year mortality after left main angioplasty was 30%, and hence not much better than that for medical therapy. However, the explosive growth of coronary stenting and the availability of potent antithrombotic agents like ticlopidine have prompted new attempts at LMCA dilatation. Karnowski et al. have shown that stenting is superior to balloon angioplasty in the LMCA. There was higher procedural success (98% v. 92%), lower procedural complications (0% v. 5.4%), lower TLR (15% v. 18%) and a higher 1-year event-free survival (78% v. 76%). More recently, several workers (Kosuga et al., O’Keefe et al., Eldar et al., Park et al., Wong et al., Tamura et al.) have published their own series. The angiographic success rate is generally high (>95%) but in-hospital mortality has been variable (0%–40%) depending on the type of patients enrolled. The incidence of TLR varied from 20% to 40%. In a study by Park et al. who reported results in 42 patients with normal left ventricular function, the angiographic success rate was 100%, there were no in-hospital complications, the TLR was 17% and 1-year mortality was 2.5%. A recent study by Fajadet and his group has also confirmed the same findings in 92 consecutive patients of unprotected LMCA disease. The procedural success rate was 100%. The in-hospital mortality was 4%, overall mortality was 3.8% in the low surgical-risk group and 20.5% in the high-risk group. Although all these studies suggest that LMCA stenting is a safe and efficacious alternative to CABG, the data should be interpreted with caution as there might have been a publication bias in favor of positive studies. Unprotected LMCA stenting should be used only in selected patients and that too by an experienced operator in high-volume centers.
Arterial Revascularization Therapies Study (ARTS)

Summary

The Arterial Revascularization Therapies Study (ARTS) was a prospective randomized trial conducted to compare the clinical outcome and cost-effectiveness of multivessel stenting and bypass surgery in 1205 patients with multivessel disease, in whom an equivalent degree of revascularization was achievable with both techniques (patients with left main coronary artery disease, recent transmural myocardial infarction (MI) and left ventricular ejection fraction (LVEF) <30% were excluded). The primary end-point of freedom from death, major cardiac or cerebrovascular event or repeat revascularization at 12 months was significantly better in the surgery group compared to the stent group (87.8% v. 73.8%, p<0.001), primarily due to a lesser need for repeat revascularization (3.5% v. 16.8%), while there was no difference in the rate of death, stroke or MI. Thrombosis occurred in 1.1% of stents (2.8% patients). Throughout the 12-month period of observation, more patients were free from angina after surgery than after stenting (90% v. 79%). Multivariate Cox regression analysis revealed that the only predictor of outcome was an elevation in postoperative creatine kinase (CK-MB) in the surgery group and diabetes mellitus in the stent group. Eight major adverse cardiac events occurred during the waiting period in the surgery group while only 1 event occurred in the stent group as the waiting period was nearly 2.5 times longer in the surgery group (27±39 days v. 11±16 days). At 1 year, there was still a substantial cost–benefit (2973 dollars per patient) in the stent group despite the higher re-intervention rate with a calculated additional cost of approximately 21000 dollars for every patient-year free of events with surgery. This led the investigators to conclude in favour of percutaneous coronary intervention (PCI) in such patients, with the caveat that the patient and the physician should weigh the possible need for further procedures prior to taking the final decision.

Comments

The results of this trial are consistent with the available data on the role of these strategies in patients with multivessel disease, wherein PCI is found to be cheaper (in western countries) and less invasive with earlier recovery, but with a much higher need for repeat revascularization. Most of the previous studies, including the BARI, GABI, EAST, CABRI, ERACI-1 and RITA-1, however, compared surgery with PCI without the use of stents or glycoprotein (Gp) IIb/IIIa inhibitors. ARTS is different in that each patient received at least 2 stents, though coated stents and Gp IIb/IIIa inhibitors were not used, which might have significantly reduced the stent thrombosis rates and thus the adverse events. The only other study with contrasting results is the ERACI-II, where PCI compared to surgery in a population of patients with predominantly unstable angina (92%) with multivessel disease was associated with a significantly better survival (96.9% v. 92.5%) and freedom from MI (97.7% v. 93.4%) at a mean follow-up of 18.5±6.4 months. However, ERACI-II has been said to be biased against surgery, with the mortality being nearly twice as high as expected in a group with equivalent risk factors. The perioperative mortality was 3.3% in the New York Cardiac Surgery and Angioplasty Case Registry. The adverse implications of diabetes mellitus in patients undergoing multivessel angioplasty bears out the results in the BARI subgroup, in which treated diabetics undergoing multivessel balloon angioplasty had a higher mortality (5-year survival of 65.5% v. 80.6% in the surgery group, p=0.003). Even though Gp IIb/IIIa inhibitors, which have been shown to improve the outcome of stenting in diabetics to levels comparable to nondiabetics, were not used in both studies, this highlights the prognostic significance of diabetes and thus the need for serious thought prior to attempting PCI in these patients. As the waiting period is much longer for surgery, it can be associated with an increased risk of major adverse cardiac events while awaiting surgery. Both strategies are thus acceptable in an individual patient provided they are feasible, the decision being based on patient preference. Of note, however, is the fact that only ≤10% of multivessel disease patients were finally randomized in these trials, emphasizing the fact that surgery remains the preferred modality in most of them.

The situation is somewhat different in our country, where the initial cost of multivessel stenting is usually higher than surgery, and the need for Gp IIb/IIIa inhibitors and repeated revascularization procedures make it costlier still. Such an approach becomes extremely expensive in our setting, where only a patient with no financial constraints and wishing to avoid the more invasive surgical option is a suitable candidate for multivessel stenting.
One-year Survival Following Early Revascularization for Cardiogenic Shock (SHOCK trial)

JS Hochman et al.  JAMA 2001; 285: 190–192

Summary

Should We Emergently Revascularize Occluded Coronaries for Cardiogenic Shock (SHOCK) trial was an unblinded, randomized, controlled trial involving 302 patients with acute myocardial infarction (AMI) and cardiogenic shock (CS), mostly due to left ventricular failure. The trial was designed to compare the utility of early revascularization with aggressive medical management. The initial medical stabilization (IMS) group of 150 patients received thrombolysis (63%), intra-aortic balloon counterpulsation (IABP) (86%) and subsequently (after 54 hours or more) revascularization (25%). The early revascularization (ERV) group of 152 patients underwent angioplasty (PTCA) (55%) or coronary bypass surgery (CABG) (38%) within 6 hours of randomization. There was a non-significant improvement in survival in the ERV group at 1 month (56% v. 47%) but at 1 year (a prespecified secondary end-point) the survival was significantly better in the ERV group (46.7%) than in the IMS group (33.6%) (p=0.03, with a relative risk [RR] of death 0.72, 95% CI: 0.54–0.95). Age was the only factor out of 10 prespecified variables that interacted significantly with the treatment, the 1-year survival being better only in patients <75 years of age (51.6% in the ERV group v. 33.3% in the IMS group, p<0.03). The investigators thus recommend early transfer of AMI patients with CS to centers with facilities for early revascularization, especially in those <75 years of age.

Comments

Cardiogenic shock (CS) in the setting of AMI is associated with a high mortality regardless of the management strategy. Previous nonrandomized trials and retrospective studies have shown that thrombolysis, IABP use and early revascularization using either PTCA or CABG reduced mortality. Survival was distinctly better in patients undergoing coronary angiography (signifying a low-risk subgroup), as well as in those who underwent successful PTCA compared to those who had a failed PTCA in previous nonrandomized studies and the prospective SHOCK Registry. The only other randomized trial was SMASH, which was limited by the small number of patients enrolled (32 in the invasive and 23 in the medical strategy group) and did not show any difference in mortality (69% v. 78%, p=ns). Even the SHOCK trial failed to demonstrate the benefit of an early revascularization strategy over aggressive medical management in 30-day mortality (primary end-point of trial 56% v. 47%, p=0.11), though there was a significant benefit at 6 months (50.3% v. 63.1%, p=0.027), which persisted till 1 year. The late survival benefit achieved is expected, as the early hazard of surgery is more than offset only after long periods of follow-up in this high-risk cohort. Previous studies have shown that thrombolytic therapy (TT) and IABP are used less often than indicated in CS patients (German 60 minute MI Project and GUSTO-1), but when used, they improve survival significantly despite the efficacy of thrombolysis being lower in these patients (42%–48%). The SHOCK Registry also reveals a lower mortality in thrombolysed patients versus those not thrombolysed (54% v. 64%, p=0.005) and in those in whom IABP was used versus those in whom it was not used (50% v. 72%, p<0.0001). There was a graded rise in mortality in subjects in whom these measures were not used, from 47% in both the TT and IABP groups, to 52% in IABP alone, 63% in TT alone and 77% in those in whom neither was used (p<0.0001). However, survival correlated best with early revascularization, where the mortality was 39% compared to 78% in those not revascularized (p<0.0001). Thus, a combination of these aggressive measures helps to stabilize patients till they are taken up for intervention (25% in the IMS group of SHOCK), leading to a similar 30-day survival as in the ERV group. However, the improved 6- and 12-month outcome of the ERV group forces one to think that the intermediate-term outcome is better in patients offered ERV, possibly due to more myocardial salvage and thus lesser events over follow-up. The net 39% reduction in 1-year mortality translated into an absolute benefit of 132 lives saved per 1000 treated, which is a major gain. Hence, it would be prudent to offer these patients aggressive therapy right from the onset, and all patients with CS (especially those <75 years of age) should be referred to centers with facilities for urgent revascularization.
Can We Eradicate Rheumatic Fever in the 21st Century?

The review article on rheumatic fever (RF) was interesting. However, the guidelines for secondary prevention need reconsideration. This is now relevant as excellent echocardiographic techniques for visualization of the valves are available.

The blanket long-term prophylaxis recommended for all cases of RF is unjustifiable. It causes much physical and psychological pain to the patient and his/her family. The main aim of secondary prophylaxis for RF is to prevent valve disease. In the case of RF, the mitral valve is the most commonly affected. The moot point is whether a recurrence of RF will have any effect on a badly damaged valve, and if so, what greater damage would it cause? In such cases, should the cumbersome prophylaxis be continued if the valve is already badly damaged?

Echocardiography can provide the answer. In a patient with a history of RF the mitral valve should be checked for fibrosis or calcification. If these are absent or minimally present, then aggressive RF prophylaxis needs to be instituted, which can even be lifelong. Such a strategy is worth the effort because it will, hopefully, prevent valve damage. However, the lenient strategy adopted in the USA for patients without rheumatic heart disease (RHD), as mentioned in the article, would sometimes be enough for such patients. As a corollary, effective prophylaxis should also be adopted for patients who have undergone balloon valvotomy.

In patients with a badly damaged fibrotic or calcified valve, continuation of the prophylaxis would not be worth the effort. Similarly, some authorities have recommended prophylaxis for patients with a prosthetic valve. Here again, I see no reason why RF would affect a biologically inert structure. In all these cases, the probable theoretical benefits would be protection of the other valves, especially the aortic valve, and prevention of fulminant forms of carditis. Fortunately, these are rare in the age of widespread use of antibiotics. The basis of any treatment is to weigh the benefits against the harm that could be done. Each patient should be optimally treated according to individual circumstances. It is time we had a thorough re-look at secondary prevention of RF.

References

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Reply

Certainly “blanket” recommendations for secondary prophylaxis of RF are made with reservations that consider the judgment of clinicians concerning individual patients in various geographical and socioeconomic settings. As Dr George Thomas suggests, “The main aim of secondary prophylaxis for RF is to prevent valve disease” and therefore, where the greatest damage to the heart has already occurred, e.g. advanced mitral stenosis, prevention of further damage is unlikely. Were every RHD patient to have the benefit of expert echocardiography to diagnose irreversible mitral valve damage (not likely to be available in all settings in which RF is rampant), and to have the further benefit of expert valve replacement in such cases (also unlikely to be available or affordable in all settings), they might indeed be able to survive repeated attacks of acute RF, even when such recurrences may be accompanied by pancarditis with pericardial effusion and myocarditis, and possible further damage to the aortic valve. Should one gamble on that assumption?

I would welcome reference to some reliable data, however, on just how well patients with advanced mitral valvular disease, with and without valve replacements, fare from recurrent acute rheumatic attacks. I recall that even in the days before echocardiography, some patients with advanced rheumatic valvular disease (well diagnosed by competent clinicians), were lost due to recurrent rheumatic attacks—valvular surgery notwithstanding. If secondary prophylaxis recommendations are to be further modified, so that patients with advanced RHD no longer require prophylaxis because of the benefits of expert modern cardiology and cardiovascular surgery, we need to see the data on which such modifications should be based. Does the alleged “suffering” from continued use of antibiotic prophylaxis by patients with advanced RHD exceed their potential suffering from repeated attacks of RF? Perhaps, if the risk of rheumatic recurrences no longer exists.

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July 6–11, 2001, XVII World Congress of the International Society for Heart Research, Winnipeg, Manitoba, Canada
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November 11–14, 2001, 74th Scientific Session, American Heart Association, Anaheim, California, USA
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February 8–10, 2002, VIth World Congress of Echocardiography and Vascular Ultrasound, New Delhi, India
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March 17–20, 2002, 51st Annual Scientific Sessions, American College of Cardiology, Atlanta, Georgia, USA
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May 5–9, 2002, XIV World Congress of Cardiology, Sydney, Australia
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July 17–21, 2002, 14th Asian Congress of Cardiology, Kuala Lumpur, Malaysia
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