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Indian Heart Journal: Onward Expedition

Dear Colleagues,

It is with a deep sense of gratitude and a measure of satisfaction that I complete my tenure as the Editor of the Indian Heart Journal. Times of transition provide good opportunity for reflection and self introspection. During my tenure, I strived to maintain high academic standards set by my predecessors, and attempted to impart more 'Indian' flavor to the Journal. The readership has increased. The Indian Heart Journal is available free on the net, and its articles can be downloaded from the Pubmed link as well. The website receives a high number of hits indicative of the wide interest generated in the readers.

We could publish only a part of what we received. At times even good articles cannot be accommodated due to space constraints. Selection of articles is always a difficult decision for any editor, but to ensure the quality and keeping in mind the interest of readers, 'Rejection Letters' have to be sent. In this task, I was assisted by a number of learned reviewers who selflessly devoted their time. Since we did not publish the list of reviewers, it may not be out of place to specially acknowledge the timely, critical and enthusiastic reviewership of many members for critically evaluating the contents and the data of the articles. The colleagues who reviewed maximum number of articles included Anil Bharani, D Prabhakaran, George Joseph, JC Mohan, Jacob Jose, Nakul Sinha, OP Yadav, Prem Pais, PK Goel, R Bajaj, Rajeev Gupta, R Krishna Kumar, SR Mittal, S Shrivastava, Yash Lokhandwala.

I would like to take this opportunity to thank my colleagues in the department for not only helping me with the journal work but also taking some of my departmental responsibilities so that I could devote more time to the journal. I specially thank SS Kothari who worked very closely with me in running the journal for last five years. I am also grateful to the advertisers and sponsors for providing unstinted financial support. I would also like to thank the printers - Thomson Press and its staff specially Rajan Khurana, and my editorial Staff - H Barthwal and ML Pahuja for their excellent support.

As the Editor of Indian Heart Journal, I was fortunate to have an overall view of the ongoing research in the country. While the number of heart hospitals in India has increased remarkably, the same is not true of the research papers being submitted

for publication. Case reports and clinical images were available in plenty, but the quantum of original research work has not shown an upward trend. The increasing complexities of cardiac care throw new challenges and demand newer innovative answers. While India is quite fit to serve as a hub for medical tourism in curative cardiac care, the overall cardiac health of the country is not satisfactory. I do sincerely hope research into preventive, promotive and curative health would continue in a balanced way. The time is ripe for more research into medical audits, quality of care issues, cost-effective analysis of various treatments in Indian scenarios and multi-centre Indian trials amongst other ingenious approaches to cardiac care. Further, there seems an urgent need to streamline our health care delivery systems and accreditation procedures. The Government needs to develop guidelines for equitable allocation of health budget, so that the benefits of advances in cardiac care, which currently only the affluent can afford, can also accrue to all sections of the society.

Scientific journals survive only on trust. The editors and reviewers have no mechanisms, nor the inclination to police research. It is indeed unfortunate that the issue of fraudulent research should ever arise anywhere in the world. I wish that the editors of Indian Heart Journal would never have to deal with questions of fraudulent research, duplicate publications or plagiarism.

I am sure, under the new Editorial team, Indian Heart Journal would continue to stimulate and foster relevant research and provide a forum for information and ideas on nationally relevant themes, as well as have its share of global presence.

Together we would scale newer academic peaks.

With best wishes

(VK Bahl)

Indian Heart J 2005; 57: 617-631 **Review Article**

Coronary Artery Disease in South Asians: Evolving Strategies for Treatment and Prevention

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"In earlier times, starvation consigned languishing bodies to death; now, prosperity plunges them into the grave"

–Lucretius

Coronary artery disease (CAD) is the number one killer in developed nations. While death rates of CAD have been declining over past three decades for the population as a whole, a disturbing trend has been noted among the persons of south Asian origin. Multiple studies on its prevalence indicate that the immigrant South Asian Indians experience a disproportionately larger burden of CAD, and are at two- to three-fold higher risk of mortality compared with native population. For the approximately 16 million Asian Indians living outside India including 1.6 million in the US and 2 million in the UK, who constitute a "high risk" subpopulation, search for various pathogenic factors and plausible solutions have attracted great interest in this area as seen in recent literature. Prevalence of risk factors including hypertension, dyslipidemia, central obesity, and diabetes, is not only higher in this subpopulation, but is also rapidly rising. This predisposition to accelerated atherosclerosis seems to have genetic predisposition but is being enhanced by changing lifestyle, dietary and cultural preferences, and suboptimal application of healthcare. Further, a similar surge in prevalence of CAD has been reported among Asian Indians living in India, specially those in the urban areas. The propensity to develop CAD generally tends to manifest early, and follows a malignant course. It afflicts individuals during the most productive years of their lives and leads to a significant loss of disability-adjusted life-years (DALY). Since the Asian Indian minority population is not significantly represented in major clinical trials, evidence-based management strategies for treatment and prevention of CAD are seriously lacking. Fortunately, a number of randomized trials of dyslipidemia therapy and risk reduction have recently been launched. Preliminary data suggest a need for lower goals for lipid levels through institution of much more aggressive therapy than is currently recommended. The control and prevention of CAD through adequate lifestyle change, dietary modification, and early screening for CAD and risk factors form the 'centerpiece' of the suggested management strategies. The pharmacotherapeutic armamentarium includes not only statins, but also fibrates, angiotensin-converting enzyme (ACE) inhibitors, and insulin sensitizing agents like peroxisome-proliferator activator receptors (PPAR-gamma), such as glitazones. Rapid incorporation of these strategies is required. In addition to aggressive application of therapeutic regimen, a broader involvement through governmental, regulatory, educational, and population-based initiatives is now urgently needed to reverse the raging CAD epidemic in this clinically disadvantaged subpopulation.

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Prevalence of Coronary Artery Disease among South Asians

The term "South Asians" includes persons that originated from nations of the Indian subcontinent - India, Pakistan, Bangladesh, Nepal, Bhutan, and Sri Lanka. They constitute both large and small immigrant populations that reside in different parts of the world. These subpopulations have come into existence at separate time points because of different waves of emigration over the past 200 years, with varying ethnic and socioeconomic characteristics. Notwithstanding such baseline differences, persons of Asian Indian descent throughout the world - whether living in UK, USA, Singapore, South Africa or Trinidad - share a common characteristic - the highest predisposition to develop CAD. In the US, the South Asians, also known as Asian Indians, exhibit the highest prevalence of CAD and coronary risk factors as compared with Caucasians.[1] The high CAD prevalence is associated with similarly higher prevalence of risk factors among this ethnic group.[2] The prevalence of central obesity, glucose intolerance, hypertension, high triglyceride (TG) levels, and low levels of high-density lipoprotein cholesterol (HDL-c)—the five

'axes of evil' of metabolic syndrome—is highest among the Indians and continues to increase at a rapid pace.[3]

All Asians, however, are not similar. There are marked differences in CAD rates among them. For example, a review of hospitalization data in the US showed that the CAD prevalence rates for Japanese and Filipino Americans were similar to that of Whites; Chinese Americans exhibited lower rates, and the CAD rates were highest for the Asian Indians. In fact, the CAD rates among Indians were 6 times higher than Chinese and 4 times higher than other Asian Americans.[4] On an average, a three-fold higher prevalence of CAD has been noted among Indians when compared to the respective native inhabitants. More recently, the Study of Health Assessment and Risk in Ethnic groups (SHARE) from Canada showed that the overall prevalence of CAD was 10.7% among South Asian Indians *versus* 4.6% in Europeans and 1.7% in the Chinese population.[5]

Prevalence of CAD among Indians living in India has also been shown to be high in multiple cross-sectional studies. Beginning as early as the 1960s, researchers in India have variously studied and reported the prevalence of CAD in both urban and rural populations.[6-18] What is even more troubling is the fact that current epidemiologic transition of 'urbanization' in India is still ongoing, and it has not shown its final impact yet. Present health transition from predominance of infections to the preponderance of cardiovascular disorders, such as hypertension, diabetes, and CAD, is now responsible for 53% of all deaths, and 44% of DALYs lost due to majority of the deaths occurring in younger working class individuals.[19] Hypertension and hypercholesterolemia not only show rapid increase in prevalence, but are ineffectively diagnosed and treated. Screening and Health awareness programs are practically absent. Similar to the immigrant Indians living abroad, native Indians living in India now constitute the largest population with diabetes in the world. There were an estimated 19.3 million Indians diagnosed with diabetes in 1995 and that number is projected to surpass 57.2 million by 2025. Effective screening strategies, application of therapeutic interventions, educational programs and regulatory mechanisms are, therefore, urgently needed in order to avert the impending explosion in prevalence of coronary risk factors and CAD in the Asian Indians.

Several special considerations need to be entertained as the initial step toward formulating effective therapeutic and preventive strategies for management of CAD in the South Asian Indians. They not only have one of the highest rates of heart disease in the world - 3 times higher than that in the US,[20] but the CAD in them tends to be more aggressive and manifests at a younger age. Over half of myocardial infarctions (MI) occur in persons less than 55 years of age, and up to 25% of MIs occur in persons less than 40 years of age.[21] The increasing incidence of Type-2 diabetes within South Asians strongly correlates with increasing central obesity and high CAD prevalence.[22] Based on a study of South Asian immigrants in Britain and the native Europeans, it can be inferred that a pattern of insulin resistance and associated metabolic abnormalities underlie the high rates of CAD and adult onset diabetes among the Asian Indians.[2,23] Furthermore, high levels of lipoprotein(a) [Lp(a)] are also seen among the Indians – both living in India or abroad, and suggest a genetic predisposition. Based on the current information, adverse interaction between a genetic predisposition and lifestyle changes appears to explain the excess vulnerability of Indians to CAD,[24] and balance of the excess risk may be explained by genetic abnormalities in triglyceride and insulin regulation that are common among Asian Indians.[25-29] Several studies have shown that such high prevalence of small dense low-density lipoprotein (LDL), together with the increased triglyceride and decreased HDL levels, forms the "atherogenic lipoprotein phenotype", a potent risk factor for coronary heart dsease (CHD), which may partly explain the excess CAD risk of Indians.[30-35] The high Lp(a) is also potentially harmful.[36] Proposed mechanisms of atherogenesis by Lp(a) include preferential uptake of Lp(a) into macrophages in the atherosclerotic plaques via binding to fibrin and plasminogen receptors. Because of the structural similarity between Lp(a) and plasminogen, it has also been hypothesized that the former interferes with plasminogen activation and produces a thrombogenic environment.

The epidemic of obesity is a huge and ever so rapidly growing public health problem. Three aspects of weight—body mass index (BMI), waist size, and weight gained after one's early twenties—are linked to increased chances of having, or dying from heart disease, strokes and other cardiovascular diseases, and diabetes. Abdominal obesity (i.e. central obesity), with increased waist circumference, is an important component of the insulin resistance – hyperinsulinemia syndrome, and has been found to be more frequent in persons of Indian origin. The average waist–hip ratio (WHR) was higher in South Asian men than in the Europeans studied.[37] The regulation of weight gain and weight loss is marvelously complex, but certain simple principles stand out, such as CICO i.e. calories in, calories out. The hypothalamus controls body weight. A lack of blood sugar stimulates secretion of hormones—ghrelin (an appetite stimulant) and leptin (an appetite suppressant). When one loses fat, leptin decreases and ghrelin increases, causing one to eat more—and gain the weight back. The

body equilibrates. Several studies have documented the clustering of metabolic abnormalities associated with the insulin resistance syndrome. High serum TG levels and low HDL levels have also been seen in studies of native Indians with CAD.[38-41] The mechanism is yet unclear. The risk of CAD, nonetheless, is increased by the associated alteration in the lipid profile, hypertension, a thrombotic tendency evidenced by elevated levels of plasminogen activator inhibitor-1 (PAI-1)[42] and by the presence of impaired glucose tolerance (IGT) or diabetes.[43] World Health Organization (WHO) projections indicate the fastest increase in the cases of new onset diabetes in Southeast Asia.[44] By the year 2025, Southeast Asia would surpass Americas, and would have the highest number of diabetics.

The higher heart disease rates are partially attributable to an "influence of affluence". As lifestyle changes in India, the degree and the duration of exposure to the CAD risk factors is on the increase as a result of increasing life expectancy due to better treatment of infectious diseases, coupled with growing number of people with higher risk factor levels.[45-49] In some studies, high prevalence of smoking, elevated serum total cholesterol levels, low HDL levels, hypertension and diabetes were noted in both the urban and rural populations.[50,51] Therefore, although conventional risk factors might not be sufficient to explain the increased prevalence of CAD among Indians, their importance in the context of disease prevention and control remains undiminished. Differences have also been observed in the exercise levels and physical activity patterns of Indians. In India a higher prevalence of both sedentary lifestyle and obesity in urban compared with rural communities has been noted.[52] Merely belonging to the Asian-Indian ethnicity places one at higher risk for CAD than having high cholesterol and being a smoker combined. It has been suggested that certain genetic defect(s) could be responsible for part of the increased risk in CAD in Asian Indians. An excess prevalence or activation of the so-called "thrifty" or "pig-out" gene [i.e., 825T allele of the B3 subunit of heteromeric G-protein (GNB3) is associated with the development of obesity and metabolic syndrome when coupled with the absence of adequate regular exercise (gene-environment interaction). Even though the environmental and behavioral responses to urbanization and westernization appear to be consistent across cultures, the genetically determined metabolic response to these environmental changes and resulting CAD risk profiles may vary in different ethnic groups.[53] Ethnicity is a strong surrogate for gene-environment interactions, and it may underlie the tendency to develop obesity and atherosclerosis due to selection of the 'thrifty gene', that increases the efficiency of fat storage as described earlier. The extent to which these variations in different ethnic groups are due to genetic or environmental factors remains unclear.[54] A group of scientists collaborated in a large international, multi-center, case-control study called INTER-HEART study. Approximately 13,000 incident cases of acute MI in men and women who were admitted to the coronary care units (CCU) in the tertiary care centers and a similar number of age- and sex-matched controls are being evaluated.[55] Smoking as a coronary risk factor has been noted to be on the rise in India and other surrounding developing nations.[56] According to WHO, populations in developing countries account for approximately 85% of the 1.15 billion smokers worldwide, and the trends toward increased tobacco consumption observed in most transitional countries contrast with trends toward decreased smoking rates observed in most developed countries. Indeed it is estimated that annual deaths due to smoking will increase from about 1 million worldwide in 1995 to over 7 million in 2025. During this period, tobacco-related mortality will rise from about 1% to 13% of total mortality in India. Several recent studies have investigated the contribution of homocysteine to CAD risk both among immigrant Indians and those living in India.[57-61] In SHARE study, the South Asians had significantly higher levels of plasma homocysteine than their European and Chinese counterparts, this did not translate into an independent association of homocysteine with CAD. Atherosclerosis of the coronary vessels in South Asian Indians is usually quite widespread and diffuse, and exhibits accelerated progression than Whites. On angiography, their coronary arteries are found to be more often smaller and tend to develop fewer collaterals as CAD progresses.[57,62]

Strategies for Treatment and Prevention

Management strategies—both established and evolving—involve careful assessment and determination of appropriate CAD risk, and application of proportionate therapeutic intervention. We now know that the increased risk of CAD among persons of South Asian descent likely results from a complex interplay of genetics and environment. The ultimate resolution of the puzzle of increased CAD in Indians will only be provided by a better knowledge of that interaction. Nationally representative distribution data are available for a few risk factors. Several community-based surveys, done in different parts of India at different times, have contributed to a patchwork profile of risk in segments of the population, but there have been few multi-center studies with standardized methodology.

Studies such as the Framingham and the Multiple Risk Factor Intervention Trial (MRFIT) have clearly shown that the coexistence of multiple risk factors confers a magnified risk which is multiplicative rather than additive. The demonstration of such multiplicative risk has given rise to the concept of "comprehensive cardiovascular risk" or "total risk", quantifying an individual's overall risk of developing cardiovascular disease resulting from the confluence of risk factors. This fact has led to the recommendations that include calculation of Framingham risk score for the 10-year probability of cardiac events. This is particularly relevant in the Indian context because of the clustering of risk factors as metabolic syndrome among ethnic Indians.

Individual-Based Strategies: Early Screening for CAD and Risk Factors

Medical check-up and screening of all south Asians for presence of CAD and coronary risk factors should begin early, preferably by 40 years of age in all, and by 30 years of age in those with family history of premature coronary disease, and should be repeated at periodic intervals. Presence and intensity of coronary risk factors should be clearly delineated at each interaction with the physician, and level of risk should be determined according to the Framingham Risk Scoring System (high risk >20%, moderate risk 10%-20%, and low risk <10% with 10-year probability of major coronary events or death). Based on the risk level, preventive interventions should be applied, and follow-up schedules instituted.

Dietary Interventions

Indian expatriates, especially the first generation immigrants in the US, are frequently busy working long hours. Often both couples work, and have very little time for planning healthier meals. Their tendency to drive through a "fast food restaurant" is as widespread as it is among the rest of the Americans. On any given day, 30% of American children aged 4-19 years eat fast food. Overall, 7% of the US population visits one of the fast food chains, such as McDonald's, each day, and 20% to 25% eat in some kind of fast-food restaurant daily. Such fast food frenzy is fueling the rapid rise in overweight and obesity seen in the west. Obesity epidemic is merely the tip of the iceberg, on top of huge societal issues. As compared with White American teenagers, teenage children of Indian parents have been shown to be more often overweight and obese, perform less leisure time activity and exercise, consume fast food with greater frequency, and spend greater time in front of television, video games and computer. Similar fast food frenzy is now spreading in India, and is becoming the driving force behind the changing dietary culture and sedentary lifestyles.

Healthy diet: Even though Asian Indian physicians comprise the highest proportion of foreign medical graduates practicing in the US, most Asian Indians do not possess adequate knowledge with regard to health issues. The majority of Asian Indians, especially the vegetarians, believe that they are eating a healthy diet, which is incorrect. The typical Asian Indian diet averages 56% of energy intake from carbohydrates, 32% from total fat and 8% from saturated fat. The high fat intake is associated with obesity and low leisure time activity. The Dietary Guidelines describe a healthy diet as one that (a) emphasizes fruits, vegetables, whole grains, and fat-free or low-fat milk and milk products; (b) includes lean meats, poultry, fish, beans, eggs, and nuts; and (c) has lower amounts of saturated fats, trans fats, cholesterol, salt (sodium), and added sugars. People generally tend to eat the same amount of bulk, no matter what the calories. They fill their plate with the same amount of food. So if the foods are energy-rich, they take in more calories, but things that have a lot of water, air, and fiber in them, like fruits and fresh vegetables, fill one up more without the caloric load. Because fat, at nine calories per gram, is the densest form of food energy we consume, it is much easier to overeat on fat. Doing so tends to add body weight more readily, because fat is more efficiently stored. (Storing 100 calories of protein, for example, takes nearly twice as much energy as storing 100 calories of fat.)

Many Indian families abroad as well as a substantial number of them in urbanized India consume "fast foods" with certain regularity. Since it is impossible for people to avoid fast foods both in US and in India, it would be prudent to advise them regarding eating "healthy" even at these places. A few general recommendations follow: (a) *Schools and Soda machines*: While school vending machines are profitable ventures economically, the health consequences for the children are alarming. Extra calories contribute to childhood obesity, diabetes, hypercholesterolemia and hypertension very early in life. Drinking soda (liquid candy) instead of milk (low-fat, of course) can also cause decreased bone mineral density, tooth decay, and caffeine addiction. Children who drink three or more sodas a day have 60% higher risk of becoming overweight. It would be prudent not to ban the vending machines, but stock them with

water and "low-fat" milk (similar to California's "healthy beverage" campaign). (b) *For most foods, one can apply the 5+15 rule*: Choose foods with no more than 5 gm of fat and 15 gm of sugar per serving. While whole milk has 8 gm of fat per serving, 2% milk has 5 gm, so a good alternative is to pick milk with 2% or 1% fat for all kids above 2 years of age. Flavored milk may be substituted for greater acceptance. Low carbohydrate diets should be avoided in children - they may hinder school performance. In "starvation" mode, extra ketones are produced that have dulling effect on the brain. For this reason, fruit juices that generally contain higher amount of sugars are still preferred because they provide the essential vitamins and minerals (micronutrients).

Physical Activity

Regular exercise improves insulin sensitivity, decreases plasma TG levels, and reduces cardiovascular morbidity and mortality. Daily physical activity of 30 min is enough to help reduce and maintain body weight. The activity should be in the form of aerobic exercise of moderate intensity like riding a bicycle, jogging, taking a brisk walk, gardening, raking leaves, or even playing actively with kids. The health benefits of regular physical activity as a primary preventive measure is beyond doubt, and physicians have a crucial role in passing this information to their patients particularly those who are overweight and have a sedentary lifestyle, when counseling them about lifestyle changes.[63] Physical activity simply means performance of movement of the various muscle groups that use energy. Walking, gardening, briskly pushing a baby stroller, climbing the stairs, playing soccer, or dancing are all good examples of being active. Physical activity is associated with successful weight reduction, and along with other therapeutic lifestyle changes, can reduce the progression of new-onset diabetes by half in patients with metabolic syndrome.

Exercise is something many Indians, specially women, do not do on a regular basis. Many Asian Indian women have been conditioned to play passive games rather than be involved in action sports. Physical activity recommendations should include practical, regular, and moderated regimens of exercise, with a daily minimum of 30 to 60 min over and above the regular day-to-day activities. An equal balance between aerobic exercise and strength training should be incorporated. In a study, effect of leisure time exercise on HDL concentrations, subclasses, and size measured by nuclear magnetic resonance spectroscopy, was assessed in 388 healthy Asian Indians. Exercise was associated with significantly greater concentrations of total HDL-c, entirely due to significant increases in the cardioprotective large HDL subclass and larger HDL-c particle sizes.[64]

Lipid Management

Management of dyslipidemia is the cornerstone of therapeutic strategy for CAD risk reduction in the south Asian population. The general guidelines for the management of dyslipidemia in Asian Indians should be according to National Cholesterol Education Program (NCEP), Adult Treatment Panel III (ATP III). However, optimal management requires consideration of ethnic-specific dietary, lifestyle and management factors to formulate individual treatment guidelines.

The five currently available classes of lipid-modifying agents—the statins, bile acid sequestrants, nicotinic acid (niacin), fibric acids, and cholesterol absorption inhibitors—produce their major effect on one lipoprotein type - LDL but have lesser effects on the others. While multiple randomized trials have proven the benefits of such agents, such randomized trial data for the south Asian Indians, both abroad and in India, are lacking. The database to support treatment recommendations is, therefore, derived primarily from studies of Caucasian populations. For any given level of risk factor, the CAD risk among Indians is at least twice that of Whites.[65,66] Therefore, the threshold for intervention and the treatment targets may need to be lower in Asian Indians than in Whites by at least 20%, which is similar to the recommended threshold for patients with diabetes. Under ATP III of the NCEP guidelines, diabetes is regarded as a CAD risk equivalent, as are peripheral vascular disease (PVD), cerebrovascular disease (CVA), and aortic aneurysm. For persons with these diagnoses, the LDL goal is less than 100 mg/dL, irrespective of the presence or absence of CAD. Those who already have CAD require even more aggressive treatment to lower LDL to less than 70 mg/dl (cholesterol <150 mg/dl), specially if they also have high levels of Lp(a). Therefore, efforts to reduce cholesterol and other CAD risk factors among South Asians of Indian ancestry appear to be specially crucial. Asian Indians constitute a rapidly growing population in the US, and consistently appear to be at higher baseline risk for CAD compared to Whites. Their very high CAD prevalence, evident early in life, is intriguing because it is often not accompanied by a corresponding proportionate increase in traditional risk factors.[67] Rather, this elevated CAD risk reflects, among other things, higher prevalence rates of non-traditional risk factors, such as insulin resistance, metabolic syndrome, diabetes, and elevated Lp(a) levels

although the possible contribution of elevated Lp(a) levels to increased risk for CAD is still debated. These elements put South Asians particularly at risk for metabolic syndrome and Type-2 diabetes, and form the basis for the NCEP ATP III recommendation that not only should extra attention be given to detection of CAD risk factors in South Asians, but that increased emphasis should be placed on therapeutic lifestyle changes (TLC) to forestall metabolic syndrome.[68] All other aspects of the NCEP ATP III risk assessment and lipid-lowering guidelines remain the same for this group, but there appears to be a need for modifying these recommendations toward stricter goals. Recent studies have correlated consideration of a lower cut off for waist circumference for Asian Americans than that currently recommended for definition of metabolic syndrome. In a study involving adolescents, South Asian children demonstrated higher average levels of insulin and insulin resistance than Caucasian children; thus, the prevention of diabetes needs to begin earlier in life. It is feared that the children and grandchildren of Indian immigrants could be at even higher risk for heart problems than their parents, given that their current lifestyle as children seems to be much more sedentary than their parents' lifestyle as children used to be.[69]

Statins (HMG-CoA reductase inhibitors): The statins block the rate-limiting step in cholesterol synthesis and have the most powerful LDL-cholesterol (LDL-c) lowering effects of all lipid-modifying agents. Results of large, randomized CAD prevention trials have consistently confirmed the effectiveness of statin monotherapy in patients with Type-2 diabetes and the metabolic syndrome. Potential clinical benefits of statin therapy generally outweigh the small risks for these adverse events. Statins have been shown to be very effective agents for LDL reduction in multiple randomized clinical trials. Asian Indians have not constituted significant percentage of subjects in these studies. Therefore, the treatment recommendation for Asian Indians is mainly patterned after the NCEP recommendations.[70] In a study from Singapore, 548 patients (77.5% Chinese, 12.1% Malays, 7.6% Asian Indians; 49.6% males, 50.4% females; 54.7% diabetics, 45.3% non-diabetic) were treated with statins. These patients had >2 coronary risk factors, diabetes mellitus or documented CAD. Duration of therapy ranged from six months to five years. The choice and titration of statins were determined by attending physicians. The median statin dose (simvastatin equivalent) was 20 mg with 52.5% requiring 20 mg or more. Statin dose did not differ between diabetic and non-diabetic subjects. The median statin dose was 15 mg for the lower two tertiles and 20 mg for the upper tertile; this difference did not achieve statistical significance. The reduction in LDL-c was 41.5% and total cholesterol was 33.0%.[71]

A long overdue randomized trial of lipid reduction in this population, called the IRIS (Investigation of Rosuvastatin In South-Asian Subjects) trial, has completed enrolment. It will assess the comparative efficacy and safety of rosuvastatin and atorvastatin in Indian Americans and provide further insight into formulating adequate risk management strategies in this high-risk subpopulation. Persons of Asian descent have been shown to have twice the drug level compared to Whites on an equivalent dose of statins, specially rosuvastatin. Although the metabolism of these drugs has not been specifically evaluated in Asian Indians it is prudent to start these medications at a lower dose in Asian Indians. A recent FDA advisory suggests starting treatment with a 5 mg daily dose of rosuvastatin and avoiding a 40 mg daily dose to minimize the risk of rhabdomyolysis. The dose should also be lowered in elderly patients and in those with renal insufficiency.

In addition to statins, fibrates and niacin frequently provide added benefit in this subpopulation with higher prevalence of metabolic syndrome. The role of newer drugs, such as glitazones and torcetrapib, has not yet been evaluated in Asian Indians but deserves serious consideration due to the potential of significant benefit from these drugs in Asian Indians. In order to control and reverse the mortality and morbidity rates from CAD in the Asian Indian population—both within and outside of India—simultaneous individual level and Governmental level interventions are necessary.

Evolving therapies and newer trends: Newer therapies, such as cholesterol absorption inhibitors, and insulin sensitizers (metformin, glitazones), could also be employed alone or in combination with other agents to optimize treatment. The basis for a multiple approach to correcting dyslipoproteinemia in visceral obesity and the metabolic syndrome relies on understanding the mechanisms of action of the individual therapeutic components. In a study from Chennai, India, new Type-2 diabetic subjects (n=97), aged 30-60 years with BMI < 30 kg/m^2 were selected and short-term efficacy of glimepiride, metformin and pioglitazone was evaluated. Glycemic control improved in all study groups, and the improvement was better in drug-treated groups than in the controls. Glimepiride improved insulin secretion including the early

phase secretion and reduced plasma triglycerides. Metformin and pioglitazone had beneficial effects on lipid levels, insulin sensitivity and insulin secretion.[72]

Strategies for raising HDL-c levels: Low HDL levels often reflect a genetic abnormality, although they can also be pushed downward by a high blood level of triglycerides or by cigarette smoking, inactivity, hypertension, or a diet very high in carbohydrates or polyunsaturated fats.

CETP inhibition therapy: Another pharmacologic approach geared toward raising HDL levels involves inhibiting cholesteryl ester transfer protein (CETP). The CETP helps exchange cholesterol between lipoproteins and can transfer it from HDL to the LDL and very low-density lipoprotein (VLDL).[73] Individuals with a genetic mutation that causes loss of all CETP activity have very high levels of HDL-c. They appear to be at lower risk of coronary disease. A small study in 2004 involving CETP inhibitor, torcetrapib, showed that the drug markedly increased HDL levels and decreased LDL levels when taken alone and also when taken in combination with a statin.[74] The increases in HDL levels were much higher than can be achieved with existing lipid drugs. However, torcetrapib needs to be tested in a larger population, and should be shown not only to increase HDL levels, but also to prevent heart problems through outcome studies.

HDL-infusion therapy: This study, in a group of 40 Italian villagers led to the discovery of a rare type of HDL that seemed to protect against heart disease even when the levels of HDL were not very high. These people had a protein in their HDL, now called *apo A-I Milano*, that seemed to be better at stimulating the removal of cholesterol from plaques than did HDL containing the normal protein, called *apo A-I*. Researchers recently tested whether a synthetic version of apo A-I Milano (recombinant ApoA-1 Milano/ phospholipid complexes, ETC-216) infused into the blood of people who didn't naturally have this protein would have the same effect.[75] The small trial randomly assigned 47 people who had recent heart attacks to receive either a placebo or a low or high dose of this chemical. Through ultrasound of the arteries, researchers found that from the beginning to the end of the five-week trial, the plaque in the treatment groups shrank by 4%, while that of the placebo group increased by a small amount. Although these results are exciting, a larger trial with such synthetic HDL infusion therapy is needed.

Estrogen replacement or *hormone replacement therapy* (HRT)*:* The HRT raises HDL by about 8% in post-menopausal women, but its use is controversial, and is not recommended for CAD prevention due to demonstrated lack of benefit and possible risk of increased thrombosis. The Heart and Estrogen progestin Replacement Study (HERS) found no net decrease in secondary prevention of CHD events over 4 years. Events increased by 50% with HRT during year 1 but then progressively decreased to 33% lower by study end. The early increase may have resulted from prothrombotic and/or proinflammatory effects of HRT, while the later decrease may have reflected the 8% increase in HDL-c and/or other antiatherosclerotic mechanisms. Results of HRT in primary prevention await completion of the Women's Health Initiative in 2007.

Fish oil capsules: Since dietary modification to increase the consumption of cold-water fish (e.g., salmon) rich in polyunsaturated fats may help to raise HDL, capsules containing omega-3 fatty acids (1.48 gm of docosahexenoic acid and 1.88 gm of eicosa-pentenoic acid) have been studied in small trials. In a recent study in patients with familial combined hyperlipidemia, treatment with this formulation for 8 weeks increased HDL by 8%, particularly the more buoyant HDL-2 subfraction. Levels of the anti-oxidant HDL-associated enzyme paraoxonase also increased by 10%.

None of these HDL-raising therapies have been studied in the Asian Indians. And, therefore, no particular treatment recommendations can be made at this juncture. The treatment strategies, nonetheless, appear well suited for this subpopulation with high prevalence of hypo-alphalipoproteinemia (low HDL-c).

Treatment of hypertriglyceridemia: Elevated triglyceride levels increase heart disease risk, and are a frequent finding in Asian Indians. In the light of these findings, the NCEP guidelines recommend treating even borderline high triglyceride levels.

The NCEP divides triglyceride levels into four categories. For people who have borderline high (150–199 mg/dl) or high (200–499 mg/dl) TG, the first goal is to bring LDL to a healthy level. Cornerstone of the treatment are the lifestyle changes that include losing weight, limiting alcohol to one drink a day, stopping smoking, increasing the level of exercise, and limiting daily calorie intake as well as the amount of fat and carbohydrate in the diet. For people with high or very high TG (200 mg/dl or above) — as well as those with a combination of high LDL or a high risk for heart disease and borderline or higher TGs — lifestyle changes are generally accompanied by drug therapy. Drug therapies, in this case, include more aggressive LDL-lowering drugs or the use of nicotinic acid or a fibrate (gemfibrozil or fenofibrate).

Combination therapy: Many patients require HMG-CoA reductase inhibitor/fibric acid derivative, HMG-CoA reductase inhibitor/niacin and HMG-CoA reductase inhibitor/fish oil combinations. Because statins have lesser effects on TG and HDL-c, statin monotherapy may not be sufficient to manage the total lipid abnormalities of patients with the metabolic syndrome or insulin resistance, such as majority of South Asian Indians. Hence, combination therapies may frequently be necessary to reduce CAD risk in these patients. The rationale for combination therapy is that drugs with complementary mechanisms of action can provide complementary effects on the lipid profile. Both niacin and fibrates have greater effects on TG and HDL levels than statins. Although safety issues have limited their use, combinations of statins with fibrates or niacin are proving safe and effective for treatment of atherogenic dyslipidemia.[76]

Fibric acid derivatives, or fibrates, were some of the earliest agents used for the management of hyperlipidemia. They are thought to affect lipid and lipoprotein metabolism by activating peroxisome proliferator activated receptors (PPAR-alpha nuclear receptors). The fibrates are very effective at lowering TG levels, are moderately effective at raising HDL levels, and have generally modest effects on LDL-c levels. Because of their complementary lipoprotein effects, statin/fibrate combinations have been recently evaluated in clinical studies of patients with diabetes.[77] In one long-term study, 148 patients with Type-2 diabetes and mixed dyslipidemia (elevated LDL and TG levels, normal HDL levels) were administered simvastatin or bezafibrate for 6 months followed by both drugs for 12 months. Combination therapy reduced LDL and TG levels by 29% and 42% while raised HDL levels by 25%. Cardiovascular event rates during the first 6 months were 6% with simvastatin and 12% with bezafibrate; during the year of combined therapy, the event rate fell to 2%. A second study of 120 patients with diabetes and similar mixed dyslipidemia but no CAD compared treatment with atorvastatin, fenofibrate, and the two agents combined over a 2-year period. Combination therapy resulted in superior lipid improvements, reducing LDL levels and TG levels by 46% and 50%, respectively, and increasing HDL levels by 22%. Combined therapy reduced the predicted 10-year risk of MI from 21.6% to 4.2%. The safety of statin/fibrate combination therapy was recently examined in a Medline and bibliographic search involving 1,674 patients enrolled in studies reported between 1988 and 2000. None of the patients developed rhabdomyolysis or acute renal failure. Myalgia or other muscle symptoms were reported in 1.9% of patients, and elevated creatine kinase (CK) levels were reported in 2.1%. Most reports of statin-fibrate-associated myopathy have involved gemfibrozil. In contrast, fenofibrate appears to be associated with a much lower risk of myopathy when combined with a statin. This may result from their different effects on statin metabolism; gemfibrozil strongly inhibits the glucuronidation pathway while fenofibrate produces less inhibition. Although there is a small increase in risk, yet, statin-fibrate therapy is overall a useful option for patients with atherogenic dyslipidemia when administered with appropriate medical care.

Niacin is the most efficacious of the currently available lipid-modifying agents for raising low HDL levels. It reduces TG levels to a degree similar to that of the fibrates and has moderate LDL-lowering efficacy. Niacin is effective in managing the dyslipidemia associated with the metabolic syndrome since it acts primarily by decreasing the mobilization of FFAs from adipose tissue. In addition, it increases the size of LDL particles. In fact, niacin appears to be most effective in patients with small dense LDL particles, producing greater decreases in TG and increases in HDL levels. As noted in NCEP ATP III, the combination of a statin and niacin corrects most forms of complex dyslipidemia. The combination of atorvastatin and niacin was evaluated in 53 patients with diabetic dyslipidemia characterized by small LDL particle size or low levels of the larger HDL-2 subclass. Combination therapy reduced LDL levels significantly more than niacin alone and increased LDL size, HDL levels, and HDL-2 mass significantly more than atorvastatin alone. It was also more effective in reducing TG levels than either monotherapy. The combination improved all components of the atherogenic lipid profile. However, the use of niacin has been limited by adverse effects, most notably flushing. Flushing occurs in the majority of patients at the start of niacin therapy, and is usually transient, but it often gets discontinued before tolerance has developed. Aspirin, given 30 min before dosing, frequently reduces the flushing. Timed-release niacins cause less flushing, but have been associated with significant hepatotoxicity. Extended-release niacin has an intermediate-release rate that has been shown to limit flushing without an increase in hepatotoxicity.[78] The use of niacin has also been discouraged in diabetic patients because it had been shown to increase insulin resistance and degrade glycemic control, particularly at high doses. Despite this concern, the long-term use of niacin in patients with Type-2 diabetes is safe as well as effective when administered with reasonable medical care.

Dietary approaches for treatment of dyslipidemia: Dietary interventions to lower lipid levels include reduction

of saturated fat intake to <10% of the total fat in the diet, reduction of the amount of dietary cholesterol intake, reduction of total fat intake to <30% of the diet, eating more soluble fiber, and maintaining ideal weight. Initial goal for management of dyslipidemia must still focus on LDL reduction in the Asian Indians. In addition, attention must be given to lowering of the TG level, a frequently elevated lipid in Asian Indians. Dietary interventions for triglyceride control include reduction of total fat and saturated fat intake, eating less sugar, avoiding alcohol, and eating more fish high in omega-3 fatty acids. HDL-c tends to increase with dietary changes that include plenty of exercise, modest alcohol intake,[79] low total and saturated fat consumption, and low consumption of trans fatty acids (trans fats). Elevated levels of Lp(a) also contribute to the enhanced atherogenecity seen in Asian Indians. There is no clarity about strategy to lower a high Lp(a) level. Some preliminary findings point to aspirin, red wine and omega-3 fatty acids from fish as possibly lowering Lp(a) levels. More research is needed before specific dietary recommendations can be made. Following general recommendations regarding dietary modification can be made.

Reduction of total fat and saturated fat intake: The risk of CAD falls sharply if fat intake is decreased to <30% of total calories (as opposed to the 34-54% that is typical for both vegetarians and non-vegetarians). Exactly how much of the diet should come from fat is still somewhat controversial. A Dean Ornish type diet which has been suggested for reversal of CAD, includes exercise, meditation, and an almost-vegetarian diet with fat intake of only 10%. Overweight people with high cholesterol and Type-A personalities may greatly benefit from such program which is rigorous, and rigid but effective. Alternatively, a Mediterranean type diet with 30% fat content may be effective as long as the fat largely comes from olive oil, fish and nuts. People can eat a good deal of cheese and yogurt, but rarely red meat and drink wine only in moderation. The carbohydrates should come from whole-grain cereals and breads, fresh fruits and vegetables. Daily cholesterol intake should be 300 mg or less. Certain animal foods are rich in cholesterol, but no plant foods contain cholesterol. Persons who eat eggs should consider egg white that has no fat or cholesterol, and is also an excellent source of protein. Organ meats and certain seafoods — shrimp, lobster and calamari — have high levels of cholesterol, and should be avoided.

Avoidance of tropical oils: The tropical oils, such as palm, palm kernel and coconut oil (widely consumed by South Indians), are highly saturated. They are also found in non-dairy coffee creamers, whipped toppings, baked goods, cookies, and chocolate candies, and must be avoided.

Reduction of trans-fatty acid intake: Trans-fatty acids are found in foods chemically modified by partial hydrogenation (e.g., hydrogenated oils). A US Department of Agriculture (USDA) study showed that trans-fatty acids raise cholesterol similar to saturated fats, and cause reduction in HDL-c levels, while raising Lp(a).

Increase in intake of monounsaturated fats: Monounsaturated fats tend to lower blood cholesterol levels. These fats are generally liquid at room temperature, and are the main fatty acids in olive oil and canola oil. Thus, olive and canola oils should be used in cooking and in salad dressings as the main oils.

Increase in intake of polyunsaturated fats (PUFA): Polyunsaturated fats are the major fat source in vegetable oils, such as safflower oil and corn oil. They lower total cholesterol, although they may also lower HDL-c. Use of hydrogenated margarine should be reduced; liquid and tub margarine are better. The primary polyunsaturated fatty acid is omega-6 (n-6), or linoleic acid, a fatty acid that is essential for our growth and development. Widespread use of omega-6, however, may upset the balance with omega-3 (n-3), which may augment cancer risk. Omega-3 fatty acids are polyunsaturated fats from plant and marine sources. Omega-3 is an essential fatty acid, linolenic acid. Its richest sources are fish that swim in cold waters, such as salmon, bluefish, mackerel, tuna, herring, and sardines. These should be consumed 3-4 times a week to achieve significant reductions in TG levels. The seafood should be baked, broiled, steamed or boiled – but not fried, and olive or canola oils should be used in preparing the recipes which call for oil. The vegetarians, and those who do not eat fish should consume walnuts, walnut oil, and flaxseed oil that are rich sources of linolenic acid.[80] In a long-term study conducted on 80 middle-aged Indian subjects (40 men and 40 women) using the subjects' own home-prepared diets to evaluate the effects of dietary n-3 PUFA on biochemical indices of CAD risk with substitution of Blend G (equal proportions of groundnut and canola oils) for groundnut oil or substitution of Blend S (equal proportions of sunflower and canola oils) for sunflower oil increased alpha-linolenic acid (ALNA) four-fold. Fish oil supplementation increased n-3 PUFA in plasma and platelet phospholipids, decreased ADP-induced platelet aggregation, but increased plasma cholesterol. Since both n-6 and n-3 PUFA play a critical role in the programming of diet-related chronic diseases in adults, an improvement in the n-3 PUFA nutritional status in cereal-based diets through long-term use of cooking oils containing 25-40% linolenic acid and 4% ALNA may contribute to the prevention of CAD in Indians.[81]

Increase in intake of soluble fiber: The soluble fiber in oats, called beta-gluca, has specifically been shown to reduce serum cholesterol level. A high daily intake of soluble fiber, through generous servings of oat- and bean-based foods, helps eliminate cholesterol-laden bile acids and fats from the body. Soluble fiber is found primarily in oats, legumes, apples, pears, plums, carrots, okra, and barley.

Increase in intake of folic acid, vitamin B6 and vitamin B12: Low levels of folic acid and other B vitamins can cause excessive homocysteine to be produced in the body. High homocysteine levels are frequently encountered in Asian Indians. Reducing homocysteine level, however, has not yet been shown to convincingly decrease cardiac event rate. In the meantime, supplementation with 400 mcg of folic acid a day to prevent heart disease may be reasonable. Foods that supply vitamin B include total cereal, lentils, asparagus, spinach, kidney beans, and orange juice.

Increase in protein intake specially for vegetarians: Soyabean (Soy) protein intake helps lower cholesterol levels. Soy contains isoflavones, called daidzein and genistein, which are the plant estrogens that play a role in cholesterol metabolism. Soy protein can be substituted for animal protein in the diet, and is found in tofu, tempeh, veggie burgers made with textured vegetable soy protein, and soy milk. Generally, a daily intake of 25-50 gm of soy protein or 60 mg of isoflavones is considered to be adequate for cholesterol lowering.

Increase in intake of anti-oxidants: Anti-oxidants retard the development of "free radicals" that are implicated in production of oxidized LDL and atherosclerotic progression. Vitamin E is an antioxidant with recommended intake of 400-800 IU daily. Vitamin C may be taken as an antioxidant at 350-500 mg a day. Beta-carotene at 15 mcg a day, may also be helpful. It must be noted, however, that these as well as mega doses of dietary antioxidants – vitamin C, vitamin E, selenium, beta-carotene, and other carotenoids – have not demonstrated protection against cardiovascular disease or diabetes. Large placebo-controlled trials have failed to show benefit and, in some instances, have suggested adverse effects of antioxidant vitamins.[82]

Increase in intake of phytochemicals: Phytochemicals are plant chemicals that may help prevent not only CAD, but also other chronic diseases and conditions such as diabetes, hypertension, and some cancers. Fruits and vegetables are rich in phytochemicals, and five servings a day is recommended. Garlic may help reduce serum cholesterol, LDL and TG. Garlic given as tablets has been studied, but the results so far have been inconclusive. It appears that raw garlic may be the active ingredient.

Management of Insulin Resistance, Metabolic Syndrome and Prevention of Diabetes

It is abundantly clear that insulin resistance and Type-2 diabetes mellitus are the result of a complex interplay between genetic and environmental factors. However, there is compelling evidence to suggest that the current worldwide metabolic syndrome and diabetes epidemic is largely due to changes in diet and lifestyle. Prospective cohort studies and randomized clinical trials have demonstrated that Type-2 diabetes can be prevented essentially through diet and lifestyle changes. Excess adiposity is the most important risk factor for metabolic syndrome and insulin insensitivity, thus maintaining a healthy body weight and avoiding weight gain during adulthood is the cornerstone of their prevention. Increasing physical activity and reducing sedentary behaviors are important both for maintenance of body weight and increase in insulin sensitivity. There is increasing evidence that the quality of fat and carbohydrate plays a more important role than does the quantity, and thus, public health strategies should promote replacing saturated and trans-fats with unsaturated fats and substituting refined grain products with whole grains. There is some evidence that addition of micronutrients, such as calcium and magnesium may influence the reduction of insulin insensitivity. Overall, a healthy diet, together with regular physical activity, maintenance of a healthy weight, moderate alcohol consumption, and avoidance of sedentary behaviors and tobacco, could nearly eliminate insulin resistance syndrome and Type-2 diabetes.

Insulin resistance without overt diabetes can be managed in two ways—by reducing the need for insulin, and by increasing the sensitivity of cells to the action of insulin. The need for insulin can be reduced by altering the diet, particularly the carbohydrates in the diet. Carbohydrates are absorbed into the body after they are broken up into their component sugars. Some carbohydrates are broken up and absorbed faster than others and are referred to as having a high glycemic index (e.g. unrefined sugars, white breads and unrefined corn products, such as bagels, mashed potatoes, doughnuts, corn chips, and french fries). These carbohydrates increase the blood glucose level more rapidly and require the secretion of more insulin to control the level of glucose in the blood. Such carbohydrates should be avoided. Instead, carbohydrates with a low glycemic index should be chosen. These include foods with higher

fiber content such as whole grain breads, brown rice, and non-starchy vegetables, such as broccoli, green beans, asparagus, carrots, and greens. The sensitivity of cells to the action of insulin can be raised by increasing physical activity. Several studies have shown that weight loss and aerobic exercise (without weight loss) increase the rate at which glucose in the blood is taken up by muscle cells as a result of improved sensitivity of the cells to insulin.

Pharmacologic management of metabolic syndrome: Although pharmacological treatment, at present, is not recommended to tackle the insulin resistance of metabolic syndrome, every opportunity should be taken to treat patients with Type-2 diabetes and metabolic syndrome with the insulin sensitizers – metformin and thiazolidinediones.

Thiazolidinediones appear to act by lowering free fatty acid levels. Like fibrates, they lower TG level and raise HDL-c level. Rosiglitazone appears to cause a shift in size of LDL particles from small to large. There is also evidence for role of acarbose in the prevention of glucose toxicity and beta-cell exhaustion and it should be an essential component of any anti-diabetic regimen in patients with Type-2 diabetes and metabolic syndrome. Metformin (glucophage) prevents the liver from releasing glucose into the blood, and increases the sensitivity of muscle and fat cells to insulin so that they remove more glucose from the blood. Because of these actions, metformin reduces blood insulin levels. In a study, metformin reduced the development of diabetes by 31%. Other medications include a class of drugs called thiazolidinediones, e.g., pioglitazone, and rosiglitazone also increase sensitivity to insulin. At present, however, these medications are not routinely used, in part because of liver toxicity that requires monitoring of blood liver tests. Because of severe toxic liver effects, another agent in this class, troglitazone, was taken off the market.

The angiotensin-converting enzyme (ACE) inhibitor, ramipril, in the HOPE trial has indisputably demonstrated reduction and even prevention of cardiovascular events in a broad range of high-risk patients with preserved LV function.[83] Ramipril should be the antihypertensive of choice in an individual with hypertension associated with metabolic syndrome. It is thought to reduce cardiovascular morbidity and mortality by slowing the progression of atherosclerotic plaque formation, preserving endothelial function, and reducing plaque activation independently of its effects on blood pressure and lipid levels. It is interesting to note that ramipril also prevented the development of Type-2 diabetes in the study participants probably by reducing insulin resistance. As a result, a large trial among individuals with impaired glucose tolerance has been started to evaluate prospectively whether ramipril prevents diabetes. Although statins only partially correct the atherogenic dyslipidemia, lowering of LDL-c remains the first target. There is evidence that statins may reduce new onset diabetes and may therefore be beneficial for individuals with metabolic syndrome.

Blood pressure management: While thresholds for risk factors are useful in making clinical decisions involving individual patients, it is being increasingly recognized that risk factors operate in a continuum of progressively increasing risk rather than an all-or-none relationship suggested by the cut-off values. For example, although a systolic blood pressure (SBP) of 140 mmHg, the widely accepted threshold for diagnosis of hypertension, carries a lower risk of adverse cardiovascular events than an SBP of 180 mmHg, the risk imparted is still greater than that posed by SBP between 130 and 139 mmHg. South Asian Indians tend to have borderline rise in blood pressure in isolation or in combination with other components of metabolic syndrome. Such borderline high pressures need to be treated because it has already been shown that a mere 2 mmHg reduction in the mean diastolic blood pressure would prevent 93% of the paralytic strokes and more than all the heart attacks that can be prevented by drug treatment of established hypertension. Such blood pressure changes can often be achieved and sustained by increasing the overall physical activity levels and decreasing salt intake in the population.

Weight reduction: In human body, amino acids and carbohydrates take priority over fat in oxidation for energy production. There is no storage depot for amino acids; carbohydrate can be stored as glycogen in limited amounts only and its conversion to fat is not energy-efficient. Human body has developed the ability to store fat (largely in adipose tissue) for periods of energy deprivation and the storage capacity is unlimited. The storage efficiency of fat is also high. Therefore, the amount of daily fat intake that is oxidized or stored, is the difference between total energy needs and oxidation of other priority fuels – protein and carbohydrates. For weight reduction, reduction in daily fat intake is essential. Saturated fat (mainly dairy and animal fat) worsens insulin resistance and increases LDL-c level. Trans-unsaturated fatty acids (formed when vegetable oils are hydrogenated) behave similarly. Therefore, their daily intake should be restricted to 7-10% of caloric intake. Dietary cholesterol should be restricted to <200 mg/day. Incorporation of monounsaturated fatty acid (fat from plant source like olive oil, soybean oil, canola oil, safflower oil, peanut oil, peanuts, peanut butter, almond, and cashew

nut) may be beneficial as it improves the atherogenic dyslipidemia. Similarly, n-3 polyunsaturated fatty acids (mainly from fish) have cardioprotective effect.[84] Polyunsaturated fatty acid should constitute approximately 10% of energy intake. Viscous (soluble) fibre (mainly in oat products, psyllium and pectin) intake of 10-25 gm/day also improves atherogenic dyslipidemia. A diet incorporating whole grain cereals, fruits, vegetables, nut, legumes and low fat milk is rich in all these ingredients. It is important to remember that carbohydrate derived from processed cereals such as white bread is as bad as saturated fat in causing weight gain.

Education: Structured programs that emphasize lifestyle changes, including education, reduced fat ($\leq$ 30% of daily energy) intake, regular physical activity, and regular participant contact, have the potential to produce long-term weight loss. Even a weight loss of 5-7% leads to significant improvement in insulin resistance. The real challenge lies in implementing these programs at community and national levels.

Population-Based Strategies

In addition to the individual level approaches, the prevention has to involve policy level interventions as well. The population-based strategy is in contrast to the individual/ high-risk approach (focused on individuals at the highest risk). It must, however, be emphasized that the two strategies are not mutually exclusive but are synergistic and complementary, and have to be applied to the population simultaneously for any meaningful impact on CAD epidemic in the Asian Indians. There is an urgent need to increase resource allocation, coordinate multi-level policy interventions, and enhance the engagement of the health system in activities related to cardiovascular disease prevention and therapy. The limited health budgets are not ready to take on the additional costs of treating chronic diseases at state expense. However, the huge expenditure that the state and society are incurring on the tertiary care of advanced chronic diseases such as CAD has only been recently recognized. This has prompted increased emphasis on prevention. A comprehensive law for tobacco control was enacted in 2003. An integrated national program for the prevention and control of cardiovascular diseases and diabetes is under development.

The policy framework needed to implement the WHO Global Strategy on Diet, Physical Activity and Health is still evolving. The existing food-based dietary guidelines should be revised to reflect the principles of chronic disease prevention and health promotion and, thereafter, widely disseminated through various Indian languages. Through amendments in the Prevention of Food Adulteration Act of 1954, limitations can be placed on the levels of salt, sugar, and saturated fats in manufactured food products. Food labeling also needs to be introduced and enforced to facilitate informed choice by consumers. In India, in the past few years, two surveillance systems have been established to provide risk factor data from different parts of the country, using WHO's STEPS methodology. In 2002, Indian Council for Medical Research (ICMR), with technical assistance from WHO, established a community-based surveillance system involving five centers. During 2000–2004, another WHO-assisted project established a sentinel surveillance system for cardiovascular risk factors and events in 10 large industries across the country, involving the employees and their family members. The results from those newly established surveillance centers should provide the much needed data regarding the prevalence of common and established coronary risk factors among Asian Indians. In addition a large prospective epidemiologic study, called the "Indian Heart Watch" study has just begun at 20 centers across various regions of India to identify the prevalence of risk factors responsible for increasing rates of diabetes and CAD in India.

Conclusions

Coronary artery disease appears to be more virulent in South Asian Indians than persons of other ethnicities.

The key to combating the increasing incidence of CAD among Indians is, an aggressive treatment of known risk factors through both an individual-based as well as a population-based approach aimed at comprehensive risk factor reduction. The presence of relatively low levels of conventional risk factors in rural population presents a window of opportunity for primordial and primary prevention in that subgroup.

Establishing surveillance systems for more accurately estimating the prevalence of risk factors in the community, and the initiation of studies to clarify the role of existing and emerging risk factors in the Indian context would greatly enhance the ability to execute appropriate preventive and control measures. Early institution of healthy lifestyle beginning with adolescence seems justified in view of the malignant nature of CAD in the Asian Indians.[85,86] Pharmacologic intervention similar to that of secondary prevention of CAD should be used as primary prevention in high-risk Indians. Therefore, it is suggested that the threshold for intervention and goals of treatment for various risk factors in this special population should be

20% lower than Caucasians for LDL-c and 10% lower for other risk factors. Preventive strategies should begin at least 20 years earlier than in other populations (men by 25-30 years of age, and women by 35-40 years of age) because of the much more frequent premature occurrence and malignant nature of CAD. Furthermore, the magnitude of the benefit of statin therapy for dyslipidemia in this subpopulation seems to far exceed that of the treatment of other risk factors, such as hypertension or glucose intolerance. Thus, lipid-lowering treatment with statins should be considered a first line of treatment rather than a second line strategy. Finally, for this special population, regular physical activity, smoking cessation, and reduced consumption of saturated fat should become the main focus of the therapeutic lifestyle changes.

On the national level, in India, where demographic transitions, and changing diet and lifestyles have instigated the CAD epidemic, prompt socio-political, and public health initiatives are required. With the initial focus on adolescents and the persons at lower socio-economic level, swift regulatory and educational interventions must be instituted to root out smoking, make foods healthier and safer through food labeling and close monitoring, and promote regular exercise for the entire population. There is no doubt that significant reduction in CAD is quite feasible in India by adopting the combined tactics at both — population and individual ranks, and incorporating primary and primordial prevention policies. This would require enthusiastic action by everyone - the medical profession, administration, media, and the people. Much can be achieved in terms of reduction of early mortality and morbidity associated with CAD in the Asian Indians with a lucid appreciation of its epidemiology and etio-pathogenesis, and concerted action toward already known risk factors.

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Burden of Coronary Heart Disease in India

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Coronary heart disease (CHD) has assumed epidemic proportions in India. The disease is more prevalent in urban populations and there is a clear gradient in its prevalence from rural to semi-urban to urban populations. The disease occurs at a younger age in Indian subjects compared to western developed nations. The burden of CHD can be measured as (a) population impact measured by premature mortality and disability, (b) burden on healthcare systems, and (c) burden on economy. The Global Burden of Diseases (GBD) study reported the estimated mortality from CHD in India at 1.6 million in the year 2000. Extrapolation of these numbers estimates the burden of CHD in India to be more than 32 million patients. Epidemiological studies show a sizeable burden of CHD in adult rural (3-5%) and urban (7-10%) populations. Thus, there could be 30 million patients with CHD in India of whom 14 million are in urban and 16 million in rural areas. This number is similar to that derived by the GBD study. There is a significant burden of CHD on healthcare systems. In urban primary health clinics 1-1.5% of all patients have CHD while in general internal medicine clinics CHD prevalence is 10-20%. In a rural internal medicine practice it was reported that 8% of all patients have CHD. Hospital statistics reveal that 20-25% of all medical admissions are due to CHD. The admissions due to acute myocardial infarction (MI) are increasing in India. The economic costs of CHD are poorly understood. We roughly calculated that annually India spends about Rs. 100 billion as direct costs of treatment. The magnitude of indirect costs is unknown and could be another Rs. 100 billion. The sum is equal to 0.8% of the Indian gross national product. There is a strong positive correlation of increase in CHD in India with primordial risk factors of urbanization, excessive fat intake, faulty diet, tobacco consumption, and sedentary lifestyle. Major coronary risk factors - high blood pressure, high cholesterol levels, low high-density lipoprotein (HDL) cholesterol, insulin resistance and diabetes are also escalating in India and correlate strongly with the increase in coronary diseases. There is an urgent need to develop CHD risk factor surveillance and prevention effort in India.

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Cardiovascular Disease : The Indian Scenario

Cardiovascular diseases account for a large proportion of all deaths and disability worldwide. GBD study reported that in 1990 there were 5.2 million deaths from cardiovascular diseases in economically developed countries and 9.1 million deaths from the same causes in developing countries.[1] However, whereas about one-quarter of all cardiovascular disease deaths occurred in persons who were under 70 years of age in the developed world, more than about half of these deaths occurred in those under 70 years in the developing world. It has been predicted that by the year 2020 there will be an increase by almost 75% in the global cardiovascular disease burden. Almost all of this increase will occur in developing countries.

The situation in India is more alarming. Reddy[2] reported that mortality from cardiovascular diseases was projected to decline in developed countries from 1970 to 2015 while it was projected to almost double in the developing countries. GBD study reported that of a total of 9.4 million deaths in India in 1990, cardiovascular diseases caused 2.3 million deaths (25%); 1.2 million deaths were due to coronary heart disease and 0.5 million due to stroke.[1] It has been predicted that by 2020 there would be a 111% increase in cardiovascular deaths in India. This increase is much more than 77% for China, 106% for other Asian countries and 15% for economically developed countries.[1]

Measuring Disease Burden

A variety of time-based measures have been used for measuring disease burden but the GBD study used an internationally standardized form called the disability-adjusted life years (DALY).[3] For the GBD 1990 study, estimates for disease burden were prepared for eight broad geographic regions of the world: Established Market Economies (EME), Formerly Socialist Economies (FSE), India, China, Latin America, Caribbean (LAC), Other Asia and Islands (OAI), and Sub-Saharan Africa (SSA).[1] CHD was the leading cause of death in both developed and developing countries in GBD 1990.[4] For the GBD 2000 study the regional composition has been adapted to the six WHO regions.[5] However, since these groups are epidemiologically significantly heterogeneous, they have been

further divided into five categories based on child and adult mortality in each country. CHD is again the leading cause of death in developed and developing countries (Table 1).

Table 1. Estimates of 10 leading causes of global death in GBD 2000 study

Developed countries			Developing countries		
Rank	Cause	% of total deaths	Rank	Cause	% of total deaths
1	Ischemic heart disease	22.6	1	Ischemic heart disease	9.1
2	Cerebrovascular disease	13.7	2	Cerebrovascular disease	8.0
3	Trachea, bronchus, lung cancers	4.5	3	Lower respiratory infections	7.7
4	Lower respiratory infections	3.7	4	HIV/AIDS	6.9
5	COPD	3.1	5	Perinatal conditions	5.6
6	Colon and rectum cancers	2.6	6	COPD	5.0
7	Stomach cancer	1.9	7	Diarrheal diseases	4.9
8	Self-inflicted injuries	1.9	8	Tuberculosis	3.7
9	Diabetes	1.7	9	Malaria	2.6
10	Breast cancer	1.6	10	Road traffic accidents	2.5

COPD: chronic obstructive pulmonary disease

Results of GBD studies clearly demonstrate that disability plays a central role in determining overall health status of a population. The leading causes of disability are shown to be substantially different from those of death, which has considerable implications for the practice of judging a population's health from its mortality statistics alone (Table 2). The key aim of the GBD was to measure the burden of fatal and non-fatal health outcomes in a single measure, the DALY. To calculate DALYs due to each disease or injury in a given year and population, the years of life lost through all deaths in that year (YLL) were added to the years of life expected to be lived with a disability of all new cases of disease or injury occurring in that year (YLD), weighted for the severity of that condition. In 1990 as well as 2000, the major causes of global disease burden are lower respiratory infections, diarrheal diseases, perinatal causes, depression and CHD.[3,5]

Table 2. Ten leading global causes of DALYs in 1990 and 2000

1990 Rank	Disease or injury	2000 Rank	Disease or injury
1	Lower respiratory infections	1	Lower respiratory infections
2	Diarrheal disease	2	Perinatal conditions
3	Perinatal conditions	3	HIV/AIDS
4	Depression	4	Unipolar depression
5	Ischemic heart disease	5	Diarrhoeal disease
6	Stroke	6	Ischemic heart disease
7	Tuberculosis	7	Cerebrovascular disease
8	Measles	8	Road traffic accidents
9	Road traffic accidents	9	Malaria
10	Congenital anomalies	10	Tuberculosis

DALY: disability-adjusted life years

Burden of Coronary Heart Disease in India

Scientific involvement in the epidemiology of CHD and hypertension in India emanated from observations that these diseases were present in significant numbers in urban subjects in metropolitan cities and contributed to a large number of hospital admissions.[6] A study from rural areas of Rajasthan reported that CHD contributes to 8% of patients attending a specialist physician's clinic.[7]

The age of presentation of acute coronary syndrome is about 5 to 10 years earlier in Indian patients. An Indian multicentre study that analyzed data from 4081 subjects reported that acute coronary syndromes occurred at a mean age of 56.6±12 years in men and 61.8±10 years in women.[8] In developed countries the average age of presentation is higher and the US National Registry of Myocardial Infarction reported an average age of 66.0±0.05 years.[9]

DALYs and absolute burden of CHD: The GBD Studies reported the DALYs lost by CHD in India in years 1990 and 2000 (Table 3).[1,5] The World Bank has reported that in India DALYs are projected to more than double in the next 20 years.[10] In 1990, CHD was responsible for 5.6 million DALYs in men and 4.5 million in women. This is projected to increase serially as shown in Table 4.

The GBD 2000 analyzes the burden in WHO zones and not in individual countries.[5] India falls in the South-East Asian Region - D (SEAR-D) that also includes other countries with high childhood and high adult mortality -

Table 3. Major causes of DALYs in India

2000 Rank	Disease or injury	2000 Rank	Risk Factor
1	Perinatal conditions	1	Underweight
2	Lower respiratory infections	2	Unsafe sex
3	Diarrheal disease	3	Unsafe water, sanitation
4	Ischemic heart disease	4	Indoor smoke, solid fuels
5	Unipolar depression	5	Zinc deficiency
6	Unintentional injuries	6	Iron deficiency
7	Tuberculosis	7	Vitamin D deficiency
8	HIV/AIDS	8	Blood pressure
9	Maternal conditions	9	Tobacco
10	Stroke / cerebrovascular diseases	10	Cholesterol

DALY: disability-adjusted life years

Table 4. Estimated DALYs (in millions) lost due to cardiovascular diseases in India

	Men				Women			
	1990	2000	2010	2020	1990	2000	2010	2020
Cardiovascular diseases	12.25	15.94	20.91	27.79	11.20	12.56	14.02	15.74
Rheumatic heart disease	0.61	0.71	0.87	1.07	0.89	0.86	0.84	0.83
Coronary heart disease	5.60	7.67	10.46	14.36	4.53	5.55	6.55	7.66
Cerebrovascular disease	2.13	2.79	3.65	4.84	2.11	2.43	2.75	3.13

DALY: disability-adjusted life years

Bangladesh, Bhutan, North Korea, Maldives, Myanmar, and Nepal. Non-communicable conditions are estimated to cause a loss of 144.7 million DALYs in the year 2001 in this region. Cardiovascular diseases caused a loss of 35.4 million DALYs. CHD resulted in a loss of 17.99 million DALYs as compared to rheumatic heart disease with 2.34 million and cerebrovascular diseases with 7.98 million. India comprises of 81.2% of population in this region and therefore the DALYs lost in India due to CHD according to the World Health Report 2002 would be about 14.61 millions.[5]

For calculating the absolute number of patients with CHD in India, extrapolation from mortality figures available from the various GBD studies can be used. According to the GBD data published by the International Institute of Health,[10] in 1990 CHD caused 0.62 million deaths in men and 0.56 million deaths in women and in 2000 this increased to 0.85 million in men and 0.74 million in women, a sum of 1.59 million deaths. Clinical studies show that untreated CHD patients die at the rate of 7-8% per year.[11] Addition of appropriate medical therapies can reduce this death rate to 2% per year.[11]

If we consider an average mortality of 5-6% per year (OASIS-2 Study, unpublished) then the absolute number of CHD patients will be 20 times the persons dying from it. This would extrapolate to a burden of 31.8 million CHD patients in India. This compares with 16.5 million patients in USA and 2.7 million in the UK.[12] Further extrapolation of this data would suggest that there would be 1.27 million acute coronary events per year in India at the rate of 4% events per year in the total CHD population. Compare this with 0.63 million acute coronary events in the European union and 0.275 million heart attacks annually in UK.[12]

Epidemiological studies: In the absence of reliable mortality data, estimates of the burden of disease have mostly been based on morbidity indicators from population-based cross-sectional surveys. Morbidity surveys involve problems of sample design, sample size, standardization, and measurement errors. Indian CHD epidemiological studies have been reviewed earlier.[13] The prevalence of CHD in various studies is shown in Table 5.[14-31] In the urban population the prevalence increased from 1.05% (Agra, 1962)[14] and 1.04% (Delhi, 1962)[15] to 6.60% (Chandigarh, 1968).[16] In recent years a consistent high prevalence of CHD has been reported from Delhi (9.67%, 1990),[17] Jaipur (7.8%, 1995),[19] Chennai (9.0%, 2001),[21] Jaipur (8.1%, 2002),[22] and Panjim (13.2%, 2004).[23] In semi-urban populations of Haryana and Kerala the prevalence has increased from 3.6% (1975)[24] to 7.4% (1993).[25]

In rural populations, its prevalence increased from 2.06% (Haryana, 1974)[26] and 1.69% (Vidarbha, 1988)[27] to 2.71% (Haryana, 1989),[28] 3.09% (Punjab, 1994),[29] 3.46% (Rajasthan, 1994)[30] and 5.00% (Himachal, 2002).[31] Rural-urban comparison shows that while prevalence has increased two-fold in rural areas (2.06% in the 1970s to 4.14% in the 1990s) the prevalence in urban areas has increased nine-fold (1.04% in the early 1960s to

Table 5. CHD prevalence in India: epidemiological studies

Author(s)	Year	Age group	Place	Sample size (*n*)	CHD (%)
Urban Populations					
Mathur KS[14]	1960	30-70	Agra	1046	1.05±0.3
Padmavati S[15]	1962	30-70	Delhi	1642	1.04±0.3
Sarvotham & Berry[16]	1968	30-70	Chandigarh	2030	6.60±0.6
Chadha et al.[17]	1990	25-65	Delhi	13723	9.67+0.5
Sinha et al.[18]	1990	30-70	Varanasi	648	6.48±1.0
Gupta et al.[19]	1995	20-80	Jaipur	2212	7.59±0.6
Begom et al.[20]	1995	30-70	Thiruvananthapuram	506	12.65±1.0
Mohan et al.[21]	2001	20-70	Chennai	1150	11.00±1.0
Gupta et al.[22]	2002	20-80	Jaipur	1123	8.12±0.6
Pinto et al.[23]	2004	35-64	Panjim	371	13.21±1.1
Semi-Urban Populations					
Gupta et al.[24]	1975	30-70	Rohtak	1407	3.63±0.5
Kutty et al.[25]	1993	25-65	Kerala	1130	7.43±0.8
Rural Populations					
Dewan et al.[26]	1974	30-70	Haryana	1506	2.06±0.4
Jajoo et al.[27]	1988	30-70	Vidarbha	2433	1.69±0.3
Chadha et al.[28]	1989	35-65	Haryana	1732	2.71±0.3
Wander et al.[29]	1994	30-70	Punjab	1100	3.09±0.5
Gupta et al.[30]	1994	20-80	Rajasthan	3148	3.53±0.3
Gupta et al.[31]	2002	20-80	Himachal	1160	5.00±0.5

CHD: coronary heart disease

9.45% in the mid 1990s).[13] There is evidence of CHD growth from rural to semi-urban and urban areas with the highest prevalence reported from metropolitan Delhi and Chennai. This clearly shows the importance of socio-economic factors associated with CHD epidemic in India.

Analyses of prevalence studies in various decades in India provide significant information regarding the absolute number of CHD cases. Decadal variations indicate that the prevalence has increased in urban areas from about 2% in 1960 to 6.5% in 1970, 7.0% in 1980, 9.7% in 1990 and 10.5% in 2000 while in rural areas it increased from 2% in 1970 to 2.5% in 1980, 4% in 1990 and 4.5% in 2000. In terms of absolute numbers there is a very steep increase in CHD cases in both urban and rural areas. In urban populations, the numbers have increased from 0.5 million in 1960 to 4.5 million in 1970, 5.6 million in 1980, 9.7 million in 1990 and 14.1 million in the year 2000. In rural populations the numbers have increased from 4.1 million in 1970 to 6.4 million in 1980, 11.8 million in 1990 and 15.7 million in 2000. Thus epidemiological studies show that there are at present 29.8 million CHD patients in this country. This number is similar to that derived from GBD studies. As epidemiological studies exclude many patients with silent and asymptomatic CHD, the actual numbers may be much greater.

Burden on Healthcare System

Pattern of various cardiovascular diseases in hospitalized patients has been reported by many authors. From 1940s to 1960s CHD formed 5-20% of all heart disease admissions in big hospitals in Delhi, Mumbai and some other cities. Wasir et al.[6] reported an increasing trend and significant burden of CHD cases in cardiology outpatient department and medical admissions to a Delhi-based tertiary care hospital. During 1966-70, CHD was present in 18.4% of all heart diseases cases seen at All India Institute of Medical Sciences, Delhi. This changed to 16.5% in 1971-75, 15.2% in 1976-80 and 19.7% in 1981-85. In the same years, proportion of CHD cases in hospital admissions increased from 20.8% to 21.0%, 20.3% and 23.9%, respectively. Pooled data from the states of Assam, Madhya Pradesh, Punjab, Kerala and Karnataka reveal that proportion of all cardiac admissions to various government hospitals, and incidence of CHD increased from 14% in 1970 to 19% in 1985. At Vellore (South India), admissions due to CHD in a non-government hospital steadily increased from 4% in 1960 to 33% in 1989 indicating increasing burden.[32]

In a single medical college hospital in Kerala there has been a more than 20-fold increase in admissions for acute MI from 1966 to 1988. Number of acute MI cases was 220/22387 in 1967, which increased to 440/23410 in 1970, 1500/33134 in 1975, 4901/43937 in 1982 and 5284/43897 in 1987.[33] In Orissa, proportion of admissions due to CHD increased from 19.9% in 1981-1990 to 28.0% in 1991-2000.[34] There are substantial regional variations in cardiovascular mortality in different parts of the country[35] but all these studies report an increasing burden from CHD on healthcare system, specially urban hospitals, in all regions of India.

Serial studies from rural areas of India have not been reported but one from Rajasthan reported that CHD contributes to 8% of patients attending a general physician's clinic.[7] Of a total of 1362 medical cases seen at a referral medical clinic there were 110 CHD cases. In terms of absolute numbers this would convert into millions of patients with CHD seen all over India in rural clinics, urban clinics and hospitals on a daily basis. The burden on population and health care system is indeed very large.

Economic and Social Burden

From the year 1995 to 2000, India has been spending about 5% of its gross domestic product (GDP) on health. Of this, direct private expenditure on health is about 82-83% and the subsidized general government expenditure is 17-18%.[5] Therefore, any disease that is as widespread as CHD would entail substantial economic burden on the population. Although no formal calculations exist of economic burden of CHD in India we have tried an evidence-based calculation that has been reported elsewhere.[36] These data are to be interpreted cautiously and the confidence intervals of the numbers are wide. It is suggested that more in-depth economic analyses be performed to exactly assess the burden of CHD on the government and private exchequer.

Considering the data in the GBD mortality statistics the number of patients with CHD in the country is about 32 million. Of this about a fourth would be aware of their disease status and therefore at any given point of time about 7- 8 million CHD patients would be under some form of medical care. For all these patients, a minimum basic prescription following the 'polypill approach[11,37] should include a beta-blocker, angiotensin-converting enzyme (ACE) inhibitor, statin, aspirin, vitamin and occasionally nitrate tablets. Many patients are on more complex pharmacotherapy and the compliance to therapy in CHD patients appears reasonable. Yusuf et al.[38] reported that in India 92% of patients with ST-segment elevation MI receive thrombolysis. A high use of other drugs was also reported:

aspirin 98%, beta-blockers 70%, ACE inhibitors 74%, and statins 62% showing a good compliance.

The average cost of generic forms of these drugs in India is about Rs. 15 per day, that amounts to Rs. 5500 per year.[36] If we consider that 8 million patients are on this form of therapy, the total burden in terms of cost of such therapy to the patient population would be Rs. 44 billion per year. Add a similar amount for ancillary services such as costs of investigations and hospital visits and add an amount of Rs. 44 billion. We have determined the cost of a single acute coronary event to the population as Rs. 5000 in terms of costs of medicines to the patient. For 1.27 million acute coronary events, the cost would be Rs. 6.5 billion. It has been reported that about 20,000 coronary bypass surgeries and 30,000 coronary angioplasty procedures are performed in the country every year.[39] At the minimum cost of Rs. 0.1 million per procedure (many hospitals charge the patient more than 5-times this amount)— this would add burden of another Rs. 5 billion to the patient. All this adds up to Rs. 99.5 billion (~100 billion) of burden in terms of direct cost of therapy to the patient (Table 6). The National Family Health Surveys report that direct medicine costs are about 45-50% of medical treatment costs in India.[40] Thus, a similar amount (Rs. 100 billion) could be spent by the healthcare system in caring for these patients in outpatient clinics, hospitals and other institutions.

Therefore, at an underestimate the economic burden of CHD in India is about Rs. 200 billion. The total economy of India annually (GDP) is about Rs. 25000 billion. Thus the burden of CHD in India is about 0.8% of the GDP. Economists would think that CHD is contributing this much amount of money to the GDP but we conclude that this is a waste as almost 80% of the heart attacks can be prevented by appropriate management and prevention strategies.[37,41] Cost calculations in terms of loss of man-hours and wages has not been performed in this study as formal economic cost-calculation studies in India are not available. WHO recommends that for estimating costs, analysts should follow the ingredients approach and collect and report information on the quantities and prices of the resources used in addition to total expenditures.[42] A complex model for cost of providing health interventions has been suggested and as macroeconomic inputs are not available from India we have not performed a formal analysis. It has been reported that population-based as well as high-risk based prevention approaches are cost-effective and should be implemented.[43]

Social burden of CHD is more difficult to gauge. In Indians, typically acute coronary events occur at least 10 years earlier than in Caucasian and Latin American countries[44] and 5 years earlier than in China.[38] Numerous reports and anthropological statements have shown that premature CHD causes significant social burden in terms of loss of support for young children, women and the elderly. Exact cost to a family of such a catastrophe is difficult to calculate. The DALY calculations include burden of premature morbidity on the individual and clearly shows that CHD contributes a large burden in India (Table 4). Formal studies that measure individual and societal burden of CHD on social structures are needed.

Table 6. Direct annual economic burden of CHD in India

Direct costs to population for CHD treatment	
Known CHD	≅ 8.0 million
Pharmacotherapy (polypill approach)[37]	@ Rs. 5500/year
Direct costs to patients	Rs. 44 billion
For ancillary medical services	Rs. 44 billion
Hospitalization procedures and costs to patients	
Acute coronary syndromes:	
1 million events/year @ Rs 5000/event	Rs. 6.5 billion
PTCA, CABG, 50,000/yr: @ Rs 1 lakh	Rs. 5.0 billion
Total costs:	Rs. 100 billion (range 40-160)
Ancillary costs (staff, clinics, hospitalization)	Rs. 100 billion
Grand total per year	Rs. 200 billion (range 80-320)
Others and indirect costs	Undetermined

Government expenditure: 17-18% (World Health Report, 2002)[5]

CHD: coronary heart disease; PTCA: percutaneous transluminal coronary angioplasty; CABG: coronary artery bypass grafting
(Adapted from Reference 36)

Prevention of Coronary Heart Disease

World Health Organization estimates that deaths attributable to cardiovascular diseases have increased in parallel with the expanding population in India. Cardiovascular diseases now account for a large proportion of DALYs lost in India as well as other developing countries. The CHD rate in India is expected to rise in parallel with the increase in life expectancy secondary to increases in per capita income and declining infant mortality rate (IMR). The average life expectancy has increased from 41 years in 1951 to 61 years in 1991 and is projected to reach 72 years by 2030, which could lead to large increases in CHD prevalence. In contrast to UK and Canada, although the CHD mortality of Indian populations remains high, a decline in CHD has been observed over the past 10 years. These data indicate that the high rates of CHD with economic changes are reversible and perhaps even

avoidable. Therefore, lessons learnt from migrant Indians may be helpful in developing prevention strategies for the Indian subcontinent.[45]

The incidence of CHD in any population is associated with positive shifts (rightward skew) in distribution of its biological characteristics - serum lipids, blood pressure, blood glucose, insulin, thrombogenic factors, and others.[43] Population-wide negative shifts are possible by suitable interventions. The epidemic of CHD in India warrants an urgent action in terms of expanding public education, control of primordial and primary risk factors by population-based and high-risk interventions and other effective preventive strategies.

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Indian Heart J 2005; 57: 639–643 **Review Article**

Management of Hypertension: Diagnosis and Lifestyle Modification

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Cardiovascular diseases (CVD) including stroke constitute the major cause of death and disability.[1] Every year, worldwide more than 15 million deaths occur due to CVD and about 9 million deaths are accounted for in developing countries. In India, CVD-related deaths rose from 1.17 million in 1990 to 1.59 million in 2000 and are expected to rise to 2.03 million in 2010[2] and significant numbers of these are premature deaths (people below the age of 55). In most developed countries CVD death rates are declining while in the developing countries, including the most populous countries such as India and China, CVD mortality and morbidity are on the rise.[1]

High blood pressure (HBP) or hypertension is the primary risk factor for CVD. Blood pressure is a continuum and the definition of HBP is an arbitrary cut off based on population epidemiological data. Conventionally an individual with systolic blood pressure (SBP) of ≥ 140 mmHg and a diastolic blood pressure (DBP) of ≥ 90 mmHg (≥ 140/90 mmHg) is considered to be hypertensive.

Screening

Measurement of blood pressure, although considered to be a simple procedure, is an important step in identifying a person to be either normotensive or hypertensive. Studies have shown that in most cases, specially in the physician's clinic, the blood pressure measurements are often not done right.[3] Poor measurement leads to either under-estimation or over-estimation resulting in absence of treatment or unnecessary treatment of individuals.[4] The Canadian guidelines on blood pressure measurement[5] outline the proper procedure.

In the recent years, use of mercury manometers has been recommended to be banned because of mercury poisoning. The development of accurate automated blood pressure measuring devices has helped to fill this void. The Canadian Hypertension Society recommends automated blood pressure measuring devices which meet the standards of the Working Group on Blood Pressure Monitoring of the European Society of Hypertension International Protocol for validation of blood pressure measuring devices in adults[6] or British Hypertension Society[7].

It is also recognized that there is transient increase in blood pressure due to anxiety as well as in the presence of a physician (known as white coat hypertension).[8] Therefore, it is recommended that the measurements are taken (i) after a minimum of 5 min rest[5]; (ii) after discarding the first reading and taking the average of next two readings; and (iii) by a nurse or a non-physician to avoid white coat hypertension. Few advanced automated blood pressure measuring devices[9] incorporate all the above recommendations. These instrument can be connected to patient in a quiet room in the absence of a physician or a healthcare provider. It takes a maximum of six readings, discards the first reading, and finds the average of remaining five readings. The readings are accurate and reproducible.[10]

Diagnosis

In light of the growing epidemic of CVD in India and in most parts of the world, number of world bodies including World Health Organisation (WHO) recommend that opportunistic screening of blood pressure is done at every visit to the physician's clinic.[11] This would allow early diagnosis of elevated blood pressure, and to take action to prevent the onset of hypertension and associated CVD.

Diagnosis of hypertension should not be made on one single measurement in a physician's clinic. If the blood pressure is elevated, the individual must be seen again within a week to reconfirm the elevated blood pressure.[12] Fig. 1 shows the algorithm and action to be followed[13] for diagnosis and confirmation of high blood pressure. Hypertensive urgencies and emergencies are indicated in Table 1.

Management

Management of hypertension should be based on global risk assessment considering other concomitant cardio-

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Table 1. Hypertensive urgencies and emergencies*

Asymptomatic diastolic BP > 130 mmHg or systolic BP > 200 mmHg
Accelerated malignant hypertension with papiledema
Cerebrovascular:
Hypertensive encephalopathy
Atheroembolic brain infarction with severe hypertension
Intracerebral hemorrhage
Subarachnoid hemorrhage
Cardiac:
Acute aortic dissection
Acute refractory left ventricular failure
Acute myocardial ischemia or infarction with persistent ischemic pain
Post-coronary bypass surgery
Renal:
Acute glomerulonephritis
Renal crisis from collagen vascular diseases
Severe hypertension following renal translantation
Excessive circulating catecholamines:
Pheochromocytoma
Tyramine-containing foods or drugs or drug interactions with monoamine oxidase inhibitors
Cocaine and sympathomimetic drug use
Rebound hypertension after cessation of some antihypertensive drugs (e.g., clonidine or guanabenz)
Toxemia of pregnancy: eclampsia
Surgical:
Severe hypertension in patients requiring emergency surgery
Severe post-operative hypertension
Post-operative bleeding from vascular suture lines
Following severe body burns
Severe epistaxis

*Adopted from Ref. 51

vascular risk factors. Global risk assessment is an important tool to assist physicians and other health care providers to identify hypertensive individuals who are most likely to benefit from management including pharmacotherapy.[13] Well established models are Framingham,[14] CV life expectancy[15] and SCORE.[16] The Canadian Heart Education Program (CHEP) recommendations on routine and optional laboratory tests for the investigation of patients with hypertension are given in Table 2.[13]

Table 2. Routine and optional laboratory tests for the investigation

For patients with hypertension:
urinalysis
complete blood cell count
blood chemistry (potassium, sodium, and creatinine)
fasting glucose
fasting total cholesterol (TC) and high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, triglycerides
standard 12-lead electrocardiogram (ECG)
For those with diabetes or kidney diseases
Assess urinary protein excretion, since lower blood pressure targets are appropriate if proteinuria is present.
During the maintenance phase of hypertension management
Tests (including electrolytes, creatinine, glucose, and fasting lipids) should be repeated with a frequency reflecting the clinical situation.

Lifestytle modifications: Increasing evidence suggests that lifestyle modification, previously termed as 'non-pharmacological therapy', is beneficial for both non-hypertensive and hypertensive individuals.[17] When applied on a population-wide basis, lifestyle modification has the potential for major benefit beyond lowering blood pressure.

In hypertensive patients, lifestyle modification should constitute initial treatment before the commencement of pharmacotherapy and serve as an adjunct to medication in patients already on drug therapy. In highly motivated drug-treated patients who are successful, and maintain lifestyle changes, these therapies could facilitate drug step-down and possibly, drug withdrawal. For patients with other cardiovascular risk factors such a hyperlipidemia, obesity and diabetes, lifestyle measures are even more important.[18]

Physical exercise: (a) For non-hypertensive individuals, to reduce the possibility of becoming hypertensive, prescribe the accumulation of 30-45 min of moderate intensity dynamic exercise (such as walking, jogging, cycling or swimming) 3 days to 5 days a week.[19,20] Higher intensities of exercise are no more effective.[21] (b) For hypertensive patients, to reduce blood pressure, prescribe the accumulation of 30-60 min of moderate intensity dynamic exercise (for example walking, jogging, cycling or swimming) on most days (4 days) of week.[22-24] Higher intensities of exercise are no more effective.[21]

Weight reduction: (a) Height and weight should be measured and body mass index (BMI) (i.e. weight in kg/height in meters squared) calculated for all adults. (b) Maintenance of an ideal body weight (BMI 18.5-24.9 kg/m^2) is recommended for non-hypertensive individuals to prevent hypertension. (c) Maintenance of a healthy BMI (18.5-24.9 kg/m^2) is recommended for hypertensive patients to reduce blood pressure. All overweight (BMI > 25 kg/m^2) hypertensive individuals should be advised to lose weight. (d) Waist circumference may more accurately measure visceral adipose tissue stores, and predicts cardiovascular risk factors, even within normal ranges of BMI.[25] Therefore, in addition to calculating BMI, measuring abdominal girth is recommended, and a waist circumference of < 88 cm in women and 102 cm in men should be maintained.[26,27] (e) Weight loss strategies should use a multidisciplinary approach and include dietary education, increased physical activity and behavioral modifications.[28,29]

Alcohol consumption: Healthy adults – both normotensive and hypertensive – should limit alcohol consumption to two drinks or fewer per day, and consumption should not exceed 14 standard drinks per

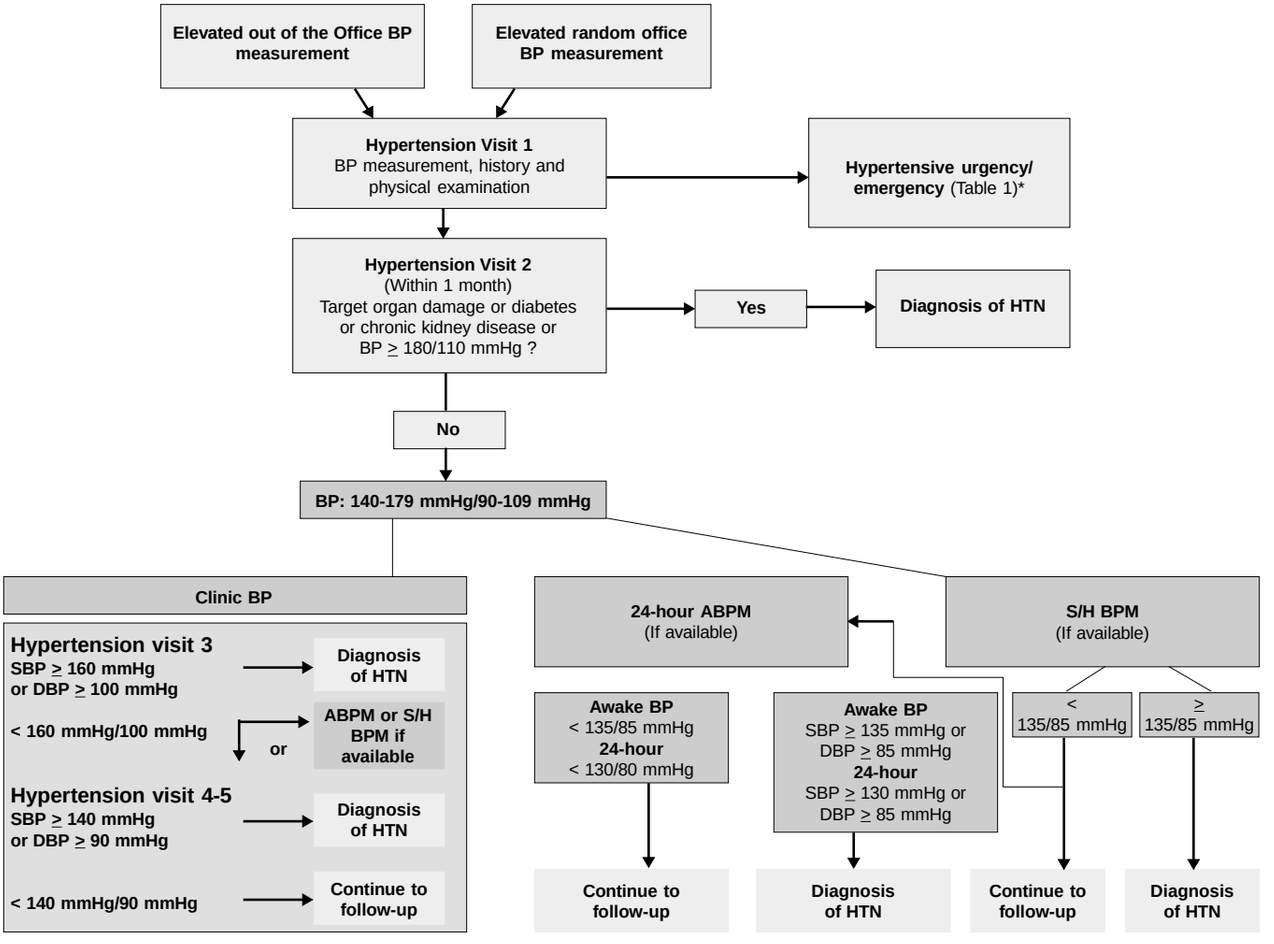

Fig. 1. *Diagnostic algorithm for high blood pressure including Office, ABPM and S/H blood pressure measurement.*
BP: blood pressure; HTN: hypertension; SBP: systolic blood pressure; DBP: diastolic blood pressure; BPM: blood pressure measurement; ABPM: ambulatory blood pressure measurement; S/H: self/home

week.[30-32] One drink is considered 13.6 gm or 17.2 ml of ethanol, or approximately 1.5 oz of 80 proof (40%) spirits, or 12 oz of 5% beer, or 5 oz of 12% wine. Binge drinking must be avoided.[33]

Dietary recommendations: It is recommended that hypertensive patients consume a diet that emphasizes fruits, vegetables and low fat dairy products and reduced fat and cholesterol.[34,35]

Salt intake: (a) In normotensive individuals at increased risk of developing hypertension who are considered salt-sensitive such as those of African descent, people > 45 years of age, and individuals with impaired renal function or diabetes, salt intake should be restricted to < 100 mmol/day.[36-38] (b) In hypertensive patients, dietary sodium intake should be limited to 65-100 mmol/day.[39,40]

Potassium, calcium and magnesium: (a) Hypertensive patients or normotensive individuals at increased risk of developing hypertension who are considered salt-sensitive such as those of African descent, people > 45 years of age, and individuals with impaired renal function or diabetes, should ensure an adequate intake of potassium, calcium and magnesium by consuming a diet which is rich in these micronutrients.[41] (b) Supplementation of potassium, calcium and magnesium is not recommended for the prevention and treatment of hypertension.[41] (c) Individuals who require a diet rich in these cations, but who cannot tolerate or afford this diet, should supplement their diet with potassium to obtain a daily intake of 80 mmol/day.[42]

Dietary antioxidants and fish oil supplements: Evidence from epidemiological studies suggest that

Mediterranean-style diet or dietary supplementation with omega-3 polyunsaturated fatty acids can reduce blood pressure.[43-45] Due to lack of sufficient evidence from large number of patient population, no recommendations are given at present.

Stress management: In hypertensive patients in whom stress may be implicated in contributing to bloods pressure elevation, stress management should be considered as an intervention.[46] Individualized cognitive behavioral interventions are more likely to be effective when relaxation techniques are used.[47]

Conclusions

Proper diagnosis with accurate measuring devices is an important first step in the management of hypertension.

Results from long-term follow-up studies demonstrate that many patients fail to sustain lifestyle changes.[48] Nevertheless, lifestyle modifications must be pursued as the first-line in the management of hypertension since such therapies are safe, inexpensive and, when combined with pharmacotheray, may result in better blood pressure control and improved quality of life.[49] Table 3 summarizes the recommendations on lifestyle management of hypertension. Experience shows that brief physician advice doubles the chances of a patient adopting many healthy lifestyles.

Table 3. Lifestyle therapies in hypertensive adults: Summary

Intervention	Target
Sodium restriction	65-100 mmol/day
Weight loss	BMI < 25 kg/m^2
Waist circumference	< 102 cm for men; < 88 cm for women
Alcohol restriction	≤ 2 drinks/day
Exercise	At least 4 times/week
Dietary patterns	DASH diet
Smoking cessation	Smoke-free environment

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Although modification of a single lifestyle factor may only have a modest blood pressure lowering effect in an individual patient, in the general population, it may lead to profound reduction in CVD on a population-wide basis.[50] Thus lifestyle modification for the treatment of hypertension is an important intervention both from a public health perspective and in the routine management of the individual hypertensive patient.

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The contents of the manuscript are largely based on the Canadian Hypertension Education Program recommendations. This program systematically reviews hypertension literature and annually updates treatment recommendations. The 2005 recommendations (www.hypertension.ca) were used for this manuscript.

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Management of Hypertension: Pharmacotherapy

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Hypertension is a major public health issue in all countries of the world. Fortunately there are effective measures to prevent and treat hypertension.

Pharmacotherapy is effective in reducing cardiovascular risk in those with established hypertension. When considering pharmacotherapy for hypertension it is important to first assess the overall risk of cardiovascular disease in the patients as most will have other risks that also require management. Except for few patients with low risk hypertension, most with sustained systolic blood pressure above 140 mmHg systolic and 90 mmHg diastolic will benefit from pharmacotherapy to reduce the blood pressure below these levels. For those with diabetes and renal disease, the threshold for therapy is 130/80 mmHg and target is below these values. This article outlines the way to individualize therapy based on current evidence. Many patients require combinations of lifestyles and two or more drugs to achieve blood pressure targets. Steps to improve the compliance of the patient for taking the medication are also discussed.

Pharmacotherapic Measures

Hypertension is a leading cause of death and disability around the world.[1,2] The prevalence of hypertension and subsequently cardiovascular disease is likely to increase.[3] The burden of cardiovascular disease can be reduced by preventing hypertension and by identifying those with hypertension and controlling their blood pressure.[1] The purpose of this article is to (i) assess the cardiovascular risk of all hypertensive patients in order to intensify therapy in those at highest risk and optimize risk reduction strategies, (ii) individualize drug therapy based on the patient's presentation, (iii) treat patients to therapeutic targets using combination of effective medications, and (iv) help patients adhere to the drug therapy.

Risk assessment: Patients with the same level of blood pressure can have over a 10-fold difference in their risk of a cardiovascular event.[4] Cardiovascular risk is dependent on the level of blood pressure with risk increasing at systolic blood pressure > 115 mmHg and diastolic blood pressure > 70 mmHg.[5] However, multiple factors contribute to a person's cardiovascular risk (Table 1). Many of the cardiovascular risks are amenable to therapy. A multi-pronged approach could reduce overall risk in a hypertensive patient by 80% and blood pressure risk by about 25%.[6] There are multiple methods of assessing cardiovascular risk; however, the routine use of a risk table has been shown to reduce systolic blood pressure.[7] Consideration should be given to lipid lowering therapy and aspirin in patients at high cardiovascular risk.[8,9]

Thresholds for Therapy

All patients are candidates for lifestyle modification regardless of their blood pressure. Several trials have shown that certain groups of high-risk patients benefit from blood pressure reduction by pharmacotherapy regardless of their blood pressure.[10-12] This includes patients with overt atherosclerotic vascular disease [e.g. past myocardial infarction (MI) or ischemic heart disease, stoke or transient ischemic attack (TIA)], congestive heart failure and those with diabetes plus additional cardiovascular risks factors. For other patients, thresholds for initiation of anti-hypertensive therapy are as follows.[8] In patients without

Table 1. Major cardiovascular risk factors

Male sex
Age 55 years or older
Smoker
Obese
Inappropriate diet*
Sedentary lifestyle
Diabetes mellitus or glucose intolerance
Dyslipidemia
Microalbuminuria or proteinuria
Left ventricular hypertrophy
Overt atherosclerotic vascular disease
Family history of premature cardiovascular disease

*A diet high in saturated fats and salt and low in fresh fruit and vegetables

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any additional cardiovascular risks, drug therapy should be initiated if the blood pressure is sustained above 160 mmHg systolic or 100 mmHg diastolic (very few hypertensive patients have hypertension as the only risk factor). For patients with additional risk factors treatment can be initiated for sustained blood pressure >140 mmHg systolic or for diastolic blood pressure > 90 mmHg. For patients with diabetes or renal disease, treatment should be initiated if the blood pressure is sustained at > 130 mmHg systolic or 80 mmHg diastolic. The thresholds for systolic blood pressure in patients with risk factors or with diabetes or renal disease are based largely on expert opinion while the other thresholds are based on entry criteria to large randomized controlled trials.

Blood pressure targets during pharmacotherapy: In most patients blood pressure should be lowered to <140 mmHg systolic and < 90 mmHg diastolic.[8] For patients with renal disease or with diabetes, the blood pressure target is <130 mmHg systolic and < 80 mmHg diastolic. If patients with renal disease have > 1 gm/24 hours proteinuria, then the target is < 125 mmHg systolic and <75 mmHg diastolic.

Initial pharmacotherapy of uncomplicated hypertension: The reduction in cardiovascular events in uncomplicated hypertension depends on degree of blood pressure lowering and not on specific blood pressure medication class used to lower blood pressure.[8,13-15] Initial therapy should be selected from classes of drugs proven to reduce cardiovascular events and include low-dose thiazide type diuretics, beta-blockers in patients under age 60, angiotensin-converting enzyme (ACE) inhibitors, long acting calcium channel blockers and angiotensin receptor blockers (ARBs). Beta-blockers are less effective in the elderly and should not be selected as initial therapy in those over age 60.[8,16-18] Alpha-blockers have not been proven to reduce cardiovascular events in hypertension and should not be selected as initial therapy.[8,19]

Patients with compelling indications for specific pharmacotherapy: Table 2 outlines initial therapeutic options for patients with specific indications for pharmacotherapy. Dyslipidemia and left ventricular hypertrophy do not modify the recommendations for initial therapy.[8]

Patients with diabetes: Patients with diabetes are generally at very high cardiovascular risk.[20] There are substantial mortality benefits from more intensive lowering of blood pressure in patients with diabetes. The cost of intensive treatment is less than the cost of treating the complications which the treatment would have prevented.[20,21] The threshold for initiation of therapy is 130/80 mmHg and the therapeutic target is <130/80 mmHg.[8] First line therapy is with an ACE inhibitor or an ARB. If there is no proteinuria, a thiazide type diuretic is an alternative first line therapy. Most patients, however, will require both a diuretic and an ACE inhibitor or an ARB and many will also require the addition of a calcium channel blocker or beta-blocker. To reduce proteinuria, many will combine an ACE inhibitor and an ARB.[8]

Combining Antihypertensive Medications

It is generally more effective to combine two drugs at low to moderate dose than to maximize the dose of a single drug. Most patients with hypertension will require two or more antihypertensive drugs to achieve the target blood pressures indicated[9,20,22] and under most circumstances, a diuretic should be one of the drugs. To optimally lower blood pressure, calcium channel blockers and diuretics should be either combined with an ACE inhibitor, ARB or beta-blocker in two-drug therapy. Other two drug combinations have either been demonstrated to have less than additive blood pressure lowering or there is controversy regarding the additive hypotensive effects of combination.

Adherence to Drug Therapy

Many patients with hypertension either do not start their prescribed therapy or stop the therapy after it is started. There are many steps that can improve the chances that the patients will continue on their therapy.[8] Patients and their families require both written information on hypertension as well as verbal explanations about the risks of hypertension, benefits of therapy and need to continue their medication, once the blood pressure is reduced. The patients need to know about common and serious side effects that could occur with the prescribed medication. Simplified medication regimes of long acting drugs that can be taken once daily make it easier for patients to adhere to therapy. It is also critical to ensure that the drugs prescribed are affordable to the patient, otherwise the prescription may not be followed. In patients who have difficulty in adhering to prescription, self-monitoring of blood pressure and self pill counts can help. If the patient is taking several medications a pill dispenser (dosette) is also useful.

Resistant hypertension: Many, if not most, patients will require at least two drugs to lower blood pressure to current targets.[9,20,22] If patients are not controlled on three or more medications they are called resistant. In this situation white coat hypertension or white coat effect is more common, and should be tested by self measurement of blood pressure or

by ambulatory monitoring. Lack of adherence to therapy is another common reason for resistant hypertension. This should be assessed by non-confrontational questioning, pill counts, examining pills bottle for refill dates and looking for physiological makers of therapy (e.g. a slow pulse on beta-blocker, an increase in plasma bicarbonate on diuretic), failure to attend clinics and lack of blood pressure lowering when drugs are prescribed at therapeutic doses. Secondary hypertension is also more common in resistant hypertension and testing for hyperaldosteronism, pheochromocytoma, renal and renal vascular hypertension should be considered.[8] Resistant hypertension is more common in obesity and can be associated with sleep apnea. In many cases resistant hypertension may also be caused by faulty lifestyle (e.g. weight gain, reduced physical activity, increased salt intake, alcoholism). Drugs that increase blood pressure [e.g. non-steroidal anti-inflammatory drug (NSAIDs)] or drugs like phenytoin or

Table 2. Considerations in the individualization of antihypertensive therapy

	Initial therapy	Second-line therapy	Notes and/or cautions
Hypertension without compelling indications for other medications	Thiazide diuretics, beta-blockers (for patients <60 years), ACE inhibitors (in non-blacks), ARBs, or long-acting CCBs (consider ASA and/or statins in selected patients)	Combinations of first-line drugs	Alpha-blockers are not recommended as initial monotherapy. Beta-blockers are not recommended as initial monotherapy in those > 60 years of age. Hypokalemia should be avoided in those who are prescribed diuretics. ACE inhibitors are not recommended as initial monotherapy in blacks.
Isolated systolic hypertension without other compelling indications	Thiazide diuretics, ARBs, or long-acting dihydropyridine CCBs	Combinations of first-line drugs	Hypokalemia should be avoided in people who are prescribed diuretics
Diabetes mellitus with nephropathy	ACE inhibitors or ARBs	Addition of one or more of thiazide diuretics, cardioselective beta-blockers, long-acting CCBs or use of an ARB/ACE inhibitor combination	—
Diabetes mellitus without nephropathy	ACE inhibitors, ARBs, or thiazide diuretics	Combination of first-line drugs or addition of cardioselective beta-blockers and/or long-acting CCBs	—
Angina	Beta-blockers (strongly consider adding ACE inhibitors)	Long-acting CCBs	Avoid short-acting nifedipine
Prior myocardial infarction	Beta-blockers and ACE inhibitors	Combinations of additional agents	—
Heart failure	ACE inhibitors (ARBs if ACE inhibitor intolerant), beta-blockers, and spironolactone in selected patients	ARBs or hydralazine/ isosorbide dinitrate; thiazide or loop diuretics as additive therapy	Avoid non-dihydropyridine CCBs
Past cerebrovascular accident or TIA	ACE inhibitor/diuretic combinations		Blood pressure reduction reduces recurrent cerebrovascular events
Chronic kidney disease	ACE inhibitors (diuretics as additive therapy)	Combinations of additional agents (ARBs if ACE inhibitor intolerant)	Avoid ACE inhibitors and ARBs if bilateral renal artery stenosis
Left ventricular hypertrophy	ACE inhibitors, ARBs, CCBs, thiazide diuretics (beta-blockers for patients <60 years)	—	Avoid hydralazine and minoxidil
Peripheral arterial disease	Does not affect treatment recommendations	—	Avoid beta-blockers with severe disease
Dyslipidemia	Does not affect treatment recommendations	—	—

*With permission from the Canadian Hypertension Education Program

ACE: angiotensin-converting enzyme; ARB: angiotensin-receptor blockers; CCB: calcium channel blockers; ASA: aspirin; TIA: transient ischemic attack

herbal preparations (i.e. St Johns' Wort) that induce the metabolism, or antihypertensive drugs can also cause resistant hypertension.

To treat resistant hypertension the cause should always be identified if possible. The therapeutic regime should include, if possible a diuretic, an ARB or ACE inhibitor, a vasodilator (long acting calcium channel blocker) and a beta-blocker. Many patients will respond to a high dose of diuretics and this should be instituted as a therapeutic trial. Some patients will respond to spironolactone even if they do not have hyperaldosteronism. In resistant hypertension, moderate to high doses of drugs are used but the attempt is always to use long acting once daily medication in a simplified regime.

Conclusions

Antihypertensive pharmacotherapy is an effective measure to reduce cardiovascular morbidity and mortality. In those under age 60 the benefits include a modest blood pressure reduction in stroke of about 40% and coronary artery disease of about 15%. For those over age 60, the proven benefits include a reduction in mortality by 20%. Greater benefits accrue with greater reduction in blood pressure. For most patients the greatest benefits are related more to blood pressure lowering than to the specific drugs used. Individually tailored antihypertensive regimes will allow blood pressure targets to be achieved in a large proportion of hypertensive patients.

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Original Article

Comparative Efficacy of Once daily Parnaparin and Unfractionated Heparin in Unstable Angina Pectoris : PRIME CARE Study

PRIME CARE Study Investigators Group

Background: This study sought to compare the efficacy of low molecular weight heparin, parnaparin and unfractionated heparin in Indian patients presenting with unstable angina pectoris.

Methods and Results: In this randomized, prospective and multicentre trial 897 adult patients of both sexes suffering from unstable angina were included. All patients also received oral aspirin and adequate anti-anginal treatment as per their individual needs. Patients in unfractionated heparin group received unfractionated heparin as an intravenous bolus of 5000 IU followed by an intravenous infusion of 800 to 1000 IU/hour for 48 hours, followed by 5000 IU subcutaneously every 6 hours for 5 days. The patients in the other group were treated with parnaparin sodium 6400 IU subcutaneously once daily for 7 days. In the unfractionated heparin group there were 446 patients (310 males, 136 females) with a mean age of 55.9 $\pm$ 12.27 years and in parnaparin group 451 patients (312 males, 139 females) with a mean age of 57.6 $\pm$ 11.19 years. Both the groups were similar with respect to age and sex (p=0.89 and 0.068, respectively). The associated cardiovascular risk factors such as diabetes, hypertension, dyslipidemia, previous myocardial infarction and previous coronary artery bypass grafting/percutaneous transluminal coronary angioplasty were similar in both the groups. At the end of 7 days, the primary end points (death, myocardial infarction, or need for myocardial revascularization) were reported in 33 (7.32%) patients in parnaparin group and 51 (11.43%) patients in unfractionated heparin group. This difference was statistically significant. At the end of 30 days, data from 330 patients from parnaparin group and 334 patients from unfractionated heparin group was available for analysis. The cumulative event rate of primary end points at the end of 30 days was reported in 40 (12.12%) patients in parnaparin group and in 73 (21.86%) patients in unfractionated heparin group. This difference was statistically significant. Two episodes of major bleeding each were reported in both the groups. Minor bleeding was reported by12 (2.66%) patients in parnaparin group and by 115 (25.8%) patients in unfractionated heparin group. This difference was statistically significant.

Conclusions: Addition of parnaparin to the standard treatment of unstable angina significantly reduced the incidence of combined triple end points of death, myocardial infarction and need for revascularization when compared to unfractionated heparin. This benefit was observed at 7 days as well as at 30 days of follow-up. The incidence of minor bleeding was significantly less in patients treated with parnaparin. Thus, once daily administration of parnaparin 6400 IU as a fixed dose is a safe and effective alternative to unfractionated heparin in the treatment of unstable angina. **(Indian Heart J 2005; 57: 648–654)**

Key Words: Unstable angina, Unfractionated heparin, Low molecular weight heparin

Ischemic heart disease (IHD) represents a spectrum with acute transmural infarction at one end and occasional silent ischemic episodes at the other. Clinical conditions such as chronic stable angina, unstable angina and acute subendocardial infarction are interspersed between the ends of the spectrum of IHD. Unstable angina and acute myocardial infarction (MI) are closely related with respect to their etiology and pathogenesis. While patients with unstable angina are often difficult to be managed, it is generally recognised that most do not culminate to MI over short-term.[1]

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In addition to platelet aggregation, active thrombotic process has also been shown to occur in patients of unstable angina.[2,3] The association of rest pain, intracoronary thrombus and adverse outcome have also been reported.[4,5] Autopsy studies have confirmed an ongoing thrombotic process in a major coronary artery during the period of unstable angina.[6] If left untreated, this process can result in a total occlusion of the coronary vessel leading to acute MI and/or sudden death.

It is recognised that a subset of patients with unstable angina appear to have worse prognosis and to be at a high risk of adverse events. These are: advanced age,[7,8] continuing rest pain with intracoronary thrombi and complex coronary morphology or multivessel disease.[4]

Involvement of platelet activation and thrombus formation[4,5,9,10] has been well established in patients with unstable angina and has led to treatment strategies that include aspirin and heparin. The combination of both these drugs has been proved to be more effective than either drug given alone,[11] reducing the incidence of MI and death in patients with unstable angina.

In recent years, subcutaneous low-molecular weight heparins (LMWH), administered in a twice-daily weight-adjusted dosage have been shown to offer an effective and safe alternative to unfractionated heparin (UFH) administration in the short-term management of unstable angina, and constitute a clear progression in anti-thrombotic therapy. Similarly, in the post-acute phase of coronary instability, trials have been published showing the efficacy of a single fixed daily dose of LMWH[12] or the administration of a double daily injection with dosage adjusted to bodyweight.[13]

Although biochemical differences do exist between patients with acute MI and patients with unstable angina or silent myocardial ischemialater.[14-17]

Parnaparin is an LMWH with a high bioavailability and a prolonged half-life whose efficacy and safety has already been established in prevention and therapy of thromboembolic conditions and in the therapy of deep vein thrombosis (DVT) including other venous disorders. In addition, it has been investigated in the treatment of peripheral arterial thrombotic occlusions.[18-20] The aim of the present study was to compare the efficacy of a once daily parnaparin with UFH when added to the standard treatment of unstable angina.

Methods

The PRIME CARE study sought to investigate the effect of parnaparin, an LMWH on the in-hospital cardiac event rates during the 7 days. It was a prospective, multicentric, randomized and parallel group in design; 29 centres located in different parts of the country participated in this study. Patients admitted to the acute coronary care unit with acute chest pain due to unstable angina were considered for the study.

Inclusion criteria : Patients were enrolled in the study provided the following criteria were met : (i) Adult patients of both sexes (ii) Unstable angina as defined by a recent onset or prolonged (>10 min) or severe and frequent (>3 episodes/day) anginal symptoms or spontaneous rest pain, (iii) Evidence of underlying IHD as shown by at least one of the following : (a) electrocardiographic (ECG) changes of MI, (b) previous (>3 months) documented MI, (c) history of typical exertional angina, (d) angina at rest without acute ECG changes where the diagnosis is confirmed independently by 2 cardiologists, (e) previous coronary artery bypass surgery, (f) positive stress test for angina, (g) previous coronary angiography showing $\geq$ 70% narrowing of the lumen in any coronary artery, and (h) echocardiographic evidence of wall motion abnormalities with a previously documented IHD.

Exclusion criteria: The patients meeting the following criteria were excluded : (i) Acute Q wave or non-Q wave MI, (ii) MI in the preceding 3 months, (iii) An episode of thromboembolic event in the previous 3 months or a hemorrhagic stroke, (iv) Any contraindication to the use of anticoagulant therapy, (v) Angioplasty in the preceding 3 months, and (vi) Pregnancy or lactation.

Randomization and treatment protocol: All the eligible patients were randomized to two groups : Group A and Group B. The randomization was carried out at each center using a treatment allocation table constructed using random numbers.

Treatment was started as soon as possible after randomization. All patients were administered 150 to 325 mg daily aspirin soon after admission to the hospital and this was continued throughout the study period. Those randomized to Group A received 5000 IU of UFH as a bolus dose followed within 1 to 2 hours by a continuous infusion at a rate of 800 to 1000 IU per hour for 48 hours. The dose of UFH was adjusted to maintain the activated prothromboplastin time (aPTT) value 1.5 to 2.5 times the control value. The infusion was then replaced by 5000 IU of UHF administered subcutaneously every 6 hours for the next 5 days. Group B patients were administered LMWH parnaparin sodium 6400 IU once daily by subcutaneous route.

The dose of parnaparin was selected based on the pharmacokinetic data available with this drug. It has been shown that peak anti-Xa activity following subcutaneous administration of parnaparin 6400 IU was approximately 3 times greater than with heparin 10,000 IU. Moreover, appreciable inhibition of factor Xa ($\simeq$ 0.1 aXaU/ml) persisted for up to 18 hours after parnaparin, compared with approximately 8 hours for heparin.[18] LMWH parnaparin sodium (Fluxum, Alfa Wasserman, Italy) was provided in the form of pre-filled syringes each containing 6400 IU. The brand of UFH was used as per the local preference. Concomitant treatment with other drugs such as beta-blockers, calcium channel blockers, diuretics, lipid lowering agents, antidiabetic medications were permitted according to the needs of the individual patient. No other anticoagulants or antiplatelet agents were permitted during the study.

Outcomes: The primary efficacy end point of the study was the composite of death, MI, and emergency myocardial revascularization procedures. Only one major event was considered for each patient : death prevailed on MI and MI prevailed on urgent revascularization. These events were recorded for 7 days immediately after randomization to either treatment. The recurrences of anginal chest pain during 7 days after the index episode and the outcome at 30 days were considered as secondary efficacy end points. Bleeding complications were monitored as adverse events during the seven days post-treatment with the study medications. All bleedings of a retroperitoneal, intracranial and intraocular location were considered as major events. In other instances, an episode of bleeding was considered as major, if there was a decrease in hemoglobin by $\geq$ 2 gm/dl or there was a need for a blood transfusion. Other bleeding episodes such as epistaxis, ecchymosis, macroscopic hematuria and hematomas or bleeding at the injection sites, which did not fulfill the criteria of a major bleeding, were classified as minor bleeding episodes.

End-point definition: Only cardiovascular deaths were considered valid to the aim of the study. A patient was considered to have suffered from an MI if the episode met at least two of the following criteria : typical prolonged chest pain, new Q waves/characteristic ST segment elevation or CK-MB > 2 times the normal upper limit of normal and an increase of 50% over the baseline (in the absence of CK-MB total CK elevated to > 2 times the upper limit of normal). Emergency revascularization procedures were coronary artery bypass graft surgery (CABG), angioplasty (PTCA) and/or intracoronary stenting.

Estimation of sample size: The sample size was calculated based on the findings of the study when a total of 200 patients were enrolled in both groups. The interim analysis showed an incidence of composite end point to be 11% in the patients treated with UFH. The sample size was calculated to detect a 50% reduction in the event rate with a 5% Type I error (two-tailed) and a power of 80%. Thus, it was necessary to enroll at least 429 patients in each group.

All patients who received at least one dose of the study medication were included in the primary analysis of the efficacy. The patients were classified according to the dichotomous variable, i. e. the end point as an occurrence or non-occurrence of an event namely, all-cause mortality or Q wave or non-Qwave MI or myocardial revascularization.

All the efficacy variables were analyzed according to an intention-to-treat principle and 95% confidence interval (CI) values were calculated for the incidence of all events. The parametric data such as age and weight were analyzed by an unpaired student's *t* test. The non-parametric data such as the incidence of composite end points, sex, associated conditions etc. were analyzed by Chi-square test.

Results

In this study, a total of 897 patients > 18 years meeting the entry criteria were randomized to antithrombotic therapy with either parnaparin sodium or UFH. The demographic characteristics of the patients are shown in Table 1. In our study male patients were more than double the female patients in both the groups. Their age, sex and risk factors such as diabetes, hypertension, dyslipidemia were similar in both the groups (Table 1). The average body weight of all the patients was similar in both the groups (Table 2). The number of patients with confirmed coronary artery disease before enrollment were similar (Table 3). The mean, median and mode of the weight were also similar in both the groups indicating a normally distributed weight pattern (Table 4). In the parnaparin group the 90th percentile was 71 kg and in UFH group it was 70 kg.

During the course of the study, 9 (2.01%) patients from UFH group and 9 (1.99 %) patients from parnaparin group were withdrawn from the study. The reasons for their withdrawal are mentioned in Table 5.

Patients who did not meet any efficacy end points and had no symptoms of unstable angina were discharged from the hospital. All of them were advised to continue treatment with aspirin and appropriate antianginal as well as other medications, if required, as per the needs.

During the follow-up of 7 days, 170 (50.8%) patients from UFH group and 146 (44.2%) patients from parnaparin group reported recurrent anginal chest pain (p=0.085). The episodes of recurrent anginal chest pain could be correlated to ST-T changes in ECG (Table 6). These differences were statistically significant (p=0.007).

Table 1. Baseline characteristics of patients enrolled in the study

	Group A (UFH) (*n*=446) (%)	Group B (parnaparin) (*n*=451) (%)	Chi-square analysis
Males	310	312	0.89 #
Females	136	139	0.89 #
Age (years)	55.98	57.64	0.068 *
Diabetes	131 (29.37)	122 (27.05)	0.57 #
Hypertension	225 (50.44)	217 (48.11)	0.48 #
Dyslipidemia	99 (22.19)	94 (20.84)	0.62 #
Previous MI	40 (8.96)	44 (9.75)	0.68 #
History of CABG or PTCA	12 (2.69)	14 (3.10)	0.13 #

Values in parantheses show percentage
#: Chi-square test; *:Unpaired *t* test UFH: unfractionated heparin; MI: myocardial infarction; CABG: coronary artry bypass grafting; PTCA: percutaneous transluminal coronary angioplasty

Table 2. Body weight of the patients enrolled in the study (data available for 618 patients)

Weight (kg)	Group A (UFH) (*n*=317)	Group B (parnaparin) (*n*=301)	Total (*n*=618)
Up to 45	12	10	22
45 - 50	25	19	44
50 - 55	41	42	83
55 - 60	52	41	93
60 - 65	64	78	142
65 - 70	57	56	113
70 - 75	42	31	73
> 75	24	24	48

UFH: unfractionated heparin

Table 3. Diagnosis of coronary artery disease confirmed prior to enrollment

	Group A (UFH) (*n*=334) (%)	Group B (parnaparin) (*n*=330) (%)
Exertional angina	212 (63.5)	225 (68.2)
Past myocardial infarction	30 (8.9)	33 (10.0)
Positive stress test	59 (17.7)	52 (15.8)
Coronary angiography	14 (4.2)	15 (4.5)
Prior CABG/PTCA	9 (2.7)	6 (1.8)
Echocardiographic wall Motion abnormalities4	9 (14.7)	45 (13.6)

UFH: unfractionated heparin; CABG: coronary artery bypass grafting; PTCA: percutaneous transluminal coronary angioplasty

Table 4. Comparison of body weight of the patients

Weight (kg)	Group A (UFH) (*n*=317)	Group B (parnaparin) (*n*=301)
Mean	61.17 ± 10.00	61.39 ± 9.51
Median	56.0	59.0
Mode	60	60
90th percentile	70	71
10th percentile	42	45

UFH: unfractionated heparin

Table 5. Reasons for patient withdrawal from the study

Reason for withdrawal	Group A (UFH) (*n*=446)	Group B (parnaparin) (*n*=451)
Adverse events	6	2
Inappropriate compliance	1	1
Protocol violation	1	1
Consent withdrawal	-	5
Cause not mentioned	1	1
Total	9 (2.01%)	9 (1.99%)

UFH: unfractionated heparin

Table 6. No of patients with recurrent anginal chest pain during 7 days

	Parnaparin (*n*=330)	UFH (*n*=334)	Relative risk (95% CI)	Odds ratio (95% CI)	Chi-square	p value
No. of patients with chest pain	146 (44.2%)	170 (50.9%)	0.87 (0.74-1.02)	0.77 (0.56-1.03)	2.95	0.085
No. of patients with chest pain and ST-T changes	76 (23.03%)	108 (32.3%)	0.71 (0.55-.92)	0.62 (0.44-0.88)	7.17	0.007

UFH: unfractionated heparin

Table 7. Incidence of study end points at end of 7 days

Event	Group B (parnaparin) (n=451)	Group A (UFH) (*n*=446)	Relative risk (95% CI)	Odds ratio (95% CI)	Chi-square	p value
Death	6	6	–	–	–	–
Acute MI (Q wave or non-Q wave)	13	21	–	–	–	
Myocardial revascularization	14	24				
Total	33	51	0.64 (0.42-0.97)	0.61 (0.39-0.97)	4.48	0.034

UFH: unfractionated heparin; MI: myocardial infarction

The primary end points of death (all-cause mortality), MI (Q wave and non-Q wave) and myocardial revascularization, at the end of 7 days (Table 7) was met by 33 (7.32%) patients in parnaparin group and 51 (11.43%) patients in UFH group. This difference was statistically significant p=0.034; RR 0.64, 95% CI: 0.42 - 0.97; OR 0.61 (95% CI: 0.39 - 0.97). The cumulative event rate of primary end points at the end of 30 days (Table 8) was reported in 40 (12.12%) patients in parnaparin group and in 73 (21.86%) patients in UFH group. This difference was statistically significant, p=0.0008; RR 0.56, 95% CI: 0.39 - 0.79); OR 0.49, 95% CI: 0.32 - 0.75).

Anticoagulant effect of UFH as well as parnaparin was monitored by measuring aPTT. The results indicate that in patients treated with parnaparin, the aPTT observed/ control ratio did not show any increase from the baseline and remained unchanged until day 7 while the aPTT observed/control ratio in the UFH group was maintained between 1.5 to 2.5 until day 7.

Adverse events recorded throughout the study are reported in Table 9. Two events, each of the major bleeding,

Table 8. Incidence of study end points at end of 30 days

Event	Group B (parnaparin) (*n*=451)	Group A (UFH) (*n*=446)	Relative risk (95% CI)	Odds ratio (95% CI)	Chi square	p value
Death	7	7	–	–	–	–
Acute MI (Q wave or non-Q wave	13	26	–	–	–	
Myocardial revascularization	20	40	–	–	–	–
Total	40	73	0.56 (0.39-0.79)	0.49 (0.32-0.75)	11.14	0.0008

UFH: unfractionated heparin; MI: myocardial infarction

Table 9. Major and minor bleeding episodes during 7 days

Event	Group B (parnaparin) (n=451)	Group A (UFH) (*n*=446)	Relative risk (95% CI)	Odds ratio (95% CI)	Chi-square	p value
Hematoma at injection site	6	58	–	–	–	–
Bleeding from injection site	3	20	–	–	–	–
Echymosis at injection site	3	30	–	–	–	–
Epistaxis	Nil	5	–	–	–	–
Macroscopic hematuria	Nil	2	–	–	–	–
Total minor bleeding	12 (2.66%)	115 (25.8%)	0.10 (0.06-0.18)	0.07 (0.04-0.14)		p<0.001
Major bleeding	2	2				
Total (major and minor)	14	117	0.12 (0.07-0.20)	0.09 (0.05-0.15)		p<0.001

UFH: unfractionated heparin

Table 10. Platelet count

	Platelet count (Mean ± SD)	
	Parnaparin	UFH
Baseline	221,267 (± 63775)	229,286 (± 58501)
At 7 days	218,077 (± 69379)	205,242 (± 62029)
p value (paired *t* test)	0.24	<0.001

UFH: unfractionated heparin

were reported in both the groups. At the end of therapy 115 (25.78 %) and 12 (2.66 %) patients in UFH and parnaparin group, respectively, experienced minor bleeding.

There was decrease in the platelet count by 3189 and 24044 in the parnaparin and UFH group, respectively (Table 10). This difference was not statistically significant in parnaparin-treated patints, whereas in UFH group the difference was statistically significant (p<0.001).

Discussion

In this open, prospective and comparative study, the efficacy of a uniform/fixed once daily dose parnaparin (6400 IU) was compared with UFH in the treatment of unstable angina. Published studies on LMWH in the treatment of unstable angina or non-Q wave MI have all employed twice daily administration of the respective LMWH. The dose is further calculated as per the body weight of the patients.

The pharmacokinetic data of subcutaneous administration of parnaparin has shown that anti-factor Xa activity is maintained up to 24 hours. It is important to consider the difference amongst various LMWHs. Individual LMWHs are manufactured using different technologies. These differences are responsible for the different composition and the average molecular weight of the drug. The length of the glycosaminoglycan is critical in ensuring the bioavailability and anti-Xa activity.

The primary efficacy end point (death, MI, myocardial revascularization) was significantly lower in the parnaparin group compared with UFH group, 7.32% *versus* 11.43%. Similar results have been reported with other LMWHs. The cumulative event rate of primary end points at the end of 30 days was also significantly lower in the parnaparin group compared with UFH group, (12.12% *versus* 21.86%). The incidence of combined triple end points at the end of 7 days, reported in the present study, was similar to that in another study comparing enoxaparin and UFH in Indian patients.[21]

Therapy with LMWH upto a certain dose does not require monitoring of coagulation parameters. This dose varies according to the LWMH used. It has been shown that administration of parnaparin upto 6400 IU per day does not require monitoring of coagulation parameters. This was reconfirmed by the data on serial aPTT monitoring. Bleeding complications specially episodes of minor bleeding episodes of minor bleeding were significantly less with parnaparin when compared to UFH.

Frequency of recurrent anginal chest pain was monitored during 7 days after enrolment in the study. The episodes of chest pain were also correlated with ECG changes of ischemia. This data was available from 664 patients (parnaparin, *n*=330; UFH, *n*=334). The overall incidence of recurrent anginal pain was less in patients in parnaparin group compared with UFH, 44.2% *versus* 50.8% (p=0.08). However, this difference was not statistically significant. The recurrent anginal chest pain associated with ECG changes was significantly less in parnaparin group compared with UFH group, 23.0% versus 32.3% (p=0.007).

The incidence of minor bleeding was significantly less in parnaparin group compared with UFH group (2.6% *v.* 25.8%). Two episodes each of major bleeding were reported in both parnaparin as well as in UFH group.

Hemorrhagic episodes of both minor and major in nature have been much less frequent in the LMWH group

than in the UFH arm. The rate of bleeding episodes in the present study is in accordance with the published data. At 6 days of therapy in the FRIC study[24], the rate of major bleedings was 1.1% with delteparin and 1.0% with unfractionated heparin. In the FRAXIS study the two nadroparin groups reached a rate of 0.7% and 1.3% in major bleedings at day 6 *versus* 1.0% with UFH. In the TIMI 11B a similar rate was reported.[25] On the whole, in our study, difference in major plus minor bleedings was more favorable to the parnaparin group than reported earlier.[21,22,24] A possible explanation could be the lower number of subcutaneous injections of parnaparin required in our study. Our results are consistent with the experimental evidence indicating that LMWHs are at least as effective and safe as heparin in the acute-phase treatment of unstable angina/non-QWMI.[25]

The average body weight of the patients in UFH group (n=317) was 61.17 ±10.00 kg and in parnaparin group (n=301) it was 61.39 kg ± 9.51 and the 90th percentile weight was 70 kg and 71 kg, respectively. This indicates that a fixed dose of parnaparin may be adequate for an average Indian patient and there is no need to modify the dose according to the body weight of the patient. It is also important to note that a fixed dose of 6400 IU irrespective of their body weights was administered to all the study patients. The present study, therefore, suggests that in patients presenting with unstable angina, a single rather than twice daily injection of a fixed dose of parnaparin (6400 IU) was effective and safe.

Conclusions: Considering the superior efficacy of parnaparin compared to UFH, it could be concluded that a uniform dose of parnaparin was adequate for all the patients irrespective of their body weight. Once daily administration will also provide additional patient convenience and reduce treatment costs.

Treatment with subcutaneous injection of parnaparin 6400 IU once daily, in addition to aspirin and standard anti-anginal therapy, should be considered at least for 7 days in all patients of unstable angina and non-Q-wave MI. This will help to ameliorate the recurrent anginal chest pain and cardiac events.

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vWf Levels As A Circulating Marker of Endothelial Dysfunction in Patients with Hypertrophic Cardiomyopathy

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Background: The aim of the present study was to investigate whether the von Willebrand factor levels, as a possible indicator of endothelial dysfunction, is increased in hypertrophic cardiomyopathy, and also whether it is related to the clinical status of hypertrophic cardiomyopathy.

Methods and Results: The study group comprised 29 patients with hypertrophic cardiomyopathy and 29 healthy age- and gender-matched control subjects. There was no significant difference in von Willebrand factor levels between study group (77.0±23.1%) and control group (88.5 ±34.2%). There was no statistically significant difference between control group (88.5±34.2%) and functional class I/II group (82.0±24.3%), between control group and functional class III group (67.6±18.3%) and between functional class I/II group and functional class III group with respect to the von Willebrand factor levels.

Conclusions: The results suggest that von Willebrand factor levels, as a possible indicator of endothelial dysfunction, are not increased in patients with hypertrophic cardiomyopathy and von Willebrand factor levels are not related to functional class in these patients. **(Indian Heart J 2005; 57: 655–657)**

Key Words: Hypertrophic cardiomyopathy, von Willebrand factor, Endothelial dysfunction

Von Willebrand factor (vWF) is a multimeric glycoprotein that is synthesized exclusively in endothelial cells and megakaryocytes.[1] vWf release is increased when endothelial cells are damaged. Numerous clinical and experimental reports suggest that high vWf levels reflect damage to the endothelium or endothelial dysfunction.[1-5] The impairment of endothelium-dependent coronary vasodilation in hypertrophic cardiomyopathy (HCM) has been shown in recent studies.[6-8] It was suggested that coronary artery system of patients with HCM shows an intrinsic endothelial dysfunction. There is no data concerning the vWf levels as a possible indicator of endothelial dysfunction in patients with HCM. In the present study we aimed to evaluate the serum levels of vWf levels in patients with HCM and its clinical implications.

Methods

We prospectively evaluated 29 HCM patients (21 males; age 50.9±18.9 years) consecutively admitted to outpatient clinic at the Department of Cardiology, Suleyman Demirel University, Isparta, Turkey. Twenty-nine healthy age- and gender-matched volunteers were taken as control group (19 males; age 50.1±13.2 years). The diagnosis of HCM was based upon M-mode and two-dimensional (2D) echocardiographic evidence of a hypertrophied, non-dilated left ventricle in absence of any identifiable causes of secondary hypertrophy.[9] Patients with uncontrolled congestive heart failure (CHF) (requiring hospital admission for deteriorating CHF within 3 months), coronary artery disease (CAD), significant renal impairment (creatinine >200 µmol/L), active infection, neoplastic or connective tissue disease, a recent (≤3 months) cerebrovascular event, atrial fibrillation or pacemakers, or previous thromboembolism and those taking warfarin, antithrombotic agents other than aspirin (e.g., non-steroidal anti-inflammatory agents, clopidogrel), or hormone replacement therapy were excluded. Patients having one or more risk factors for CAD that would be expected to cause endothelial dysfunction, such as cigarette smoking, hypertension, hypercholesterolemia, advanced age or diabetes mellitus were closely associated with abnormal endothelial function, even in patients with "normal" findings on coronary arteriography. We also

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excluded HCM patients having at least one or more risk factors mentioned above.

All patients underwent clinical examination, electrocardiography, 2D Doppler echocardiographic examination and venous blood sampling for vWf analysis. The clinical status and functional capacity were assessed according to the New York Heart Association (NYHA) classification. 2D echocardiography was performed with commercially available equipment. Measured variables included: left ventricular end-diastolic (LVEDD) and end-systolic diameters (LVESD), using 2D guided M-mode. The left ventricular ejection fraction (LVEF) was calculated using the Simpson method from the apical four-chamber view. All patients and volunteers gave informed consent and the study was approved by the local ethics committee.

Serum vWf measurements: We have set up a rapid assay for measuring the activity of the vWf using an automated coagulometer (BCS, Dade-Behring, Germany) and commercially available lyophilized platelet reagents (Dade-Behring, Marburg, Germany; lower and upper normal limit: 50-150% d.n.)

Statistical analysis: All measurements are presented as mean ± SD. The differences between the two groups were assessed by using the student's *t* test and one-way or two-way analysis of variance for repeated measures with *post hoc* Scheffé correction. A p value < 0.05 was considered statistically significant.

Results

Clinical characteristics of study population are listed in Table 1. Mean age and sex distribution did not differ in groups. The mean serum level of vWf was 77.0±23.1% in the study group (*n*=29) and 88.5±34.2% in the control group (*n* =29). There was no statistical difference between study group and control group (p=0.1). Serum vWf levels in HCM patients were classified according to NYHA functional class.

There was no statistically significant difference between control group (88.5±34.2%) and functional class I/II group (82.0±24.3%), between control group and functional class III group (67.6±18.3%) and between functional class I/II group and functional class III group with respect to the vWf levels.

Discussion

The present study is the first one evaluating the relationship between vWF levels and HCM. In this study we could not find a relationship between vWf levels and HCM. Also, vWf levels did not change with the severity of HCM in respect to NYHA functional class. In the setting of left ventricular dysfunction, levels of vWf have been shown to be abnormal, with the highest level associated with left ventricular aneurysms.[10] Levels of vWf were also positively correlated with NYHA class in chronic heart failure.[11] This could be explained in two ways. Firstly, patients with the highest vWf levels may be at highest cardiovascular risk, resulting in the largest myocardial infarctions or recurrent infarctions, thus resulting in the most cardiac damage and subsequently, aneurysm formation. Alternatively, these patients may have severe endothelial dysfunction, leading to greater intravascular thrombogenesis.

Table 1. Clinical characteristics of patients with HCM (*n* =29)

Age (years)	50.9 ± 18.9
Males	21 (66%)
NYHA functional class	
I	3 (10%)
II	16 (55%)
III	10 (35%)
LA diameter (mm)	43.5 ± 5.5
LVEDD (mm)	41.7 ± 4.4
EF (%)	67.5 ± 13.7
LV outflow tract gradient > 30 mmHg	7 (24%)
Prior therapy	
Verapamil	9 (31%)
Beta-blocker	18 (65%)

HCM: hypertrophic cardiomyopathy; NYHA: New York Heart Association; LA: left atrial; LVEDD: left ventricular end-diastolic diameter; EF: ejection fraction; LV: left ventricular

Clinical and epidemiological studies on the risk of thromboembolism in patients with cardiac impairment do not, however, differentiate between the contribution of systolic and diastolic dysfunction to heart failure. This is pertinent as up to 30%-40% of patients with CHF have normal systolic function.[12,13] Endothelial dysfunction may thus be related to abnormalities of diastolic function seen in ischemic heart disease. In studies on ischemic heart disease, no significant differences were observed in vWf levels between patients with and without diastolic dysfunction despite correcting for the interaction with systolic dysfunction when it was present in individual patients.[12,13] Patients with the greatest systolic abnormalities (with aneurysm formation) had the highest vWf levels.[13] However, to our knowledge there is no report exploring the vWf levels in HCM patients with respect to endothelial dysfunction/damage.

von Willebrand factor reflecting endothelial dysfunction or damage, a marker of atherosclerosis risk associated with a higher rate of atherothrombotic events,[14] is a complex glycoprotein that plays an important role in hemostasis by promoting platelet adhesion and aggregation and acting

as a carrier of coagulation factor VIII.[15] Furthermore, baseline plasma vWf levels have been predictive of an adverse prognosis in cardiovascular disease.[16,17]

Congestive heart failure has been found to be associated with impaired endothelium-dependent vasodilation and impaired release of endothelium-derived nitric oxide in response to stimuli, which contributes to the peripheral vasoconstriction that is characteristic of heart failure.[18] Consequently, the elevated baseline vWf levels have been accepted to reflect pre-existing endothelial dysfunction in CHF, and as a procoagulant product of the endothelium, vWf may further enhance the prothrombotic state through its effects on platelet aggregation and platelet adhesion to the endothelium.[19] The impairment of endothelium-dependent coronary vasodilation in HCM in response to intracoronary acetylcholine injection and to the cold pressor test (another stressor testing endothelium-dependent vasomotor reactivity) has been shown in some studies raising the question of endothelial dysfunction in HCM patients.[6-8] Yokohoma et al.[20] found for the first time that endothelial function is preserved in patients with HCM.[20] However, vWf levels as an indicator of endothelial dysfunction/damage has not been studied in HCM patients previously.

Study limitations: Our study included a relatively small number of patients. This is important specially for negative results. Decreased vWf levels in patients with NYHA class III could have attained a statistically significant level if more number of study patients were included. The studies with greater number of patients must be done in these patients.

Conclusions: To our knowledge, this the first study evaluating the vWf levels in HCM patients. In the present study we could not find relationship between vWf levels and HCM. Also, vWf levels did not change with the severity of HCM in respect of NYHA functional class.

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Original Article

Profile and Prevalence of Aspirin Resistance in Indian Patients with Coronary Artery Disease

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Background: Aspirin resistance is considered to be an enigma and the data available on aspirin resistance is scarce. This study was initiated to prospectively evaluate the prevalence of aspirin resistance in patients with stable coronary artery disease by using an established method of optical platelet aggregation.

Methods and Results: We studied 50 patients who were on 150 mg of aspirin for the previous 7 days. Fasting blood samples were assessed using optical platelet aggregation (Chronolog Corp, USA). The mean platelet aggregation with 10 µm of adenosine diphosphate in our patient group was 49.42 ± 23.29% and with 0.5 mg/ml of arachidonic acid it was 13.58 ± 21.40%. Aspirin resistance was defined as a mean aggregation of ≥70% with 10 µm of adenosine diphosphate and a mean aggregation of ≥ 20% with 0.5 mg/ml of arachidonic acid. Aspirin semi responders were defined as those meeting only one of the criteria. Based on these criteria, 2.08% patients were found to be aspirin-resistant, 39.58% were aspirin semi responders and 58.33% were aspirin responders. Females tended to be more aspirin semi responsive (p = 0.08). All other parameters tested, namely, age, smoking, diabetes mellitus, hypertension, obesity, lipids, hemoglobin, platelet count, ejection fraction and drug intake did not show any statistically significant difference among the groups. Thus, in our group 41.66% patients showed inadequate response to aspirin.

Conclusions: This study shows that aspirin resistance and aspirin semi responsiveness do occur in the Indian patients and there are no reliable clinical predictors for this condition. The diagnosis therefore relies primarily on laboratory tests. **(Indian Heart J 2005; 57: 658-661)**

Key Words: Aspirin resistance, Platelet aggregation, Coronary artery disease

Since the time of introduction of aspirin in 1897 and the elucidation of the mechanism of its benefit, aspirin has become a cornerstone in the treatment of coronary artery disease (CAD).[1] The beneficial role of aspirin in the secondary prevention of vascular events is now well established.[2,3] The Antithrombotic Trialist Collaboration's meta-analysis with approximately 100,000 subjects treated with aspirin showed a 25% reduction in death, myocardial infarction (MI) and stroke in the high risk patients.[4,5] However, it has been recently shown that its effect may not be uniform in all patients. Various laboratory parameters assessing its efficacy, like bleeding time, platelet reactivity, thromboxane A_2 (TXA_2) production and measurement of platelet aggregation have confirmed the lack of its uniform effect on the platelets, among patients who manifest breakthrough events with thrombotic and embolic complications despite being on therapeutic doses. It has been suggested that one out of every eight high-risk individuals may experience an event in the next 2 years despite aspirin therapy.[6] Based on this fact, the concept of aspirin resistance has emerged. Few studies have estimated that 5% to 45% of patients with vascular disease are aspirin-resistant.[7-10] This variability in incidence is due to non-standardization of method and definition of aspirin resistance used in these studies.

The present study was initiated to prospectively evaluate the prevalence of aspirin resistance in patients with stable CAD as there is scarce data on this subject from the Indian sub-continent. The test was carried out by using an established traditional method of optical platelet aggregation which, although tedious to accomplish, is considered the gold standard. Optical platelet aggregation utilizes a modified spectrophotometer in which platelet-rich plasma is assessed using optical density changes, which detect photoelectrically, as platelets begin to aggregate. Adenosine diphosphate (ADP), when added to platelet-rich plasma, promotes the release of additional endogenous ADP, causing irreversible aggregation. The addition of arachidonic acid (AA) to platelet-rich plasma produces TXA_2, which enhances platelet aggregation.[10]

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Methods

The present study was done on a group of 50 patients attending our outpatients department as follow-up patients of CAD. The inclusion criteria for the study were patients with a documented history of previous MI, or with angiographically proven coronary disease. All patients who were ≥ 21 years old and who had taken 150 mg of aspirin for the previous 7 days were eligible for enrolment. We relied on statement of our patient group to ascertain that adequate dose of aspirin had been taken. Age, sex, occupation, clinical history, previous history of diabetes, smoking, hypertension, family history, hospitalization for ischemic heart disease were noted. A thorough clinical examination and 12-lead electrocardigram (ECG) was done. Fasting blood samples were taken for biochemical tests, which were conducted at the Central Drug Research Institute, Lucknow. An informed consent was obtained from each patient and the study protocol conformed to the standard ethical guidelines. Exclusion criteria included use of clopidogrel, dipyridamole, non-steroidal anti-inflammatory drugs (NSAIDs), administration of heparin/ other antithrombotics in last 48 hours, family or personal history of bleeding disorders, platelet count < 150×10^3/µl or > 450×10^3/µl, hemoglobin <8 gm/dl, history of blood dyscrasias, heparin-induced thrombocytopenia, major surgical procedure within one week before enrolment or malignant paraproteinemias.

Optical platelet aggregation utilizes a modified spectrophotometer in which platelet-rich plasma is incubated, stirred, and evaluated as aggregating agents are added. It assesses optical density changes which are detected photoelectrically as platelets begin to aggregate.[11] Whole blood (9 ml) was drawn within 24 hours of administration of the last dose of aspirin and tests were done within 4 hours of sampling. The sample was added to 1 ml of 3.8% trisodium citrate (pH=6.5) solution and centrifuged for 20 min at 20°C. The platelet-rich plasma was removed, and followed by centrifugation of remaining specimen to obtain platelet-deficient plasma. Platelet count was adjusted to 2×10^8/ml with the spectrophotometer (absorption of 0.650 at 6.30 mm refers to the 2×10^8/µl). Platelet-rich plasma (400 µl) was taken in the aggregometer (whole blood Lumi Aggregometer-Chronolog Corp, USA). After 5 min of incubation, ADP (10 µm) and AA (0.5 mg/ml) was added to get the respective aggregation. Aggregation was monitored for 7-10 min. The inhibition of aggregation was compared with the control value. Another sample of 2 ml blood anticoagulated with EDTA was collected for hemoglobin and platelet count analysis.

Aspirin resistance was defined as a mean aggregation of ≥ 70% with 10 µm ADP and a mean aggregation of ≥ 20% with 0.5 mg/ml AA. Aspirin semi responders were defined as those meeting only one of the criteria.[10] This is a stringent definition, as other studies have defined aspirin resistance by merely a lack of aggregation inhibition by ADP. Laboratory standards were established by screening 35 age- and sex-matched healthy controls without any history or family history suggestive of CAD and they were not on any drugs for the past 7 days.

Statistical analysis: All analysis were done on SPSS 11.5 software. The analysis of continuous variables was done using the paired *t* test with equal variance. The chi-square test and Fisher's Exact test was calculated to see the association between variables. All variables were expressed as mean ± SD .

Results

Fifty patients having stable CAD underwent platelet aggregation studies. Two patients were excluded from the statistical analysis due to hemolysis of the sample. Amongst the remaining 48 patients there were 18.75% females, 18.75% smokers, 12.25% diabetics and 33.3% obese patients. There were 52% post-MI patients, 39% with chronic stable angina, 4.2% post-coronary artery bypass grafting (CABG) and 4.2% with ischemic cardiomyopathy. In the patient group (n = 48), with 10 µm of ADP the mean platelet aggregation was found to be 49.42 ± 23.29% and with 0.5 mg/ml of AA it was 13.58 ± 21.40% while in the controls (n=35) with 10 µm of ADP the mean platelet aggregation was found to be 54.53 ± 16.81% and with 0.5 mg/ml of AA it was found to be 56.00 ± 21.93%.

Out of 48 patients, 1 (2.08%) was found to be aspirin-resistant, 19 (39.58%) were aspirin semi responders and 28 (58.33%) were aspirin responders. The mean age in the aspirin semi responder group (n=19) was 56.69 ± 10.14 years and aspirin responder group (n=28) was 53.36 ± 8.35 years (p = 0.2). There were 6 (31.57%) females in the semi responder group and 3 (10.7%) females in the responder group (p = 0.08). All other parameters tested like smoking, diabetes, hypertension, obesity, lipid fractions, hemoglobin, platelet count, ejection fraction and drug intake did not show any statistically significant difference among the two groups (Table 1).

Thus in our group, 41.66% patients showed inadequate response to aspirin i.e. 2.08% aspirin resistant plus 39.58% aspirin semi responders. Among females there was a trend to be more aspirin semi responsive (31.67% *v.* 10.7%, p = 0.08).

Discussion

The concept of aspirin resistance is receiving increasing attention in recent literature. Till now the data available on aspirin resistance is scarce, and to the best of our

Table 1. Characteristics of patients as per sensitivity to aspirin

Variable	Aspirin-resistant (*n*=1; 2.08%)	Aspirin semi responder (*n*=19; 39.58%)	Aspirin-sensitive (*n*=28; 58.33%)	p value*
Age (years)	72	56.59±10.14	53.36±8.85	0.20
Females	0	6 (31.57%)	3 (10.7%)	0.08
Smokers	0	2 (10.52%)	7 (25%)	0.20
Diabetes	0	3 (15.78%)	9 (32.14%)	0.18
Hypertension	0	10 (52.63%)	11 (39.28%)	0.37
Obesity	0	5 (26.31%)	11 (39.28%)	0.36
Hemoglobin (gm%)	14	13.75±1.22	13.45±1.18	0.40
Platelet count ($\times 10^5$)	2.75	2.44±0.30	3.09±3.72	0.35
Ejection fraction (%)	45	57.89±7.51	55.89±8.06	0.40
Total cholesterol	162	165.95±29.58	181.82±42.85	0.25
LDL-cholesterol	117	98.66±22.35	114.97±37.38	0.12
HDL-colesterol	28	37.66±10.26	34.82±8.25	0.30
Triglycerides	83	131.26±60.74	157.39±79.06	0.25
Beta-blockers	1	17	23	0.40
Calcium blockers	0	3	8	0.26
Statins	1	10	16	0.76
Fibrates	0	1	1	0.65
Nicorandil	0	2	1	0.36
Trimetazidine	0	2	1	0.36

*p values between aspirin semi responders plus resistant (41.66%) *versus* aspirin sensitive (58.33%)
LDL: low-density lipoprotein; HDL: high-density lipoprotein

knowledge, no study has been reported on this subject from the Indian subcontinent. Data using varying methodologies have given inconsistent results with aspirin resistance reported in 5% to 50% patients depending on the type of test used.[7-10] In fact a study by Tantry et al.[12] showed that only one out of 143 patients studied was aspirin-resistant. The present study enrolled patients taking 150 mg aspirin daily because this is the most commonly used dosage in clinical practice in our country. Among these patients of stable CAD, 2.08% were aspirin-resistant and an additional 39.58% were aspirin semi responders, thus a cumulative inadequate response of 41.66% was noted.

In a study by Gum et al.[10] aspirin resistance was found in 5.5% while 23.3% were semi responders thus giving an inadequate response of 28.8%. The patients were taking 325 mg aspirin and those who showed inadequate response were more likely to be females (34.4% *v.* 17.3% p = 0.001) and less likely to be smokers (0% *v.* 8.3% p= 0.004). There was a trend toward increased age of patients showing inadequate response (65.7 *v.* 61.3 years, p = 0.06). They used the same methodology of measuring aspirin resistance which was carried out in our work. Hung et al.[13] have shown that smoking was significantly associated with aspirin resistance ($p<0.05$). A recent study has also shown that aspirin resistance was significantly more in men (p=0.02)and those using tobacco (p=0.03).[14] In our study there was no difference related to age (p = 0.2). There was only a trend for females to be semi responders (31.67% *v.* 10.7%, p = 0.08). We could not find any statistically significant difference related to smoking among the groups (p = 0.2). All other parameters tested including diabetes, hypertension, obesity, lipid fractions, hemoglobin concentration, platelet count, ejection fraction and concomitant drug intake did not show any statistically significant difference among the groups.

Thus it was shown that inadequate response to aspirin is prevalent in Indian patients and there are no predictors for this condition. The diagnosis is primarily laboratory-based, and this incomplete therapeutic response may be of clinical importance. Although, much is currently known about aspirin's effect on platelets, the mechanism by which some platelets are resistant has not been ascertained. The proposed mechanisms for the aspirin resistance can be broadly classified into extrinsic and intrinsic factors.[15] The extrinsic factors like smoking have been shown to accentuate platelet thrombosis.[12,13] However, some studies have also refuted this claim by showing that aspirin resistance was less likely among smokers.[10] Other factors such as use of NSAIDs, which act through the same pathway, may compete with aspirin.[16] There is also a suggestion of a dose response curve and up to 8% of patients appear to be resistant even at 1300 mg daily doses.[7] There are proposed intrinsic mechanisms also leading to failure of adequate suppression of TXA_2. Recent evidence has established that platelets may contain Cox-2 mRNA[17] and this could provide an alternate pathway for the platelets to act. Besides platelets, the nucleated cells are also rich sources of TXA_2 and single nucleotide polymorphism of Cox-1 has been reported, which imparts resistance.[18]

A few long-term studies have suggested the clinical importance of aspirin resistance. In a cohort of stroke patients, 30% of subjects were found to be aspirin non-

responders and after a follow-up of 2 years, major clinical vascular end points were higher in this group compared to responders ($p<0.0001$).[9] In yet another study, aspirin non-responder status was seen in 34% of patients with recurrent cerebrovascular ischemic events, despite regular use of aspirin for more than 5 years.[19] A subgroup analysis from the HOPE trial,[20] reported higher adverse outcomes at a follow-up of 5 years in patients showing aspirin resistance. Gum et al.[10] showed that among stable patients with CAD over a mean follow-up period of 679±185 days, aspirin resistance was associated with an increased risk of composite end points of death, MI or cerebrovascular accident ($p=0.03$) and the multivariate analysis showed aspirin resistance to be a significantly independent predictor of long-term major adverse outcome.

Limitations of the study: It has been suggested by some researchers that aspirin resistance may not be absolute over time, that measurement of aspirin resistance should be done more than once as a single measure may overestimate its prevalence.[21] Use of aspirin needs to be confirmed by serum salicylate levels to assess the adequacy of the dose used but in the present study we relied on the history of drug intake given by our patient group to ascertain that adequate dose of aspirin had been taken prior to assessment of resistance. In our study, the sample size was small and we measured aspirin resistance only once which may have a bearing on the final results.

Conclusions: Aspirin resistance and aspirin semi responsiveness occurs frequently in the Indian patients and there are no reliable clinical predictors for this condition. The diagnosis relies primarily on a laboratory assessment of platelet functions and we may be overestimating its risk by using different methods and definitions.

Further, we need to formulate a policy on aspirin usage and ascertain whether all patients taking aspirin need to be investigated, whether all patients with so-called aspirin resistance be put on clopidogrel and lastly whether there is a serious issue of clopidogrel resistance at hand as well. We also foresee further advancements in the diagnostic tests for aspirin resistance like PFA-100 and estimation of 17 hydroxy TXA_2 which are user-friendly. Once these are commercially available, the true picture of aspirin resistance may come to light.

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Original Article

Morphometric Analysis of Fossa Ovalis in Rheumatic Heart Disease

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Background: Rheumatic heart disease is an important cause of valvular disease in India, with resultant alterations in the interatrial septum and fossa ovalis. Morphometric details of fossa ovalis may help in its localization during transseptal catheterization so as to prevent complications.

Methods and Results: Autopsy heart specimens of rheumatic heart disease (n=30) and non-cardiac death (n=30) patients between 15-45 years of age were studied as case and control group, respectively. The dimensions of fossa ovalis and interatrial septum were measured. The ratio of area of fossa ovalis to septum was calculated. Case group showed a significant increase in surface area of septum and fossa as compared to control group. The septal area was significantly increased in 15-30 years and 31-45 years groups, specially females in the former group. The fossa area was increased only in 31-45 years age group. The ratio of area of fossa to septum was not statistically altered in cases *versus* controls. Case group, specially females of 15-30 years, showed a significant horizontal orientation of fossa as compared to controls. Cases having both mitral and aortic stenosis showed highest increase in the areas of fossa and septum, as also the most horizontal orientation of fossa.

Conclusions: The enlargement of the septal area begins at an early age in rheumatic heart disease along with initial hemodynamic and valvular alterations. There is a categorical horizontal orientation of fossa ovalis in these cases. Varying dynamics in stenotic and regurgitant valves leads to varying morphological changes in dimensions of fossa ovalis and septum. **(Indian Heart J 2005; 57: 662–665)**

Key Words: Rheumatic heart disease, Fossa Ovalis, Transseptal catheterization

Rheumatic heart disease (RHD) is an important cause of valvular disease in India. Balloon valvuloplasty/ commissurotomy is commonly performed for treatment of rheumatic valvular disease. This involves transseptal catheterization (TSC), which is done through fossa ovalis (FO). It is a blind procedure and puncture at improper site may result in fatal complications. Rheumatic valvular disease will necessarily result in alterations in the interatrial septum (IAS)/fossa ovalis. Morphometric details of fossa ovalis in RHD may therefore help in localization of fossa ovalis and reduce the complications. To the best of our knowledge, no morphometric study has been carried out to identify alterations in IAS and fossa ovalis. Our study was carried out with the aim to compare and contrast morphometric parameters of the interatrial septum and fossa ovalis in rheumatic disease hearts and age-matched normal hearts as controls.

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Methods

Thirty autopsy heart specimens of RHD patients in age groups 15 to 45 years were included as case group and as many autopsy heart specimens of non-cardiac death patients of the same age range were included as control group. The case group showed moderate to severe valvular lesions. Formalin-fixed specimens were not flaccid and thus made demarcation and measurement of parameters easy.

The margins of the IAS were delineated using landmarks (Fig. 1).[1] It is a blade-shaped structure with three margins. The tip of the blade is directed into the orifice of the superior vena cava (SVC). The anterior margin is slightly concave and it outlines the curvature of the adjacent aorta. It begins at the tip and extends inferomedially to terminate in the fibrous trigone (FT), posterior to the membranous ventricular septum. The posterior margin extends from tip of the blade through a convex curvature posterior to fossa ovalis, terminating at the os of coronary sinus (CS). The short inferior margin extends from coronary sinus ostium to fibrous trigone.

Inked pins were used to mark the boundaries, with the septum under uniform tension. Boundaries were then successively transferred to butter paper and graph paper and the area (SA) was measured. The fossa ovalis was delineated using trans-illumination technique from right atrial (RA) aspect. The vertical (length) and horizontal (breadth) dimensions of fossa ovalis were measured directly. A line joining superior and inferior vena cavae was taken as a reference for vertical dimension. The horizontal dimension was taken perpendicular to the vertical dimension (Fig. 1). The ratio of length to breadth was calculated to study the orientation of fossa ovalis. Area of fossa ovalis (FOA) was calculated from the graph paper. The ratio of area of fossa ovalis to interatrial surface was calculated.

The point corresponding to the midpoint of rim of the non-coronary cusp of the aortic valve was marked on the IAS on the right atrial surface. This is a point at which aortic valve pulsations are felt during cardiac catheterization. The distance between this point and the anterior margin of fossa ovalis was calculated and considered as shortest distance. The shortest distance was seen to correspond to the anterior isthmus i.e. the distance of the aortic root from the anterior border of interatrial surface.

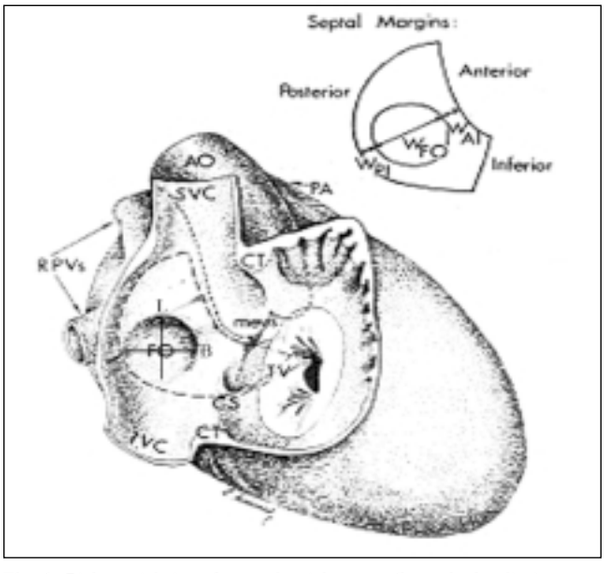

Fig. 1. *Right atrial view of normal atrial septum (heavy broken line). Position of the aorta (AO) is indicated by light broken line.*
CS: coronary sinus; CT: crista terminalis; FO: fossa ovalis; IVC: inferior vena cava; SVC: superior vena cava; MVS: membranous ventricular septum; PA: pulmonary artery; RPV: right pulmonary vein; TV: tricuspid valve; W FO: width of fossa ovalis; W AI: width of anterior isthmus; W PI: width of posterior isthmus; L: length (vertical dimension) of fossa; B: breadth (horizontal dimension) of fossa

Statistical analyses were performed on Statistical Package for Social Science (SPSS) V.10.1. In addition to calculation of mean and standard deviation, the statistical test of significance used was unpaired *t* test.

Results

The distribution of cases and controls according to age and sex is shown in Table 1. The study showed that the mean age in RHD group was 28.67 ± 16.50 years (mean ± 2 SD) while that for control group was 27.90 ± 15.82 years. The case group was further divided based on type of valvular disease as: Group A (mitral and aortic stenosis) *(n*=5), Group B (mitral and aortic regurgitation with mitral stenosis) (*n*=2) and Group C (only mitral stenosis) (*n*=23).

Table 1. Age and sex distribution of cases and controls

Age group (years)	Case group (RHD) (*n*=30)		Control group (*n*=30)	
	Male	Female	Male	Female
15-30	7	10	12	7
31-45	4	9	6	5
Total	11	19	18	12

RHD: rheumatic heart disease

Case group showed a significant increase in surface area of IAS and fossa ovalis as compared to control group (Table 2). On further division of the groups as per age into 15-30 years and 31-45 years, the septal area was significantly increased ($p < 0.05$) in both age groups, while fossa ovalis area was increased only in > 30 years age group ($p > 0.05$). The increase in septal area was statistically significant specially in female cases of 15-30 years ($p < 0.05$) (Table 3). In comparison to case group, the females in the control group showed a pattern of increasing septal area ($p < 0.05$) and decreasing fossa ovalis area ($p > 0.05$) in the age groups of 15-30 years and > 30 years. The control group of males showed increasing septal area ($p > 0.05$) while the fossa ovalis remained constant in the two age groups. In the two age groups, the male subjects in the case group showed an increase in both septal area and fossa ovalis area ($p > 0.05$).

Table 2. Comparison between case and control groups irrespective of age and gender

Variables	Cases		Controls		Unpaired *t* test	
	Mean	SD	Mean	SD	p value	Significance
SA	811.50	369.80	536.13	136.92	0.000	Significant
FOA	239.17	142.94	167.67	59.22	0.014	Significant
FOA/SA	0.33	0.19	0.34	0.15	0.831	Not significant
Shortest distance (mm)	13.37	6.87	14.50	6.14	0.503	Not significant
Length (mm)	15.57	6.73	13.63	4.20	0.187	Not significant
Breadth (mm)	18.67	6.51	14.47	4.46	0.005	Significant

SD: standard deviation; SA: interatrial septal area; FOA: fossa ovalis area

The ratio of areas of fossa ovalis to IAS was not statistically altered in cases (0.33±0.19) *versus* controls (0.34±0.15). The same trend was seen in subgroups irrespective of age and sex (p>0.05) (Tables 2 and 3).

Cases of RHD showed a significant increase in breadth to length ratio of fossa ovalis, as compared to controls (Table 2). This was statistically significant in females of 15-30 years age group (Table 3). The other subgroups also showed an increase in breadth as compared to length, although it was not statistically significant. This emphasizes the horizontal orientation of fossa ovalis in RHD cases, specially females of 15-30 years age.

Table 3. Comparison between case and control group females aged 15 to 30 years

Variables	Case group		Control group		Unpaired *t* test	
	Mean	SD	Mean	SD	p value	Significance
Age (in years)	21.00	4.93	21.40	3.05	-	-
SA	919.63	327.61	416.00	38.63	0.006	Significant
FOA	277.50	139.16	177.00	38.99	0.149	Not significant
FOA/SA	0.31	0.18	0.44	0.15	0.229	Not significant
Shortest distance (mm)	15.88	9.76	14.40	5.64	0.766	Not significant
Length (mm)	16.00	5.26	13.40	2.97	0.339	Not significant
Breadth (mm)	20.75	7.13	12.60	0.55	0.029	Significant

SD: standard deviation; SA: interatrial septal area; FOA: fossa ovalis area

The distribution of cases as per valvular disease is given in Table 4. The highest increase in the SA and FOA is seen in Group A (mitral and aortic stenosis), followed by Group B (mitral and aortic regurgitation with mitral stenosis) and then Group C (only mitral stenosis) (p>0.05). The change in the shortest dimension can be represented as A<C<B (p>0.05). The ratio of length to breadth in above group is A<C<B. Thus, fossa is most horizontally oriented in Group A (p>0.05).

Table 4. Comparison of variables in Groups A, B and C

Variables	Groups					
	A		B		C	
	Mean	SD	Mean	SD	Mean	SD
SA	855.78	391.03	805.00	148.49	610.40	288.28
FOA	254.57	155.58	190.00	56.57	188.00	91.49
FOA/SA	0.33	0.22	0.25	0.12	0.31	0.06
Shortest distance (mm)	12.65	7.54	17.00	0	15.20	3.96
Length (mm)	15.87	7.63	14.50	0.71	14.60	2.51
Breadth (mm)	19.17	6.94	16.50	4.95	17.20	5.50

A: mitral stenosis (MS)+aortic stenosis (AS) (*n*=5); B: mitral stenosis+mitral regurgitation (MR)+aortic regurgitation (AR) (*n*=2); C: mitral stenosis only (*n*=23); SD: standard deviation; SA: interatrial septal area; FOA: fossa ovalis area

Discussion

Rheumatic heart disease is one of the most common forms of valvular heart disease in India. The juvenile RHD is a special feature of both public health as well as clinical importance.[2]

Mitral and aortic balloon valvuloplasties have sparked a renewed interest in transseptal approach, whereby localization of the fossa ovalis is imperative.[3] Modifications are important to avoid complications[3-5] which include puncture of unintended structures like pericardial puncture resulting in cardiac tamponade, aortic/cardiac chamber puncture and displacement thromboembolism. High atrial puncture may lead to septal dissection. Too anterior atrial septal puncture can cause injury to tricuspid valve or coronary sinus leading to intractable hemorrhage. A 'stitching' phenomenon can occur due to a puncture from right atrium to left atrium.

Normally, the IAS has an oblique angulation from right posterior to left anterior plane so that RA is alongside and anterior to left atrium. IAS occupies posterior half of the medial wall of the RA, whereas anterior half abuts on the proximal ascending aorta, aortic valve (AV) at its right coronary and non-coronary cusps and right ventricular outflow tract. Normally FO is concave toward RA and lies at the junction of the lower and middle one-third of the IAS. These anatomic relations assume importance in the transseptal catheterization procedures.[6]

Our study was focused on morphometric parameters of fossa ovalis with respect to IAS in RHD specimens. It involved 30 cases of RHD and 30 control subjects. The cases showed moderate to severe valvular lesions. The male to female ratio was 0.57 and 0.67, respectively. Among the control group, the females showed a pattern of increasing septal area (p< 0.05) and decreasing fossa ovalis area (p>0.05) between the age groups of 15-30 years and > 30 years. The case group females of 15-30 years showed a significant increase in septal area as compared to controls. No statistically significant increase was noted in area of fossa ovalis in the above group. Thus it can be concluded that there is significant enlargement of the septal area as compared to fossa ovalis area in the younger age group in RHD along with hemodynamic and valvular alterations. The control group showed a mean length (13.63 mm) to breadth (14.47 mm) ratio to be almost unity (0.92). This indicates that the normal fossa ovalis is round to oval in shape. The case group showed a mean ratio of 0.83. Thus there was an emphatic horizontal orientation of fossa ovalis in the RHD cases (p<0.05). As all our cases had mitral stenosis, this horizontal orientation of fossa ovalis is in accordance with an earlier report by Clugston et al.[3]

The highest increase in the SA and FOA is seen in Group A followed by Group B and then Group C (p>0.05). The change in the shortest dimension can be represented as A<C<B (Table 4) (p>0.05). The ratio of length to breadth in above group is A<C<B. Thus fossa is most horizontally

oriented in Group A ($p>0.05$). Therefore, valvular stenoses, specially involving mitral valve tend to produce greater alterations in the parameters studied (areas of IAS and fossa ovalis, shortest distance and horizontal orientation). Group A will have pressure overload in both left atrium and ventricle. Group B will have volume overload in LV and pressure as well as volume overload in LA. Group C will have pressure overload on LA. These varying dynamics will thus produce varying morphological changes. In aortic valve disease, the dilated aorta draws fossa ovalis superiorly and anteriorly, so that the IAS becomes vertically oriented. Antegrade aortic valvuloplasty requires lower (but not posterior) puncture. In mitral stenosis (MS), LA progressively enlarges, so that the fossa ovalis becomes horizontal, ultimately completely averted and lies lower than the normal. Hence, in mitral valve disease, transseptal puncture is generally performed caudally and in middle third of septum. In tricuspid stenosis and regurgitation, RA enlargement is marked, making transseptal puncture difficult, if not impossible.[3,4]

Our study is applicable to post-mortem pathological specimens. This leaves further scope to study and correlate the same parameters in living subjects using 3 dimensional echocardiography.

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Original Article

Acute Hemodynamic Effects of Nicorandil in Patients with Primary Pulmonary Arterial Hypertension

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Background: Pulmonary arterial hypertension is managed with vasodilators, and till date no specific drug has been identified with sufficient degree of success. Potassium channels have been implicated in the pathogenesis of primary pulmonary arterial hypertension. We undertook this study to assess the acute effect of oral nicorandil in patients of pulmonary arterial hypertension.

Methods and Results: We studied acute hemodymanic response of 40 mg oral nicorandil in 10 patients with primary pulmonary arterial hypertension aged between 15 and 39 years (mean age 27.2±6.7 years). Responders (Group I) were defined as those with ≥20% reduction of pulmonary vascular resistance index and no change or increase in cardiac index; and non-responders (Group II) were those with <20% reduction of pulmonary vascular resistance index. There were 7 responders (pulmonary vascular resistance index decreased from 22.8±9.3 to 17.9±6.5 Wood units) and 2 non-responders (pulmonary vascular resistance index decreased from 26±3.5 to 25±1.0 Wood units). The maximum reduction in pulmonary vascular resistance index from baseline was 29.77±6.53% (23.7-40.5%) in responders and 7.3±4.2% (4.3-10.3%) in non-responders. The study was halted prematurely in one patient who developed hypotension, requiring intravenous inotropes.

Conclusions: Our results suggest that nicorandil significantly decreases pulmonary artery pressure in primary pulmonary arterial hypertension acutely and can be cautiously tried for the therapeutic use in primary pulmonary arterial hypertension. Further studies are warranted. **(Indian Heart J 2005; 57: 666–669)**

Key Words: Pulmonary arterial hypertension, Nicorandil, Vasodilators

Primary pulmonary arterial hypertension (PAH) is a serious disease of unknown etiology characterized by raised pulmonary vascular resistance (PVR). Pathogenesis of the disease is not well understood. However, significant progress has been made recently in this area. Vasoconstriction of pulmonary arteries along with smooth muscle proliferation and fibrotic, inflammatory, thrombotic changes in pulmonary arteries forms an important part of the pathologic process.[1,2] The treatment of primary PAH is generally unsatisfactory, although oral and intravenous vasodilators and anticoagulants have met with some success.[3-5] The potassium channel has been shown to play an important role in development of various cardiovascular disorders,[6] including the pathogenesis of pulmonary hypertension.[7-9] In animal models ATP-sensitive potassium channel openers have been shown to decrease pulmonary vasoconstriction, pulmonary artery pressure and pulmonary smooth muscle cell proliferation.[10-13] In this respect, potassium channel openers may be of some interest as alternate therapy. Nicorandil is an ATP-sensitive potassium channel opener and has been shown to decrease pulmonary artery pressure and resistance both in animals and humans.[11,12,14,15] Hence, we hypothesize that oral nicorandil may be useful in the treatment of primary PAH, and report our initial experience of acute hemodynamic changes with oral nicorandil in patients with primary PAH.

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Methods

Ten patients with primary PAH aged between 15 and 39 years (mean age 27.2±6.7 years) were included in the study. None of the patients were receiving vasodilators. Patients with New York Heart Association (NYHA) functional class IV symptoms, systolic blood pressure <90 mmHg or concomitant systemic illness were excluded from the study. Informed consent was obtained from all the patients. A diagnosis of primary PAH was made when PAH was present in the absence of any demonstrable cause. After clinical examination and routine blood investigations, all

patients underwent chest X-ray, electrocardiogram (ECG), and echocardiography. All drugs were stopped for at least five elimination half-lives prior to the study. The study was performed after overnight fast, at rest in supine position during daytime. Right heart catheterization was performed through the right femoral vein using a Swan-Ganz flow-directed catheter under fluoroscopic guidance. Baseline oxygen saturations were estimated from superior vena cava, right atrium, right ventricle and pulmonary arteries. Right femoral artery was cannulated by a 4 F sheath for direct intra-arterial pressure measurement and for arterial blood sampling. Baseline right atrial pressure, pulmonary arterial pressure, pulmonary wedge pressure and systemic arterial pressure were recorded. Cardiac output was calculated using the thermodilution principle.

After recording baseline parameters, a single oral dose of nicorandil 40 mg was given. All the hemodynamic parameters and blood samples for oxymetry were taken at 30 min intervals for 3 hours following nicorandil administration. All hemodynamic parameters were measured in triplicate and averaged. Cardiac index, pulmonary vascular resistance index (PVRI) and systemic vascular resistance index (SVRI) were calculated each time using the standard formula.

The hemodynamic response to nicorandil was classified into two groups: responders (Group I), those with ≥20% reduction of PVRI with no change or increase in cardiac index; and non-responders (Group II), those with <20% reduction of PVRI.

Statistical analysis: Statistical analysis was done following the compilation of data. The arithmetic mean and standard deviation was calculated for all the descriptive parameters. Paired *t* test was used for comparison of post-nicorandil parameters with baseline parameters.

Results

Baseline characteristics are shown in Table 1. All patients had a history of dyspnea, three had syncopal episodes, two had hemoptysis and two presented with congestive cardiac failure. ECG showed right ventricular hypertrophy and right axis deviation in all patients. All patients showed evidence of PAH on chest X-ray (dilated central pulmonary arteries with pruning of peripheral vessels). Seven patients had mild, and three had moderate to severe tricuspid regurgitation. Echocardiography was performed in all patients and none had evidence of left ventricular (LV) dysfunction, valvular abnormality or congenital shunt lesions.

The study was stopped prematurely in one patient who developed hypotension 30 min after the nicorandil administration and required treatment with intravenous inotropes. This patient did not differ in baseline hemodynamic parameters from other patients. Data from nine patients who completed 3 hours of serial hemodynamic study were analyzed. Serial hemodynamic effect of nicorandil is presented in Tables 2 and 3 and Figs 1 and 2. Heart rate did not change significantly from baseline values after nicorandil administration. There was a

Table 1. Baseline characteristics in 10 patients with primary pulmonary arterial hypertension

Age (years)	27.2±6.7
Sex (M/F)	8/2
NYHA functional class II	5
NYHA functional class III	5
Mild TR	7
Moderate to severe TR	3
PAMP (mmHg)	60.13±13.9
CO (L/min/m^2)	2.07±0.62
PVRI	25.39±10.0

NYHA: New York Heart Association; TR: tricuspid regurgitation; PAMP: pulmonary artery mean pressure; CO: cardiac output; PVRI: pulmonary vascular resistance index

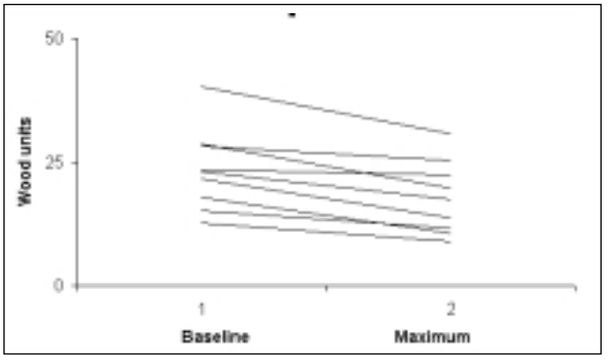

Fig. 1. *Line diagram showing maximum fall in pulmonary vascular resistance in each patient after administration of oral nicorandil.*

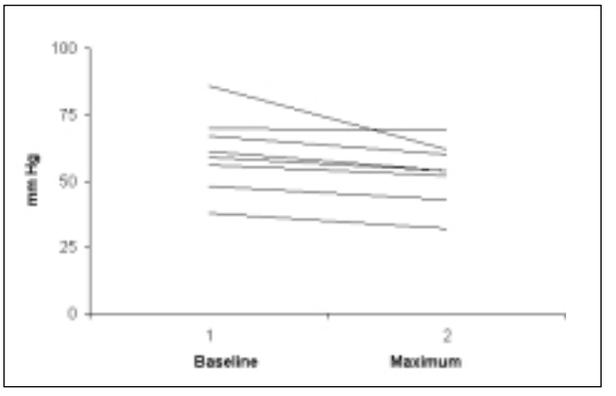

Fig. 2. *Line diagram showing maximum fall in mean pulmonary artery pressure in each patient after administration of oral nicorandil.*

Table 2. Serial hemodynamic changes after administration of oral nicorandil in 7 responders with primary pulmonary arterial hypertension

Parameters	Time of estimation after drug administration (min)					
	0	30	60	90	120	180
HR (beats/min)	86.9±8.7	85.4±10.9	87.6±11.4	87.9±12.8	90.1±9.8	87.9±12.0
RAP (mmHg)	8.7±1.4	7.4±1.4	8.3±1.4	8.4±1.6	7.7±1.4	6.3±1.0
PAMP (mmHg)	57.1±15.9	55.6±14.3	51.4±10.6	51.2±11.1	50.1±11.7	51.4±14.2
PAWP (mmHg)	10.1±1.2	10.3±1.1	10.3±1.1	10.7±2.3	9.4±3.3	9.3±1.7
SAMP (mmHg)	81.9±7.3	79.8±9.0	76.0±10.2	73.0±10.0	72.9±10.9	72.9±9.9
CO (L/min/m^2)	2.1±0.7	2.3±0.9	2.4±0.7	2.6±0.8	2.3±0.6	2.3±0.8
SVRI (Wood units)	36.3±11.5	35.2±14.4	30.1±10.6	28.0±9.6	29.1±9.2	30.4±10.0
PVRI (Wood units)	22.8±9.3	21.4±10.9	18.2±8.2	17.1±7.2	17.9±6.5	18.3±9.1

HR: heart rate; RAP: right atrial pressure; PAMP: pulmonary artery mean pressure; PAWP: pulmonary artery wedge pressure; SAMP: systemic artery mean pressure; CO: cardiac output; SVRI: systemic vascular resistance index; PVRI: pulmonary vascular resistance index

Table 3. Serial hemodynamic changes after administration of oral nicorandil in two non-responders with primary pulmonary arterial hypertension

Parameters	Time of estimation after drug administration (min)					
	0	30	60	90	120	180
HR (beats/min)	89.0±7.1	91.5±5.0	92.0±2.9	90.0±5.6	93.0±7.1	94.0±5.8
RAP (mmHg)	9.5±0.7	7.3±0.7	8±0	9±2.8	8.5±2.1	8.5±2.1
PAMP (mmHg)	65.5±6.4	66.0±5.8	66.5±3.5	64.5±6.4	64.5±9.2	68.5±16.3
PAWP (mmHg)	12±0	13±0	13±0	14±0	11±1.4	10±1.4
SAMP (mmHg)	78.5±7.9	79.5±9.2	76.0±10	76.0±1.4	76.5±5.0	78.0±1.4
CO (L/min/m^2)	2.1±0.0	2.1±0.1	2.1±0.1	2.0±0.2	2.1±0.1	2.0±0.1
SVRI (Wood units)	33.3±3.9	35±2.9	32.5±0.7	32.8±0.7	32.4±2.3	37.7±2.3
PVRI (Wood units)	26.0±3.5	26.0±2.0	26.0±3.4	25.0±1.0	26.0±4.5	28.0±7.2

HR: heart rate; RAP: right atrial pressure; PAMP: pulmonary artery mean pressure; PAWP: pulmonary artery wedge pressure; SAMP: systemic artery mean pressure; CO: cardiac output; SVRI: systemic vascular resistance index; PVRI: pulmonary vascular resistance index

significant fall in PVRI in seven patients (responders) and no significant change in PVRI in two patients (non-responders). The maximum reduction from baseline PVRI was 29.77±6.53% (23.7-40.5%) in responders and 7.3±4.2% (4.3-10.3%) in non-responders.

Discussion

The therapy of primary PAH is severely limited due to non-availability of prostacycline in many parts of the world. Any new drug with some benefit is of immense clinical interest. The role of potassium channels has been emerging in the pathogenesis of pulmonary hypertension.[7] Recent evidence suggests that potassium channel abnormality plays an important role in the development of anorectic drugs-induced pulmonary hypertension.[9] Among various pathological changes occurring in the pulmonary artery, pulmonary vasoconstriction and vascular smooth muscle hypertrophy greatly contribute to the elevated pulmonary vascular resistance in patients with primary PAH.[1,2] Activity of potassium channels regulates the membrane potential, which in turn regulates cytoplasmic free calcium concentration. A rise in cytosolic free calcium in pulmonary artery smooth muscle cells triggers vasoconstriction and stimulates cell growth. Vasoconstriction further elevates intravascular pressure and elastic stretch of the smooth muscle cells, both of which cause smooth muscle growth, creating a vicious cycle of cellular hypertrophy, proliferation, and vascular remodeling. Dysfunction of potassium channels has also been linked to decreased apoptosis in pulmonary arterial smooth muscle cells, a condition that contributes further to the medial hypertrophy of the arterial walls and vascular remodeling.[7,13]

Nicorandil is an ATP-sensitive potassium channel opener and a balanced vasodilator that has been used in patients with coronary artery disease (CAD), valvular regurgitant lesion and congestive heart failure.[16-20] Administration of nicorandil 5 to 80 mg either intravenously or as a single oral dose at rest in patients with CAD and congestive heart failure decreased systolic blood pressure by 9-28%, mean arterial pressure by 4-24%, pulmonary artery wedge pressure by 14-45% and systemic vascular resistance by 8-27%. The effect of nicorandil on cardiac output is variable in patients with CAD and congestive heart failure.[16] We previously found a significant fall in mean pulmonary artery pressure (23.6±13.6 mm

Hg to 19.1±11.7 mmHg) and PVRI (from 2.2±1.5 to 1.6±1 Wood units) shortly after administration of nicorandil in patients with severe valvular regurgitation.[16]

The favorable hemodymanic response of nicorandil in decreasing pulmonary artery pressure in ischemic heart disease and valvular regurgitant lesions and the role of ATP-sensitive potassium channel opener in decreasing pulmonary artery tone and pressure in pulmonary hypertension, suggested that nicorandil may be useful in the management of primary PAH. In the present study, 7 of 9 (77.8%) patients were responders. The percentage of responders reported in literature with other vasodilators in this condition ranges from 55% to 89%.[21-26]

Various acute complications have been reported after administration of vasodilators in patients with primary PAH. The incidence of serious complications ranged from 6-10%.[25,26] Weir et al.[25] reported three adverse events in 29 patients among 422 patients included in drug trials. The nature and severity of adverse events varied from drug to drug. In our study, only one patient developed systemic hypotension which required treatment with inotropes. Otherwise, the drug was well tolerated in the remaining patients.

Conclusions: Oral nicorandil decreased pulmonary artery pressure in acute hemodynamic testing in patients with primary PAH and the drug was well tolerated. Larger and long-term studies are required to further validate the effects of nicorandil in the management of primary PAH.

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Original Article

Prevalence, Prognostic Importance and Therapeutic Implications of Anemia in Heart Failure

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Background: Despite advances in its management, heart failure, once established, remains highly prevalent and lethal. Anemia can exacerbate the hemodynamic burden in heart failure. The present study was undertaken to assess the presence of anemia and analyze how its control impacts the outcome in heart failure patients.
Methods and Results: From a cohort of 238 heart failure patients, 55 (231%) patients were found to be anemic. Twenty-nine patients (Group A) were given recombinant human erythropoietin for 12 weeks along with iron, and followed up for a mean period of 24±6 months. The patients improved substantially in terms of functional capacity (6 min walk test improved from 232±35 m to 278±41 m, $p < 0.001$), hemoglobin level from 10.1±0.90 gm/dl to 12±0.7 gm/dl, ($p \leq 0.001$), and ejection fraction from 33±7.1% to 41±6.9% ($p \leq 0.001$). Twenty-six patients (Group B) who were age- and sex-matched with Group A and had similar degree of functional disability and left ventricular dysfunction as that of Group A were not given erythropoietin and iron. Thus, Group B patients served as controls. In comparison to Group B, Group A patients demonstrated not only higher hemoglobin level (12±0.7 gm/dl *v*. 9.8±0.9 gm/dl, $p \leq 0.001$), and ejection fraction (41±6.9% *v*. 26±7%, $p \leq 0.05$), but also better survival (16/29 *v.* 7/26, $p < 0.05$, odds ratio 1.27).
Conclusions: Anemia is a significant predictor of poor outcome in patients with heart failure. Administration of erythropoietin can correct anemia and help improve survival. **(Indian Heart J 2005; 57: 670–674)**

Key Words: Heart failure, Anemia, Erythropoietin

Heart failure (HF) is a major clinical and public health problem. Patient survival has improved by the advances in the treatment of overt HF and its predisposing factors such as hypertension, myocardial ischemia and valve diseases, but the overall morbidity and mortality remains considerable. The exact magnitude of the problem is difficult to assess because we lack broadbased population estimates of its prevalence, and mortality rates.[1] It is estimated that nearly 23 million people have heart failure worldwide.[2] Estimates from European countries indicate that heart failure consumes 1-2% of total health care budget.[3]

Despite significant success of pharmacologic blockade of neurohumoral activation in HF, the negative or neutral results of multiple recent trials suggest that we have reached a ceiling of benefit with regard to this approach.[4] This has led to the search for novel and newer mechanisms to address the persistent high morbidity and mortality associated with HF. Anemia has recently been demonstrated to be a common comorbid condition in patients with HF, and multiple observational studies have demonstrated an independent association between lower hemoglobin and adverse clinical outcome in this syndrome.[5] In patients with HF, the presence of anemia is associated with reduced exercise capacity, greater hospital admission rates, lower quality of life and symptoms score.[6] The prevalence of anemia in patients with HF depends on the level of hemoglobin (Hb) that is chosen as lower limit of normal, varying between 14.4% when an Hb level of 11 gm/dl is chosen and 15.6% when an Hb level is 12 gm/dl is chosen.[7,8] Clinical trials with recombinant human erythropoietin in patients with chronic kidney disease and concomitant structural heart disease have demonstrated beneficial effects on ventricular remodeling but variable effects on clinical outcome.[9] Excessive cytokine production, which is common in HF, causes reduced erythropoietin secretion and interferes with activity of erythropoietin in bone marrow.[10] Preliminary trials in anemic patients with HF demonstrate that erythropoietin therapy is well tolerated and associated with short-term clinical

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improvement, though the optimum target hemoglobin and dosing regimen of erythropoietin is not known.[9]

The aim of present study was to quantify the presence of anemia and its influence on symptoms and exercise tolerance in a group of patients with HF. We also tried to assess the impact of erythropoietin therapy on functional capacity and survival in patients with heart failure having anemia.

Methods

The study was carried from January 2002 to December 2004. Presence of symptoms like effort dyspnea, orthopnea and paroxysmal nocturnal dyspnea were noted. Detailed physical examination was done in all. Heart failure was diagnosed clinically according to Framingham criteria which defines a series of major and minor criteria to establish the diagnosis of heart failure.[11] The patients were subjected to echocardiographic examination and were enrolled to the study protocol if they had left ventricular ejection fraction (LVEF) of < 40% with the Simpson's measurement.[12] Besides ejection fraction, the other echocardiographic parameters specifically studied were end-diastolic dimension (EDD), end-diastolic volume (EDV), end-systolic dimension (ESD), and end-systolic volume (ESV). Each patient was subjected to full blood count including hemoglobin estimation and blood tests for renal function. The definition of anemia used was that of the World Health Organization (Hb < 13 gm/dl in men and Hb < 12gm/dl in women).[5] Serum iron was estimated in all anemic patients. All patients underwent 6 min walk test. The patients excluded from the study were those having anemia due to known secondary causes, i.e. malignancy, inflammatory diseases, chronic renal disease, active bleeding, and deficiency of iron, Vitamin B_{12} or folic acid. Patients having surgically correctable causes of heart failure were not included in the study. Those patients who had clinical evidence of heart failure but normal ejection fraction by echocardiography (diastolic heart failure), were also excluded from the study protocol. Those patients who did not return for follow-up were not considered for final analysis.

One group of anemic patients with heart failure (Group A) was given intravenous recombinant human erythropoietin (rHuEPO) 50 units/kg of body weight per dose twice weekly for 12 weeks. These patients were also administered iron (sodium ferric gluconate complex in sucrose equivalent to 62.5 mg of elemental iron) intravenous (IV) twice a week. Iron therapy was withheld if serum ferritin exceeded 800 ng/ml. Target Hb level was 12 gm/dl. Hemoglobin, hematocrit, and serum ferritin were estimated before therapy and every month for 3 months. Group B patients also had anemia with heart failure, similar functional disability and poor left ventricular (LV) function. This group of patients was not given erythropoietin, and served as controls. Group C patients were those with heart failure without anemia.

Follow-up: The total duration of follow-up was 36 months with a mean period of 24±6 months. Besides the blood tests carried out in anemic patients given erythropoietin and iron as described above, all the patients were subjected to symptomatic evaluation, routine blood estimation, 6 min walk test and detailed echocardiographic examination first at 3 months and then at 6 monthly intervals during the follow-up period.

Statistical analysis: Variables were expressed as mean ±SD The students' *t* test and chi-square test were used to test the significance between the study groups. Risk analysis was carried out by calculating the odds ratio (OR) and relative risk (RR). SPSS 11.0 software was used for the analysis purpose.

Results

Initially, a total of 259 HF patients were taken up for study, 21 did not return for follow-up examination and were excluded from the study protocol. Data of 238 patients were finally analyzed. Group A comprised 29 patients with anemia and HF, who were administered erythropoietin and iron. In Group B, 26 subjects were included with anemia and HF who were not given erythropoietin and served as controls. Group C comprised 183 HF patients without anemia. Thus, out of 238 HF patients, 55 (23.1%) had anemia.

Patients of HF with and without anemia were nearly evenly matched as regards age (64.8±7.9 years *v.* 69.0±7.2 years) and sex (61.1% *v.*61.4% males) without any statistically significant difference. Mean Hb level was 10.2±0.9 gm/dl and 13.7±0.8 gm/dl ($p < 0.001$) in the two groups, respectively. HF patients with anemia were more likely to have advanced symptoms (30.9% *v.* 18.1%, $p < 0.05$). They were also unable to walk more in standard 6 min walk test (236±31 m *v.* 250±27 m, $p < 0.05$). HF patients having anemia tended to have inceased EDV (165±24.9 ml *v.* 151±21 ml, $p < 0.001$) and ESV (97± 14.8 ml *v.* 83±10.1 ml, $p < 0.05$). The ejection fraction was also low in HF patients with anemia. Pattern of drug therapy like use of digoxin, furosemide, angiotensin-converting enzyme (ACE) inhibitors, beta-blockers and

angiotensin receptor blockers (ARB) were same in both the groups.

Baseline characteristics of heart patients with anemia who received erythropoietin and iron (Group A) and HF patients with anemia who did not receive erythropoietin and iron (Group B) were almost similar without any statistically significant difference. Both the groups were thus evenly matched for age (63.5±8.1 years *v.* 65.1±7.6 years), sex (31.8% *v.* 30.0% males), EDV (164±27 ml *v.* 168±25.7 ml), ESV (97.6±14.9 ml *v.* 101±13.9 ml), ejection fraction (33±7.1% *v.* 32.4±6%), 6 min walk test (232±35 m *v.* 239±37 m), and serum iron level (12.9±5 µmol/L *v.* 11.6±4.7 µmol/L).

Alterations in various parameters following erythropoietin and iron administration have been shown in Table 1. The Hb level rose from 10.1±0.9 gm/dl to 12±0.7 gm/dl ($p \leq 0.001$). The patients' 6 min. walk test improved from 232±35 m to 278±41 m, $p < 0.001$. The LV dimensions deceased and ejection fraction improved significantly (from 33±7.1% to 41±6.9%, $p < 0.001$). Adverse effects were minimum with erythropoietin therapy. Only two patients developed transient hypertension following the first dose which did not require any intervention.

Table 1 depicts the comparison between the Group A (n=16) and Group B (n=7) patients at the end of follow-up. The patients belonging to Group A had better functional capacity (6 min walk test 278±41 m in Group A *v.* 227±16 m in Group B, $p < 0.05$), higher Hb level (12±0.7 gm/dl *v.* 9.8±0.9 gm/dl $p < 0.001$). The ejection fraction also was significantly higher in group A (41±6.9% *v.* 26±7%, $p < 0.05$). The survival was better in Group A (55.1% *v.* 26.9%, $p < 0.05$, OR=1.27).

Comparison was made between Group B (anemic patients with HF, not given erythropoietin and iron) and Group C patients (HF without anemia). The patients belonging to the former group had poorer functional capacity (6 min walk test: 227±16 m *v.* 251±10 m, $p < 0.05$), and lower ejection fraction (26 ± 7% *v.* 37±5.1%, $p < 0.05$). There were also fewer survivors in Group B (26.9% *v.* 53%, $p < 0.05$); the relative risk (RR) of chance of survival was 0.51:1.

Discussion

The present study demonstrates that the prevalence of anemia in patients, with HF is 23.1%. The frequency of anemia in patients with HF varies widely. The reasons for this wide variation include differences in the HF population studied, in study methods, and in the definition of anemia used.[5] While Silverberg et al.[8] report a prevalence of 55%, Al-Ahmad et al.[13] described a lowly 4% prevalence of anemia in HF patients. Horwich et al.[6] and Felker et al.[14] who adopted the WHO definition of anemia (as in present study) have reported 30% and 49% prevalence of anemia, respectively.

In our study, more number of anemic patients had advanced symptoms than the heart failure patients without anemia. Similar observation has been made by Szachniewicz et al.[15] Silverberg et al.[8] reported very high prevalence of anemia (79%) in class IV population.

As the anemia was a significant problem in patients with heart failure and was associated with severe symptoms, attempt was made to correct it by giving erythropoietin and parentral iron; 29 patients received the therapy, while 26 served as controls. There was significant improvement in functional capacity along with rise of (Table 1). The LV dimensions got reduced with improvement in ejection fraction. Fig. 1 shows ejection fraction in different groups

Table 1. Pre- and post-therapy parameters within GroupA and between Group A and Group B at end of follow-up

	Group-A			Group B (n=7)	
	Before EP therapy (n=29)	After EP therapy (n=16)	p value	Without EP therapy	p value*
6 Min walk test (m)	232±35	278±41	< 0.001	227±16	< 0.05
Hemoglobin (gm/dl)	10.1±0.9	12.0±0.7	< 0.001	9.8±0.9	< 0.001
LVEDD (mm)	59±6.4	53±5.1	<0.01	63±5.8	<0.001
LVESD (mm)	48±7.0	42.1±6.0	<0.01	51.0±7.0	<0.05
LVEDV (ml)	164±27	130±18.9	<0.001	170±24.9	<0.001
LVESV (ml)	97.6±14.9	84.6±11.0	<0.01	105±12.9	<0.05
LVEF (%)	33±7.1	41.0±6.9	< 0.001	26±7	< 0.05
Survivors	-	16/29 (55.1%)	-	7/26 (26.9%)	< 0.05

*p value is obtained after comparing the patients (n=16) at end of EP therapy with those having not received EP (n=7).
EP: erythropoietin; LVEDD: left ventricular end-diastolic dimension; LVESD: left ventricular end-systolic dimension; LVEDV: left ventricular end-diastolic volume; LVESV: left ventricular end-systolic volume; LVEF: left ventricular ejection fraction

at baseline at end of follow-up. In an uncontrolled study, Silverberg et al.[8] also demonstrated that use of erythropoietin and iron resulted in marked improvement in functional capacity, with patients being able in many instances to return to work and live quite normal lives. These positive findings were accompanied by improvement in LVEF. In another study,[16] the same group conducted a small randomized trial of recombinant human erythropoietin and intravenous iron in 32 patients with functional class III to IV heart failure, which demonstrated that treatment of anemia in this patient population resulted in improved functional class and decrease in need for hospitalization. Mancini et al.[17] reported that 3 months therapy with erythropoietin significantly improved exercise capacity in anemic HF patients. There were significant increases in Hb level, peak oxygen consumption and exercise duration, but these two studies did not address the issue of any reduction in mortality. The present study showed survival benefit following use of erythropoietin. At the end of follow-up, out of 29 patients, 16 (55.1%) were alive whereas only 7 (26.9%) managed to survive out of 26 who were not given erythropoietin. Fig. 2 shows percentage of survival in different groups of patients.

The present study showed that anemic HF patients continued to deteriorate with worsening of functional capacity and ejection fraction during the follow-up period. At the end of follow-up, 26.9% were alive in contrast to 53% survival in HF patients without anemia. Anemia contributes to the exercise intolerance that is a major morbidity in chronic heart failure.[5] Kalra et al.[18] found that Hb was a significant independent predictor of maximal exercise tolerance as measured by peak oxygen consumption, even after controlling for ejection fraction, age and renal function. Anemia was a relevant and independent indicator of poor outcome in unselected, prospectively evaluated HF patients.[15] In the Outcome of Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure (OPTIME-CHF) study which involved patients hospitalized with decompensated HF, hemoglobin levels were also found to be independently associated with adverse outcomes, with a 12% increased risk of death or rehospitalization at 60 days for every decrease of 1 gm/dl of hemoglobin.[14]

Although a precise definition for a cut-off value of hemoglobin level for anemia continues to be elusive, it has been found to be a common complication in HF patients. There are several possible pathogenetic mechanisms for anemia in HF and a precise underlying cause is found in only a minority. Potential mechanisms include hemodilution, renal dysfunction, proinflammatory

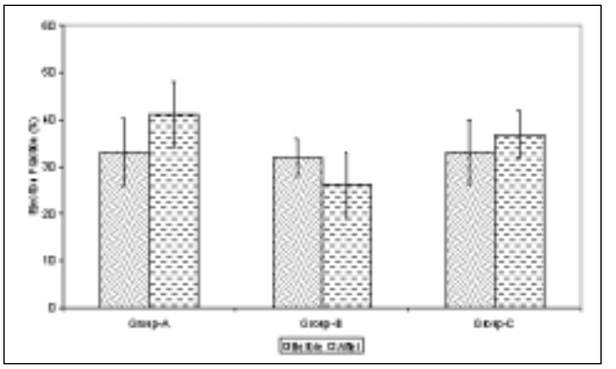

Fig. 1. *Ejection fraction (%) at baseline and at end of follow-up.*

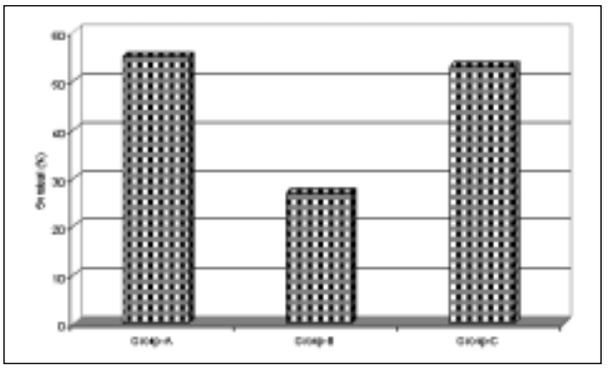

Fig. 2. *Survival (%) in different groups at end of follow-up.*

cytokines, malnutrition due to right-sided heart failure, decreased perfusion to the bone marrow, and drug therapy (such as ACE inhibitors).[5] Elevated levels of circulating proinflammatory cytokines can lead to deceased erythropoietin production and resistance to the effects of erythropoietin on bone marrow production of red blood cells.[5] In both the cases, the true anemia or the one due to hemodilution, prognosis is worse than for patients with a normal Hb level.[19] Another potentially important cause for anemia in HF is treatment with ACE inhibitors, which can significantly decrease Hb level via the inhibition of erythropoietin synthesis.[20] In the present study, however, no difference was found in pharmacologic therapy between anemic and non-anemic patients.

Limitations of the study: Total numbers of HF patients having anemia were rather small in the present study. Also, the optimal range for Hb needed for benefits cannot be established from the study. The study was also a non-randomized and non-blinded one. Though echocardiography is the most useful and convenient approach for assessment of resting LV function, it is highly

operator-dependent and there can be significant intra- or inter-observer variability in the data obtained.

Conclusions: A significant number of patients with heart failure can have anemia, which further worsens the already bleak outcome of heart failure patients. Correction of anemia by erythropoietin therapy may tilt the balance and improve survival in such patients who are doubly beset by heart failure and anemia. Current guidelines provide no specific recommendations for evaluation or treatment of anemia.[21] Hence, studies involving large number of patients are needed to find out whether anemia is an important prognostic indicator in patients with heart failure. Large scale, double blind and placebo-controlled trials are also necessary to confirm further whether erythropoietin offers any survival benefit to anemic heart failure patients.

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Prevention of Atherosclerosis Progression Using Atorvastatin in Normolipidemic Coronary Artery Disease Patients - A Controlled Randomized Trial

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Background: Statins have been known to reduce progression of atherosclerosis when used in high dosage in patients with elevated cholesterol. A large majority of Indian patients, however, develop coronary artery disease with average or below average cholesterol level. There is insufficient data on effect of low-dose statins on progression of atherosclerosis in such patients with normal / average lipid levels.

Methods and Results: In this prospective study, 150 patients with angiographically proven coronary artery disease and baseline total cholesterol <200 mg/dl and low-density lipoprotein cholesterol <130 mg/dl were randomized to treatment with low-dose atorvastatin (10 mg) or placebo. Both groups were comparable in demographic characteristics. Progression of atherosclerosis was assessed using carotid intima media thickness as surrogate marker using standard protocol on B-mode ultrasound including common carotid artery, common carotid bifurcation and internal carotid artery measurements. Follow-up study for carotid intima media thickness was done at end of one year. A decrease in mean maximum carotid intima media thickness was recorded for all the three carotid segments individually from basal to end of one year in atorvastatin group [common carotid artery –0.008 mm (p = 0.01), common carotid bifurcation –0.022 mm (p = 0.001), internal carotid artery –0.009 mm (p = 0.01)] while the same showed an increase in placebo group [common carotid artery +0.011 mm (p = NS), common carotid bifurcation +0.013 mm (p = NS), internal carotid artery +0.007 mm (p = NS)]. The average mean carotid intima media thickness (all three segments included) decreased from 0.739 ± 0.114 mm to 0.726 ± 0.115 mm (difference –0.013 mm) in statin group and increased from 0.733 ± 0.124 mm to 0.742 ± 0.117 mm (difference + 0.009 mm) in placebo group (p<0.001). Along side, there was a reduction in the total cholesterol from 144 ± 26 mg/dl to 130 ± 18 mg/dl (↓9.7%, p = 0.05) and in low-density lipoprotein cholesterol from 86 ± 24 mg/dl to 74 ± 19 mg (↓13.9%, p = 0.05) in study group and an increase in total cholesterol from 148 ± 32 mg/dl to 154 ± 8 mg/dl (↑4.05%, p = NS) and in low-density lipoprotein cholesterol from 84 ± 19 mg/dl to 87 ± 16 mg/dl (↑3.57%, p = NS) in placebo group at end of one year (p=NS). No adverse effects of statins were reported in the treatment arm.

Conclusions: We conclude that low-dose statins reduce progression of atherosclerosis as observed by carotid intima media thickness in Indian patients with known coronary heart disease and normal lipid values independent of lipid lowering. The study favors use of this therapy in patients with normal / below average cholesterol levels. **(Indian Heart J 2005; 57: 675–680)**

Key Words: Intima media thickness, Atherosclerosis, Statins

National cholesterol education program (NCEP)-III guidelines recommend drug therapy for low-dose lipoprotein (LDL) >130 mg/dl with target of <100 mg/dl in patients with known coronary artery disease (CAD).[1-3] Statins are known to reduce coronary events in patients of CAD with elevated cholesterol levels.[4-7] Many studies have shown a decrease in major adverse cardiovascular events (MACE) in patients with average or above average cholesterol with statin.[8-12] Decreased progression or reversal of atherosclerosis has been reported in patients with elevated cholesterol using statin therapy.[8-16] Few recent reports suggest reversal of atherosclerosis in patients with

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average cholesterol using statins.[17,18] The dosage of statin used in most such trials, however, is high and all trials are from the western literature.

A large majority of Indian patients develop CAD with mean cholesterol within normal range, so to say, with average/ below average cholesterol levels.[19,20] The decrease in adverse events with statin therapy is explained by both, a decrease in cholesterol level and over and above, the beneficial pleiotropic effect of statins.[21,22] If one follows the NCEP guidelines strictly on the Indian patients, many of them would not call for statin therapy and thus be devoid of the beneficial pleotropic effects of statins. Also there is no data on reversal of atherosclerosis as detected through carotid intima media thickness (IMT) in this subgroup of patients with average/below average cholesterol levels and that too with low-dose atorvastatin which could be effective because of the smaller build of Indian patients. Therefore, we aimed to study the effect of low-dose statin therapy in the Indian CAD patients with average or below average cholesterol levels and assess atherosclerotic progression using carotid IMT as a surrogate marker.

Methods

Inclusion and exclusion criteria: In this prospective randomized study, 150 consecutive patients undergoing coronary angiography and showing angiographically proven CAD were enrolled if LDL was <130 mg/dl and total cholesterol (TC) < 200 mg/dl. Patients with history of recent myocardial infarction (MI) (<6 weeks), altered liver function test (SGPT/SGOT >3 times of normal), altered renal parameters (raised serum creatinine of > 2 mg/dl), triglycerides (TG)>200 mg/dl, those already receiving lipid lowering drug therapy or daily alcohol intake > 3 peg per day, were excluded. Patients with secondary causes of elevated cholesterol levels were also excluded (steroid therapy, hypo/hyperthyroidism, antacid containing aluminum) and so were the patients with any major systemic illness. Basal demographic characteristics, risk factors profile and associated drug therapy was also studied.

Method of measuring lipid value: The lipid values of all the patients were measured in a fasting state on the morning of the day the coronary angiography was done. Fresh fasting samples (after 12 hours of overnight fasting) were used for the estimation of lipid profile. Lipid profile included TC, TG, high-density lipoprotein cholesterol (HDL-c) and very low-density lipoprotein cholesterol (VLDL-c) measured by the enzymatic method (Autoanalyzer, Technicom RX XT). The reagent was added to the serum according to the method described in the kits. VLDL-c was estimated by dividing the TG levels by a factor of 5. LDL-c was obtained by subtracting the sum of VLDL-c and HDL-c fractions from TC by applying the Friedewald formula.

Randomization: Patients taken for diagnostic coronary angiography and showing definite significant CAD (>50% diameter stenosis in at least one major coronary vessel) were randomized into two groups viz. atorvastatin 10 mg/ day (Group I) and placebo (Group II), once the inclusion criteria were fulfilled. The allocation was made on an alternate basis with atorvastatin 10 mg (study group) as a part of treatment medicine while placebo group got no statin in treatment protocol. All patients received dietary advice and lifestyle modification at time of randomization.

Follow-up: Follow-up was done at 1 year on an outdoor basis for reassessment of carotid IMT measurement. To look for dietary compliance, lifestyle modification advice and monitor for any side effects of statins, an in-between visit at 6 months was also done. Average of two fasting lipid profile values, was taken both at basal and at one year.

Carotid ultrasound: Carotid IMT was assessed at basal and after one year of study period by B-mode on HP Sonos 5300 machine by standard protocol.[23-28] Carotid artery was divided into three segments based on anatomy and geometry (Fig. 1). The first segment was common carotid artery (CCA), which is the straight distal 10 mm of vessel that lies immediately proximal to the beginning of bifurcation. The carotid bifurcation was the second segment that begins at the point of the dilation and ends at arc of the blood flow divider separating the internal and external carotid arteries. The third segment was proximal 10 mm of internal carotid artery. For each segment of carotid artery, far and near wall measurements were done on both sides (right and left). For the total of 12 walls thus identified viz. right far (RF), right near (RN), left far (LF) and left near (LN) of distal CCA, common carotid bifurcation (CCB) and proximal internal carotid artery (ICA), the sonographer attempted to record as many images as possible to find the thickest wall or to say, the maximum IMT. The measurement areas were magnified (×10) for clear resolution. An average of right and left side for each of the three segments individually was calculated to give the mean IMT of each segment individually. The average of values thus obtained for all 12 segments gave the average mean maximum IMT, which was then taken for analysis. A single reader blinded to study group performed all carotid IMT measurements on recorded images. The intra-observer variation was <1%. To minimize the effect of cardiac cycles on IMT measurements, each IMT was obtained through an average of values obtained from 4 frames chosen

randomly at different times in the cardiac cycle. The changes in the overall mean maximum IMT at basal study and one year follow-up were evaluated in both study groups and statistical analysis applied. Ultrasonographer was blinded to treatment allocation during both basal and follow-up IMT study.

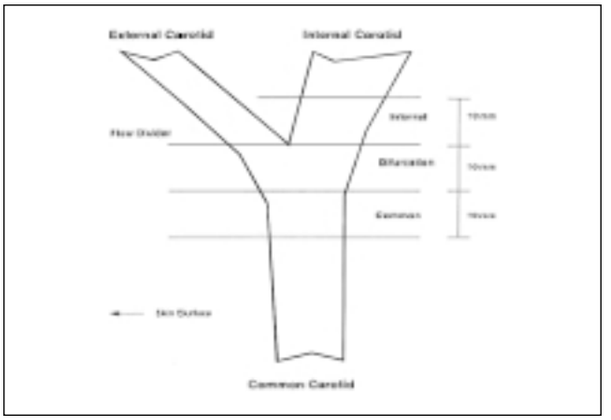

Fig. 1. *Sites for measurement of carotid intima-media thickness.*

Study end points: The primary end point of the study was to assess the change if any, in carotid IMT at end of one year in both groups secondary end point was to assess the effect of treatment on lipid profile in the two groups.

Statistical analysis: All statistical analyses were performed using SPSS software version 11. Values were reported as mean ± standard deviation (SD). A 2-sided probability value of ≤ 005 was considered statistically significant. Comparison of the treatment effect between two groups for primary end point i.e. change in maximum carotid IMT in all three segments individually and combined, was performed with *t* test for independent group.

Results

Basal demographic profile: Basal demographic profile is shown in Table 1. In this study, a total of 150 patients were randomized, 75 in each group. Group 1 constituted the treatment arm (atorvastatin 10 mg) and Group 2 placebo. Mean age was similar in two groups (57.23 ± 8 years *v.* 55.03 ± 3 years). The proportion of females was 18.7% and 24%, diabetes was noted in 32% and 28%, hypertension in 44% and 50.7% and smoking history was positive in 16% and 18.7% in Groups I and II, respectively (p= NS). Positive family history of premature CAD and/or peripheral arterial disease was present in a small percentage

Table. 1. Demographic characteristics.

	Drug: *n* (%)	Placebo: *n* (%)	p value
Age (years)	57.23	55.03	0.56
Male	61 (81%)	57 (76%)	0.48
Female	14 (19%)	18 (24%)	0.61
HTN	33 (44%)	38 (51%)	0.51
DM	24 (32%)	21 (28%)	0.53
Smoker	12 (16%)	14 (19%)	0.60
F/H premature CAD	9 (12%)	7 (9%)	0.62
Peripheral arterial disease	4 (5%)	3 (4%)	0.58
Beta-blockers	70%	64%	0.41
CB	21.3%	22.4%	0.45
ACE-I	77%	81%	0.49
Aspirin	All	All	–

HTN: hypertension; DM: diabetes mellitus; F/H: family history; CAD: coronary artery disease; ACE-I: angiotensin-converting enzyme inhibitor; CB: calcium blockers

of patients in both groups; 145 patients completed one-year follow-up. Two patients in treatment group and three patients in placebo group were lost to follow-up.

Lipid profile: Lipid profile in the two groups is shown in Table 2. Basal lipid profile was comparable in both groups except slightly higher TG level in placebo arm. Over the 12 months of follow-up, there was a significant reduction in TC from 144 ± 26 mg/dl to 130 ± 18 mg/dl (↓9.7%, p = 0.05), LDL-c from 86 ± 24 mg/dl to 74 ± 19 mg/dl (↓13.9%, p = 0.05) and TG from 142 ± 66 mg/dl to 119 ± 45 mg/dl (↓16%, p = 0.04) compared to basal in atorvastatin group while there was no significant change in TC from 148 ±32 mg/dl to 154 ± 28 mg/dl (↑4.05%, p = 009), LDL from 84 ± 19 mg/dl to 87 ± 17 mg/dl (↑3.57%, p = 015) and TG from 152 ± 38 to 156 ± 34 mg/dl (↑2.63%, p = 014) in placebo group. Increase in HDL occurred in both the treatment and placebo arms by 6.6% and 5.9%, respectively. All patients continued statin therapy during study period and no adverse effects were reported. Liver and muscle enzymes done at 6 months and one year were in normal range.

Basal study: Carotid IMT measurements in each segment are shown in Tables 3 and 4. Basal carotid IMT was comparable in both the study groups viz. treatment and placebo as shown in Table 3, with mean maximum basal IMT in drug and placebo group being 0.648 ± 0.099 mm and 0.631 ± 0.093 mm for CCA; 0.836 ± 0.109 mm and 0.840 ± 115 mm for CCB and 0.733 ± 0.104 mm and 0.729 ± 104 mm for ICA (p= NS), respectively.

Follow-up study: All the three carotid segments analyzed independently showed decrease of carotid thickness at end of one year in the treatment group [CCA (–)0.008 mm, CCB (–)0.022 mm and ICA (–)0.09 mm] while the same showed

Table 2. Lipid profile: basal and after one year

	Drug		% change	p	Placebo		% change	p value
	Basal	After 1 year			Basal	After 1 year		
TG (mg/dl)	142 ± 66	119 ± 45	16.0%(↓)	0.04	152 ± 38	156 ±34	2.63%(↑)	0.14
TC (mg/dl)	144 ± 26	130 ± 18	9.7% (↓)	0.05	148 ± 32	154 ± 28	4.05%(↑)	0.09
HDL (mg/dl)	30 ± 5	32 ± 5	6.6%(↑)	0.12	34 ± 5	36± 5	5.9%(↑)	0.13
LDL (mg/dl)	86 ± 24	74 ± 19	13.9% (↓)	0.05	84±19	87±16	3.57%(↑)	0.15

TG: triglycerides; TC: total cholesterol; HDL: high-density lipoprotein; LDL: low-density lipoprotein

an increase in placebo group [CCA (+)0.011 mm, CCB (+)0.013 mm and ICA (+)0.007 mm] as shown in Table 4. The change in mean maximum IMT (all three segments combined) was (–)0.013 mm and (+)0.009 mm in drug and placebo group, respectively (p<0001). The change of carotid IMT between two groups at end of one year was statistically highly significant (Table 4).

Table 3. Basal carotid IMT in two study groups (mm)

Arterial segment		Treatment	Placebo	p value
CCA	Right	0.646 + 0.090	0.627 + 0.089	0.21
	Left	0.650 + 0.096	0.635 + 0.090	0.24
	Mean	0.648 + 0.099	0.631 + 0.093	0.20
CCB	Right	0.828 + 0.106	0.842 + 0.111	0.19
	Left	0.828 + 0.106	0.838 + 0.114	0.18
	Mean	0.836 + 0.109	0.840 + 0.115	0.18
ICA	Right	0.723 + 0.096	0.733 + 0.101	0.21
	Left	0.743 + 0.098	0.725 + 0.099	0.16
	Mean	0.733 + 0.104	0.729 + 0.104	0.21
Mean IMT*		0.738 + 0.123	0.733 + 0.124	0.20

IMT: intima-media thickness; CCA: common carotid artery; CCB: common carotid bifurcation; ICA: internal carotid artery
* All three segments included

Discussion

Our study primarily shows a decrease in progression of atherosclerosis with low dose of atorvastatin in patients with normal/below average cholesterol levels. This is evidenced from the significant decrease of IMT in all three segments of carotid artery in the treatment group at one year [CCA (-)0.008 mm, CCB (-)0.022 mm and ICA (-)0.009 mm]. The placebo group, on the other hand, on a similar follow-up protocol showed an increase in thickness [CCA (+)0.011 mm, CCB (+)0.013 mm, and ICA (+)0.007 mm]. The degree of change in carotid IMT between the two groups was statistically highly significant (p<0.001). Studies done in the past on progression of atherosclerosis as assessed using carotid IMT have made similar observations but on patients with either elevated basal TC or with much higher mean levels even if within normal range.[10,11,15,17,18] In PLAC-II[10] and CLAS[15] studies, patients with elevated TC showed a reduction in their carotid IMT over three and four years, respectively, but with mean basal LDL-c of 150 mg/dl and above.[10,15] ARBITER[18] and

Table 4. Change in carotid intima media thickness (mm) at one year: Follow-up in two study groups

	Basal		One year		Change in IMT at 1 year from baseline		p value
Arterial segments	Atorvastatin	Placebo	Atorvastatin	Placebo	Atorvastatin	Placebo	
CCA: Right	0.646 + 0.090	0.627+0.089	0.640+0.091	0.640+0.088	-0.006	0.013	00.09
Left	0.650+0.096	0.635+0.090	0.641+0.089	0.644+0.092	-0.009	0.009	0.10
Mean	0.648+0.099	0.631+0.093	0.640+0.098	0.642+0.097	-0.008	0.011	0.01
CCB: Right	0.828+0.106	0.842+0.111	0.807+0.104	0.851+0.108	-0.021	0.009	0.07
Left	0.845+0.112	0.838+0.114	0.823+0.104	0.854+0.116	-0.022	0.016	0.06
Mean	0.836+0.109	0.840+115	0.815+0.106	.852+0.119	-0.022	0.013	0.001
ICA: Right	0.723+0.096	0.733+0.101	0.715+0.096	0.740+0.103	-0.008	0.007	0.11
Left	0.743+0.098	0.725+0.099	0.733+0.097	0.731+0.098	-0.010	0.006	0.10
Mean	0.733+0.104	0.729+0.104	0.724+106	0.735+108	-0.009	0.007	0.01
Mean IMT*	0.739+0.114	0.733+0.124	0.726+ 0.115	0.742+117	-0.013	0.009	0.01

p value for change in intima-medial thickness at 1 year between atorvastatin and placebo
CCA: common carotid artery; CCB: common carotid bifurcation; ICA: internal carotid artery

* all three segments included

LIPID[11,17] substudy with average basal LDL-c still had values much higher than our study group, which had a mean basal LDL of only 85 mg/dl.

The decrease in carotid IMT in most studies is associated with significant decrease in lipid levels. The magnitude of decrease in LDL-c and TC in our study was, however, small compared to other trials. This could be explained by an already low (one of the lowest basal TC amongst all studies done so far) LDL in our study when compared with other studies till date and a limit to which drugs could lower cholesterol levels.

Also the decrease in carotid IMT seen in previous trials was secondary to use of large-dose statins. In PLAC-II study,[10] there was a significant reduction in carotid IMT (35%) as against placebo observed with pravastatin but at a dose of 20 mg to 40 mg per day. Similarly in CLAS study[15] lovastatin showed a decrease in carotid IMT compared to placebo at follow-up of two years but with 80 mg/kg of this drug. Lovastatin group showed a decrease in carotid IMT of (–)0.038 mm $\pm$ 0.004 mm/year while the placebo group had an increase of (+)0.019 $\pm$ 0.004 mm/year ($p<0001$). Also, LIPID atherosclerosis substudy showed a 0.014 mm decrease in carotid IMT but with pravastatin 40 mg/day while an increase of 0.048 mm occurred in placebo group over this same period of four years.[11,17] ARBITER study[18] showed that a higher dose of statin (atorvastatin 80 mg/day) used to reduce LDL-c by 50% was associated with decrease of 0.038 mm in carotid IMT while the low dose of statin (pravastatin 40 mg/day), despite showing a reduction of LDL-c by 27%, was associated with a mean progression of carotid IMT to the tune of 0.026 mm. We feel that our positive results with low-dose statin could be explained by the smaller build of our patients who probably need lesser statin dose for similar effects and a much low basal lipid levels in our patients. Also, with mean cholesterol being one of the lowest in our patients among all studies done in past, the amount of cholesterol reduction to have beneficial effect of statin treatment might be of a much lesser magnitude. Karter et al.[22] have already shown improvement in endothelial dysfunction with statins occurring irrespective of the dosage used which further support our results.

Carotid IMT being a surrogate marker of progression of atherosclerosis, the decrease in IMT in treatment group could be judged as a marker of decrease in progression of atherosclerosis secondary to statins.[23-32] The retardation of progression in carotid IMT is probably related to lipid lowering as well as beneficial pleotropic effects of statin. Our study suggests that even patients with normal / below normal TC show retardation in progress of atherosclerosis using statins which may be beneficial in these patients.

Experimental data from mammals suggest that physiological LDL level is only 50 to 70 mg/dl. Observational studies have shown a continuous positive relationship between CHD risk and LDL levels beginning from 50 to 70 mg/dl onward. Cardiovascular event rate approaches zero at LDL-c level of 57 mg/dl for primary prevention and 30 mg/dl for secondary prevention. The LDL level of healthy neonates is only 30 to 70 mg/dl and healthy adult primates 40 to 80mg/dl. An LDL level of 50 to 70 mg/dl, which although seems excessively low, is precisely normal for humans living a lifestyle of and eating a diet for which they are genetically adapted.[33]

Study limitations: This study included small number of patients; it was a single center trial and follow-up was limited to one year only. A larger number of patients studied with longer follow-up would be required to establish our results in a wider range of patients. The adverse clinical outcome at follow-up has not been addressed, primarily because follow-up was limited to one year and small number of patients studied. To properly address this issue, a minimum follow-up of at least 4-5 years in a much larger number of patients would be needed. We do intend to continue follow-up of the current patient cohort for a longer period of time.

Conclusions: The patients of CAD with truly low cholesterol level also benefit from statin therapy and even in low dose as suggested by the decrease in carotid IMT in treatment group at one year in our study. This would be more applicable to Indian patients in whom the LDL and TC levels are much lower even in presence of CAD and patients are at high risk of development of cardiovascular events. Thus, there is lot more to lipid lowering than just going by the current NCEP guidelines. The latest NCEP guidelines (2004)[3] have infact already been modified to an LDL goal of 75 mg/dl.

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Transradial Primary Angioplasty and Stenting in Indian Patients with Acute Myocardial Infarction: Acute Results and 6-month Follow-up

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Background: Coronary angioplasty and stent implantation is effective as primary intervention in acute myocardial infarction. Because of fewer puncture site complications and improved patient comfort, transradial access has been increasingly used as an alternative to transfemoral access for percutaneous coronary interventions.

Methods and Results: We studied 103 patients (94 men, 9 women; mean age 52.5±11.96 years) with a diagnosis of acute myocardial infarction (<12 hours after onset), who underwent primary percutaneous coronary intervention. Transradial access was used in all patients with a normal Allen's test and transfemoral access was used additionally only if intra-aortic balloon counterpulsation was required. Follow-up duration was 6 months. Transradial access was successfully achieved in all patients. Radial artery cannulation took <2 min in more than 85% patients. During percutaneous coronary intervention, cannulation to balloon inflation times and total procedure times were 11.3±5.2 min and 19.9±10.8 min, respectively. Stents were implanted in 99 (96.1%) patients and plain balloon angioplasty was performed in 3.9%. The primary success rate was 98.1%, with no major bleeding complications. Total length of hospitalization averaged 2.4±0.8 days. In-hospital major adverse clinical events rate was 5.9%. Six-month clinical follow-up was achieved for 84 (86.6%) patients. Six (7.1%) patients died during follow-up. Follow-up coronary angiography was performed in 22 (26.2%) patients. After 6 months, 7 patients required revascularization of the target lesion. The rate of survival without myocardial infarction, bypass surgery or repeat coronary angioplasty was 88.5% at 6 months.

Conclusions: Transradial access may represent a safe and feasible technique for performing primary percutaneous coronary intervention with good acute results and without major bleeding complications. **(Indian Heart J 2005; 57: 681–687)**

Key Words: Primary angioplasty, Myocardial infarction, Stent

Randomized studies have shown that primary percutaneous transluminal coronary angioplasty (PTCA) and stenting is superior to thrombolysis in acute myocardial infarction (AMI).[1-4] The outcome after this intervention has dramatically improved with use of newer antiplatelet agents in post-procedural therapy.[5] However, the use of intense anticoagulation or antiplatelet therapy, such as glycoprotein IIb/IIIa (Gp IIb/IIIa) receptor blockers, potentially increases the risk of bleeding complications during a percutaneous coronary intervention (PCI) performed via transfemoral access (TFA).[6-8] Recently, transradial access (TRA) has been increasingly used as an alternative means of performing elective diagnostic and interventional coronary procedures.[9,10] This approach is shown to be associated with a lower incidence of vascular access site complications, and allows an earlier mobilization of patients, with a reduced hospital stay and hospitalization costs.[11] The very low incidence of access site bleeding complications suggests TRA is an interesting alternative to TFA in primary PCI, particularly when performed under an aggressive anticoagulation/antiplatelet regimen.[12-17] Nevertheless, the possibility of using TRA for primary PCI in Indian subjects has not yet been thoroughly investigated.

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In our hospital, TRA has been used as a routine procedure since December 2001. More than 96% of coronary procedures were performed through TRA in the last 18 months. We retrospectively analyzed our acute results and 6-month follow-up of TRA primary PCI in patients with AMI.

Methods

Study population: 182 consecutive patients with AMI admitted to our hospital on an emergency basis, within 12 hours of the onset of chest pain were considered for primary angioplasty via TRA. AMI was defined as typical chest pain lasting for >30 min, resistance to nitrates, with ST segment elevation >0.1 mV in the limb leads or >0.2 mV in two or more chest leads. Primary angioplasty was offered as an alternative to thrombolytic therapy in such patients. Clinical exclusion criteria included prior administration of thrombolytic agents for index infarction, current use of warfarin, stroke within 1 month, women with childbearing potential, unless a recent negative pregnancy test existed, and contraindications to aspirin, clopidogrel or heparin. Exclusion criteria for TRA were an abnormal (negative) Allen's test, previous coronary artery bypass grafting (CABG) using both the right and left radial arteries, and absence of both radial pulses. Of these 182 patients, 117 opted for primary angioplasty. Among the remaining 65 patients, 7 had cardiogenic shock and their radial arteries were not palpable. Rest 58 patients did not give consent for primary PCI. The 117 patients gave their formal written consent before the procedure and were submitted to urgent coronary angiography, after which 14 patients did not undergo further interventions because of infarct-related arterial stenosis <50% with Thrombolysis In Myocardial Infarction (TIMI) flow grade 3. The remaining 103 patients (94 males and 9 females: mean age 52.5±11.96 years) underwent a primary PCI and form the basis of the present report. The right TRA was used in 96 patients and the left in 7. TFA was used in 12 patients as an additional route because intra-aortic balloon counterpulsation (IABP) was required.

Arterial cannulation: Radial artery cannulation was performed with the right arm positioned beside the patient's body and the wrist hyperextended. After local anesthesia with 1 ml of 2% xylocaine, the radial artery was punctured with a 20G Jelco needle (Ethicon Endo-surgery, Johnson & Johnson) and a 0.025" straight tip Terumo guidewire was inserted through the needle. Upon removal of the cannula, a 10 cm long 6 F sheath (Radifocus, Terumo, Terumo Corporation) was placed over the guidewire. To reduce spasm and discomfort, an intra-arterial drug cocktail containing 200 µg of nitroglycerin, 2 mg of diltiazem and 1 ml of 2% xylocaine was delivered through the sheath. Diagnostic angiography was performed using 5 F catheters and PCI using 6 F guiding catheters, manufactured by either Boston Scientific/Scimed (Maple Grove, USA) or Medtronic (Minneapolis, USA) and with inner luminal diameter of 0.064".

Angioplasty and stent implantation: Before PCI, all patients received aspirin, intravenous nitrates and a 2,500 IU bolus of unfractionated heparin. An adjunctive bolus of heparin was administered during coronary angioplasty. The dose was determined on the basis of the patient's body weight (100 IU/kg) and the activated clotting time was monitored (therapeutic range 250-350 s) during the procedure. Gp IIb/IIIa inhibitors were administered as clinically indicated during the procedure. The bolus dose of unfractionated heparin was reduced to 70 IU/kg if Gp IIb/IIIa was administered. After the procedure, unfractionated heparin or low molecular weight heparin was continued for 24 hours. Patients were treated with 150 mg aspirin daily plus 75 mg clopidogrel twice a day for 1 month. Beta-blockers, angiotensin-converting enzyme (ACE) inhibitors and lipid-lowering drugs, if well-tolerated and not contraindicated, were routinely administered to all patients.

Definitions: Primary success was defined as a residual obstruction of <30% with TIMI grade 3 flow and no major complications. Failure was defined as the impossibility of achieving primary success due to difficulty in crossing or dilating the area of obstruction appropriately, or not achieving TIMI grade 3 flow in absence of major complications. Major complications were defined as death, emergency surgical revascularization or worsening of the clinical picture (Killip-Kimbal class 3-4). Major adverse clinical events (MACE) were defined as death, new AMI and myocardial revascularization.

Sheath management : In all cases, the arterial sheath was removed immediately following completion of the procedure and hemostasis of the puncture site was achieved by a custom-made hemostasis device. Patients were then transferred to the coronary care unit.

Clinical and metabolic data: All patients were screened for electrocardiographic (ECG) changes; creatine-kinase (CK) and CK-MB values were assessed every 12 hours during the first day and then every day before discharge, unless clinical events prompted repeat measurements. Adverse clinical events, including death, ventricular

arrhythmias, reinfarction, recurrent angina, target lesion revascularization (TLR) and heart failure, were evaluated during the in-hospital follow-up. Bleeding was defined according to the criteria of the TIMI trial 18; major bleeding was defined as a decrease in the hemoglobin basal level of 5 gm/dl, intracranial hemorrhage or cardiac tamponade; minor bleeding was defined as a decrease in the hemoglobin basal level of 3 gm/dl, spontaneous gross hematuria, hematemesis, hemoptysis or puncture site bleeding.

Early ambulation protocol: All the patients were asked to follow an early ambulation protocol. On day 0, they were asked to sit on the bed, stand beside the bed and use the bedside toilet. On day 1, they were asked to walk in the wards. On day 2, the patients were discharged from the hospital to home or to the index hospital. The patients were hospitalized for more than 3 days if they developed any of the following complications: sustained ventricular arrhythmias or ventricular fibrillation, continued bradycardia, prolonged hypotension, congestive heart failure, pericarditis with pericardial effusion, residual ischemia or any severe non-cardiac complications.

Follow-up: Clinical follow-up data were obtained by either a review of the hospital records or telephone contact with the patients or their referring physicians. The major clinical events studied were death, myocardial infarction, bypass surgery and TLR. Death was defined to include death from any cause. Myocardial infarction was defined as an increase in serum CK activity to more than twice the normal value, in association with new, pathological Q waves. Bypass surgery was defined as any surgical revascularization, even if the stented segment was patent. TLR was defined as either bypass surgery or balloon angioplasty involving the stented/balloon angioplasty segments. Clinical follow-up events were studied at 1 and 6 months. In-hospital events were not included in the analysis of follow-up events. Repeat balloon angioplasty for subacute stent thrombosis was considered to constitute TLR in the analysis of clinical follow-up data.

As per our protocol, follow-up angiography was performed at six months, or earlier if there was evidence of clinical recurrence or if a stress test was positive on follow-up. Subacute stent thrombosis was not considered to constitute angiographic restenosis, because the underlying mechanisms appeared to be different; therefore, lesions that underwent successful revascularization for subacute stent thrombosis were considered to be eligible for subsequent angiographic follow-up. The view showing the most severe stenosis after stent implantation, but with no substantial overlapping of the study vessel with other branches and no foreshortening, was selected from among multiple projections. Analysis of the control and follow-up angiograms was performed in nearly identical views.

Catheters that did not contain contrast medium were used for calibration whenever possible. Proximal and distal reference points were defined by the operator before the intervention, and length of the lesion, minimal luminal diameter, reference diameter, and percentage of stenosis between those points were calculated by visual assessment. In the post-intervention and follow-up studies, the same reference points were selected by the operator, and the minimal luminal diameter between the two points was assessed visually by the operator, even when the most severe narrowing was outside the stent. Restenosis was defined as stenosis of $\geq$50% observed at follow-up.

Statistical analysis: Categorical data are presented as absolute values and percentages; continuous data are summarized as mean values ± SD.

Results

The baseline demographic, clinical characteristics and coronary lesions are shown in Table 1.

Procedural data (Table 2): The primary success rate was 98.1%; in 2 (1.9%) patients TIMI grade 3 final flow could not be achieved. Right TRA was performed in 96 (93.2%) patients and in the remaining 7 patients the procedure was performed through the left radial. Left TRA was used in 4 patients due to an abnormal Allen's test on the right side, and in another 3 patients the radial artery could not be cannulated on the right side. None of the patients were switched to TFA, but it was used as an additional route for IABP insertion in 12 (11.7%) patients. The time necessary for radial artery cannulation was < 2 min in 85% of the patients (range 30 s - 6 min). The cannulation-to-balloon inflation times (from coronary artery cannulation to the time of angioplasty balloon inflation) and the total procedure times (from patient arrival at the catheterization room to the completion of the procedure) were 11.3±5.2 min and 19.9±10.8 min, respectively. Plain optimal balloon angioplasty (POBA) was performed in 4 (3.9%) patients. Fifty-eight (56.3%) patients received Gp IIb/IIIa inhibitors. Multivessel disease was diagnosed in 36 patients. The culprit vessel angioplasty was performed in all patients and in 23 patients non-culprit vessel intervention was also performed during the same sitting. Vessel distribution and lesion morphology are summarized in Table 2.

In-hospital results (Table 3): Among the 103 patients, 99 (96.1%) underwent successful stent implantation. There

Table 1. Patient characteristics (*n*=103)

Male gender (%)	94 (91.3)
Age (years)	52.5±11.96
Range	30– 82
Diabetes	28 (27.2)
Hypertension	49 (47.6)
Hyperlipidemia	22 (21.4)
Smoking	33 (32)
Prior myocardial infarction	10 (9.7)
Killip classification (%)	
1	22 (21.4)
2	43 (41.7)
3	32 (31.1)
4	6 (5.8)
Onset to arrival (hours)	5.2 ±2.3
Number of diseased vessels (%)	
Single	67 (65)
Multivessel	36 (35)
Culprit artery (%)	
Left anterior descending artery	73 (70.9)
Left circumflex	10 (9.7)
Right coronary artery	18 (17.5)
Others	2 (1.9)
Initial TIMI flow (%)	
0	43 (41.8)
1	38 (36.9)
2	20 (19.4)
3	2 (1.9)
Absence of collaterals (%)	76 (73.8)
Left ventricular ejection fraction (%)	26.7±14.1
<40%	86 (83.5)
<30%	71 (68.9)

TIMI: thrombosis in myocardial infarction

Table 2. Characteristics of coronary interventions (*n*=103)

Right radial approach	96 (93.2%)
Left radial approach	7 (6.8%)
Fluoroscopy time (min)	6.8±4.6
Range	1.8-21.3
Procedure time (min)	19.9±10.8
Range	7.3-60.2
Cannulation-to-balloon inflation time (min)	11.3±5.2
Guiding catheters used (*n*)	1.1±0.4
Total amount of dye used (ml)	60±27.5
Reference vessel diameter (mm)	3.3±0.5
Minimum lumen diameter (mm)	
Pre-	0.14±0.28
Post-	3.14±0.6
Diameter stenosis (%)	
Pre-	95.9±7.5
Range	60–100
Post-	1.7±6.6
Stent diameter (mm)	3.2±0.6
Number of stents	1.2±0.6
Total stent length (mm)	18.3±8.9
Lesion morphology (%)	
A	10
B1	32
B2	35
C	23
Final TIMI flow (%)	
0	0 (0)
1	1 (0.9)
2	1 (0.9)
3	101 (98.1)
Balloon angioplasty (%)	4 (3.9)
Direct stenting (%)	36 (35)
Conventional stenting (%)	63 (61.1)
IABP support (%)	12/103 (11.7)
Glycoprotein IIb/IIIa inhibitor	58/103 (56.3)
Primary success rate (%)	101/103 (98.1)

TIMI: thrombosis in myocardial infarction; IABP: intra-aortic balloon counterpulsation

was clinical success in 101 (98.1%) patients. Major bleeding complications requiring either surgery or blood transfusion were not observed in any of the patients; however, minor bleeding was seen in 6 (5.8%) patients. Ninety-eight (95.1%) patients had a palpable radial artery at discharge and none of the patients had symptoms or physical signs of hand ischemia. However, Doppler examination was not routinely performed; thus, the incidence of asymptomatic radial artery occlusion could not be determined. Major complications included death in 4 (3.9%) patients, repeat myocardial infarctions in 2 (1.9%) and 1 (0.97%) patient requiring TLR for subacute thrombosis. This patient had a recurrence of angina on the second day after the procedure and repeat coronary angiography revealed subacute thrombosis of the target vessel. He underwent successful revascularization and was subsequently discharged with a patent stent. None of the patients required emergency bypass surgery. Therefore, out of 103 patients, 97 patients who survived to discharge with patent stents were eligible for the six-month follow-up. The average total length of hospitalization was 2.4±0.8 days.

Six-month follow-up results (Table 4): Of 103 patients, 97 were eligible for follow-up. In 86.6% cases (84/97), follow-up was possible. Of these, 77% were asymptomatic and 13 (15%) had a recurrence of angina. All 65 asymptomatic patients were asked to undergo a stress test; 48 (73.9%) were tested. The specific reason for the failure of patients to undergo stress test after 6 months was refusal by either the patient or the referring physician. Stress tests were positive for reversible ischemia in 9 (18.8%) cases. Repeat coronary angiography was advised and performed in 22 patients. Of these, 7 patients had significant restenosis, and they received TLR. Nine patients had new coronary lesions and 6 patients had insignificant restenosis (<50%) at the target vessel site. Echocardiography was obtained in all 78 patients and only 23.8% had severe left ventricular (LV) dysfunction (<30%) at 6 months, as compared to 68.9% patients prior to the procedure. The cumulative survival rates was 93.1% (78/84) 6 months

Table 3. In-hospital results (*n*=103)

In-hospital MACE (%)	
Death	4 (3.9)
TLR	1 (0.97)
Reinfarction	2 (1.9)
Bypass surgery	0
Composite end points (%)	6 (5.9)
Switch to femoral approach	0
Major bleeding complications	0
Minor bleeding complications (%)	
Access site	6 (5.8)
Excluding patients with in-hospital death	
Length of hospital stay (days)	2.4±0.8
Range	2 - 7
Successful day 2 discharge (%)	70 (68)

MACE: major adverse clinical events; TLR: target lesion revascularization

Table 4. Six month follow-up

Clinical follow-up	
Eligible for follow up (*n*)	97 (94.2)
Follow-up completed	84 (86.6)
Free of angina	65 (77.4)
Clinical restenosis	13 (15.5)
Death	6 (7.1)
Stress test	
Number	48 (73.9)
Positive	9 (18.8)
Negative	39 (81.2)
Left ventricular ejection fraction, %	47.4±15.6
<40%	32 (38.1)
<30%	20 (23.8)
Angiographic follow-up	
Number	22 (26.2)
Restenosis	7 (9.0)
Insignificant restenosis (<50 %)	6 (7.7)
New lesions	9 (11.5)
MACE after discharge	
TLR	7 (9.0)
Myocardial infarction	3 (3.9)
Bypass surgery	0
Death	6 (7.7)
Composite MACE	15 (19.2)

Values in parentheses show percentage
MACE: major adverse clinical events; TLR: target lesion revascularization

after implantation of the stent. Besides the 4 patients who died in hospital, an additional 6 patients died during the first 6 months. Four died of cardiac causes, 3 of progressive heart failure and the fourth of reinfarction. Two died of non-cardiac causes. The rate of survival free of myocardial infarction, bypass surgery, and TLR was 88.5% (69/78) at 6 months.

Discussion

Our results are consistent with recent studies of TRA primary PCI for AMI in selected patients.[12-17] Radial cannulation should not take long because it may have a negative impact on results, particularly in patients with AMI. Ochiai et al.[13] reported that radial artery puncture was achieved within 15 min in all patients and within 5 min in 79%. In the study by Kim et al.[16] the cannulation time was <10 min in the majority of patients (only in 1 patient it was impossible to gain access to the radial artery) and Louvard et al.[17] have shown similar results. The mean cannulation time was < 2 min in the study reported by Valsecchi et al.[8] with no significant difference in transradial or transfemoral cannulation times. In the TEMPURA trial[18] the two approaches were similar in overall results, the number of guiding catheters used, the total amount of dye used, total fluoroscopy time, in-hospital mortality and costs, although the total procedure time was significantly lower in the TRA group. In studies where the two approaches have been compared with each other, TRA has been as effective as TFA and probably safer as far as local site complications are concerned.[8,18] In the present study, the incidence of access site bleeding complications (5.8%), was as low as has been reported in a controlled study of patients with AMI. Johnson et al.[19] reported an incidence of vascular complications of 2.4% out of 1579 PCI procedures performed using the femoral and brachial techniques. Popma et al.[20] reported a 5.9% incidence of vascular complications after 1413 PCI procedures with different techniques; the highest incidence (14%) was observed after coronary stenting. Valsecchi et al.[8] had only one access site bleeding complication in the radial group (0.6%). Kiemeneij et al.[9] compared the results of using the radial approach with those of brachial and femoral access in a randomized study. They found that the vascular access site complication rate was significantly lower with the radial (0%) as compared to the femoral (2.0%) or brachial (2.3%) approaches ($p<0.05$).[10] Another randomized study, which compared radial and femoral access for coronary stenting in patients with acute coronary syndromes, showed similar reductions of access site complications in the radial group (0 *v.* 4%; $p<0.04$).[11] The safety of TRA is mainly determined by the favorable anatomic relations of the radial artery to its surrounding structures. No major veins or nerves are located near the artery, minimizing the chance of injury to these structures. Thrombotic or traumatic arterial occlusion does not compromise the viability of the hand if an adequate collateral blood supply from the ulnar artery is present. The superficial location of the radial artery allows easy hemostasis, and the use of a mechanical compression device reduces the need of personnel.[21,22] An additional advantage of TRA is the passive achievement of hemostasis by a pressure device or by a pressure bandage, reducing the workload of nursing and medical staff.[8]

In this study 99 (96.1%) patients received one or more stents in the infarct-related artery and direct stenting was attempted in 36 (35 %) patients. Stenting via the radial route is technically more challenging. However, almost all recently designed stents can be delivered through the 6 F guiding catheters. Stent embolism or dislodgement was not encountered in our series and in no case did we fail to deliver the stent. These results are consistent with those of previous studies reporting smaller numbers of patients in which it was concluded that in hemodynamically stable patients, primary stenting or PCI can be performed expeditiously and safely using TRA.[8,13,16] In the TEMPURA trial,[18] primary stent implantation by TRA was proved to be as feasible as by TFA.

An important criticism of TRA is that it is not suitable for every patient. Moreover, radial arteries in Asians are thought to be smaller than those of Europeans. However, Wu et al.[23] and Saito et al.[24] have clearly demonstrated the feasibility of TRA in Chinese and Japanese populations, respectively. Since the size of the radial artery is generally enough for the insertion of a 6 F introducer,[25] the size of the artery will not negatively influence TRA in patients with AMI, provided that 6 F guiding catheters are used. Several reports have attested to the use of TRA in virtually all clinical situations;[8,23,26,27] in our study the PCI was successfully performed in almost all (98.1%) patients. Of course, patient selection before the procedure, on the basis of the clinical status (Killip class <4) and the anatomic characteristics of the radial artery (normal Allen's test), is very important. Other possible disadvantages of TRA are difficulty in learning the technique and the smaller size of the radial artery, as compared to the femoral. However, the procedural and fluoroscopy times are similar in a well-equipped laboratory where both approaches are frequently used by operators.[18] None of the procedures was associated with inadequate support of the guiding catheter, despite the fact that most guiding catheters are not designed for the right radial approach. Good backup support for the right coronary artery could be achieved by means of Judkins right, Patel 1/2 and Amplatz right 1/2 guiding catheters. For the left main coronary artery, Judkins left, Voda or Q curve, Patel 1/2 and Amplatz left 1/2 guiding catheters were used.

Study limitations: (i) Ours being a retrospective study, we cannot apply its results to other hospitals where TRA is not frequently performed. TRA has a definite learning curve and it may limit the possibility of transferring our results to less experienced, low-volume centers and operators. (ii) Cannulation-to-balloon inflation time and total procedure times are not part of standard terminology of AMI timings. They only represent that the PCI can be quickly performed through transradial route. (iii) There is lack of follow-up Doppler information on the patency of the radial artery through which the procedure was performed. Although no patient in the present study had an absent pulse or symptoms suggesting vascular ischemia of the hand, it is likely that asymptomatic radial artery occlusion occurred in a small percentage of patients. Previous series[28,29] have demonstrated the incidence of asymptomatic radial artery occlusion in the 3-5% range, but the benign nature of this problem has been emphasized. (iv) The need for the use of small guide catheters (6 F) has been felt to be a significant limitation of TRA in lesions requiring complex devices (e.g. thrombus removal or distal protection) or techniques (kissing balloon). However, with experience and the recent continued miniaturization of interventional devices, this is no longer a serious drawback. Indeed, in the present study no patient crossed over to TFA for these reasons. (v) The number of cases discussed in our study is not large. Financial constraints and a lack of infrastructure for patient transport make primary intervention for AMI a difficult option in Indian patients.

Conclusions: Transradial access performed in Indian patients by experienced operators may represent a safe and feasible technique for performing primary percutaneous coronary intervention with good results and without major bleeding complications. It is specially useful for hemodynamically stable patients who are suitable for transradial access by normal Allen's test.

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Original Article

Port-Access Approach for Cardiac Surgical Procedures: Our Experience in 776 Patients

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Background: Recent advances in minimally invasive technology has expanded the application of the right thoracotomy approach for mitral valve surgery and atrial septal defect closure. The present study examines the feasibility, safety and efficacy of this technique.

Methods and Results: Between September 1997 and December 2004, 430 patients underwent mitral valve surgery through right anterolateral thoracotomy. The mitral valve was repaired in 62 patients, and 368 patients underwent mitral valve replacement. During same period, 336 patients underwent surgical closure of atrial septal defect. In all cases femoral artery and femoral venous cannulation was used for cardiopulmonary bypass. There was no approach-related limitation to surgical exposure, nor complication in cannulation of femoral vessels through the groin. Mean duration of cardiopulmonary bypass and cross-clamp time was 90±48 min and 51±29 min, respectively. Mean intubation time was 14.8 hours (range: 8-28 hours). Mean duration of intensive care and hospital stay was 26 hours (range: 18-38 hours) and 7 days (range: 5-17 days), respectively. In the atrial septal defect group, the mean cardiopulmonary bypass time and aortic cross-clamp time was 29±14 min and 19±8 min, respectively. Mean intensive care unit stay and mean hospital stay was 9.8±2.6 hours and 4.0 ±1.9 days, respectively. Hospital mortality was 0.46% (2/430) in the mitral valve group while there was no hospital mortality in atrial septal defect group. At a mean follow-up of 38.0±6.2 months there was one late death and two re-operations in the patients who underwent mitral valve surgery.

Conclusions: Port-access approach is safe, offers faster recovery, cosmetic advantage, more patient satisfaction; it obviates the complications due to re-entry in redo cases and offers same efficacy as conventional operation. Furthermore, it is an excellent approach for mitral valve surgery in patients who had previous cardiac procedures. It has become our standard approach for repair of atrial septal defect and isolated mitral valve procedures. **(Indian Heart J 2005; 57: 688–693)**

Key Words: Minimally invasive surgery, Atrial septal defect, Mitral valve replacement

Recent evolution of minimally invasive technology has expanded the application of the right thoracotomy approach for mitral valve surgery and atrial septal defect (ASD) closure. Several authors have shown encouraging operative results with a low surgical mortality using minithoracotomy.[1-3]

A major breakthrough in the ability to widen the application of minimally invasive surgery was the development of port-access endovascular cardiopulmonary bypass (CPB) system (Endo CPB, Heartport, Inc., Redwood City, CA), which is a catheter-based system of devices that permit the heart to be arrested and maintain bypass. The system also includes specially designed long fine instruments enabling access to the surgical field. The port-access approach was initially tested by the research laboratories of Stanford and New York Universities. The concept was refined technologically by an industry (Heartport Inc., CA). Minimally invasive approach results in less pain, a faster recovery, a better cosmetic result, less infection and more satisfaction to the patient, and is as safe and effective as conventional approach.

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Methods

Between September 1997 and December 2004, 430 patients underwent mitral valve surgery by means of

minimally invasive approach through right anterolateral minithoracotomy through 4th intercostal space. There were 140 males and 290 females. The mean age was 42.2±8.4 years. The video-assisted approach was used in 250 patients, while in 180 patients, the surgery was carried out under direct vision. The patient characteristics are shown in Table 1. In the same period (September 1997- December 2004), 336 patients with primary diagnosis of ASD underwent surgical repair. There were 206 males and 130 females. The video-assisted approach was used in 180 patients, while in 156 patients, it was performed under direct vision. The patient profile is shown in Table 2.

Table 1. Profile of patients (*n* = 430) with mitral valve disease

Age in years (mean ±SD)	14-76 (42.2 ± 8.4)
Male	140 (32.6)
NYHA class	
I	10 (2.3)
II	38 (8.8)
III	102 (23.7)
IV	280 (65.1)
CVD	42 (9.8)
COPD	110 (25.6)
Diabetes mellitus	118 (27.4)
Morbid obesity	36 (8.4)
Renal failure	72 (16.7)
Pulmonary hypertension	172 (40)
Atrial fibrillation	186 (43.3)
Valvular pathology	
Rheumatic	390 (90.7)
Degenerative	40 (9.3)
Predominant mitral insufficiency	288 (67.0)
Predominant mitral stenosis	142 (33.0)
Tricuspid regurgitation	
Severe	18 (4.2)
Mild to moderate	42 (9.8)
Redo cases (%)	92 (21.4)
LVEF % (mean ± SD)	42±7

SD: standard deviation; NYHA: New York Heart Association; CVD: cerebrovascular disease; COPD: chronic obstructive pulmonary disease; LVEF: left ventricular ejection fraction
Value in parentheses show percentage

Table 2. Characteristics of patients (*n*=336) with atrial septal defect

Age, years	12-61
Sex- Male	206 (61.3)
Female	130 (38.7)
NYHA class	
I-II	154 (45.8)
III	142 (42.3)
IV	40 (11.9)
LVEF ≤ 30	24 (7.1)
>31	312 (92.9)
Mean pulmonary artery systolic pressure, mmHg	34 (10.1)
COPD	86 (25.6)

NYHA: New York Heart Association; LVEF: left ventricular ejection fraction; COPD: chronic obstructive pulmonary disease
Value in parentheses show the percentage

The data was collected using the Society of Thoracic Surgeons National Cardiac Surgery Database (STS/NCSD) variables and definitions. The clearance of hospital ethical committee was obtained before starting the study.

To achieve the potential benefits of minimally invasive mitral valve surgery, the following modifications have been applied over the conventional operative technique.

1. The endovascular CPB and cardioplegic system (Endo CPB) - this includes (i) Y-shaped femoral arterial returns cannula and a femoral venous cannula for CPB, (ii) centrifugal pump-assisted venous drainage, (iii) triple lumen, balloon tipped endo-aortic balloon catheter (endo-clamp) used for endovascular ascending aortic occlusion, antegrade cardioplegia infusion, aortic root venting and aortic root pressure monitoring, and (iv) pulmonary artery venting and retrograde coronary sinus cardioplegia catheters via the internal jugular or subclavian vein.
2. Minithoracotomy incision.
3. Use of specially designed instruments for this surgery.

In later part of the study, few more modifications were made. These included (i) doing away with double lumen tube which did not provide any added advantage, as after initiation of CPB, the lungs were deflated, (ii) direct transthoracic aortic clamp occlusion, (iii) endopulmonary vent was not used, (iv) only antegrade application of cardioplegic solution was used and coronary sinus catheter was not required, and (v) use of fluoroscopy was decreased as transesophageal echocardiography (TEE) was quite effective.

Surgery: Patients were positioned in a supine position with the right side of the chest slightly elevated. A 5-6 cm long anterolateral thoracotomy was performed through the 4th intercostal space. A double-lumen endotracheal tube was used in initial cases for endotracheal intubation.

Transjugular coronary sinus catheter (Heartport Inc., CA) was inserted under TEE and C-arm guidance for retrograde cardioplegia in 23 cases. Transjugular endo-vascular pulmonary vent (Heartport Inc., CA) was used in 21 cases. Flow-directed pulmonary artery catheter was inserted only in those patients who had very high pul-monary artery pressure on pre-operative evaluation.

After systemic heparinization, a 21 F, Y-shaped or 21 F straight cannula (DLP Inc. MI) was placed in the femoral artery depending on whether an endoaortic (EAC) or trans-thoracic occlusion clamp was being used. A 28 F venous return cannula (Heartport Inc., CA) was placed in the femoral vein and advanced to the right atrium and then to the superior vena cava (SVC) under TEE control.

A conventional CPB system with roller pump and membrane oxygenator was used. In addition, a centrifugal pump (Sarns Inc., MI) was placed in the venous line to enhance venous drainage.

The aorta was screened for atheromas with the aid of TEE, to avoid cerebral embolization with retrograde perfusion. The endovascular clamp was placed 1 cm above the level of the sinotubular junction under multiplane TEE (Sonos 5500 Hewlett Packard Inc. MA) and fluoroscopic guidance (Sieremobil 2000, Siemens, Germany). The EAC was inflated to endoluminally block the ascending aorta while the heart was vented through the endovascular pulmonary vent. After clamping, the balloon pressure was maintained between 250 and 340 mmHg. Additional volume was injected to inflate the EAC in case the balloon pressure dropped below 250 mmHg. Warm-blood cardioplegic solution was delivered antegradely through the distal endovascular clamp lumen while maintaining aortic root pressure between 50 and 70 mmHg. The distal migration of EAC was detected by difference in mean pressure of right and left radial arteries, while proximal migration was monitored by intra-operative TEE. Aortic root diameter > 3.5 cm was a relative contraindication to use of the EAC. In initial 23 cases, retrograde cardioplegia was also used as an adjunct to antegrade cardioplegia through coronary sinus catheter placed through transjugular vein. The EAC was used in 72 cases, and we preferred the trans-thoracic, sliding-rod aortic clamp (Scanlan International Inc., USA) which was used in 358 cases in present series. The clamp is passed through the 2nd intercostal space in the anterior axillary line through a 3 mm port. The DLP cardioplegia catheter (DLP Inc. MI) was used, for antegrade cardioplegia delivery, and for aortic root suction during de-airing. After cardiac arrest was established, the left atrium was opened and the mitral valve was exposed using specially designed atrial retractor (Heartport Inc., CA), which was inserted through another 3 mm port at 5th or 6th intercostal space parasternally.

The mitral valve repair or replacement was performed under direct vision with using specially designed instruments (Heartport Inc., CA). After completion of the procedure, the left atrial vent was positioned across the mitral valve and the left atrial incision was closed.

In patients undergoing tricuspid valve repair as well, the SVC was separately cannulated and the venous cannula was withdrawn into the inferior vena cava (IVC), both the cavae were taped, and the right atrium opened, while the blood from SVC was sucked into the cardiotomy reservoir. After completion of tricuspid valve repair, the right atrium was closed, and the venous cannula was pushed back to the right atrium.

De-airing was performed by reduction in venous drainage, with the patient in Trendelenburg position and the inflation of the lungs. Aortic root air was removed by suction through the distal lumen of EAC or cardioplegia catheter (depending on which was in place). The EAC was deflated and the catheter was left in place for further venting until air was completely removed. If necessary, defibrillation was performed using external defibrillation pads. A temporary pacing wire was put in the right ventricular epicardium before the aortic cross clamp was released. Once air removal was complete, the EAC or cardioplegia catheter at aortic root was removed. The patient was weaned off CPB and the arterial and venous cannulae were removed, and the femoral vessels were repaired. The chest wound was closed after inserting a drainage tube into the pleural space.

This surgical technique for repair of the ASD varied from mitral valve procedure in terms of venous return: separate cannulation of the SVC via the internal jugular vein and IVC via the femoral vein. The intrapericardial cavae were dissected and taped.

In our series, 92 patients were redo cases, 31 had undergone previous mitral valve repair, 6 had undergone aortic valve replacement, 10 coronary artery bypass grafting (CABG) and 44 patients had undergone closed mitral commissurotomy. One patient had a post-mitral valve replacement paravalvular leak. In all redo cases except those who had previous closed mitral commissurotomy, the EAC was used as it avoids the excessive dissection needed to clear the aorta for external clamping.

Two hundred fifty patients undergoing mitral valve surgery and 180 patients undergoing surgical repair of ASD, were put on video-assisted approach. The exposure was facilitated with an endoscope attached to a voice-controlled robotic arm (AESOP 3000) allowing stabilization and voice activated camera positioning.

Follow-up: Post-operative follow-up included 3-month, 6-month and annual check ups. All the data was prospectively collected and stored in a prescribed form and database.

Results

Placement and positioning of the endovascular pulmonary vent was successful in all cases and transjugular coronary sinus catheter was successful in 23 cases, but could not be negotiated in 3 cases. There was no complication in cannulation of femoral vessels through the groin. Injection of initial volume of 20 ml to 35 ml saline resulted in sufficient aortic occlusion with a balloon pressure of 240 mmHg to

360 mmHg. Additional saline was required to be added in 4 patients to maintain the desired pressure. Migration of the balloon during initial placement was observed in 4 patients but was easily corrected under TEE control. During the later part of the study, we used transthoracic sliding rod aortic cross-clamp and there were no aortic clamp-related injuries.

Surgical technique: In all patients, the mitral valve was accessible through the right anterolateral minithoracotomy. The mean length of incision was 5.0±1.7 cm (range: 4.6-8.6 cm). Mitral valve repair was undertaken in 62 cases, and was successful in all cases (Table 3).

Table 3. Operative procedure in patients with mitral valve disease (*n*= 430)

MVR	258 (60.0)
MVR ± tricuspid valve repair	16 (3.7)
MVR ± atrial septal defect closure	3 (0.7)
Mitral valve repair + atrial septal defect closure	6 (1.4)
Mitral valve repair	51 (11.8)
Mitral valve repair + left atrial clot removal	2 (0.5)
Mitral valve and tricuspid valve repair	2 (0.5)
Redo MVR	91 (21.2)
Redo repair of paravalvular leak	1 (0.2)

MVR: mitral valve replacement
Values in parentheses show the percentages

Of the 368 patients who underwent mitral valve replacement, there were 318 with preservation of posterior mitral leaflet. In remaining 50 cases the posterior leaflet was heavily calcified and could not be preserved. We preferred using the Starr Edward mitral valve prosthesis (Baxter Healthcare Corp, Edwards CVS Division, Irvine CA) for the ease of anticoagulation management in our patients. In 14 patients, Carpentier Edward bioprosthesis (Baxter, Healthcare Corp, CA) was used and Perimount was used in 8 cases. In 18 patients with severe tricuspid regurgitation, tricuspid valve was also repaired with mitral valve. The mean duration of CPB and cross clamp times was 90±48 min and 51±29 min, respectively (Table 4).

Post-operative course and complications- *Mitral valve*: The mean time on ventilator was 14.8 hours (range 8-28 hours). The mean duration at intensive care unit (ICU) and hospital was 26 hours (range 18-38 hours) and 7 days (range: 5-17 days), respectively. Mean blood loss was 260 ml (range: 140 - 940 ml). Four patients required re-exploration for bleeding, which could be performed through the same incision. Two patients were found to have left hemiparesis on post-operative day 1 from which patients fully recovered.

Table 4. Perioperative variables and complications in patients with mitral valve disease

No. of patients	430
Mean duration of CPB (min)	90± 48
Mean cross clamp time (min)	51±29
Mean blood loss (cc)	260 (140-940)
Mean intubation time (hours)	14.8 (8-28)
Mean ICU time (hours)	26 (18-38)
Mean post-operative hospital stay (days)	7 (5-17)
Hemiparesis	2 (0.46%)
Reoperation for bleeding	4 (0.93%)
Heart block	2 (0.46%)
Atrial fibrillation	12 (2.79%)
Renal failure	2 (0.46%)
Operative mortality	2 (0.46%)
Major gastrointestinal bleeding	1 (0.23%)

CPB: cardiopulmonary bypass; ICU: intensive care unit

One patient died on post-operative day 12 due to upper gastrointestinal bleeding. He was 85 years old, and had uneventful recovery until post-operative day 5, when he had massive hematemesis, which was managed conservatively. However, it recurred, and he expired on post-operative day 12.

At discharge, all patients with mitral valve repair had none or trivial regurgitation. All implanted valves were functioning normally, as seen by post-operative echo-cardiographic studies.

Atrial septal defect: Thirty-four patients had direct closure of the ASD, while 302 patients required pericardial patch closure. Mean CPB time for repair of ASD was 49±14 min and mean aortic cross clamp time was 29±8 min. Mean ventilation time after surgery was 6.1±3.0 hours and the mean ICU stay time was 9.8±2.6 hours. The mean hospital stay was 4.0±1.9 days. There was no in-hospital mortality, nor neurological dysfunction. Mean post-operative blood loss was 180±31 ml and three patients required re-exploration because of excessive bleeding. There was no femoral arterial cannulation-related complication and no residual ASD was observed by TEE in any patient.

Follow-up: The mean follow-up time was 38.0±6.8 months (Table 5). There was one late death because of late prosthetic valve endocarditis. There were 2 reoperations, in whom mitral valve repair had been performed. Two patients had anticoagulation-related bleeding, which required transfusion of fresh frozen plasma to control the elevated prothrombin time. The New York Heart Association (NYHA) functional class improved by 1.4± 0.6.

All except four patients had improvement in their activity level compared to their pre-operative status. These patients

Table 5. Follow-up results in patients with mitral valve disease (*n* = 430)

Mean follow-up (months)	38.0 ± 6.8
Late death	1 (0.23%)
Reoperation	2 (0.46%)
Anticoagulation-related complications	2 (0.46%)
Echocardiographic results	
Mitral valve repair	
Residual stenosis	0 (0.0%)
Pre-operative MR (0-4)	3.1± 0.3
Post-operative MR (0-4)	0.4 ± 0.3
Mitral valve replacement	
Paravalvular leak	0 (0.0%)
Functional class (I-IV)	
Pre-operative	2.8 ±0.4
Post-operative	1.4±0.6

MR: mitral regurgitation

had long standing mitral regurgitation with high pulmonary artery pressure.

Discussion

The right anterolateral minithoracotomy for minimally invasive mitral valve surgery and closure of ASD seems very promising because the incision provides an excellent visualization of the mitral valve and ASD in the arrested heart. The surgeon uses specially designed long instruments and 'knot pushers' to facilitate the technical process. It is devoid of complications such as wound infection, back pain, sternal dehiscence and visible scar and the incidence of post-operative bleeding in quite low. Majority of patients in our series were young women; this incision gives better cosmetic results, because the incision remains hidden underneath the breast. The length of the thoracotomy incision has steadily decreased, and none of the patients required rib resection. Using a video- and voice-controlled robotic arm (AESOP 3000) it was possible to minimize the length of incision and obtain good visualization of the entire mitral apparatus.

The patient satisfaction in the present series was very high. In addition, there was faster return to normal activity as was also concluded in Port Access International Registry (PAIR) study. The quality of life was better with port-access approach than with standard open-chest techniques.[4] Improvement in NYHA function class as noted by Grossi et al.[5] was 0.85±0.61. In the present series there was improvement in NYHA class by 1.4±0.6.

The femoral vessel cannulation enables the operative field to be devoid of cannulas and thus facilitates the exposure even through a small incision. Significant atherosclerosis of the ascending aorta and severe deformity of the superior chest wall are conditions, where femoral arterial cannulation is specially advantageous. On the contrary, relative contraindications for femoral arterial cannulation are small femoral artery size, aorto-iliac disease, obesity and ageing population. There have been concerns with femoral arterial cannulation including groin wound infection, wound seroma, arterial injury requiring reconstruction, aortic dissection, atheroembolism, and limb ischemia. However, most of studies have reported femoral arterial cannulation to be quite safe. Galloway et al.[6] in the first report of Port Access International Registry observed the incidence of aortic dissection to be 0.75% which decreased further, as registry progressed from 1.30% in the first half of study to 0.18% in the last 532 patients. The risk was minimized because of progressive development of improved catheters with more flexible guidewires, conversion to an open-chest approach when guidewire would not pass and pre-operative screening for severe perepheral vascular disease. In present series, in accordance with previous experience,[7] no femoral artery injury was noted, probably due to younger age of our patients and because precautions described earlier were taken.

Our strategy of switching to transthoracic aortic clamp in place of the EAC, is because of its safety and economy. Moreover, transthoracic clamp occlusion is not difficult and antegrade cardioplegia provides excellent cardiac protection. In our experience, there was no incidence of aortic dissection with the use of the endoclamp as also reported by Mohr et al.[8] but this may be because our patient population was much younger. In 4 patients we observed inadvertent balloon migration, which was easily detected by differences in mean pressure of right and left radial arteries due to innominate artery occlusion and reconfirmed on TEE. In all the four cases, balloon position was easily adjusted without causing any damage.

With increasing experience, cardiopulmonary bypass and cross clamp times became shorter in present series.

The decision to repair a mitral valve was not influenced by the operative approach, but rather by the abnormality of the valve. In the present series we were able to carry out repair procedure in only 62 cases, which is 14.4% of the total number. This is because we mainly deal with rheumatic pathology, which leads to significantly deformed and calcified mitral valves, which are not suitable for repair.

The incidence of post-operative renal complication in patients undergoing cardiac surgery is around 7%,[9,10] and much more in patients undergoing mitral valve surgery.[11] McCreath et al.[11] found evidence of reduced acute renal injury associated with the minimally invasive technique in

mitral valve surgery patients than in patients undergoing mitral valve surgery through conventional approach. The other major complication i.e. development of new onset of atrial fibrillation was lower with port-access technique than with full sternotomy in mitral valve patients in the PAIR study.[4-6] Low incidence of new onset post-operative atrial fibrillation was attributed to absence of a right atriotomy incision and suture line with the post-access technique. The right atrium is manipulated less and not exposed to light and heat resulting in less inflammation.[6]

Concern regarding de-airing also seems unfounded, and is same as in conventional open-chest procedures with the proper use of technique under TEE surveillance described earlier.[6] In present series, there were two (0.46%) patients who had left hemiparesis, but they recovered.

Patients having minimally invasive mitral valve surgery had much less chest tube drainage and required fewer blood transfusions and re-exploration for bleeding.

In a multi center port-access valve registry, Glower et al.[4] noted the mortality rate similar to that reported by means of a sternotomy. They also concluded that the procedure is technically reproducible even in smaller centers with equally good results and that the patient outcome is not related to institutional case volume. Galloway et al.[6] in report of the port-access international registry of 1063 patients from 121 centers found that post-access mitral valve operations can be performed safely with morbidity and morality rates similar to those associated with open-chest operations. There was only one (0.2%) in-hospital mortality. Others have reported similar in-hospital mortality of 0%,[12] 1.1%[13] and 3.7%.[5] At a mean follow-up of 38.0 ± 6.8 months, there was one late death and two patients required reoperation. Grossi et al.[5] reported cumulative freedom from reoperation to be 94.4% at one year.

Conclusions: Minimally invasive cardiac surgery is safe and benefits the patient by lesser blood loss, minimal post-operative pain, low risk of wound infection and faster recovery with shorter ICU stay, earlier hospital discharge and better cosmetic results.[14] It is technically reproducible, obviates the complications due to re-entry in redo cases and there is reduced tissue trauma. The use of transthoracic aortic clamp in place of endoaortic clamp further reduces the cost. As it offers excellent exposure, mitral valve repair as well as replacement, and closure of ASD can be done safely with this approach with good operative results. It is also an excellent approach for mitral valve surgery in patients who had previous cardiac procedures. The low operative mortality and excellent post-operative echocardiographic results attest to the safety and efficacy of this approach, similar to those of conventional methods.

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Original Article

Left Ventricular Systolic and Diastolic Functions in Patients with Sickle Cell Anemia

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Background: Sickle cell anemia is a formidable problem in India, and is more prevalent in Maharashtra. Cardiovascular involvement in this condition has not been well studied. The present study therefore sought to investigate the systolic and diastolic left ventricular function of children with sickle cell anemia.

Methods and Results: This prospective controlled study comprised of 25 cases of sickle cell anemia, 25 cases of anemia (hemoglobin <11 gm/dl) with 'AA' types of hemoglobin electrophoresis and 25 non-anemic controls (hemoglobin > 11 gm/dl) with normal hemoglobin electrophoresis pattern. M-mode, 2-dimensional and Doppler echcardiographic measurements of patients and controls were performed according to criteria of the American Echocardiography Society. In the study cases, age ranged from 5 years to 15 years with the mean age of 9.91 years. There were 14 males and 11 females in the study cases. Patients with sickle cell anemia had significantly larger left atrial (23.26±3.6 mm, 22.9±2.56 mm, 20.72±2.79 mm; $p < 0.05$), left ventricular (34.88±4.53, 33.28±3.28, 30.72±3.68; $p< 0.05$) and aortic root (19±2.7, 18.91±2.24, 17.56±1.44; $p<0.05$) dimensions. They also had higher indexed end-diastolic left ventricular volumes (101.84±22.74 ml/m^2 *v.* 65.05±10.81 ml/m^2; $p< 0.001$), and higher stroke volume (29.32±11.32 ml, 27.12±7.82 ml, 22.4±6.67 ml; $p<0.05$). Left ventricular mass (62.24±18.44 gm, 52.53±16.23 gm, 50.2±15.68 gm; $p<0.05$) was greater in sickle cell anemia patients than in controls. No statistically significant differences were detected in the Doppler finding of patients with or without anemia. No statistically significant correlation was found between echocardiographic parameters (M-mode and Doppler) and the hemoglobin in the sickle cell patients.

Conclusions: Echocardiography is a useful non-invasive technique to study the changes in cardiac structure and function. In spite of left ventricular volume load and dilation in sickle cell anemic patients, left ventricular contraction was good and systolic function was normal, and there was no correlation between the echocardiographic findings and hemoglobin level. **(Indian Heart J 2005; 57: 694–697)**

Key Words: Sickle cell anemia, Echocardiography, Left ventricular function

Sickle cell anemia (SCA) was first described in a west Indian student by Herrick in 1910.[1] It is a significant health problem in India mainly in the central part of Maharashtra. The prevalence of sickle cell disease in different communities of Maharashtra ranges from 1.9% to 33.5%.[2] Abnormal cardiac finding are present in most patients with SCA and are primarily the result of chronic anemia and the compensatory increased cardiac output.[3] Low hemoglomin levels are associated with an elevated cardiac output at rest, cardiac enlargement and frequently heart murmurs, presumably due to increase in stroke volume.[4] Cardiovascular involvement is not well studied in children with SCA. The aim of this study was to evaluate the echocardiographic parameters of the children with SCA.

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Methods

It was a prospective controlled study conducted from 1st January 2005 to 31st July 2005 at our institute. The study comprised of 25 cases of sickle cell anemia, 25 cases of anemia (Hb < 11 gm/dl) with "AA" types of hemoglobin electrophoresis and 25 non-anemic controls (Hb > 11 gm/dl) with normal hemoglobin and electrophoresis pattern. The control group patients were comparable in age and sex, free from any cardiovascular disorder and not taking any cardioactive drugs. Detailed clinical examination and investigation including hemogram, chest X-ray and electrocardiography were obtained in the study cases.

Hemoglobin was measured when subjects were at a steady state (free of any acute process that might alter its level) on the same day as the echocardiography. Subjects were crisis free for 2 weeks prior to the study and had not been transfused in the preceding 3 months. Echocardiography [two-dimensional (2D), M-mode and Doppler) was performed in study cases and control groups. The examination was conducted with the patient lying in supine position. The parasternal long axis and short axis views, parasternal right ventricular (RV) outflow view and apical view were obtained in all study cases and control groups.

Echocardiographic measurement: The aortic root, left artial dimension, left ventricular (LV) end-systolic and end-diastolic dimension, LV posterior wall thickness and septal thickness were measured by M-mode according to the recommendation of the American Society of Echocardiography. The LV ejection fraction (EF), fractional shortening (FS) and left ventricular mass (LVM) were calculated.[5,6]

To record LV inflow velocities, the apical four-chamber view was used, and the pulsed-wave Doppler sample volume was placed at the level of the leaflets tips of the mitral valve, where the highest peak velocity was recorded. Peak flow velocities of the LV inflow in early diastole (E) and late diastole with atrial contraction (A) were measured. E/A velocity ratios were calculated for each cardiac cycle.

Statistical anaysis: Data were expressed as mean± standard deviation (SD). Statistically, comparison of SCA patients and controls was made by using unpaired *t* test. A value of $p < 0.05$ was considered statistically significant.

Results

In the study cases, age range was from 5 years to 15 years with the mean age of 9.91 years. There were 14 males and 11 females in the study group. Maximum cases belonged to the Kunbi caste (*n*=8, 32%) followed by Teli and Mahar. On cardiovascular examination, mean heart rate was 89±11 beats per minute (bpm), mean blood pressure was 94±12/63±7 mmHg. On auscultation, 6 (24%) cases revealed an ejection systolic murmur heard maximally in 3rd left intercostal space parasternally. Mean hemoglobin was 8.5±2.12 gm% in study cases. Severe anemia (Hb<7 gm%) was present in 6 (24%) cases whereas 8 (32%) cases had moderate anemia. On chest X-ray, cardiomegaly was detected in 11 (44%) cases.

The electroardiographic changes of LV hypertrophy were present in 1 (4%) case. Echocardiographic measurements in patients with sickle cell anemia were compared with those of anemic and non-anemic controls with a normal hemoglobin electrophoresis pattern (Table 1). Patients with anemia (study cases and controls) had higher left ventricular internal dimension in diastole (LVIDd), left atrial dimension in systole (LADs), Stroke volume (SV) and left ventricular mass (LVM) in comparison to those who were non-anemic (controls) with a normal hemoglobin electrophoresis pattern. No statistically significant differences were detected in the Doppler finding of patients with or without anemia. On Doppler study, 'E' and 'A' wave amplitude was higher in SCA cases as compared to the control. No statistically significant correlation was found between echocardiographic parameter (M-mode and Doppler) and severity of anemia in the sickle cell patients (Table 2).

Discussion

Sickle cell disease is an inherited disorder associated with significant morbidity, characterized by the presence of an abnormal hemoglobin within the red blood cells. Valine is substituted for glutamic acid as sixth amino acid in the beta polypeptide chain of this abnomal hemoglobin.[6] The cardiovascular system is stressed by chronic anemia, recurrent small pulmonary artery occlusion, and myocardial hemosiderosis. Autopsies have revealed that right and left venticular dilation is common in both children and adults.[7] LV hypertrophy may result from systemic hypertension secondary to chronic renal failure. SCA results in chronic volume overload of the heart due to hemodilution. Previous echocardiographic studies of cardiac function in children with SCA have not accounted for these abnormality loading conditions.[8] The typical physical examination in SCD reveals cardiomegaly, a hyperdynamic precordium, and a grade II/III systolic ejection murmur with wide radiation. Wali et al.[9] reported that the dilated chamber in SCA was not associated with any abnormality in systolic or diastolic ventricular function nor with significant hypertension. Cipolotti et al.[10] observed that early hemodynamic changes occur with progressive cardiac chamber dilation and diastolic dysfunction becomes increasingly abnomal with growth. Chung et al.[3] reported that left ventricular internal dimension in systole (LVIDs), LVIDd, LVEDV, and cardiac output are significantly increased in patients with SCA. However, Lester et al.[11] concluded that the major echocardiographic abnormality in SCA children was enlargement of left heart chambers; our study had similar findings.

Batra et al.[8] also demonstrated that SCA results in a volume-overloaded heart with a significant increase in LV cardiac mass, both proportional to the degree of anemia. Despite these abnormal loading conditions, systolic function is preserved. However, Kilinc et al.[12] found that

Table 1. Echocardiographic measurements in patients with sickle cell anemia versus anemic and non-anemic controls with normal hemoglobin electrophoresis

Echocardiography	SCA cases Hb, Electro. 'SS' (*n*=25) Mean ± SD	Anemia Hb, Electro. 'AA' (*n*=25) Mean ± SD	Non-Anemic Hb, Electro. 'AA' (*n*=25) Means ± SD	p[@] value	p[#] value	p* value
M-Mode/2D						
LAD (mm)	23.26±3.60	22.90±2.56	20.72±2.79	0.006*	0.615	0.005*
Aod (mm)	19.00±2.70	18.91±2.24	17.56±1.44	0.038*	0.703	0.146
LA/Ao	124.88±10.89	123.00±13.26	122.72± 16.48	0.833	0.586	0.463
IVSd (mm)	7.36±1.44	6.99±1.32	7.08±1.89	0.686	0.374	0.558
IVSs (mm)	10.10±1.20	10.24±1.30	9.52±1.38	0.120	0.164	0.118
LVIDd (mm)	34.88±4.53	33.28±3.28	30.72±3.68	0.001*	0.184	0.0007*
LVIDs (mm)	23.80± 3.75	24.60±2.28	22.60± 3.29	0.086	0.345	0.234
LVPWd (mm)	6.52±1.47	6.21±1.36	6.76±1.47	0.400	0.441	0.566
LVPWs (mm)	9.20±1.52	8.92±1.42	8.96±2.24	0.832	0.503	0.659
IVS/PW (%)	119.98±36.23	115.51±32.48	112.60±24.70	0.707	0.651	0.404
SV (ml)	31.32±9.32	27.12±7.82	22.40±4.67	0.015*	0.429	0.046*
FS %	31.68±5.80	31.14±6.80	30.20±3.50	0.635	0.763	0.302
EF %	67.00±7.50	65.00±5.85	66.00±4.40	0.507	0.290	0.452
LVM (gm)	62.24±18.44	52.53±16.23	50.2±15.68	0.032*	0.053	0.016*
Doppler						
FVI (ms)	12.23± 2.64	12.68±2.79	12.48±2.29	0.826	0.560	0.721
IVRT (ms)	72.60±11.60	69.80±10.33	67.24±5.40	0.143	0.371	0.143
'E' wave (m/s)	112.20±18.07	109.00±17.05	107.84±19.07	0.678	0.545	0.384
'A' wave (m/s)	61.00±16.50	56.58±14.50	53.80±12.82	0.216	0.295	0.127
E/A	2.08± 12.60	2.01±0.78	1.97±0.49	0.908	0.629	0.908
AT	67.90±14.50	72.80±13.57	73.56±15.65	0.333	0.222	0.395
DT	126.96±51.88	120.83±32.66	112.72±17.04	0.393	0.483	0.262

LAD: left atrial dimension in systole; Aod: Aortic root dimension in diastole; IVSd: interventricular septum in diastole; IVSs: inteventricular septum in systole; LVIDd: left ventricular internal dimension in diastole; LVIDs: left ventricular internal dimension in systole; LVPWd: left ventricular posterior wall in diastole; LVPWs: left ventricular posterior wall in systole; SV: stroke volume; FS: fractional shortening; EF: ejection fraction; LVM: left ventricular mass; IVRT: isovolumic relaxation time; AT: acceleration tme; DT: deceleration time; SCA: sickle cell anemia

[@] p value compared the SCA cases with that of anemic and non-anemic controls

[#] p value compared between SCA cases with that of anemic controls

* p value compared the SCA cases with that of non-anemic controls

posterior LV thickness and LVM were increased in SCA group compared with controls ($p=0.001$, $p<0.05$ respectively). Kingue et al.[13] reported that the dimensions of the cardiac chambers and the LVM were increased in the SCA patients. Same result was found in the present study. Posterior LV wall thickness and septal thickness were increased in the study group when compared with normal subjects although the differences were not statistically significant.

Wasi et al.[9] showed that left atrium dimensions were significantly increased as compared to the controls. Kilinc et al.[12] reported that mean left atrial dimension was increased in SCA group compared with controls ($p<0.001$), which is in concordance with the present study. No statistically significant correlation was found between the echocardiographic parameters and the hemoglobin value. Studies by Rees et al.[14] and Cipolotti et al.[10] have failed to established correlation between LV performance and the hemoglobin level. Chung et al.[3] documented that there is no significant correlation between Hb, end-diastolic volume and ejection fraction in patients with SCA. Kane et al.[15] emphasized the frequency of the heart involvement in SCD, particularly in the homozygous type, and pointed out the importance of the cardiac screening of these patients.

Kilinc et al.[12] showed that in spite of LV volume overload and dilation, LV contraction was good and systolic function was normal, and there was no correlation between the echocardiographic findings and hematological indices. Same result was found in our study. Kingue et al.[13] reported that the amplitudes of the mitral inflow 'E' and 'A' waves were increased, and the deceleration time (DT) was longer in the sickle cell group whereas in our study, 'E' and 'A' wave amplitude were increased in SCA cases as compared to the controls although the difference was not statistically significant. There were no abnormalities in the ejection fraction or shortening fractions. These results suggest early hemodynamic changes with progressive cardiac chamber dilation that become increasingly abnormal with growth.

Table 2. Comparison of the echocardiographic parameters with respect to the hemoglobin values in the study group (*n*=25)

Echocardiography	SCA cases (*n*=6) Hb <7 gm/dl Mean±SD	SCA case (*n*=8) Hb 7-9 gm/dl Mean±SD	Non-Anemic Mean±SD	p value
M-Mode/2D				
LAD (mm)	24.00±2.36	22.76±3.44	23.09±4.08	0.827
Aod (mm)	19.50±2.16	18.50±3.04	18.54±2.73	0.747
LA/Ao	126.66±6.67	123.62±11.32	125.54±9.98	0.840
IVSd (mm)	7.83±1.94	7.25±1.29	7.18±1.25	0.658
IVSs (mm)	9.83±1.60	10.37±0.99	9.81±0.40	0.434
LVIDd (mm)	35.83±4.66	35.62±3.96	33.81±4.85	0.588
LVIDs (mm)	25.83±4.07	24.50±2.69	22.18±3.73	0.118
LVPWd (mm)	6.33±1.63	6.50±1.11	6.63±1.68	0.925
LVPWs (mm)	8.50±1.64	9.00±1.58	9.72±1.27	0.251
IVS/PW (%)	135.93±42.83	116.88±33.11	113.54±33.91	0.460
SV (ml)	32.33±19.34	31.50±11.53	27.72±11.56	0.891
FS %	28.83±5.94	32.12±3.96	33.45±7.04	0.325
EF %	62.33±8.52	66.50±3.90	69.72±7.97	0.143
LVM (gm)	69.33±22.94	62.95±19.69	58.00±19.47	0.554
Doppler				
FVI (ms)	12.11±4.05	11.87±1.36	12.54±2.62	0.864
IVRT (ms)	75.83±12.60	70.87±11.32	72.18±11.54	0.727
'E' wave (m/s)	106.5±20.63	114.63±15.01	113.54±19.09	0.616
'A' wave (m/s)	50.66±17.59	60.37±13.59	67.00±15.80	0.137
E/A	2.77±2.50	1.97±0.41	1.78±0.37	0.296
AT	67.16±15.31	71.12±17.20	65.90±10.52	0.722
DT	128.33	121.50±51.19	130.18±47.12	0.630

LAD: left atrial dimension in systole; Aod: Aortic root dimension in diastole; IVSd: interventricular septum in diastole; IVSs: interventricular septum in systole; LVIDd: left ventricular internal dimension in diastole; LVIDs: left ventricular internal dimension in systole; LVPWd: left ventricular posterior wall in diastole; LVPWs: left ventricular posterior wall in systole; SV: stroke volume; FS: fractional shortening; EF: ejection fraction; LVM: left ventricular mass; IVRT: isovolumic relaxation time; AT: acceleration tme; DT: deceleration time; SCA: sickle cell anemia

Conclusions: Sickle cell anemia in children results in a volume-overloaded heart with a significant increase in left ventricular dimension and left ventricular cardiac mass, both proportional to the degree of anemia. Despite these abnormal loading conditions, systolic function is preserved.

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Original Article

Transcatheter Closure of Perimembranous Ventricular Septal Defect with Amplatzer Membranous Occluder

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Background: Use of trancatheter device closure for membranous ventricular septal defect is still in evolving phase. We report the early and mid-term results of our experience with the new asymmetric Amplatzer membranous ventricular septal defect occluder.

Methods and Results: We attempted, transcatheter closure of perimembranous ventricular septal defect using asymmetric Amplatzer occluder in 26 patients. The patients were selected on the basis of transthoracic and transesophageal echocardiographic assessment of the ventricular septal defect. The procedure was successful in 21 (81%) patients. The age ranged from 3 to 23 years, weight from 10 to 59 kg and defect size ranged from 3 to 9 mm (mean: 5 ± 1.8 mm). One patient had situs inversus with dextrocardia; 11 had aneurysmal tissue partly occluding the defect and the device was deployed either across (n=6) or within the aneurysmal sac (n=5). Three patients developed high degree atrioventricular block on attempts to cross the defect with the sheath and the procedure was discontinued. In two patients it was not possible to place the sheath in left ventricle despite repeated attempts. There was a residual flow in 4 (19%) patients at 24 hours. Two patients developed bundle branch block and none had complete heart block. At follow-up (1-9 months, n=20), residual flow was seen in two patients. None developed late conduction defect, aortic regurgitation, infective endocarditis or hemolysis.

Conclusions: Transcatheter closure of perimembranous ventricular septal defect can be performed safely and effectively with the new asymmetric Amplatzer occluder device in selected patients with good short- and mid-term results. These devices can be deployed safely in and across and the aneurysmal sacs. In selected cases, this procedure is a satisfactory alternative to surgery. **(Indian Heart J 2005; 57; 698-703)**

Key Words: Ventricular septal defect, Amplatzer occuder, Echocardiography

Surgical closure of perimembranous ventricular septal defects (VSD) is generally safe with low mortality.[1,2] Nevertheless, the procedure is associated with significant morbidity and involves considerable patient discomfort.[1-3] Transcatheter device closure has evolved as an alternative to open heart surgery and its use has been well established with muscular VSDs.[4-8] On the contrary, the role of transcatheter closure of perimembranous VSDs with the new membranous asymmetric Amplatzer ventricular septal defect occluder (AAVSDO) is in the evolving phase.[8-12]

We report our initial experience in closure of perimembranous VSD with the new membranous Amplatzer occluder.

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Methods

The objective of the study was to describe the case selection strategy, the technique and the results of closure of perimembranous VSDs with the membranous Amplatzer VSD occluder. An informed consent was obtained from all patients after explaining the procedure and the risks involved. All patients underwent a detailed transthoracic (TTE) and transesophageal echocardiogram (TEE) before the procedure. The following information was sought in these studies: (i) The maximum size of the defect as assessed in multiple views, (ii) The distance of separation of the defect from the aortic annulus was measured in the apical five-chamber view and in the parasternal long axis view, and (iii) In patients with septal aneurysm covering the VSD from the right ventricular aspect, the following additional information was sought so as to decide the optimal site for device deployment- (a) dynamic mechanism of the closure of the defect by the aneurysm in various phases of cardiac

cycle, (b) the relationship of the septal tricuspid leaflet to the aneurysm, (c) the effective orifice, (d) multiple orifices, and (e) the presence of a narrow proximal neck (entry point) for the aneurysm.

Patients with perimembranous VSDs with 2 mm separation of the aortic annulus from the superior edge of the defect were selected for device closure. In patients who had septal aneurysm, this was not considered mandatory. Children weighing less than 10 kg were excluded. Patients with aortic valve prolapse with significant aortic regurgitation were not offered the procedure. Patients who had tricuspid septal leaflet tissue which was a part of the aneurysm that potentially would be entrapped by the device on deployment were not selected for transcatheter closure.

Device and delivery system: The AAVSDO is a self centering and repositionable device, comprising of two disks of nitinol wire mesh (AGA Medical Corporation, USA) with a short waist to minimize the entrapment of tricuspid valve tissue.[11,12] The left ventricular (LV) disc extends 5 mm toward the platinum marker (which should be facing the apex) and 0.5 mm toward the aorta. This helps in firm anchoring on the ventricular septum, and at the same time avoids contact with the aortic valve. The delivery system has a stainless steel cable (0.038") to be passed through a plastic delivery sheath (which is curved, so as to direct the device to the apex) and has a metallic slot that has to match the micro screw on the device. Once the stainless steel cable is screwed on to the device and the micro screw attachment pulled into the metallic slot of the delivery catheter, the stainless steel cable is pulled and the traction maintained by tightening the screwing device against the hub of the plastic delivery catheter. This prevents the rotation of the device as it is advanced through the delivery sheath and ensures that the LV disc is released with the platinum marker toward the apex. For introduction into the delivery sheath, the device is pulled into the loader.

Procedure: The procedure of transcatheter closure of perimembranous defects is similar to the transcatheter closure of muscular defects.[4-8,11,12] All patients received 5 mg/kg of aspirin one day before the procedure. The patients were intubated and underwent a right and left heart study under general anesthesia. A pre-procedure TEE was repeated to confirm the location, the size of the defect and its relationship to adjacent structures. All patients received 100 IU/kg of heparin and the ACT was maintained above 250 ms during the procedure. An LV angiogram was done in angled angiographic views and the VSD was crossed from the left ventricle using either 4 F or 5 F right coronary catheter (RCA) or a 5 F cut pigtail (Fig. 1). In the first few patients we used the soft 0.035", 300 cm Rope wire (AGA Medical Corporation, USA) to cross the VSD and this was snared from the pulmonary artery using a 10 or 15 mm snare (120 cm, Amplatz Goose Neck; Snare, USA) and brought out through the femoral vein to establish an arteriovenous wire loop. In subsequent patients, we used the 0.035 terumo wire (300 cm) for crossing the VSD and this was guided into the pulmonary artery and later exchanged for a regular 0.032", 300 cm guidewire. The catheter was removed from the femoral vein and the appropriate sized delivery catheter (7 F to 9 F) was advanced over the wire across the VSD into the ascending aorta. The dilator was removed and the sheath tip was positioned in the LV apex by deflecting the guidewire into the ventricular cavity using the RCA catheter placed in the aorta. The device size was selected to be 1-2 mm larger than the largest diameter of the defect (on TEE).

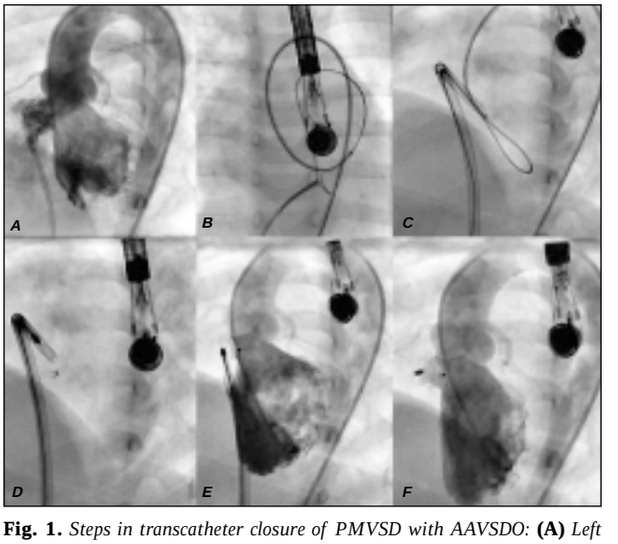

Fig. 1. *Steps in transcatheter closure of PMVSD with AAVSDO:* **(A)** *Left ventricular angiogram in long axial oblique view showing perimembranous VSD,* **(B)** *Cine-radiographic frame showing the 0.032" exchange length wire being snared from the pulmonary artery to form an arteriovenous wire loop,* **(C)** *Cine-radiographic frame showing the sheath deflected into left ventricle with a wire loop formed by introducing the 5F RCA catheter into the left ventricle from the aorta,* **(D)** *LV disc deployed with the marker toward the apex,* **(E)** *Angiogram in long axial oblique view showing the device in position before release,* **(F)** *LV angiogram in long axial oblique view showing the device in position after release.*

PMVSD: perimembranous ventricular septal defect; AAVSDO: asymmetrical Amplatzer membranous VSD occluder; VSD: ventricular septal defect; RCA: right coronary artery; LV: left ventricular

In patients with aneurysm, the device size was selected by the size of the entry point or by the size of the largest orifice of the opening of the aneurysm. The delivery catheter was flushed and its position was checked on TEE (Fig. 2). The device was loaded as described previously and the LV disc was partly released in the left ventricle and

slowly withdrawn into the LV outflow tract away from the mitral valve. The left disc was fully deployed and pulled back gently against the septum on TEE and fluoroscopic guidance. After making sure that the position of the left disc is optimal (with the platinum marker facing toward the apex and the device well away from the aortic valve), the right disc was deployed. This was done by gently unhitching the metallic slot of the plastic delivery sheath from the micro screw of the device while maintaining the pull on the left disc by the stainless steel cable. After this maneuver, the RV disc was deployed by pulling back the delivery catheter. The device was released after confirming that the device was deployed optimally with no interference with the aortic and tricuspid valve structures by TEE. After release of the device a selective left ventriculography was done to check for the device position and residual flows. All patients were put on aspirin (5 mg/kg) daily for 6 months.

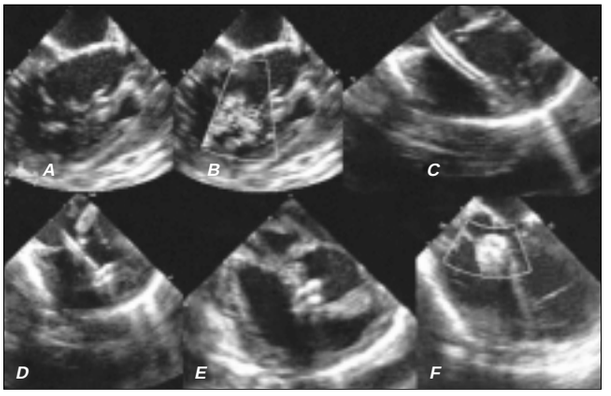

Fig. 2. *Transesophageal two-dimensional echocardiogram and color Doppler images of short and long axis views.* **(A)** *Perimembranous ventricular septal defect with aneurysm,* **(B)** *Aneurysm with two jets into right ventricle,* **(C)** *The long sheath deep in left ventricle,* **(D)** *Left ventricle disc deployed after sheath is withdrawn,* **(E)** *Right ventricular disc deployed and device in good position,* **(F)** *No residual flow across the device.*

In patients with aneurysm, the site of deployment of the device was decided on TEE. In case the aneurysm had multiple openings, care was taken to make sure that the arteriovenous wire loop was through the largest opening of the aneurysm with the help of TEE. In cases where the aneurysm had a narrow proximal neck, the device was completely in the sac (both discs on either side of the narrowest portion of the aneurysm). In cases where the aneurysm had a single large opening, the device was deployed across this (LV disc in the aneurysm and the RV disc in the RV cavity) (Fig. 3).

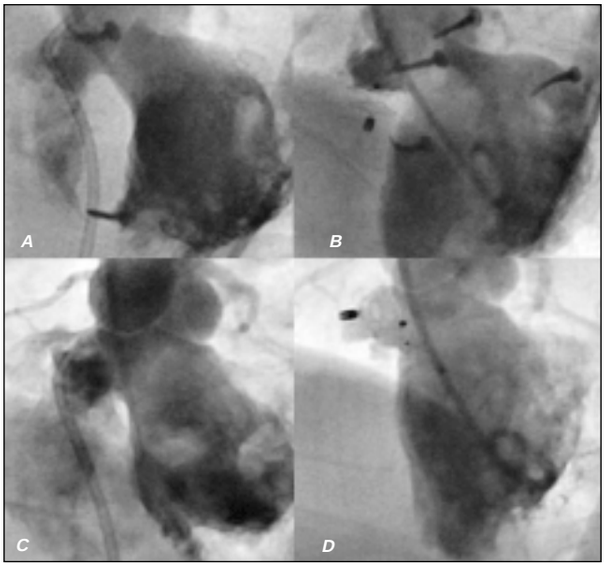

Fig. 3. *Left ventricular angiogram in long axial oblique view showing perimembranous ventricular septal defect and the device position.* **A** *and* **B***: Device deployed across the aneurysm,* **C** *and* **D***: Device deployed in the aneurysm.*

Follow up: All patients were reviewed after one month and then every three months. At review, a complete physical examination along with 12-lead electrocardiogram (ECG), chest X-ray and echocardiogram was done.

Results

The procedure was attempted in 26 patients (intention-to-treat success rate: 81%) and 21 of them had successful closure of their defects with the new AAVSDO (Table 1). The age ranged from 3 years to 23 years with a median age of 6 years. Eleven patients were male with their weight ranging from 10 to 59 kg with a median weight of 15 kg. The mean pulmonary artery pressure (PAP) ranged from 18 to 55 mmHg and 15 of them had a mean PAP of > 25 mmHg. The Qp-Qs ratio ranged from 1:2 to 3:1 for the whole group, with 12 patients having a shunt ratio > 1.8:1. The maximum diameter of the defect on TEE ranged from 3 mm to 9 mm (mean diameter was 5±1.8 mm). The mean device diameter was 8 mm and the largest device used was 12 mm.

In 11 patients, aneurysmal tissue was partly covering the defect. In this subset, seven patients had multiple openings into the right ventricle (5 patients had two jets and 2 had 3 jets opening into right ventricle) by echocardiography. In 5 patients, the device was deployed within the aneurysm (both the discs in the aneurysm). In six

patients the device was deployed across the aneurysm (LV disc in the aneurysm and the RV disc in the right ventricle) and in the rest (n=10) the device was deployed across the ventricular septum (occluder discs on either side of the ventricular septum).

In patients with aneurysm with multiple openings, the device was either deployed in the aneurysm or across the larger of the opening of the aneurysmal sac. In two such patients the aneurysmal sac had a narrow neck across which the device was deployed and this ensured complete closure even with the sac having multiple secondary openings. In one patient, a relatively oversized device was deployed across the larger opening to cover an additional smaller defect. Two patients had their devices deployed directly in the aneurysm because the sheath could not be placed initially into the LV even after repeated attempts. The procedure time ranged from 120 to 335 min (mean 178 ± 58 min). Immediate complete closure of the defect was possible in 15 patients. In patients with aneurysm (n=11), there was immediate residual flow in 4 patients. The average hospital stay was 5 ± 2 days. At discharge, there was mild residual flow in only two patients (both had flows from additional orifice of the aneurysm). Of the 26 patients attempted, the procedure was not successful in five. Three of these patients developed AV nodal conduction abnormalities (2 patients had 2:1 AV block, 1 had transient AV dissociation) on attempts to place the long sheath across the defect. In the other two patients, it was not possible to place the sheath in the left ventricle despite multiple attempts. Two patients developed bundle branch block [incomplete right bundle branch blcok (RBBB): 1, left anterior hemiblock (LAHB):1] before discharge. Two patients developed repeated supraventricular tachycardia with hemodynamic compromise on attempts to cross the defect with the sheath and required cardioversion and eventually the procedure was completed successfully in them. There was no mortality and no patient developed complete heart block immediately after the procedure. The follow-up (n=20, duration 1-9 months) showed mild residual flow in two patients. The conduction block observed in the two patients persisted at 3-month visit. There were no new onset conduction abnormalities and none had new onset tricuspid or aortic valve regurgitation.

Discussion

There are only few published reports of transcatheter closure of perimembranous VSDs with good results.[10-12] The new eccentric Amplazter VSD occluder has been specifically designed for closure of perimembranous VSDs and offers significant advantages over the previous devices.[4,10-12] In contrast to the other occluders, the AAVSDO has a short connecting waist, is less rigid and more importantly, has an asymmetric LV disc designed to avoid contact with the aortic valve. The AAVSDO requires only 2 mm rim of tissue between the defect and the aortic valve

Table 1. Demographic and hemodynamic characteristics of patients who underwent device closure with AAVSDO

S.N.	Age (years)	Sex (M/F)	Wt (kg)	PAP (mean)	Qp-Qs ratio	VSD size (mm)	Device size	Aneurysm (Y/N)	Residual flow -immediate	Residual flow at 1 month
1	6	F	25	36	2:01	8	12	N	No	No
2	5	M	11	22	1.20	5	6	Y	Mild	No
3	3	F	13	45	2:01	9	10	Y	Mild	Mild
4	4	F	10	55	2:01	6	10	N	No	No
5	11	M	30	25	2.00	6	8	Y	No	No
6	8	F	24	35	2.00	4	6	Y	No	No
7	3	M	10	19	2.00	4	4	Y	No	No
8	4	M	15	27	1.60	4	6	N	Mild	No
9	20	F	45	28	2.10	6	10	N	Mild	No
10	9	F	33	33	2.00	4	6	Y	No	No
11	5	M	14	25	1.20	4	6	N	No	No
12	10	M	25	27	1.40	3	8	Y	Mild	Mild
13	4	M	14	20	1.40	4	6	N	No	No
14	3	M	10	18	1.40	3	4	Y	Mild	No
15	23	M	59	27	2.00	6	10	N	No	No
16	5	F	11	35	2.50	6	8	N	No	No
17	5	F	12	26	2.00	3	4	Y	No	No
18	7	M	18	22	2.50	6	8	N	No	No
19	6	F	14	19	1.80	3	6	Y	No	No
20	13	F	38	45	3.00	8	12	N	No	No
21	6	M	15	35	1.80	6	8	y	No	NA

AAVSDO: asymmetric Amplatzer ventricular septal defect occluder; PAP: pulmonary artery pressure, mmHg; VSD: ventricular septal defect

and this allows many of the perimembranous defects amenable to non-surgical closure. Various studies have emphasized the technical difficulties that are associated with percutaneous closure of perimembranous VSD.[4, 8-11] These septal defects are close to the mitral, tricuspid and aortic valve. In addition, the AV node is situated in the posterior upper membranous ventricular septum and branches into left and right bundle in the posterior lower margin. This increases the risk of transcatheter closure of perimembranous VSDs.[10-12] Arrhythmias are a common complication and various types of conduction abnormalities have been reported with the procedure.[10-12]

In our study, we used the AAVSDO for transcatheter closure of PMVSD in 21 patients. Complete occlusion with no residual flow was possible in 19 patients without major complications on short-term follow-up. In this series, a sizable proportion (11/21) of patients had aneurysmal tissue covering the VSD and all these defects were successfully closed with the asymmetric device. In these patients the device size was not selected according to the size of the defect across the ventricular septum. The device was chosen considering various parameters like the size of the entry point, size of the aneurysmal sac, size of the exit point(s). In 5 patients we deployed the device across the entry point or within the aneurysmal pouches. This relatively pliable device with its narrow waist allows the device to position itself in the aneurysm without overt distortion. In patients that did not have a narrow entry (similar to a duct ampulla), we deployed the device across the largest exit orifice. In one patient we used a relatively larger device (4 mm) more than the effective orifice to cover an additional exit opening of the aneurysm. The use of TEE and an understanding of the nature of the defect and its dynamics in various phases of cardiac cycle are necessary to determine the site of deployment of the device.[13] In all our patients the site of deployment was decided by the pre-procedure echocardiogram. There was residual leak in 4 patients at discharge (all had aneurysm) and this resolved in all patients except two at one month follow-up. The device position remained stable on short-tem follow-up.

In our series, a significant proportion (8 patients) had relatively small defects (< 4 mm). Although patients with small defects have excellent prognosis, they are at risk for endocarditis and late cardiac arrhythmias.[14-17] These patients were offered this procedure in the expectation that complete closure of these defects will obviate the risk of endocarditis and arrhythmias.

There was no incidence of complete heart block in this relatively small series but the reported incidence in larger series is around 1.7%.[17] Our strategy has been to discontinue the procedure in the event of any serious conduction abnormalities. This probably decreases the incidence of complete heart block associated with this procedure, which needs to be substantiated in larger studies.

Conclusions: Transcatheter closure of perimembranous VSD can be performed safely and effectively with the new AAVSDO device. These devices can be deployed safely across and in the aneurysmal pouches that partly cover the membranous defects. Short-term follow-up showed neither a change in device position nor new onset tricuspid regurgitation in patients in whom the device was deployed partly or completely in the aneurysm. Two patients developed bundle branch block on follow-up. There was no incidence of complete heart block in this series. Our strategy has been to discontinue the procedure if any serious conduction abnormalities develop. This strategy needs to be further evaluated in larger studies. Further follow-up is required to establish the long-term safety of this procedure.

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Original Article

Stenting the Patent Arterial Duct to Increase Pulmonary Blood Flow

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Background: Use of surgically created aoropulmonary shunt is well-established for improving pulmonary blood flow in infants with critical reduction in pulmonary blood flow. Recently, stenting the patent ductus arteriosus has emerged as an alternative in selected infants with congenital heart disease and reduced pulmonary blood flow.

Methods and Results: We reviewed records of consecutive infants undergoing stenting of patent ductus arteriosus between August 2003 and October 2005 at our institution. Two of 12 patients underwent patent ductus arteriosus stenting to facilitate preparation of left ventricle for transposition with intact septum. We report the case selection, technique, immediate and short-term follow-up outcome in the remaining 10 patients [median age: 16 days (range 4-290 days); weight 2.7 kg (range 2-6 kg)] with reduced pulmonary blood flow who underwent stenting of patent ductus arteriosus as an alternative to conventional surgical aortopulmonary shunts. Five of the 6 newborns were prostaglandin-dependent and 4 had previously undergone guidewire perforation of the pulmonary valve (n=2) or balloon dilation (n=2). Successful stent implantation was accomplished in all with no major patient-related complication (median fluoroscopy time: 18.6 min; range: 7.7-72 min). The intensive care unit and hospital stays were prolonged in 3 patients because of sepsis (n=2) and pulmonary over-circulation with sepsis (n=1). On follow-up (median 5.5 months; range 1-19 months) all implanted stents were patent. One patient underwent re-dilation of the implanted stent for declining saturations.

Conclusions: The immediate and short-term follow-up results of stenting of the patent arterial duct, as an alternative to the surgical aortopulmonary shunt in carefully selected newborns and infants is encouraging.

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Key Words: Patent ductus arteriosus, Stents, Aortopulmonary shunt

Maintaining the patency of the arterial duct by stenting is evolving as an effective alternative to surgical aortopulmonary shunts. Surgical shunts improve and maintain the pulmonary blood flow in neonates with duct dependent pulmonary circulation (DDPC), allow growth of the pulmonary arteries and are well established as an effective initial palliation till these children become suitable for definitive repair. However, these procedures carry significant morbidity and some mortality.[1,2] In addition, they increase the complexity of the subsequent definitive repair. Though stenting the arterial duct was introduced nearly 15 years ago,[3] it remained largely unpopular due to the technical difficulties. With the advancement in the transcatheter interventional techniques and better hardware including flexible stents, stenting arterial ducts has been shown to be safe and effective in straight ducts[4] as well as in ducts with more complex anatomy.[5,6] We report our experience in stenting arterial ducts in children with critically reduced pulmonary blood flow.

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Methods

Between August 2003 and October 2005, 10 children with critically reduced pulmonary blood flow underwent stenting of the arterial duct. Two other children with D-transposition of great arteries, who presented late, underwent stenting of the arterial duct as a means to prepare the left ventricle for subsequent arterial switch operation and were not included in this study.

The suitability for the procedure was assessed by detailed echocardiography performed in children presenting with reduced pulmonary blood flow. The origin of the duct (undersurface of the arch, descending aorta, base of innominate artery etc), its course (straight *v.* tortuous), length and diameter at aortic and pulmonary ends, were recorded. In children with small-sized pulmonary arteries (<3 mm), arterial duct stenting was offered as the primary procedure since surgical aortopulmonary shunt carried significant risk. Informed consent was obtained from the parents after explaining the advantages and potential disadvantages of the stenting procedure as compared to surgery. Children with significant stenosis of branch pulmonary artery origin were not considered suitable for the procedure.

The procedure was performed under general anesthesia in all. Femoral route was used. If the patient was receiving prostaglandin infusion, it was stopped 0-4 hours prior to the procedure to allow the ductal constriction to occur. Stenting was performed from the venous route whenever right ventricle to pulmonary artery continuity was present or established by a prior intervention. In the rest of the patients with pulmonary atresia, the procedure was performed from the femoral arterial route via 4 F long sheath (Cooks Inc., Indiana). Aortogram was performed in appropriate views to define the course of the arterial duct. A 4 F pigtail catheter with its loop cut or a 4 F RIM catheter (Cordis) was used to engage the arterial duct from the arterial side. A 0.014" coronary guidewire was advanced across the arterial duct and lodged in the distal pulmonary artery. When the duct was approached from the venous side, the wire was taken across the duct and parked in the descending aorta. A Prolink (Vascular Concepts, Bangalore, India) coronary bare metal stent was crimped over a 3.5 or 4 mm coronary balloon of appropriate length and was deployed across the arterial duct in 9 children; one child received a pre-mounted stent. The stent was distended to a diameter of 3.5 mm in neonates and to a diameter of 4 mm in older infants.

Following the procedure, mechanical ventilation was continued electively for a minimum period of 10 hours to allow the hemodynamic readjustments. Heparin was administered at 20 units/kg/hour till adequate enteral feeding was established when aspirin (3-5 mg/kg/day) and clopidogrel (2 mg/kg/day) were added. These two medications were continued till these children were subjected to a definitive surgical procedure. The patency of stented arterial duct and the growth of pulmonary arteries were assessed by repeat echocardiography performed 1 month after the procedure and 3 monthly thereafter.

Results

Stenting was done in 10 patients at a median age of 16 days (range 4 – 290 days), 7 (70%) of them aged ≤ 30 days. The median weight was 2.7 kg (range 2-6 kg), 6 (60%) of them weighed ≤ 3 kg. The details of the diagnoses are shown in Table 1. Five (50%) children were dependent on prostaglandin infusion while being taken up for the procedure. Initial pulmonary valve intervention was done in 4 patients prior to stenting. Two children with valvular pulmonary atresia with intact interventricular septum (IVS) underwent guidewire-assisted perforation of the pulmonary valve and subsequent balloon pulmonary valvotomy. Pulmonary valvotomy was performed in two other children - one had critical valvular pulmonary stenosis with IVS and the other child had tetralogy of Fallot. In all these four situations, pulmonary balloon valvotomy had not resulted in satisfactory improvement in systemic saturation. While stenting was done immediately following inadequate response to pulmonary valvotomy in the child with tetralogy of Fallot, it was performed 2-5 days later in other children.

Table 1. Details of diagnosis of patients

S. No.	Age (days)	Weight (kg)	Diagnosis	Stent (mm)		Fluoro time (min)
				Length	Diameter	
1	9	2.6	PA/IVS	15	3.5	22.0
2	5	3.2	PA/IVS	10	4.0	18.6
3	90	3.4	PA/IVS	10	3.5	7.7
4	5	2.4	PA/ TOF	10	3.5	55.7
5	8	2.6	PA /TOF	15	3.5	56.2
6	290	6.0	PA/ LTGA/VSD	18	4.0	29.0
7	23	2.7	PA/ LTGA /VSD	15	3.5	13.2
8	30	2.0	PA/TA	10	3.5	56.7
9	4	2.8	Critical PS / IVS	15	3.5	17.0
10	120	4.5	Critical PS/TOF	10	4.0	72.2

PA: pulmonary atresia; IVS: interventricular septum; TOF: tetralogy of Fallot; LTGA: corrected transposition of great arteries; VSD: ventricular septal defect; TA: tricuspid atresia; PS: pulmonary stenosis

In four children, the size of the right pulmonary artery was < 3.5 mm, and in two of them it measured <3 mm. These children were considered to be relatively unsuitable for surgical aortopulmonary shunt. We encountered four types of ducts depending on the arch-sidedness, origin and course of the patent arterial ducts (Fig. 1). In the majority (50%), the duct had a straight course from the proximal descending aorta (type A). Two (20%) of them had straight but vertically coursing ducts from the base of the innominate artery (type C). In both these types, positioning the wire and implanting the stent were done without much difficulty. Two (20%) children with tetralogy of Fallot and pulmonary atresia had vertical ducts arising from the undersurface of the arch with a tortuous course (type B). Significant difficulty was encountered in these children for

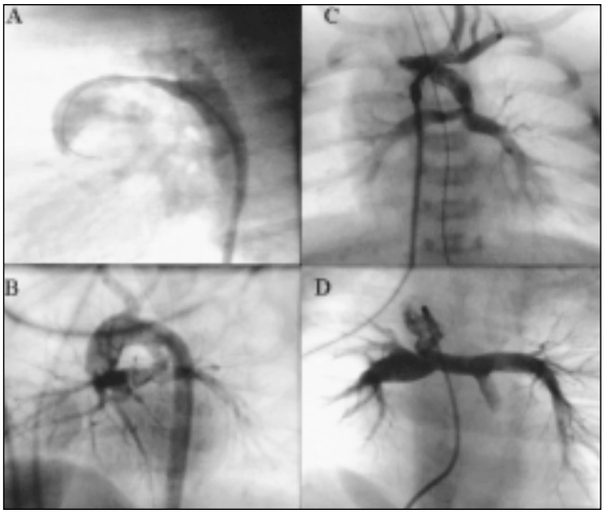

Fig. 1. (**A**) *Type A - Straight horizontal duct,* (**B**) *Type B - Vertical tortuous duct from the undersurface of arch of aorta.* (**C**) *Type C - Straight vertical duct from the base of innominate artery from right aortic arch.* (**D**) *Type D - Vertical duct from undersurface of right aortic arch inserting into mid segment of right pulmonary artery.*

obtaining a stable wire position. In addition, these ducts were straightened by the balloon and needed a longer stent than anticipated.

The procedure was most difficult in the patient with type D duct where it arose from the undersurface of right aortic arch and inserted into the mid segment of right pulmonary artery, well away from the pulmonary artery confluence. The arterial route necessitated 180° turning of the wire from the descending aorta and was unsuccessful despite trying various wire catheter combinations. From the venous side, a 0.014" coronary guidewire was passed antegradely into the main pulmonary artery. With the help of a 4 F Judkin's right coronary catheter, the wire was guided across the duct into the descending aorta. It was snared from the arterial end to establish an arteriovenous loop. However, this wire loop distorted the duct anatomy significantly and subsequent stenting from the arterial route was quite challenging necessitating multiple check angiograms both from arterial and venous ends.

Stenting was done from the venous route in 3 (30%) and from the arterial route in the rest. The length of the stent varied between 10-18 mm, median length being 10 mm. The stents were expanded to a diameter of 3.5 mm in 6 patients and to 4 mm in 4 patients. The median fluoroscopic time was 25.5 min (range 7.7 – 72.2 min). Single stent was used in all patients. The length of the stent was selected aiming to cover the entire length of the arterial duct. Unobstructed flow to both branch pulmonary arteries was achieved in all (Fig. 2). Ideal stent placement was achieved

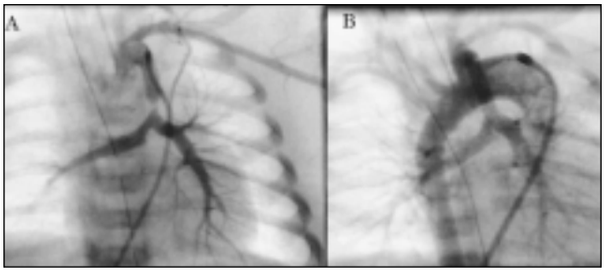

Fig. 2. (**A**) *Straight duct seen arising from innominate artery with severe constriction at its pulmonary artery insertion (arrow).* (**B**) *Angiogram done following stent deployment.*

in all except in one child in whom it was protruding more toward right pulmonary artery. However, there was no significant obstruction to the left pulmonary artery flow. The mean systemic arterial saturation at admission was 65±8% which increased to 90±2% after the procedure. There was no procedure failure, and no procedure-related mortality.

Procedural complications: In one child with valvular pulmonary atresia with intact IVS, there was improper expansion of the 3.5 mm balloon resulting in partial and uneven expansion of the stent. During manipulation, the stent was accidentally deployed in the pulmonary end of the arterial duct with the major portion protruding into the roof of main pulmonary artery. In order to reposition the stent, a 4 mm coronary balloon was chosen, manipulated into the stent and partially inflated. This partially inflated balloon-stent combination could be advanced to achieve proper positioning of the stent when the balloon was further inflated to deploy the stent. In another child with corrected transposition of great arteries, while negotiating the duct, the stent got dislodged from the balloon catheter. Using a snare, one end of the stent could be crushed and withdrawn into a 7 F femoral venous introducer sheath and thus it could be retrieved. Subsequently another stent was deployed successfully.

Post-procedural course: Two patients had impending stent block, manifesting as sudden fall in the systemic arterial saturation, despite heparin infusion. Echocardiography demonstrated reduction in the flow across the stented arterial duct. In one patient, it occurred 4 hours after the procedure, and promptly responded to additional fluid therapy. In the other child, it occurred just after shifting to the intensive care unit (ICU) and responded to fluid therapy and phenylephrine infusion.

The neonate who received 4 mm stent inadvertently showed features of increased pulmonary blood flow. In addition, she developed gram-negative septicemia on post-

procedural day 4, and needed prolonged ventilation for 11 days. Gram-negative sepsis occurred in 2 other children who also required prolonged ventilation for 6 days and 7 days, respectively. All of them responded to appropriate antibiotic therapy and other supportive measures. The mean duration of post-procedural ventilation in the rest of the children was 1.27 ± 0.7 days. The median post-procedural intensive care unit stay was 3.5 days (range 2-15 days) and the median post-procedural hospital stay was 5.5 days (median 4-22 days).

Follow-up: The median duration of follow-up was 5.5 months (range 1-19 months). The systemic saturation was consistently >80% in 7 patients and >75% in 2 patients. In a patient with corrected transposition with ventricular septal defect and pulmonary atresia, the saturation fell to 70%, 13 months after the procedure. The pulmonary artery sizes were still inadequate to consider any definitive surgical repair. She was subjected to repeat cardiac catheterization. There was mild intimal lining of the stent with no localized obstruction. The stent was re-dilated with a 5 mm balloon following which the systemic saturation rose to 88%. Cardiac catheterization was done in another patient who had pulmonary atresia with intact IVS, at 4 months of age with the aim of subjecting to one and a half ventricle repair. Ductal angiogram showed no significant stenosis of the stent with good blood flow into the pulmonary arteries. This patient awaits a cavopulmonary shunt.

Echocardiographically, there was steady increase in the size of the pulmonary arteries in all other patients with no significant distortion of the branches. One child who had critical pulmonary stenosis has been planned for one and a half ventricle type of repair and 2 other children have been planned for elective bi-directional cavopulmonary shunt. No acute stent thrombosis was encountered during follow-up.

Discussion

In the current era with advancements in the pediatric cardiac surgery, palliative aortopulmonary shunts are done predominantly on neonates and young infants. The surgical mortality of neonatal aortopulmonary shunts compares with that of relatively complex open heart operations.[2,7] In addition, the associated morbidity, pulmonary artery distortion and differential growth of branch pulmonary arteries could potentially influence the outcome of subsequent definitive surgery.[1,8] Though the initial experience by Gibbs et al.[3] in arterial duct stenting was not fruitful, there have been encouraging reports recently.[4-6]

The success of this procedure depends on appropriate case selection, which in turn depends on the anatomy of the arterial duct and presence or absence of branch pulmonary artery stenosis. Fifty percent of our children had straight duct anatomy similar to that observed by Gewillig et al.[4] These authors chose only those with straight ducts and showed the safety of stenting. Subsequently, the feasibility of stenting the arterial duct with more complex anatomy has been shown by Alwi et al.[5] and Schneider et al.[6] Presence of branch pulmonary artery stenosis had an adverse impact on the outcome of arterial duct stenting in the series by Alwi et al.[5] who considered it as an absolute contraindication for stenting the arterial duct. Hence, we decided not to consider this procedure for those children who had significant branch pulmonary artery stenosis.

Post-procedure management after stenting patent arterial duct is similar to that of post-operative management following surgical aortopulmonary shunts. Because of the increase in the pulmonary blood flow, the systemic ventricle would be volume overloaded. To allow the hemodynamic adjustments, it is generally recommended to continue mechanical ventilation in these children for a minimum period of 6-12 hours following the procedure. In some children, the shunt can result in excessive pulmonary blood flow resulting in pulmonary edema needing prolonged mechanical ventilation as occurred in one of our patients who inadvertently received a larger stent than what was intended. Maintenance of adequate intravascular volume and systemic vascular resistance is essential for good flow across the stented arterial duct. Two of our children had documented transient reduction in the flow across the stented arterial duct associated with fall in the systemic saturation. While one of them responded to fluid therapy alone, the other child needed phenylephrine infusion in addition. Three of our children developed systemic sepsis. However, seedling of the stent with bacteria or features of endarteritis did not develop in any of the children. Potential reasons could include gut ischemia due to pulmonary over-circulation and need for relatively prolonged ICU stay. Adequate palliation was achieved in all the children who underwent ductal stenting including those who had pulmonary artery sizes not ideal for surgical aortopulmonary shunt.

The relatively long fluoroscopic times reported by us and others suggest that this is a technically challenging procedure.[5] The use of pre-mounted stents instead of hand-crimped stents may allow for better stability of the stent during deployment. Difficulties relating to crossing the duct and obtaining a stable wire position can be overcome by the axillary artery approach in selected situations.[9] The patients in our study have not yet undergone subsequent

surgical procedure and it remains to be seen if any difficulty is encountered to interrupt the stented arterial duct during surgery. There are potential advantages of stenting of the arterial duct as compared to surgery. The procedure can be accomplished relatively expeditiously at a lower overall cost, specially in severely hypoxic children where cardiopulmonary bypass is needed for the aortopulmonary shunts.

Conclusions: This study demonstrates the feasibility of stenting the arterial duct as initial palliation for a selected group of newborns and infants with congenital heart disease with reduced pulmonary blood flow. Although this initial experience is encouraging, additional numbers and longer follow-up is needed. With progressive refinements in hardware and growing experience, it may emerge as an alternative to aortopulmonary shunt in selected situations.

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Angioplasty of Congenital Pulmonary Vein Stenosis

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We present a unique case of idiopathic pulmonary vein stenosis in an adult who presented with progressive dyspnea and severe pulmonary arterial hypertension. Magnetic resonance imaging confirmed the diagnosis. The patient was treated by balloon angioplasty and is well at 6 months post-treatment follow-up. The etiology of pulmonary vein stenosis in this case is difficult to ascertain, but is likely to be congenital. **(Indian Heart J 2005; 57: 709–712)**

Key Words: Pulmonary vein stenosis, Angioplasty, Congenital heart disease

Pulmonary vein (PV) stenosis is an uncommon condition, which usually presents in early childhood and carries a poor prognosis. Some cases of PV stenosis are acquired and these are readily amenable to treatment. We report a case of congenital PV stenosis who presented very late at the age of 36 years, and had good outcome with balloon angioplasty.

Case Report

A 36-year-old male patient presented with progressively increasing dyspnea of 2 years duration, which was of NYHA class III severity at presentation. He had no history of any surgery, radiofrequency ablation (RFA) or any drug intake in the past. Clinical examination showed left parasternal heave, loud pulmonary component of second heart sound with narrow splitting and ejection systolic murmur in left upper sternal edge signifying pulmonary arterial hypertension (PAH). Chest X-ray showed severe pulmonary venous congestion, which was more marked in right lung (Fig. 1). Echocardiography confirmed severe pulmonary hypertension with mild tricuspid regurgitation (TR) with a gradient of 66 mmHg (estimated right ventricular pressure of 66 + right atrial pressure). There was no evidence of mitral stenosis (MS) or left ventricular (LV) dysfunction, thus excluding other causes of PAH. On Doppler study there was a well appreciable jet coming out of the pulmonary venous drainage site from the right side into the left atrium (LA). The jet was continuous and had a gradient of 24 mmHg, which gave suspicion of pulmonary venous stenosis of the right-sided pulmonary veins. Magnetic resonance imaging (MRI) further confirmed pulmonary venous stenosis of the right-sided PV at their confluence just before their entry into LA (Fig. 2). There was no evidence of any mediastinal fibrosis or mass.

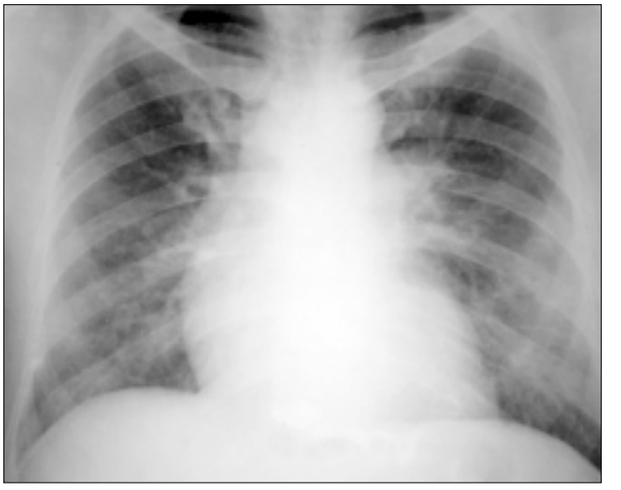

Fig. 1. *Chest X-ray PA view showing marked pulmonary venous congestion more marked on right side.*

In view of the symptoms and confirmed diagnosis, we proceeded to perform angioplasty of the pulmonary veins. Arterial and venous access was established from the right groin with Seldinger technique. Right heart catheterization was performed. The pulmonary artery (PA) pressure was 78/56 (mean 66) mmHg. Mean LA pressure was 8 mmHg. The cardiac index was 4.1 L/min/m^2. Transseptal puncture was performed with the help of Brockenbrough's needle (Cook Inc., USA) and Mullin's sheath (AVE Ireland Ltd., Ireland). LA access was secured using coiled LA wire over

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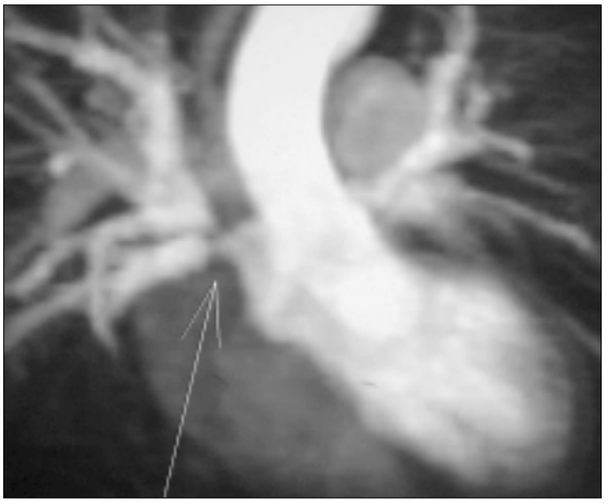

Fig. 2. *Magnetic resonance imaging with Gadolinium showing tight stenosis of the confluence of the right-sided pulmonary veins (arrow).*

which the septal puncture was dilated with the help of a 12 F dilator (Toray Industries Inc., Japan). An 8 F multi-purpose guide catheter (Boston Scientific Target, USA) was passed into the LA and right-sided pulmonary veins were cannulated with the help of Terumo wire (TERUMO Corp., Japan) which was exchanged for a 0.035" Amplatzer superstiff guidewire (Boston Scientific Corp., USA). With-drawal gradient was seen across the stenosis, the mean being 24 mmHg. Angiogram of right pulmonary veins showed that all veins from the right lung were forming a confluence at the entry site into the LA which had a tight stenosis (Fig. 3). The stenosis was tight and had a pre-stenotic dilation. Balloon sizing for the dilation was difficult and likely to be fallacious because of the pre-stenotic dilation on one side and LA on the other side. We performed quantitative measurements and also had visual assessment of the likely size of the balloon required. We chose a 15 mm × 30 mm Tyshak II (NuMed Canada Inc,. Canada) balloon. The guide catheter was withdrawn and the balloon passed directly over the Amplatzer wire (Figs 4 and 5). It was inflated to a pressure of 2 atm till the waist was abolished and continued for 10 s. During balloon inflation the patient developed bradycardia and hypotension, which immediately responded to deflation of the balloon. There was hypertension and tachycardia after deflation of the balloon akin to valsalva maneuver. Otherwise the patient tolerated the procedure well. There was no dissection or residual stenosis necessitating stent deployment. There was prompt fall in the mean PA pressure from 66 to 36 mmHg. There was no demonstrable withdrawal gradient across the stenotic segment after the procedure. The patient has

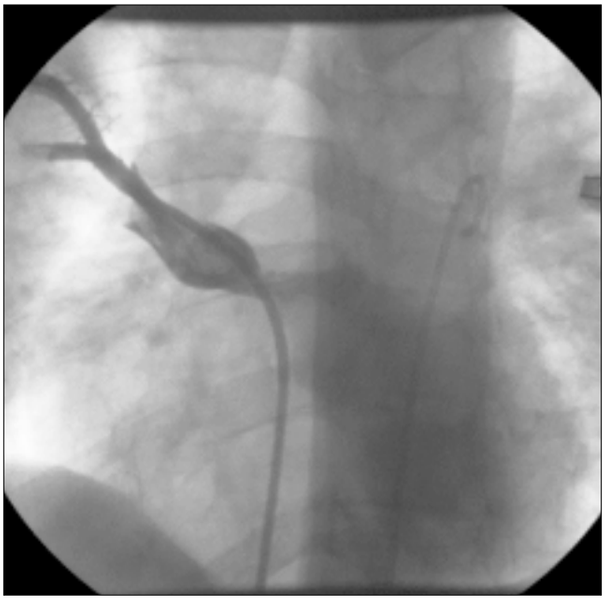

Fig. 3. *Pulmonary vein angiogram in 15° left anterior oblique view showing pulmonary vein stenosis at the site of entry into left atrium with pre-stenotic dilation.*

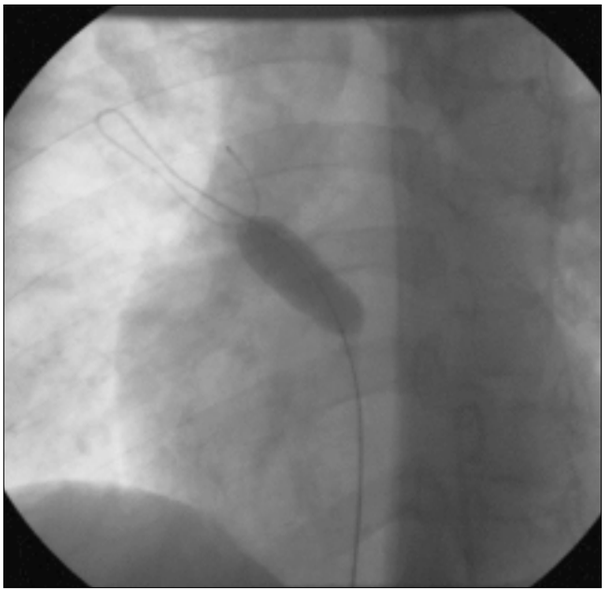

Fig. 4. *Balloon dilation of right upper pulmonary vein with 15 mm × 30 mm balloon shown in 15° left anterior oblique view.*

remained asymptomatic after 5 months of the procedure (NYHA class I). Estimated right ventricular systolic pressure by TR jet was 36 mmHg on echocardiography. The gradient across right PV as measured with the help of the Doppler jet was 7 mmHg on follow-up.

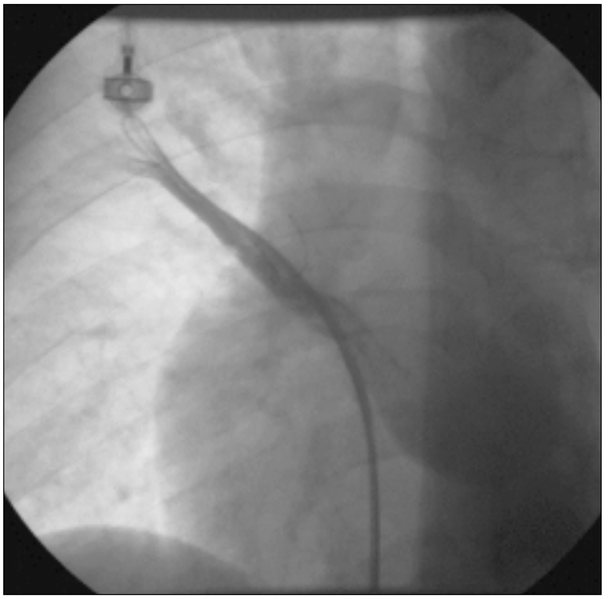

Fig. 5. *Post-balloon angioplasty angiogram in 15° left anterior oblique view showing no residual stenosis of pulmonary vein and disappearance of pre-stenotic dilation.*

Discussion

Pulmonary vein stenosis is a rare entity.[1-7] Pulmonary vein stenosis is an uncommon cause of PAH. After excluding common causes i.e. valvular heart disease, coronary artery disease, cardiomyopathies, chronic obstructive pulmonary disease, chronic thromboembolism etc. PV stenosis should be thought of. PV stenosis cannot be easily differentiated from other causes of PAH on history, clinical examination, electrocardiogram (ECG) and chest X-ray. Chest X-ray with findings of PAH, and pulmonary venous hypertension without left atrial enlargement may suggest pulmonary venous stenosis. In our case, diagnosis was suggested by a high pressure jet in the LA. Hemodyanamic hallmark of PV stenosis is the dichotomy between high pulmonary wedge pressure and normal left atrial pressure. Imaging modalities like MRI are very helpful in diagnosing this entity. PV stenosis is usually congenital and may be associated with other congenital heart diseases.[4-6] Congenital PV stenosis presents in infancy with congestive cardiac failure (CCF) with severe PAH. Other commonly recognized etiologies are mediastinal fibrosis,[7] post-cardiac surgery[8-10] and RFA.[2]

Unilateral PV stenosis can occur due to incomplete incorporation of PV into LA during cardiac development. Patients with congenital PV stenosis present late in their childhood[8] or in adulthood.[9,10] Oldest patient in Alamrani's series was 17 years of age, and there was no adult patient.[8] Our patient presented at the age of 36 years with progressively increasing dyspnea. He was a soldier in armed forces who performed rigorous military duties till 2 years prior to onset of symptoms. He never had dyspnea till 34 years of age despite rigorous duties. It is very unusual for congenital PV stenosis to present at this age. Other possible etiologies like RFA, surgery, radiotherapy or external compression were also excluded clinically, and on MRI. The etiology of PV stenosis is likely to be congenital in this patient.

Pulmonary vein stenosis have been treated surgically[11-13] or more recently by percutaneous angioplasty with or without stenting.[1-7] The results are drastically different in infancy[1,4,5,6,8] and adulthood.[2,7] In infancy, the poor prognosis is due to associated congenital cardiac defects[6] and early restenosis.[1,3,4,6,8] Despite repeat dilations, the overall long-term prognosis remains poor and majority of infants die.[1,4,6,8] In the largest series of transcatheter interventions in childhood, Alamrani et al.[8] treated 33 patients of PV stenosis, who underwent 45 balloon angioplasties and 12 stent implantations. They found that stenting achieved greater vessel diameter and lesser residual gradient as compared to balloon angioplasty. There were very low complication rates. Despite good acute results, 15 of the 33 patients died within 9 months follow-up. Majority of deaths were in infancy and in those with bilateral or multiple PV stenosis. The results with balloon angioplasty and stenting were similar. In this series, all cases were in pediatric age group and were therefore congenital PV stenosis.

In adults the etiology is varied[2,7] and the prognosis is far better because there are no associated cardiac defects; only one or two pulmonary veins are affected and larger lumen is achieved after balloon dilation which makes restenosis less common.[2,7] Qureshi et al.[2] reported 19 adult patients with post-RFA pulmonary vein stenosis. Of the 17 patients followed up for average 43 weeks, 8 developed restenosis that responded to redilation with good outcome. Similarly, Doyle et al.[7] reported good results after angioplasty and stenting in patients with PV stenosis secondary to mediastinal fibrosis. Our patient, also an adult, showed good outcome till 6 months after balloon angioplasty without stenting.

Pulmonary vein stenting has been reserved for cases where results after balloon angioplasty are inadequate or as bail out procedure due to dissection.[2,8] Other authors have stented all their patients.[1,3] The outcome after stenting has been poor in infancy and good in adults. Factors

responsible for this difference are likely to be same as detailed above rather than stenting *per se*.

To conclude, in this report we describe an adult patient with congenital pulmonary vein stenosis that responded well to balloon angioplasty with good outcome over 6 months follow up.

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Single Therapeutic Catheterization for Treatment of Native Coarctation of Aorta and Large Patent Ductus Arteriosus Using a Covered Stent

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A 20-year-old girl was diagnosed to have severe coarctation of the aorta, large patent ductus arteriosus and severe pulmonary artery hypertension. She underwent single therapeutic catheterization for the treatment of native coarctation of aorta and closure of ductus arteriosus using 39 mm long Cheatham-Platinum covered stent. The procedure was done successfully under local anesthesia without any complication. This appears to be a safe strategy while dealing with an adolescent or an adult with this combination of lesions. **(Indian Heart J 2005; 57: 713–716)**

Key Words: Covered stent, Coarctation of aorta, Patent ductus arteriosus

Balloon angioplasty with stent implantation is accepted as a primary management for coarctation of aorta in adolescents and adults.[1] At the same time, coils and several types of devices are used for closure of patent ductus arteriosus (PDA). There are reports of both the lesions being treated successfully in cardiac catheterization laboratory with the help of balloons, stents and devices, either simultaneously or in two settings.[2-5]

Covered stents are used for treatment of coarctation of aorta with aneurysm formation.[6] This is the first report where a bare covered Cheatham-Platinum (CP) stent has been used for treatment of PDA with coarctation. There has been a similar report where balloon-mounted covered stent was used in similar situation.[7]

Case Report

A 20-year-old girl presented with history of recurrent respiratory tract infection. Her physical examination revealed weak femoral pulses with brachiofemoral delay. Blood pressure was 160/90 mmHg in right arm and 110/80 mmHg in right leg. She had grade 4/6 continuous murmur over the left second intercostal space. Pulse oxymetry showed oxygen saturation of 98% in all four limbs. Chest radiography showed significant cardiomegaly [cardiothoracic ratio (CTR) 70%] with increased pulmonary vascularity. Two-dimensional echocardiography with color flow imaging revealed presence of large ductus arteriosus measuring 7 mm, which was shunting left to right. The estimated right ventricular systolic pressure by tricuspid regurgitation jet was 90 mmHg. The descending aorta could not be visualized from suprasternal view beyond the origin of left subclavian artery. Cardiac catheterization was performed under local anesthesia with adequate sedation. Right femoral artery and vein were cannulated. Heparin was given at 100 units/kg body weight. Pulmonary artery pressures were significantly elevated (83/42 mmHg with a mean of 57 mmHg), with Q_p- Q_s ratio of 2.5:1. Aortogram in descending aorta in lateral view showed a large type I ductus arteriosus measuring 6 mm at its pulmonary end and severe juxtraductal coarctation with the narrowest diameter of 7 mm (Fig. 1). The isthmus measured 20 mm and the descending aorta at the level of the diaphragm was 19 mm. The pressure gradient across the coarctation was 50 mmHg. The coarct segment was crossed with the help of right coronary artery diagnostic catheter and a 0.035" Amplatz extra stiff wire was placed in the ascending aorta through the diagnostic catheter. A 14 F 80 cm long Cook sheath was passed over the guidewire. A 39 mm long CP covered stent (NuMed, Hopekinton, NY) was hand-crimped on the BIB balloon (outer balloon 18 mm × 4 cm, inner balloon 9 mm × 3 cm) with prior balloon preparation. The covered CP stent consists of the bare CP stent composed of a 0.013" platinum/iridium wire that is covered with an expandable sleeve of the polytetrafluoroethylene. The hand-

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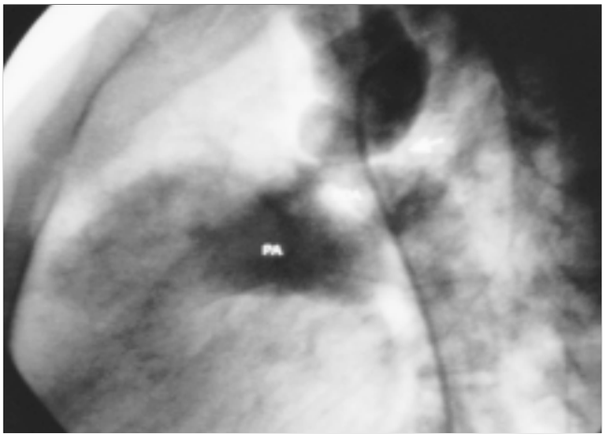

Fig. 1. *Descending aortogram in lateral view showing a large PDA with severe coarctation of aorta. Narrowest aortic diameter at the site of coarctation is 7 mm and PDA measures 6 mm in diameter.*
PDA: patent ductus arteriosus

crimped stent balloon assembly was passed through the Cook sheath placed over the guidewire. The stent was positioned across the coarctation segment and was repositioned after inflation of the inner balloon. Position was reconfirmed by angiography and stent was deployed at 4 atm pressure by inflation of outer balloon. Both balloons were deflated and removed through the sheath. Post-procedure, there was no gradient across the coarctation with an ascending aortic pressure of 130/80 mmHg. Pulmonary artery pressure decreased to 50/18 mmHg with a mean of 30 mmHg. Final angiogram revealed complete closure of ductus arteriosus with relief of coarctation (Figs 2 and 3). The diameter of the stented coarctation segment measured 18 mm. Total fluoroscopy time was 20 min and total procedure time was 65 min. No complications occurred during the procedure. She did not require any antihypertensive medication during or following the procedure. The patient was discharged on the following day with oral aspirin for six months.

At 3 months and one year follow-up she remained completely asymptomatic with normal blood pressure. There was no difference in upper and lower limb blood pressures. Echocardiography revealed complete closure of ductus and there was no gradient across the stented coarct segment.

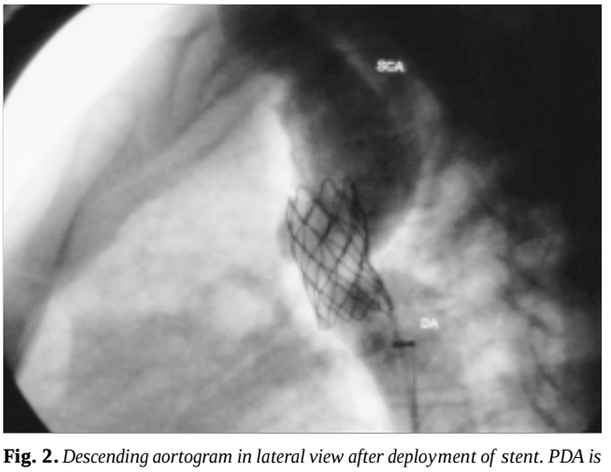

Fig. 2. *Descending aortogram in lateral view after deployment of stent. PDA is completely closed and coarct segment is dilated.*
PDA: patent ductus arteriosus

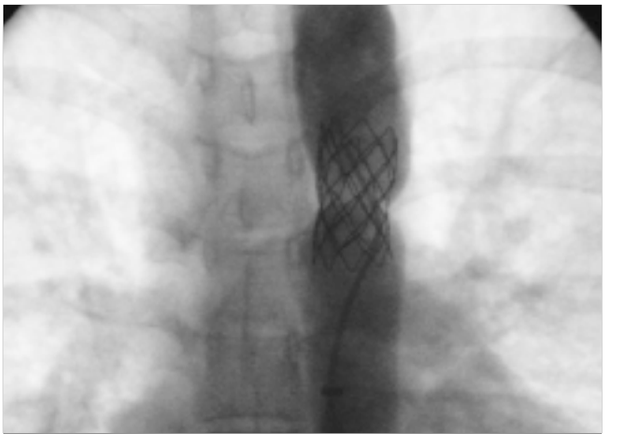

Fig. 3. *Descending aortogram in PA view after stent deployment. Coarct segment is dilated completely.*

Discussion

Coarctation of aorta and PDA is a common association in infancy, but is seen quite rarely in adults.[8] The recommended treatment for this combination of lesions in infants and children is surgery. This combination can be successfully treated in cardiac catheterization laboratory with the help of balloons, stents and devices either simultaneously or sequentially at different sittings.[2-5] During sequential sittings, balloon dilation of coarctation was carried out first, followed by PDA occlusion at a later date as there was a concern regarding aortic dissection or aneurysm formation at the site of newly dilated coarctation site by further catheter or wire manipulation during ductal closure.[2,3] Sequential therapy is possible, if the PDA is small and it can be closed after the dilated coarctation site heals completely. This may not be possible in cases with a large hemodynamically significant PDA as in ours, where simultaneous closure of PDA was needed. Simultaneous closure of PDA with a coil and balloon dilation of the

coarctation has also been reported earlier.[5] The procedure appears feasible in dealing with a young child with a combination of these lesions and a small PDA, but the technique is cumbersome and serious complications like aneurysm formation, aortic dissection, mediastinal hematoma have been reported during catheter manipulation for ductal closure.[9] PDA may enlarge in size following balloon dilation of coarctation and needs to be measured again. Utmost care needs to be taken in handling the catheter that should not cross the freshly dilated coarctation site, which may warrant use of transseptal puncture to obtain an ascending aortogram for re-measuring the correct ductal size. Failing this, if the PDA dimension increases following coarctation dilation, the misjudgement of the size of the coil may lead to coil embolization and subsequent need for retrieval. Thus, in smaller infants with a small size PDA and coarctation amenable to balloon dilation, the sequential angioplasty of coarctation first followed by closure of PDA appears a rational approach.

Recoiling, recoarctation and aneurysm formation are known complications after balloon coarctoplasty. By buttressing the vessel wall, intravascular stents plaster the flaps induced by the balloon inflation and overcome the problem of recoil and recoarctation. Providing a rigid vascular stent may help avoiding the significant arterial wall weakening and theoretically, may reduce the incidence of aortic aneurysm. Thus, stents have become the primary management option for treatment of coarctation in adolescents and adults.

Hakim et al.[10] reported the first successful simultaneous stent implantation for native coarctation of aorta and closure of an associated PDA using Amplatzer duct occluder.[10] They implanted the PDA occlusion device antegradely before the implantation of Palmaz balloon-expandable stent. The stent was expanded against the aortic wall and subsequently the device was released. The authors claimed that use of coil in this situation may be hazardous. The coils may protrude into the struts of the stent leading to balloon rupture.

Palmaz stent was originally designed for peripheral vascular lesions, and has significant limitation when used for large elastic vessel as aorta with significant intimal and medial injury during its overexpansion.[11] Covered CP stent has been developed to overcome this problem and also to successfully treat the complications like dissection/ aneurysm.[11,12] The primary therapeutic indication of covered stent is completion of third stage Fontan in cardiac catheterization laboratory in patients with hypoplastic left heart syndrome.

We used the covered CP stent for simultaneously closing PDA and dilating the coarctation. PDA was closed during expansion of the stent at the site of coarctation, as do all PDA devices, by apposition of the stent against the wall of the aorta. It avoided the need for an additional device for closure of PDA. Use of BIB balloon allowed proper stent repositioning before deployment by inflation of inner balloon. A single case report[7] is available in the literature on simultaneous closure of PDA and stent implantation for coarctation of aorta using covered CP stent with good results. Unlike in our case where the stent was hand-crimped over the balloon, a pre-mounted balloon stent was used in that case.

Limitations: A minor limiting factor may be use of larger sheath (14 F). As our patient was a 20- year girl, we could use it without much difficulty. Due care needs to be taken while deploying the stent to avoid arch vessel obstruction. As spinal artery usually originates at the level of lower thoracic aorta, covered stent used for treatment of coarctation of aorta is unlikely to cause damage to spinal arteries.

Conclusions: The technique described is safe, simple and can be carried out under local anesthesia with adequate sedation even in patients with severe hyperkinetic pulmonary artery hypertension in mature children and adults. When possible, an effort should be made to treat both the conditions simultaneously in one setting.

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Implantable Cardioverter Defibrillatory Implantation in a Patient with Persistent Left Superior Vena Cava and Right Superior Vena Cava Atresia

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Persistence of a left superior vena cava has been observed in 0.3% of the general population as established by autopsy findings. In the adult population, it is an important anatomic finding if a left or right superior vena cava approach to the heart is considered for device implantation. We present a case with persistent left superior vena cava and right superior vena cava atresia in whom a dual chamber implantable cardioverter defibrillator was implanted and was technically challenging. **(Indian Heart J 2005; 57: 717–719)**

Key Words: Venous anomaly, Heart failure, Arrhythmia

There has been tremendous increase in number of implantation of implantable cardioverter defibrillator (ICD) in recent years due to the ease of placement offered by the transvenous puncture technique. However, in the presence of a congenital venous anomaly such as a persistent left superior vena cava (LSVC), manipulation and placement of the leads may be technically challenging. The choice of the appropriate hardware is vital in these cases as this may affect the vectors of defibrillation and the eventual outcome of the procedure. We present the case of a patient with persistent LSVC with right superior vena cava (RSVC) atresia in whom a dual chamber ICD was implanted.

Case Report

A 50-year-old male in congestive heart failure was admitted for an episode of frank syncope. History was positive for syncopal episodes in the past. Baseline electrocardiogram (ECG) showed right bundle branch block (RBBB) with left anterior hemiblock and a PR interval of 200 ms. Echocardiography revealed global hypokinesia of the left ventricle with an ejection fraction (EF) of 20%. Angiography documented normal coronaries.

A sustained monomorphic ventricular tachycardia [left bundle branch block (LBBB) with superior axis morphology] with hemodynamic compromise was induced by programmed electrical stimulation of the right ventricle (RV) during electrophysiological study. The HV interval was measured to be 75 ms. In view of these findings, the decision was made to implant a dual chamber ICD.

A conventional left-sided subclavian puncture was made (the majority of implants done at our institution are via a left subclavian puncture route), but resistance was encountered when attempts were made to negotiate the guidewire through the puncture needle. A venous anomaly was confirmed by injecting dye in the left subclavian vein. Anatomically, an acute angle was demonstrated which made the negotiation of the guidewire into the LSVC impossible, hence, strategy of implantation was changed and a right subclavian puncture was made. The dye was injected through the right subclavian puncture and it was seen that the RSVC was absent but the right subclavian vein was connected to LSVC through a large venous channel (Fig. 1). The guidewire could be negotiated through the puncture needle to the LSVC, to the coronary sinus (CS) and finally to the right atrium (RA).

An active fixation, single-coil lead was placed at the right ventricular (RV) apex using stylet which was manually shaped resembling a distal rounded “C”. This procedure required skilled manipulation. The R wave measured 11.8 mV with a pacing threshold of 0.8V. Placement of an active-fixation lead into the right atrial (RA) appendage was accomplished using another manually shaped stylet resembling a distal rounded “L”. The P wave measured 4 mV with a pacing threshold of 0.5 V.

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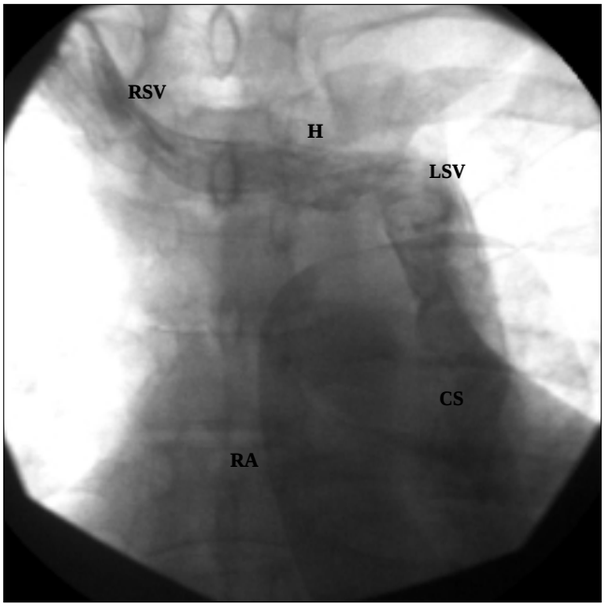

Fig. 1. *The anatomical relations between the right subclavian vein (RSV), connection (H), the persistent left superior vena cava (LSVC), the dilated coronary sinus (CS), and the right atrium(RA).*

Attempts to achieve defibrillation threshold (DFT) by inducing ventricular fibrillation giving a T wave shock through the device were unsuccessful at 20 J and 35 J. External defibrillation was carried out to revert the patient to sinus rhythm. The polarity of shock therapy was reversed and successful defibrillation was achieved with a 20 J shock, administered through the device. The patient's course was uneventful post-implant, and over 12 months follow-up.

Discussion

Albert and Geissler,[1] in a large study of unselected autopsies (> 4000), and other investigators[2] have documented persistence of LSVC in approximately 0.3% of the general population. In their 10-year experience, Biffi et al.[3] showed that persistence of LSVC in adults undergoing pacemaker or automatic cardioverter-defibrillator implantation is similar to that of the general population (0.47%). The prevalence of this anomaly is much higher in patients with congenital cardiac abnormalities compared to the general population, ranging from 2.8% to 4.3%.[4,5]

Left superior vena cava is the most common form of anomalous venous drainage involving the SVC and represents the persistence of the left vein of the embryonic sinus venosus, which involutes during normal development to become the CS. Embryologically, it results from the failure of the left common cardinal vein to become occluded.[6] Almost always, a persistent LSVC enters the RA through the orifice of an enlarged CS.[7] This anomaly is usually asymptomatic. There are isolated reports of LSVC persistence in patients undergoing ICD implantation.[8-10] With an increase in the number of pacemakers and ICDs being implanted worldwide, this anomaly is encountered more frequently. The nature of this unusual anatomic access to the heart makes it difficult to find a convenient site to ensure stable lead placement.[4]

Favale et al.[8] presented a case of LSVC with RSVC atresia, where a single chamber ICD was implanted with a dual coil RV lead. They used a right subclavian puncture access successfully. Mattke et al.[9] reported two cases of ICD implant in the presence of LSVC. In one patient, an ICD was implanted via a left subclavian vein puncture and a subcutaneous patch was used for effective defibrillation. In the second case, the ICD lead was implanted through the right subclavian vein and a defibrillation threshold (DFT) was achieved with a 5 J shock administered through the device. Brooks et al.[10] implanted an ICD in a patient with LSVC via a left subclavian puncture approach and used a subcutaneous patch to improve DFT.

The left subclavian vein is the preferred approach due to the defibrillation envelope formed in left ventricle.[11,12] However, the left-sided anatomy of our patient, with its acute angulation, made this approach technically difficult, hence we were required to use a right subclavian approach (Fig. 2).

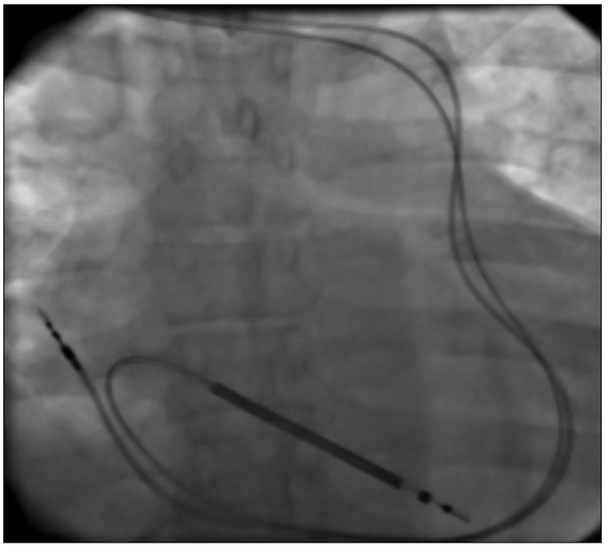

Fig 2. *Anterior-posterior view showing the position of the screw-in leads in the RA and the RV. The course taken by the RV lead is from right subclavian vein to the persistent LSVC, CS, RA and TV to the RV apex. Note the loop formed by the RV lead, which is technically difficult to manipulate.*
RA: right atrium; RV right ventricle; LSVC: left superior vena cava; CS: coronary sinus; TV: tricuspid valve

A single-coil active-fixation ICD lead was selected for implantation in the RV in view of the angulation, the loop, and to enhance the stability of the lead position. This lead was chosen based on the anatomical delineation, but also to avoid the possibility that the SVC coil might get caught in the RV or RA due to the large loop formed by the lead while passing through the CS and the RA. There is little documentation of the superiority of the dual-coil lead system over the use of a single-coil lead as far as energy requirements for defibrillation are concerned.[13,14]

Conclusions: This case report documents a successful dual-chamber ICD implant in the presence of LSVC and demonstrates the effectiveness of the available technology in a setting requiring a right-sided subclavian approach.

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Brief Report

Balloon-Expandable Covered Stent Repair of Massive Abdominal Pseudoaneurysm

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Pseudoaneurysms of descending aorta have usually been treated surgically or using self expanding endovascular stent grafts through open femoral arteriotomy. Here we report an unusual case of massive abdominal peseudoaneurysm in a young woman who was managed successfully with balloon-expandable covered stent deployed percutaneously. **(Indian Heart J 2005; 57: 720–722)**

Key Words: Pseudoaneurysm, Covered stent, Abdominal aneurysm

An important potential advancement in management of aneurysmal disease was the first clinical application of endovascular stent graft (self-expanding stent) to treat abdominal aneurysm reported by Parodi et al.[1] Aortic pseudoaneurysm is a rare entity and usually secondary to trauma, post-aortic graft placement, post-endovascular stent placement, or secondary to mycotic etiology and rarely due to Takayasu's arteritis.[2] Most peudoaneurysms have been treated surgically or using endovascular self-expanding stent grafts otherwise used to treat sacular abdominal aneurysm.[3-7] We herein report an unusual case of abdominal pseudoaneurysm in a young woman who was managed successfully with a balloon-expandable covered stent.

Case Report

A 35-year-old asthenic female presented with the chief complaint of epigastric pain of 10 days duration. There was no history of fever. On examination she had resting tachycardia with systolic blood pressure of 90-100 mmHg. On routine investigations, hemoglobin was 7.2 gm%, total leucocyte count was marginally raised (11,000 per mm^3) and high erythrocyte sedimentation rate (ESR) (64 mm 1st hour). She had an elevated C-reactive protein (CRP) (6.1 IU as against normal of <0.6 IU) but rheumatoid factor and other IGG / IGM antibody titers were normal. The PPD test was positive over 15 mm. Blood culture was sterile after one week for aerobic and anaerobic incubation. Abdominal examination showed epigastric tenderness with no organomegaly. Ultrasound of the abdomen showed a large pseudoaneurysm arising from left lateral aspect of aorta just above the celiac axis, and measured 55 × 45 × 40 mm in dimension. Abdominal computerized tomographic (CT) scan showed the large pseudoaneurysm arising from descending aorta just above the celiac axis level and size as observed on ultrasound was reconfirmed. In view of the large aneurysm and poor general status of the patient, non-surgical repair using stent graft was considered. Patient was initially stabilized with blood transfusion. In the absence of any known organism being picked up, a presumptive diagnosis of tubercular etiology was considered, and the patient started on anti-tuberculosis treatment.

Stent graft procedure: Bilateral femoral arterial puncture was done under local anesthesia and 6 F sheath introduced in the left groin for aortogram and 12 F sheath in the right groin for introduction of the covered stent graft percutaneously under cover of 5000 IU of heparin. Ascending aortogram done in AP and lateral projection showed the large pseudoaneurysm with a narrow neck of about 11 mm arising from the left lateral aspect of the descending abdominal aorta just above the celiac trunk (Figs 1a and 1b). The descending aorta showed mild smooth narrowing all along the extent of the aneurysm secondary to compression from the aneurysm *per se* which extended from the lower border of T9 to the upper border of L1. There was no evidence of any other aortic disease and the aorta above and below was absolutely clean and regular. The normal segment of aorta above measured 18 mm and below, about 17 mm with dimension at the aneurysm site being 14 mm. The neck of the aneurysm was located at upper border of T12. To prevent accidental blockage of the celiac trunk during covered stent placement a selective

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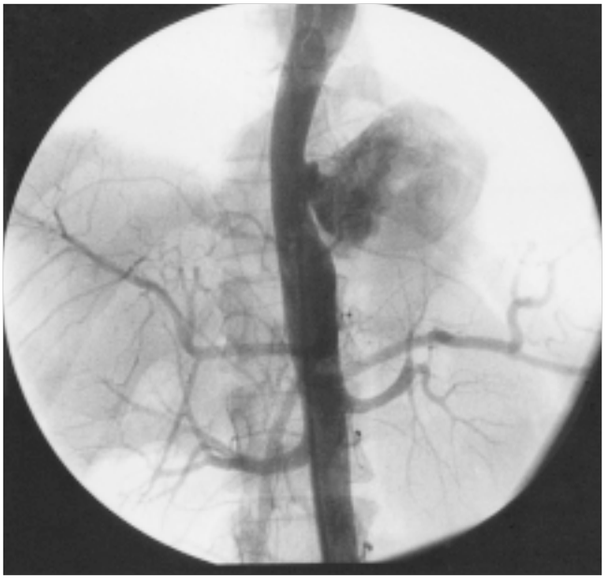

Fig. 1a. *Aortogram in AP view showing large pseudoaneurysm.*

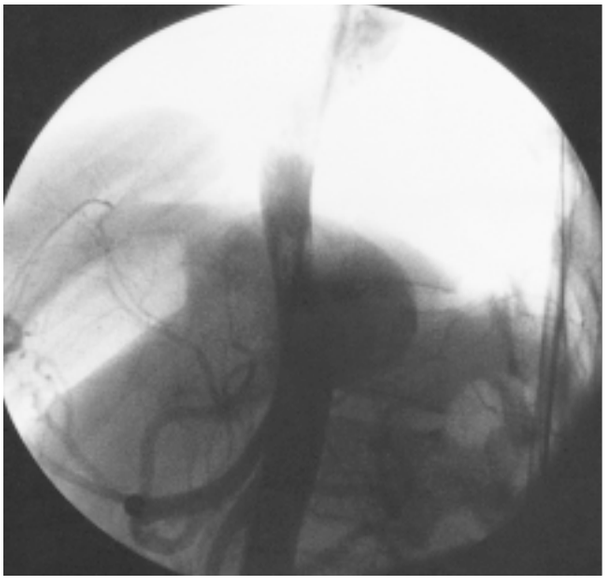

Fig. 1b. *Aortogram showing large pseudoaneurysm in lateral view.*

hooking of the celiac axis was done with a 6 F IMA catheter passed through the left groin so as to keep a constant vigil on the celiac trunk origin all through during the procedure. Then, through the right femoral arterial 12 F sheath, an Amplatz extra stiff 0.035" guidewire was passed into the descending thoracic aorta. A covered CP stent was mounted on a 16 mm diameter × 45 mm long over the wire balloon (Neumed) and deployed successfully in the descending abdominal aorta just above the coeliac trunk covering the opening of the pseudoaneurysm and keeping off the celiac trunk. After stent deployment (Fig. 2) no leak could be seen from the pseudoaneurysm neck and there was no compromise of any major vessel of the descending abdominal aorta (Figs 3a and 3b). Post-procedure, the sheath was removed in the catheterization laboratory itself and the patient mobilized next day. A post-procedure ultrasound and abdominal CT done 48 hours later confirmed absence of any leak.

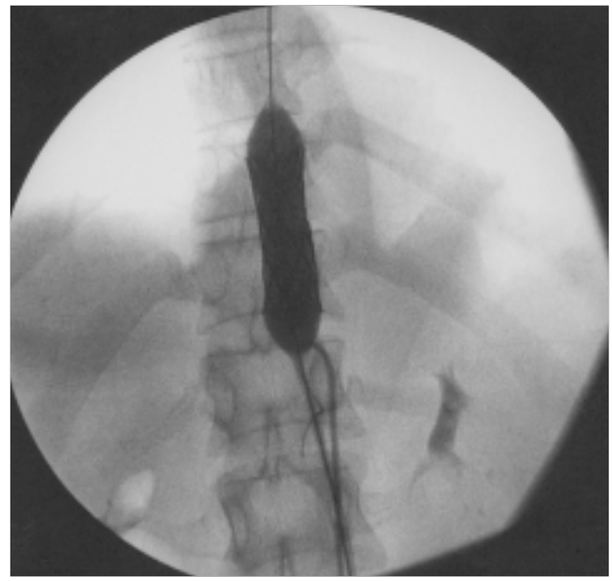

Fig. 2. *Balloon expandable covered stent repair of massive abdominal pseudo-aneurysm-AP view.*

Discussion

A pseudoaneurysm of abdominal aorta located at the level of celiac artery, if repaired surgically, involves a major thoraco-abdominal surgery with considerable morbidity. The self-expanding intravascular stent grafts are rather expensive and large profile devices requiring large sized sheaths (21F-24F) to be introduced through the groin which is not possible percutaneously, and requires open arteriotomy. We achieved good result after placement of a balloon-expandable covered stent percutaneously and without any complication. This approach was cost effective and minimally invasive as the covered balloon-expandable stent requires only a 12 F introducer which can be easily placed percutaneously. Such a stenting technique has only rarely been used in this setting primarily because of non-

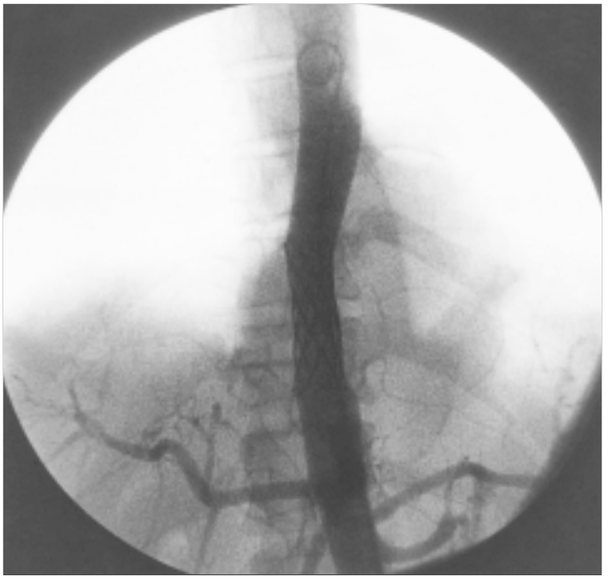

Fig. 3a. *Balloon expandable covered stent repair of massive abdominal pseudo-aneurysm.*

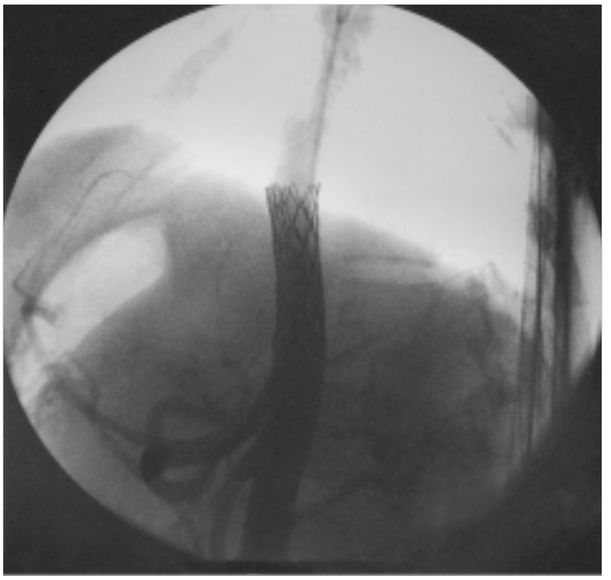

Fig. 3b. *Balloon expandable covered stent repair of massive abdominal pseudo-aneurysm.*

availability of covered stents in the sizes required to be put in the abdominal aorta. The only report of balloon-expandable covered stent has been by Khan and Moore[8] who treated false aneurysm formation in a patient with post-coarctation dilation where a Palmaz P308 stent was used with maximum expanded size requirement being 12 mm as the patient was of the pediatric age group. Our patient being an adult, the expanded size requirement was much larger, in the range of 16 mm. This was possible using the CP stent which has been made available recently and is meant primarily for treating aortic coarctations and to the best of our knowledge this would be the first report of its successful use to treat the abdomen aortic pseudo-aneurysm.

As far as etiology of the aneurysm in this case, we feel this to be mycotic in nature specially in view of the high ESR/CRP with borderline elevation of total leucocyte count. A presumptive tuberculous etiology was considered, this being a common disease in the Indian setting. A biopsy was out of question because of the aneurysmal nature of the swelling which would have involved damaging the vessel and exaggerating the leak. There was no history of trauma so as to favor a traumatic etiology and aortoarteritis which is also a common disease in India seemed unlikely in this case specially in view of the absolutely clean aortic margins and no other vascular site involvement.

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Heart Failure: A Unique Presentation of Typical Atrioventricular Nodal Reentrant Tachycardia

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Cardiomyopathy due to various ventricular and supraventricular arrhythmias, including isolated cases of atypical atrioventricular nodal reentrant tachycardia, have been described. In this case report typical slowfast atrioventricular nodal reentrant tachycardia resulting in cardiomyopathy is being documented for the first time. In the setting of depressed left ventricular function, an episode of tachycardia pushed this patient into heart failure. Radiofrequency ablation of the slow pathway was successful in eliminating her tachycardia with the return of left ventricular function to normal. A follow-up of two years post-ablation revealed the patient to be symptom-free. **(Indian Heart J 2005; 57: 723–724)**

Key Words: Heart failure, Tachyarrhythmia, Electrophysiology

Dilated cardiomyopathy is arguably the most depressing diagnosis with more than 50% of patients being labeled as "idiopathic" and condemned to a poor prognosis. Occasionally potentially curable causes are identified, tachycardiomyopathy being one such. Incessant atrial tachycardia and permanent form of junctional reciprocating tachycardia[1] are the commonest implicated culprit arrhythmias. Atypical atrioventricular nodal reentrant tachycardia (AVNRT) has been very rarely reported to cause tachycardiomyopathy[2] but there have been no reported incidences of typical AVNRT leading to depressed left ventricular (LV) function.

Case Report

A 69-year-old lady presented with a history of increasing breathlessness, palpitation and near syncope of 2 days duration. Over the previous 3 months she often complained of uneasiness and was noted to have a pulse rate of 130 to 140 beats per minute (bpm), which had been passed off as anxiety. Five years ago, she had been documented to have an episode of supraventricular tachycardia following acute gastroenteritis.

During the current episode she was admitted to a peripheral hospital where the monitor strip revealed incessant tachycardia (Fig. 1A). Occasionally, 2:1 atrioventricular (AV) conduction was seen during tachycardia with the blocked P wave lying exactly between 2 QRS complexes. Clinical examination revealed an orthopneic elderly lady with a pulse rate of 100 bpm, blood pressure of 90/60 mmHg and raised jugular venous pressure with bilateral basal crepitations. There was an auscultable LV third heart sound but no murmurs. The chest X-ray showed an enlarged heart with the pulmonary congestion. Echocardiography demonstrated a dilated and globally hypokinetic LV with a left ventricular ejection fraction (LVEF) of 0.2 and grade I mitral regurgitation. Her routine blood investigations and thyroid profile were normal. She was treated with diuretics and angiotensin-converting enzyme (ACE) inhibitors.

The tachycardia could be transiently terminated by 12 mg of adenosine. At this time the electrocardiogram (ECG) revealed marked T wave inversion in the inferior leads and in leads V_1 to V_3 (Fig. 1B). After this, she again lapsed into narrow QRS tachycardia at the rate of 130 bpm (Fig. 2). P waves could not be discerned but there was evidence of r' in lead V_1 and "pseudo-S" wave in inferior leads.

The next day she was taken up for electrophysiological

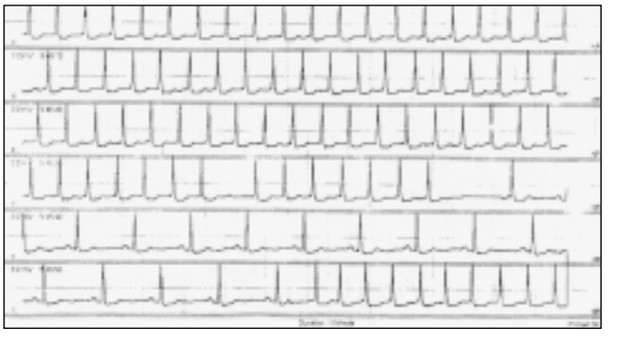

Fig. 1A. *Monitor strip of tachycardia. The blocked P wave lies exactly between the two QRS complexes. Tachycardia restarts with a premature atrial complex with a long PR interval.*

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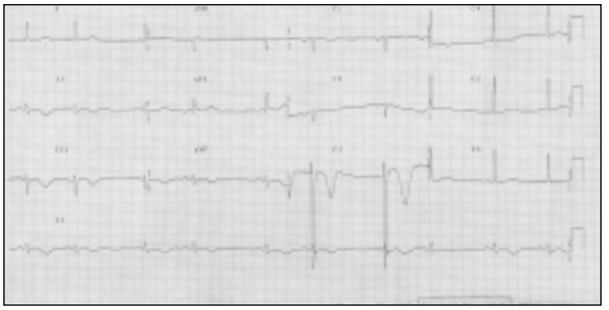

Fig. 1B. *12-lead electrocardiogram after tachycardia termination showing sinus arrhythmia with T wave inversion in inferior leads and V_1 and V_3. The deep S in lead V_3 is suggestive of left ventricular enlargement.*

(EP) study. Initially her coronary angiogram was performed which was normal. The tachycardia could be terminated by overdrive atrial stimulation or by 3 ventricular extrastimuli. During tachycardia, the His bundle electrocardiogram (HBE) showed a large distal His-potential preceding the QRS complex by 30 ms (Fig. 3). During 1:1 AV relationship, the septal A was always simultaneous with the QRS complex; the HA time was < 60 ms. Antegrade AV nodal duality was also demonstrable. During right ventricular (RV) pacing, the retrograde atrial sequence was identical as that during tachycardia. The EP study thus confirmed the mechanism of this incessant tachycardia as typical slow-fast AVNRT (Fig. 3). Successful RF ablation of the slow pathway was performed. Subsequently no other tachycardia was inducible. The patient made an uneventful recovery. After 3 days, the LVEF had increased to 0.4 with normalization of the heart size on X-ray. At the 2 years follow-up she had no recurrence of symptoms. LV function returned to normal with normal chamber dimensions on the echocardiography. There was grade I mitral regurgitation.

Discussion

Breathlessness and palpitation with T wave inversion in the precordial leads on ECG and globally depressed LV function gives the first impression of coronary artery disease (CAD) or idiopathic dilated cardiomyopathy (DCM) as the causal diagnosis. The occurrence of incessant narrow QRS tachycardia during hospitalization could erroneously be interpreted as an effect of cardiomyopathy. However, this patient's symptoms started off as palpitation and only later, there was increasing dyspnea. Since the tachycardias were not very rapid, they were attributed to anxiety. Tachycardias at rates of 130-140 bpm are more likely to become incessant; the more rapid tachycardias come to light immediately and are therefore treated. Our patient thus progressed into pulmonary edema and only then came for proper medical attention.

Incessant atrial tachycardia, atrial flutter/fibrillation, permanent form of junctional reciprocating tachycardia and idiopathic ventricular tachycardia have all been known to lead to cardiomyopathy.[1] An incessant nature of tachycardia rather than the rate is more likely to lead to depression of cardiac contractility. Isolated cases of AVNRT, mostly atypical, have also been reported to lead to tachycardiomyopathy.[2] This is the first report of typical slow-fast AVNRT leading to cardiomyopathy.

Usually recovery of cardiac function after restoration of sinus rhythm is gradual. Repletion of mitochondrial and energy stores and reversal of intercellular alteration take several weeks. In basic study, the recovery of LV systolic function requires about 2 weeks from the termination of pacing. However, in clinical situations, this may be quite variable both spatially and temporally because the length of tachycardia and underlying heart disease are different in each patient.[2] Intriguingly, in our patient most of the recovery was seen within 3 days.

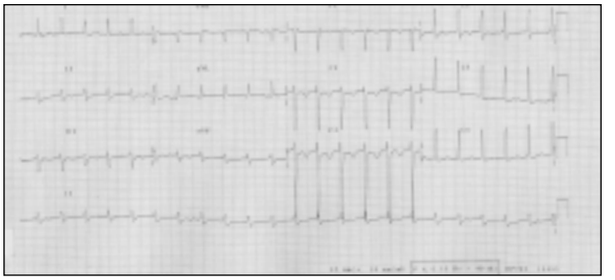

Fig. 2. *12-lead electrocardiogram of narrow QRS complex tachycardia. Note the r' in lead V_1.*

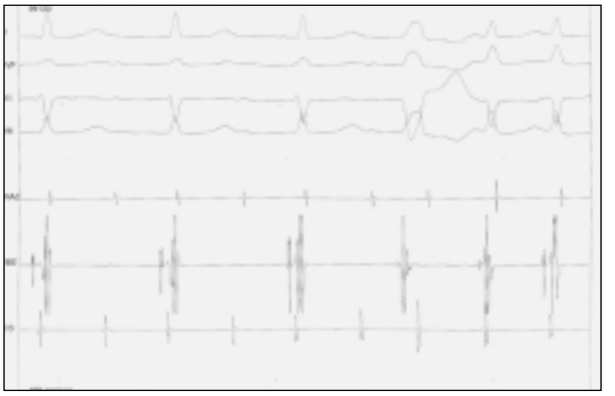

Fig. 3. *Intracardiac electrocardiogram showing tachycardia. Initially there is a 2:1 AV conduction. 1:1 AV relationship is seen in the last 2 complexes, the atrial activation being simultaneous with the QRS complex. A large distal His deflection is seen 30 ms prior to the QRS complexes.*
HRA: high right atrium; HBE: His bundle electrocardiogram; CS: coronary sinus; AV: atrioventricular

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Left Internal Mammary Artery to Pulmonary Vasculature Fistulae Closed with Particle Embolizaton: New Form of Percutaneous Intervention

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The left internal mammary artery is frequently employed as a conduit in coronary bypass surgery. We report a 42-year-old male post-coronary artery bypass grafting patient with, angina on exertion who was found to have multiple atrioventricular fistulae arising from left internal mammary artery to pulmonary vasculature leading to coronary steal and positive stress thallium in left anterior descending territory. These fistulae were selectively embolized with polymer particles leading to improved flow in distal left anterior descending artery. Post-intervention, the patient has been asymptomatic for more than 8 months. **(Indian Heart J 2005; 57: 725–727)**

Key Words: Coronary artery disease, Coronary intervention, Coronary bypass grafting

Patients with recurrent angina following coronary bypass surgery are often referred for investigation of progressive disease in the native and graft circulations. Several cases of internal mammary artery (IMA) to lung vessel fistulae have been reported as complications following conventional coronary artery bypass graft (CABG) surgery.[1-8] We describe a patient with recurrent angina 6 months after off-pump coronary bypass surgery in whom an acquired left internal mammary artery (LIMA) to pulmonary artery fistula was documented.

Case Report

A 42-year-old male, known hypertensive for the past 8 years, non-smoker, non-diabetic, dyslipidemic was admitted with progressive angina of few days duration. Patient had undergone a CABG (off-pump) 6 months back with 3 conduits for severe triple vessel disease with normal left ventricular (LV) functions [LIMA to left anterior descending artery (LAD), left radial artery to obtuse merginal (OM)-1 and reverse LSV to posterior descending artery (PDA)]. His operative and post-operative period were uneventful. However, he started having progressive angina after 5 months for which he had undergone stress thallium evaluation which revealed large area of reversible ischemia in the anterior territory. Patient underwent coronary angiography which showed native triple vessel disease with patent graft to OM and PDA with good LV functions. LIMA to LAD was also patent. However, the flow in LIMA was sluggish, with competitive flow seen at the LIMA - LAD junction. A leash of vessels was seen from the upper portion of LIMA confluencing to drain into a large vessel and subsequently draining into the pulmonary vasculature (Fig. 1). This was causing steal in the flow of distal LIMA and hence appeared to be responsible for ischemia in the anterior territory. After considering all options, a novel technique of particle embolization of the fistulae was contemplated.

LIMA was selectively cannulated using 7 F IMA guide catheter. Every individual leash of vessel was selectively and serially wired with 0.014" floppy guidewire and subsequently Tracker catheter was positioned in respective vessel. Each vessel was embolized using 500-750 micron embolic particles (Emboli Contour™, Boston Scientific) mixed with saline. Repeat angiography 2 days post-embolization showed that majority of fistulae had been closed, and there was increased flow in the LIMA - LAD graft (Figs 1 and 2). Two weeks after the procedure, the patient underwent repeat stress thallium which showed significantly smaller area of reversible ischemia in the anterior territory. Patient has been asymptomatic now for more than 8 months, and is under regular follow-up.

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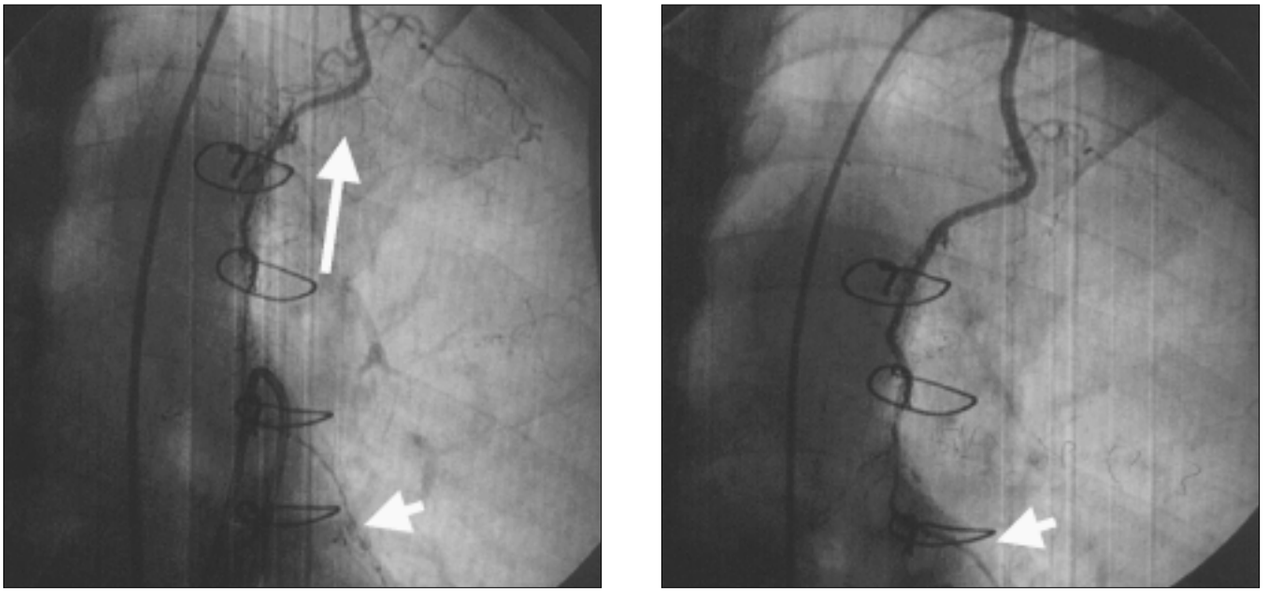

Fig. 1. *Coronary angiogram (Left LAO 2° Cranial 41° view) showing LIMA to pulmonary vasculature fistulae(long arrow) and stealing of flow in LAD distal to anastomosis(short arrow). On the right-same view after closure of fistulae with polymer particles demonstrating significant improvement in LAD flow(short arrow).*
LAO: left anterior oblique; LIMA: left internal mammary artery; LAD: left anterior descending

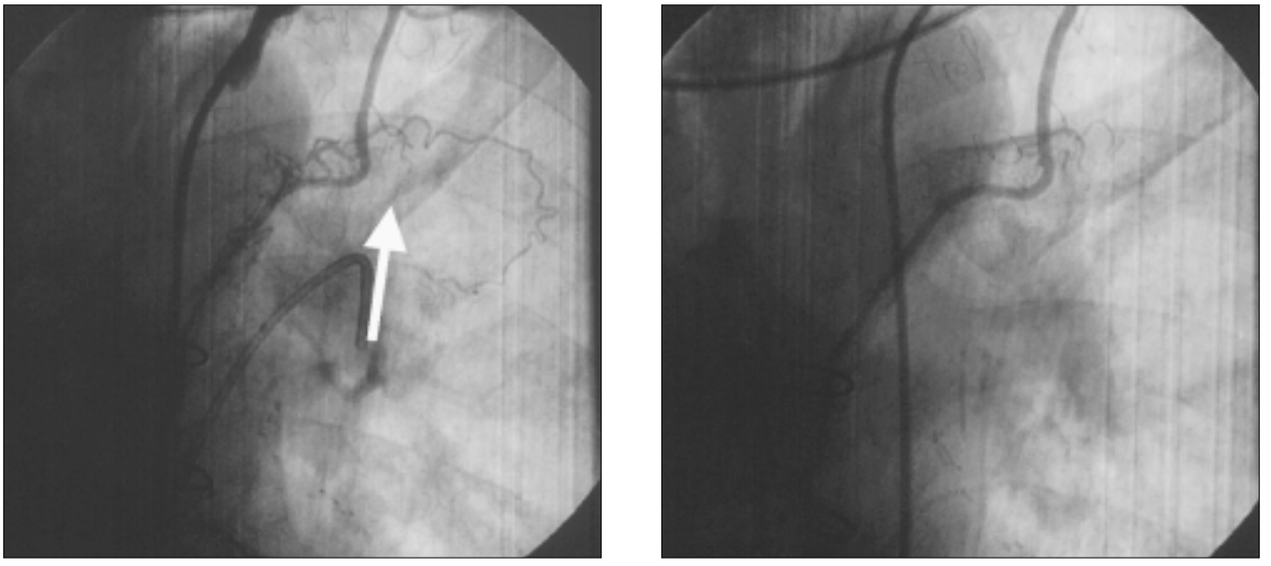

Fig. 2. *Coronary angiogram (Left RAO 1° Cranial 43°view) showing LIMA to pulmonary vasculature fistulae(long arrow). On the right-same view after closure of fistulae with polymer particles.*
RAO: right anterior oblique; LIMA: left internal mammary artery

Discussion

The LIMA-to-pulmonary vasculature fistulae can be congenital or acquired. The more common congenital variety occurs as an isolated anomaly or in association with other congenital defects. Suggested etiologies of acquired LIMA-to-pulmonary artery fistulae are iatrogenic, pulmonary infections, neoplasia, trauma, lymphoid neoplasia and chronic granulamatous disease. Iatrogenic fistulae have been associated with inadvertent anastomosis of aortocoronary saphenous vein grafts and LIMA grafts into a cardiac vein[9] or after the placement of parasternal wires following median sternotomy.[10-12]

After conventional CABG[1-8], the LIMA-to-pulmonary vasculature fistula may result from only electrocoagulating but not clipping branches of the IMA. Visceral pleural injury may be an important denominator in the development of this fistula.[13-16] This may occur from repeat sternotomy or from the mere presence of metal clips in close proximity to the visceral pleura. This local injury may be further aggravated by respiratory movements and the beating heart, and may eventually result in a local inflammatory response leading to neovascularization and formation of a tuft of multiple small fistulous communications between the IMA and pulmonary vasculature.

The diagnosis of this condition requires a high index of suspicion. Patients who present with recurrent angina and who have had IMA grafts implanted should undergo selective IMA injection, specially when a new systolic murmur is discovered post-operatively. The management of LIMA-to-pulmonary vasculature fistulae is dictated by the presence and the severity of symptoms. The choices are conservative medical management,[2,4,5] surgical division of the fistula,[3] or percutaneous coil spring closure.[4] This can potentially cause distal coronary artery embolization and is not recommended for most cases. Observation without intervention is recommended in asymptomatic patients with small fistulae.[12] However, in symptomatic patients with a large shunt, or in those in whom complications develop such as angina pectoris, mycotic aneurysm, congestive heart failure, endocarditis, aneurysmal expansion, rupture, hemoptysis, or eventually pulmonary hypertension, intervention is clearly indicated.[1,10] Surgical intervention via a left thoracotomy and staple division of a small portion of the lung may be an effective method of management.[17] One of the reported case, caused by Hodgkin's disease, was treated by therapeutic embolization of the fistula with gelfoam and alcohol[10] and another by percutaneous transvenous insertion of a coil-spring occluder;[2] most of the remaining ones were treated by surgery.

In the present case, we embolized the fistulae with polymer particles (Emboli Contour™, Boston Scientific) by selective cannulation of the fistulae which is shown to be highly effective in occluding communicating vessels, and may be the modality of choice when anatomically feasible. To the best of our knowledge, this is the first reported case using this modality of intervention. It is well known that fistulae can regrow with time and therefore, close follow-up in all these patients is indicated.

Some surgical techniques have been developed to prevent mammary artery fistula formation after coronary surgery.[8] One method is to separate the internal mammary artery pedicle from the lung by interposing a pericardial flap[8]. Another is to clip rather than electrocoagulate the small side branches of the internal mammary artery.[8]

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Brief Report

Complete Heart Block following Occlusion of the First Septal Perforator after Coronary Stenting

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We report a case of transient complete heart block following occlusion of the first septal perforator branch after stent deployment in the left anterior descending coronary artery. The patient was treated with temporary transvenous pacing and reverted spontaneously to normal atrioventricular conduction after 3 days. **(Indian Heart J 2005; 57: 728–730)**

Key Words: Coronary angioplasty, Complete heart block, Stents

Complete heart block (CHB) in association with localized infarct because of first septal perforator (FSP) occlusion is not a common occurence after stenting of left anterior descending (LAD) artery. This report describes the case of an elderly woman who developed this complication and required temporary transvenous pacing for 12 hours before normal atrioventricular (AV) conduction was restored.

Case Report

A 67-year-old post-menopausal woman, known to have hypertension and dyslipidemia, was admitted with a history of unstable angina. She had significant ST segment depression in leads V_1 to V_5 during the episodes of chest pain. Her troponin T (Trop-T) levels were mildly elevated. Echocardiogram showed good left ventricular (LV) function with no regional wall motion abnormalities. She was treated with optimal anti-ischemic measures including beta-blockers. Coronary angiography was performed, which revealed tight stenosis in proximal LAD artery involving the ostium of the FSP (Fig. 1). Left circumflex (LCx) and right coronary artery (RCA) were normal.

The patient underwent percutaneous transluminal coronary angioplasty (PTCA) to LAD under tirofiban cover. The lesion was pre-dilated with 2 mm × 11 mm balloon. A 3.5 mm × 18 mm sirolimus-eluting stent was deployed and expanded at 14 bar. The middle part of the stent had a mild residual waist, which was post-dilated with a 3.5 mm × 14 mm balloon at 18 bar. Subsequent arteriography revealed TIMI III flow through LAD with no residual stenosis, dissection or thrombus. A flush occlusion of FSP was noted (Fig. 2). The patient was asymptomatic at the end of the procedure. An electrocardiogram (ECG) immediately after the procedure revealed normal sinus rhythm with no significant abnormalities.

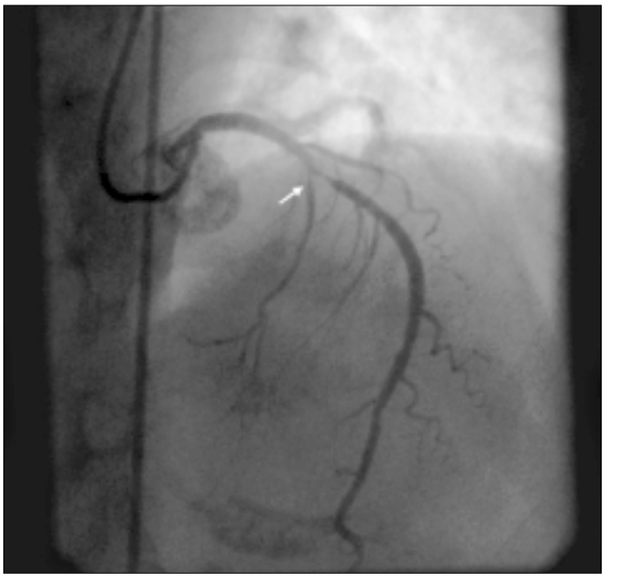

Fig. 1. *Initial angiogram demonstrating proximal LAD stenosis involving the ostium of the first septal perforator branch (arrow).*
LAD: left anterior descending artery

The patient was observed in the intensive coronary care unit (ICCU) after her angioplasty. Cardiac markers obtained 12 hours after the procedure were found to be elevated (CK-MB 30 ng/ml and Trop-T 0.28 ng/ml). The ECG did not

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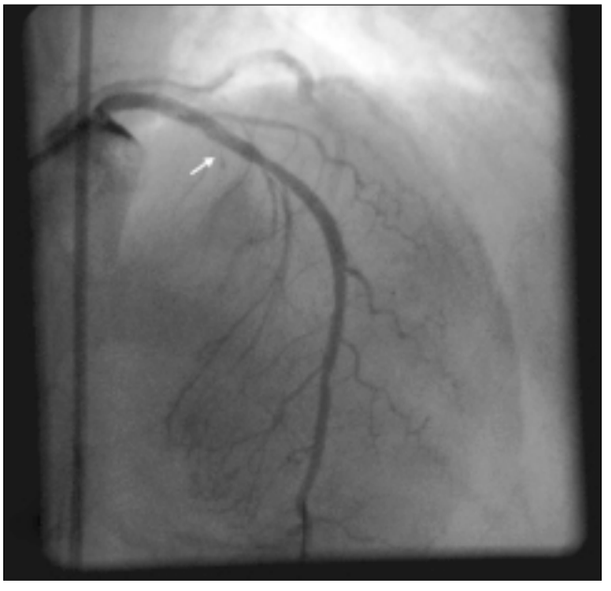

Fig. 2. *Left anterior descending artery after stent deployment to the proximal portion of the vessel with occlusion of the first septal perforator branch (arrow).*

show any significant changes. She was transferred to her room after 24 hours.

Approximately 48 hours after the procedure, the patient had a syncopal attack. Her ECG showed CHB with sinus cycle length of 600 ms, and a ventricular escape rhythm [right bundle branch block (RBBB) configuration] at a rate of 41 beats per minute (bpm) (Fig. 3). Emergency transcutaneous pacing was instituted. She was taken back to the catheterization laboratory where transvenous pacing was performed. Coronary angiogram revealed a well patent stent in LAD. Sluggish flow into the FSP was noted.

Two hours after the onset of CHB, she reverted to 1:1 AV conduction with left bundle branch block (LBBB) pattern and prolonged PR interval (Fig. 4). The sinus cycle length at this time was 800 ms. The next day (12 hours

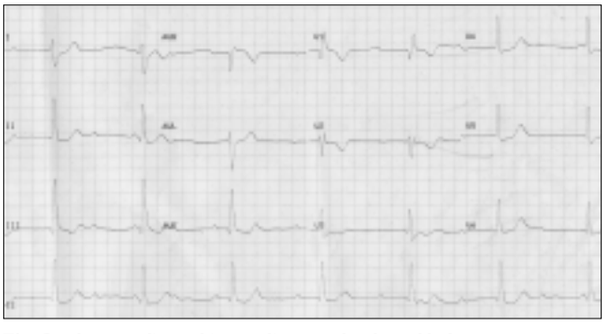

Fig. 3. *Electrocardiographic revealing complete heart block.*

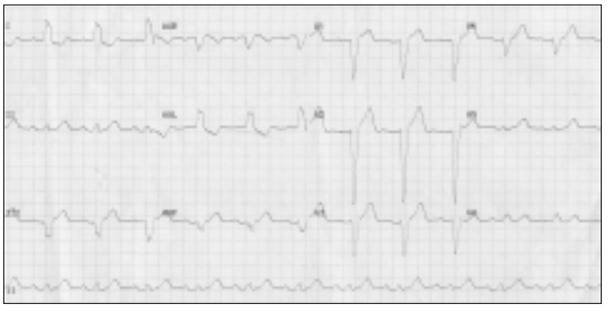

Fig. 4. *Electrocardiographic revealing sinus rhythm with left bundle branch block (LBBB) pattern and prolonged PR interval.*

after the onset of CHB), the ECG reverted to sinus rhythm with normal PR interval and QRS complexes. The patient was observed for a period of 5 days and discharged in stable condition without the need for a permanent pacemaker.

Discussion

An important limitation of coronary artery stenting is a possible risk of side branch occlusion (SBO) described in up to 18% of patients.[1] Occlusion of small side branches is generally well tolerated. However, at times the occlusion becomes clinically significant. The presence of ostial narrowing of the side branch has been reported as the most powerful predictor of SBO immediately after stenting.[2] In our patient, the diagnostic angiogram had demonstrated ostial narrowing. The possible mechanism of SBO after stenting is the 'snow plough' effect, causing a shift of atheromatous material into the ostium of the side branch from the parent vessel.[3]

The occurrence of CHB due to the loss of FSP after LAD stenting is a rare event; we were able to find only one such report in the literature.[4] We postulate that the CHB in our patient was due to a small localized infarct related to the occlusion of the FSP. The location of block is likely to be distal to the bundle of His, as the escape rhythm had RBBB configuration. Restoration of 1:1 AV conduction could be explained by resolution of pathological changes in the infarct region or perhaps by the restoration of blood flow into the FSP. It has been noted that the majority of side branches occluded after stenting regain patency spontaneously.[5] Alternatively, augmentation of blood supply to the bundle of His and proximal bundle branches from the right coronary artery may have resulted in improvement in AV conduction.

The development of CHB in the setting of occlusion of the FSP may be analogous to the occurrence of CHB in patients undergoing percutaneous transluminal myo-

cardial septal ablation for hypertrophic cardiomyopathy. CHB as a complication of septal reduction by intracoronary alcohol injection of the first major septal branch has been reported in 60% to 70% of patients.[6] In the absence of any chemical injury added to ischemic insult, our patient had greater chances of resolution of the infarct by means of recanalization of the FSP or by collateral supply from other septal vessels. AV block following LAD occlusion, as in anterior wall myocardial infarction, usually develops as a result of extensive septal necrosis that involves the bundle branches.[7]

Conclusions: Complete heart block associated with a localized small infarct in the septum due to occlusion of the FSP following proximal LAD stenting is a rare and interesting phenomenon with a relatively favorable outcome. Conduction disturbances including CHB in this setting may become more commonly recognized in future.

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A Case of Giant Aneurysm following Percutaneous Coronary Intervention

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The incidence of restenosis has significantly reduced following introduction of drug-eluting stents. However, complications i.e. subacute thrombosis and aneurysm formation may be higher with these stents. We report a case of giant aneurysm formation following drug-eluting stent implantation. **(Indian Heart J 2005; 57: 731–733)**

Key Words: Stents, Coronary artery disease, Coronary aneurysm

With the coming of age of percutaneous coronary intervention it has been thought of as a panacea of all ills, more so with the advent of drug-eluting stents (DES). Whereas the rate of restenosis with bare metal stents was 15-27%[1] it has been shown to be much less, to the tune of 5% for DES[2] and thus in recent times they have been used with greater frequency. The complications following their implantation are different from those of bare metal stents, with subacute thrombosis being more common. We report a case of giant aneurysm following a sirolimus-coated stent implantation. Complications such as these must be kept in mind as more and more DES are being implanted due to their other potential benefits.

Case Report

A 58-year-old male, diabetic, non-hyertensive, non-smoker was admitted for elective percutaneous transluminal coronary angioplasty (PTCA) and stenting to left anterior descending (LAD) in our institution. The patient had an anterior wall myocardial infarction (AWMI) one month ago for which he was admitted in a private institution and managed conservatively. He had not received thrombolytic therapy at that time due to his late presentation. After 10 days of hospital stay, which was uneventful, he was discharged. About 4 weeks of his discharge, the patient started developing exertional chest pain inspite of adequate dose of nitrates, beta-blockers and antiplatelets. His echocardiography showed adequate left ventricular (LV) function [ejection fraction (EF) 51%] and anterior wall hypokinesia. Later, coronary angiography (CAG) showed a 90% lesion in proximal LAD along with thrombus (Fig. 1).

Considering the diabetic status of the patient, decision for revascularization with a DES was taken. A floppy wire was passed across the lesion, a 2.5 mm×15 mm Stormer balloon inflated at 10 atm and a 3 mm×18 mm Cypher stent was deployed at 12 atm pressure. Pre- and post-operatively the patient received standard anticoagulant and antiplatelet medication. Post-procedure there was TIMI grade III flow (Fig. 2) and the patient had an uneventful recovery. He was discharged from hospital in the 2nd week after CAG with usual antiplatelet (aspirin 150 mg, clopidegrol 75 mg/day) and other standard medications (atorvastatin 20 mg, beta-blockers, and antidiabetics. His high sensitive C-reactive protein (hs CRP) at that time was 5 mg/L.

Three weeks post-discharge, the patient had an episode of low grade fever and abdominal pain with distension of

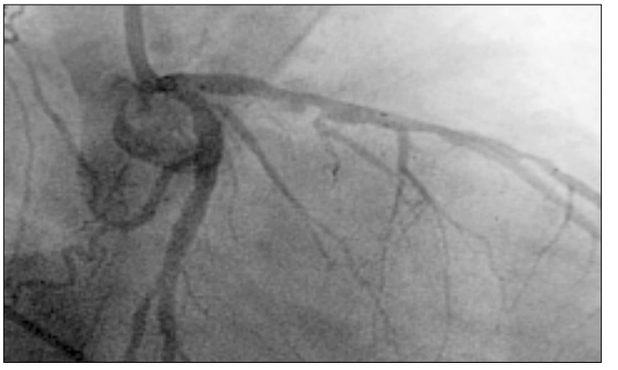

Fig. 1. *Angiography showing 90% thrombus-containing lesion in left anterior descending artery.*

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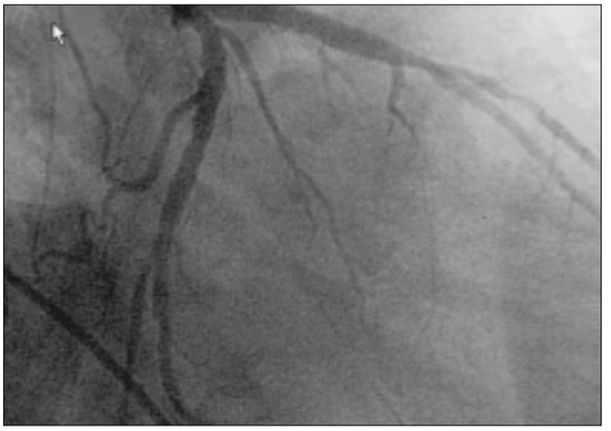

Fig. 2. *Post-angioplasty showing deployment of stent with TIMI III flow.*

2 days duration for which he consulted his local doctor. He was prescribed some medicines, and recovered from this episode in about 7 days. After this, the patient started experiencing left precordial pain. The pain was constant, dull aching and had a dragging character. On occasions the pain had anginal character and was relieved with sublingual nitrates, but most of the times it was constant and not relieved with his usual medications. In this background, a decision for repeat angiography was taken and CAG done. All along his glycemic status was normal with a postprandial sugar of 120-140 mg/dl. His renal status (serum urea and creatinine) was also normal. The repeat angiography showed aneurysmal dilation in proximal part of the stent along with lesion proximal to the stent and a significant lesion at origin of circumflex artery also (Figs 3 and 4). The patient's hsCRP was found to be 9 mg/L at this time.

Considering the multiple lesions and the hyperglycemic state of the patient he was advised to undergo coronary artery bypass grafting (CABG) and resection of the aneurysmal sac, and is well on follow-up.

Discussion

Coronary aneurysms are noted in 0.3%-4.9% of all CAGs. Aneurysms after coronary interventions are uncommon and are more likely to occur after ablative techniques particularly excisional atherectomy with or without stenting.[3] With the coming to age of DES with a restenosis rate of 0-5%, it was thought that we are at last winning the battle over restenosis which was around 27% with bare metal stents. However DES brought its own complications

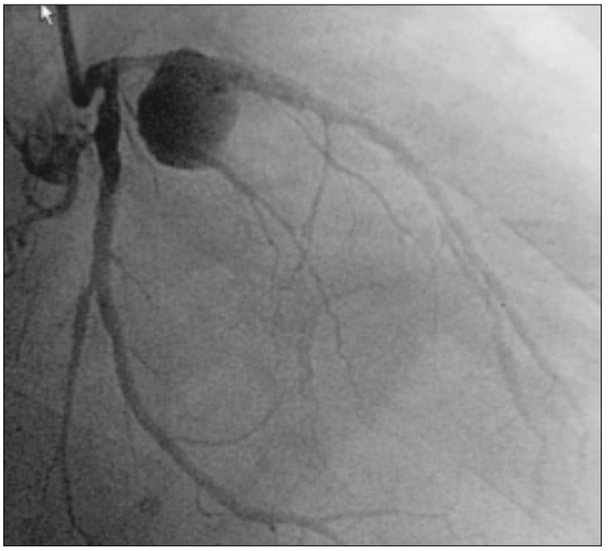

Fig. 3. *Giant aneurysm proximal to stent and progression of lesion in proximal left anterior descending artery and circumflex.*

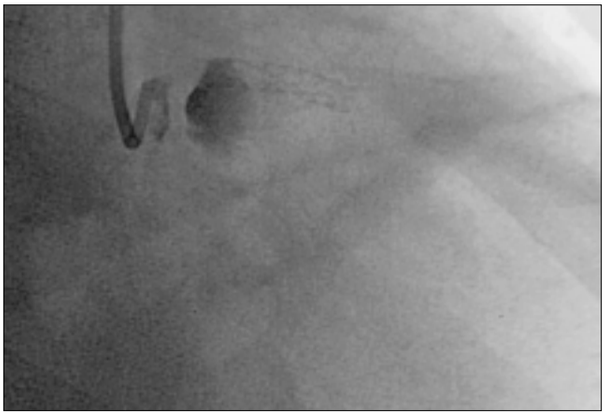

Fig. 4. *Giant aneurysm proximal to stent.*

like formation of aneurysms[4] which were reported to be higher in the initial reports but subsequently not substantiated. The mechanism involved in prevention of restenosis by DES, the antimitotic effects of the anticancer drugs, were considered responsible for the delayed healing effects following balloon dilation resulting in aneurysm formation. Accelerated atherosclerosis proximal and distal to QP2-coated stents have also been reported, though their clinical relevance is not yet established.[5]

In present case the patient had a giant aneurysm, which was probably because of the disease process of atheros-

clerosis, which had prevented proper healing. This is evident from the progression of the lesion in other territories in the repeat angiography after angioplasty. Also, the hsCRP following readmission after percutaneous transluminal coronary angioplasty (PTCA)/stenting was much higher than just after angioplasty. The use of this marker for prediction of complications of stent implantation over short-term can probably be used, although much larger randomized studies need to be conducted to determine their role.

Intravascular ultrasound (IVUS) would be essential in planning a therapeutic strategy. One could verify whether it was a pseudoaneurysm or true aneurysm by the presence of the 3 layered appearance, typical of coronary artery.[6] Simply stenting over the origin of the dilated segment will often cover the entrance of the dilated system resulting in closure of the aneurysm area. A PTFE-covered stent could be employed to seal off the area. A recently presented method by Iakovou et al.[7] used a custom-modified PTFE-covered stent. However, in our case since there was progression of the lesions in the proximal part of the stent as also in the circumflex territory, the patient was advised bypass surgery with resection of the aneurysm.

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Brief Report

Acute Myocardial Infarction Secondary to Myocardial Bridge Treated with Drug-Eluting Stent

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We report a case of myocardial bridge in left anterior descending coronary artery associated with acute anterior wall myocardial infarction. The patient had many unusual features like coronary ectasia and atherosclerosis within the myocardial bridge segment. The patient was treated with drug-eluting stent under intravascular ultrasound guidance with good result over 6 months follow-up. **(Indian Heart J 2005; 57: 734–737)**

Key Words: Myocardial infarction, Coronary ectasia, Drug-eluting stents

Myocardial bridging of coronary arteries is a frequent congenital anomaly that is almost exclusively confined to the left anterior descending (LAD) artery. Myocardial bridge (MB) is usually benign, but can be associated with unstable angina, myocardial infarction (MI), ventricular arrhythmias and sudden cardiac death. We report an unusual case of MI in a young male due to myocardial bridge with coronary ectasia, which was treated with drug-eluting stent (DES) in LAD under intravascular ultrasound (IVUS) guidance. There has been no previous report on coronary ectasia at the site of MB and drug-eluting stent implantation for treating MB in the literature.

Case Report

A 34-year-old male patient suffered from acute anterior wall MI which was not thrombolyzed due to late presentation. He was referred to our hospital after 12 days with history of post-MI exertional angina. He was a non-obese, non-diabetic, non-hypertensive and non-smoker with normal lipids. Clinical examination was normal. His electrocardiogram (ECG) showed QS pattern in V_1 to V_3 and T inversions in V_1 to V_4. Echocardiography showed normal left ventricular (LV) dimensions with ejection fraction (EF) of 60%. There was hypokinesia of septum, anterior wall and apex. He was taken up for angiography 16 days post-MI. Left main coronary artery (LMCA), left circumflex (LCx) and right coronary arteries (RCA) were normal with right dominant circulation. His LAD showed complete occlusion in the distal segment after the second diagonal branch. There was a small area of ectasia before the occlusion. The ectatic segment was contracting like a muscle bridge with complete obliteration of lumen during systole and well developed ectasia during diastole (Fig.1). We proceeded with the angioplasty. The LMCA was hooked with a 7 F JL 3.5 guide catheter and the lesion was crossed with a BMW guide wire (Guidant Corporation, Santa Clara, USA) without any difficulty. The lesion was pre-dilated with a 2 × 15 mm balloon at 8 atm. The lesion opened partially with restoration of TIMI 3 flow which revealed complete extent of the myocardial bridge (Fig. 2). The lesion and the MB site were further dilated with 3 × 12 mm balloon at 6 atm for 60 s. The angiographic picture did not improve any further. The exact contribution of the MB, atherosclerotic lesion and/or intimal dissection, if any, was difficult to ascertain from the angiographic picture. We, therefore, performed IVUS (Atlantis SR, Boston Scientific Scimed Inc., USA). IVUS confirmed MB, atherosclerotic lesion as well as dissection which was non-flow limiting. The myocardial bridge was severe with complete obliteration of the lumen during systole (figure not shown). Stenting the lesion was considered but not done in view of long tight muscle bridge and significant ectasia in the middle of the MB which could predispose to stent thrombosis and stent collapse. After IVUS, predominant problem seemed to be tight MB which was completely occluding the lumen during systole with lesser contribution from atherosclerotic lesion and dissection. Since TIMI 3 flow had been restored and the dissection was non-flow limiting, we decided to follow-up the patient without stenting and try out beta-blockers (metoprolol 50 mg twice daily) in addition. Patient was kept

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under close out patient follow-up, and he did well. He was called after 3 months for repeat angiogram. At 3 months follow-up he reported angina of effort of 3 weeks duration. There was no history to suggest acute coronary syndrome. Repeat coronary angiogram showed 70% eccentric lesion at the site of MB and ectasia as before. Since the patient had angina, we decided to stent the lesion with 2.75 mm × 28 mm Cypher Select (Cordis Europa NV, The Netherlands) stent at 12 atm for 20 s. The lesion and the entire length of the MB were carefully covered with the stent (Fig. 2). IVUS was performed to check for the complete coverage of the MB and also for stent apposition. Stented area showed complete obliteration of the milking action of the MB except in the region of the ectasia. The ectatic region continued to show MB-like activity around the stent (Fig. 3). The stent cross section area was 6.1 mm^2. Abciximab (Centocor BV, CB Leiden, The Netherlands) and 5000 IU of unfractionated heparin was administered during the procedure and activated clotting time was 286 s. Six months follow-up angiogram and IVUS showed no intimal thickening, thrombus, or stent compression but continued presence of myocardial bridge around the stent.

Discussion

Myocardial bridge occurs when bands of heart muscle overlie the intramural course of epicardial arteries. The first detailed postmortem analysis of a series of patients with this anomaly was reported by Geiringer in 1951.[1] Autopsy studies have reported the incidence from 5% to 86%[2,3] while angiographically the reported incidence has ranged from 0.5 to 12%.[4,5] The bridging segment can vary in length from less than a centimeter to long segments involving the majority of the length of the vessel.[6]

Mechanism of MI in MB is not settled. Thrombotic occlusion[7,8] and atherosclerotic lesions[9] were seen in only some of them. Vasospasm has also been implicated.[10] In the remaining cases, the coronaries were found to be patent with evidence of only MB. Even on IVUS, evidence of atherosclerotic process is uncommon. Coronary atherosclerosis, therefore, does not explain and is not necessary to cause MI in MB. Whenever atherosclerosis is associated it is the segment proximal to the bridge which is involved[9,10] but the tunneled segment is typically spared.[6] Our case had atherosclerotic lesion within the tunneled segment which is unusual and also had ectasia within the tunneled segment (unreported association). Hemodynamic forces may explain atherosclerotic plaque formation at the entrance to the tunneled segment. There is low shear stress in the tunneled segment but high shear stress proximal to

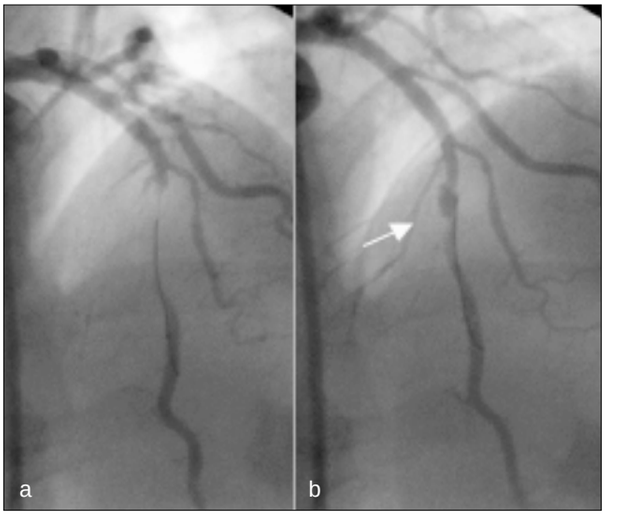

Fig. 1. *RAO cranial view of left anterior descending coronary artery after balloon dilation showing the myocardial bridge and tight lesion,* ***(a)*** *systolic frame showing ectatic myocardial bridge totally collapses during systole* ***(b)*** *diastolic frame showing ectasia at the site of myocardial bridge (arrow).*

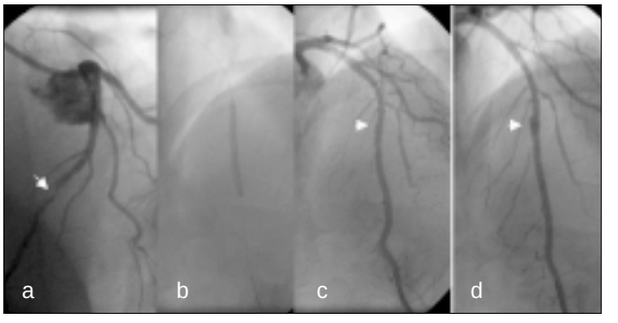

Fig. 2. ***(a)*** *LAO cranial view of left anterior descending coronary artery showing eccentric lesion in mid segment (arrow). RAO cranial view during and after stent implantation.* ***(b)*** *Stent deployment* ***(c)*** *systolic frame showing ectatic myocardial bridge contracts around the stent with complete obliteration of ectasia.* ***(d)*** *Diastolic frame clearly shows ectatic myocardial bridge around the stent (arrow).*

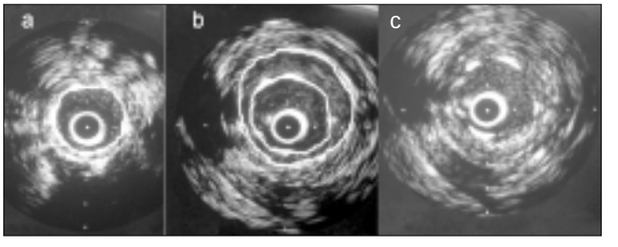

Fig. 3. *Intravascular ultrasound images showing* ***(a)*** *good stent apposition in the myocardial bridge segment with stent area of 6.1 mm2.* ***(b)*** *image at the site of ectasia within the myocardial bridge showing stent malapposition in diastolic frame. The stent cross-sectional area is 6.8 mm2 and EEM cross-sectional area of the ectatic zone is 14.6 mm2* ***(c)*** *Systolic frame at the same site showing complete obliteration of ectasia due to contraction of the myocardial bridge around the stent.*

the tunneled segment which may predispose to atherosclerosis.[9,10] Ectasia at the site of MB in this case was possibly secondary to the atherosclerotic lesion within the tunneled segment coupled with milking action of severe MB resulting in weakness of the vessel wall.

Three treatment strategies have been explored for symptomatic patients of MB (i) Negative ionotropic and/or negative chronotropic agents i.e. beta-blockers[11,12] and calcium channel antagonists,[13] (ii) Surgical myotomy / coronary artery bypass grafting (CABG),[14] and (iii) Stenting of tunneled segments.[15-21] Stables et al.[16] first reported coronary stenting as interventional approach for MB in 1995.

Stenting of MB is not always necessary. Cases of myocardial ischemia and acute MI secondary to MB have been managed medically as well.[22-24] Usual indications of revascularization in MB are similar to any other case of coronary artery disease viz. persistent ischemia and/or angina despite drugs.

Stenting of MB segment and the post-procedural period can have many potential complications. Coronary artery dissections, perforations,[25] abrupt vessel closure,[22] inadequate stent expansion,[17] and subacute thrombosis[21] have been reported. Long-term concerns are restenosis (nearly 50%) predominantly due to neointimal hyperplasia and stent compression due to MB.[17] It is therefore necessary to implant stents with good radial strength and completely cover the MB segment.[17] This requires long stents in many cases. Therefore, DES (e.g. Cypher Select™ as in this case) may be better choice as they would protect against neointimal hyperplasia in these long stented segments. There is no previous report of use of any DES in MB. Use of IVUS is strongly recommended while stenting MB segments to correctly chose the stent length and also achieve adequate deployment of stent.[19] Stables et al.[16] demonstrated that intracoronary stent implantation could achieve internal stabilization of the squeezing action at the MB. Hagger et al.[17] described 11 cases of stenting in MB. The procedure was uneventful in all their cases but 6 of 11 cases showed inadequate expansion of the stent even at 10-12 atm which was corrected with IVUS guidance. Six of their cases had early restenosis at 7 week angiograms. IVUS showed that in majority of these cases mechanism of restenosis was neointimal hyperplasia. One patient showed severe collapse of the stent due to compression which could not be redilated necessitating coronary bypass surgery. We therefore decided to use IVUS guidance in our case. Since the mechanism of restenosis happens to be neointimal proliferation we used sirolimus-eluting stent, use of which has not been reported earlier for MB. Presence of ectasia proximal to the MB was a concern as it was expected that the drug-eluting stent will not have adequate stent apposition in that area. Malapposition of this nature might predispose to subacute stent thrombosis. We therefore administered abciximab to the patient. At the same time, active squeezing action in the ectatic area is likely to prevent any stasis and reduce the chances of thrombus formation. Six-month angiogram and IVUS showed no thrombus, neointimal hyperplasis or stent compression.

Conclusions: Our case had MB of LAD associated with acute anterior wall MI. The patient had unusual features like coronary ectasia and atherosclerosis within the MB segment. He was treated with DES under IVUS guidance with good result till 8 months follow-up. This report is first experience of drug-eluting stent in MB producing MI.

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Brief Report

Risk Factors for Coronary Heart Disease In Indians: A Case-Control Study from Eastern India

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We conducted a hospital-based case-control investigation (150 cases and 176 controls) to examine the putative role of conventional risk factors in subjects with and without coronary heart disease from Eastern India. Multivariate binary logistic regression revealed the following as significant risk factors for coronary heart disease: male sex (OR=4.6, p=0.001), elevated total cholesterol/high-density lipoprotein ratio (OR=4.0, p=0.001), systolic blood pressure (OR=3.0, p=0.004), diastolic blood pressure (OR=3.6, p=0.002), fasting plasma glucose (OR=3.0, p=0.05), post-pondrial plasma glucose (OR=3.2, p=0.005), Impaired fasting glucose (OR=3.7, p=0.002), elevated triglyceride (OR=3.1, p=0.018), increased total cholesterol (OR=3.0, p=0.029), low-density lipoprotein (OR=3.1, p=0.001), low-density lipoprotein/high-density lipoprotein ratio (OR=3.4, p=0.004), central obesity (OR=3.0, p=0.006), smoking (OR=3.7, p=0.001) and urban residence (OR=3.1, p=0.003). In this study, the discriminant analysis showed that 77.2% of all entry for cases and 72.6% of all entry for controls were correctly classified using conventional risk factors and warrant early intervention for conventional risk factors. **(Indian Heart J 2005; 57; 738-740)**

Key Words: Coronary heart disease, Epidemiology, Dyslipidemia

The prevalence of coronary heart disease (CHD) is known to be high in people of south Asian descent (subjects originally from India, Pakistan and Bangladesh). Moreover, CHD among them is often premature and occurs a decade earlier than that seen in Europeans and/or Americans.[1-3] However, its precise etiology and mechanisms remain incompletely understood. Although prevalence of conventional risk factors such as smoking, hypertension and hypercholesterolemia is no higher in South Asians than in other ethnic groups, yet it is quite clear that some metabolic abnormalities are more prevalent among them, including high triglyceride (TG) concentration, increased total cholesterol (TC) and high-density lipoprotein (HDL) ratio (TC/HDL), diabetes mellitus (DM) and central or visceral obesity.[3-5] In Asian populations, mortality and morbidity from CHD is occurring in people with lower body mass index (BMI).[6] The metabolic syndrome that has been defined as the constellation of CHD risk factors is associated with striking tendency to central obesity in south Asians although they are no more overweight than Europeans or Americans.[7]

We conducted a hospital-based case-control investigation to examine the putative role of conventional risk factors in subjects with and without CHD from the Eastern part of India.

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Brief Report

This case control study enrolled 150 consecutive patients (120 males and 30 females) aged 30-77 years admitted to Kolkata Medical College with acute coronary syndrome (ACS). Further 176 individuals (132 males and 44 females) aged 30-78 years, who were prospectively recruited from those attending the outpatient clinics for various reasons, served as controls. These controls had no complaints pertaining to cardiovascular system; they had a normal electrocardiogram (ECG), denied history for any cardiac ailment and did not have any clinical evidence of atherosclerotic vascular disease. Participants from Kolkata

and suburbs were considered as urban dwellers and those who came from nearby districts were asked whether they live in town or village and accordingly categorization was made.

Anthropometric variables like height, body, weight, circumferences of waist (WC) and hip were taken using standard techniques.[8] BMI and waist-hip ratio (WHR) were computed accordingly.

For metabolic profile, blood was taken from patients within 12 hours of the onset of chest pain and available medical records were also considered in this regard. A fasting blood sample was collected from each control for the determination of metabolic variables. Values of low-density lipoprotein (LDL) were estimated using standard formula TC – (HDL+ TG/5) provided TG was < 400 mg/dl. It was directly estimated if TG was > 400 mg/dl. All metabolic variables were measured in mg/dl unit.

Systolic (SBP) and diastolic (DBP) blood pressure measurements were taken twice using sphygmomanometer and stethoscope and averaged for analyses. A third measurement was taken only when the difference between the two measurements was > 5 mmHg and the average of three was calculated. Prior medical records regarding blood pressure were also considered.

Subjects were categorized into two groups of central body fat distribution using the JNC-V criterion (1993):[9] centrally obese (CO)= WHR > 0.95 (for males) and >0.85 (for females); centrally non-obese (CNO)= WHR $\leq$ 0.95 (for males) and $\leq$ 0.85 (for females). Cut-off values for elevated TC were taken as TC $\geq$ 240 mg/dl,[10] elevated TG as TG $\geq$ 200 mg/dl,[11] elevated TC/HDL ratio as ratio $\geq$ 4.4 [12] and impaired fasting glucose (IFG) as IFG = >- 125 mg/dl.[13]

Age in both groups was comparable (55.0 ± 9.0 years in patients *v*. 53.0 ± 12.0 years in controls, p=NS) validating the age-matched case-control nature of the study. For cases, 40% and 55% were present smokers and urban dwellers, respectively, as compared to 32% and 48%, respectively in the control group. More than 80% for both the groups were leading more or less sedentary lifestyle. Most of the participants were non-vegetarians. Mean and standard deviation for anthropometric, metabolic and blood pressure variables are presented in Table 1. No significant group difference was evident for height, weight, BMI and hip circumference. However, significant differences were observed for metabolic parameters (except HDL), blood pressure, and central obesity measures. The results of the multivariate binary logistic regression revealed the followings as significant risk factors for CHD outcome: male sex (OR:4.6, p=0.001) and TC/HDL ratio $\geq$ 4.4 (OR: 4.0, p=0.001), SBP (OR: 3.0, p=0.004), DBP (OR: 3.6, p=0.002), fasting glucose (FPG) (OR: 3.0,p=0.05), post-prandial glucose (PPG) (OR: 3.2, p=0.005), IFG (OR: 3.7, p=0.002), elevated TG (OR: 3.1, p=0.018), elevated TC (OR: 3.0, p=0.029), LDL (OR: 3.1, p=0.001), LDL/HDL ratio (OR: 3.4, p=0.004), central obesity (OR: 3.0, p=0.006), smoking (present smokers + previous smokers) (OR: 3.7, p=0.001) and urban residence (OR: 3.1, p=0.003). Discriminant analysis (corrected for group size) was undertaken to determine how well individuals in the two groups (cases *v*. controls) could be correctly classified utilizing these variables. Results revealed that 77.2% of all entries for cases (with CHD) and 72.6% of all entries for controls (without CHD) were correctly classified. In fact, the overall percentage of grouped cases correctly classified was 75%.

Discussion

Our results revealed that male sex, blood pressure, plasma glucose, elevated level of total cholesterol, elevated TG, elevated TC/HDL ratio, LDL (used as continuous variable), increased LDL/HDL ratio, central obesity and urban residence were independent risk factors for CHD.

In our study, when we used present smoking as independent variable, the odd ratio was 2.1. But when we clubbed present smokers with previous smokers, the odd ratio increased to 3.7. Large-scale longitudinal and/or case-control studies are necessary in the Indian population to assess the atherogenic effect of smoking in this ethnic group. To the best of our knowledge no such initiative has been undertaken so far in India. Furthermore, the low HDL (HDL concentration <40 mgl/dl) is often considered as an independent coronary risk factor. In our study, the level of HDL was almost same in the two groups (mean HDL 46.0 mgl/dl in patients *v*. 46.7 mg/dl in controls). A lack of difference in HDL concentration in the two groups may be attributed to the frequent consumption of n-3 polyunsaturated fatty acid (PUFA) through fish eating.[7] Both fasting and post prandial glucose (FPG and PPG) concentrations were significantly higher in cases than controls. In fact, fasting (OR=3.01, p=0.002) and post-pondrial glucose (OR=3.23, p=0.004 concentrations had significant impact on CHD in our study. The American Diabetes Association introduced IFG recently as a category of abnormal glucose metabolism surrogate to impaired glucose tolerance (IGT). Our outcome revealed that IFG is also a good predictor (OR=3.72, p=0.002) of CHD.

Significant positive impact of central obesity (OR=3.0, p=0.006) and not absolute body fat content (as assessed by BMI) ratify previous findings that CHD in people of

Table 1. Descriptive statistics for variables considered in individuals with (n=150) and without (n=176) coronary heart disease (CHD)

Variables	With CHD (*n*=150) Mean ± SD	Without CHD (*n*=176) Mean ± SD
Age (years)	55.0 ± 9.0	53.0 ± 12.0
Height (cm)	161.1 ± 8.4	157.8 ± 9.4
Weight (kg)	60.1 ± 8.6	59.5 ± 9.0
BMI (kg/m^2)	23.1 ± 2.6	23.9 ± 4.0
Waist circumference (cm)**	89.2 ± 8.3	86.7 ± 11.2
Hip circumference (cm)	92.0 ± 6.3	94.0 ± 9.7
WHR**	0.96 ± 0.06	0.92 ± 0.07
TC (mg/dl)***	224.2 ± 7.7	164.0 ± 7.2
TG (mg/dl)***	230.2 ± 74.2	144 ± 70.6
HDL (mg/dl)	46.0 ± 8.8	46.7 ± 10.0
LDL (mg/dl)*	142.3 ± 38.6	121.0 ± 42.5
TC/HDL***	5.0 ± 1.3	4.5 ± 1.2
LDL/HDL**	3.5 ± 1.4	2.7 ± 0.91
FPG** (mg/dl)	102.6 ± 21.6	90.0 ± 23.4
PPG*** (mg/dl)	153.2 ± 41.4	129.7 ± 43.4
SBP*** (mm Hg)	149.6 ± 8.6	134.4 ± 8.2
DBP*** (mm Hg)	90.3 ± 12.3	84.2 ± 13.2
MAP*** (mm Hg)	110.0 ± 16.8	101.0 ± 13.4

ANOVA-revealed significant group difference at * $p<0.05$; ** $p<0.01$; *** $p<0.001$
BMI: body mass index; WHR: waist-hip ratio; TC: total cholesterol; TG: triglyceride; HDL: high-density lipoprotein; LDL: low-density lipoprotein; FPG: fasting plasma glucose; PPG: post-load plasma glucose; SBP: systolic blood pressure; DBP: diastolic blood pressure; MAP: mean arterial pressure

Indian descent occurred even at lower body fat with higher central obesity. Positive significant impact of urban residence on CHD outcome could have been attributed to changing life style including food habit changes as well as decreased physical activity invariably associated with an urban lifestyle. The result of the discriminant analysis, which is useful to build a predictive model of group membership based on observed characteristics of each case, revealed that overall 75% of all subjects could be correctly classified (people with and without CHD) using blood pressure, plasma glucose, elevated lipids, central obesity, smoking and urban residence. The subjects in the study were predominantly male. Therefore any extrapolation of these results to women would have to be done with great care.

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Brief Report

Recanalization of a Single Functioning Kidney

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For patients with renal artery stenosis, percutaneous transluminal angioplasty is generally the treatment of choice. This report describes the case of an elderly lady with type III aortoarteritis whose right renal artery was successfully recalized and stented. There was satisfactory improvement in renal function and blood pressure post-procedure, and at one-month follow-up. **(Indian Heart J 2005; 57: 741–743)**

Key Words: Renal artery stenosis, Renal angioplasty, Aortoarteritis

Percutaneous transluminal renal angioplasty (PTRA) is the preferred therapeutic option for hemodynamically significant renal artery stenosis (RAS).[1-3] We report a case where recanalization and stenting was done to an occluded renal artery of a single functioning kidney, in a 51-year-old lady with type III aortoarteritis. She had had left nephrectomy nine years ago for a non-functioning left kidney and uncontrolled hypertension.

She presented with acute pulmonary edema, worsening renal function and uncontrolled hypertension despite four antihypertensive agents. The right renal artery was successfully recanalized and stented. Improvement of renal function, control of blood pressure with minimal medication and clinical recovery occurred in the immediate post-procedure period and was sustained at one-month follow-up.

Case Report

A 51-year-old lady was referred to our hospital with history of worsening dyspnea, decreased urine output and anasarca of two week duration. She also complained of orthopnea for two days prior to presentation. She had been diagnosed to have aortoarteritis nine years ago when she underwent left nephrectomy for secondary hypertension due to a non-functioning left kidney with occluded renal artery on the same side.

On admission her blood pressure in the right upper limb was 190/110 mmHg and in the lower limb 180/110 mmHg. Pulse and blood pressure were not recordable in the left upper limb (she was diagnosed to have occluded left subclavian also, nine years ago). She was orthopneic, had tachypnea, tachycardia and bilateral crepitations on clinical examination. Chest X-ray revealed evidence of pulmonary edema and electrocardiogram (ECG) showed left ventricular (LV) hypertrophy. Echocardiography demonstrated normal LV function and normal chamber dimensions. Her serum creatinine was 3.6 mg/dl.

Renal ultrasonography showed damped flow in the distal right renal artery and its branches. The ostial and the proximal part of right renal artery could not be visualized. The right renal parenchyma was preserved and the kidney size was 8 cm.

She was stabilized medically by dialysis and four antihypertensive drugs including intravenous diuretics and nitrates. In view of the recent onset of symptoms, >300 ml urinary output, preserved renal parenchymal sonographic pattern and >7 cm kidney size (marker of functional kidney), it was decided to go ahead with angiography and renal revascularization, if feasible. Surgery was considered as the second option in view of her poor clinical status.

Abdominal aortogram was done using a 6 F pigtail through the left femoral approach as the right groin was accessed for dialysis. The right renal artery was occluded at the ostium with late filling from collaterals with the occlusion segment of almost 2 cm in length (Figs 1 and 2). The abdominal aorta as a whole was diseased with 50% stenosis at the iliac bifurcation. There was a gradient of 20 mmHg from the abdominal aorta to the iliacs. Renal guiding catheter did not give adequate support and hence 6 F right coronary guiding catheter was used. The occluded right renal was wired successfully with an 0.14" Shinobi wire, after initial attempts with 0.018" Roadrunner and 0.014" Stabilizer wires failed. A 2.0 × 15 mm coronary dilation balloon was used to pre-dilate the lesion.

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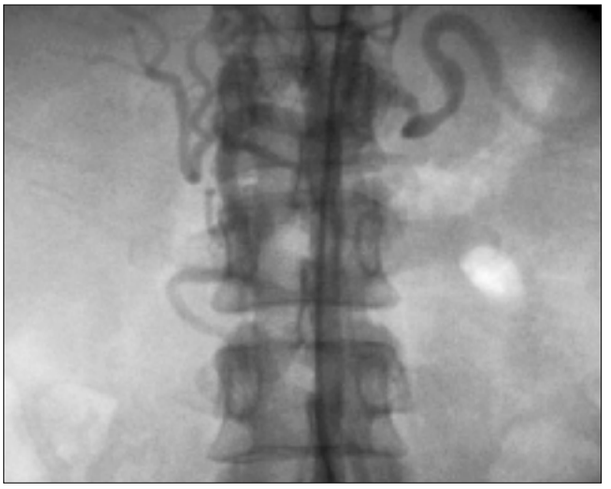

Fig. 1. *Early phase of abdominal aortogram showing absence of renal arteries.*

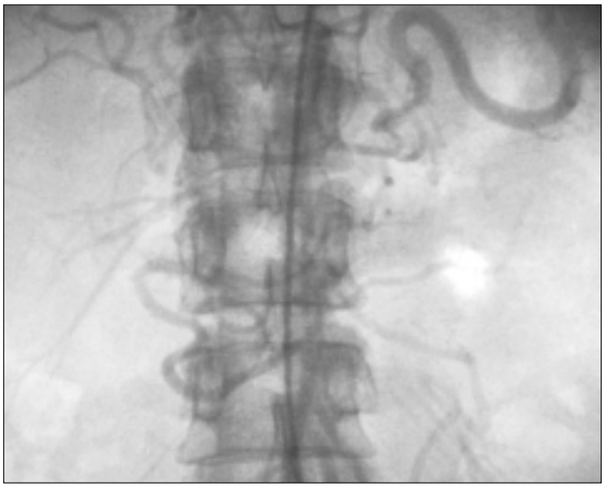

Fig. 2. *Late filling of right renal artery through collaterals.*

A check angiogram revealed that the wire had entered a branch, which was arising from the diseased segment. The main branch continued further before division into intra renal branches. The main artery was wired carefully with a Choice standard 0.014" wire and further pre-dilated to 4 mm at 16 atm. The entire lesion including the ostium was stented with a 5 × 20 mm stent at 18 atm. The check angiogram showed a small plaque at the ostium, which did not give way with further dilation. Another 5 mm short stent was deployed at the ostium with 2 to 3 struts protruding into the aorta, overlapping with the previous stent. The ostium and overlap segments were post-dilated with a 5 mm balloon at 18 atm. The final result was good with the brisk renal blood flow (Fig. 3).

The blood pressure continued to decline steadily and her urine output improved post procedure. Her creatinine level

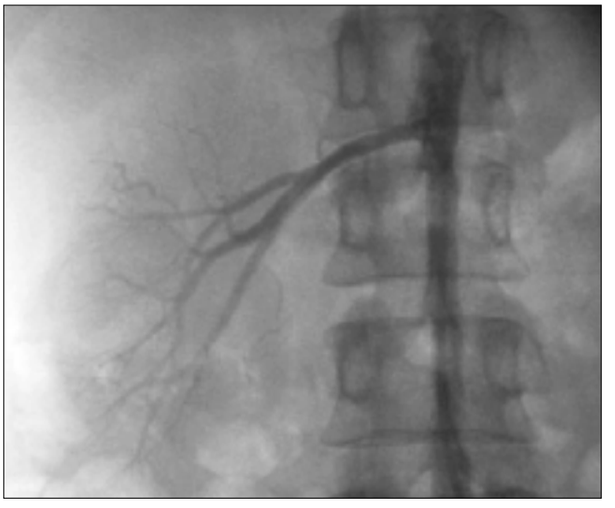

Fig. 3. *Aortogram showing recanalized and stented right renal artery.*

came down to normal in two days time (3.4 mg/dl to 1.0 mg/dl) and she was discharged on two anti-hypertensives and steroid for her active stage of aortoarteritis. Her blood pressure in the right upper limb at the time of discharge was 130/80 mmHg.

Follow-up: She was reviewed after three weeks in the outpatient department and her creatinine and blood pressure were found to be stable.

Discussion

Renal artery stenosis can result in renovascular hypertension and accounts for 1-2% of all cases of hypertension.[1] It can also lead to renal insufficiency. An aggressive treatment of RAS is recommended for patients with uncontrolled hypertension, renal insufficiency, congestive heart failure, unstable angina, and in patients with solitary or single functioning kidney.

The treatment of RAS includes medical therapy, balloon angioplasty with or without stenting and surgery. Surgery remains at high risk with a 2-7% peri-operative mortality rate, a 17-31% morbidity and deterioration of renal function in 11-31% of patients, re-occlusion and restenosis in 5-18%.[2-4] Indications for surgery are limited: failed percutaneous approach, hostile aorta, infra-renal total occlusion and in association with aortic surgery. PTRA technique is the therapeutic strategy of choice for RAS.[5-9] Although it is still controversial with some investigators questioning the rationale for intervention as the renal

function may not improve from the baseline and the need for antihypertensive may not change.[10] Parameters to predict whether intervention would result in improvement are available.[11-13]

This case, though anecdotal, clearly suggests dramatic improvement in clinical and biochemical renal parameters after renal artery recanalization. The dosage and number of antihypertensive drugs decreased after revascularization. The long-term results will have to be awaited considering the disease process.

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Brief Report

Isolated Thrombus-producing Right Ventricular Outflow Tract Obstruction: An Unusual Presentation of Primary Antiphospholipid Antibody Syndrome

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Right ventricular outflow tract obstruction secondary to an isolated organized thrombus is a rare entity. Proper diagnosis of this condition is essential for the survival of such patients. We describe the case of a middle aged woman who presented with dyspnea and decreased effort tolerance, and was managed with surgical excision of a firm mass which was identified as organized thrombus. **(Indian Heart J 2005; 57: 744–746)**

Key Words: Echocardiography, Right ventricular outflow obstruction, Antiphospholipid syndrome

Obstruction of right ventricular outflow as a sequel to organized thrombus is not a common occurence. This report describes an usual presentation of a middle-aged female patient who presented with dyspnea and decreased effort tolerance. Transthoracic echocardiography revealed a lobulated mass in right ventricular outflow tract (RVOT) which was excised.

Case Report

A 40-year-old post partum lady with previous history of recurrent abortions, presented with class III dyspnea and decreased effort tolerance of four months duration. Physical examination of chest showed a short systolic precordial murmur. On abdominal examination, liver was enlarged reaching up to about 3 cm below the costal margin.

Chest X-Ray demonstrated an increased cardiothoracic ratio (0.54) with bilaterally congested lung fields. Electrocardiography (ECG) showed sinus rhythm. Transesophageal echocardiography (TEE) revealed a large lobulated mass in the right ventricular outflow tract 4.1 cm×2.4 cm with peak RVOT gradient of 35.5 mmHg. Left and right ventricular functions were normal. There was minimal pericardial effusion (Fig. 1).

Ultrasound abdomen confirmed an enlarged liver; the rest of the abdominal viscera were normal. A 16-slice computerized tomographic (CT) pulmonary angiography of the chest was done to assess the mass and pulmonary vasculature. CT angiography showed a well defined, lobulated soft tissue attenuation, minimally enhancing mass lesion in the right ventricular cavity measuring 4.1 × 3.2 × 2.5 cm arising from its anterolateral wall. The mass was stopping short of the pulmonary valve (Fig. 2). Bilateral pulmonary arteries, their branches and peripheral venous system was normal (Figs 3 and 4). Minimal pericardial effusion was noted.

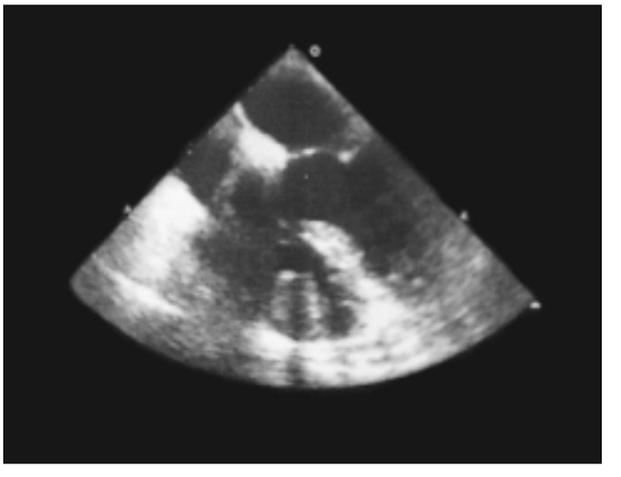

Fig. 1. *Transesophageal echocardiography showing right ventricular mass.*

Hematology results including platelet count, bleeding time, and activated partial thromboplastin time and clotting time were normal. There was mild normocytic, normochromic anemia. Serum levels of homocystine, protein C and protein S and antithrombin III were also

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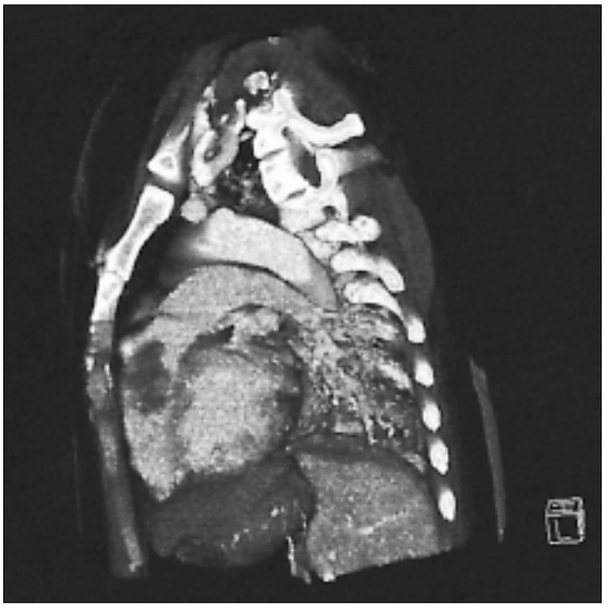


Fig. 2. *MIP axial image (2) and saggital reconstructed MIP image (3) through the cardiac chambers showing an irregular, well defined, low-density filling defect within the right ventricle outflow tract stopping short of the pulmonary valve. Mild pericardial effusion is also seen.*

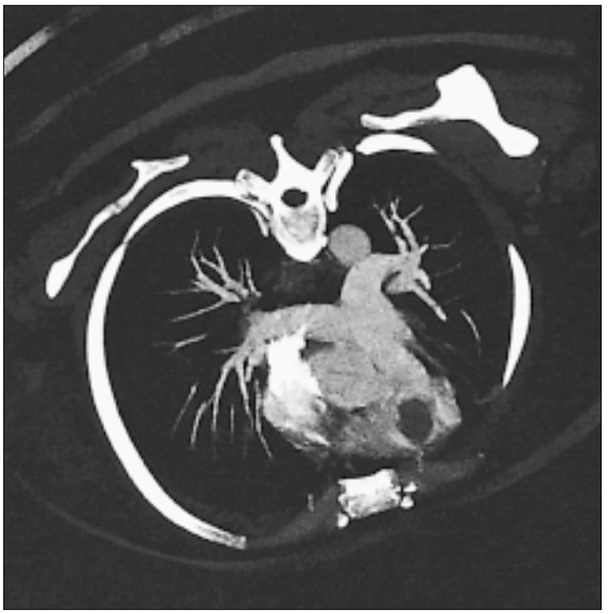


Fig. 3. *Volume rendered image of the right ventricular outflow tract.*

normal. Anticardiolipin antibodies estimation showed raised levels of both lgG (20 micro/ml) and lgM (16 micro/ml). Surgical excision and removal of the mass was done through an incision on the pulmonary artery 1 cm above the pulmonary valve. A firm to hard mass measuring about 4 cm × 2.5 cm was attached to the free wall of the right ventricle and anterior papillary muscle. The pulmonary artery was closed with prolene continuous sutures (Figs 5a and 5b).

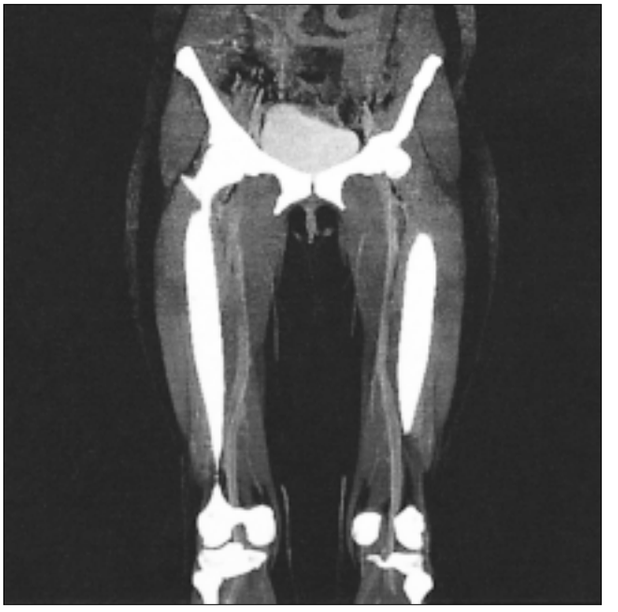


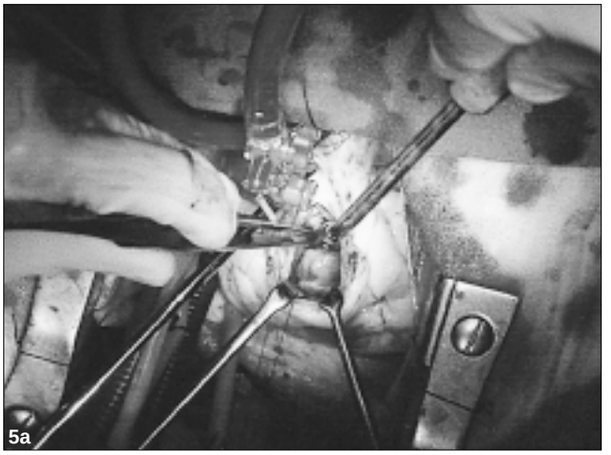
Fig. 4. *Coronal MIP reconstruction images of bilateral femoral veins showing normal opacification of contrast with no filling defect.*

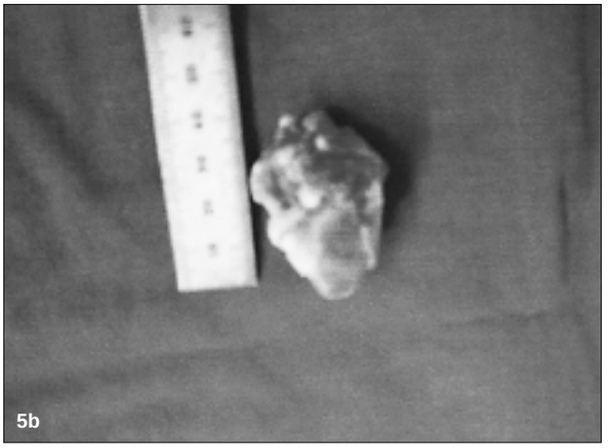
Pathological findings: Microscopically the tumor was composed of a mass of fibrin with neovascularity in the form of blood capillaries and proliferation of fibroblasts. No myxoid cells were seen. Features were suggestive of organizing thrombus (Fig. 6).

Discussion

Scientific data on isolated right ventricular thrombus in the absence of right ventricular dysfunction is sparse. Although Ebato et al.[1] have reported isolated thrombus formation on structurally normal tricuspid valve, Mottram et al.[2] and Nickele et al.[3] reported thrombus on mitral valve in patients with antiphospholipid antibody syndrome. Right ventricular thrombus may be a source of pulmonary embolism, a potentially fatal condition, hence accurate diagnosis is considered emergent.

Definitive diagnosis of antiphospholipid antibody syndrome requires demonstrating an elevated level of antiphospholipid antibody associated with clinical evidence of thrombosis occurring in the absence of identifiable causes of hypercoagulability.[4] As all the above features were





Figs. 5. *(a) Surgical excision of the mass, (b) Excised mass.*

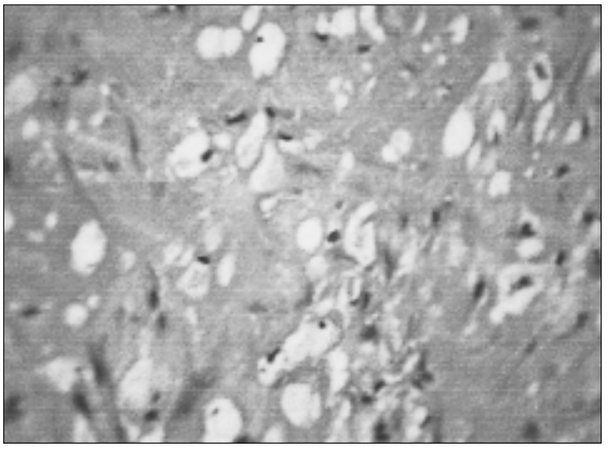


Fig. 6. *High power image showing the fibrin and few fibroblasts.*

present in our case, a probable diagnosis of antiphospholipid antibody syndrome was made. The cardiac pathology associated with antiphospholipid antibody syndrome includes valvular abnormalities and intracardiac thrombus. The diagnosis should be considered in all cases of intracardiac thrombosis with structurally normal heart without deep vein thrombosis and in the absence of other identifiable hypercoagulable states.

The present case is interesting, as the patient had an unusual presentation of RVOT obstruction secondary to an isolated organized thrombus without any evidence of venous thrombosis. Such a presentation, to the best of our knowledge, has not been reported in literature. Further, accurate diagnosis of this condition can be lifesaving as it may be associated with potentially fatal pulmonary embolism.

Conclusions: Antiphospholipid antibody syndrome associated with right cardiac thrombosis, though difficult to assess clinically, is as common as left cardiac thrombosis and is associated with an increased risk of pulmonary emboli. The diagnosis should be considered in all cases of intracardiac thrombosis in structurally normal heart, in the absence of deep vein thrombosis and other hypercoagulable states.

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Peripheral Vascular Diseases : An Update on Endovascular Therapy

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Peripheral arterial diseases (PAD) are frequent and one of the major manifestations of systemic atherosclerosis and affect approximately 10 to 14 million Americans every year. PAD are estimated to be present in 3% of people in the age range 40-59 years and in 20% of people over 70 years as documented by non-invasive testing.[1,2] PAD are therefore increasing dramatically as the population ages. Unfortunately, PAD are often under-diagnosed and many of these patients are misdiagnosed and their symptoms are attributed to ostearthritis or the normal aging process.

Approximately 30% to 50% of the patients with PAD will progress from intermittent claudication to critical limb ischemia (CLI) in due course of their disease. CLI is estimated to have an incidence of approximately 500 to 1000 per million per year. The risk factors that result in this advanced form of PAD are advanced age, tobacco use and diabetes mellitus. Patients on dialysis are also at increased risk of presenting with CLI.[3-5] CLI is associated with an extremely poor prognosis. Mortality rates are alarming: 25.0% at 1 year, 31.6% at 2 years and more than 60.0% after 3 years.[3,6,7] Moreover, CLI results in 150,000 amputations per year in the US and Europe. Within 1 year of the onset of CLI 25% of the patients will die and another 25% will require major amputation.[8,9] Significant mortality is due to coexistent cardiovascular and cerebrovascular diseases. Multivascular disease also entails significant mortality.

In the PARTNERS study of 6900 patients, either over 70 years of age regardless of medical history, or over 50 years of age with a history of smoking and diabetes mellitus, 13% suffered from isolated PAD, 16% had combined PAD and cardiovascular diseases (CVD) both and 25% had CVD alone, 47% were healthy normal patients without atherosclerosis.[10]

The primary goal of any treatment of patients with PAD will be either limb salvage or relief of significant lifestyle-limiting symptoms that cannot be controlled by risk factor modification, exercise therapy or medication. At the same time, evaluation and treatment of coexistent cardiovascular and cerebrovascular diseases should be completed.

From an interventional perspective, nearly 30% of the arterial lesions are located in the iliac arteries, 70% in the femoro-popliteo-tibial track. Isolated lesions below the knee are present in only 15% of the cases. Approximately 30% of the symptomatic PAD patients have diffuse arterial disease, and the majority of CLI patients, most of whom are diabetic, have distal arterial disease with occlusions in the tibial arteries.

For a long time, surgery has been considered as the gold standard treatment. With the rapid introduction of new wires, debulking devices, low-profile balloons and stents, endovascular technology has improved during the last 10 years. Furthermore, endovascular specialists have adopted coronary techniques, particularly in the small vessels. As a result, endovascular intervention has become a first line therapy to treat PAD and even complex arterial diseases.

Iliac Occlusive Diseases

Approximately one-third of the obstructive lesions in PAD affect the aorto-iliac segment. As in the case with most PADs, iliac artery disease is commonly found in patients who either smoke, have diabetes, hypertension, and/or high cholesterol. Their symptoms are somewhat different from patients with infrainguinal lesions in that they commonly present with more proximal symptoms, which manifest through discomfort in the hip, thigh, or buttocks during ambulation that subsides when the patient stops the activity.[11]

Many physicians either overlook the presence or misdiagnose the symptoms as musculoskeletal in nature. Patients with symptomatic iliac artery disease often have normal pulse in the groin while at rest, which may falsely indicate a non-vascular cause to physicians.

Iliac artery diseases may be treated for a number of reasons, including relief of claudication, relief of limb-threatening ischemia and maintaining vascular access for

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other vascular-based procedures, such as intra-aortic balloon pump placement or cardiac catheterization.[12] Iliac artery obstructions have traditionally been treated with open surgery. Although highly effective, these surgical interventions are associated with a substantial procedure-related risks for the patient. In a meta analysis of data published after 1975, the aggregate operative mortality rate for aorto-femoral bypass surgery was 3.3% and the aggregate systemic morbidity rate was 8.3%.[13] Open bypass surgery appears to be relegated to a secondary role for treating patients without an endovascular option. Percutaneous transluminal angioplasty (PTA) is a less invasive treatment alternative and should be the first treatment to be proposed.

To optimize and maintain international medical standards in the management of PAD, a consensus expert opinion of key professional societies, the TransAtlantic Inter-Society Consensus (TASC) working group, developed a consensus document.[6] It made recommendations about the treatment of choice, depending on the morphologic stratification of iliac lesions (Table 1). According to these guidelines, PTA is generally considered for more focal diseases (Type A and B lesions). For complex, multifocal or totally occluded atherosclerotic segments of the iliac arteries (Type C and D lesions) TASC recommends surgery as the procedure of choice.

Table 1. TASC recommendations for the treatment of iliac lesions

Endovascular procedures are the treatment of choice for type A lesions, and surgery is the procedure of choice for type D lesions. More evidence is needed to make any firm recommendations about the best treatment for Type B and C lesions.

Type A iliac lesions
- Single stenosis < 3 cm of the CIA or EIA (unilateral/ bilateral)

Type B lesions
- Single stenosis 3-10 cm in length, not extending into the CFA
- Total of two stenoses < 5 cm long in the CIA and/or EIA and not extending into the CFA
- Unilateral CIA occlusion

Type C lesions
- Bilateral 5-10 cm long stenoses of the CIA and/or EIA, not extending into the CFA
- Unilateral EIA occlusion not extending into the CFA
- Unilateral EIA stenosis extending into the CFA
- Bilateral CIA occlusion

Type D lesions
- Diffuse, multiple unilateral stenoses involving the CIA/EIA, and CFA (usually >10 cm)
- Unilateral occlusion involving both the CIA and EIA
- Bilateral EIA occlusions
- Diffuse disease involving the aorta and both iliac arteries
- Iliac stenoses in a patient with an abdominal aortic aneurysm or other lesion requiring aortic or iliac surgery.

TASC: Trans Atlantic inter-society consensus; CIA: common iliac artery; EIA: external iliac artery; CFA: common femoral artery;

Now, the guidelines might need to be updated. The development of new endovascular devices and stents has progressed extremely quickly. Currently, the length and morphology of iliac lesions has less influence on technical success and long-term results for experiences and well-skilled interventionists. The advancement of interventional techniques allows the treatment of complex lesions in the aorto-iliac segment.

Balloon angioplasty alone: With balloon angioplasty alone, the technical success rate in iliac artery stenosis is up to 92%, while the 2- and 5-year primary patency rates are 81% and 75%, respectively as indicated by an analysis of 2697 interventions.[14] Limitations of balloon angioplasty are elastic recoil, flow-limiting dissection, residual pressure gradient, distal embolizations, especially when occluded arteries are recanalized.

PTA and stenting: The development and introduction of endovascular stents have revolutionized the treatment and improved the immediate and long-term hemodynamic results. With the use of Palmaz balloon-expandable stents (Cordis Endovascular, Miami, FL), a high primary success rate and a patency rate of > 90% may be obtained at long-term follow-up.[15,16] In a series of 118 patients, Vorwerk et al.[17] obtained a 2- and 4-year patency rate of 88% and 82%, respectively. As self-expanding, stainless steel stents were introduced, more complex diseases could be treated with similar success rates.[18] Six-year primary patency in patients treated for claudication of nearly 80% has been seen in a study utilizing the stainless steel Wallstent (Boston Scientific Corporation, MA).[19]

Advanced engineering had led to the development of more flexible balloon-expandable stents, and nitinol self-expandable stents with low-profiles, good radial strengths and minimal foreshortening, allowing an accurate placement, even in tortuous arteries. These nitinol stents exert a constant pressure on the vessel wall. It is not compressible, and therefore, is a good choice for arteries that are affected by muscle movements or located close to the body surface. We published a series of 172 iliac arteries stented with nitinol stents with a 3-year patency rate of > 80%.[20]

Iliac stenting is generally indicated if PTA fails (dissection, residual stenosis etc.). Chronic iliac occlusion is also a primary indication for stent placement. Long segment stenoses with irregular surfaces, aneurysm formation or marked ulcerations are among the complex

lesions that need stenting. Eccentric stenoses or ostial lesions also are indications for primary stenting. However, there is a tendency among specialists to perform primary stenting for the majority of iliac lesions.

As documented in a meta analysis, stenting of iliac artery stenoses contributed to a relative risk reduction of 39% *versus* balloon angioplasty with respect to failed long-term patency. Direct stenting improved primary patency by ~ 10%.[21] In a prospective multicenter trial, the direct comparison between primary stenting and balloon angioplasty of the iliac artery in over 300 patients resulted in a 5-year patency rate of 90% for stenting *versus* 68% for balloon angioplasty.[22] In contrast, Tetteroo et al.[23] suggested balloon angioplasty with selective stenting being equivalent to primary stenting with similar 2-year patency rates of 77% and 78%, respectively. However, 43% of the patients in the balloon-only group were stented due to unsatisfactory angioplasty results. Complication rates were almost doubled (4% *v*. 7%) in the angioplasty group. Primary stenting appears to reduce the rate of peripheral embolization compared to pre-dilation.[24]

Predictors of adverse outcome after PTA/stenting have to be pointed out. Timaran et al.[25] compared the results of PTA/stenting of the external iliac artery (EIA) and common iliac artery (CIA) lesions. Overall primary patency was significantly decreased in patients with EIA lesions compared with CIA lesions at 1, 3 and 4 years: 76%, 56% and 56%, respectively for patients with EIA stents, 92%, 85% and 76%, respectively for those with CIA stents. Furthermore, women with EIA stents had the poorest outcome with a primary patency of 23% at 5 years.

However, in our study,[20] we found no significant difference after stenting with nitinol stents of EIA or CIA in men or women. At 3 years, the primary patency rate was 85.5% for CIA lesions, 91.5% for EIA lesions; 89.3% for men, 84.0% for women (p=NS). Lee et al.[26] also reported a series of EIA and CIA stenting with a comparable patency rate at both sides despite more ischemic limbs in patients receiving EIA stents. In other studies, Timaran et al.[27,28] identified renal insufficiency as an independent predictor of decreased primary stent patency and hormone replacement therapy also appeared as a significant risk factor for decreased primary patency.

Poor infrainguinal run off is the main risk factor for decreased primary patency after surgical reconstruction but also after iliac stenting to treat TASC Type B and C iliac lesions.[29]

To maximize the accuracy of stent deployment and improve long-term outcome, intravascular ultrasound (IVUS) may be useful. Buckley et al.[30] observed sub optimal stent deployment in 40% of the 49 stented limbs with IVUS. Their iliac stent patency rate was improved at 6 years (100% *v.* 69%, p <0.001) when using IVUS to monitor the adequacy of stent expansion.

Iliac occlusions: Recanalization of a totally occluded iliac artery can be a technically demanding procedure. Several approaches may be used, including the retrograde, the crossover and the brachial access. The ipsilateral retrograde approach is frequently used, but with the disadvantage of a more difficult puncture distal to the occluded segment, as well as difficulties to navigate the guidewire intraluminally through the occlusion, which may result in extensive dissection of the vessel wall extending in the region of the aortic bifurcation.

The crossover technique is the preferred primary access for recanalization of total occlusions. A primary stenting is recommended to treat an iliac occlusion and reduce the risks of distal embolization. In patients with acute thrombosis, thrombolysis, and mechanical devices may be used. In patients with chronic occlusions, thrombolysis may also be proposed before angioplasty and stenting but if the occlusion is older than 3 months, a mechanical recanalization followed by a primary stenting could be the technique of choice.

In a recently published series, a high technical success rate and good long-term follow-up have been obtained. Vorwerk et al.[31] reported on a series of 103 chronic iliac occlusions with a technical success rate of 98%, a primary and secondary patency rates of 78% and 88% at 4 years. Uher et al.[32] reported on a series of 73 chronic iliac occlusions with a technical success rate of 97% and a 3-year primary and secondary patencies of 69% and 81%, respectively. In a series of 212 patients, Scheinert et al.[33] obtained a technical success of 89.6% with a primary patency rate of 81.2% at 2 years and 75.7% at 4 years. We have published a series of 173 lesions[34] with a technical success rate of 90% and an 8-year follow-up. These results are reported in Table 2 (all lesions, on an intention-to-treat basis including initial technical failures) and in Table 3 (results for recanalized patients).

With a good technique, it is possible to recanalize the majority of total iliac occlusions and even long lesions (TASC Type C and D lesions). Angioplasty and stenting of these lesions is a safe and durable alternative to surgical therapy. Subintimal angioplasty has been proposed in case of failure of intraluminal recanalization,[35-37] but this technique could be risky at aortic bifurcation and does not seem to give better results.

Table 2. Eight-year follow-up: all lesions (*n*=173)

	No. of lesions	PI (%)	PII (%)
All lesions	173	66	77
CIA	106	66 (NS)	80 (NS)
EIA	67	67 (NS)	72 (NS)
<3 months	89	68 (NS)	86 (p<0.01)
≥3 months	84	63 (NS)	67 (p<0.01)
Length < 6 cm	52	78 (p<0.01)	90 (p<0.01)
Length ≥ 6 cm	121	61 (p<0.01)	71 (p<0.01)
Diameter < 8mm	80	67 (NS)	76 (NS)
Diameter ≥ 8 mm	93	65 (NS)	78 (NS)
Calcified	36	50 (p<0.01)	53 (p<0.008)
Non-calcified	137	70 (p<0.01)	53 (p<0.008)
Good run off	98	71 (NS)	80 (NS)
Poor run off	75	58 (NS)	7 (NS)

PI: primary patency; PII: secondary patency; CIA: common iliac artery; EIA: external iliac artery; NS: non-significant

Table 3. Eight-year follow-up: recanalized patients (*n*=155)

	Number of lesions	PI (%)	PII (%)
All lesions	155	73	86
CIA	95	74 (NS)	90, p<0.05
EIA	60	75 (NS)	80, p<0.05
< 3 months	88	69 (NS)	87 (NS)
≥ 3 months	67	79 (NS)	84 (NS)
Length < 6 cm	51	80 (NS)	92 (NS)
Length ≥ 6 cm	104	71 (NS)	83 (NS)
Diameter < 8mm	75	71 (NS)	81 (NS)
Diameter ≥ 8 mm	80	76(NS)	90 (NS)
Calcified	23	78 (NS)	82 (NS)
Non-calcified	132	72 (NS)	86 (NS)
Good run off	89	79 (p<0.04.)	88 (NS)
Poor run off	66	66 (p<0.04.)	83 (NS)

PI: primary patency; PII: secondary patency; CIA: common iliac artery; EIA: external iliac artery; NS: non-significant

Reconstruction of the aorto-iliac bifurcation: Over the years, lesions of the abdominal aorta and of the aortoiliac bifurcation were mainly surgically treated, with good long-term results. There is only limited experience with PTA for the treatment of these lesions, involving the aortic bifurcation. The potential of contra-lateral embolism or contralateral iliac artery occlusion due to dislodgment of atherosclerotic or thrombotic material during unilateral PTA has prevented the common use of interventional techniques in this vessel segment. To avoid such complications, we recommend the kissing balloon and the kissing stent technique for bilateral simultaneous angioplasty and stent implantation into the common iliac arteries and the distal abdominal aorta. Good immediate technical success and long-term outcomes may be obtained. Scheinert et al.[38] reported a series of 48 patients with a technical success in all patients and a primary patency rate of 86.8% at 2 years. In a study by Haulon et al.[39] Three-year primary and secondary patency rates were 78% and 98%, respectively. In our series of 72 patients (162 lesions), we obtained a technical success in 70 (97%) patients, a 5-year primary patency rate of 74% and a secondary patency rate of 90.8%.[40]

PTA and stenting can also be proposed as the first treatment for these aorto-iliac bifurcation lesions and it is the same for stenotic lesions involving only the abdominal aorta. Theoretically, there is a greater risk of vessel wall rupture. The fear of aortic rupture may be exaggerated but it has been shown that underdilation of these lesions still produces sufficient flow to relieve symptoms of the patients. Calcified lesions must be dilated with extreme caution and overdilation has to be avoided. Long-term outcomes are encouraging and comparable to those of surgery.[40]

Covered stents: These devices, composed of either stainless steel or nitinol stents covered with Dacron or polytetra fluoroethylene (PTFE), have the theoretical advantage of excluding the diseased segment from the circulation. In the iliac segment, stent grafts may be used to treat occlusive diseases but they are predominantly used to treat aneurysmal disease or rare cases of rupture, perforation or fistula.

Several studies were published with differently covered stents. Lammer et al.[41] reported the results of an international study using the Hemobahn (Gore and Associates, Flagstaff, AZ) for occlusive diseases in 61 iliac arteries. The primary and secondary patency rates at 12 months were 91% and 95%, respectively. Rzucidlo et al.[42] used the Wallgraft (Boston Scientific, Natik, MA) or Viabahn (Gore and Associates, Flagstaff, AZ) in 34 patients (85% had TASC C or D lesions, mean lesion length 13.7±8 cm). The primary patency rate was 70% at 12 months and the primary assisted patency was 88%.

The Aspire stent (Vascular Architects Inc., San Jose, CA) is a flexible spiral-shaped nitinol stent with only the spiral struts covered with PTFE. It has a unique design that may minimize the potential for intimal hyperplasia. Early results showed a promising efficacy in the treatment of complex, long stenoses and occlusions in iliac arteries.[43]

We found very good long-term results with covered stents.[44,45] We treated 64 patients with Cragg Endopro/ Passager stent (Boston Scientific, Natik, MA). The 5-year primary patency rate was 88% and the secondary patency rate 100%. We treated 38 patients with the Corvita stent (Boston Scientific, MA), and obtained a 3-year primary patency rate of 87% and a secondary patency of 95%.

The majority of patients with iliac aneurysms are asymptomatic, but some of them may present with symptoms, due to local compression of adjacent pelvic structures, thrombosis, embolism or rupture. Overall, the prognosis of patients with untreated iliac artery aneurysm is poor. Endoluminal treatment of these aneurysms with

covered stents offers a good option and an alternative to surgery. Long-term patency is encouraging as reported in various studies.[45,46]

Superficial Femoral Artery and Popliteal Artery Diseases

The superficial femoral artery (SFA) is the most commonly diseased vasculature. More than 50% of all PAD cases involve the SFA and popliteal arteries. These vessels are long vessels, and femoropopliteal disease is often characterized by long, diffuse lesions, long occlusions (as opposed to mild focal stenoses) with relatively low flow and high resistance outflow, relatively small target vessels and exposure to mechanical stress due to joint flexions.

SFA and popliteal arteries are unique in that they move dramatically in multiple planes during limb motion. These arteries not only compress, bend and rotate, but they also shorten and extend in response to movement.[47] All these factors are known to negatively impact the long-term outcome of any endovascular procedure. Femoropopliteal occlusive diseases remain the Achilles heel of the vascular specialist.

The TASC document[6] divided the femoropopliteal lesions into 4 categories (Table 4). TASC A lesions are more suitable for endovascular procedures, whereas surgery is recommended for TASC D lesions. The TASC document clearly states that more evidence is needed to make firm recommendations about the role of balloon PTA for TASC B and C lesions. TASC recommendation states that femoropopliteal stenting as a primary approach to the interventional treatment of intermittent claudication or chronic limb ischemia is not indicated. Stents may, however, have a limited role in salvaging acute PTA failures or complications. In fact, this recommendation is based on earlier experience of PTA/stenting using balloon expandable stainless steel stents or Wallstent stents. Today, a large number of new technologies, new stents with new material, new design are being evaluated to treat femoropopliteal diseases.

Table 4. TASC recommendations for femoropopliteal lesions

Classification	Characteristics	Recommendation
TASC A	Single restenosis < 3 cm	Endovascular treatment
TASC B	Single stenosis 3-10 cm (not involving popliteal artery) or Multiple stenosis, each <3 cm; or Single or multiple lesions without continuous runoff	Endovascular treatment is more frequent, but more evidence needed to make a recommendation
TASC C	Single stenosis or occlusion >5 cm Multiple stenosis or occlusions each 35 cm	Surgical treatment is more frequent, but more evidence needed to make a recommendation
TASC D	Complete CFA or SFA occlusion; or Popliteal & trifurcation occlusion	Surgery

CFA: common femoral artery; 5FA: superficial femoral artery

Vascular access is a point of consideration. Antegrade access offers improved wire control but post-procedure hemostasis appears to be more problematic. It is also more difficult in an obese patient with an increased risk of puncture site complications and retroperitoneal hemorrhage. Contralateral vascular access is often the preferred technique for safest hemostasis but requires braided non-kinking vascular sheaths. The popliteal access is useful for total occlusions that cannot be accessed from above and must be well known. The brachial access is rarely used.

With a good technique (approach, guiding catheters, wires, etc.) we can expect to cross about all stenoses and at least 90% of occlusions, even long occlusions. In case of failure to cross an occlusion with a single glidewire, we can utilize one of the recently available devices designed to cross total occlusions such as: (i) Frontrunner CTO Catheter (Lu Med Inc., Redwood City, CA) (ii) Safe-cross Radiofrequency Total Occlusion System (Intraluminal Therapeutics, Carlsbad, CA) (iii) Cross Point (Medtronic, Santa Rosa, CA)

However there is cost consideration associated with these more sophisticated crossing techniques.

Balloon PTA remains the simplest technique and may be the first treatment to be proposed for some lesions, but its technical success and durability strongly correlate with lesion morphology.[14,48-50] In general, the results obtained after treating longer stenoses and/or occlusions have not been encouraging. A 5-year cumulative patency rate of 75% can be expected for short focal stenoses, but the one-year cumulative patency rate for occlusions > 3 cm is significantly lower.[50] Similarly, reported 6-month cumulative patency rates have been 86.8% for stenoses <7 cm and 23.1% for those >7 cm.[49]

Balloon PTA of lesions <5 cm is generally more durable than PTA of lesions >10 cm.[48] The STAR registry[51] published in 2001 (219 limbs, 205 treated patients) showed that PTA alone could still be proposed. The technical success rate was 95% with a primary patency rate of 87% at 1 year, 80% at 2 years, 69% at 3 years, 55% at 4 and 5 years, which is encouraging. If we analyze the lesions according to the TASC categories, 36 months patency rate was 87% for category A, 69% for category B and 67% for category C, which demonstrated that category C lesions may be treated with PTA results similar to those in category B.

Factors for long-term patency have been well described: (i) Presence of diabetes and renal failure (ii) lesion length (iii) Stenosis *versus* occlusion (iv) Percentage stenosis pre-

and post-PTA, calcification, eccentricity, post-PTA dissection (v) ≥3 *versus* 1 or 2 sites (74% *v.* 87% patency, p=0.04), (vi) tibial run off: poor run off : patency 40.6%, p<0.001; good run off : patency 92%, p<0.001.

Can we improve long-term results with stents ? Recently, Schillinger[52] reported the randomized ABSOLUTE study with 104 patients. Mean lesion length was 8 cm. The 6 months patency rate after PTA and selective stenting was 55% and after primary stenting 75% (p = 0.044). Primary stenting seems to improve the results.

Stents' designs have changed over the years. In the early Wallstent data, SFA reocclusion rates were up to 70% at 3-years.[53-55] Balloon-expandable stents like Palmaz stents, and Strecker stents were also implanted at femoro-popliteal level and several series were published showing acceptable results but only for short lesions.[16, 55-61]

Three randomized studies[62-64] comparing PTA alone and PTA and stenting with balloon-expandable stents reported no significant patency rate improvement, a high restenosis rate and the possibility of stent compression. These studies do not support balloon-expandable femoro-popliteal stenting as a primary approach. These stents may have a limited role in salvage of acute PTA failure or complications and should be abandoned at femoro-popliteal location.

A promising new option on the horizon is modern nitinol mesh stents. They offer numerous advantages: improved deliverability precision, minimal foreshortening, 5F/6F sheath compatibility, longer lengths and radiopaque makers for enhanced visibility on fluoroscopy.

Several studies have demonstrated the significant improvement of the new generation of nitinol stents for the SFA:

- The German Multicenter experience, a retrospective review of 111 SFA compared Smart stents (Cordis Corporation, Miami, FL) used in 76 procedures with Wallstents used in 35 procedures. The 6 months patency rate for Smart stents was 82% *versus* 37% for the Wallstent.[65]
- Hayerizadeh[66] compared 163 Smart stents (lesion length: 178±110 mm) with 166 Wallstents (lesion length: 197±101 mm). The 1-year patency rate was 61±5% with Smart stents *versus* 30±5% with Wallstent (p < 0.0001).
- Sabeti et al.[67] did a retrospective study in 175 patients comparing nitinol stents and stainless steel stents. The 2-year patency rate was 69% with nitinol stents and 34% with stainless steel stents (p = 0.008).
- More recently, Sabeti et al.[68] reported a study of 65 patients with a lesion length ≥ 20 cm and found encouraging mid-term results in non-diabetic patients. The 1-year patency rate was 7% in non-diabetic and 22% in diabetic patients (p < 0.01).
- Mewissen[69] implanted 246 stents in 137 limbs (12 TASC Type A lesions, 125 TASC B and C lesions). Mean lesion length was 12.6 cm. The technical success rate was 98%. The patency rate was 92% at 6 months, 76% at 12 months, 66% at 18 months, 60% at 24 months.
- We have recently published a series[20] with the Optimed stent (Optimed, Ettlingen, Germany); 204 lesions were treated at femoral level, 27 at popliteal level. The 3-year patency rate was 62.1% for femoral lesions, 66.1% for popliteal lesions with better results when we treated stenoses rather than occlusions (69.9% *v*. 49%, p < 0.004).

In the category of nitinol stents, the Intracoil (EV3, Plymouth, MN) has a coil-shaped design and is the only stent presently approved by the Food and Drug Administration (FDA) for treating the SFA. Its design allows implantation at joint location. Its applications has shown good short and long-term results.[70-73]

Recently, hopes that a drug-eluting stent (DES) might prove a useful solution to long-term restenosis in the SFA was dashed by the SIROCCO I and II trials.[74,75] These trials did not show any difference between the DES and the bare nitinol Smart stents. It is hoped that further refinement in drug dosing and elution formula will show the benefits of DES in this vascular bed.

A concern with nitinol is the problem of stent fractures, recently pointed out in the SIROCCO study[74,75] and by Scheinert et al.[76] The authors studied 93 patients (121 legs) treated with nitinol stents and stent fractures were found in 37.2% of the cases with complete separation in 25%. The 1-year patency rate was 84.3% without stent fracture and 41.1% with stent fracture.

So, while stenting remains the preferred interventional therapy for many cases, it does not appear as the ideal solution to treat femoro-popliteal lesions. There are many emerging technologies for the treatment of special cases that are revolutionizing the way we approach treatment of the SFA.

- Plaque removal with the Silverhawk plaque excision technique (Fox Hollow Technologies, Redwood City, CA) was recently proposed for vessels over a wide range of diameters (2-7 mm). Long, diffuse, even calcified lesions can be treated. Acute and 6 months data from TACON study[77] demonstrate promising results. 90% of the patients remained free of target lesion revascularization (TLR) at 6 months. Ramaiah[78] treated 104 patients with this device. 77%

of the lesions were type B, C, D as per TASC classification. The 1-year patency rate was 86%. Long-term follow-up is awaited.

- A new thrombectomy and atherectomy device has been recently proposed.[79,80] The ROTAREX (Straub Medical, Wango, Switzerland) system can be applied for thrombotic occlusions both in acute and chronic phases and for long restenosis with promising results.
- The cryotherapy is an angioplasty system that simultaneously dilates and cools the plaques and vessel wall. Laird[81] published a multicenter registry with 102 patients and lesions < 10 cm. The technical success was 96% (13% of the lesions were stented). The 9-month patency rate was 85%. We do not know the long-term results.
- The cutting balloon may be a good alternative to treat femoro-popliteal lesions and avoid stenting. Calcified lesions, and lesions at bifurcation can be treated with this device. Ansel et al.[82] found that at 1 year, results compare favorably with surgery.
- Excimer Laser Angioplasty can be used to treat long femoral lesions and long occlusions. A multicenter randomized study (PELA study)[83] compared excimer laser-assisted PTA with PTA alone for long SFA occlusions ≥10 cm. The procedural success was 85% for laser, and 9% for PTA. The complications rate was 12.8% with laser and, 11.4% with angioplasty and the 1-year patency rate was 49% with laser and angioplasty. The available data do not indicate a significant long-term benefit compared to conventional angioplasty. Laser angioplasty does not seem to have a significant role in the treatment of femoro-popliteal diseases.
- Brachytherapy has been proposed by few centers. Based on the promising results of the pilot Vienna 1 study, the role of femoropopliteal brachytherapy for the treatment of *de novo* lesions and recurrent lesions after PTA was established with the Vienna 2 trial.[84] However, this technique is difficult to be used routinely in many hospitals.
- The subintimal angioplasty remains controversial. It is an inexpensive method which seems to give good long-term results for long lesions and for patients with critical limb ischemia. Bell[85] reported more than 1000 procedures with a technical success rate of 86%, a 6-year patency of 55% and a 3-year limb salvage of 85-90% which competes with surgery.

All these techniques notwithstanding, the treatment of the SFA lesions is still controversial although, the use of SFA angioplasty with or without stenting is expanding with an increasingly aggressive management strategy for all TASC lesions. It is widely accepted that TASC A and B lesions can be treated endoluminally. The new techniques may allow us to extend endovascular procedures to TASC C lesions. But the role of endovascular therapy for TASC D lesions remains debated, and many advocate that these patients should be considered for surgical intervention. Surgical bypass remains the gold standard for these more advanced SFA diseases, though surgery is not perfect. If the distal anastamosis involves the above the knee popliteal artery, and autogenous vein grafts are used, patency rates are good, and based on one study involving 3005 limbs, the 5-year primary patency rate is 70% and the secondary patency rate 81%. The patency rate is lower if prosthetic grafts are used and if we treat patients for limb salvage. Complications are not infrequent, wound infections 1.6 to 3.4%, early graft failures 0 to 24%, acute leg ischemia 1 to 2%, surgical reversion rate > 20% and operative mortality 1.3 to 6%.[86]

So, as recently suggested, if the 5-year patency rate of endoluminal interventions exceeds 30%, endoluminal intervention should be the preferred initial invasive strategy. [87,88]

New techniques should lead to higher success rates, and should be now in competition with surgical bypass. Two recent techniques are:

- The remote endarterectomy,[89] which is an hybrid of minimally invasive surgical and endovascular techniques that offers a safe and effective option for treatment of long segment SFA diseases with a single small incision in the groin. Extensive debulking can be performed with specifically designed surgical instrumentation combined with standard endovascular equipment. Recent clinical study has involved performing this technique in combination with placement of a distal Aspire-covered stent (Vascular Architects Inc., San Jose, CA). A primary patency of 70% at 30 months was recently published.[90] For Rosenthal et al.,[91] with the Aspire stent, the primary patency rate was 68.6±13.5% at 18 months, and the primary-assisted patency 88.5±8.5% at 15 months.
- Endografts could be one of the solutions to treat long SFA diseases (TASC D lesions). These endografts can be implanted by percutaneous approach[44,45,90] but results have been far better with second generation devices[92-95] and we believe they currently have a major role to play in the treatment of longer SFA lesions and that they should be competitive with surgical bypass. Saxon et al.[96] reported a 79%

primary patency rate and 93% secondary patency rate at 4 years follow-up for lesions of an average length > 10 cm, using Hemobahn or Viabahn stent grafts (Gore and Associates, Inc., Flagstaff, AZ). Furthermore, these endografts allow the treatment of femoro-popliteal aneurysms.[44,45]

Tibioperoneal Arterial Diseases

Tibioperoneal disease generally presents as a critical limb ischemia (CLI). However, in roughly 25% to 30% of the cases infrapopliteal disease presents as claudication, particularly in concert with SFA and popliteal lesions.

The accepted indications for below-knee endovascular intervention are primarily confined to patients with limb ischemia and for limb salvage; it is rarely done for disabling claudication. An attempt should ideally be made to restore in-line flow to the foot.

Only 1.4% of patients with PAD develop ischemic rest pain or tissue loss, though it is more frequent in diabetics and smokers. Acute ischemia is caused either by embolus or thrombosis. When pain, pallor, polar (cold) are accompanied by paresthesias and paralysis, urgent revascularization, usually surgical embolectomy is required. Percutaneous techniques assume a greater relevance when encountering the more frequent subacute or chronic manifestations of ischemic rest pain, trophic skin changes, tissue loss or simple claudication. As techniques have evolved and success has become more assured, only patients with severe claudication are now being treated. An additional important indication for below-knee angioplasty is to improve run-off and subsequent long-term patency after femoro-popliteal angioplasty/stenting or bypass grafting.[97] Several techniques can be proposed to treat these peroneal arterial diseases.

Balloon angioplasty: Balloon angioplasty remains the easiest and the most often used technique to treat infrapopliteal arteries and the methods learnt from coronary interventions are directly translatable to below the knee interventions and range from simple balloon angioplasty to kissing balloons, to total occlusions. We used small balloons (1.5 to 5 mm in diameter, and lengths up to 10 cm need to be available) and fine 0.014" or 0.018" wires. Initial technical success rate is satisfactory, particularly in patients with non-calcified arteries. Unfortunately, the tibioperoneal vessels are frequently calcified which may not allow PTA to stretch the vessel walls easily. Some lesions seem to be favorable anatomical indications: (i) The ideal lesion should be short, focal stenoses, little, or not calcified (ii) Lesions <5 cm in length in any single vessel (iii) Occlusions <5 cm (iv) Fewer than 4 to 5 lesions in any single vessel.

Table 5[98-108] summarizes different series reported in the literature with PTA showing that technical success, and limb salvage rates are high. A technical success of 95-100% for stenosis, 60 to 90% for occlusions can be expected. Despite a high restenosis rate of 30 to 50%, a 2 years limb salvage rate of 80-90% with “straight line flow” to the foot in at least one vessel may be expected. Nevertheless, when the distal outflow remains obstructed, the limb salvage rate is very low (0 to 5 %).[100,107,108]

Dorros et al.[109] reported his experience in treating 284 patients (529 lesions). The technical success rate for tibioperoneal angioplasty was 95%. Dilation of 333 ipsilateral inflow obstructions was required to access and successfully dilate 485 (92%) lesions; 215 patients were clinically followed for 5 years. Bypass surgery was performed in 8% of them and significant amputation in 9% of limbs. The limb salvage rate was 91%. The overall probability of survival was 56 to 58% for Fontaine’s class

Table 5. Infrapoliteal occlusive diseases: PTA results

Authors	Years	Limbs	CLI (%)	Diabetes (%)	Technical success (%)	Limb salvage/ follow-up period
Schwarten et al.[98]	1988	114	100	60	97.0	86/24 months
Bakal et al.[99]	1990	57	98	85	78.0	67/24 months
Matsi et al.[100]	1993	84	100	74	88.0	75/24 months
Motarjeme[101]	1994	361	100	66	92.5	73/36 months
Varty. et al.[102]	1995	40	50	45	98.0	77/12 months
Wagner et al.[103]	1997	158	68	46	95.0	88/17 months
Hanna et al.[104]	1997	29	100	100	90.0	79/12 months
Nydahl et al.[105]	1998	28	100	33	84.0	85/12 months
Vraux et al.[106]	2000	40	100	72	78.0	81/12 months
Soder et al.[107]	2000	72	100	76	78.0	80/21 months
Boyer et al.[108]	2000	49	100	82	92.0	87/36 months

PTA: percutaneous transluminal angioplasty; CLI: critical limb ischemia

III patients and 33% for class IV patients. Compared with class IV patients, those in class III had significantly fewer surgical bypasses and amputations. The authors concluded that tibioperoneal angioplasty, often combined with inflow interventions, is effective in the primary treatment of CLI. The low cumulative survival rate is an indication of severe comorbidities, which may be ameliorated by aggressive cardiovascular diagnostic and treatment options.

Stenting: At present, we lack evidence-based guidelines related to the indications for the stenting of tibioperoneal arteries. Furthermore, there are no dedicated stents for these arteries. In cases in which stenting is necessary, coronary balloons pre-mounted stents or peripheral self-expandable stents are used.

Stenting is currently considered only in cases of major or flow limiting dissection that cannot be controlled by prolonged balloon inflation. Primary stenting is limited to more diffuse restenoses or to heavily calcified lesions, showing a tendency to recoil. In the majority of the cases, we use coronary stents with a diameter of 2.5 to 4 mm. The concern about the applicability of coronary stents in leg arteries with regard to the potential crush of the stent by the surrounding tissues could not be confirmed by the clinical experience. Self-expanding stents may be implanted in more proximal vessel segments including the tibioperoneal trunk.

Biamino[110] reported his experience of 365 lesions treated in 282 patients who had Rutherford class 3 to 4 claudication. The global primary success rate was 93%. The 1-year primary patency was 65.2%, the primary-assisted 81.2% and the secondary patency rate 91.3%. A stent was used for 42 (12%) lesions with a 1-year primary patency rate of 69%. However, the clinical patency rate connected to a relevant improvement of the clinical status was 93%. The related limb salvage rate was 95%. In another analysis of 51 patients treated with the Flexmaster stent (Abbott Laboratories, Abbott Park, IL) the primary patency rate was only 44.2% after a mean follow-up of 10.7 months. So the restenosis rate appears high after stenting of tibioperoneal arteries with coronary stents.

Drug-eluting stents were recently proposed to treat infrapopliteal arteries. The first studies were disappointing. Scheinert[111] reported no difference in the 6 months angiographic restenosis rate for tacrolimus-coated *versus* bare metal stents (60.9% *v.* 56.5%).

Biodegradable stents were also recently proposed. Peeters et al.[112] reported a series of 20 patients with Rutherford category 4 or 5 CLI. The primary patency was 78.9% at 6 months, 72.4% at 1 year, the secondary patency 78.9% at 1 year, with a limb salvage rate of 94.7%.

Cutting balloon: This technique can be used for recalcitrant lesions such as calcified or ostial plaques and instent restenosis.[113] These lesions are commonly seen in diabetics.

Atherectomy devices: Rotational atherectomy can be used for calcified lesions as in coronary angioplasties. A high technical success rate may be obtained, but the high restenosis rate in long lesions limits the indications to very short lesions.[114,115]

As in SFA the Silverhawk atherectomy device may be used, allowing the removal of large portions of plaque through continuous shaving. Mid and long-term follow-up data are missing.

Initial enthusiasm for laser angioplasty has been tempered by disappointing long-term patency rates. Under the recent LACI trial,[116] 145 patients (155 limbs) with CLI Rutherford category 4 to 6 were treated. The procedural success was 85%, a straight line foot established in 89 % of the cases. The 6-month survival with limb salvage was 93%.

Subintimal angioplasty: This technique, pioneered in the United Kingdom, permits the treatment of longer lesions or hard long-term occlusions. Lesions as long as 30 cm can be successfully recanalized. The technical success rate for total occlusions > 5 cm is over 80%. The 12-month patency rates are in order of 50% with a 1-year limb salvage rate of 85%.[107] Vraux et al.[106] reported a 78% technical success rate in 40 patients with CLI with a limb salvage rate of 81%.

All these techniques can be combined allowing better technical success rates and maybe better long-term results. Complications can occur in 2-6% of the cases. Some are specific to the chosen technique, but most commonly, these complications occur at the access site. Spasm and thrombosis are the most likely complications. As in coronary procedures, intra-arterial nitroglycerin (NTG) and calcium antagonists are effective. All patients need to be anticoagulated. An alternative anticoagulant, the bivalirudine (Angiomax, The Medicines Company) has recently been proposed. Glycoprotein (Gp) IIb/IIIa inhibitors and thrombolytics may be used in case of thrombosis. Vessel perforation, distal embolism may also occur during the procedure and must be recognized and quickly treated.

One of the main concerns linked to these techniques is the high restenosis rate. As for surgical practice,[117,118] post-intervention surveillance and subsequent reintervention can prolong long-term patency.[102] Repeat PTA performed to enhance secondary patency is probably underutilized,

yet relatively inexpensive and non-invasive compared to surgery. The goal of interventions in patients with CLI is in fact not long-term patency, but rather the avoidance of a major amputation. Recurrent CLI is unlikely to redevelop in vessels that restenose. If they result in a clinical failure, endovascular techniques almost never preclude surgery and if successful, spare precious vein for later surgical use, if necessary.[97] The results of these techniques have to be compared to the gold standard of surgical distal bypass grafting. One can expect primary and secondary one-year patency rates of saphenous vein grafts of 70-75%, declining to around 50% at 3 years, with substantially inferior results when using PTFE grafts. The limb salvage rate exceeds the primary patency rate by >10% in almost all series. These operations are technically demanding and associated with a peri-operative mortality rate of 1.8-6%.[119,120] In a retrospective analysis Nasr et al.[121] did not find any disadvantage on treating CLI patients with angioplasty compared to surgery.

Endovascular procedures are becoming the first treatment to be proposed to treat tibioperoneal arteries and CLI.

Acute Limb Ischemia

Acute limb ischemia is a medical emergency that causes a threat to extreme mobility and necessitates a prompt diagnosis and rapid initiation of therapy, as acute ischemia is not only limb threatening, but also a potentially life-threatening event.

The incidence of acute limb ischemia is increasing due to aging of the population. Acute occlusion may be due to thrombus formation in a native artery or a bypass graft, or to embolization of material from a distant site (cardiac arrhythmia, cardiomyopathy, aneurysm). Iatrogenic causes such as thrombus from a sheath or debris embolization during endovascular procedures are becoming more frequent. The severity of symptoms depends primarily on the location of the occlusion and the status of the collateral vascular supply. Patients with pre-existing non-occlusive arterial diseases have often developed collateral vessels and therefore may present with less acute ischemic symptoms. Embolization into an arterial bed without previous collateral development may produce severe ischemia.

Several treatments may be proposed for acute limb ischemia. For years, surgery has been the gold standard, offering various possibilities such as embolectomy, bypass, amputations etc.

Amputation should be limited to limbs with prolonged ischemia, irreversible major tissue loss.

Embolectomy may be performed for limbs with acute profound ischemia with immediate limb threat, specially secondary to embolization, with motor function and neurosensory changes.

This surgery is high-risk. In-hospital mortality following surgery had been found to exceed 20% in some series.[122,123] Furthermore, Fogarty thromboembolectomy has several limitations: residual thrombus is frequently left, branch vessel occlusions are not cleared, the balloon causes endothelial injury that may be thrombogenic. These limitations and the high mortality rates have prompted the investigation and subsequent widespread use of endovascular procedures (local thrombolysis, mechanical devices, thromboaspiration) as an alternative form of therapy for patients presenting with acute limb ischemia and at least for patients without immediate threatening of the limb.

Thromboaspiration: It is the easiest method to reopen an occluded artery using a single lumen straight 6F to 8F catheter and a syringe (20-50 cc) to create a vacuum and aspirate clots or any embolic material. This technique can be the first intention method; it is at low cost, without limits in all sites. It appears a very safe and effective procedure.

We published[124] a series of 85 procedures (74 for native arteries, 11 bypass grafts) with a technical success of 92%; 52 underlying stenoses were treated. This technique was completed by fibrinolysis in 19 cases and mechanical devices in 4 cases.

Starck[125] reported a series of 158 procedure with a limb salvage rate of 93.7%, a 30-day mortality rate of 3.2%, a 5-year patency rate of 80% with coumadin, 40% without coumadin.

Thrombolysis: Randomized studies[126-128] have shown that thrombolysis is generally as efficacious as surgery. Thrombolysis has become the treatment modality of choice in appropriately selected patients that present with acute limb ischemia.

Thrombolytic therapy is used when patient's clinical conditions allow for delay in restoration of blood flow. The rationale for this approach includes the advantages of slowly restoring flow, identifying the underlying arterial lesion which has to be treated in most of the cases, restoring collateral circulation and avoiding trauma to the vessel endothelium. Using thrombolytic therapy and avoiding emergency surgery appears to be associated with a lower mortality rate for patients with acute limb ischemia. Nevertheless, for patients presenting with more chronic limb ischemia, surgery appears to offer superior limb salvage.[125-128] Furthermore, thrombolytic therapy may not

provide rapid enough restoration of flow to be used as a sole modality when significant neurovascular symptoms are present.

Different thrombolytic agents may be used: (i) Urokinase[129] with variable dose: 60,000 to 240,000 units infused per hour until antegrade flow is achieved, (ii) Rt-PA[130]: 0.5-2 mg/hour, (iii) R PA[131]: 0.25 U/hour, (iv) TNK: a third generation of thrombolytic drug was recently proposed[132]: 10 to 20 mg.

To date, there have been little data comparing the various lytic agents in the same patients population. Mahler et al.[133] reported a trial comparing urokinase to Rt-PA. In this study, bleeding complications were nearly equal (12.8% Rt-PA *v.* 9.1% urokinase). Because of a relative paucity of data, decisions to use one thrombolytic drug over another are based more on a personal experience.

Thrombolytic agents are infused through a catheter placed close to the occlusions or inside the thrombus. Several techniques may be used: (i) Continuous infusion; this is the most common method. This may or may not be proceeded by intrathrombus lacing, (ii) Stepwise infusion consisting of stepwise advancement of the tips of the infusion catheter as the thrombus dissolves, (iii) Pulse spray technique[132] which refers to the technique of forcibly injecting thrombolytic agent into the thrombus to fragment it so as to increase the surface area available for the action of plasminogen activators and to accelerate lysis. Technical success may be obtained in 70 to 90% of the cases with a limb salvage rate of 80-90%.

In our earlier series of 113 procedures to treat native arteries (n=74) or bypass grafts (n=39), the average duration of fibrinolysis (urokinase) was 18 hours. A complete lysis was obtained in 81% of the cases. A significant underlying lesion was treated in 70 cases.[124]

A new technique of isolated thrombolysis was recently proposed. The Trellis device (Bacchus Vascular, Santa Clara, CA) is a pharmacomechanical percutaneous infusion system that can isolate and treat a clot with any standard thrombolytic in a single setting. A unique dual balloon system maintains the concentration of the infused liquid while its mechanical dispersion wire effectively disperses the fluid throughout the treatment area. This system allows the physician to aspirate the treatment area and the risk of downstream emboli is reduced.

Mechanical thrombectomy devices: Mechanical devices for continuous active aspiration have already been developed. The most extensively studied device is the Rheolytic thrombectomy catheter (Angiojet, Possis, Inc, Minneapolis, MN). This device includes a drive unit console, pulsatile jets, and various specifically tailored catheters. The device uses a complex mixture of rapid fluid streaming and hydrodynamic forces to fracture thrombus, allowing extraction at the distal catheter tip using a negative pressure (Venturi effect).

Several studies have shown procedural success with low amputation and mortality rates.[134-137] These studies illustrate the need for adjunctive treatment with low dose thrombolysis in 18% to 58% of patients; however, with recent improvements in the device, there is a decrease in the need for post-procedure thrombolysis. The major limitation common to all of the mechanical thrombectomy devices is a lack of effect on the non-organized thrombi which could be too firm for complete removal. Downstream embolization may also complicate the procedure.

Ansel et al.[138] reported a multicenter registry of 99 patients with a 30-day limb salvage rate of 96% and a mortality rate of only 7.1%. This technique seems promising to remove quickly fresh thrombi and reopen an occluded artery, to reduce the amount of thrombolytic and reduce its hemorrhagic complication rate. Other devices used were: (i) The Hydrolyzer catheter (Cordis Corporation, Miami, FL). In a series of 50 patients, we had a technical success rate of 82% and at 30 days; 74% of the vessels remained patent.[139] (ii) The Rotarex catheter, as previously described.[79,80]

Thoracic and Abdominal Aortic Aneurysms and Dissections

Abdominal aortic aneurysms: Although abdominal aortic aneurysms (AAAs) were first described during the 16th century by the anatomist Vesalius, durable and successful repair of AAAs was not achieved until 1951 when resection and graft replacement was first performed. AAAs most commonly represent a degenerative process in elderly white males probably secondary to atherosclerosis. There appears to be also a correlation between both hypertension and smoking and the development of AAAs. Recent studies have documented a strong genetic component to this disease, while several biochemical abnormalities have been reported in patients with aortic aneurysms, including increased proteolysis (elastolysis and collagenolysis).[140]

The goal of elective AAA repair is to prevent rupture and thus prolong life. Consequently, it should be performed when the rupture risk is higher compared to operative risk, and in patients expected to live long enough to enjoy the long-term benefit. Aneurysm rupture risk, elective

operative mortality risk, life expectancy and patient preference are the main factors that affect the decision for AAA elective surgical or endovascular repair.

The diameter of AAA is considered to be the best predictor of rupture risk and based on the best available current data, AAAs with diameter ≥5.5 cm should be electively repaired. Other factors that increase rupture risk include high annual sac expansion rate, smoking/chronic obstructive pulmonary disease, family history, hypertension, eccentric sac shape and female gender.[141,142]

The current standard surgical procedure, endoaneurysmography with intraluminal graft placement was introduced by Creech,[143] DeBakey, and their colleagues almost half a century ago. Reported mortality from elective surgery varies between 4% and 8%.[144] It is influenced by several factors such as patient's age and gender, cardiac, renal, or pulmonary comorbidities and anatomic or pathologic features of the AAA.[145] Early post-operative complications of this approach include cardiac ischemic events, hemorrhage, hemodynamic complications, iatrogenic injuries, renal failure, gastrointestinal complications, distal embolization, paraplegia, and impaired sexual function. Late complications after successful AAA surgical repair including anastomotic pseudoaneurysm formation, graft infection, secondary aortoenteric fistula, graft thrombosis etc. are uncommon and only 7% of treated patients experience such complications within 5 years after surgery.[146] The five- and ten-year survival rates after successful AAA surgical repair are approximately 70% and 40%, respectively.[147]

Endovascular aneurysm repair (EVAR) has been used as an alternative approach for infrarenal AAAs since the early 1990s, and has already gained an important role in current clinical management of patients with AAAs. Suitable anatomy concerning the aneurysm neck and the iliac arteries is required for the initial success of the procedure. Many studies[148,149] have demonstrated early safety and efficacy of EVAR comparable with conventional open surgical repair. In addition, the endoluminal approach usually requires shorter intensive care unit and hospital stay, while it also provides some other benefits such as reduced blood loss, fewer major complications, and more rapid recovery. Because of its less invasive nature, most investigators feel that EVAR offers lower perioperative mortality risk than surgical repair. However, a recent DREAM clinical trial group.[150] demonstrated that the perioperative survival advantage with endovascular repair as compared with open repair is not sustained after the first post-operative year. Besides, the rate of survival free of moderate or severe complications was found to be similar for both approaches. EVAR trial[151] also indicated that EVAR offers no advantage to all-cause mortality and health-related quality of life compared with conventional open repair, while it carries a greater number of complications and reinterventions as well.

Other limitations of the endovascular approach include: (a)*Endoleak* (leakage at the anchor sites (Type I); leakage due to collateral arteries (Type II); modular disconnection (Type III); leakage due to porosity of the graft material (Type IV);) primary or secondary occurs in 10-20 % of cases and although the true clinical significance of this entity is poorly defined, there is consensus that Types 1 and 3 endoleaks may be associated with adverse effects such as continued AAA enlargement and ongoing rupture risk. (b) *Endotension***,** which is another issue that may lead to further aneurysm expansion and rupture despite the absence of detected endoleak. In addition, changes in the sac morphology (e.g. shrinkage) even when the latter is completely excluded, may lead to later complications related to the stent graft such as limb kinkage or occlusion, modular junction separations, or device migration.[152,153] As a consequence of such potentially adverse effects following EVAR, secondary reinterventions are required in almost 10% of patients per year[154] while only 2% of patients undergo surgery for a second time in the first five years after open surgical repair. Although the high rate of reintervention after endovascular approach does not necessarily reflect failure of EVAR, it is certain that patients should be informed about the possibility of reoperation.

Now-a-days both surgical and endovascular techniques provide a safe management of AAAs that need to be repaired. Although the initial results concerning EVAR have been very promising, concerns have been raised about several limitations of the method such as endoleaks, endotension, ongoing risk of rupture, need for periodic follow-up and possible reintervention, anatomic limitations etc. Thus, EVAR should be performed to carefully selected patients who meet specific anatomic criteria and are aware of potential complications and later failure of the method even after initial success.

Thoracic aortic aneurysms: Thoracic aortic aneurysm (TAA) is a highly morbid disease with reported rupture rate of 31% for aneurysms >6 cm at five years.[155] Most TAAs are degenerative in nature and many studies suggest that primary connective tissue weakness is involved in their pathogenesis.

Open surgical repair with graft replacement has been the traditional management for aneurysms > 6 cm in diameter. Complications of this approach include major

perioperative hemorrhage, respiratory and renal insufficiency. However, the most serious non-fatal complication is spinal cord ischemia which manifests clinically as paraplegia or lesser degrees of lower extremity paraparesis with reported incidence between 5% and 21%.[156,157] Thirty-day mortality varies between 5% and 20%[158] while 5-year survival was approximately 56% in recent studies.[158]

Endovascular TAA repair was reported for the first time in 1994 by Dake et al.[159] Since then, important progress in adopting endoluminal techniques for TAAs repair has been reported, however slower than in the AAAs territory. Several studies[160-162] have demonstrated the feasibility of the method with acceptable perioperative mortality (6%) and morbidity particularly with regards to a low incidence of the spinal cord ischemia (4%), pulmonary and cardiac studies.[160-162]

However, these reports highlight certain shortcomings of current stent-graft technology in treating thoracic aorta disease: (i) The extent of coverage of the thoracic aorta remains unclear; the need for durable repair must be balanced against preservation of blood flow in the intercostals, (ii) Inspite of the use of iliac conduits, deployment of large and long devices, often necessary to fit the size of the descending thoracic aorta, remains a problem, (iii) Accurate proximal device placement in the aortic arch can be challenging due to high blood flow and substantial movement of the arch. This is very important as distal migration of even few millimetres during deployment may result in poor proximal fixation, (iv) Inherent limitations of commercially available devices may also complicate accurate deployment, (v) Definite long-term results are not available yet; late type I and III endoleak, and also the possibility of device fatigue are important issues.

Endovascular stent-graft repair of descending TAAs is still in evolutionary stage, and shows promising results in treating the disease. However, there are certain device limitations. Improvements in delivery systems, materials engineering and fixation devices are necessary to make this approach an effective and safe alternative to conventional surgical treatment. In addition, surgical procedures such as carotid subclavian transposition, combined open and endovascular elephant-trunk procedures and use of iliac conduits may expand the applicability of the method.

Type B dissection of the descending thoracic aorta: Aortic dissection is characterized by separation of the aortic wall layers by extramural blood that usually enters the aortic wall through an intimal tear.[163] Potential complications of type B dissections (no involvement of the ascending aorta) combine those of aneurysmal aortic disease with those of occlusive disease of the aortic branches.

Symptomatic or complicated type B dissections have been managed with several surgical techniques including graft replacement, aortoplasty, the "elephant trunk" technique and fenestration. All these techniques carry significant mortality and morbidity rates specially in poor surgical candidates. Endovascular procedures (stenting) have been used for treatment of both the aortic lesions and ischemic complications. Nathanson et al.[163] reported technical success of 95%, perioperative death rate of 2.5%, and endoleak rate of 3%; 38% patients experienced post-operative complications, mainly renal or pulmonary, while the incidence of post-operative paraplegia that did not resolve was 3%. The 1-year survival was 85%. Other series report similar results.[164] In addition, thoracic stent-grafts have been used for emergent repair of acute type B dissections with very low mortality and perioperative morbidity.[165]

These early results indicate that thoracic endografts offer a realistic alternative to surgery for complicated type B thoracic aortic dissections with acceptable morbidity and mortality. However, further analysis of the long-term outcomes is required.

Renal Artery Stenosis

Renal artery stenosis (RAS) is more and more frequently diagnosed, thanks to technical improvements in duplex ultrasound, magnetic resonance angiography, CT scan and systematic angiography during catheterization.

RAS is most of the time atheromatous (80% of the cases and over 40 years) but can also be due to fibromuscular dysplasia, arteritis (Takayasu's disease), neurofibromatosis and post-radiations. It can also be diagnosed after renal transplant, in a renal bypass graft. The prevalence of RAS is high. Rihal et al.[166] found a RAS > 50% in 19.2% of patients during cardiac catheterization of 297 hypertensive patients. RAS prevalence is 35 to 45% in patients with PAD, 14 to 24% in patients with cerebrovascular disease, 7% to 30% in patients with coronary heart disease.[167-169] In patients with renal insufficiency, the incidence of unsuspected RAS is as high as 24%.[170]

RAS can result in renovascular hypertension but can also lead to renal insufficiency, cardiac failure with pulmonary edema and unstable angina. Renovascular hypertension occurs in response to a significant hemodynamic obstruction to renal blood flow. The resultant

stimulation of renine and angiotensin production causes systematic hypertension and fluid retention.

The natural history of RAS is to progress over time resulting in renal artery occlusion, loss of renal mass and subsequent decrease in renal function. The incidence of progression in angiographic studies ranges from 39% to 49%. Vessels with the most severe stenoses result in total occlusion in 16% of the patients.[171-174] In a prospective study of patients with RAS treated medically, progression occurred in 42% (11% progressed to occlusion) in patients over a 2-year period.[173] Of particular importance is the realization that progression of RAS and loss of renal function are independent of the ability to medically control blood pressure.[175]

The treatment of RAS includes medical therapy, endovascular procedure and surgery. Surgery remains at high risk with a 2-7% perioperative mortality rate, a 17-31% morbidity and deterioration rate in renal function in 11-31% of the patients, reocclusion and restenosis in 5-18%.[176-178] Indications for surgery are limited: failed percutaneous approach, hostile aorta infrarenal, total occlusion and in association with aortic surgery.

Percutaneous transluminal renal angioplasty (PTRA) technique has become the cornerstone for the therapeutic strategy for addressing RAS and is now the treatment of choice. Balloon angioplasty alone was first proposed but several series reported the success of endovascular stents for treating suboptimal angioplasty and as a primary intervention for atherosclerotic lesions and particularly ostial lesions with better immediate and long-term results than with PTA alone.[179-184] Primary stenting is now the procedure of choice in most cases of atherosclerotic RAS. PTA alone should be reserved for non-ostial RAS and fibromuscular dysplasia. Cutting balloon seems a good indication to treat arteritis.

Renal angioplasty stenting can be performed by femoral approach in the majority of cases. The brachial or radial approach can be used as well. The technique benefits from the improvements of coronary technique: monorail system for balloon and stents, low profile devices, 0.01"or 0.018" guidewires allowing a direct stenting in 80-90% of the procedures.

Indications for treatment of RAS are debated but a consensus is now developing that patients with significant RAS ($\geq$70% diameter stenosis and/or 15 mmHg pressure gradients) in the setting of uncontrolled hypertension or renal insufficiency are appropriate candidates for PTRA. Other indications include patients with congestive heart failure (flash pulmonary edema) and unstable angina. Patients on hemodialysis whose parenchyma is supplied by stenotic renal arteries may also be considered candidates for PTRA.[185]

Treatment of RAS without hypertension or renal insufficiency is debated but could be envisaged to preserve the renal function and the renal artery patency, to delay aggravation of the stenosis and the possible manifestation of renal insufficiency. The procedural success is excellent (98-100%) with a low complication rate, a low restenosis rate (10-15%) and a long-term patency rate of 85-98%.[180-186] Restenosis rate is higher for arteries 6 mm in diameter. Indications for DES could be envisaged in these cases.

In a personal series of 602 renal angioplasty stenting, we had a successful stent deployment in 600 cases (99.8%), 6 major complications: 3 renal ruptures, 2 successfully treated by covered stent, the other surgically (death from myocardical infarction), one stent thrombosis treated by fibrinolysis and 2 arterial perforations, one treated by surgery, the other by interventional procedure (coils). The restenosis rate was 11.5%, the primary patency 82.8% and the secondary patency 98.5% at 9 years follow-up.

Numerous studies reported PTRA with or without stenting as beneficial on blood pressure control and on renal function.[175-182, 186-195]

Effects on blood pressure: Renal artery stenting of atherosclerotic lesions has been associated with a statistically significant decrease in blood pressure in need of medication during long-term follow-up. About 15 to 20% of the patients are cured, 50-60% are improved.

Better results can be expected in patients with fibromuscular dysplasia or arteritis. Hypertension is cured or improved in 60 to 92% of the cases.

Effects on renal function: Recent studies regarding the effects of PTRA or stenting on renal function showed that a large percentage of patients seem to benefit from the procedure, with a stabilization or improvement in renal function.[180,188-192] Renal stenting in selected patients could slow the progression of renovascular renal failure.[190, 193]

However, in many published series a decline in renal function is noted in 20 to 30% of the patients even after successful initial technical results and a good long-term patency of the renal artery. Dorros et al.[184] reported a deterioration of the renal function in 47% of the patients with a creatinine >2 mg/dl. Subramanian et al.[194] showed a worsening in renal function in 24% of non-diabetic patients and 27% of diabetic patients with renal insufficiency, Guerrero et al.[195] in 31% of patients with renal insufficiency. Recently, Nolan et al.[196] reported a deterioration of the renal function in 24% of the patients

at 1 year even with new techniques, low profile systems.

In contrast to other series, Zeller[197] found the highest proportion (36%) of patients with deteriorated renal function in patients with normal baseline serum creatinine. Many factors may account for this functional deterioration: contrast media-induced nephrotoxicity, progression of concomitant nephrosclerosis, lesions recurrence, hyperperfusion syndrome etc. However, atheroembolism during the procedure seems to play an important role as well demonstrated recently by Hiramoto et al.[198] Contrary to earlier beliefs that atheroembolization is a non-issue during percutaneous angioplasty, there is now mounting evidence that distal atherosclerotic debris commonly embolizes from lesions in many vascular territories during percutaneous intervention.

Distal embolization seems to be the root cause of many procedural complications whenever atherosclerotic lesions are treated.

Cholesterol atheromatous embolism is an increasingly recognized cause of renal function deterioration, due to instruments manipulation in the aorta and renal arteries, which result in detachment and embolism of atheromatous debris. The true incidence of atheroembolism in uncertain. Many patients can have a silent course because of the large functional kidney reserve, which allows normal serum creatinine values despite a significant decline in total glomerular filtration capacity. Therefore, only the most severe cases may be detected, specially in patients with pre-procedural renal dysfunction and limited functional reserve. An abnormal serum creatinine may only be observed if 50% of nephron population is destroyed. Most patients reach a peak serum creatinine level over 3 to 8 weeks but onset is usually sooner. Atheroembolism can give rise to different degrees of renal impairment but its diagnosis is difficult and the prognosis severe. No specific treatment can be proposed.

The main problem is indeed to avoid atheroembolic events during renal intervention. Selection of the patients and technical considerations may limit atheroembolism, but protection devices similar to those used for carotid angioplasty are the main technique to avoid renal atheroembolism during renal angioplasty and stenting. Some studies[199,200] have shown that protection devices with occlusion balloon or filters are efficient to reduce the risk of embolization to the brain, and that these techniques are mandatory in this field and are the standard of care. We postulated that the same technique could be suitable in the management of renal angioplasty and stenting to reduce the risk of atheroembolism and of renal function deterioration.[201-203]

We performed 111 renal angioplasties and stenting under protection with different devices (occlusion balloons, filters), with excellent immediate and long-term results. At 6 months follow-up, only one (1.2%) deterioration of the renal function, and at 3 years only 2 (4%) deteriorations were observed. Similar results were reported by Holden and Hill.[204]

This technique of renal protection maybe the way for the future to improve the long-term results of renal angioplasty and stenting and avoid renal function deterioration. The beneficial effects of this technique should be evaluated by randomized studies.

Conclusions

Endovascular treatment is the first treatment to be proposed to the majority of patients suffering from PAD. The improvements in techniques, devices and drugs have enlarged the indications for TASC Type C and D lesions. Procedures are becoming easier and safer while at the same time long-term outcomes are improving.

In the near future, we can expect solutions for patient with long lesions, long occlusions and for patients with limb threatening ischemia. New covered stents, drug-eluting stents, gene therapy, angiogenesis should be developed and help avoid major surgery even amputation in patients who often are elderly, at high risk or with multivascular morbidity.

Surgery should be reserved for failure of endovascular procedures, some complications and for a limited number of patients impossible to be treated by percutaneous approach.

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Induced Subcutaneous Nodules in the Diagnosis of Acute Rheumatic Fever

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The diagnosis of acute rheumatic fever (ARF) depends on clinical criteria combined with investigations identifying presence of an active disease as well as evidence for recent Group-A beta hemolytic streptococcus infection. The original Jones' criteria (1944)[1] were subsequently modified (1956),[2] revised (1965)[3] and updated (1992)[4] by the American Heart Association.

Evaluation of investigations required for the diagnosis of ARF indicates that there has been very little change over the years. Since there are no specific and diagnostic investigations, there is a need to reassess investigations, which have been tried but not utilized as they should have been.

One of the major clinical manifestations of ARF is the presence of subcutaneous nodules (SCN) occurring with a frequency of 1-21%.[5,6] The SCN have a predilection for bony prominences. Hypothesizing that trauma may be an important factor in the genesis of SCN, Massel et al.[7] injected whole autologous blood on the elbows of patients and applied frictional pressure over the site of injection thus inducing development of SCN with a sensitivity of 90% in ARF. Surprisingly, artificially induced SCN with a high sensitivity utilized by Massel were not pursued as a diagnostic test for ARF. Bhattacharya et al.[8] replicated this study in a larger sample size, but found a high specificity (100%) although with a much lower sensitivity (29%) than Massel et al. Subsequently Vasan,[9] with the reasoning that it is the leucocytes which are involved in immunological perturbations and not the red blood cells, modified the test and used only the white cell concentrate instead of the whole blood. He centrifuged 3 ml of venous blood in sterile tubes and obtained buffy coat by removing the plasma. The buffy coat was withdrawn in a sterile disposable syringe for immediate injection under strict aseptic conditions. This was followed by local frictional pressure 6 to 10 times a day.

Patients were divided in two groups and each group into two sub-groups: Group I(a) consisted of 20 patients of ARF and Group I(b) had two patients with pure chorea. Group II(a) included 15 patients of inactive rheumatic heart disease (RHD) and Group II(b) had three patients with infective endocarditis. The buffy coat was injected over the right elbow of all patients. Then, 1 to 2 ml of autologous blood was injected subcutaneously over the left elbow in all of Group II patients and 18 of the 22 Group I patients. In four Group I patients, plasma obtained by centrifugation was injected instead of the whole autologous blood. Steroids were not withheld from any patient during the study.[9] Patients were evaluated for the presence of SCN by two observers, one of them being the consultant cardiologist supervising the study. The buffy coat-induced SCN appeared between 4th to 7th day and the whole blood-induced SCN appeared in 5 to 7 days. In four patients with buffy coat-induced SCN who could be reevaluated after 12 weeks, the nodules were still present inspite of receiving steroid therapy. Histologically, the induced subcutaneous nodule was identical to the naturally occurring SCN.

Eighteen of the 20 patients with ARF [Group 1(a)] developed induced SCN from buffy coat injection. Of the remaining two, one developed ulceration at the site of injection due to excess rubbing and one left the hospital on the 4th day and was lost to follow-up. Seven of the 16 patients of Group 1(a) developed SCN with whole blood as well. None of the four patients injected with autologous plasma developed SCN.

Of the two patients with chorea [Group 1(b)], one developed SCN with buffy coat but not with whole blood and the other was lost to follow-up after five days during which she did not have SCN.

None of the Group II(a) patients with inactive RHD developed a nodule. Of the three patients with infective endocarditis, one developed a buffy coat-induced nodule but not with the whole blood.

Use of buffy coat resulted in a sensitivity and specificity of 86% and 94%, respectively compared to whole blood with a sensitivity of 38% and specificity of 94%.[9] It is possible that the buffy coat is more sensitive since cell-mediated immune response is involved in the pathogenesis of ARF. Buffy coat contains a leucocyte concentrate providing a larger dose of leucocytes than the whole blood injection, which could also alter the response.

The study establishes the utility of induced SCN using autologous buffy coat for the diagnosis of active rheumatic

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fever (RF). It is a simple, inexpensive, safe, accurate and sensitive investigation when performed with strict aseptic care for identifying active RF. The utility of the test lies in its simplicity, universal availability and the very low cost. It needs further evaluation in a larger sample size.

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Short QT Syndrome. What is it? Where is it?

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Presence of a long QT interval (LQTI) in the electrocardiogram (ECG) has been associated with sudden cardiac death (SCD). This congenital long QT syndrome (LQTS) was first described with structurally normal heart way back in 1957;[1] however, little was known about the significance of a short QT interval (SQTI). This entity has received considerable attention over the last couple of years. Only a few families have been reported with this syndrome till date, which has a propensity for ventricular tachyarrhythmias (VT), atrial fibrillation (AF) and associated high risk for SCD. In 1993, Algra et al.[2] analyzed 6693 consecutive Holter recordings and concluded that an increased risk of SCD was present not only in patients with long QT interval but also in patients with a QT interval of < 400 ms,[2] thus giving birth to a new entity 'the short QT interval'.

Later, Gussak et al.[3] formally proposed the 'short QT syndrome' (SQTS) as a new congenital clinical syndrome in report of two siblings and their mother, all of whom persistently demonstrated SQTI on their ECGs. One of the sibling had several episodes of paroxysmal lone AF requiring repeated cardioversion.[3] A series of descriptions and reports have subsequently helped to establish the entity of SQTS. The familial nature of SQTS was further emphasized by Gaita et al.[4] in 2003 in their study of six patients from two unrelated European families presenting with syncope, palpitations, resuscitated cardiac arrest and a positive family history of SCD.

Genetics of Short QT Syndrome

Short QT syndrome has been described to have an autosomal dominant (AD) inheritance.[5] The first gene responsible for SQTS was reported by Brugada et al.[6] in 2004. Till date, three different mutations in genes encoding for cardiac potassium channels (KCNH2, KCNQ1 and KCN J2) have seen identified.[7] The mutations in KCNH2 (HERG) have been noted in the familial forms and a mutation in KCNQ1 in the sporadic form of the disease.[8] The substitution of lysine for asparagine at position 588 of KCNH2 was found to cause a loss of the normal rectification of the current at plateau voltages, thus resulting in a large increase of rapidly activating delayed rectifier channel, IK(r) during the action potential plateau. This led to a marked abbreviation of the action potential duration and setting the substrate for increased arrythmogenesis. All mutations lead to gain in function of the affected current IK(r), IK(s) and IK(1). Thus N588K seems to be a hotspot for familial form of the SQTS.[7,8] Recently, two further mutations in the KCNQ1 gene encoding the α-subunit of the KvLQT1 [IK(s)] channel and in the KCNJ2 gene encoding the strong inwardly rectifying channel protein Kir2.1 confirmed SQTS as a genetically heterogeneous disease. The possible substrate for the development of VTs may be a significant transmural dispersion of the repolarization due to a heterogeneous abbreviation of the action potential duration.[9]

Clinical Spectrum

Short QT syndrome occurs in all age groups and even in newborns.[10] It is a clinically heterogeneous disease with most of the affected patients not manifesting any clinical symptoms. Symptomatology ranges from palpitations due to paroxysmal or permanent AF, to dizziness, syncope and even sudden death. It is recommended that young patients with lone AF should be screened for SQTS.[7] During programmed electrical stimulation (PES), atrial and ventricular effective refractory periods (ERP) are shortened, and in a high percentage, VTs are inducible. Sudden cardiac death occurs in all age groups and even in newborns.[7] Hong et al.[8] identified a family with SQTS with a high incidence of paroxysmal AF in their members and no known history of SCD. QT interval ranged from 225 to 240 ms within normal heart rate ranges in the affected individuals. PES was performed in all affected members, which revealed a remarkably short atrial and ventricular ERP, and inducibility of atrial and ventricular fibrillation (VF).[8] Another case reported was of a 20-year-old male presenting with exertional dyspnea. An electrophysiologic study revealed AF with a very high frequency, short ventricular ERP and easily inducible VF. ECG was consistent with SQTS; however, the patient was free of arrhythmia and denied any syncope or pre-syncope.[11] Viskin et al.[5] have proposed that idiopathic VF might also represent underlying SQTS. In the

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presence of structurally normal heart, the secondary causes of SQTI should be suitably ruled out like the presence of tachycardia, hyperthermia, hyperkalemia, hypercalcemia, acidosis, alterations of autonomic tone and the use of digoxin before concluding a diagnosis of SQTS.[10]

Diagnosis and Prevalence

Electrocardiographically, an SQTS is characterized by a shortened QTc interval of <300 ms with an absolute QT interval of <320 ms.[7,12] A tall, symmetrical peaking T wave in the right preccordial leads is often striking. However, this has not been described in every patient; asymmetrical T waves have been reported in some cases. Individual risk assessment of patients with a SQTS is still diffcult due to genetic and clinical heterogeneity and low number of patients with a short follow-up. SQTS has been separately defined as a 'Predicted QT' (QTp = 656/(1+Heart rate/100) of < 80%,[12] QTp has been derived from a study of 14,379 North American children and adults aged 0 to 75 years with normal ECG.[13]

A large study from Italy looked at the prevalence of SQTI in 12,012 healthy individuals using QTp < 80% as the diagnostic cut off and came up with a prevalence of 0.12%, that is a total of 15 patients. Clinical information was available for 13 of these patients and no sudden death or significant arrhythmias were recorded in them at a mean follow-up of 11.56±5.2 years.[14] In another study on the prevalence of SQTI and SQTS, QTc was measured as < 300 ms; this study examined 479,120 automated ECG recordings and 215 of these were found to have QTc<300 ms; however 67% of these were errors due to pacemaker spike, 17% had supraventricular tachycardia and 16% had error in cycle length calculation.[15] Therefore, none of the ECGs were found to have a QTc <300 ms, further emphasizing the rarity of this intriguing clinical syndrome. In 400 consecutive apparently healthy young individuals with mean age of 42.3±13.1 years (42% males) who presented to our outpatients department with non-specific complaints or routine medical examination and in whom we had suitably ruled out the possibility of secondary QT shortening e.g. dyselectrolytemia, QTc was measured using an automatic 12- lead ECG machine. All ECGs were subsequently verified by a cardiologist and QTc cross-checked manually wherever required. Out of the subjects screened, the average QTc for males was 420±20 ms and 435±16 ms for females. The shortest QTc screened was 330 ms. QTp <80% was found in only one patient who was also incidentally found to be taking digoxin. Only 5 subjects were reported by the automated machine to have a QTc <300 ms. Four ECGs were found to have calculation errors in the cycle length and 1 subject was on digoxin and thus none of the screened subjects were found to have the classical idiopathic SQTS.

Treatment Options

Till now only a few studies have reported the response to drugs in SQTS patients. The impact of sotalol, ibutilide, flecainide, and quinidine on QT prolongation has been evaluated. Only quinidine effectively suppressed gain-of-function in IKr, along with prolongation of the QT interval and rendered VTs non-inducible. It may serve as an adjunct to implantable cardioverter defibrillator (ICD) therapy or as possible alternative treatment especially for children and newborns.[7] In yet another study, quinidine was shown to prolong the QT interval to normal range and prevented the inducibility of VF in all 4 patients studied while sotalol failed to prolong QT interval in any of the patients.[16] Hong et al.[8] showed that in a family with SQTS, treatment with propafenone maintained the individuals free of AF.[8] Thus, pharmacological treatment of patients with a SQTI may be considered to prolong QT interval and suppress arrhythmias.

In patients with a history of resuscitated cardiac arrest, symptomatic patients with a family history of SCD, ICD remains the only treatment option, and has been reported in a single article.[17] However, ICD therapy has an increased risk for inappropriate shock therapies due to possible T wave oversensing.[9] Pharmacological treatment should be reserved for patients for treatment or prevention of ventricular tachyarrythmias, if ICD is denied or impossible due to other reasons.

Conclusions

Short QT syndrome is probably a rare isolated phenomenon restricted to a few families so far. The criteria for its diagnosis and evaluation need to be studied further. This is an accidental finding with a clinical spectrum ranging from no-symptoms in most patients to sudden cardiac death, presumably due to arrhythmias in a few. The clinical significance thus remains uncertain with few cases being reported and the search is continuing for these patients.

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COX-2 Inhibitors and Heart

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Non-steroidal anti-inflammatory drugs (NSAIDs) are among the most commonly used medications in the world.[1] They act by inhibiting cyclo-oxygenase (COX), a key enzyme in arachidonic acid metabolism.[2] The COX enzyme catalyzes the initial steps in the conversion of arachidonic acid to various eicosanoids including prostaglandins (PGs) and thromboxanes. COX is present in two isoforms, COX-1 and COX-2 (Fig.1). The COX-1 is a naturally occurring house keeping enzyme which generates PGs for physiological functions. It plays a role in the protection of gastric mucosa and is also responsible for the action on kidney, platelets and smooth muscles. In contrast, COX-2 is an inducible enzyme which appears during cell injury and synthesizes PGs for an inflammatory response. The inhibition of COX-2 produces the much desired anti-inflammatory response.[3]

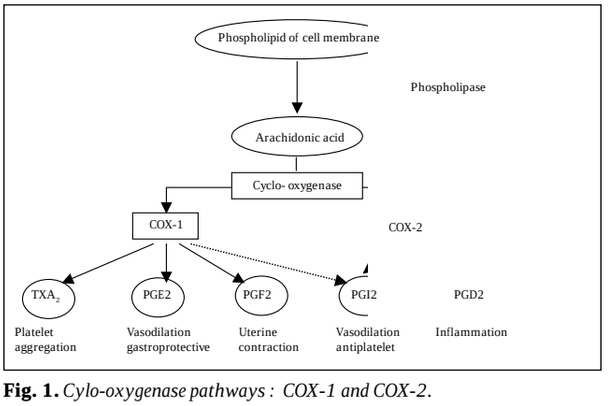

Fig. 1. *Cylo-oxygenase pathways : COX-1 and COX-2.*

Selective COX-2 Inhibitors

Since the conventional NSAIDs inhibit both COX-1 and COX-2 enzyme, it was postulated that the efficacy of NSAIDs (attributable to COX-2 inhibition) could be achieved without gastrointestinal toxicity (due to COX-1 inhibition). This realization rekindled the efforts of the pharmaceutical industry to produce a safe NSAID via selective inhibition of COX-2, which were allowed to reduce inflammation without influencing normal physiological function. The first selective COX-2 NSAID approved by Food and Drug Administration (FDA) was celecoxib.[4] Table 1 enlists the various coxibs which have been introduced in the market.

Table 1. Classification of COX-2 inhibitors

	Name	Cox-2: Cox-1 selectivity
First generation	Celecoxib	30
	Rofecoxib	276
Second generation	Valdecoxib	261
	Lumiracoxib	433
	Etoricoxib	344

Adverse Cardiovascular Effects of Coxibs

COX-2 inhibitor may decrease vascular prostacyclin (PGI2) production and may affect the balance between pro-thrombotic and antithrombotic eicosanoids and may tie the balance in favor of prothrombotic eicosanoids (thromboxane A_2) and lead to increased cardiovascular events.[5,6] It was initially assumed that PGI2, which causes vasodilation and inhibits platelet aggregation, is derived mainly from COX-1. This assumption later proved incorrect since studies on mice and humans showed that COX-2 was the dominant source. Whereas aspirin and traditional NSAIDs inhibit both thromboxane A_2 and PGI2, the coxibs decrease the production of PGI2 alone leaving thromboxane A_2 generation unaffected. Thus the suppression of the COX-2-dependent formation of PGI2 by the coxibs predisposes the patients to myocardial infarction (MI) and thrombotic stroke.[7] The various cardiovascular effects of coxibs[8-11] are enlisted in Table 2.

Table 2. Cardiovascular effects of coxibs[8-11]

Effects	Probable pathogenesis
Myocardial infarction	Decreased vasodilator PGI2 and increased proaggregatory TXA_2
Sudden cardiac death	Decreased PGl2 and proarrythmic effect
Elevation of blood pressure	Alteration of RAS pathway and inhibition of vasodilating PGs
Worsening heart failure	Sodium and water retention; augmentation of blood pressure
Endothelial dysfunction	Increased oxidative stress and free oxygen radical injury
Accelerates atherosclerosis	Decreased concentration of essential fatty acids, lipoxins and resolvins
Stroke	Prothrombotic tendency

PG : prostaglandins; TX : thromboxane; RAS : renal artery stenosis

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Withdrawal of rofecoxib from the market: On 30 September 2004, a press release from Merck announced the withdrawal of rofecoxib because of an increased cardiovascular risk in patients taking the drug for more than 18 months.[12] The story of rofecoxib is a strange combination of stunning commercial success and dramatic calamities. Though the question regarding cardiovascular safety of rofecoxibs was raised right from the day it was launched and there were evidences against its usage also but neither the FDA, nor the Merck fulfilled its responsibilities to the public and it was after five and half years of its launch with more than 80 million patients having taken this medicine and annual reaching $ 2.5 billion level that the company withdrew the drug because of an excess risk of MI and stroke. This represented the largest prescription drug withdrawal in history. Had the many warning signs along the way been heeded, such a debacle would have been prevented.[13] Of late, on 7 April 2005, valdecoxib has also been voluntarily withdrawn by the company.

Evidence of cardiovascular toxicity with coxibs: The summary of various trials of cardiovascular toxicity of coxibs is illustrated in Table 3.

In the CLASS trial,[14] celecoxib was compared with ibuprofen or diclofenac. In the original report, celecoxib appeared to have a more favorable gastrointestinal side effect profile and no increase in cardiovascular risk was revealed. However, this report contained only half the data (from only six months of a one-year study).[15] When the full data set became available, it was clear that celecoxib did not differ from the traditional NSAIDs in its effect on the predefined gastrointestinal end points.[16] Indeed, the most powerful evidence supporting claims of celecoxib's superiority over traditional NSAIDs in terms of gastrointestinal effects rests on a post-hoc analysis of the CLASS data for patients who did not use aspirin. However, a similar retrospective approach to the data also reveals signs of increased cardiovascular risk.[17]

The Vioxx Gastrointestinal Outcome Research (VIGOR) trial[18] recruited 8076 rheumatoid patients to either 50 mg/day rofecoxib or 500 mg twice daily naproxen over a median period of 9 months. The rate of serious gastrointestinal events among those with rofecoxib was half of those receiving a traditional NSAID naproxen (2% *v.* 4%). However, a significant increase by a factor of five in the incidence of MI was observed. The cumulative risk of developing serious cardiovascular thrombotic events was 1.7% in rofecoxib group compared with 0.7% in the naproxen group. But this was attributed to cardioprotection of naproxen rather than a cardiotoxic effect of rofecoxib. However, later epidemiological studies of possible cardioprotection afforded

Table 3. Major trials showing coxibs and cardiovascular effects

Trial	Drug	Duration of treatment	Control group	Cardiovascular outcome
CLASS[14] (*n*=8059)	Celecoxib 800 mg/day	1 year	Ibuprofen 2400 mg/day and diclofenac 150 mg/day	CVS effects were not reported initially but a retrospective approach to data showed signs of increase cardiovascular risk
VIGOR[18] (*n*=8076)	Rofecoxib 50 mg/day	9 months	Naproxen 500 mg/ day	5 times increase in the risk of MI in rofecoxib group
TARGET[23] (*n*=18,000)	Lumiracoxib	52 weeks	Naproxen Or ibuprofen	Trend toward more CVS event in lumiracoxib (0.86 *v.* 0.75 per 100 patients-years)
APPROVe[25] (*n*=2600)	Rofecoxib 50 mg/day.	18 months	Placebo	Incidence of MI was 3.5% in rofecoxib *versus* 1.9 % in placebo (p<0.001)
CRESCENT[31] (*n*=404)	Rofecoxib 25 mg/day	12 weeks	Celecoxib Or naproxen	At equally effective doses, rofecoxib but not celecoxib or naproxen induced a significant increase in 24-hour systolic BP
APC study[26] (*n*=2035)	Celecoxib 200 mg twice daily Or 400 mg twice daily	2.8 to 3.1 years	Placebo	Celecoxib was associated with dose-related increase in the composite end point of death from cardiovascular causes, MI, stroke or heart failure
CABG[27] Surgery Study (*n*=1671)	Parecoxib (40 mg/day i/v) and valdecoxib (20 mg/day)	30 days	Placebo	CVS events were more frequent among the patients given parecoxib and valdecoxib than placebo (2% *v.* 0.5% RR=3.7; p=0.03)

i/v: intravenous; CVS: cardiovascular; MI: myocardial infarction; BP: blood pressure

by naproxen have proved inconclusive.[19-22] Also, the total cardiovascular effect of rofecoxib in the trial were not reported to FDA and only the increased rate of MI was mentioned in the VIGOR publication[18] and not the overall increase in the cardiovascular events. Moreover, the increased MI rate reported was in a subgroup of patients only, which was defined retrospectively. FDA data later clearly showed that increased cardiovascular events were found in not only those subgroup of patients in whom aspirin was indicated [(relative risk ratio RR) 4.89; 95% CI. 4.1-16.88), but also in patients not needing aspirin (RR 1.89; 95% CI 1.03 –3.45).

The Therapeutic Arthritis Research and Gastrointestinal Event Trial (TARGET)[23,24] compared lumiracoxib with naproxen or ibuprofen. The primary end point was incidence of serious gastrointestinal events, which was reduced significantly among patients receiving lumiracoxib. However this difference was observed in patients who were not taking aspirin. Although this trial was not powered to detect a difference in the rate of cardiovascular events in non-aspirin users, more such events occurred in the lumiracoxib group than in the other group (0.86 *v.* 0.75 per 100 patient-years; odds ratio 1.14), although the difference was not significant (p=0.50). Concomitant use of aspirin did not provide any cardioprotection.

Adenomatous Polyp Prevention On Vioxx (APPROVe) was a placebo-controlled trial of rofecoxib for the prevention of recurrence of colorectal polyp in 2600 patients with a history of colorectal adenoma.[25] This trial was prematurely terminated because it was discovered that 3.5% of the patients assigned to rofecoxib had MI or stroke as compared to 1.9% of the patients assigned to placebo (p< 001). Blood pressure (BP) was elevated in patients in the rofecoxib group early in the course of the study but the incidence of MI and thrombotic stroke in the two groups began to diverge after a year or more of treatment.

The Adenoma Prevention with Celecoxib (APC) study group[26] reviewed all potentially serious cardiovascular events among 2035 patients with a history of colorectal neoplasia who were enrolled in a trial comparing two doses of celecoxib (200 mg or 400 mg twice daily) with placebo for the prevention of colorectal adenoma. Celecoxib use was associated with a dose-related increase in the composite end point of death from cardiovascular causes, MI, stroke or heart failure (1% for placebo, 2.3% for patients receiving 200 mg celecoxocib twice daily and 3.4% for patients receiving 400 mg celecoxib twice daily). As a result of this trial, Pfizer stopped advertising of celecoxib to consumers.

The coronary artery bypass graft (CABG) surgery study[27] was a randomized double blind study to assess the safety of valdecoxib and its intravenous product parecoxib after CABG. It included 1671 patients who were randomly assigned to receive intravenous parecoxib 40 mg daily for 3 days, followed by oral valdecoxib 20 mg daily for 10 days; intravenous placebo followed by oral valdecoxib; or placebo for 10 days. The cardiovascular events were more frequent among the patients given parecoxib and valdecoxib than among those given placebo (2% *v.* 0.5%; RR 3.7; 95% CI 1-13.5; p= 0.03) and interestingly the curves for cardiovascular events began to diverge within few days of initiation of treatment.

Recently, there was a meta-analysis published in Lancet[28] regarding the risk of cardiovascular events and rofecoxib. The researchers identified 18 randomized controlled trials and 11 observational studies before September 2004. MI was the primary end point of analysis. By the end of 2000 (52 MIs, 20742 patients) the relative risk from randomized controlled trials was 2.30 (95% CI 1.22- 4.33 , p= 0.010) and 1 year later (61 events, 21432 patients) it was 2.24 (95% CI 1.24-4.02; p= 0.007) There was little evidence that relative risk differed depending on the control group (placebo, non-naproxen NSAID, or naproxen ; p = 0.41) or trial duration (p=0.82). This cumulative meta analysis of randomized controlled trial indicated that an increased risk of MI was evident from 2000 onward and rofecoxib should have been withdrawn several years earlier.

COX-2 inhibitor and hypertension: COX-2 inhibition has been shown to increase blood pressure.[29] Several factors may explain their blood pressure raising effects[30] like alteration in renin angiotensin pathway, changes in sodium and water retention by the kidney, inhibitor of vasodilating PGs, production of various vasoconstrictors including endothelin-1 and P450-mediated metabolite of arachidonic acid.

In the VIGOR trial, patients in the rofecoxib developed higher elevation of blood pressure in comparison with naproxen group (4.6 mmHg increase in systolic BP and 1.7 mmHg increase in diastolic BP in the rofecoxib group as compared to a 1.0 and 0.1 mmHg increase in systolic and diastolic BP, respectively with naproxen).

In the latest CRESCENT study,[31] at equally effective dose for ostearthritis management, treatment with rofecoxib, but not celecoxib or naproxen induced a significant increase in 24-hour systolic BP. Similarly, in the APPROVe study[25] there was more increase in the blood pressure in rofecoxib group than placebo group and these effects were seen as early as at 4 weeks.

Cardiovascular toxicity and relation with dose of rofecoxib:[32,33] There had been variable result of dosage comparison and cardiovascular toxicity of rofecoxib. While previous studies have shown that high dose rofecoxib >25 mg could be associated with a higher risk of cardiovascular events than rofecoxib ≤ 25 mg but the latest meta analysis published in Lancet[28] this year found little evidence to suggest that relative risk differed depending the dosage of rofecoxib (RR 2.71 for 12.5 mg; 1.37 for 25 mg and 2.83 for 50 mg, p=0.69). However, there was dose-related increase in cardiac toxicity with celecoxib in the APC study.

Duration of treatment and cardiovascular toxicity: In a subset of population like in APPROVe study[25] in which patients were not screened for coronary artery disease, the cardiac toxicity of rofecoxib was evident after 18 months of treatment whereas in the recent CABG surgery study[27] the curves for cardiovascular events began to diverge within few days of initiation of treatment. Thus there is an increase in cardiac toxicity with both short and long duration treatment and use of coxibs particularly in patients with pre-existing cardiac disease can be detrimental.

Rofecoxib *versus* other COX-2 inhibitors: The cardiotoxicity of rofecoxib has already been established and it has been withdrawn last year. More unwelcome data from placebo-controlled trials of rofecoxib's competitors followed: valdecoxib taken after CABG was shown to be associated with increased incidence of cardiovascular event and it has also been withdrawn by FDA this year. The APC trial reported an increased risk of cardiovascular events associated with use of celecoxib, a drug known to be less selective for COX-2 than rofecoxib or valdecoxib. A small increase in the risk of MI was also observed for the highly selective lumiracoxib. No data on the cardiovascular safety of etoricoxib from large trials have been published so far. Patients and doctors are anxious to know whether cardiotoxicity is a class effect applicable to any COX-2 inhibitors, or even to NSAIDs in general.

Coxibs in patients with a history of cardiovascular disease : Because of restrictive inclusion criteria, most trials included only few individuals with a history of cardiovascular disease. This contrasts with the situation encountered in routine clinical settings. For example, in middle-aged and elderly people from the Tennessee Medicaid programme, Ray et al.[34] reported that more than 40% of rofecoxib users had a history of cardiovascular disease and that compared with trial population, the risk of fatal or non-fatal MI was eight times higher (11.6 *v.* 1.45 per 1000 patient-years). This risk translates into number needed to treat for 1 year to cause one MI to 556 patients in trial population, but only 70 patients in routine population in Tennessee. Similarly in the CABG surgery study, the curves for cardiovascular events began to diverge within few days of initiation of treatment. Therefore, use of coxib in patients with pre-existing cardiac disease can be detrimental.

Coxibs and congestive cardiac failure:[35] The role of COX-2 inhibition in congestive heart failure is complex. On the one hand, both NSAIDs and COX inhibitors have various renovascular side effects, which include increased volume retention, edema, and blood pressure, all of which can exacerbate heart failure. On the other hand, the COX-2 enzymes are induced in the myocardium of the failing heart, and associated with myocardial scarring. Selective COX-2 inhibitors can therefore be cardioprotective at the level of the failing myocardium. Data, however, suggest that differences exist between the two types of drugs as well as between the COX-2 inhibitors themselves, with some but not all studies showing that rofecoxib is assoicated with more renovascular side effects, including increased edema and blood pressure, than are NSAIDs and celecoxib. Recently, two population-based studies have been undertaken in which users of rofecoxib and NSAIDs, but not celecoxib had a higher risk of death or admission for congestive heart failure.[35]

Coxibs and endothelial functions:[36-41] Selective COX-2 inhibitor has a variable response to endothelial function. Studies have shown that celecoxib but not rofecoxib improves endothelial function and reduces oxidative stress. This differential effect of various coxibs on endothelial function suggests that COX-2 independent activities may be involved. It should also be noted that celecoxib is more extensively distributed into tissues than rofecoxibs and more selectively reduces oxidative stress.

Coxibs and stroke: Rofecoxib has been found to increase risk of stroke, although the number of events was small and 95% CIs wide.[28] In the recent APPROVe and APC trials there was a significant increase in the incidence of ischemic stroke and transient ishchemic attack. But there is little data on increased incidence of venous thrombosis and arterial occlusion with coxibs.

Can Cox-2 Inhibitor-Induced Increase in Cardiovascular Toxicity be Modified ?

Role of aspirin : COX-2 inhibitors-mediated cardiotoxicity has been attributed to uninhibited TXA_2 production and since aspirin reduces the formation of TXA_2, there is a theoretical possibility that it might reduce cardiac

complication. In the CLASS trial, lack of adverse cardiac toxicity with celecoxib was attributed to the concomitant aspirin use. However, in the APC and APPROVe trials, there was no significant difference in the cardiovascular risk whether patient took aspirin or not. Similarly concomitant use of aspirin did not provide cardioprotection in the TARGET trial.

Role of essential fatty acids (EFAs):[42] In contrast to aspirin, COX-2 inhibitors do not increase the concentration of diloma-gamma-linolenic acid (DGLA), arachidonic acid, eicosapentenoic acid (EPA) and docosahexenoic acid (DHA). These essential fatty acids augment the formation of PGI2, lipoxins resolvins and eNO that not only have anti-inflammatory action but also have anti-arrhythmic, anti-atherosclerotic and neuroprotective action. Therefore, there is an emerging concept, that combining EFAs with COX-2 inhibitors could prevent these cardiovascular complications. However, these will need validation through clinical trials.

Unanswered Questions

We have still many concerns regarding usage of coxibs which need to be resolved. These include: (i) Whether cardiovascular effects of rofecoxib are a class effect applicable to all COX-2 selective inhibitors, (ii) How selective the COX-2 inhibition needs to have this adverse effect, and (iii) What are the modalities of preventing these adverse effects.

Conclusions

The cardiovascular toxicity of coxibs is well established.[43] Rofecoxib and valdecoxib have already been withdrawn by FDA and strong evidences against other coxibs are quickly emerging. Of late, there are reports to put all categories of NSAIDs under scrutiny.[44,45] Hence these pain killers should be used on the basis of their relative gastrointestinal and cardiovascular safety profile rather than the selectivity of their class.

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50 Years of the Asian Pacific Society of Cardiology in Retrospect: Long-Term Perspective

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As is well known, Cardiology became a distinct speciality after World War II and several cardiac societies emerged in various countries of Europe, the Americas and Asia between 1945 and 1950 (Table 1). This is true of the Cardiological Society of India (CSI), American Heart Association (AHA) and American College of Cardiology (ACC). Continental Societies had also begun to take shape at this time, Inter-American in 1944 and European in 1950. The World Society of Cardiology came into being in 1950, thanks to the efforts of stalwarts such as Paul Dudley White, Ignazio Chavez and Pierre Laubry. White suggested to Samia and Kempson Maddox at the 2nd World Congress in Washington DC in 1954 that they should also form an Asian Pacific Society. It was after considerable effort that Samia managed to call a meeting of regional representatives in April 1956 at Manila. Dr Paul White was there with his guiding spirit and the Asian Pacific Society of Cardiology (APSC) was born. The Charter Members of the APSC were Australia, India, Japan, Pakistan and the Philippines. Today the APSC has over 25 national societies affiliated to it. Subsequent conferences have been regularly held, earlier 4 yearly and from 2001, every 2 years. It was held for the first time in India after 50 years of founding (Table 2). Conferences of only smaller branches of the Society such as that of Cardiac Pacing and Rehabilitation have been held here earlier.

Table 1. Origins of continental and international societies of cardiology/foundations

1950	World Society of Cardiology
1969	International Cardiology Federation
1978	International Society and Federation of Cardiology
1998	World Heart Federation
1944	Inter American Society of Cardiology
1950	European Society of Cardiology
1956	Asian Pacific Society of Cardiology
1985	Pan African Society of Cardiology
	Foundations
	European Heart Network
1994	Inter-American Heart Foundation
1998	Asian Pacific Heart Network
	African Heart Network

Table 2. Asian Pacific Congresses of Cardiology - date and venue

1st	19–23 April, 1956	Manila, Philippines
2nd	June, 1960	Melbourne, Australia
3rd	10–14 May, 1964	Kyoto, Japan
4th	1–7 September, 1968	Jerusalem & Tel Aviv, Israel
5th	8–13 October, 1972	Singapore
6th	3–8 October, 1976	Honolulu, Hawaii
7th	26–30 November, 1979	Bangkok, Thailand
8th	27th Nov–2 Dec, 1983	Taipei, Taiwan
9th	11–16 February, 1987	Auckland, New Zealand
10th	6–11 October, 1991	Seoul, Korea
11th	17–22 September, 1995	Bali, Indonesia
12th	17–21 October, 1999	Lahore, Pakistan
13th	3 – 6 October, 2001	Manila, Philippines
14th	17–21 January, 2004	Singapore
15th	1–4 December, 2005	Mumbai, India

Development of the APSC

Special features: Unlike some other continental societies, the APSC has some special features. Large far-flung areas over land and sea are involved; it has both developed (Australia, New Zealand, Hawaii and Japan) and developing countries as members and has only one language of communication, English. It has 7 zones and the original 4 committees have grown into 7. Conferences have been regularly held. Special diseases predominate here viz. rheumatic heart disease (RHD), Kawasaki disease and now hypertension and ischemic heart disease (IHD). A Newsletter, which served a very useful purpose of communication, was unfortunately discontinued in 1988. Most of information about the APSC has been available in these Newsletters in which Samia and Maddox had covered its history for its 30th Anniversary in 1985.[1-3]

Main Achievements

Catalyst in development of Cardiology in Southeast Asia: Many national societies were formed after 1956. Two societies sprang directly from its committees viz. the Asian

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Pacific of Pacing and Electrophysiology and the Asian Pacific Society of Rehabilitation. Others formed later were the Asian Pacific Society of Pediatric Cardiology, Asian Pacific Society of Cardiac Surgery, ASEAN Society of Cardiology and the SAARC Society of Cardiology. These hold regular conferences by rotation in the countries of the region.

Bonding: Over time, close friendships have developed and due to developments in information technology (IT) there is now almost a countinuous flow of scientific communication between the countries of this region.

Training: Initially, training emanated from the United States of America (USA) to countries such as Australia and New Zealand. Later Australia, New Zealand and Japan took on the role of mentor to the less developed areas of the region. Today, thanks to such training, the cardiac services in the underdeveloped areas have improved considerably, specially from a technology standpoint and Interventional Cardiology and Surgery are easily available in many of these countries.

Research: Although there is a Research Committee in existence since 1956, it has not made much headway because of the distances involved and lack of finances. Much collaborative research can be done in epidemiology and methods of control of cardiovascular disease by the use of low-cost methods. According to World Health Organization (WHO), 80% of deaths due to cardiovascular diseases and hypertension occur in the low and middle income countries including Southeast Asia.

Role of World Heart Federation (WHF): The Paul Dudley White Fellowship and the Twin Centers program have helped to train doctors from the developing countries (mainly Southeast Asia), in the very best institutions in the USA and Europe in technology. World Heart Day started in 2000 at the instance of Bayes de Luna, and has increased awareness of the dangers of heart disease and its prevention, and is becoming increasingly popular all over the world.

Role of Foundations: Conceived initially as the awareness-creating and fund-raising arm of cardiac societies, they have had a difficult time in survival except in Australia and Japan. The establishment of the Asian Pacific Heart Network (APHN) in 1998 with its permanent headquarters in Jakarta Indonesia, will hopefully solve some of these problems.

Future Prospects

Conferences: Some difficulties are envisaged regarding holding conferences. The conferences will now be held every 2 years. The number of participants are increasing and space for conferences very limited. This is happening with other societies as well. A solution will have to be found such as smaller meetings on selected subjects and meetings of small committees.

Health tourism: This "Mantra" is now prevalent in some of the APSC countries. With a large number of trained personnel and many privately-funded institutions with state-of-the-art equipment and highly trained doctors, nurses and technical personnel with expertise, although expensive for their own countries, are attractive to the developed countries because of the long waiting list there and much lower cost here. Countries such as Thailand, Singapore, Malaysia and India are making a big bid for custom from the developed world fairly successfully. The cost of bypass surgery in India is 1/5 that of the United Kingdom (UK) or USA. With an attractive tourism program to follow such surgery, patients are lining up for this venture. Although cardiac surgery is only one of the subjects, it is a money spinner. Other subjects are bone marrow transplant, joint replacement, sex change and plastic surgery, to mention a few.

It is not impossible to combine training with this program. Already surgeons from India regularly do cardiac surgery in China, East Africa and Sri Lanka, thereby also training the local doctors and other staff.

The wheel appears to have come full circle from the 1950s and there is every indication that it will grow. Action on three issues by the outgoing and incoming Presidents needs consideration: (i) Revive the Newsletter, and preferably have an Editor in an English speaking country, initially for 3-5 years. (ii) Explore research program on Epidemiology and Prevention using low-cost methods for rheumatic fever (RF)/RHD, hypertension and IHD. (iii) Explore the inclusion of training in the Medical Tourism projects for treatment.

The APSC has survived for 50 years, held regular meetings and attained some of its lofty objectives. The enthusiasm and dedication of its pioneers appears to have borne fruit. It has become a healthy, mature entity and it is for the next generation to carry the message forward. We should be optimistic.

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Magnetic Resonance Imaging of Effusive Constrictive Pericarditis

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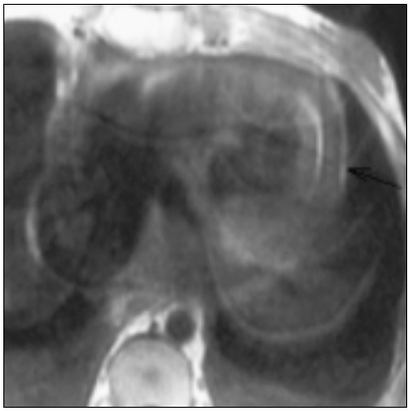

Fig. 1. *Axial SE image: thickened hypointense band of pericardium and pericardial effusion seen between the high signal stripes of epicardial and pericardial fat.*

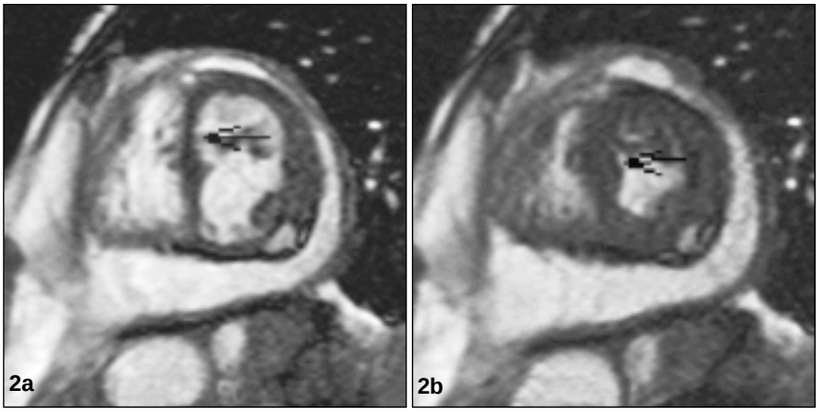

Fig. 2. *Short axis plane (cine GRE) in* **(a)** *diastole and* **(b)** *systole: Paradoxical motion of interventricular septum in early diastole seen as septal flattening. Normal septal configuration is seen in the systolic phase. Thickened pericardium and pericardial effusion are well contrasted.*

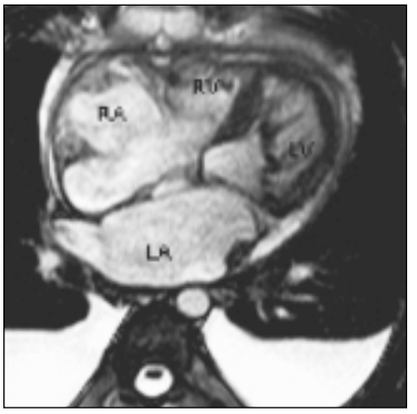

Fig. 3. *Four-chamber plane (GRE): Small ventricular and enlarged atrial chambers. Bilateral pleural effusions are also noted.*

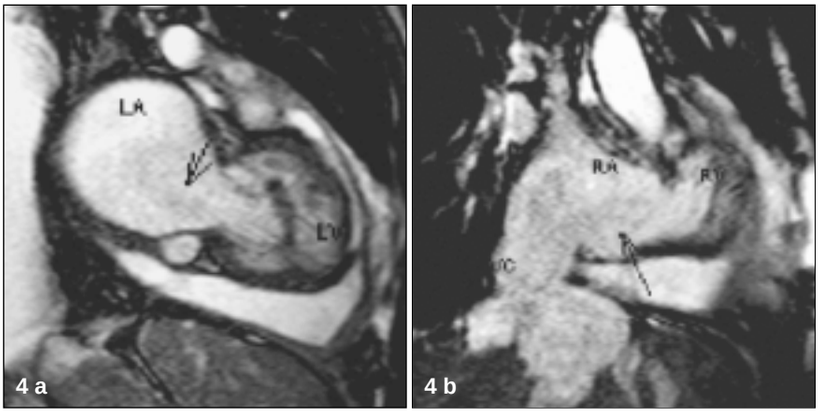

Fig. 4. *Two-chamber planes (GRE)* **(a)** *LA-LV plane and* **(b)** *RA-RV plane: Regurgitant jets noted through the mitral and tricuspid valves (arrow marked).*

SE: spin echocardiography; GRE: gradient recalled echocardiography; LA: left atrium; LV: left ventricle; RA: right atrium; RV: right ventricle

The pericardium may be involved in acute bacterial or viral infections such as pneumonia, in chronic infections such as tuberculosis, and in generalized conditions such as uremia, systemic lupus erythematosus, scleroderma, serum sickness, radiation therapy, rheumatoid arthritis, or even in lymphoma and malignant disorders. Long standing pericardial inflammation (pericarditis) may present as the classic chronic constrictive pericarditis or as subacute effusive constrictive pericarditis.

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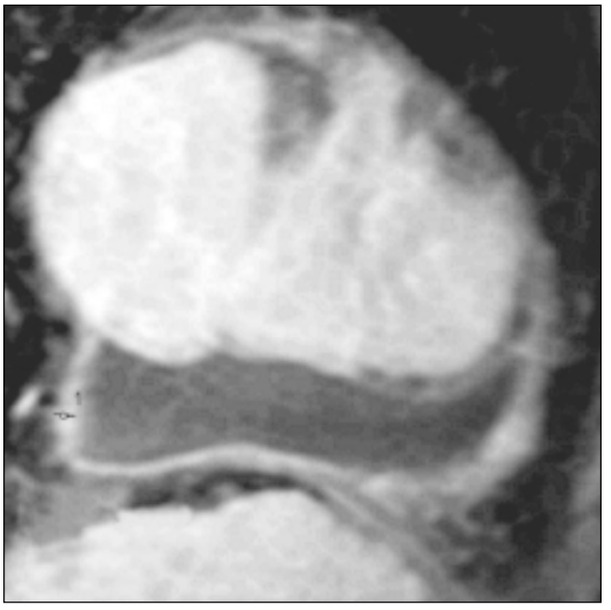

Fig. 5. *Post-gadolinium coronal image: Thickened enhancing pericardium is noted.*

The latter combines elements of effusion-tamponade and constriction.[1]

We present here the magnetic resonance (MR) images of a 31-year-old male who presented with a year-long history of slowly progressive swelling of the abdomen and lower limbs, with increasing dyspnea for the past 2 months. His clinical examination revealed ascites, bilateral pleural effusion and lower limb edema. The heart sounds appeared distant. His chest X-ray revealed an enlarged cardiac silhouette showing a triangular/moneybag configuration with evidence of bilateral pleural effusion. A cardiac MR was performed during the patient's work up. A prospective electrocardiogram (ECG)-gated cardiac magnetic resonance imaging (MRI) examination was performed on a 1.5 Tesla MR using spin echo (SE) and gradient recalled echo (GRE) techniques for morphological and functional evaluation. Axial T1-weighted SE (Fig. 1) images acquired for evaluation of cardiac morphology revealed biatrial enlargement with a thickened hypointense stripe (representing pericardial space and the parietal pericardium) between the epicardium and mediastinal fat. The thickened pericardium and the pericardial effusion were well identified separately on T2-weighted GRE sequences (Figs 2-4). Cine cardiac evaluation in the short axis plane revealed early diastolic flattening of the interventricular septum (IVS) with return of normal septal convexity toward the right ventricle during systole (Fig. 2a, 2b). Ballooned right and left atria were noted on the four-chamber plane (Fig. 3). Cine evaluation in two-chamber planes (Figs 4a and 4b) revealed regurgitant jets through the mitral and tricuspid valves during ventricular systole with grossly dilated inferior vena cava (IVC) and hepatic veins. Contrast-enhanced MR scans revealed a thickened enhancing pericardium suggesting pericardial inflammation (Fig. 5). The MR finding of pericardial thickening combined with early diastolic septal flattening, abnormal diastolic ventricular function and the resultant hemodynamic changes confirm presence of pericardial constriction. In the presence of an associated pericardial effusion a diagnosis of effusive-constrictive pericarditis was reached. The patient subsequently underwent a pericardiectomy, and a diagnosis of tubercular pericardial constriction was confirmed.

The pericardium is visualized as a low signal intensity band between the intermediate to high signal mediastinal fat and epicardium on ECG-gated T1-weighted spin echo scans and gradient echo MR. The thickness of the normal pericardium averages 1 to 2 mm.[2] The hallmarks of pericardial constriction are pericardial thickening, pericardial calcification, and abnormal diastolic ventricular function. In pericardial constriction, the morphology of the right ventricle is frequently abnormally tubular. Gradient reversal acquisition reveals limited diastolic excursion of the ventricles with resultant dilation of the right atrium, vena cavae, coronary sinus, and hepatic veins are also noted. Abnormal septal motion seen as left-sided septal flattening during early diastolic filling has been described as a very specific feature of constrictive pericarditis. Ventricular interdependence is increased owing to the presence of a non-compliant pericardium, which impedes the outward movement of the ventricular free wall during filling. Consequently, the instantaneous diastolic transseptal gradient changes and leads to septal reconfiguration and paradoxical motion during filling. The ventricular diastolic filling patterns help to distinguish from restrictive cardiomyopathy, which shows a uniformly impaired filling in contrast to the rapid early diastolic filling in constrictive pericarditis.[3] Pericardial thickening on its own is not diagnostic of pericardial constriction. It is the demonstration of pericardial thickening >4 mm in the face of characteristic hemodynamic findings that help distinguish constrictive pericarditis from restrictive cardiomyopathy. Computerized tomography (CT) is a significantly more sensitive technique than echocardiography for evaluation of pericardial thickness. CT is also exquisitely sensitive to pericardial calcification, which is present in nearly half the cases of pericardial constriction, in which case a tubercular etiology is strongly

suggested. ECG-gated MRI is an ideal method of investigating the pericardial thickness and assessing the morphologic and functional changes in the atria and ventricles resulting from pericardial disease. Reliable measurement of pericardial thickness cannot be made on echocardiography unless the pericardium is surrounded by both pleural and pericardial fluid. At times it cannot differentiate small pericardial effusions from pericardial thickening and may not identify loculations within pericardial effusions.[4] CECT and gradient reversal MRI can also accurately identify posterior left ventricular (LV) wall atrophy in patients with constrictive pericarditis, which has a prognostic significance post-pericardiectomy. Cases with atrophy of the free wall of the left ventricle are associated with markedly increased mortality following pericardiectomy.[5]

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Traumatic Pseudoaneurysm and Arteriovenous Fistula of Common Carotid Artery

A 30-year-old man, with history of progressively increasing swelling in his neck following blunt trauma two days before, was referred to us for urgent angiography. Clinical examination revealed a diffuse pulsatile swelling in the anterior and lateral aspect of his neck on the right side associated with a palpable and audible bruit. From the femoral route, an arch aortogram was done followed by selective angiogram of the right common carotid artery (RCCA). Angiogram of the RCCA showed a large false aneurysm arising from it with an associated fistula to the internal jugular vein (IJV) (Fig. 1). After informed consent, he was taken up for transcatheter repair after pre-treatment with a combination of aspirin and loading dose of clopidogrel (300 mg). Following insertion of a long 12 F sheath (Cook, Bloomington USA) into the abdominal aorta, a 0.032" guidewire (Terumo, Tokyo, Japan) and a 5 F Judkin's right coronary catheter were passed into the internal carotid artery well beyond the level of the false aneurysm. This was then exchanged with a 0.038" Amplatz extra stiff guidewire (Boston Scientific, USA) over which a 12 mm × 3 cm covered stent (Wallgraft, Boston Scientific, USA) was placed across the defect with its distal end just short of the bifurcation. Check angiogram following deployment of the stent showed good stent position within the RCCA with no filling of the false aneurysm or the IJV from the RCCA (Fig. 2). Doppler study of the RCCA at follow-up of 3 months has shown no evidence of recurrence of the fistula and there was good flow through the stent.

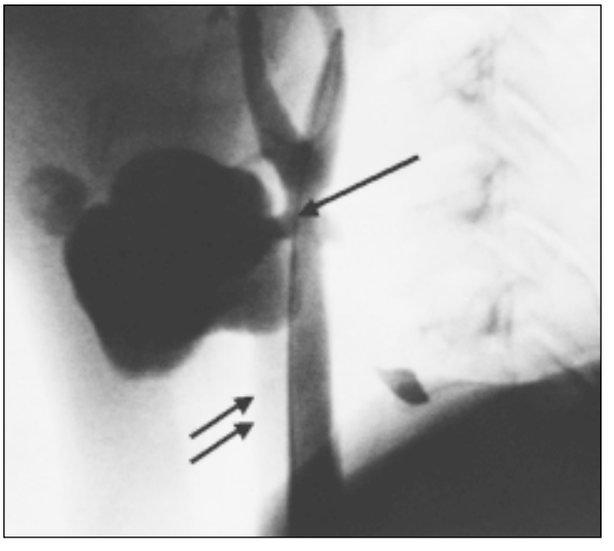

Fig.1. *Angiogram of the right common carotid artery showing rapid filling of the false aneurysm (↑) and the internal jugular vein (↑↑) via the arteriovenous fistula.*

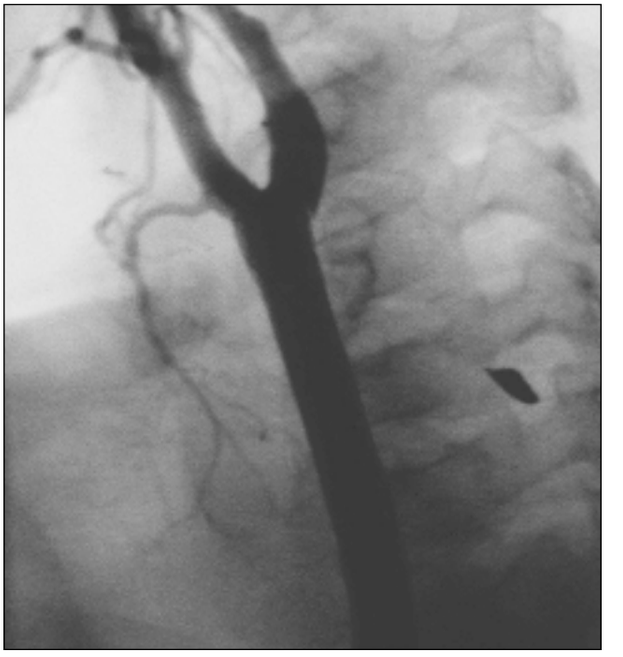

Fig. 2. *Check angiogram following stent graft deployment showing no-flow into the false aneurysm or the internal jugular vein.*

False aneurysms of the extra-cranial carotid arteries are uncommon and might be associated with arteriovenous fistulae, particularly following blunt or penetrating trauma.[1] The cases that do not present immediately, might present later with progressive enlargement causing compressive symptoms, distal embolization or rupture.[2] Though traditionally treatment has been surgical, recently various endovascular techniques have been reported. These include permanent balloon occlusion of the internal carotid artery,[3] covered stents[4, 5] or stenting with coil embolization of the false aneurysm.[6] So instead of surgery, endovascular therapy should be considered as an alternative treatment in such cases.

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ST Elevation is Not Always a Sign of Coronary Artery Disease

Coronary artery disease (CAD) is on the rise in south-east Asia in the younger population without any conventional risk factors. With changing social environment, drug abuse is increasing in younger population, and cocaine or heroin abuse can present as acute coronary syndrome (ACS).

A 35-year-old male was brought to the emergency of our institution after collapsing while having dinner. The patient was gasping and not responding to commands. The pulse rate was 100 beats per minute (bpm), regular, with low volume. Non-invasive blood pressure was 112/72 mmHg and oxygen saturation was 74% on room air. There was a bilateral wheeze and basal crepitations on auscultation of the chest. After endotracheal intubation, the patient was ventilated with a volume-controlled mode. Post-intubation hemodynamics deteriorated and dopamine infusion was started at the rate of 5 µg/kg/min, which was later increased to 10 µg/kg/min. The 12-lead electro-cardiogram (ECG) revealed ST segment elevation in leads V_2 to V_5. A diagnosis of extensive anterolateral wall ST elevation myocardial infarction (MI), with cardiogenic shock was made. Patient received oral aspirin 325 mg and streptokinase 1.5 million units. Troponin-T test was negative. As ST elevation started to normalize, there was improvement in hemodynamics. Dopamine infusion was tapered and stopped. A transthoracic echocardiography (TTE) revealed no evidence of MI in the form of segmental wall motion abnormality and left ventricular ejection fraction (LVEF) was 0.54. After overnight ventilation, there was marked improvement in chest condition. The patient was fully conscious and after weaning to CPAP mode, patient's trachea was extubated. The patient was asked for history of any addiction and he confessed to taking a large dose of cocaine on the night of the incident. The patient was later referred to the institutes' de-addiction clinic.

Any physician, who finds a young person with unexplained ECG changes suggestive of MI without any of the conventional risk factors, should consider cocaine use to be a possible cause for the ACS.

Cocaine may cause MI by (i) increasing myocardial oxygen demand through increases in the heart rate and blood pressure, (ii) diminishing coronary artery flow either from coronary vasospasm or thrombosis, or (iii) active myocarditis.

There are few reports of documented MI in cocaine abusers in the literature.[1] Cardiac specific troponin T or I is useful for detecting myocardial necrosis in these patients.[2] Myocardial perfusion imaging with technetium 99m sestamibi has been found to be useful in excluding infarction in patients with cocaine-associated chest pain.[3] Treatment of cocaine-induced myocardial ischemia consists of nitrates, β-adrenergic blockers, calcium antagonists and thrombolytic therapy for MI. β-blockers probably should be avoided because cocaine causes α-adrenergic-induced coronary vasoconstriction and can further reduce coronary blood flow.[4]

Thus, ST elevation in a young patient may not always be due to atherosclerotic CAD and may not be a sign of acute MI. Because of the social stigma attached to drug abuse, patients may hide this crucial information. In such situation the probability of drug abuse should be kept in mind and patient's urine sample should be sent for detection of cocaine or its metabolites.

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Mild Mitral Regurgitation on Color Doppler Echocardiography: A Diagnostic Dilemma

Color Doppler echocardiography is a sensitive and useful modality for diagnosis and quantitation of regurgitant lesions. Color Doppler echocardiography is more sensitive in picking up minor degrees of valvular regurgitation than clinical examination.[1] However, because of the higher sensitivity there is a chance of overdiagnosis and it should be remembered that trivial regurgitant on color Doppler may occur even in normal subjects.[2] While evaluating a child with insignificant murmur and unequivocal history for rheumatic fever, if a trivial or mild mitral regurgitation is detected the first step is to confirm that it is pathological mitral regurgitation and not the so-called Doppler regurgitation. The pointers for pathological mitral regurgitation being the typical regurgitant color jet clearely seen in two planes with a velocity of >1.2 m/s systolic signal of mitral regurgitation of >200 m/s and the mitral regurgitation signal on pulsed Doppler being recorded > 1 cm away from the coaptation point of the mitral valve.[3-5]

The next important dicision is to ascertain whether mitral regurgitation is rheumatic or not? The valvular nodularity and thickening of the valve leaflets and chordae, if present, do suggest a rheumatic etiology. Often these may not be very typical in a patient with mild mitral regurgitation. In such a case, if the short axis view of the mitral valve shows commissural mitral regurgitation then it is most likely to be rheumatic in etiology (Figs 1 and 2). This is collaborated by the pathology of rheumatic mitral valve disease – commissural involvement being the hallmark.[6]

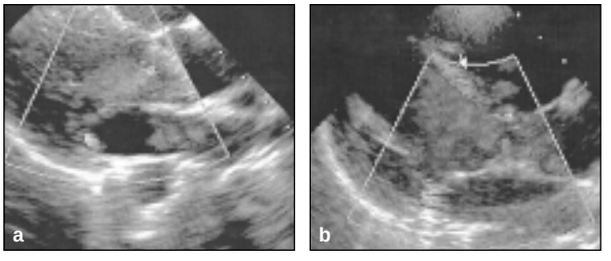

Fig. 1(a). *Long axis view showing mild mitral regurgitation on color Doppler echocardiography*. **(b)** *Apical 4-chamber view showing mild mitral regurgitation on color Doppler echocardiography*.

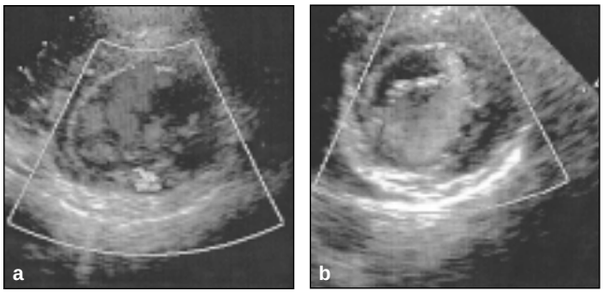

Fig. 2. *Two-dimensional echocardiogram short axis view at mitral valve level:* **(a)** *mitral regurgitation through posteriomedical commissure,* **(b)** *mitral regurgitation through anterolateral commissure,*

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Screening for Pre-Clinical Hypertrophic Cardiomyopathy by Tissue Doppler Imaging

I read with interest the article by Seth et al.[1] However, their methodology needs clarification. In the case of tissue Doppler analysis they state that "sample volumes were placed at the lateral aspect of mitral valve annulus, septal side of mitral annulus, mid lateral wall and mid septum." These are vague areas. Where exactly were the sample volumes placed? Was is say, 0.5 cm, 2 cm, 3 cm etc. from the cavity or from the apex. Tissue Doppler values change with minor changes in position. This is seen in the wide variability of the three values used for averaging. Even if there is no variability, were they interrogating similar points in the patients, relatives and controls.

Without going into the complexities of the vector components of cardiac motion, are they confident that they are measuring the peak velocities consistently. For example, at the lateral regions could they align the Doppler beam in the apparent line of motion. Or, did they apply angle correction, or maintained the same angle for all the measurement.

The authors state, "velocities were measured in the apical 4-chamber and 2-chamber views". However, the values of the 2-chamber views were not documented. Is it that these values do not conform to their hypothesis? Similarly, "color tissue Doppler images were acquired". Why? And what was the inference?

Basic echocardiology tells us that myocardial thickening is the gold standard of regional systolic function. These are best explored from the parasternal short and long axis views. What were the tissue Doppler recordings from these views? Or are these velocities of no consequence? This paper presents methodological inaccuracies and so the data obtained and the inferences derived should be viewed with caution.

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Reply

With reference to the letter by Dr George Thomas, we provide the following clarifications: (i) The technique we have used is the standard technique used in tissue Doppler studies. The pulse Doppler probe was paced at the lateral corner and medial corner of the mitral annulus in the apical 4-chamber view. It is not possible to measure this point by using an absolute distance from the apex as this would not be fixed for all patients. The minimum possible gate length was used, the view used was apical 4-chamber view and each wall was aligned to the cursor prior to recording, to the extent possible (angle correction was done for the lateral wall). To avoid errors, an average of three cycles, where all three cycles were showing a similar configuration, were used, (ii) The color tissue Doppler images were acquired for quality control to ensure that the recorded pulse Doppler wave forms were from the correct site, (iii) 2-chamber views were recorded in these patients but were not presented since they did not provide significant additional information, and (iv) Tissue Doppler was not recorded from any parasternal view because the movement here is perpendicular to the Doppler line and therefore the myocardium moves out of the cursor range and results are not consistent. Therefore, tissue Doppler studies generally do not use parasternal views.

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Transmitral Doppler Flow Velocities in Uncomplicated Maturity Onset Diabetics below 50 years

Left ventricular (LV) diastolic dysfunction is known in diabetes. Hypertension, obesity, microangiopathy, coronary artery disease and autonomic neuropathy are frequent in diabetes and can independently influence ventricular diastolic functions.[1-3] Diastolic dysfunction is also common in the elderly. Previous studies[4-6] have not rigidly excluded these coexisting abnormalities. It is, therefore, not clear whether diabetes mellitus *per se* produces diastolic dysfunction independent of the co-existing conditions.

Transmitral Doppler flow velocities were evaluated in 25 patients with maturity onset diabetes. Patients with hypertension or history of antihypertensive therapy, body mass index ≥35 kg/m^2, microangiopathy and autonomic neuropathy were excluded. Other conditions known to independently affect transmitral flow velocities were also excluded. These included age >50 years, history of regular isometric or endurance exercise, heart rate < 60/min or > 100/min. Patients with history of angina, abnormal resting electocardiogram (ECG), positive stress test, inadequate echocardiographic evaluation or presence of any valvular lesion, regional wall motion abnormality or systolic dysfunction on echocardiography were also excluded. Twenty-five asymptomatic persons matched for age, sex, systolic and diastolic blood pressure without any abnormality on clinical examination, ECG, stress testing and echocadiography formed the control group.

Demographic and hemodynamic variables were not statistically different in the two groups. Transmitral peak E wave velocities were 74.3±14.2 cm/s in control group and 69.7±14.8 cm/s in diabetics (p>0.05). Peak A wave velocities were 58.7±14.6 cm/s in control group and 56.1±11.5 cm/s in diabetcs (p >0.05). E wave/A wave ratios were 1.47±0.38 in control group and 1.30±0.28 in diabetics (p=0.05). Pressure half-time was 55.8±10.8 ms in control group and 49.8±12.3 ms in diabetics (p=0.05).

Transmitral Doppler flow velocities may be influenced by age, heart rate, rhythm, loading conditions, ventricular systolic functions and atrial functions. All these variables were excluded in this study. Diastolic LV functions can also be evaluated by color flow propagation velocity and mitral annulus tissue Doppler evaluation if variables that affect transmitral flow cannot be excluded categorically. We did not perform these studies as we strictly excluded various confounding factors. However, we cannot be dogmatic that our patients did not have any diastolic function abnormalities not detected by transmitral flow velocity.

We observed that uncomplicated maturity onset diabetics <50 years of age have normal transmitral flow velocities if various confounding factors are excluded.

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Acute Effects of Smoking on Blood Pressure: Implications for Blood Pressure Measurements

There is consensus that there are a large number of factors including smoking which can contribute to the variability in blood pressure (BP).[1] In an attempt to negate the acute effects of smoking on BP, it is recommended that patients should refrain from smoking for 30 min preceding the BP measurement.[2]

We analyzed the BP responses to a single cigarette (Gold Flake Kings, ITC Ltd.) consumed within 5 min in 32 healthy male smokers [young group, <30 years (n=16); old group, >60 years (n=16)] for a period of 2 hours after cessation of smoking. BP at each of the time points indicated in the table below, was the avearage of two measurements made with an automated BP device (Welch Allyn, NY, USA, meeting SP10-1992 AAMI standards). When the data for all subjects were pooled, elevation in systolic BP (~ 4 mmHg) persisted for 45 min and diastolic BP (~ 3 mmHg) for 15 min following cessation of the cigarette smoking. In contrast, in the young subjects alone, the elevation in systolic BP (peak change ~11 mmHg) persisted for 2 hours and diastolic BP (peak change ~ 6 mmHg) for 45 min following the cigarette smoking. There was no significant elevation in BP in the old subjects.

	Basal	15 min	45 min	90 min	120 min
All subjects					
Systolic BP	119.4±20.0	125.9±2.2*	123.3±2.1*	122.3±1.9	123.5±2.1
Diastolic BP	72.3±1.3	75.6±1.4*	74.1±1.3	73.0±1.2	72.8±1.2
Young					
Systolic BP	116.1±2.9	126.9±3.2*	123.6±3.0*	120.7±2.7*	121.0±2.8*
Diastolic BP	69.8±1.4	76.2±1.8*	74.0±1.7*	72.3±1.6	72.2±1.6
Old					
Systolic BP	122.5±2.5	125.0±3.0	122.9±3.1	124.0±2.8	126.1±3.1
Diastolic BP	74.7±2.1	75.1±1.8	74.2±1.8	73.8±1.8	73.4±1.7

All mean±SD
* significantly different from basal (paired t test, after Bonferroni correction for multiple comparisons)

The data indicated that the magnitude and duration of BP elevation with cigarette smoking is variable, and may not be limited to the 30 min following a cigarette smoking. It underscores the need for physicians to document time interval of smoking in relation to a BP measurement; this is not standard practce. There is also a need for more data to be generated to determine the effects of age and cumulative cigarette exposure on the acute effects of smoking on BP.

Acknowledgements

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References

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Rescue Angioplasty after Failed Thrombolytic Therapy for Acute Myocardial Infarction

Gershlick AH et al. For REACT investigators. N Engl J Med 2005; 353: 2758-2768

Summary

The multicenter randomized controlled trial, Rescue Angioplasty versus Conservative Treatment or Repeat Thrombolysis (REACT), was conducted in 35 centres in the United Kingdom to evaluate the various strategies of management after failed thrombolysis for acute ST elevation myocardial infarction (STEMI). Four hundred and twenty-seven patients (age range: 34 - 84 years), who received various licensed thrombolytic agents within 6 hours of onset of chest pain and had resolution of ST segment elevation of less than 50% in the lead with maximum ST elevation at 90 min after thrombolytic therapy were included in the study. The patients were randomized to one of the three arms, i.e. repeat thrombolysis with fibrin-specific thrombolytic agents (alteplase or reteplase) (n=142) patients, conservative treatment (n=141) or rescue percutaneous coronary intervention (PCI) if needed, as decided by angiography (n=144). The primary end point was a composite of death, reinfarction, cerebrovascular events or severe heart failure within six months. Secondary end points included components of primary end point as well as bleeding and revascularization. Occurrence of composite primary end point was significantly lower in the rescue PCI group as compared to the other two groups (15.3% in rescue PCI group *v.* 31% and 29.8% in repeat thrombolysis and conservative arm, respectively, $p<0.01$). However, individually incidence of death from any cause, death from cardiac causes, cerebrovascular accident (CVA) or severe heart failure was not different in the three groups. Recurrent mycardial infarction (MI) was significantly lower in rescue PCI arm (2.1% *v.* 10.6% and 8.5% in repeat thrombolysis and conservative arms, $p<0.01$). Revascularization at six months tended to be lower in the rescue PCI group (13.2%) *versus* 20.6% in the conservative arm and 23.2% in the repeat thrombolysis arm. At six months, incidence of major bleeding was not significantly different in three groups: 0%, 3%, 5% in the rescue PCI group, conservative arm, and repeat thrombolysis group, respectively. Minor bleeding episodes were significantly more frequent in the rescue PCI group. The rate of event-free survival among patients treated with rescue PCI was 84.6%, as compared with 70.1% in conservative arm and 68.7% in repeat thrombolysis group ($p=0.05$).

Comments

Various trials have proven the prognostic importance of an open infarct-related artery. Primary PCI has been shown to be superior to thrombolysis in achieving a higher patency rate in the infarct-related artery. However 30% to 70% of MI cases worldwide get thrombolyzed mainly due to non- availability of intervention facilities. The optimum management for unsuccessful thrombolysis is not clear at present. It was to address this important clinical issue that the present REACT study was undertaken. The data to support rescue PCI is limited. Recently reported Middlesbrough Early Vascularization to Limit Infarction (MERLIN) trial results showed benefit of rescue PCI only in terms of reducing revascularization rates. The contradictory results obtained in REACT trial have been discussed by the authors and the reason put forth may be two-fold. First, in MERLIN trial eligibility of entry into study was decided on the basis of electrocardiogram (ECG) obtained after 60 min of giving thrombolytic therapy and streptokinase was the initial thrombolytic agent used (96% *v.* 59% in the MERLIN trial). Hence there might be some more patients in the conservative arm who had an open vessel at 90 min and hence resulting in improvement in the clinical outcome of patients included in the conservative arm. Moreover, for some unexplained reason there was increased incidence of CVA and mortality in PCI arm of MERLIN trial. There was a lower rate of stenting and of glycoprotein IIb/IIIa inhibitor use in the MERLIN trial which may have contributed to a higher reinfaction rate in the rescue PCI group. Also there was around 12% of patients in the conservative group who underwent repeat thrombolysis, which probably confounded the results further. Another important aspect of this trial was that only 61% of the patients were enrolled from centers in which there was facility for intervention whereas the rest were transferred at a median time of 85 min from centers where there were no interventional capabilities. Stents were deployed in 68.5% and abciximab was administered in 43.4% of patients. As for the safety concerns, there was no difference in the incidence of a major bleeding complication in the three arms although there was a higher incidence of minor bleeding in the rescue PCI group. In conclusion, the REACT trial found that rescue PCI is better than repeat thrombolysis or conservative management following failed thrombolysis. There was a significant reduction in major cardiac and cerebrovascular events with most of the benefit obtained by rescue PCI because of a reduction in the rate of reinfarction and reduced revascularization rates. Therefore, rescue PCI should be considered for failed reperfusion following thrombolysis even if it entails transfer to a tertiary center.

High-Dose Atorvastatin vs Usual- Dose Simvastatin for Secondary Prevention after Myocardial Infarction

Pedersen TR et al. For IDEAL study group. JAMA 2005; 294: 2437-2445

Summary

The Incremental Decrease in End points through Aggressive Lipid lowering (IDEAL) study was undertaken to address the hypothesis that there is an incremental benefit of intensive lowering of low-density lipoprotein cholesterol (LDL-c) with high dose of atorvastatin compared to the regular, moderate dose of simvastatin. The IDEAL study was a multicenter, prospective randomized, open label, blinded trial carried out in 6 European countries over a 2-year period. Patients under the age of 80 years with a definite history of past myocardial infarction (MI) were included. Patients enrolled were randomized after dietary counseling to receive simvastatin 20 mg daily or atorvastatin 80 mg daily. Patients were regularly followed up and the dose of simvastatin was increased to 40 mg daily if the plasma total cholesterol was higher than 190 mg daily. The dose of atorvastatin was reduced to 40 mg daily in case of adverse effects. The primary clinical outcome was time to first occurrence of a major coronary event defined as coronary death, confirmed non-fatal acute MI or cardiac arrest with resuscitation. Eight thousand eight hundred and eighty-eight patients met the eligibility criteria and were randomized. Baseline characteristics were comparable between the two groups. The median follow-up time was 4.8 years. During treatments, patients in the simvastatin group had a mean LDL level of 104 mg daily and those in the atorvastatin group had a mean LDL of 81 mg daily. The primary outcome (a major coronary event) occurred in 10.4% of the simvastatin patients and in 9.3% of the atorvastatin patients (p=0.07). This corresponds to a relative risk reduction of 11% with atorvastatin. Non-fatal MI occurred in 6% on atorvastatin and 7.2% on simvastatin (p=0.02). There were 4% coronary deaths in the simvastatin group *versus* 3.9% in the atorvastatin group (p=0.90). Non- fatal MI occurred in 321 patients (7.2%) in the simvastatin group and in 267 (6.0%) patients in the atorvastatin group (p=0.02). The risk of death from any cause was similar in both groups and non-cardiovascular death occurred in 156 (3.5%) and 143 (3.2%) in the two groups, respectively (p=0.81). Major cardiovascular events including stroke occurred at a lower rate in the atorvastatin group 12% *versus* 13.7% in simvastatin group (p=0.02). These results indicate that more intensive lowering of LDL-c than usual in patients with previous MI might prevent 68 first cardiovascular events per 1000 patients over 5 years.

Comments

The Scandinavian Simvastatin Survival Study (4S) reported by Pedersen and colleagues was the landmark trial that first reported a significant 30% reduction in total mortality with the daily use of simvastatin at a dose of 20-40 mg daily. In this particular study the LDL-c reduction was 35%. The majority of statin trials in the recent past have evaluated the effect of lowering of LDL-c by 25-40%. The PROVE IT- TIMI 22 trial evaluated a more intensive strategy using high dose atorvastatin that achieved a median LDL-c level of 62 mg daily. There emerged a 16% reduction in the risks of death and major cardiovascular events which was observed over the subsequent two years following an acute coronary syndrome. The Treating to New Targets (TNT) trial expanded the benefit of intensive statin therapy to patients with stable coronary artery disease. However, there was a question mark over the issue of non-cardiovascular deaths. The IDEAL trial was undertaken to explore whether there is an incremental benefit of reducing LDL-c in patients with chronic coronary artery disease and also to assess the safety of high dose atorvastatin therapy. This study showed that with the use of atorvastatin 80 mg daily (the intensive statin treatment) there was a 23 mg/dl lower LDL-c level compared with simvastatin 20-40 mg daily. This reduction translated clinically to an 11% reduction in the primary end point of coronary heart disease death, non-fatal MI or cardiac arrest with resuscitation (p=0.07). The primary end point was thus not met. However, if a major cardiovascular event such as stroke is included, as was done in the TNT trial, there was a significant 13% reduction (p=0.02). Similarly if any cardiovascular event including revascularization was used, there was a 16% reduction (p<0.01). There were no differences in all-cause, cardiovascular or non-cardiovascular mortality. This study has shown that there is no enhanced risk of dying due to non-cardiovascular causes including cancer in the 5 years follow-up period. Other safety concerns included liver and muscle toxicity that was also assuaged satisfactorily. However, there was a higher rate of discontinuation of therapy with atorvastatin due to non-serious adverse events (elevated transaminases) (9.6% *v.* 4.2%). To summarize, this study has shown that "lower is better" for preventing MI, stroke and in reducing the need for cardiac procedures.