Hormone Replacement Therapy and Coronary Artery Disease: Buried Alive?

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The onset of the menopause has been linked to a rise in cardiovascular risk in women. Epidemiologic studies have shown that the risk of cardiovascular events rises steadily with increasing age in the postmenopausal period. Data from the Framingham Heart Study showed that the annual incidence of myocardial infarction (MI) in the age group 45–64 years was 424 000 in men and 136 000 in women; this increased to 440 000 in men and 374 000 in women in those ≥65 years of age.1 As life expectancy increases, more women spend a longer period in the estrogen-depleted state. The public health importance of this increased cardiovascular risk is evident from the mortality data available from developed countries—more than 250 000 deaths/year in women in the United States result from MI alone.7 Also, the mortality rate in women with established coronary artery disease (CAD) is much higher than that in men. Cardiovascular diseases are also a leading cause of disability. The economic impact of cardiovascular diseases for 1999 in the United States— including work absences, lost productivity and premature death—has been estimated to be nearly $300 billion.2 As epidemiological data strongly suggested that the incidence of CAD in women rose dramatically after the age of 50 years, the approximate age of natural menopause when endogenous estrogen levels dropped, exogenous estrogens have increasingly been used to restore the “hormonal imbalance”.

Results from numerous case-control, observational and angiographic trials as well as from meta-analysis of these trials supported the use of hormone replacement therapy (HRT) for the prevention of CAD in postmenopausal women.3–6 Data from these trials showed a 35%–50% reduction in coronary events in women on HRT. Both estrogen replacement therapy and combination estrogen-progestin therapy have been shown to reduce the incidence of fatal and nonfatal MI in these studies. Numerous biologically plausible mechanisms support these epidemiological observations. Hormone replacement therapy has been shown to favorably affect the lipid profile; it lowers LDL-cholesterol and total cholesterol levels and increases HDL-cholesterol levels.7 It also favorably affects other biochemical factors such as fibrinogen, lipoprotein (a) [Lp(a)], tissue plasminogen activator, plasminogen activator inhibitor-1, insulin resistance and homocysteine.7,8 By acting on estrogen receptors on the vasculature, estrogen also modulates vasomotor tone and improves endothelial cell function. However, these favorable results on CAD were not replicated in the only large, randomized, placebo-controlled, secondary prevention trial conducted so far,9 prompting a serious re-look at the body of evidence supporting HRT for CAD.

Hormone Replacement Therapy in Secondary Prevention of CAD

The HERS trial: The Heart and Estrogen/progestin Replacement Study (HERS) was the first large, randomized, double-blind, placebo-controlled trial to be conducted in women taking HRT.9 It was a secondary prevention trial that enrolled 2763 postmenopausal women with CAD who were randomized to HRT (n=1380) or placebo (n=1383). A prior Q wave MI was seen in 17% of patients, approximately 45% had undergone a previous angioplasty while 42% had had prior bypass surgery. Women who had a coronary event within 6 months prior to the onset of the trial were excluded from the study. Lipid-lowering therapy was prescribed to 45% of women on HRT and 47% of women on placebo. These women were followed up for a mean period of 4.1 years. Their mean age was 67 years and the mean duration since menopause was 18±8 years. All women on HRT received 0.625 mg of conjugated equine estrogen along with 2.5 mg medroxyprogesterone acetate. The mean reduction in LDL-cholesterol levels was 10% while HDL-cholesterol levels rose by 11% (p<0.001). Despite this favorable effect on lipids, there was no overall difference in coronary events in either arm at 4 years of follow-up. Within this overall null effect, there was an increase in cardiovascular events in the first year of use (the risk for a recurrent MI or cardiovascular death was 50% higher in the treatment arm in the first year of therapy). In absolute numbers, there were 57 coronary events in the HRT arm.
Corroborative evidence from other trials: The results of the HERS trial were contrary to observations in nonrandomized trials. However, the greater number of cardiovascular events in women on HRT in the first year of use is not likely to be due to chance alone. Data from some previous observational studies including the Coronary Drug Project and Nurses Health Study had also suggested an increase in coronary events in patients on HRT. In the Coronary Drug Project, men with a previous MI who were randomized to 5 mg/day of conjugated equine estrogen had a significant increase in recurrent MI rates, necessitating premature termination of this arm of the trial. In the Nurses Health Study also, a two-fold increase in the risk of MI or CAD was reported in the first year of initiation of HRT amongst women with a prior MI compared to non-users.

Similarly, in an interim report, investigators from the Women's Health Initiative, a large, randomized, placebo-controlled, double-blind, primary prevention trial comparing HRT versus placebo, reported an increased incidence of MI in the initial two years of use.

Active intervention trials initiating HRT soon after acute MI have also demonstrated an increase in cardiovascular events on follow-up. The Coumarin Aspirin Reinfarction Study (CARS) was a randomized, double-blind trial involving 8803 post-MI patients who were randomized to low-dose aspirin plus low-dose coumadin or standard-dose aspirin. It included a subgroup of 1857 postmenopausal women of whom 107 (6%) were new users. The use of HRT was not randomized. In a retrospective analysis of this subgroup of patients, Alexander et al. found that those who had been given HRT soon after an acute MI had a higher incidence of unstable angina on follow-up than nonusers (39% vs. 20%, p=0.001). However, in contrast to the HERS trial the risk of death or recurrent MI was lower among users than nonusers (4% vs. 15%, p<0.05). In another population-based cohort study, 981 postmenopausal women who survived to hospital discharge after their first MI, were followed for a mean period of 3.5 years. Compared to women who were not on hormones, those on HRT had an increased risk of recurrent coronary events during the first 2 months of hormone use (adjusted RH 2.16; 95% confidence interval 0.94–4.95). However, the risk of coronary events was lower in those who continued to use HRT for longer than 1 year (adjusted RH 0.76; 95% confidence interval 0.42–1.36).

A recent, randomized, angiographic study also failed to substantiate the beneficial effect of HRT on coronary atherosclerosis in contrast to the numerous observational studies that had documented an improvement in the angiographic profile of coronary arteries in women on HRT. The Estrogen Replacement and Atherosclerosis (ERA) study randomized 309 postmenopausal women (mean age 65.8 years) to one of the three arms: 0.625 mg of conjugated equine estrogen/day (n=100), 0.625 mg of conjugated equine estrogen plus 2.5 mg of medroxyprogesterone acetate/day (n=104) or placebo (n=105). These women were followed for a mean period of 3.2±0.6 years. Forty-eight percent of women who were in the estrogen arm had a prior MI while 41% and 55% of women in the estrogen plus progesterone and placebo arms had a prior MI, respectively. Thirty-four percent, 38% and 37% of women in these age groups were on lipid-lowering agents as well. Though estrogen and estrogen plus progesterone produced significant reduction in LDL-cholesterol levels (9.4% and 16.5%, respectively) along with a significant improvement in HDL-cholesterol levels (18.8% and 14.2%, respectively), no significant alteration in progression of coronary atherosclerosis was seen with either drug. The investigators suggested that, based on these results, estrogen replacement should not be used in women with established CAD for cardiovascular benefits.

Possible mediatory mechanisms for adverse outcome: Numerous hypotheses have been proposed to explain the excess cardiovascular events in these trials, including a prothrombotic effect, proinflammatory actions, plaque instability, an adverse effect on lipid composition of LDL. Hormone replacement therapy has been shown to exert a prothrombotic effect; an excess of venous thromboembolic events has clearly been shown to occur in the HRT arm in numerous trials. Whether this process can extend into the arterial tree is unresolved. Procoagulant factors such as Factor VII, Factor X and protein C have been showed to be raised while levels of antithrombin III are low in HRT users. Hormone replacement therapy has also been shown to increase serum levels of inflammatory markers such as C-reactive protein (CRP). It has been shown that
this could possibly initiate or aggravate inflammation in atherosclerotic plaques leading to plaque rupture or thrombosis. Data from both men and women have identified CRP as an independent risk factor for future cardiovascular events. Importantly, data from the Women’s Health Study has shown that CRP predicts future cardiovascular events even among low-risk subgroups of women with no apparent risk factors. Overall, the risk of cardiovascular events is 5-fold higher in those in the highest quartile of CRP level (>7.3 mg/L). Similarly, the risk of MI and stroke is increased 7-fold.

Other inflammatory mediators that adversely affect plaque stability are also stimulated by HRT. Zanger et al., demonstrated that the serum level of matrix metalloproteinase-9 (MMP-9) is increased with short-term HRT. This is due to estrogen-mediated increase in expression of the gene encoding for MMP-9. As HRT also reduces plasma levels of plasminogen activator inhibitor-1, the principal inhibitor of plasmin, plasmin-mediated activation of MMP-9 is possible in vulnerable plaques. These two mechanisms result in digestion of matrix proteins that comprise the fibrous part of atherosclerotic plaques, predisposing them to rupture and thrombosis.

An adverse effect on lipid profile may also contribute to the unfavourable results. Although HRT decreases LDL-cholesterol levels significantly, studies have shown that it unfavorably alters LDL particle size. It has been shown that exogenous estrogens produce an increase in plasma triglyceride concentrations. This increase in plasma triglyceride levels reduces LDL particle size due to changes in lipid transfer; hypertiglyceridemia results in triglyceride-rich and cholesterol ester-poor LDL particles. The triglyceride content then gets hydrolyzed by lipolytic enzymes which results in smaller than usual LDL particles. As the menopause has been shown to be associated with small LDL particle size, HRT may further increase the small LDL subfraction content in postmenopausal women. This may partially offset the benefits of decreasing LDL-cholesterol levels as small dense LDL subfraction is more susceptible to oxidative modification.

An epidemiological illusion? The results from the HERS trial could have been similar to that from non-randomized trials had the patients been recruited in an observational study design. Although HRT decreases LDL-cholesterol levels significantly, studies have shown that it unfavorably alters LDL particle size. It has been shown that exogenous estrogens produce an increase in plasma triglyceride concentrations. This increase in plasma triglyceride levels reduces LDL particle size due to changes in lipid transfer; hypertiglyceridemia results in triglyceride-rich and cholesterol ester-poor LDL particles. The triglyceride content then gets hydrolyzed by lipolytic enzymes which results in smaller than usual LDL particles. As the menopause has been shown to be associated with small LDL particle size, HRT may further increase the small LDL subfraction content in postmenopausal women. This may partially offset the benefits of decreasing LDL-cholesterol levels as small dense LDL subfraction is more susceptible to oxidative modification.

HRT and CAD: Newer Fronts

A subgroup that benefits? These results from randomized trials have dampened the use of estrogen/progestins for the prevention of future coronary events in women with established CAD. It is not currently recommended to start HRT in such women for cardiovascular benefits alone. Efforts are being targeted to identify women with established CAD who may be at an increased risk for coronary events while on HRT. Prospective identification of such women would permit prescription of these drugs to appropriate postmenopausal women only. Subanalysis from the HERS trial has suggested that a subgroup with increased coronary events on HRT may be identifiable—women who have Lp(a) levels below the
median at baseline have an increased risk of cardiovascular events in the first year of use (relative risk 2.1 v. placebo, p≥0.05). On the other hand, women with Lp(a) levels above the median had less early harm (p=0.04). In a recent publication, the HERS investigators showed that increased Lp(a) levels (>25 mg/dl) remained a possible positive modifier in women on HRT throughout the study. Many other clinical, demographic and laboratory parameters, however, did not identify patient subgroups who would or would not benefit from HRT. As one of the hypotheses for an increase in coronary events in HERS was postulated to be a thrombotic event, possible risk factors are being looked for that could explain these results. Such a prothrombotic risk factor would need to have a prevalence of 3%–5% in the population and have a risk ratio of 13–15 amongst HRT users to reproduce results similar to those of HERS. Psaty et al. reported that the prothrombin variant 20110 G to A was a prothrombotic genetic mutation that could predispose such women to adverse events while on HRT. This has been previously shown to produce an increased risk of venous thrombosis though its effects on coronary events are unclear. Amongst postmenopausal hypertensive women on HRT, current users with this prothrombin variant had an 11-fold increased risk of nonfatal MI compared to nonusers. This interaction was not seen in nonhypertensive women. Factor V Leiden, which has been shown to be associated with an increased risk of venous thrombosis, did not predispose to increased coronary events amongst either users or nonusers in this study.

Additional subgroups in whom the role of HRT is still unclear include those women who are on estrogens alone. In the HERS trial, only combined therapy with both estrogens and progestogens was used and hence these results do not apply to users of estrogens alone. A patients enrolled in the HERS trial were started on HRT late into the menopause (nearly 20 years later), these results also cannot be extrapolated to younger postmenopausal women.

**Newer agents, different composition, newer routes of administration?** It needs to be explored whether altering the components of HRT, their doses, or their mode of administration may affect outcome. The role of progestogens in HRT is solely to counter the effects of unopposed estrogen on uterine endometrium. As they remain a weak link in HRT, with numerous studies showing that they attenuate the effect of estrogens, alternative progestogens are being explored. In one study it was demonstrated that natural progesterone, but not medroxyprogesterone acetate, augmented the beneficial effects of estrogen. In this study, time to exercise-induced myocardial ischemia was increased by estradiol/progesterone therapy compared to estradiol/medroxyprogesterone acetate therapy. These findings are in concordance with other data that have reported a detrimental effect of medroxyprogesterone acetate on coronary vasomotor tone and plaque development. Miyagawa et al. demonstrated that the addition of medroxyprogesterone acetate to 17-beta-estradiol in ovariectomized rhesus monkeys increased the risk of coronary vasospasm while progesterone did not have any adverse effect. Adverse effects of medroxyprogesterone acetate on coronary atherosclerosis in the animal model have also been reported. Bellinger showed that the beneficial effects of conjugated equine estrogens on coronary atherosclerosis were opposed by medroxyprogesterone acetate. In the balloon-induced injury model of rat carotid arteries, medroxyprogesterone acetate has been shown to attenuate estrogen-mediated inhibition of neointimal proliferation. On the other hand, in vitro models have shown that progesterone has an anti-smooth muscle proliferative effect. Thus the effect of adding a more appropriate progestogen to HRT needs to be examined.

Concerns have also been raised about the dose and route of estrogen administration. Retrospective analysis from the Nurses Health Study showed that a dose of 0.3 mg of conjugated equine estrogen conferred a similar protection against major coronary events as 0.625 mg. Some other studies have also demonstrated that low-dose HRT is effective in improving lipid profile, reducing osteoporosis and improving endothelial function. Whether a lower dose of HRT (0.3 mg of conjugated equine estrogen) will have a lesser prothrombotic effect acutely remains to be seen. This could reduce the increased risk of coronary events seen after initiating HRT. Moreover, as low-dose HRT is as effective in countering climacteric symptoms and is not associated with withdrawal bleeding, drug compliance is significantly better, especially in older postmenopausal women. The dose of progestogen required in low-dose HRT is also much lower—this should further reduce the adverse effect of progestogens in HRT. Sattar et al. reported that plasma CRP levels were lowered when they used transdermal rather than oral estrogen. This differential effect of transdermal versus oral delivery of estrogens may relate to bypassing the first-pass metabolism in the liver. As plasma levels of CRP relate to hepatic synthesis, transdermal estrogens may not adversely influence CRP levels. Also, the investigators used norethisterone, which is
more triglyceride neutral, instead of medroxyprogesterone acetate. These differences may account for the discordant effects between these two modes of delivery. These issues, however, are yet to be resolved as some studies, including a recent retrospective, population-based, nested, case-control study conducted in the UK demonstrated that the incidence of acute MI was similar in women on oral as well as transdermal HRT.33

**Hormone Replacement Therapy in Primary Prevention of CAD**

Epidemiological data from observational studies have shown a marked reduction in the risk of future cardiovascular events in women on HRT. A recent meta-analysis demonstrated a 35% reduction in cardiovascular events among estrogen replacement therapy (ERT) users.6 It has been demonstrated from animal studies in cynomolgus monkeys fed an atherogenic diet that ERT significantly reduced the extent of atherosclerosis as compared to untreated estrogen-deficient monkeys.34 These data suggest that results of ERT may also depend on the presence of underlying coronary atherosclerosis at the time of initiating ERT. In those with established CAD, the effects of ERT may differ, at least in some individuals, due to its pro-inflammatory effects leading to plaque instability. However, no randomized, controlled trials are presently available that have evaluated the role of HRT in primary prevention. The Women’s Health Initiative recently reported an early increase in cardiovascular events among women on HRT as compared to placebo at 2 years’ follow-up. However, results of long-term follow-up will not be available before 2005. As data are even more scanty regarding the role of HRT in primary prevention, no firm conclusions either supporting or rebutting the role of HRT can be drawn. Till then, its use should be individualized and preferably should be part of a randomized trial. However, it should be realized that while randomized trials draw their strength in being able to eliminate bias due to the process of randomization, observational studies are able to enrol a very large population base that is followed for a significantly longer time period. The Nurses Health Study at its last publication had accumulated 400 000 woman-years of follow-up, which is not possible in a randomized study design.

**Phytoestrogens and SERMS: Viable Alternatives?**

Phytoestrogens are naturally occurring plant estrogens that have estrogenic activity in human beings. Interest in this group of estrogens developed with the observation that cardiovascular diseases and menopausal symptoms are less frequent in Asian women.35,36 As consumption of soy protein among Asians, a rich source of phytoestrogens, is much higher than in the West, the role of these agents as a potential supplementary source of exogenous estrogens has been studied. These agents, predominantly isoflavones, have selective proestrogenic action, although weak, in some tissues while being anti-estrogenic in others.37 Data from animal studies and from limited, small, human studies have reported a beneficial effect on serum levels of total cholesterol and LDL-cholesterol with a neutral effect on triglyceride levels.38,39 They also normalize vascular reactivity in postmenopausal monkeys. These agents do not increase the risk for breast or uterine cancer and have not been shown to be prothrombotic. However, data on their use in humans is scarce and there are insufficient data to recommend their use in postmenopausal women.

Selective estrogen receptor modulators (SERMS), as the name suggests, are proteins that interact with the estrogen receptor to produce pure agonist, antagonist or a mixed response. These drugs theoretically act selectively on vascular receptors, sparing uterine and breast tissues from unwanted physiological effects.40,41 The best studied of these drugs is raloxifene that favorably affects biochemical markers of CAD risk—it lowers total and LDL-cholesterol levels without affecting HDL-cholesterol and triglyceride levels. It also exerts a protective effect on bone mass and decreases the incidence of invasive breast cancer. However, there is no evidence yet to suggest that SERMS reduce the risk of CAD. This is being evaluated in the RUTH (Raloxifene Use for The Heart) study, in which over 10 000 postmenopausal women have been enrolled in a multi-institutional, randomized, placebo-controlled trial.42 The primary end-point is to evaluate its effects on coronary events as well as risk of breast cancer.

**Ongoing Trials**

Several other randomized trials are presently under way that will shed more light on the role of HRT in preventing CAD. The Women’s Health Initiative (WHI) is a large, randomized, placebo-controlled primary prevention trial in which 27 500 postmenopausal women have been enrolled. They have been randomized to estrogens (0.625 mg conjugated estrogen) with and without a progestin (2.5 mg medroxyprogesterone acetate) or placebo. These patients will be followed for more than 7 years and the results will be available by 2005. The Women’s International Study of Long Duration Oestrogen after Menopause (WISDOM) trial
is another large randomized trial in which 34,000 women between 50 and 69 years are being randomized to either estrogen with/without progestin versus placebo. These patients will receive ten years of therapy followed by another ten years of follow-up. The primary outcome being evaluated in this trial is fatal and nonfatal coronary events.

The Women's Angiographic Vitamin and Estrogen trial (WAVE) is a secondary prevention trial evaluating the effects of vitamins and HRT on progression of angiographically documented CAD (15%-75% stenosis on coronary angiogram). The primary outcome being measured is angiographic changes in these lesions after a mean follow-up of 3 years. The HERS investigators are also following 2,297 of the trial participants for at least 3 more years in HERS II to exactly quantify the late benefit seen in years 4 and 5 of this trial. The Women's Estrogen/Progestin Lipid Lowering Hormone Atherosclerosis Regression (WELL-HART) trial is another randomized, multicenter, placebo-controlled, secondary prevention trial in which the primary end-point is progression/regression of coronary atherosclerosis on angiography. In the EAGAR (Estrogen and Graft Atherosclerosis Research) study the effects of HRT on saphenous vein graft atherosclerosis are being documented and results are expected by 2002. The ESPRIT—UK (Estrogen in the Prevention of Reinfarction Trial: a multicenter trial in the UK) is evaluating the effects of estrogen in postmenopausal women with a recent MI. Follow-up is planned for 2 years and the primary outcome being measured is all-cause mortality, cardiovascular mortality, nonfatal and fatal MI. The Women's Hormone Intervention Secondary Prevention Pilot Study (WHISP) is a small secondary prevention trial evaluating the safety and tolerability of HRT after an acute MI (after 48 hours but within 7 days of MI).

**Conclusions**

In conclusion, the role of hormones in preventing CAD in postmenopausal women is still not well established. Based on current evidence available from the HERS trial, it is presently not advisable to initiate HRT in women with established CAD for the sole purpose of preventing recurrent coronary events. A statement issued by the American Heart Association recommends that the decision to continue or stop HRT in women with cardiovascular disease should be based on established noncoronary benefits and risks, taking patient preference into account. Whether subsets can be identified from amongst women with established CAD who are at a high risk of adverse events will be a point of major interest. Little data are available from randomized trials on the role of HRT in primary prevention of CAD. Whether initiating HRT soon after the menopause will be able to further delay the onset of coronary atherosclerosis in women needs to be established. If the benefits from HRT are only modest, and long duration of use is required to produce this benefit, then the utility of HRT would be greatly limited. It will need a high degree of motivation on the part of the user to continue these medications for prolonged periods. Indeed, the benefits from the HERS trial were seen in women who strictly adhered to HRT—pill compliance was nearly 80% in this trial. Similar benefits would not accrue to an unselected patient population. If this pattern of early harm is reproduced in other randomized trials, then HRT would actually confer an increased risk of coronary events to the short-term user. Whether decreasing the dose of estrogen or altering the progestogen component will be able to overcome this pattern of early harm also needs to be established. With other well established modalities (such as lifestyle modification and lipid lowering) demonstrating a clear and significant reduction in future coronary events, caution needs to be exercised before using HRT for the sole purpose of prevention of CAD. On the other hand, when HRT is needed for other indications (such as the prevention and treatment of osteoporotic fractures), the same may be continued. Nevertheless, it would be premature to bury HRT based on the results of one randomized trial alone. Future trials, especially the WHI, should be able to address these issues better.

**Table 1. Ongoing trials of HRT**

**Primary prevention trials**
- Women's Health Initiative (WHI)
- Women's International Study of long Duration Oestrogen after Menopause (WISDOM)

**Secondary prevention trials**
- HERS II
- Estrogen in the Prevention of Reinfarction Trial (ESPRIT)
- Women's Angiographic Vitamin and Estrogen (WAVE) trial
- Women's Estrogen/progestin Lipid Lowering Hormone Atherosclerosis Regression Trial (WELL-HART)
- Estrogen And Graft Atherosclerosis Research (EAGAR) study
- Women's Hormone Intervention Secondary Prevention Pilot (WHISP) study

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Management of Asymptomatic Valvular Aortic Stenosis

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Valvular aortic stenosis is characterized by a long asymptomatic latent period preceding the onset of symptoms. The widespread use of echocardiography has led to an increase in the number of patients diagnosed with hemodynamically significant but asymptomatic aortic stenosis. This finding raises the question of optimal medical management and timing of surgical intervention, with the primary concerns being the risk of sudden cardiac death and the functional effect of prolonged outflow obstruction on the left ventricular myocardium. In addition, the ability to make the diagnosis earlier in the course of the disease has led to further consideration of the impact of patient co-morbidities, such as advanced age, on the timing of surgical intervention.

Etiology

The most common cause of acquired aortic stenosis is calcific or degenerative valve disease leading to a reduction in leaflet mobility. This disease process encompasses a wide spectrum ranging from mild leaflet thickening without outflow obstruction, termed aortic sclerosis, to significant outflow obstruction and stenosis. While patients with aortic sclerosis are asymptomatic, there is an increased risk of adverse cardiovascular outcome, with a recent study demonstrating a 50% increased risk of myocardial infarction and cardiovascular death over an average follow-up of 5.5 years. Population-based studies indicate that aortic sclerosis is present in approximately 20% of people aged 65–74 years and in 48% of people older than 84 years, with aortic stenosis present in 1.3% and 4% of the same age groups, respectively. Although this progressive disorder affects normal trileaflet valves, a similar disease process affects congenitally bicuspid aortic valves, which occur in approximately 2% of the population. Cusp abnormalities lead to increased turbulence of blood flow and instigation of the calcific disease process at an earlier age. Therefore, patients with bicuspid aortic valves tend to have symptoms in the fourth or fifth decades of life compared to calcific degenerative disease in normal trileaflet valves where presentation is typically in the sixth decade of life or older.

Clinical factors that have been correlated with aortic stenosis include male sex, hypertension, diabetes mellitus, smoking, elevated lipoprotein (a) and low-density lipoprotein levels, renal failure, and abnormalities of calcium metabolism. However, the presence of these risk factors alone is not specific for aortic stenosis due to the high prevalence of coexisting conditions including atherosclerotic heart disease.

In comparison to industrialized countries where rheumatic fever has virtually disappeared, rheumatic heart disease is still prevalent in the developing countries of Africa, Asia, Latin America and the Pacific, representing a significant cause of acquired aortic stenosis. Rheumatic heart disease typically involves the mitral valve, with isolated aortic stenosis accounting for only 5% of rheumatic valve disease. Disease progression in rheumatic aortic stenosis is slow, slightly slower than that for calcific degenerative disease and aortic stenosis only develops in one-third to one-half of patients with mitral stenosis. In 131 patients with rheumatic disease undergoing mitral valve surgery, only 2 patients with mild aortic valve disease at the time of surgery progressed to severe aortic stenosis, and subsequently underwent aortic valve surgery 17 and 22 years after the initial procedure. Rheumatic fever is a disease of children and young adults. The age at diagnosis of symptomatic valve disease is geographically variable, ranging from teenagers in Africa to the third or fourth decades of life in European and North American populations.

Pathophysiology

Acquired aortic stenosis is an active disease process rather than a nonspecific degeneration. Calcific valve disease is characterized by thickening and irregularities on the aortic side of the valve, progressing from the base of the cusps toward the edges, with commissural sparing and an effective reduction in valve area due to increased leaflet stiffness. At the tissue level, there are focal areas of displacement of the subendothelial elastic lamina with protein and lipoprotein deposition and an inflammatory cell infiltrate. Calcification is present, localized to areas of lipoprotein accumulation. Additionally, the production of proteins such as osteopontin, associated with tissue calcification has been identified in these lesions. Later in
the disease process, calcification becomes prominent and there is increased fibrosis, leading to leaflet immobility and obstruction of left ventricular outflow.

In contrast, rheumatic valvular aortic disease is characterized by commissural fusion producing a triangular valve orifice with reduced systolic opening. In addition, superimposed calcific changes may occur, with time-dependent progressive leaflet thickening and fibrosis.

Regardless of the underlying mechanism, cusp calcification and leaflet immobility lead to obstruction of left ventricular outflow and increased intracavitary systolic pressure, a process termed left ventricular pressure overload. The basic compensatory mechanism for pressure overload is myocardial hypertrophy, to maintain normal wall stress. Left ventricular systolic function remains normal although the increased afterload due to valve obstruction may lead to some reduction in ejection fraction. Diastolic function is impaired as a consequence of increased wall thickness and abnormal myocardial relaxation, with increased interstitial fibrosis that persists even after relief of valve obstruction. If compensatory hypertrophy is inadequate, wall stress will increase, leading to an eventual decrease in ejection fraction in the latest stages of aortic stenosis. This decline is at least partially reversible with improvement in ejection fraction following surgical aortic valve replacement due to afterload reduction.

**Clinical Presentation**

Prognosis in acquired aortic stenosis is largely determined by the symptom status of the patient. As a consequence, therapeutic decisions related to surgical intervention are based primarily on the presence or absence of symptoms. Therefore, a thorough assessment of the clinical condition is crucial to determine if a patient is truly "asymptomatic". Although classic teachings of aortic stenosis refer to the cardinal triad of angina, congestive heart failure and syncope, aortic stenosis identified in the earlier stages may present with more subtle symptoms such as a decrease in exercise tolerance or exertional dyspnea. Because the asymptomatic time period can last decades, symptom onset is often insidious. Patients often minimize symptom development, attributing their condition to "older age" or other causes. As a consequence, asymptomatic patients must be carefully educated in layman's terms to recognize the clinical features of symptomatic disease.

Recognition of aortic stenosis occurs in the asymptomatic patient when a systolic outflow murmur is auscultated on physical examination. The diagnosis should be considered particularly in the elderly, given the long latent period of the disease. Physical examination is useful in screening patients with a cardiac murmur. Findings associated with a more severely stenotic valve include intensity of the systolic murmur, time to peak murmur intensity, a single second heart sound, and a delayed (parvus et tardus) or diminished carotid pulse contour.

However, echocardiography in conjunction with the physical examination is still necessary to reliably exclude severely stenotic lesions. In a study of 123 asymptomatic patients with aortic stenosis, no single finding on physical examination or combination of findings had both high specificity or sensitivity for detecting severe valvular aortic stenosis.

**Sudden Cardiac Death**

In previous retrospective autopsy series, sudden cardiac death in patients with severe aortic stenosis has been reported to have an incidence as high as 20%. This observation highlighted the concern that sudden death might occur in asymptomatic patients. However, more recent prospective studies have demonstrated either no or very low sudden death rates, typically less than 1% per year (Table 1). In a prospective study of 123 asymptomatic patients with moderate aortic stenosis followed for an average of 32 months, there were no

<table>
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<tr>
<th>Study</th>
<th>Number of patients</th>
<th>Follow-up duration (months)</th>
<th>Severity of aortic stenosis</th>
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<td>22</td>
<td>PV =5.0±0.6 m/s</td>
<td>1</td>
<td>Prospective</td>
</tr>
</tbody>
</table>

*Sudden cardiac death not preceded by symptoms
AVA: aortic valve area; PV: peak instantaneous velocity
episodes of sudden death.32 Similarly, in 113 patients with moderate to severe aortic stenosis followed for a mean duration of 20 months, only 2 patients suffered sudden death, but both events were preceded by symptoms for at least 3 months. In another prospective series of 126 asymptomatic patients with severe aortic stenosis followed for an average of 22 months, only one patient suffered sudden cardiac death.33 Therefore, contemporary studies demonstrate the relative rarity of sudden death in adults with aortic stenosis in the absence of preceding symptoms.

**Echocardiographic Assessment**

Whenever clinical history or physical examination suggests the presence of aortic stenosis, an echocardiogram provides visualization of valvular anatomy, measurement of the aortic jet velocity and calculation of the aortic valve area. Aortic jet velocity provides a direct measure of the severity of valve obstruction, with a jet velocity greater than 2.5 m/s indicating the presence of stenosis. In addition, aortic valve area (AVA) can be calculated on the principle of continuity of flow based on the outflow tract cross-sectional area (CSA) (calculated from the outflow tract diameter), the velocity–time integral (VTI) in the outflow tract (recorded with pulsed Doppler echocardiography), and the velocity–time integral in the aortic stenosis jet (recorded with continuous-wave Doppler ultrasound).35

\[
AVA = \text{CSA}_{\text{LVOT}} \times \left( \frac{\text{VTI}_{\text{LVOT}}}{\text{VTI}_{\text{AS}}} \right)
\]

The continuity equation can be simplified by substituting maximum velocities (V) for velocity–time integrals:35

\[
AVA = \text{CSA}_{\text{LVOT}} \times \left( \frac{V_{\text{LVOT}}}{V_{\text{AS}}} \right)
\]

Both maximum and mean pressure gradients (ΔP) across stenotic valves can also be measured noninvasively, and can be calculated from the aortic jet velocity (v) using the simplified Bernoulli equation:35–36

\[
\Delta P = 4v^2
\]

However, these echocardiographic measures alone cannot identify clinically significant outflow obstruction as there is considerable overlap in hemodynamic severity between symptomatic and asymptomatic individuals. It is not unusual to see asymptomatic individuals with a jet velocity greater than 4 m/s.32,33 Also, the calculations themselves are subject to variability in echocardiographic data recording, measurement variability, and patient physiologic variability such as interim changes in transaortic flow rate due to a decline in systolic function or increasing aortic regurgitation. In addition, changes in myocardial oxygen demand may lead to symptoms with no intervening change in the severity of obstruction. Other useful information derived from the echocardiogram includes measurement of left ventricular size, assessment of its function and the presence of concomitant valvular disease.

Using a variety of hemodynamic and natural history data, current clinical guidelines grade the severity of aortic stenosis as mild (jet velocity <3.0 m/s, AVA >1.5 cm²), moderate (jet velocity 3–4 m/s, AVA 1.0–1.5 cm²), or severe (jet velocity >4 m/s or AVA <1.0 cm²).21 The area of a normal adult aortic valve ranges between 3.0 and 4.0 cm² and is dependent on the body mass area of the individual. Therefore, aortic valve area calculations that fall within a range of “severe” aortic stenosis may represent a more critical lesion in a larger patient compared to a patient with a smaller body mass index. However, in the clinical setting, the absolute valve area or jet velocity should not be the primary determinant of the need for aortic valve replacement as there is significant overlap in hemodynamic severity between symptomatic and asymptomatic patients. Because clinical outcome is most dependent on the presence or absence of symptoms, current guidelines regarding surgical intervention are based primarily on symptom status, given that significant obstruction is present.21

**Rate of Hemodynamic Progression**

Once aortic stenosis is identified, there is a gradual increase in the severity of outflow obstruction over time in most patients. Studies of hemodynamic progression of aortic stenosis have demonstrated an average rate of increase in aortic jet velocity of 0.3 m/s per year, with an increase in mean transaortic pressure gradient of 7 mmHg per year and a decrease in aortic valve area of 0.1 cm² per year.31,37–42 These rates are relatively uniform for groups of patients and between studies; however, there is marked individual variation precluding prediction of progression in a specific patient. Clinical studies of risk factors associated with an increased rate of hemodynamic progression have identified gender, elevated serum creatinine, higher left ventricular mass index, morphologic features of the aortic valve,43 smoking status, elevated serum calcium, hypercholesterolemia,44 and flow-dependent change in the aortic valve area45 as predictors of disease progression. However, these clinical variables have not been tested prospectively on independent data and have not been demonstrated to reliably predict the rate of progression in individual patients.

Given the variability in progression rates for aortic stenosis, serial echocardiograms can assist in following hemodynamic progression as well as assessing changes in left ventricular hypertrophy and function. The frequency of echocardiograms obtained should be determined by the
severity of stenosis and by changes in physical examination or clinical status. Current clinical guidelines suggest that in patients with moderate aortic stenosis, serial studies be performed every 2 years and, in patients with mild aortic stenosis, every 5 years. Most clinicians obtain an annual echocardiogram in patients with asymptomatic severe stenosis, even though the primary indication for surgical intervention is symptom onset.

**Role of Exercise Testing**

In patients with aortic stenosis, symptoms of angina, syncope or unequivocal heart failure are an absolute contraindication to exercise testing. Exercise testing in patients with asymptomatic aortic stenosis has limited accuracy for the diagnosis of ischemic coronary artery disease due to an abnormal baseline electrocardiogram, left ventricular hypertrophy and limited coronary flow reserve. Some clinicians utilize exercise testing in patients with asymptomatic aortic stenosis and equivocal symptoms to ascertain if symptoms are, in fact, present. Exercise testing is relatively safe in this situation when performed by an experienced physician with close monitoring of blood pressure. The exercise test should be ended promptly if there is a decrease or minimal increase (less than 20 mmHg) in blood pressure, or the patient experiences symptoms.

**Clinical Outcomes in Asymptomatic Aortic Stenosis**

The prognosis in patients with asymptomatic aortic stenosis is excellent, and conservative management with diligent clinical follow-up to monitor for development of symptoms is reasonable. Once symptoms occur, prompt surgical intervention is needed, as evidenced by one report of 7 deaths in 99 symptomatic patients on a six-month waiting list for surgery. When severe stenosis (jet velocity >4 m/s) is present, 38% of asymptomatic patients develop symptoms within 2 years, and 79% within 3 years. Given the rarity of cardiac death before the onset of symptoms, it is reasonable to wait for the patient to become symptomatic before considering surgical intervention.

Prospective studies on clinical predictors of symptom onset include baseline aortic jet velocity, baseline functional status score, rate of change in jet velocity over time and degree of aortic valve calcification. Clinical factors such as age, gender, cause of aortic stenosis, presence of coronary artery disease, hypertension, hypercholesterolemia, and diabetes are not multivariate predictors of outcome. The etiology of aortic stenosis has not been identified as a predictor of adverse outcome as clinical outcome in rheumatic aortic stenosis is similar to that of degenerative disease. However, disease progression in rheumatic aortic stenosis is slow and if multi-valve involvement is present, the dominant clinical lesion may be mitral stenosis or aortic insufficiency. The timing of surgical intervention may then be based on clinical guidelines for a valve lesion other than aortic stenosis.

**Timing of Intervention**

In the absence of serious co-morbid conditions, aortic valve replacement is indicated in symptomatic patients with severe aortic stenosis. Operative mortality is acceptable given the poor prognosis if symptomatic patients are left untreated. In recent surgical series, the reported operative mortality rates vary between 2% and 9% with a long-term survival of 80% at three years. Percutaneous balloon aortic valvotomy is currently not the accepted therapy for calcific aortic stenosis as it has no effect on clinical outcome. The potential role of balloon valvuloplasty for rheumatic aortic stenosis has been less well studied.

Advocates of prophylactic surgery in asymptomatic patients argue for intervention prior to irreversible myocardial hypertrophy, fibrosis and progressive systolic dysfunction, and to decrease the risk of sudden cardiac death. However, the benefit of prophylactic surgery for aortic stenosis has not been proven in clinical trials. Although operative mortality for aortic valve replacement is low, routine early surgery cannot be universally advocated for all patients with aortic stenosis, given the risk of surgery and the late complications of a prosthetic valve. Mortality estimates as a consequence of the aortic valve prosthesis occur at a rate of 1% per year. Significant complications such as thromboembolism, hemorrhagic complications due to anticoagulation, prosthetic valve dysfunction, and endocarditis occur at the rate of at least 2% to 3% per year. The risk of sudden cardiac death is lower than the operative mortality of valve replacement so that decreasing the risk of sudden cardiac death is inadequate justification for proceeding to prophylactic surgery.

There are some clinical scenarios where surgical intervention in asymptomatic patients may be appropriate. These include a demonstrated decline in left ventricular systolic dysfunction as a consequence of aortic stenosis, women with severe aortic stenosis who are contemplating pregnancy, and patients with asymptomatic aortic stenosis who plan activities that involve severe exertion or who live in areas remote from medical care. In addition, earlier surgical intervention should be considered in patients with very severe stenosis, in whom symptom onset is inevitable.
in the short term and an elective procedure is preferred.

In asymptomatic patients with aortic stenosis undergoing other cardiac surgical procedures such as coronary artery bypass grafting, concurrent aortic valve replacement should be performed if severe obstruction is present. Decision-making is more difficult when moderate stenosis is present, and this decision must be individualized based on the expected rate of disease progression, extent of valve calcification, co-morbidity and patient preferences. In patients with mild aortic stenosis, valve replacement should be deferred as disease progression is slow and the patient may not need subsequent surgical intervention.

**Special Patient Populations**

**Elderly:** Regardless of age, aortic valve replacement is warranted for symptomatic patients. Valve replacement for aortic stenosis in the elderly has an operative mortality and morbidity of 2%-3% and long-term results comparable to those in younger patients with an 85% age-corrected 10-year survival. In addition, the quality of life is improved in the elderly who survive surgery. However, investigations have demonstrated underusage of appropriate surgical intervention in the elderly. In a study of 205 elderly patients with significant aortic stenosis, only 59% of patients who were eligible candidates for aortic valve replacement were offered the intervention, even though patients who did undergo aortic valve replacement had an operative mortality of only 2.2%. At 6 months, survival was similar (85%) in both the medical and surgical treatment arms, but after further follow-up the two survival curves diverged. The three-year survival rate was 80% in the surgical group compared to only 49% in the medically treated group. The most commonly cited reason for not recommending surgery was advanced age; however, a recent estimate of life expectancy in 1557 individuals above 75 years of age included an additional cognitive impairment-free life expectancy of 8.4 years for men and 9.9 years for women. Therefore, after taking into consideration patient preferences and severe co-morbidity such as advanced malignancy, the symptom status of an elderly patient should dictate intervention, as in the general population.

**Pregnancy:** Given the increased cardiac output and hemodynamic burden of pregnancy, severe aortic stenosis is associated with a higher risk of maternal and fetal complications so that valve surgery should be considered before pregnancy. However, when women with aortic stenosis present during pregnancy, many can be managed with careful clinical monitoring and aggressive medical therapy. Vaginal delivery with optimal pain control and invasive hemodynamic monitoring is recommended unless contraindicated for obstetrical reasons, followed by valve surgery in the early post-partum period if needed. The strongest predictors of an adverse maternal or fetal outcome in women with aortic stenosis is the severity of outflow obstruction and functional status before pregnancy. However, even minor illnesses, such as a viral syndrome, superimposed on the hemodynamic burden of pregnancy, may result in cardiovascular decompensation with pulmonary edema and the need for emergent intervention. Both valvuloplasty and surgical valve replacement have been performed in pregnancy in the setting of severe aortic stenosis, but carry the risk of adverse fetal outcomes in addition to the risks otherwise inherent in the procedure.

**Medical Management**

Because prognosis in acquired aortic stenosis is largely determined by the symptom status of the patient, a thorough assessment of a patient’s clinical condition should be made periodically and the patient educated about the disease process. A baseline echocardiogram should be obtained if clinical history or physical examination suggests the presence of aortic stenosis. Subsequently, serial echocardiographic examinations are helpful to track disease progression in asymptomatic patients. Current clinical guidelines suggest serial studies every 2 years in patients with moderate aortic stenosis and every 5 years for mild stenosis.

Acquired aortic stenosis carries a moderate risk for bacterial endocarditis. Therefore, education on antibiotic prophylaxis prior to dental, oral, respiratory tract, esophageal, genitourinary and gastrointestinal procedures for prevention of endocarditis is necessary. Standard prophylaxis regimens in adult patients recommend a single administration of antibiotic therapy prior to the procedure. Current recommendations are available for standard prophylaxis, for patients unable to take oral medication, and for those who are allergic to penicillins (Table 2). Patients with aortic stenosis needing genitourinary or gastrointestinal procedures undergo the same prophylaxis regimen if penicillins are tolerated (i.e. amoxicillin or ampicillin). However, if these patients are penicillin-allergic, then vancomycin 1 g intravenously within 30 minutes of the procedure is recommended. Cephalosporins should be avoided in patients with intermediate-type hypersensitivity to penicillins.

In patients located in geographical areas where rheumatic fever is prevalent, or those who have an established prior history of rheumatic fever, rheumatic fever prophylaxis should also be provided to prevent occurrence of incident and recurrent episodes (Table 3).
duration of therapy in secondary prophylaxis is dependent on the severity of cardiac involvement during the initial episode of rheumatic fever. For rheumatic fever with evidence of carditis and persistent valvular disease, current recommendations are to continue antibiotic therapy for at least 10 years from the last episode and until 40 years of age, with consideration of lifelong therapy. For rheumatic fever with carditis and no valvular disease, recommendations are to continue antibiotic therapy for at least 10 years or into adulthood. For rheumatic fever without carditis, recommendations are to continue antibiotic therapy for at least 5 years or until 21 years of age.71

Lastly, evaluation for coronary artery disease risk factors is important, given the high frequency of concurrent disease in adults with aortic stenosis. It remains unknown whether treatment of associated clinical factors, such as hyperlipidemia, hypertension or smoking, will affect the disease process in the aortic valve itself. However, treatment based on current guidelines for primary prevention of coronary atherosclerosis is clearly appropriate.

Conclusions

Given the long latent period, conservative medical management is reasonable with asymptomatic aortic valve stenosis. However, once cardiac symptoms develop, morbidity and mortality are significant. Therefore, aggressive clinical monitoring with intermittent clinical evaluation and echocardiography is warranted, coupled

### Table 2. Adult endocarditis antibiotic prophylaxis for aortic stenosis: dental, oral, respiratory and esophageal procedures (Bonow et al.)

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amoxicillin</td>
<td>2.0 g p.o. once 1 hour prior to the procedure</td>
</tr>
<tr>
<td>For individuals unable to take oral medications</td>
<td>2.0 g i.m. or i.v. once within 30 minutes of the procedure</td>
</tr>
<tr>
<td>Ampicillin</td>
<td>2.0 g i.m. or i.v. once within 30 minutes of the procedure</td>
</tr>
<tr>
<td>Cefazolin</td>
<td>1.0 g i.m. or i.v. once within 30 minutes of the procedure</td>
</tr>
<tr>
<td>Clindamycin, one of the following regimens:</td>
<td>600 mg once 1 hour prior to the procedure</td>
</tr>
<tr>
<td>Cephalaxin</td>
<td>2.0 g p.o. once 1 hour prior to the procedure</td>
</tr>
<tr>
<td>Cephaloxin</td>
<td>2.0 g p.o. once 1 hour prior to the procedure</td>
</tr>
<tr>
<td>Azithromycin</td>
<td>500 mg p.o. once 1 hour prior to the procedure</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>500 mg p.o. once 1 hour prior to the procedure</td>
</tr>
<tr>
<td>Clindamycin, for individuals allergic to penicillin and unable to take oral medications</td>
<td>600 mg i.v. once within 30 minutes of the procedure</td>
</tr>
<tr>
<td>Cefazolin</td>
<td>1.0 g i.m. or i.v. once within 30 minutes of the procedure</td>
</tr>
</tbody>
</table>

p.o.: oral route; i.m.: intramuscular route; i.v.: intravenous route

### Table 3. Antibiotic regimens for primary and secondary prophylaxis (Dajani et al.)

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary prevention of rheumatic fever</td>
<td>Adults: 1 200 000 U i.m. once</td>
</tr>
<tr>
<td>Benzathine penicillin G</td>
<td>Adults: 500 mg p.o. 2–3 times daily for 10 days</td>
</tr>
<tr>
<td>Penicillin V (phenoxymethyl penicillin)</td>
<td></td>
</tr>
<tr>
<td>For individuals allergic to penicillin</td>
<td>20–40 mg/kg/day p.o. 2–4 times daily (max 1 g/day) for 10 days</td>
</tr>
<tr>
<td>Erythromycin estolate</td>
<td>40 mg/kg/day p.o. 2–4 times daily (max 1 g/day) for 10 days</td>
</tr>
<tr>
<td>Erythromycin ethylsuccinate</td>
<td></td>
</tr>
<tr>
<td>Secondary prevention of rheumatic fever</td>
<td>Benzathine penicillin G</td>
</tr>
<tr>
<td>Adults: 1 200 000 U i.m. every 4 weeks</td>
<td></td>
</tr>
<tr>
<td>Penicillin V</td>
<td>250 mg p.o. twice daily</td>
</tr>
<tr>
<td>Sulfadiazine</td>
<td>Adults: 1.0 g p.o. once daily</td>
</tr>
<tr>
<td>For individuals allergic to penicillin and sulfadiazine</td>
<td>Erythromycin</td>
</tr>
<tr>
<td>Adults: 250 mg p.o. twice daily</td>
<td></td>
</tr>
</tbody>
</table>

p.o.: oral route; i.m.: intramuscular route
with patient education on symptom identification and prophylaxis regimens for endocarditis and rheumatic fever. Once symptoms develop, surgery is the treatment of choice. Surgical intervention should not be withheld in elderly patients due to age alone. Prophylactic surgical intervention should be considered for moderate to severe asymptomatic aortic stenosis in the setting of scheduled concurrent cardiac surgery.

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Predictive Accuracy of Commissural Morphology and its Role in Determining the Outcome Following Inoue Balloon Mitral Valvotomy

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Department of Cardiology, Sanjay Gandhi Post Graduate Institute of Medical Sciences, Lucknow

Background: Commissural morphology is an important predictor of outcome following balloon mitral valvotomy. The aim of this prospective study was to assess if the site of commissural splitting could be reliably predicted by echocardiography and whether the extent of commissural split affected the result of balloon mitral valvotomy.

Methods and Results: A total of 140 patients (mean age 29.1±8.6 years) were studied. Prediction of splitting was done based on the presence of echolucent dark zones as seen in the parasternal short-axis view on echocardiography. Of 102 patients in whom a split of both commissures was predicted, the prediction was accurate in 86% (88/102). Of 33 patients with a predicted unilateral split, the accuracy of prediction was 82% (27/33). In the 5 patients with bilateral commissural fibrosis (in whom none of the commissures were predicted to split), all had a unilateral split. Overall, 93 patients (66%) had a bilateral commissural split, 43 (31%) had a unilateral split, and 4 had no commissural split. All the latter 4 developed moderate-to-severe mitral regurgitation. Those with bilateral commissural split following balloon mitral valvotomy had lower transmitral gradients (5.53±1.46 v. 7.4±1.23 mmHg, p= 0.03) and greater mitral valve area (1.83±0.15 v. 1.64±0.15 cm², p<0.02), as compared to those with unicommissural split. The incidence of an increase in mitral regurgitation by > grade 1 was also lower in the former group (7.5% v. 28%). An optimal result with the first dilatation (using a balloon size <2 mm of the predicted size) was achieved more frequently in those with a bilateral split (18% v. 8%). Oversizing of the balloon by 2 mm (of the predicted size) was done more frequently (19% v. 7%) in those with unicommissural split.

Conclusions: We conclude that the assessment of commissural morphology is possible with excellent predictive accuracy. In this study, those with bilateral commissural split had more favorable hemodynamic results with lower transmitral gradients, greater mitral valve area and lesser frequency of mitral regurgitation in contrast to those with unicommissural split. (Indian Heart J 2002; 54: 39–45)

Key Words: Balloon mitral valvotomy, Mitral stenosis, Rheumatic heart disease
The aim of this study was to prospectively assess (i) whether the site of commissural split could be reliably predicted by echocardiography, and (ii) if the extent of commissural split following BMV has any correlation with the hemodynamic results [in terms of decrease in transmitral gradients, increase in MVA and the degree of mitral regurgitation (MR) produced].

Methods

A prospective study of 140 patients undergoing BMV for severe rheumatic MS was carried out at our institution. The mean age of the patients was 29.1±8.6 years with a range of 10–54 years. There were 49 males and 91 females. Atrial fibrillation was present in 14 patients (10%). Patients with calcific MS, documented left atrial clot on cross-sectional echocardiography or more than mild MR were excluded from the study.

Mitral valvotomy procedure: Balloon mitral valvotomy was performed by the Inoue technique. The balloon size was chosen according to the height of the patient (height/10+10=balloon size). Graded inflations were done, starting at 2 mm less than the predicted size. Inflations at an increasing size of 1 mm were performed till the reduction in transmitral gradients was deemed sufficient, or there was appearance of the murmur of MR. The balloon size was, however, never increased to 2 mm more than that predicted by the above formula.

Echocardiography: All patients underwent a transthoracic echocardiographic examination with a Hewlett-Packard Sonos 5000 or ATL VM 9 machine. Transmitral gradients were estimated from the continuous wave Doppler recordings and the MVA was derived by the pressure half-time method. The presence of MR was detected by color flow and spectral Doppler imaging and its severity graded quantitatively.

Commissural morphology was determined from the parasternal short-axis view and examined independently by two observers. The extent of commissural fibrosis, fusion, calcification and asymmetry of disease, if any, was noted and commissural splitting predicted according to the following criteria:

1. Both commissures were predicted to split if both were diseased and the extent of involvement was symmetric. This entailed visualization of a definite plane of cleavage seen as bilateral echolucent dark zones at the site of both the commissures (Fig. 1).

2. If both commissures were diseased but the extent of involvement was asymmetric, the less diseased commissure was predicted to split. In such cases the echolucent dark zone, signifying the potential cleavage line of the commissure, was visualized only on one (the less diseased) side (Fig. 2).

3. If both commissures were severely diseased and fibrosed, neither was predicted to split. In such cases the above-described dark zones were not visible at either of the commissural sites (Fig. 3).

Echocardiographic examinations were repeated 48 hours after BMV, and the transmitral gradients and extent of commissural splitting determined independently by two observers.
observers, both of whom were blinded to the hemodynamic results of the BMV. Commissural splitting was defined as:

(i) Increase in the apparent opening angles of either commissure (in cases where the dark zones had been visualized pre-BMV) (Figs 1b, 2b).
(ii) Visualization of the dark zone post-BMV (in cases where it had not been visualized before the procedure) implied a commissural split on that side.

A successful BMV was defined as a final MVA exceeding 1.5 cm² and an increase in valve area exceeding 25% of the baseline MVA.11

Statistical analysis: The significance of differences in various parameters observed before and after BMV was determined by the pooled estimate of variance using the Student’s t test. A p value of <0.05 was considered as significant. All values were expressed as mean ± standard deviation.

Results

Following BMV, there was a significant fall in the mean transvalvular gradients (16.6±2.9 to 6.3±1.5 mmHg), mean PA pressure (34.2±8.5 to 18.9±6.5 mmHg), and pulmonary capillary wedge (PCW) pressures (27.5±5.9 to 9.2±2.4 mmHg). There was significant increase in MVA (0.80±0.12 to 1.79±0.17 cm²), all p values were highly significant.

Based on the criteria of the predicted site of commissural split, as assessed by pre-BMV echocardiography, the patients were divided into two groups—group 1 in which both the commissures were predicted to split and group 2 in which neither or only one commissure was predicted to split. There were no intra-observer differences for the determination of commissural splitting while the inter-observer difference was <1%.

Overall, 102/140 patients (73%) were included in group 1 and 38 (27%) were included in group 2. Of the latter 38 patients, 33 were predicted to split at only one of the two commissures— either anterolateral (ALC), or posteromedial (PMC). In the remaining 5 patients in group 2, there was bilateral commissural fibrosis and neither of the two commissures was predicted to split. Both these groups did not have any significant differences in their clinical (age, NYHA class, gender distribution) or hemodynamic parameters (pre-BMV mean PA pressure, PCW pressure, mean transmitral gradients or MVA) as shown in Table 1.
Table 1. Baseline clinical and hemodynamic characteristics of the two groups based on predictability of commissural split pre-BMV

<table>
<thead>
<tr>
<th>Variable</th>
<th>Both commissures predicted to split (n=102)</th>
<th>Single or none predicted to split (n=38)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (years)</td>
<td>28.8±8.7</td>
<td>30.4±7.7</td>
<td>ns</td>
</tr>
<tr>
<td>Male/female</td>
<td>36/66</td>
<td>11/27</td>
<td>ns</td>
</tr>
<tr>
<td>NYHA class (mean)</td>
<td>2.7±0.6</td>
<td>2.6±0.6</td>
<td>ns</td>
</tr>
<tr>
<td>NYHA class II</td>
<td>37</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>class III</td>
<td>56</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>class IV</td>
<td>9</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>SR/AF</td>
<td>96/6</td>
<td>35/3</td>
<td></td>
</tr>
<tr>
<td>Height (cm)</td>
<td>158.2±9.6</td>
<td>156.8±11.8</td>
<td>ns</td>
</tr>
<tr>
<td>MPA (mmHg)</td>
<td>33.9±8.9</td>
<td>34.6±8.8</td>
<td>ns</td>
</tr>
<tr>
<td>PCWM (mmHg)</td>
<td>27.9±5.9</td>
<td>25.6±5.5</td>
<td>ns</td>
</tr>
<tr>
<td>MG (mmHg)</td>
<td>16.5±2.5</td>
<td>16.9±3.6</td>
<td>ns</td>
</tr>
<tr>
<td>MVA (cm²)</td>
<td>0.76±0.14</td>
<td>0.73±0.14</td>
<td>ns</td>
</tr>
</tbody>
</table>

SR: sinus rhythm; AF: atrial fibrillation; MPA: mean pulmonary artery pressure; PCWM: pulmonary capillary wedge mean pressure; MG: mean gradient; MVA: mitral valve area; ns: not significant

Table 2. Predictive accuracy of commissural morphology in relation to the split achieved following BMV

<table>
<thead>
<tr>
<th>Predicted bilateral split</th>
<th>Unilateral split achieved</th>
<th>No split achieved</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bilateral split (n=102)</td>
<td>88 (86%)</td>
<td>11 (11%)</td>
</tr>
<tr>
<td>Predicted unilateral split (n=33)</td>
<td>5 (15%)</td>
<td>27 (82%)</td>
</tr>
<tr>
<td>Predicted no split (n=5)</td>
<td>-</td>
<td>5</td>
</tr>
<tr>
<td>Total (n=140)</td>
<td>93</td>
<td>43</td>
</tr>
</tbody>
</table>

Of 102 patients in group 1, both commissures did split in 88/102 patients (an accuracy of 86%, Table 2). Of the remaining 14 patients in this group, in 11 patients only one commissure was split (PMC in 8 and ALC in 3) and in 3 neither of the commissures was split. The latter 3 patients developed moderate MR following BMV.

Of the 33 patients in group 2, in whom the commissures were predicted to split unilaterally, the prediction was accurate in 27 patients (an accuracy of 82%), while 5 had a bilateral split and 1 patient had no commissural split. This 1 patient, however, developed severe MR following BMV. Of the 33 patients predicted to split unilaterally, in 18 this occurred at the ALC, and in 15 at the PMC. Of the former 18, 14 had a split at the ALC, while 3 had a bilateral split and 1 developed severe MR. Of the 15 who were predicted to split only at the PMC, the prediction was true in 13, while 2 had a bilateral commissural split.

Of the 5 patients in whom neither of the commissures was predicted to split, all had a demonstrable split of at least one commissure (ALC in 2 and PMC in 3 patients).

Therefore, post-BMV a total of 93 patients (66%) had splitting of both commissures, 43 (31%) had splitting of only one of the commissures and 4 (3%) had no commissural splitting. Significantly, all of these 4 patients developed moderate-to-severe MR following BMV (moderate in 3 and severe in 1).

Comparison of the hemodynamic variables following BMV: Comparisons were performed between patients with bilaterally split commissures following BMV (n=93) and those with only unilaterally split commissures (n=43) (Table 3). It was observed that the mean age, NYHA class, gender distribution and balloon size used were not significantly different among the two groups. The pre-BMV parameters were also similar in the two groups [mean PA pressure 33.9±8.9 vs. 33.8±7.3 mmHg, PCW mean pressure 27.7±6 vs. 27.2±5.5 mmHg, mean gradient (MG)16.8±3.1 vs. 16.2±2.6 mmHg, MVA 0.76±0.13 vs. 0.73±0.15 cm²; all p=ns]. However, following BMV, those with bilaterally split commissures had lower transmural gradients (5.53±1.46 vs. 7.4±1.23 mmHg, p=0.03) as compared to those with unilaterally split commissures. The final MVA was also higher in those with bilaterally split commissures (1.83±0.15 vs. 1.64±0.15 cm², p<0.02).

Analysis of mitral regurgitation following BMV: Of 140 patients, 125 had no or trivial MR prior to BMV, while 15 (11%) had mild MR. Of the latter 15 patients, only 1 had an increase in the grade of MR following BMV, which became moderate, while it remained mild in the rest. Overall, moderate MR occurred in 8 (5.7%) patients and

Table 3. Clinical, pre- and post-BMV parameters of the two groups based on the site of commissural split

<table>
<thead>
<tr>
<th>Variable</th>
<th>Bilateral commissural split achieved (n=93)</th>
<th>Unilateral or no commissural split (n=43)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (years)</td>
<td>28.6±8.2</td>
<td>30.6±9.8</td>
<td>ns</td>
</tr>
<tr>
<td>NYHA class</td>
<td>2.7±0.6</td>
<td>2.6±0.6</td>
<td>ns</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>156.7±10.7</td>
<td>158.8±9.2</td>
<td>ns</td>
</tr>
<tr>
<td>BS recommended (mm)</td>
<td>26±1.05</td>
<td>25.8±1.19</td>
<td>ns</td>
</tr>
<tr>
<td>BS final (mm)</td>
<td>25.6±1.43</td>
<td>26±1.52</td>
<td>ns</td>
</tr>
<tr>
<td>*MG1</td>
<td>16.8±3.1</td>
<td>16.2±2.6</td>
<td>ns</td>
</tr>
<tr>
<td>*MG2</td>
<td>5.53±1.46</td>
<td>7.4±1.23</td>
<td>0.03</td>
</tr>
<tr>
<td>*MVA1 (cm²)</td>
<td>0.76±0.13</td>
<td>0.73±0.15</td>
<td>ns</td>
</tr>
<tr>
<td>*MVA2 (cm²)</td>
<td>1.83±0.15</td>
<td>1.64±0.15</td>
<td>&lt;0.02</td>
</tr>
<tr>
<td>*MVA1 (mmHg)</td>
<td>33.9±8.9</td>
<td>33.8±7.3</td>
<td>ns</td>
</tr>
<tr>
<td>*MVA2 (mmHg)</td>
<td>18.05±4.26</td>
<td>18.1±4.4</td>
<td>ns</td>
</tr>
<tr>
<td>*PCWM1 (mmHg)</td>
<td>27.7±6</td>
<td>27.2±5.5</td>
<td>ns</td>
</tr>
<tr>
<td>*PCWM2 (mmHg)</td>
<td>8.6±2.0</td>
<td>8.9±2.1</td>
<td>ns</td>
</tr>
</tbody>
</table>

BS: balloon size; MG: mean gradient; MVA: mitral valve area; MP A: mean pulmonary artery pressure; PCWM: pulmonary capillary wedge mean pressure
*The notations 1 and 2 denote pre- and post-BMV values, respectively
severe MR in 1 patient following BMV. Only 1 of these patients had mild MR, while the rest had no or trivial MR before dilatation.

**Site of commissural split in patients with MR:** Of the 8 patients with moderate MR, there was splitting of both commissures in 4, single commissure splitting in 2 and no demonstrable split in any of the commissures in 2 (with a tear in the anterior mitral leaflet producing MR in both). In the patients with single commissural splitting, the site of MR was through the split commissure. In the patients with bilaterally split commissures, MR occurred through either one of the split commissures. The only patient with severe MR following BMV also had no demonstrable commissural split (with a tear in the anterior mitral leaflet). Post-dilatation, among the 93 patients with bilaterally split commissures, 80 (86%) had no or trivial MR, 9 (10%) had mild and 4 (4%) had moderate MR. Among the 43 patients in whom only 1 commissure was split, 27 (63%) had no or trivial MR, 15 (35%) had mild and 1 had moderate MR.

**Change in grade of MR following BMV:** In those with bilateral commissural split, a change in MR >1 grade occurred in 7/93 patients (7.5%). This was in contrast to 12/43 patients (38%) with a single commissural split. Thus a higher proportion of patients with unicommissural split had a >1 grade change in MR.

**Relation of balloon size used to the commissural morphology:** This parameter was analyzed to see whether there was any difference in the balloon size used among the patients based on the degree of commissural split achieved post-BMV (Table 4). The mean height of the patients and mean balloon size used in the two groups of patients (those with bilateral commissural split versus those with unilateral or no commissural split) was not significantly different (Table 3). Subgroup analysis revealed that in the former group, 17/93 patients (18%) had an optimal result with the first dilatation (using a balloon size <2 mm of the predicted size, e.g. 24 mm in a 160 cm tall patient). However, in those with a single or no commissural split, this occurred in only 4/47 patients (8%). Oversizing of the balloon by 2 mm (of the predicted size) had to be done more often in the latter group of patients (9/47 (19%) v. 7/93 (7%), e.g. using 28 mm size balloon in a 160 cm tall patient). Overall, dilatation with a balloon size <2 mm of the optimal size was done in 83% (77/93) of patients with bilateral commissural split as compared to 55% (26/47) in those with unilateral or no split.

Analysis of balloon size used in the 4 patients with no demonstrable commissural split (all of whom developed MR post-BMV, moderate in 3 and severe in 1) revealed that in 3 of them the balloon size was 1–2 mm less than that predicted and in only 1 it was oversized by 2 mm.

**Discussion**

Percutaneous BMV by the Inoue technique is now an established mode of management for patients with rheumatic MS. The results of both surgical as well as catheter balloon commissurotomy have been shown to be highly dependent on the morphology of the mitral valve and the subvalvular apparatus. Various two-dimensional echocardiographic scoring systems based on leaflet mobility, thickness, valve calcification and subvalvular disease have been devised to predict the results of mitral valvotomy. However, the use of these scoring systems to prospectively select patients for BMV and correlate them with the outcome of the procedure is still debatable because of their poor negative predictive accuracy.

Commissural fusion is a major contributor to the underlying pathologic process in cases of rheumatic MS, and commissural split has been shown to be the predominant mechanism for increase in MVA following surgical as well as balloon commissurotomy. Hence echocardiographic analysis of commissural morphology may have a possible bearing on the prediction of post-BMV results. There are sparse data available on echocardiographic prediction of commissural morphology.

**Accuracy of prediction:** Our study demonstrates that commissural morphology is reliably predicted on echocardiography (an accuracy of 86% for patients predicted to split bilaterally and 82% for those predicted to split at only one commissural site). Overall, bilateral commissural splitting was the most frequent outcome in our patients (93/140 (66%)), while unilateral splitting occurred in 43/140 (31%). This is in contrast to the results of Fatkin et al. who demonstrated that the most frequent result was that of single commissural splitting. Contrary to these results, we also found that even in patients in whom

<p>| Table 4. Balloon size used amongst patients (analysis according to the site of commissural split) |</p>
<table>
<thead>
<tr>
<th>Balloon size used (mm)</th>
<th>Bilateral split (n=93)</th>
<th>Unilateral split (n=43)</th>
</tr>
</thead>
<tbody>
<tr>
<td>-2</td>
<td>17 (18%)</td>
<td>4 (8%)</td>
</tr>
<tr>
<td>-1</td>
<td>24 (26%)</td>
<td>7 (15%)</td>
</tr>
<tr>
<td>Optimal (height/10+10)</td>
<td>36 (39%)</td>
<td>15 (32%)</td>
</tr>
<tr>
<td>+1</td>
<td>9 (10%)</td>
<td>12 (26%)</td>
</tr>
<tr>
<td>+2</td>
<td>7 (7%)</td>
<td>9 (19%)</td>
</tr>
</tbody>
</table>

In a 160 cm tall patient, the 1st to 5th rows, respectively denote use of 24, 25, 26, 27 and 28 mm size balloon.
neither of the commissures was predicted to split, commissural splitting occurred in at least one of the commissures in all of them. Hence it is possible to achieve a successful result following BMV even in patients with bilateral commissural fibrosis. Possibly the presence of planes of cleavage in commissural sites (which may not be visible on standard echocardiographic imaging planes) plays a role.

**Relation of commissural split to hemodynamics following BMV:** Patients with bilateral commissural split had similar pre-BMV parameters as compared to those who achieved unicommissural split (Table 3). However, following BMV, those with bilateral split had more favorable hemodynamic results as compared to those with a single commissural split. This is reflected in the lower transmitral gradients (5.53±1.4 mmHg) and higher MVA (1.83±0.15 cm²) in the former group of patients.

**Commissural splitting as a determinant of MR following BMV:** Among patients with bilaterally split commissures, there was less increase in the severity of MR following BMV than in patients with unilaterally split commissures. The chance of ≥1 grade change in MR post-BMV was much higher in patients in whom only one commissure was split (28%) as compared to those with a bilateral split (7.5%). Thus the possibility of obtaining adverse hemodynamic results (in terms of higher post-BMV transmitral gradients, lower MVA and producing new or an increase in the degree of pre-existing MR) may be greater in patients with inadequate commissural splitting.

The mechanism of MR was predominantly commissural. However, we also observed that in patients in whom commissural splitting could not be achieved (n=4), there was a tear of the anterior mitral leaflet. This is possibly related to a “give way” at a point of least resistance in the presence of fixed and rigid commissures not amenable to splitting. Tear of a leaflet as a cause of MR has been related to a “give way” at a point of least resistance in the presence of fixed and rigid commissures not amenable to splitting. Bilateral commissural fibrosis. Possibly the presence of planes of cleavage in commissural sites (which may not be visible on standard echocardiographic imaging planes) plays a role.

**Analysis of balloon size:** We found that the mean balloon size used among patients with bilateral commissural splitting was not different from that used in patients with no or single commissural splitting. It was observed that an optimal balloon size (height/10+10, i.e. a 26 mm balloon in a 160 cm tall patient) was used more frequently in the former group of patients (39% v. 32%, Table 4). Conversely, oversizing of the balloon (by 2 mm, which is usually the maximum permissible) had to be done more frequently in patients in whom only single commissural splitting was achieved (19% v. 7%). A balloon size of ≤2 mm of the optimal predicted was used in 77/93 cases (83%) while oversizing by 1–2 mm was done in only 16/93 cases (17%) with bilateral commissural split. The corresponding values for those with single or no commissural split were 26/47 (55%) and 21/47 (45%), respectively. Hence, according to this study, bilateral commissural split is achieved more often if the balloon size is ≤2 mm of the optimal predicted. Oversizing by 1–2 mm, when required, more often leads to asymmetric commissural splitting, and hence may also increase the chances of adverse results.

**Conclusions:** We conclude that commissural morphology is an important predictor of results following BMV, and it is possible to predict the commissural morphology and likelihood of the site of commissural split by routine echocardiography. The observation that patients with inadequate commissural splitting tend to have higher transmitral gradients and slightly lower MVA following BMV (as compared to those with bilateral splitting) highlights the importance of commissural morphology as a determinant of outcome following BMV. The fact that there was more frequent need for oversizing the balloon in patients with single or no commissural splitting and thus a greater chance of producing new or increasing any pre-existing MR, also reflects the role of commissural morphology in these patients.

Whether the inferior hemodynamic results in those with inadequate commissural splitting play a role in restenosis remains to be ascertained.

**Limitations of the study:** (i) Our study had only 5 patients in whom commissural morphology was thought to be severe enough for them to be categorized in the group in which none of the commissures were predicted to split. However, at least one commissure did split in all these patients. A larger number of patients could be studied to see whether such patients could be candidates for BMV. (ii) Since commissural morphology is a predictor of the immediate results following BMV it could also affect the long-term results following BMV. Thus patients with unilateral split might be more prone to restenosis as compared to those with bilateral commissural splitting following BMV. This study, however, did not address this specific issue, which may be dealt with in further studies.

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Chlamydia pneumoniae Infection and Nonspecific Aortoarteritis: Search for a Link with a Nonatherosclerotic Inflammatory Arterial disease

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Background: The association between Chlamydia pneumoniae infection and atherosclerosis has gained recognition. However, the nature of this association is controversial. The infective link may not be specific for atherosclerosis and may also exist in other nonatherosclerotic arterial diseases. We investigated patients with nonspecific aortoarteritis for serological evidence of prior Chlamydia pneumoniae infection.

Methods and Results: Fifty patients each of nonspecific aortoarteritis and coronary artery disease with angiographic evidence of significant (>70%) coronary artery lesions were tested for the presence of IgG antibodies against Chlamydia pneumoniae by micro-immunofluorescence assay and compared with 50 age- and sex-matched normal healthy controls. The number of patients with nonspecific aortoarteritis who tested positive for Chlamydia pneumoniae antibodies (IgG) was not significantly different from controls (8 v. 7, p=ns). The mean titer amongst positive subjects in the two groups was also similar (1:40±40 v. 1:50±25; p=ns). Patients with coronary artery disease were significantly older than patients with nonspecific aortoarteritis and controls (53.2±5.8 v. 21.2±9.9 years and 24.5±5.2 years, p<0.01 for both) and showed a higher seroprevalence of prior Chlamydia pneumoniae infection (18 v. 8 and 7, p< 0.05 for both). The mean IgG titers of patients with coronary artery disease who tested positive were also significantly higher than the other two groups (1:98±34 v. 1:40±40, p<0.001 and 1:98±34 v. 1:50±25, p<0.01, respectively).

Conclusions: In patients with nonspecific aortoarteritis, the seroprevalence of prior Chlamydia pneumoniae infection is not more than that in healthy individuals of the same age group, but is significantly lesser than that in patients with coronary artery disease. Thus Chlamydia pneumoniae infection may not be associated with all forms of chronic inflammatory arterial lesions. (Indian Heart J 2002; 54: 46-49)

Key Words: Chlamydia pneumoniae, Nonspecific aortoarteritis, Coronary atherosclerosis

Introduction

Chlamydia pneumoniae (CP), a widespread respiratory pathogen, is present in several atherosclerotic plaques. A number of epidemiological studies have also shown serological evidence of prior CP infection in patients with coronary artery disease (CAD). However, the nature of the association and the exact role of CP in the etiopathogenesis of atherosclerosis has been widely debated. Chlamydia pneumoniae persists chronically inside macrophages and could passively reach the atheromatous lesions without having any specific affinity for arterial lesions. Thus it is possible that the organism may not be a specific primary agent for causing atherosclerosis but may only be a "bystander" or a "secondary invader". However, if this is true, other inflammatory arterial lesions may also harbor the same organism. This hypothesis could be tested in nonspecific aortoarteritis (NSAA), which is a chronic inflammatory disease of the aorta and its branches. The exact etiopathogenesis of NSAA has remained elusive and although infectious agents such as CP have been proposed as etiological agents, these associations have not been validated. We, therefore, investigated the presence of humoral immune response against CP in patients with NSAA.
Methods

**Patients:** Fifty patients with NSAA, satisfying the clinical criteria (Table 1) for the diagnosis of NSAA and 50 cases with proven CAD were screened for the presence of anti-CP antibody. Patients with NSAA included 28 males and 22 females, ranging in age from 5 to 40 years (mean 21.2±9.9 years). Patients of CAD were cases of chronic stable angina with evidence of significant (>70%) coronary artery lesion on coronary angiography. These included 32 males and 18 females (mean age 53.2±5.8 years). Of the 50 patients with CAD, 10 had single-vessel disease, 15 had double-vessel disease and the remaining 25 had triple-vessel disease. Fifty healthy blood donors served as controls. The controls consisted of 30 healthy males and 20 females (mean age 24.5±5.2 years). Patients with chronic bronchitis, those receiving steroids or immunosuppressive agents and those who cross-reacted to *Chlamydia trachomatis* and *Chlamydia psitacci* were excluded from the study. All patients underwent a detailed clinical examination and an intra-arterial digital subtraction angiography (DSA). Serum IgG antibodies against CP were estimated using micro-immunofluorescence assay.

**Micro-immunofluorescence assay:** The micro-immunofluorescence assay (Multiscreen Chlamydia, IO International, UK) was used for detecting type-specific antibodies against CP. This assay is based on testing the serial dilutions of samples and visualizing the antigen-antibody reaction. Each kit contains 8 teflon-coated slides, antihuman IgG conjugated with fluorescein isothiocyanate compound, positive and negative sera, coverslips, phosphate buffer saline (PBS) tablets and a mountant. Serial dilutions of the test serum were prepared at 1/16, 1/64 and 1/128 dilutions and added to each slide containing 18 wells with panels of the chlamydia antigen. The slides were then incubated for 30 min at 37 ºC followed by washing with PBS for 10 min. Conjugate was then added to each well. A positive reaction was indicated by the presence of elementary bodies that were evenly distributed with a bright apple-green fluorescence. A titer of >1:16 was considered as positive evidence of humoral response to CP infection.

**Statistical analysis:** Data are presented as mean±standard deviation unless stated otherwise. Continuous variables were compared using the Student’s *t* test. Sample proportions were compared by the Chi-square test with Yates’ correction. A *p* value <0.05 was considered significant.

**Results**

The overall study comprised 150 subjects (50 cases each of NSAA and CAD, and 50 controls). Baseline characteristics for all the three groups are shown in Table 2. Of the study subjects with NSAA, 36 (72%) presented with hypertension, 7 (14%) had claudication, 12 (24%) had neurological complaints including headache in 5 (10%), visual problems in 3 (6%), paresthesia in the upper extremities in 3 (6%) and episodes of presyncope in 2 (4%). Seven patients (14%) had left ventricular dysfunction and 3 (6%) presented with congestive heart failure. Three patients (6%) were asymptomatic. On DSA, 13 patients (26%) had type I disease, 9 (18%) had type II and 28 (56%) had type III disease. The DSA findings are shown in Table 3.

The number of subjects who tested positive for IgG

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**Table 1. Clinical criteria for diagnosing cases of nonspecific aortoarteritis**

<table>
<thead>
<tr>
<th>Obligatory criterion</th>
<th>Two major criteria</th>
<th>Nine minor criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &lt;40 years</td>
<td>Left mid subclavian artery lesion</td>
<td>High ESR</td>
</tr>
<tr>
<td></td>
<td>Right mid subclavian artery lesion</td>
<td>Carotid artery tenderness</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hypertension</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Aortic regurgitation or annuloaortic ectasia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pulmonary artery lesion</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Left mid common carotid lesion</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Distal brachiocephalic trunk lesion</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Descending thoracic aorta lesion</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Abdominal aorta lesion</td>
</tr>
</tbody>
</table>

Nonspecific aortoarteritis was diagnosed if in addition to the obligatory criterion, two major or one major and two or more minor criteria or four or more minor criteria were present.

<table>
<thead>
<tr>
<th>NSAA (n=50)</th>
<th>CAD (n=50)</th>
<th>Controls (n=50)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (in years)</td>
<td>21.2±9.9*</td>
<td>53.2±5.8*</td>
</tr>
<tr>
<td>Males: females</td>
<td>28:22</td>
<td>32:18</td>
</tr>
<tr>
<td>Hypertension</td>
<td>36*</td>
<td>24*</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>-</td>
<td>12</td>
</tr>
<tr>
<td>Smoking</td>
<td>14*</td>
<td>23*</td>
</tr>
<tr>
<td>Obesity</td>
<td>-</td>
<td>28</td>
</tr>
<tr>
<td>Family history of CAD</td>
<td>4*</td>
<td>14*</td>
</tr>
<tr>
<td>Old myocardial infarction</td>
<td>-</td>
<td>15</td>
</tr>
<tr>
<td>Cardiomegaly (X-ray)</td>
<td>8</td>
<td>6</td>
</tr>
</tbody>
</table>

NSAA: nonspecific aortoarteritis; CAD: coronary artery disease; *p<0.05
antibodies against CP were significantly more in patients with CAD than in those with NSAA and controls (18 v. 8, p=0.03; 18 v. 7, p<0.01). The mean IgG titers of patients with CAD who tested positive were significantly higher than those with NSAA and controls (1:98±34 v. 1:40±40, p<0.001 and 1:98±34 v. 1:50±25, p<0.01). The number of subjects with NSAA who tested positive were not significantly more than controls and their mean IgG titers were also similar (8 v. 7, p=ns; 1:40±40 v. 1:50±25, p=ns).

### Discussion

Chlamydia pneumoniae infection is detected by a rise in IgA, IgG and IgM antibodies and has been shown to be associating with systemic vasculitis of small and large vessels. Ljungstrom et al. reported 5 cases with vasculitis in whom serological evidence of CP infection was seen based on the detection of species-specific IgA, IgG and IgM antibodies. Four of the 5 cases exhibited a four-fold increase in antibody titer and the fifth case was found to have high level of IgG and IgA antibodies, indicating a recent infection. Wissler et al. have proposed that infective agents like CP could be etiologically linked to NSAA, a chronic large vessel vasculitis with a predilection for the aortic arch and its branches. To the best of our knowledge, ours is the only study which investigated the possibility of an association between serological evidence of CP infection and lesions of NSAA.

Weymann et al. analyzed the T cells infiltrating the vessel wall in NSAA and showed that a small proportion of CD4+ T cells proliferated in situ, probably following an antigen recognition. It has been postulated that an infective agent could either directly infect the vessel wall or trigger an autoimmune reaction against some component of the vessel wall in NSAA as shown by the presence of autoantibodies against vascular endothelium in some of these patients. Chlamydia pneumoniae infection constitutes an attractive explanation since it is known to cause chronic intracellular infection with poor healing tendency. It has been recognized for causing isolated or systemic vasculitis. However, unlike atherosclerosis, we did not find any serological evidence of prior chlamydial infection in patients with NSAA.

It is not clear whether CP is a primary causative agent or a secondary invader of the atherosclerotic lesion, although the association with atherosclerotic disease is well established. It has also been postulated that CP may be an innocent bystander which is carried inside the lesion by macrophages. Chlamydia pneumoniae requires living cells for replication and is the only example of internal bacterial flora in human tissue that is not propagated by passive cultivation of necrotic tissue. This point favors the innocent bystander hypothesis. However, the hypothesis of a secondary infection appears equally plausible. Although the progression of atherosclerosis is a slow, ongoing process, the agent may contribute to the instability of plaques at some time during the disease process. Chlamydia pneumoniae produces a chronic intracellular infection with poor healing tendency and frequently, arteritis can be induced in experimental animals. The overwhelming seroepidemiologic data that has shown the association between CP and CAD support a causative role for CP. Our study argues against the innocent bystander or secondary invader hypothesis. Arterial lesions were widespread in our patients with NSAA. However, we did not find any humoral evidence of chlamydial infection in these cases.

### Limitations

Serological assay alone was used for assessing the presence of prior CP infection. However, to the best of our knowledge, this is the only study that has searched for a possible role of CP infection in NSAA. The lesions of NSAA and atherosclerosis are both examples of chronic arterial inflammation, but they differ from each other in cholesterol content and degree of fibrosis. Macrophage movement may also be different in the two conditions. Similarly, since the study was primarily designed to evaluate the presence of serological evidence of CP infection in NSAA, the controls were matched to cases of NSAA and not to cases with CAD. Therefore, these limitations need to be kept in mind.

### Conclusions

There is epidemiological evidence to suggest an association between CP infection and atherosclerosis. This study investigated the presence of a similar association for a nonatherosclerotic arterial disease such as NSAA. The proportion of patients with NSAA who tested positive for
anti-CP IgG antibodies was not significantly different as compared to controls. Therefore, CP infection is not seen in all forms of arterial lesions, and may be specific for atherosclerosis.

**References**


Lipoprotein (a) Phenotypes in South Indian Patients with Coronary Artery Disease

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Background: Plasma lipoprotein (a) levels in the Indian population are varied; this study was undertaken to determine the relationship between plasma lipoprotein (a) levels and their phenotypes in a group of south Indian patients with coronary artery disease.

Methods and Results: A total of 104 patients with angiographically proven coronary artery disease were compared with 104 age- and sex-matched controls with no risk factors such as hypertension, diabetes, and smoking. Lipoprotein (a) levels were measured by an in-house ELISA method and its phenotyping was done by SDS agarose gel electrophoresis. Plasma lipoprotein (a) levels were significantly elevated in patients with coronary artery disease as compared to controls (33.4±26.1 mg/dl v. 21.4±12.8 mg/dl; p<0.01). Lipoprotein (a) phenotyping showed that low-molecular weight isoforms were found only in 19.2% of the patients with coronary artery disease and their plasma lipoprotein (a) levels were significantly elevated compared to coronary artery disease patients with higher molecular weight isoforms (50.9±34.2 mg/dl v. 29.24±20.06 mg/dl; p<0.001). Conclusions: Plasma lipoprotein (a) levels are significantly elevated in patients with coronary artery disease as compared to controls. The commoner phenotype in a South Indian population is the larger apolipoprotein (a), in which the lipoprotein (a) levels are lower. Hence the contribution of lipoprotein (a) phenotype to the lipoprotein (a) levels in our population, if any, is modest.

Key Words: Lipoprotein (a), Coronary artery disease, Apolipoproteins

Lipoprotein (a) [Lp(a)] was identified in the plasma by Berg in 1963. It is a low-density lipoprotein (LDL) particle to which an apoprotein called apolipoprotein a (apo a) is covalently linked by a disulfide bond. Serum Lp(a) levels are largely determined by an apolipoprotein (apo [a]) gene localized on the long arm of chromosome 6 accounting for more than 90% of variations in its serum level. Different isoforms have been categorized based on their molecular size and there exists an inverse relationship between the isoform size and plasma Lp(a) levels.3

Numerous studies carried out in several countries over the past 25 years have suggested that Lp(a) could be an independent risk factor for premature coronary artery disease (CAD).2 Six prospective studies concluded that Lp(a) is a risk factor for CAD1–9 but three other case-control studies did not arrive at this conclusion.10–12

We had earlier reported that serum Lp(a) levels are elevated in Indian patients with CAD.13 We noticed that the levels have a wide scatter and a definite cut-off level could not be established. Hence we carried out this study in a larger number of patients; we also studied the relationship of serum Lp(a) levels with their phenotypes.

Though there are a few studies from India in which the isoforms were studied, they were all done in a north Indian population.14–16 Since apo (a) has ethnic variation, it seemed appropriate to carry out this study in a south Indian population.

Methods

Blood was collected in tubes containing potassium EDTA from a total of 104 angiographically proven CAD patients. The control group consisted of 104 age- and sex-matched normal healthy volunteers without any CAD risk factors such as hypertension, diabetes, and smoking. Plasma was separated and kept frozen until analysis.

Lipid profile: The lipid profile tests, namely determination of cholesterol and triglyceride levels, were done by enzymatic methods on a Hitachi 911 auto analyzer using reagents supplied by Boehringer Mannheim, Germany.
High-density lipoprotein (HDL) cholesterol was measured by the same method after precipitating the apo B-containing lipoproteins with magnesium chloride and phosphotungstate. Low-density lipoprotein cholesterol was calculated using the Friedewald's equation.

Lipoprotein (a) quantitation: Plasma Lp(a) levels were measured by an in-house double antibody sandwich ELISA based on the method of Menzel et al. The capture antibody was an affinity-purified apo (a) polyclonal antibody raised in rabbits against human apo (a). The detection antibody was a mouse monoclonal antibody 1A2, conjugated with horseradish peroxidase. Orthophenylenediamine was used as the substrate and the final absorbance was read at 490 nm; standards were prepared from a commercial reference material from Immuno, Vienna and used for construction of the standard graph. The results were expressed in mg/dl.

Apolipoprotein (a) phenotyping: apo (a) phenotyping was done by SDS agarose gel electrophoresis described by Kamboh et al. The plasma samples were treated with reducing buffer containing SDS, ethylmorpholine, bromophenol blue and mercaptoethanol and then loaded onto the gel. After electrophoresis, the separated bands were transferred to a nylon membrane by the Western Blot technique. The bands were identified by immunoblotting followed by detection with ECL Western Blot chemiluminescence substrate (Amersham) and subjected to autoradiography. A standard containing a mixture of five different isoforms from Immuno, Vienna was used for reference.

Initially, Utermann identified six types of apo (a) isoforms and named them F, B, S1, S2, S3 and S4 based on their electrophoretic mobility. Later, these isoforms were identified based on their kringle (IV) repeat numbers such as 21, 23, 40, etc. According to Kraft et al., these phenotypes can be interconverted into the six different phenotypic groups as F (with 11–13 repeats), B (14–16), S1(17–19), S2 (20–22), S3 (23–25) and S4 (>25).

Statistical analysis: All results are expressed as mean±1 standard deviation. The differences between the two groups were analyzed using the Student's t test for independent samples. Since Lp(a) distribution was highly skewed, the nonparametric Mann Whitney U test was used for analysis.

Results

The baseline characteristics of the patient population are summarized in Table 1. Controls were selected from age- and sex-matched healthy individuals without any cardiac risk factors such as hypertension, diabetes and smoking. The mean age of the cases and controls was 52.5±6.8 years.

Lipid profiles are summarized in Table 2. Plasma Lp(a) levels were significantly elevated in cases compared to controls (33.4±26.1 mg/dl v. 21.4±12.8 mg/dl).

Table 1. Baseline characteristics of cases (n=104)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Number of patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smokers</td>
<td>28 (26)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>49 (47)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>24 (23)</td>
</tr>
<tr>
<td>Single-vessel disease</td>
<td>26 (25)</td>
</tr>
<tr>
<td>Two-vessel disease</td>
<td>36 (35)</td>
</tr>
<tr>
<td>Three-vessel disease</td>
<td>42 (40)</td>
</tr>
</tbody>
</table>

Table 2. Lipid profile and Lp(a) values

<table>
<thead>
<tr>
<th>Variable</th>
<th>Cases</th>
<th>Controls</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholesterol (mg/dl)</td>
<td>188±34</td>
<td>181±34</td>
<td>ns</td>
</tr>
<tr>
<td>Triglycerides (mg/dl)</td>
<td>189±85</td>
<td>148±45.5</td>
<td>&lt;0.01*</td>
</tr>
<tr>
<td>HDL-c (mg/dl)</td>
<td>40.3±7</td>
<td>44±8.6</td>
<td>ns</td>
</tr>
<tr>
<td>LDL-c (mg/dl)</td>
<td>109±28</td>
<td>108±30</td>
<td>ns</td>
</tr>
<tr>
<td>Lp(a) (mg/dl)</td>
<td>33.4±26.1</td>
<td>21.4±12.8</td>
<td>&lt;0.01*</td>
</tr>
</tbody>
</table>

ns: statistically not significant; * statistically significant; HDL-c: high-density lipoprotein cholesterol; LDL-c: low-density lipoprotein cholesterol; Lp(a): lipoprotein (a)

The frequency distribution of plasma Lp(a) levels and their phenotypes are given in Figs 1 and 2, respectively. Since the number of individuals in each of these types was few, we divided them into two major groups—A and B—as shown in Table 3.

In group A, we included types B, S1 and S2 (kringles up to 22). In this group comprising 20 cases and 12 controls, the Lp(a) levels were higher in cases than in controls (mean

![Fig. 1. Frequency distribution of plasma Lp(a) levels in patients with CAD and controls.](image-url)
In our study, the larger isoforms of Lp(a) were the most common variety. Only 19.2% of cases and 11.5% of controls had smaller isoforms. Lipoprotein (a) levels were significantly higher in the group with smaller isoforms than in the group with large isoforms (50.9±34.2 mg/dl v. 29.24±20.06 mg/dl; p<0.001). This confirms that individuals with smaller phenotypes have higher Lp(a) levels than those with larger phenotypes as seen in the West.12

Our results are similar to those of a study published by Luthra et al.14 from north India. Since individuals with the smaller isoforms form only a small group, the contribution of this phenotype will be modest in our population.

In conclusion, Lp(a) levels are significantly elevated in our patient population and there exists an inverse association between the size of apo (a) and blood levels of Lp(a) both in north and south Indian patients. In India, the larger apo (a) is the commoner phenotype in which case the Lp(a) levels are relatively low. Hence the contribution of Lp(a) phenotype to the Lp(a) levels in our population, if any, is modest.

**Acknowledgment**

We are grateful to Dr G Utermann of Austria for providing the necessary antibodies and materials needed in our biochemistry laboratory for this study.

**References**

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A Community-Based Rheumatic Fever/Rheumatic Heart Disease Cohort: Twelve-Year Experience

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Background: A pilot rheumatic fever and rheumatic heart disease control project was started in 1988 in blocks of district Ambala (Haryana) to test the feasibility of early detection, treatment and secondary prophylaxis for rheumatic fever/rheumatic heart disease cases. School teachers, students and health workers were trained to identify and refer suspected cases of rheumatic fever/rheumatic heart disease to the community health center where physicians examined the suspected cases and monthly secondary prophylaxis was provided to the confirmed cases.

Methods and Results: A survey of registered cases was done in 1999 to determine the compliance rate of secondary prophylaxis and to describe clinical and epidemiologic features of the registered cohort of rheumatic fever/rheumatic heart disease patients. A total of 257 patients had been registered till the end of 1999 with 1263 person-years of follow-up. Out of these registered patients, 132 were receiving secondary prophylaxis, 52 had died, 17 had migrated, 8 were lost to follow-up, 18 had stopped prophylaxis and 30 completed the prophylaxis course. The mean age at registration was 18 years. Half of the cases were in the 6-15 years age group at registration. Over half of the patients were registered with a history of rheumatic fever. Fever was the most common symptom (75.9%). Carditis was more common among cases with recurrent attacks of rheumatic fever than after a first attack. The mortality in rheumatic fever/rheumatic heart cases was 32.5/1000 person-years. The mean age at death was 24.4 years. Compliance with secondary prophylaxis was 92% during the past 12 years.

Conclusions: A rheumatic fever/rheumatic heart disease control program can be sustained within the primary health care system and the case registry can be utilized not only for monitoring the program but also to gain insight into the epidemiology of the disease. (Indian Heart J 2002; 54: 54-58)

Key Words: Rheumatic heart disease, Prevention, Epidemiology
healthcare (PHC) system. As part of this international initiative, a program for the prevention of RF/RHD was started in a rural community development block of Ambala district of Haryana in 1987.  The program is continuing in collaboration with the state health services staff. This study was carried out to determine the compliance rate of secondary prophylaxis among registered patients and to describe clinical and epidemiologic features of the registered cohort of RF/RHD patients.

**Methods**

The control strategies at the time of initiation of the program were to identify RF/RHD patients with the active help of teachers, students and health personnel, to register them and to provide regular secondary prophylaxis in the form of monthly injections of benzathine penicillin or oral antibiotics in case of penicillin sensitivity, in community development blocks of Haryana (population approximately 140 000). The number of children in the 5–14 years age group was estimated to be 27% of the total population. Although full details of the program design are discussed elsewhere, a summary is presented below.

Records of various health centers were scrutinized initially to determine the number of RF/RHD cases registered in the two years prior to the program. Health workers, pharmacists, government ayurvedic medical practitioners and anganwadi workers were trained to screen for possible cases and to refer them to medical officers for confirmation of the diagnosis. Similarly, health education was also imparted to teachers and students of 147 schools so that they could identify the symptoms and signs among the students for referral to the nearest health center. They were trained to identify children in the age group of 5–14 years who had fever and pain or swelling in the upper or lower limb joints, fatiguability or breathlessness, or involuntary movements of the limbs. Health education was repeated at regular intervals. Posters, pamphlets and acrylic heart models were designed, pre-tested and used in these health education sessions.

Medical officers were given reorientation training regarding the disease. They were to examine the suspected cases of RF/RHD referred by health workers, teachers and students; register them and reach a probable diagnosis of RF or RHD based upon the revised Jones’ criteria. Any child with a pansystolic or mid-diastolic murmur at the apex or early diastolic murmur at the base or atrial fibrillation (irregularly irregular heartbeat) at the time of presentation to the medical officer was registered as a probable case of RHD. Any child with two major criteria or one major and two minor criteria was registered as a probable case of acute RF. The major criteria were: arthritis (swelling of one or more big joints), carditis (cardiomegaly, acute murmur, heart failure, pericardial rub), chorea (jerky involuntary movements), erythema marginatum and subcutaneous nodules. The minor criteria were fever, arthralgia, history of previous acute RF, pre-existing RHD, prolonged P–R interval on ECG (more than 0.2 s), or elevated ESR (more than 30 mm/hour) or C-reactive protein (CRP). Persons in whom acute RF was suspected were subjected to antistreptolysin O (ASO) titer estimation by the semi-quantitative method (ASO titer >200 TU) for which facilities were available at the community health center (CHC).

For the present study, a semi-structured interview schedule was developed and pre-tested. A field worker was given training to conduct personal interviews with patients or a responsible relative. Past records of the patients were scrutinized. Patients who were not coming to the CHC for prophylaxis were identified. Thereafter, the trained field worker visited the home of these persons and interviewed them. The attending physician interviewed the compliant patients at a monthly RF/RHD follow-up clinic at the CHC.

Health education was imparted to the patients during home visits and contact was made with health workers, anganwadi workers, teachers, students and other relevant persons to spread health education messages regarding RF/RHD. Houses of 40 non-compliant patients were visited during March and April 1999. The compliance rate and new registration till 1996 are reported elsewhere. The field worker also visited the households of the registered cases who had died, and a pre-tested verbal autopsy schedule was filled up to determine the probable cause of death. Out of the 52 reported deaths, the verbal autopsy schedule could not be completed in 4 cases due to migration of the family. Two physicians assessed the completed verbal autopsy schedules to arrive at a probable cause of death as “related” or “unrelated” to RF/RHD.

Data so obtained were entered in the computer. Analysis was done through the Epi Info computer package, ver. 6.02. The total person-years of follow-up were calculated by adding up the number of years each patient was in our registry. The date of registration was the entry point in the registry and date of death or date when the patient left the area was taken as the date of exit from the registry. The Chi square and t-tests were applied for statistical significance, wherever required.

**Results**

A total of 257 patients had been registered till the end of 1999. The total person-years of follow-up were 1263. Figure 1 shows the annual registration of cases. The age and sex distribution of the cohort is presented in Table 1. Most of the cases (70.8%) were aged 6–20 years at the time.
of registration. The mean age was significantly higher (p<0.01) in females than males. Over half of the patients were registered either with RHD (44.7%) or with the presence of RHD and history of recurrence of acute RF (11.7%) (Table 2). More males (51.2%) were registered with a history of acute RF as compared to females (36.8%), who were more likely to report with RHD (with or without recurrence of RF). Among those registered with a history of RF, fever (75.9%) was the most commonly reported symptom followed by arthritis (58.9%), arthralgia (42.9%) and carditis (22.3%). Carditis was significantly more prevalent in recurrent attacks of RF (70%) compared to the first attack (p<0.01) (Table 3).

By the end of 1999, there were 132 patients in the registry. Fifty-two patients had died during the past 12 years, 17 had migrated, 8 were lost to follow-up, 30 patients completed their prophylaxis and 18 stopped prophylaxis on their own. The mean compliance with secondary prophylaxis was 92% from 1988 to 1999. The annual compliance varied from 82.4% to 100% (Table 4). The reasons for noncompliance were many; 1 patient was frightened when a fellow patient died after receiving the injection, another patient used to feel weak after the injection and 2 patients stopped taking the injection because of pain. Two patients felt that they had no health problem now and hence did not need any injection, whereas 1 patient...
stopped because of lack of awareness about the importance of prophylaxis. Five women stopped taking the injection after marriage because these services were not available locally and they did not want to reveal the disease to their husbands for the fear of divorce, etc. No specific reason could be assigned in 6 cases. Eleven of these patients restarted prophylaxis after counseling. The source of secondary prophylaxis was the government health center in 84% of the patients, 13% were taking it sometimes from the government health center and at other times from a private source, and only 3% consistently took it from private sources.

The analysis of 48 completed verbal autopsy schedules revealed that 41 deaths were probably related to RF/RHD. This gives a case fatality rate of 16%. The mortality rate due to RF/RHD per thousand person-years was estimated to be 32.5 (Table 5) which is high compared to the crude mortality rates of 9/1000 in the general population.14 The mean age at death was 24.4±12.7 years. The difference in mean age at death of males and females was not statistically significant. Compliance with secondary prophylaxis among those who died was 69% in the year preceding death.

Table 5. Mortality due to RF/RHD among registered cases

<table>
<thead>
<tr>
<th>Registered cases</th>
<th>257</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total person-years of follow-up</td>
<td>1262.7</td>
</tr>
<tr>
<td>Total deaths</td>
<td>52*</td>
</tr>
<tr>
<td>Death related to RF/RHD</td>
<td>41</td>
</tr>
<tr>
<td>Mean age at death (in years)</td>
<td>24.4±12.7</td>
</tr>
<tr>
<td>Median age at death (in years)</td>
<td>20</td>
</tr>
<tr>
<td>Case fatality rate</td>
<td>16%</td>
</tr>
<tr>
<td>Mortality per 1000 person-years of follow-up</td>
<td>32.5</td>
</tr>
</tbody>
</table>

*Cause of death could not be ascertained in 4 cases as the families had migrated before the verbal autopsy survey

Discussion

Studies carried out by WHO concluded that it is feasible to maintain a program for control of RF/RHD through secondary prophylaxis.9,10 These studies followed patients for 5 years.9 Our study shows that it is possible to maintain the program for long periods within the existing health infrastructure. However, constant supervision is required for registration of new cases and repeated motivation of the patients is also needed for continuation of prophylaxis. An average compliance rate of 92% was maintained in the past 12 years. The median age at registration indicates that cases were registered early. However, gender bias is also evident from the analysis as more males were registered at an early age with a history of RF in comparison to females who were more often registered with RHD at a later age.

Our findings confirm the conclusion that the clinical profile of RF does not differ from that of developed countries.15,16 Fever was the most common symptom of RF in our study and arthritis was found in half the cases. Carditis was observed in 22% of the patients and chorea in 16%. In one study15 febrile arthritis was found in 68% and chorea in 16%, and another hospital-based study16 found joint involvement and chorea in 69% and 18% of children, respectively, during the first attack of RF.

In our study, mortality was found to be very high (32.5/1000 person-years). Among children with RF/RHD the mortality was reported as 20/1000.16 The reasons for the high mortality in our study are that most of the patients were registered in the advanced stages of the disease and in a few cases the heart valves were either inoperable or the patients could not afford the cost of surgical treatment. Four patients died following administration of injection benzathine penicillin. Some of these deaths could be due to penicillin allergy. Sudden atrial fibrillation as a consequence of RHD may also be the cause of death in some. It was difficult to confirm the cause of death in these cases, as diagnostic facilities in the CHC set-up were limited. All these 4 patients were taking penicillin prophylaxis for months/years. Three of them had severe valvular damage with congestive heart failure; 2 had pulmonary hypertension, 1 had atrial fibrillation, and 1 had mitral stenosis and regurgitation. It is possible that pre-existing heart disease or treatment for such disease might have exacerbated the cardiovascular effects of anaphylaxis or hindered the attempts at resuscitation. The incidence of anaphylactic reactions has been reported to range from 0.8 to 4/10 000 courses of benzathine penicillin treatment.17–20

We found a decline in the registration of new RF and RHD cases in recent years (Fig. 1). However, whether this is due to a decline in the occurrence of cases is not clear since active case finding is not being pursued and an active program for treatment of sore throat is not being implemented. A decline in the registration of RF cases was reported by some workers. In a hospital-based, retrospective study, a fall in the number of admissions for RHD (800/year to 500/year) and RF (85/year to zero) was observed over a period of 30 years in Christian Medical College, Vellore.21 In Jammu, a survey of over 10 000 schoolchildren aged 6–16 years did not find any child with RF though valvular lesions were found in 14 children.3 A resurgence of RF occurred in the USA in the 1980s. A change in the virulence of the pathogen is suspected to be the reason for these changes in incidence.9,22 A population-based study is required in other regions to confirm the time trend of RF in India.

For the success of a community-based RF/RHD control program, early case detection is crucial in preventing
serious complications and mortality. Health education of the community, especially children, therefore, should be given more emphasis so that they can identify the cases among themselves at an early stage. Primary prophylaxis is another measure that can prevent the initial attack, thereby decreasing the disease load. The usefulness of primary prophylaxis in reducing the incidence of RF has been confirmed by two studies in Baltimore and Costa Rica. In the first study, throat culture was used for diagnosis but in the second all pharyngitis cases were treated with injection benzathine penicillin without any throat culture. The WHO had recommended this treatment for suspected cases of streptococcal sore throat without culture. The implementation of any primary prophylaxis program on a large scale, however, requires a well developed and dedicated primary healthcare system accessible to everyone, availability of antibiotics, culturally relevant health education and community participation. Secondary prophylaxis is more cost-effective but it needs regular surveillance, reporting, motivation and antibiotic injection.

References

Prevalence of Coronary Heart Disease and Risk Factors in an Urban Indian Population: Jaipur Heart Watch-2

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Background: The prevalence of risk factors for coronary heart disease has been inadequately studied in India. A repeat cross-sectional survey was carried out to evaluate the changes in the major coronary risk factors in the urban population of Jaipur previously studied in the early 1990s.

Methods and Results: Randomly selected adults >20 years of age were studied using stratified sampling. The target study sample was 1800 with a population proportionate gender distribution (males 960, females 840). Coronary risk factors, anthropometric variables, blood pressure, ECG, fasting blood glucose and lipids were evaluated. A total of 1123 subjects (62.4%) (males 550, females 573) were examined. Fasting blood samples were available in 523 males and 559 females. Overall coronary heart disease prevalence, diagnosed by history or ECG changes, was found in 34 males (6.18%) and 58 females (10.12%). Risk factor prevalence showed that smoking/tobacco use was present in 201 males (36.5%) and 67 females (11.7%). Physical inactivity, either work-related or leisure time, was seen in 157 males (28.5%) and 130 females (22.7%). Hypertension (>140 and/or 90 mmHg) was present in 200 males (36.4%) and 215 females (37.5%). Diabetes diagnosed by history or fasting glucose >126 mg/dl was found in 72 males (13.1%) and 65 females (11.3%). Obesity, body mass index >27 kg/m² was present in 135 males (24.5%) and 173 females (30.2%), while truncal obesity (waist:hip >0.9 males, >0.8 females) was found in 316 males (57.4%) and 392 females (68.4%). The most common dyslipidemia in both males and females was low HDL-cholesterol (<40 mg/dl: males 54.9%, females 54.2%). High total cholesterol levels of >200 mg/dl (males 37.4%, females 4.1%), high LDL-cholesterol levels of >130 mg/dl (males 37.0%, females 45.8%) and high levels of triglycerides >150 mg/dl (males 32.3%, females 28.6%) were also seen in a significant number. Hypertension, obesity, truncal obesity, diabetes and dyslipidemias increased significantly with age in both males and females (Mantel-Haenzel χ² for trend, p<0.05).

Conclusions: There is a high prevalence of standard coronary risk factors—smoking, physical inactivity, hypertension, hypercholesterolemia, diabetes and obesity—as well as factors peculiar to south Asians—truncal obesity, low HDL-cholesterol and high triglycerides—in this urban Indian population. As compared to a previous study in the early 1900s in a similar population, there is a significant increase in the number of people with obesity, diabetes and dyslipidemias. (Indian Heart J 2002; 54: 59-66)

Key Words: Coronary risk factors, Coronary artery disease, Epidemiology

The epidemic of cardiovascular diseases has taken deep roots in India and many other developing countries. The burden of death and disability due to coronary heart disease (CHD) continues to increase, and in the absence of suitable preventive efforts is not being controlled. The focus of policy-makers, the press, politicians and physicians is on novel genetic and biochemical factors and not on traditional risk factors. A large number of studies have highlighted that the primordial prevention strategy of CHD involving control of three lifestyle-related risk factors—smoking, physical inactivity and aberrant diet—is the most cost-effective method. The major coronary risk factors [smoking, hypertension, high low-density lipoprotein (LDL)-cholesterol, diabetes, obesity, truncal obesity, insulin resistance, high low-density lipoprotein (HDL)-cholesterol] are secondary manifestations of these deviant lifestyles and explain more than 90% of the incidence of CHD worldwide.

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Retrospective analysis of previous Indian CHD and risk factor epidemiological studies have reported increasing prevalence of the major coronary risk factors such as smoking, hypertension, diabetes, hypercholesterolemia, obesity and truncal obesity. The increase in these risk factors correlates positively with the increasing CHD in India.

In the Jaipur Heart Watch-1 (JHW-1), we studied the prevalence of CHD and coronary risk factors among the urban and rural populations of Rajasthan in the early 1990s using a cross-sectional survey design and stratified random sampling. Comparison of urban–rural differences identified that risk factors more prevalent in urban subjects (hypertension, LDL-cholesterol, diabetes, obesity, truncal obesity, low HDL-cholesterol) are important in Indians. We have hypothesized that these standard coronary risk factors are increasing in India, but no study is available that systematically evaluates the trends of coronary risk factor prevalence. Therefore, we performed a repeat cross-sectional survey—the Jaipur Heart Watch-2 (JHW-2) using the previous methodology to evaluate the changes in the prevalence of the major coronary risk factors in the same urban population, though not on the same subjects.

Methods
The study was approved by the institution’s Ethics Committee. A proforma was prepared that incorporated information regarding demographic, anthropometric and clinical data. This included the family history of hypertension and CHD, various lifestyle-related factors such as education and type of job. Details of major cardiovascular risk factors such as smoking, alcohol intake, amount of physical activity, diabetes and hypertension were inquired into. The physical examination emphasized measurement of height, weight, waist–hip ratio (WHR) and blood pressure. Height was measured in centimeters and weight in kilograms using a calibrated spring balance. The supine waist girth was measured at the level of the umbilicus with the person breathing silently and the standing hip girth was measured at the intertrochanteric level according to the World Health Organization (WHO) guidelines. The blood pressure was measured using a standard mercury sphygmomanometer. At least two readings at 5-minute intervals as per the WHO guidelines were recorded. If a high blood pressure (>140/90 mmHg) was noted, a third reading was taken after 30 min. The lowest of the three readings was taken as the blood pressure. A 12-lead routine electrocardiogram (ECG) was taken of all the subjects using proper standardization. Fasting blood samples were obtained from all individuals for the estimation of glucose, total cholesterol levels, HDL- and LDL-cholesterol, and triglycerides using previously standardized techniques.

Sample: The study was designed to investigate people at random and to cover large and varied areas of Jaipur with a view to include persons from all walks of urban life. The same areas were studied as previously. In brief, Jaipur is divided into 70 wards according to the latest publication of the Jaipur Municipal Council. Randomly chosen wards from different regions of the city were identified so as to cover different socioeconomic groups. We studied the population in the colonies of Jawahar Nagar, Janta Colony, Ramganj Bazar, Chandpole Bazar, Moti-Doongri Road and Jaipur South. Details of the population in these wards were available from the Voters’ Lists. The male:female ratio in the adult population (≥20 years) of Jaipur is 1000:865 (Census of India, 1991). We randomly selected 300 persons (160 males, 140 females) from each locality employing the random number technique on the Voters’ Lists. The total study sample was 1800 (960 males and 840 females) with a population proportionate male:female ratio. This sample size was considered adequate for the identification of major coronary risk actors. The formulae for calculating the sample size have been reported earlier. The study was preceded by meetings with local leaders who cooperated in identifying and ensuring participation of selected subjects. Comparison of the age structure of the present study with the Jaipur population of the Indian Census 2001 is shown in Table 1. The literacy rate in the study sample is also not significantly different from the Jaipur Census data 2001 (males 86.9% v. 82.3%, females 69.1% v. 63.3%).

Diagnostic criteria: Smokers in India consume tobacco in various forms—rolled tobacco leaves (bid), Indian pipe (chillum, hookah), cigarettes and chewing tobacco—and more than one form is used by many, making it difficult to accurately measure the amount of tobacco consumed. Therefore, users of all types of tobacco products and present and past smokers were included in the smokers category.

Table 1. Comparison of the study population with Jaipur-2001 population

<table>
<thead>
<tr>
<th>Age group (years)</th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Jaipur (%)</td>
<td>Study (%)</td>
</tr>
<tr>
<td>20–29</td>
<td>34.0</td>
<td>18.0</td>
</tr>
<tr>
<td>30–39</td>
<td>24.9</td>
<td>27.8</td>
</tr>
<tr>
<td>40–49</td>
<td>18.4</td>
<td>21.3</td>
</tr>
<tr>
<td>50–59</td>
<td>12.4</td>
<td>18.2</td>
</tr>
<tr>
<td>60+</td>
<td>10.2</td>
<td>14.7</td>
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<td>Literacy rate</td>
<td>86.9</td>
<td>82.3</td>
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</tbody>
</table>
The diagnostic criteria for tobacco use as well as other coronary risk factors have been advised by the American College of Cardiology clinical data standards. Physical activity was assessed by asking about both work-related and leisure-time activities as per the criteria defined by Paffenberger et al. as used in the previous study. Hypertension was diagnosed if the systolic blood pressure was $\geq 140$ mmHg and diastolic blood pressure $\geq 90$ mmHg or the person was a known hypertensive. Body mass index (BMI) ($\text{kg/m}^2$) was calculated and obesity was defined as BMI $\geq 27$ kg/m$^2$. Truncal obesity was diagnosed if the WHR was $>0.9$ in males and $>0.8$ in females. Dyslipidemia was defined as the presence of high total cholesterol ($>200$ mg/dl), high LDL-cholesterol ($>130$ mg/dl), low HDL-cholesterol ($<40$ mg/dl) or high triglycerides ($>150$ mg/dl) according to the USA-ATP-III guidelines. Diabetes was diagnosed either by history of previously known disease or fasting glucose $>126$ mg/dl. The three diagnostic criteria [clinically documented CHD, WHO-Rose questionnaire-positive angina, or ECG changes (ST, T or Q waves)] for CHD have been reported earlier. Fulfilment of any of these three criteria was taken as confirmation of the diagnosis. However, there could be either an over- or underdiagnosis due to poor interpretation of symptoms in an uneducated population. Therefore, the diagnosis of CHD was also confirmed on the basis of ECG findings (ST, T, Q wave changes or Q wave changes only).

Statistical analysis: The data were pooled and computerized. Continuous variables were reported as mean±1SD. The prevalence rates are given as percentages. Age-related trends were examined by the Mantel-Haenzel $\chi^2$ test. Continuous variables were compared using the $t$-test and categorical variables by the $\chi^2$ test. $p$ values $<0.05$ were considered significant. The direct method of age adjustment was used to compare the prevalence rates of various risk factors in the present with the previous study.

Results

The overall response rate was 62.4% and 1123 of 1800 eligible subjects were examined. The response rate was 550/960 (57.3%) in males and 573/840 (68.2%) in females. Response rates for lipid estimation in males was 523/550 (95.1%) and in females 559/573 (97.6%). The prevalence of CHD is shown in Table 2. According to the combined clinical and ECG criteria, CHD was present in 34 males (6.18%) and in 58 females (10.12%) with an age-associated increase in both (Mantel-Haenzel $\chi^2$ for trend, $p<0.05$).

The prevalence of major coronary risk factors is shown in Table 3. Smoking or tobacco use was present in 201 males (36.5%) and 67 females (11.7%). Physical inactivity, either work-related or leisure time, was seen in 157 males (28.5%) and 130 females (22.7%). Prevalence of the leisure-time physical inactivity alone was very high (males 61.5%, females 63.2%). Hypertension was present in 200 males (36.4%) and 215 females (37.5%). Diabetes was present in 72 males (13.1%) and 65 females (11.3%). Truncal obesity was widely prevalent. The most common dyslipidemia in both males and females was low HDL-cholesterol (males 54.9%, females 54.2%). Prevalence of high total- and LDL-cholesterol and triglycerides was also seen in significant proportions (Table 3).

Table 4 shows the age-specific prevalence of various major coronary risk factors. The prevalence of smoking and physical inactivity did not show an age-related increase but all the other risk factors—hypertension, obesity, truncal obesity, diabetes and dyslipidemias—increased significantly with age in both males and females.
Discussion

The present study shows a striking prevalence of coronary risk factors in an urban Indian population. The prevalence of standard coronary risk factors—smoking, physical inactivity, hypertension, hypercholesterolemia, diabetes, and obesity—as well as factors peculiar to South Asians—truncal obesity, low HDL-cholesterol and high triglycerides—are high in both males and females. There is also a significant burden of CHD in this population.

This study is a continuation of an earlier epidemiological study (JHW-1) that we performed in this population in the

Table 3. Prevalence of major coronary risk factors

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Males (n=550)</th>
<th>Females (n=573)</th>
<th>Total (n=1123)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoking/tobacco use</td>
<td>201 (36.55)</td>
<td>67 (11.69)</td>
<td>268 (23.9)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>200 (36.36)</td>
<td>215 (37.52)</td>
<td>415 (36.9)</td>
</tr>
<tr>
<td>Physical inactivity (work-related or leisure-time)</td>
<td>157 (28.5)</td>
<td>130 (22.6)</td>
<td>287 (25.5)</td>
</tr>
<tr>
<td>Diabetes (history or fasting glucose &gt;126 mg/dl)</td>
<td>72 (13.1)</td>
<td>65 (11.1)</td>
<td>137 (12.2)</td>
</tr>
<tr>
<td>Obesity (body mass index &gt;27 kg/m²)</td>
<td>135 (24.5)</td>
<td>173 (30.2)</td>
<td>308 (27.4)</td>
</tr>
<tr>
<td>Truncal obesity, waist:hip ratio males &gt;0.9, females &gt;0.8</td>
<td>316 (57.4)</td>
<td>392 (68.4)</td>
<td>708 (63.0)</td>
</tr>
<tr>
<td>High total cholesterol &gt;200 mg/dl</td>
<td>199/332 (37.4)</td>
<td>241/559 (43.1)</td>
<td>440/1091 (39.1)</td>
</tr>
<tr>
<td>High LDL-cholesterol &gt;130 mg/dl</td>
<td>197/332 (37.0)</td>
<td>252/559 (45.8)</td>
<td>449/1091 (41.5)</td>
</tr>
<tr>
<td>Low HDL-cholesterol &lt;40 mg/dl</td>
<td>292/332 (54.9)</td>
<td>303/559 (55.1)</td>
<td>595/1091 (55.0)</td>
</tr>
<tr>
<td>High triglycerides &gt;150 mg/dl</td>
<td>172/332 (32.3)</td>
<td>160/559 (28.6)</td>
<td>332/1091 (30.4)</td>
</tr>
</tbody>
</table>

Values in parentheses are percentages

BMI: body mass index; FBG: fasting blood glucose; HDL: high-density lipoprotein; LDL: low-density lipoprotein

Table 4. Age-specific prevalence of coronary risk factors

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Age 20–29 years</th>
<th>Age 30–39 years</th>
<th>Age 40–49 years</th>
<th>Age 50–59 years</th>
<th>Age 60+ years</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoking/tobacco (n=lipids)</td>
<td>99 (98)</td>
<td>153 (147)</td>
<td>117 (111)</td>
<td>100 (98)</td>
<td>81 (78)</td>
<td>550 (532)</td>
</tr>
<tr>
<td>Physical inactivity</td>
<td>31 (31.3)</td>
<td>60 (39.2)</td>
<td>36 (30.8)</td>
<td>33 (33.0)</td>
<td>15 (18.5)</td>
<td>157 (28.5)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>25 (25.3)</td>
<td>48 (31.4)</td>
<td>36 (30.8)</td>
<td>33 (33.0)</td>
<td>15 (18.5)</td>
<td>157 (28.5)</td>
</tr>
<tr>
<td>Obesity (BMI &gt;27 kg/m²)</td>
<td>13 (13.1)</td>
<td>42 (27.4)</td>
<td>46 (39.3)</td>
<td>54 (54.0)</td>
<td>45 (55.6)</td>
<td>200 (36.4)</td>
</tr>
<tr>
<td>Truncal obesity (WHR &gt;0.9)</td>
<td>15 (15.2)</td>
<td>35 (22.9)</td>
<td>32 (27.4)</td>
<td>33 (33.0)</td>
<td>20 (24.7)</td>
<td>135 (24.5)</td>
</tr>
<tr>
<td>Diabetes (history or FBG &gt;126 mg/dl)</td>
<td>2 (2.0)</td>
<td>9 (5.9)</td>
<td>15 (12.8)</td>
<td>26 (21.8)</td>
<td>20 (24.7)</td>
<td>72 (13.1)</td>
</tr>
<tr>
<td>High total cholesterol (&gt;200 mg/dl)</td>
<td>24 (24.5)</td>
<td>57 (38.8)</td>
<td>50 (45.1)</td>
<td>41 (41.8)</td>
<td>27 (34.6)</td>
<td>199 (37.4)</td>
</tr>
<tr>
<td>High LDL-cholesterol (&gt;130 mg/dl)</td>
<td>24 (24.5)</td>
<td>55 (37.4)</td>
<td>45 (40.5)</td>
<td>46 (46.9)</td>
<td>27 (34.6)</td>
<td>197 (37.0)</td>
</tr>
<tr>
<td>Low HDL-cholesterol (&lt;40 mg/dl)</td>
<td>48 (49.0)</td>
<td>82 (55.8)</td>
<td>68 (61.3)</td>
<td>51 (52.0)</td>
<td>43 (55.1)</td>
<td>292 (54.9)</td>
</tr>
<tr>
<td>High TG (&gt;150 mg/dl)</td>
<td>21 (21.4)</td>
<td>61 (41.5)</td>
<td>37 (33.3)</td>
<td>38 (38.8)</td>
<td>15 (19.2)</td>
<td>172 (32.3)</td>
</tr>
</tbody>
</table>

Number (n=lipids)          90 (89) | 151 (143) | 132 (127) | 113 (113) | 87 (87) | 573 (559) |

Values in parentheses are percentages

BMI: body mass index; FBG: fasting blood glucose; HDL: high-density lipoprotein; LDL: low-density lipoprotein

Numerical distribution of age-specific systolic blood pressure, diastolic blood pressure, BMI and WHR are reported in Table 5 and age-specific lipid levels in Table 6. In males a significant increase was seen in the systolic blood pressure, BMI, LDL-cholesterol and triglycerides while in females there was a significant age-related increase in systolic blood pressure, diastolic blood pressure, BMI, WHR, total cholesterol, LDL-cholesterol and triglycerides.
In JHW-1, we reported the CHD prevalence and risk factor data among 2212 subjects (males 1415, females 797). The prevalence of CHD was 5.96% in males and 10.54% in females which is not significantly different from the present study (JHW-2) where the prevalence is 6.18% in males and 10.12% in females (p<0.05) (Table 2).

Although the sample size is smaller than that in the previous study, for purposes of comparative analysis it was considered statistically adequate. The mean age of the present study population is marginally different from the previous study in males (42.3±14.1 years v. 37.4±14.0 years) but not in females (42.9±13.2 years v. 44.1±14.9 years). Therefore,

Table 5. Age-specific blood pressure, body mass index and waist:hip ratio levels

<table>
<thead>
<tr>
<th>Age group (years)</th>
<th>Males (n=550)</th>
<th>Females (n=573)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number</td>
<td>Systolic BP</td>
</tr>
<tr>
<td>20-29</td>
<td>99</td>
<td>117.2±12</td>
</tr>
<tr>
<td>30-39</td>
<td>153</td>
<td>119.0±28</td>
</tr>
<tr>
<td>40-49</td>
<td>117</td>
<td>120.1±22</td>
</tr>
<tr>
<td>50-59</td>
<td>100</td>
<td>127.7±23</td>
</tr>
<tr>
<td>60+</td>
<td>81</td>
<td>131.2±28</td>
</tr>
<tr>
<td>Total</td>
<td>550</td>
<td>122.3±24</td>
</tr>
</tbody>
</table>

Values are mean±1 SD
BP: blood pressure; BMI: body mass index; WHR: waist:hip ratio

Table 6. Age-specific lipid levels

<table>
<thead>
<tr>
<th>Age group (years)</th>
<th>Males (n=532)</th>
<th>Females (n=559)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number</td>
<td>Cholesterol</td>
</tr>
<tr>
<td>20-29</td>
<td>96</td>
<td>180.6±35</td>
</tr>
<tr>
<td>30-39</td>
<td>147</td>
<td>200.1±47</td>
</tr>
<tr>
<td>40-49</td>
<td>111</td>
<td>196.7±43</td>
</tr>
<tr>
<td>50-59</td>
<td>98</td>
<td>200.1±41</td>
</tr>
<tr>
<td>60+</td>
<td>78</td>
<td>192.7±40</td>
</tr>
<tr>
<td>Total</td>
<td>532</td>
<td>194.4±43</td>
</tr>
</tbody>
</table>

Values are mean±1 SD
LDL: low density lipoprotein; HDL: high density lipoprotein

Table 7. Age-adjusted coronary risk factor prevalence in Jaipur Heart Watch-1 (1994) and Jaipur Heart Watch-2 (2001)

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>JHW-1</th>
<th>JHW-2</th>
<th>JHW-1</th>
<th>JHW-2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoking/tobacco</td>
<td>548/1415 (38.7)</td>
<td>196/550 (35.6)</td>
<td>149/797 (18.7)</td>
<td>69/573 (12.1)</td>
</tr>
<tr>
<td>Leisure-time physical inactivity</td>
<td>1003/1415 (70.9)</td>
<td>338/550 (61.5)</td>
<td>577/797 (72.4)</td>
<td>362/573 (63.2)</td>
</tr>
<tr>
<td>Diabetes (history)</td>
<td>15/1415 (1.1)</td>
<td>42/550 (7.6)*</td>
<td>8/797 (1.0)</td>
<td>49/573 (8.6)*</td>
</tr>
<tr>
<td>Obesity (BMI ≥27 kg/m²)</td>
<td>158/1415 (11.2)</td>
<td>123/550 (22.3)*</td>
<td>105/797 (13.2)</td>
<td>170/573 (29.7)*</td>
</tr>
<tr>
<td>Truncal obesity (WHR: males&gt;0.9, females&gt;0.8)</td>
<td>128/250 (51.2)</td>
<td>280/550 (50.9)</td>
<td>131/193 (67.9)</td>
<td>388/573 (67.8)</td>
</tr>
<tr>
<td>Diabetes (history of fasting blood glucose) &gt;125 mg/dl</td>
<td>-</td>
<td>72/550 (13.1)</td>
<td>-</td>
<td>65/573 (11.3)</td>
</tr>
<tr>
<td>Hypertension (≥140/90 mmHg)</td>
<td>417/1415 (29.5)</td>
<td>165/550 (30.0)</td>
<td>267/797 (33.5)</td>
<td>174/573 (30.3)</td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>175.8±43</td>
<td>194.4±43*</td>
<td>173.2±49</td>
<td>197.7±41*</td>
</tr>
<tr>
<td>High cholesterol (≥200 mg/dl)</td>
<td>49/199 (24.6)</td>
<td>183/532 (34.4)*</td>
<td>22/98 (22.5)</td>
<td>243/559 (43.5)*</td>
</tr>
<tr>
<td>LDL-cholesterol</td>
<td>107.6±39</td>
<td>124.9±39*</td>
<td>103.3±42</td>
<td>130.1±39*</td>
</tr>
<tr>
<td>High LDL-cholesterol (≥130 mg/dl)</td>
<td>44/199 (22.1)</td>
<td>182/532 (34.2)*</td>
<td>28/98 (28.6)</td>
<td>254/559 (45.4)*</td>
</tr>
<tr>
<td>HDL-cholesterol</td>
<td>43.1±12</td>
<td>39.5±8*</td>
<td>44.8±16</td>
<td>39.7±9*</td>
</tr>
<tr>
<td>Low HDL-cholesterol (≥40 mg/dl)</td>
<td>86/199 (43.2)</td>
<td>284/532 (53.4)*</td>
<td>45/98 (45.9)</td>
<td>303/559 (54.2)*</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>126.1±55</td>
<td>149.8±79*</td>
<td>125.6±49</td>
<td>139.4±62*</td>
</tr>
<tr>
<td>High triglycerides (≥150 mg/dl)</td>
<td>53/199 (26.6)</td>
<td>163/532 (30.6)*</td>
<td>28/98 (28.6)</td>
<td>160/559 (28.7)*</td>
</tr>
</tbody>
</table>

Values in parentheses are percentages
A direct method of age-standardization was used for comparisons of risk factors. Age-standardized CHD prevalence in the present study is 4.7% in males and 11.0% in females, not significantly different from JHW-1 (p>0.05).

The age-standardized comparison of coronary risk factors in JHW-1 and JHW-2 is shown in Table 7, which shows that the prevalence of smoking, leisure-time physical inactivity, truncal obesity and hypertension have not increased significantly over a period of about 8 years. There is a significantly increased prevalence of diabetes (diagnosed by history), obesity, and all types of dyslipidemia in both males and females (Fig. 1).

The increase in diabetes may indicate either a true increase in obesity or increased awareness. However, the prevalence of diabetes diagnosed by history or abnormal fasting blood glucose is high and comparable to recent Indian studies. The low prevalence of diabetes in the earlier study may therefore be an underestimate.

In JHW-1, we studied the lipid profile in a smaller number of subjects (males 199, females 98) while in the present study the biochemical risk factors (fasting blood glucose, lipids) have been assessed in much larger numbers (males 532, females 559). Thus, the present study has greater power to study the biochemical coronary risk factors in this population. The mean levels of total cholesterol, LDL-cholesterol and triglycerides increased significantly in JHW-2 compared with JHW-1 along with a decrease in HDL-cholesterol levels (Fig. 2). This change was associated with a significant increase in the prevalence of various forms of dyslipidemias. The prevalence of high total cholesterol (>200 mg/dl), high LDL-cholesterol (>130 mg/dl), low HDL-cholesterol (<40 mg/dl), and high triglycerides (>150 mg/dl) increased in both males and females (Table 7, Fig. 1). The cause of this increase is speculative as we did not study the dietary habits in detail in the study population. This is a limitation of this study. Misra et al. recently reported a highly adverse diet in an urban population characterized by the low intake of monounsaturated fatty acids, low ratio of n-6/n-3 fatty acids, high ratio of polyunsaturated to saturated fats, high intake of erucic acid and low intake of fiber and antioxidant vitamins. In a previous study in urban subjects of this area, Singhal et al. reported a high intake of saturated and n-6 fats and a low intake of monounsaturated fats and antioxidants. Therefore, the increase in dyslipidemias in the present study could be due to increasing trends in the consumption of saturated fat in urban subjects.

The increase in obesity despite declining leisure-time physical activity habits in the study population could be due to declining occupational physical activity levels. Bharathi et al. recently reported that the traditional physical activity questionnaires do not accurately measure work-related physical activity in Indians and more complex tools are
required to accurately assess such activities. We did not use a comprehensive physical activity questionnaire and thus the data on physical activity may not reflect the true status.

These results cannot be compared with previous Indian studies. There is no study that has systematically examined changes in multiple coronary risk factors in a similar population over a period of time. We previously reported that the prevalence of CHD, hypertension, systolic blood pressure and cholesterol levels appear to be increasing in India in various meta-analyses. Ramachandran et al. reported an increasing prevalence of impaired glucose tolerance and diabetes in urban residents of Chennai. Recent cross-sectional surveys have shown that the prevalence of coronary risk factors among Indians is similar to those in the present study. Anand et al. studied the coronary risk factors in south Asians settled in Canada (n=342) and reported smoking in 32.4% males and 2.1% females, history of diabetes in 6.2%, BMI 26.0±5.3 in males and 26.5±6.1 in females, WHR 0.93±0.1 in males and 0.84±0.1 in females, total cholesterol 209.9±81 mg/dl, LDL-cholesterol 127.6±35 mg/dl, HDL-cholesterol 40.2±12 mg/dl, triglycerides 173.6±115 mg/dl and fasting glucose of 98.5±20 mg/dl. Mohan et al. reported age-adjusted CHD prevalence of 5.0% in males and 12.49% in females in 1150 urban subjects in Chennai and also reported a high prevalence of hypertension, diabetes and dyslipidemias.

Secular trends in coronary risk factors are available from various cohorts of the Seven Countries Study. Koga et al. reported that in 1958, 1977 and 1989 in a Japanese rural population, there was a significant increase in the total cholesterol levels (150±41 mg/dl, 161±32 mg/dl and 188±37 mg/dl, respectively), overweight and obesity (8%, 11%, 18%, respectively), and diastolic hypertension (8%, 20%, 13%, respectively) while the prevalence of smoking and isolated systolic hypertension declined. In rural and urban Yugoslavian cohorts there was a declining trend in cigarette smoking on the one hand and increase in the mean levels of systolic blood pressure and cholesterol on the other, associated with an increase in the consumption of meats, eggs, dairy products, fats and oils and desserts.

In urban areas of Greece from 1968 to 1988, there was an increase in the BMI, blood pressure, cholesterol levels and diabetes, but the dietary consumption of vegetables and fruits, olive oil and bread also increased, associated with a decline in cardiovascular disease mortality. In cohorts from developed countries of the Seven Countries Study (the Netherlands, Italy, North America and Finland), there has been a decline in CHD mortality associated with a declining trend in smoking, hypertension and cholesterol levels. A recent increase in obesity in the USA and many other developed countries of Europe has been reported. This is associated with a rising prevalence of diabetes.

In conclusion, the present study shows a significant burden of standard coronary risk factors in this urban Indian population. The prevalence of coronary risk factors such as diabetes, hypertension and dyslipidemias has significantly increased as compared to our previous studies in the same population. Urgent population-based measures are needed to control this trend in coronary risk factors for primary prevention of CHD in India.

Acknowledgments

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References

Ventricular Septal Defect with Congenital Mitral Valve Disease: Long-Term Results of Corrective Surgery

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Departments of Cardiothoracic Surgery and Cardiology, Cardiothoracic Centre, All India Institute of Medical Sciences, New Delhi

Background: A retrospective analysis of the mortality, morbidity and long-term follow-up of patients undergoing corrective surgery for ventricular septal defect and congenital mitral valve disease is presented.

Methods and Results: Between January 1991 and December 2000, 69 consecutive patients aged 2 months to 45 years (median 18 months) underwent repair of ventricular septal defect and associated mitral valve disease. In 52 patients (75%), the ventricular septal defects were located in the perimembranous and subarterial area. Forty-six patients had congenital mitral incompetence and 23 had congenital mitral stenosis. The ventricular septal defect was repaired through the right atrium in all. Sixty-five patients underwent reconstruction of the mitral valve and 4 underwent primary mitral valve replacement. Another 4 patients underwent mitral valve replacement after a failed repair. Associated procedures included: patent ductus arteriosus ligation (n=12), aortic valve replacement (n=6), coarctation repair (n=13), interrupted aortic arch repair (n=1), atrial septal defect closure (n=17) and Takeuchi repair (n=1). There were 6 early deaths (8.6%). Three deaths were due to pulmonary arterial hypertensive crisis and one due to residual mitral stenosis. One death was due to intractable congestive heart failure. Another patient died due to persistent low cardiac output. Follow-up ranged from 6 months to 120 months (mean 64.4±33.6 months). Reoperation was required in 22 patients, mainly for recurrent/residual mitral valve dysfunction or hemodynamically significant left ventricular outflow tract obstruction. There were 4 late deaths, 2 due to residual mitral stenosis and the other 2 as a result of a thrombosed prosthetic valve. At 10 years, the actuarial survival rate was 85%±5.0% and freedom from reoperation was 45%±10.0%.

Conclusions: Reconstruction of the mitral valve along with closure of VSD is possible in most cases. However, careful follow-up is recommended to detect changes in the mitral valve status over a course of time. (Indian Heart J 2002; 54: 67-73)

Key Words: Ventricular septal defect, Congenital mitral valve disease, Congenital heart disease

Correspondence: Professor Balram Airan, Department of Cardiothoracic and Vascular Surgery, All India Institute of Medical Sciences, Ansari Nagar, New Delhi 110029. e-mail: airanbalram@hotmail.com
of Medical Sciences, New Delhi. Of these, 69 patients (7.0%) had associated MVD. Patients with atrioventricular septal defects, diffuse fibromuscular type of left ventricular outflow tract obstruction, Shone's syndrome, hypoplastic left heart syndrome and acquired mitral valve stenosis were excluded from the study. The age and weight distribution of the population is given in Table 1.

**Table 1. Preoperative patient characteristics**

<table>
<thead>
<tr>
<th>Age</th>
<th>Number</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;3 months</td>
<td>9</td>
<td>13.0</td>
</tr>
<tr>
<td>4–12 months</td>
<td>23</td>
<td>33.3</td>
</tr>
<tr>
<td>1–2 years</td>
<td>9</td>
<td>13.0</td>
</tr>
<tr>
<td>2–5 years</td>
<td>19</td>
<td>27.5</td>
</tr>
<tr>
<td>&gt;5 years</td>
<td>9</td>
<td>13.0</td>
</tr>
</tbody>
</table>

Age range: 2–540 months
Median age: 18 months

<table>
<thead>
<tr>
<th>Weight</th>
<th>Number</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;5 kg</td>
<td>14</td>
<td>20.3</td>
</tr>
<tr>
<td>5–15 kg</td>
<td>38</td>
<td>55.1</td>
</tr>
<tr>
<td>16–30 kg</td>
<td>14</td>
<td>20.3</td>
</tr>
<tr>
<td>31–45 kg</td>
<td>2</td>
<td>2.9</td>
</tr>
<tr>
<td>&gt;45 kg</td>
<td>1</td>
<td>1.5</td>
</tr>
</tbody>
</table>

Weight range: 3–50 kg
Median weight: 10.5 kg

Cardiac morphology was investigated by echocardiography, cardiac catheterization and angiocardiography. Failure to thrive was the commonest presenting feature. Pulmonary edema was present in 5 patients (7.2%) and required preoperative ventilatory and inotropic support. The average mean pulmonary artery pressure was 49.2±15.5 mmHg, mean pulmonary artery wedge pressure 18.4±6.0 mmHg and mean pulmonary vascular resistance index 4.3±3.4 IU/m². In all patients, the mean pulmonary artery pressure was >18 mmHg.

The VSD was perimembranous in 25 patients (36%), subarterial in 27 (39%), inlet type in 9 (14%) and trabecular muscular in 8 (11%). The VSD was large, nonrestrictive and hemodynamically significant in all the patients.

**Mitral valve assessment:** The description of the mitral valve lesions was based on Carpentier's classification. The various mitral valve lesions are shown in Table 2. Congenital mitral stenosis was diagnosed when a small mitral valve apparatus which appeared abnormal was demonstrated on two-dimensional (2-D) echocardiography. Because of the associated VSD with increased transmitral flow and the frequent association of an atrial septal defect, the transmitral gradient alone was not the single criterion for judging the severity of congenital mitral stenosis. The mitral valve was measured in each patient and the largest diameter obtained from the apical 4-chamber view was indexed for body surface area (BSA) and compared with the normal values, and Z values were calculated.

Preoperative echocardiographic data in the mitral stenosis group revealed the following: (i) the mean anteroposterior mitral valve diameter was 11.6±4.3 mm/m²; (ii) the mean transmitral gradient was 12.8±6 mmHg; and (iii) the mean Z value for the mitral valve was −0.98±0.6. In the entire group, only 1 patient had a hypoplastic mitral valve annulus with a Z value of −1.5. The degree of mitral regurgitation (MR) was quantified using the criteria of Sellers and associates. MR was 1+ in 3 patients, 2+ in 14, 3+ in 11 and 4+ in 18.

**Table 2. Morphology and functional lesions of the mitral valve**

<table>
<thead>
<tr>
<th>Functional lesion</th>
<th>Sub-type</th>
<th>Malformation</th>
<th>Number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mitral valve incompetence</td>
<td>Type I Normal leaflet motion</td>
<td>Isolated annular dilatation</td>
<td>16</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cleft anterior mitral leaflet</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cleft posterior mitral leaflet</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Type II Prolapsed leaflet</td>
<td>Elongated chordae</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Elongated chordopapillary apparatus</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>Type III Restricted leaflet motion</td>
<td>Commissure fusion with retracted</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>anterior mitral leaflet and normal papillary muscles</td>
<td>3</td>
</tr>
<tr>
<td>Mitral stenosis</td>
<td>Type A Normal papillary muscles</td>
<td>Supravalvular ring</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Supravalvular ring with commissure fusion</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Papillary–commissure fusion</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Annulus hypoplasia</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Type B Abnormal papillary muscles</td>
<td>Parachute valve</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hypoplastic papillary muscles</td>
<td>2</td>
</tr>
</tbody>
</table>

Total 69
Intraoperative transesophageal echocardiography was carried out in all patients before and after mitral valve repair. Intraoperative exploration of the valve allowed recognition of the different components causing obstruction or regurgitation.

**Surgical procedure:** The VSD could be repaired through the right atrium in all. The mitral valve was approached directly through the left atrium in 40 patients, and through the atrial septum in 29.

Morphological abnormalities of the mitral valve were systematically assessed. Mitral valve function was assessed by an injection of cold saline into the left ventricle using a syringe and a fine catheter. The goal of mitral valve repair was to provide a functional valve rather than restore normal mitral valve anatomy.

A supra-annular ring, when present, was resected. In 2 patients, the ring extended onto the valve leaflets and there was mild commissural fusion. The abnormal tissue was carefully separated from the valve tissue without cutting holes in the valve. Papillary muscle–commissural fusion was treated by commissurotomy, fenestration, papillary muscle splitting and resection of accessory chordae.

Parachute mitral valves \((n=2)\) were initially treated by thinning and cutting the single papillary muscle and resecting all the chordae and bands that were not attached to the free leaflet margins. Due to persistent moderate regurgitation, both patients underwent primary mitral valve replacement.

Annular dilatation was treated by segmental annuloplasty using braided polyester sutures. Segmental annuloplasty was used in the case of pediatric patients to allow for annular growth.

Anterior leaflet prolapse secondary to chordal elongation \((n=19)\) was repaired by chordal shortening. A pericardial pledgeted braided polyester suture was used to plicate the elongated chordae to the anterior papillary muscle or to the adjacent papillary muscle.

True cleft of the posterior mitral leaflet \((n=3)\) was left unrepaired because the mitral valve was competent at the time of the initial operation and the intraoperative echocardiogram revealed trivial MR.

True cleft of the anterior mitral leaflet was repaired by placing interrupted sutures. A associated accessory chordae were excised and an annuloplasty was performed at each commissure.

Advancement of the anterior mitral leaflet \((n=3)\) was done using glutaraldehyde-treated autologous pericardium with concomitant commissurotomy and splitting of the papillary muscles. All repairs were assessed by the use of a matched Hegar’s dilator and by intraoperative transesophageal echocardiogram.

Mitral valve replacement \((n=8)\) was performed using the largest possible St Jude mechanical prosthesis in a supra-annular position. Four patients underwent primary mitral valve replacement and the other 4 underwent replacement following a failed mitral valve repair. Valves sized 21–27 mm were used. For valves sized 21 mm and 23 mm, the reverse aortic valve was used while for 25 mm and 27 mm sizes the mitral valve was used.

The details of the additional operative procedures are outlined in Table 3. Forty-five patients with associated anomalies underwent a single-stage operation, and 14 with coarctation of the aorta or interrupted aortic arch underwent a staged operation.

### Table 3. Associated anomalies and additional operative procedures

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>PDA ligation</td>
<td>12</td>
</tr>
<tr>
<td>Aortic valve replacement</td>
<td>6</td>
</tr>
<tr>
<td>Resection of infundibular stenosis</td>
<td>3</td>
</tr>
<tr>
<td>Excision of subaortic membrane</td>
<td>5</td>
</tr>
<tr>
<td>Closure of secundum atrial septal defect</td>
<td>17</td>
</tr>
<tr>
<td>Repair of unroofed coronary sinus</td>
<td>1</td>
</tr>
<tr>
<td>Repair of coarctation of the aorta</td>
<td>13</td>
</tr>
<tr>
<td>Repair of the interrupted aortic arch</td>
<td>1</td>
</tr>
<tr>
<td>Takeuchi repair for anomalous left coronary artery from pulmonary artery</td>
<td>1</td>
</tr>
</tbody>
</table>

**Total** 59

**Postoperative care and follow-up:** All patients were routinely started on oral angiotensin-converting enzyme (ACE) inhibitors from postoperative day 1 prior to weaning away from dopamine and sodium nitroprusside. Digoxin, diuretics and ACE inhibitors were discontinued within 6 months of operation in the majority of patients.

Oral anticoagulation was started using acenocoumarin on postoperative day 1 in patients undergoing mitral valve replacement. The international normalized ratio (INR) was maintained between 3.0 and 3.5. In addition to anticoagulants, low-dose aspirin (5 mg/kg/day) was also used.

**Statistical methods:** Interval-related variables were expressed as mean ± standard deviation (±SD) and categorical variables were expressed as percentages. Actuarial estimates were calculated using the Kaplan–Meier technique and reported with the standard error (SE) of the estimate.

### Results

**Early results:** Six patients (8.6%) died shortly after surgery (Table 4). Three of them, aged 2 months, 37 months and 48 months, died due to intractable paroxysmal pulmonary
hypertensive crisis. These patients did not respond to pulmonary vasodilators including phenoxybenzamine. One patient died of severe residual mitral stenosis. He was operated at 3 months of age for a multilevel left ventricular obstruction and small mitral valve annulus. One patient died of low cardiac output without apparent residual anatomic lesions. In one patient, the chordae were abnormally adhesive to the anterior mitral leaflet on the side of the anteromedial commissure. The adhesions were released and concomitant annuloplasty was performed. Twenty-four hours later he underwent mitral valve replacement using a St Jude mechanical prosthesis. He died on the postoperative day 5 due to intractable congestive heart failure. Post-mortem study of the cardiac muscles revealed the presence of endocardial fibroelastosis in the last 2 patients.

The remaining 63 patients had an uncomplicated postoperative course. Forty-five patients were extubated within 48 hours after operation. Eighteen patients remained ventilator dependent for 5–7 days due to various reasons such as chest infection, pulmonary hypertension and residual cardiac lesions. Echocardiography was performed in all these patients.

Reoperation: Reoperation was required for 22 patients; of these, 9 were reoperated because of residual or recurrent mitral stenosis, and 4 for isolated hemodynamically significant left ventricular outflow tract obstruction which manifested after the initial operation.

Late postoperatively, of the 3 patients undergoing anterior mitral leaflet advancement with glutaraldehyde-treated autologous pericardium, 2 developed moderate to severe mitral stenosis and one developed mixed MVD. All 3 required mitral valve replacement 4 and 5 years after the first operation.

Three patients with VSD and isolated cleft of the posterior mitral leaflet underwent primary repair of the VSD. The MR worsened gradually in these patients. The mitral valve was competent at the time of initial operation and intraoperative echocardiography revealed trivial MR. Hence, the clefts were not repaired at this time.

Four patients with isolated cleft of the anterior mitral leaflet had accessory chordae attached to the ventricular septum causing MR and subaortic stenosis in addition. The cleft was sutured and the accessory chordae were excised in all of them. One patient required mitral valve replacement 6 years after the first operation due to severe MR from a prolapsing anterior mitral leaflet.

Six patients with mechanical mitral prosthesis developed valve thrombosis 3–8 years after the first operation. Administration of streptokinase was unsuccessful in relieving the obstruction in 4 of them. Two patients underwent successful thrombectomy of the prosthetic valve, while 2 succumbed to the procedure.

Long-term results: There were 4 late deaths (6.3%). Of these, 2 were related to residual mitral stenosis, and the other 2 died of a thrombosed valve.

Follow-up ranged from 6 months to 120 months (mean 64.4±33.6 months). Patients were evaluated every 6
months, both clinically and echocardiographically, by the operating surgeon as well as by the cardiologist.

Overall actuarial survival rate was 70%±13.0% at 120 months. The actuarial survival rate for the isolated mitral valve repair group was 85%±5.0% at 120 months (Figs 1 and 2). Overall actuarial freedom from reoperation at 120 months was 41.0%±10.0%. The actuarial freedom from mitral valvureoperation at 120 months was 45.0%±10.0% (Figs 3 and 4). The majority (91.5%) were in New York Heart Association functional class I or II at their last follow-up visit with good left ventricular function. The mean transmitral gradient was 2.1±2 mmHg. Eight patients had mild MR.

Discussion

Congenital MVD remains a surgical challenge particularly when associated with other cardiac defects.1-5 Important confounding lesions include VSD, coarctation of the aorta, subaortic stenosis, left ventricular outflow tract obstruction, atrioventricular septal defect, univentricular heart and hypoplastic left heart syndrome.1-5 Left ventricular inflow obstruction may occur due to pulmonary venous obstruction, cor-triatriatum, membrane within the left atrium, and/or an obstructed mitral valve.1-3 Congenital MR is usually associated with other cardiac anomalies and isolated MR is rarely seen.
Preoperatively, 2-D echocardiography provided excellent information for defining the supramitral ring, annular and leaflet size, leaflet motion, morphology of the subvalvular apparatus, ventricular function, and in predicting the likelihood of valve repair rather than replacement. In our experience as well as that of others, this assessment influences the timing of surgery. Hemodynamic data of 903 patients with isolated VSD and 69 patients with VSD and associated left ventricular inflow tract problems were retrospectively analyzed. In patients with isolated VSD, we observed inflow mitral gradients of up to 15 mmHg.

Because of the frequent association of an atrial septal defect, the transmitral gradient alone could not be the single criterion for assessment of the severity of mitral stenosis.

A large number of patients with this disease combination require an operation either in infancy or early childhood. There is a universal consensus about early repair in order to minimize the long-term distortion of the valve components, myocardial dysfunction and progressive pulmonary venous hypertension.

However, as exposure of the mitral valve apparatus might be difficult in young children, the accepted target for the reparative procedure is to have a normally functioning mitral valve rather than reconstructing an anatomically perfect mitral valve. We attempted conservative mitral valve repair for all patients with moderate to severe MR and selected patients with congenital mitral stenosis.

Segmental annuloplasty was used in the majority of patients (n=19) undergoing mitral valve repair to allow for annular growth. Several investigators have demonstrated that the annuloplasty ring and sutures promote scar tissue formation, and limited appropriate annulus growth and leaflet motion.

Our results with anterior mitral leaflet advancement suggest that late postoperatively repaired mitral valves tend to be stenotic. However, this procedure may allow children to grow and undergo valve replacement at a later age. Retrospective analysis further revealed that in patients with VSD and mitral clefts, suturing of the mitral clefts is mandatory at the initial operation, even if the MR is not substantial. Cleft anterior leaflet of the mitral valve, when not associated with atrioventricular septal defect, is rare. Accessory chordae, a raphe structure or both, extended from the cleft leaflet to the ventricular septum or to the anterior wall of the left ventricle. The latter was responsible for left ventricular outflow tract stenosis in patients. Our experience reveals that a cleft mitral valve may simultaneously cause mitral insufficiency and subaortic stenosis and needs to be distinguished from hypertrophic muscular subaortic stenosis. Suturing of the cleft and resection of the accessory chordae are probably both necessary for a complete correction.

Choosing the appropriate operation required for patients with an abnormal subvalvular apparatus (including parachute valves, hypoplastic papillary muscles) appears to be complicated. Several investigators have reported that mitral valve replacement is required in 22%-30% of congenital mitral valve lesions with restricted leaflet motion and abnormal papillary muscles. Valve replacement may be difficult even in the supra-annular position in a small infant. An extracardiac valved conduit between the left atrium and left ventricle is a feasible option in this difficult subset of patients. However, we have not yet performed this procedure.

We performed mitral valve replacement in a cohort of patients with complex valve anomaly (n=4), and in those patients requiring reoperative mitral valve procedures (n=4). It was possible to preserve the entire chordopapillary apparatus in the majority of patients. Prosthetic mitral valve replacement with total chordal preservation may improve postoperative hemodynamics.

In general, continued growth of the child, overgrowth of pannus on the prosthetic valves, and early calcific degeneration of the bioprosthetic valves are factors directly responsible for valve failure in pediatric patients. Long-term anticoagulation management in children is an additional concern. In infants undergoing mitral valve replacement, xenografts have not improved early survival as compared to the use of mechanical valves.

Published reports reveal that the long-term results of mitral valve repair are superior to those of valve replacement in children. The actuarial survival rate following mitral valve repair at 10 years varies between 63% and 90% in different series. The comparable survival rate following mitral valve replacement varies between 30% and 60% at 10 years for children with congenital MR or stenosis. The actuarial survival rate of 70% at 10 years and the freedom from reoperation rate of 41% at 10 years in this series compares favorably with those of others.

Balloon dilatation was not performed in our patients because of a large VSD which was hemodynamically significant enough to warrant surgical treatment in all. During direct visualization of the valvular and subvalvular lesions, none was believed to be an anatomical substrate for improvement after dilatation.

In summary, a combination of MVD and VSD is not infrequent. Associated anomalies require careful evaluation. Reconstruction of the mitral valve is possible in most of the cases along with closure of the VSD. However, careful long-term follow-up is recommended to detect changes in mitral valve status.
References

A 56-year-old man was evaluated for exertional dyspnoea. Chest X-ray showed mild cardiomegaly and a dilated main pulmonary artery. On echocardiogram he was found to have ostium primum atrial septal defect with moderate tricuspid insufficiency. Cardiac catheterization revealed an oximetry step-up of 14% at low right atrium with angiogram demonstrating a cleft in the mitral valve, an elongated left ventricular outflow tract and ventricular septal defect closed by a septal aneurysm. Coronary angiogram revealed ostial compression of the left main coronary artery with the rest of the coronary artery anatomy being normal. (Indian Heart J 2002; 54: 74–76)

Key Words: Endocardial cushion defect, Pulmonary artery dilatation, Coronary artery compression
respiratory system were normal. The chest X-ray showed cardiomegaly with a cardiothoracic ratio of 60% and a prominent main pulmonary artery (Fig. 1). The electrocardiogram (ECG) showed sinus rhythm, right atrial enlargement and a QRS axis of +90°.

Hematological investigations revealed a hemoglobin level of 12.0 g%, total leucocyte count of 7700/cmm and a normal differential count. Routine biochemical parameters were within normal limits. The pulmonary function tests were normal. Echocardiography showed an ostium primum ASD with moderate tricuspid regurgitation. Cardiac catheterization suggested nonrestrictive ASD with mild PAH (Table 1). The oximetric analysis revealed an oxygen step-up of 14% at low right atrium. The pulmonary blood flow was 8.2 L/min and systemic blood flow was 4.08 L/min with a Qp/Qs ratio of 2.01. A left ventricular angiogram showed an elongated left ventricular outflow tract (Fig. 2); cleft mitral leaflet (Fig. 2); and ventricular septal defect closed by a septal aneurysm (Fig. 3). There was no mitral insufficiency and left ventricular function was normal.

<table>
<thead>
<tr>
<th>Site</th>
<th>Pressure (mmHg)</th>
<th>Oxygen saturation (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SVC-Right atrial junction</td>
<td></td>
<td>67</td>
</tr>
<tr>
<td>Mid right atrium (mean)</td>
<td>3</td>
<td>67</td>
</tr>
<tr>
<td>Low right atrium (mean)</td>
<td>3</td>
<td>81</td>
</tr>
<tr>
<td>Right ventricle (systolic)</td>
<td>56</td>
<td>83</td>
</tr>
<tr>
<td>Pulmonary artery (systolic) mean</td>
<td>40</td>
<td>83</td>
</tr>
<tr>
<td>Aorta (systolic)</td>
<td>110</td>
<td>95</td>
</tr>
<tr>
<td>Left atrium (mean)</td>
<td>3</td>
<td>95</td>
</tr>
<tr>
<td>Left ventricular (end-diastolic)</td>
<td>8</td>
<td>95</td>
</tr>
</tbody>
</table>

Qp=8.2 L/min; Qs=4.08 L/min; Qp/Qs=2.0

SVC: superior vena cava

Fig. 1. Chest X-ray showing cardiomegaly and prominent pulmonary artery.

Fig. 2. Left ventricular angiogram showing an elongated outflow tract and cleft mitral valve.

Fig. 3. Left ventricular angiogram showing a ventricular septal defect closed by an aneurysm.

Fig. 4a. Left coronary angiogram in AP caudal view showing 90% stenosis of the ostium.
Coronary angiogram showed 90% stenosis of the ostium of the LMCA which persisted despite intracoronary nitroglycerine and change in the size of the diagnostic catheter to 5 F (Fig. 4). The other coronary arteries were normal. The patient was offered surgical closure of the ostium primum ASD and bypass grafts to the left anterior descending and left circumflex coronary arteries; but he opted for medical therapy. During the 4 months of follow-up he remained in class 2 dyspnea without any other symptoms including chest pain.

Discussion
A dilated pulmonary trunk causing compression of the ostium of the LMCA has been uncommonly reported in patients with ASD,1,2 tetralogy of Fallot with absent pulmonary valve3 and primary pulmonary hypertension.4 Kothari et al.2 in their retrospective analysis of 41 adult (mean age 47.3±7.4 years) patients of ASD, found only 2 patients (4.8%) who had a left main coronary artery stenosis. Mitsudo et al.5 in their series of 38 patients of ASD (age range 15–62 years) reported that 18% of their patients had a stenosis of 50% or more in the LMCA. To the best of our knowledge, this is the first case report of endocardial cushion defect with a dilated pulmonary artery causing compression of the ostium of the LMCA.

Acknowledgment
The author is grateful to Dr JS Verma, former Head of the Department of Cardiology, PGI for his help and guidance.

References
**Giant Pulmonary Artery Aneurysm with Right Ventricular Outflow Tract Obstruction**

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All India Institute of Medical Sciences, New Delhi

Aneurysm of the main pulmonary artery is rare. Its natural history is not well understood and there are no clear guidelines regarding its optimal treatment. We present a case of a huge saccular aneurysm of the main pulmonary artery which was associated with infundibular and valvular pulmonary stenosis. It was repaired using a pericardial patch with concomitant pulmonary valvotomy and infundibular resection. Postoperative recovery was uneventful and the patient is doing well. Follow-up echocardiogram revealed good repair. *(Indian Heart J 2002; 54: 77-79)*

**Key Words:** Pulmonary artery aneurysm, Right ventricular outflow tract obstruction, Congenital heart defects

**Case Report**

A 54-year-old man was admitted with a complaint of shortness of breath (NYHA class II) of 25 years' duration which had progressed to NYHA class III for the past 2 years. There was no history of orthopnea, cyanosis, cough, fever, hemoptysis, chest pain or syncope. On examination, the patient was in atrial fibrillation with a ventricular rate of 90 beats/min. A left parasternal heave and a grade 4/6 systolic murmur were present in the left parasternal area. Chest X-ray revealed a homogeneous rounded opacity with a clear-cut margin in the pulmonary area (Fig. 1). Two-dimensional echocardiogram revealed a large aneurysm in the main pulmonary artery. The pulmonary valve was thickened, stenotic and bicuspid with a gradient of 80 mmHg across it. Infundibular stenosis was also present. There was no evidence of pulmonary regurgitation. An angiogram revealed a large saccular aneurysm arising from the proximal main pulmonary artery with concomitant dilatation of the right and left pulmonary arteries (Fig. 2). There was infundibular and valvular pulmonary stenosis (Fig. 3). Pulmonary artery pressures were normal with a systolic pressure of 28 mmHg and a mean pressure of 22 mmHg on catheterization.

The patient was operated on through a median sternotomy. There was a 10×10 cm saccular dilatation of the main pulmonary artery. The aneurysm was opened on...
cardiopulmonary bypass. There was no thrombus or vegetation in the aneurysm. The pulmonary valve was bicuspid with thickened leaflets and mild commissural fusion, and infundibular stenosis was present. The redundant sac was excised and pulmonary valvotomy along with infundibular resection was done. The pulmonary artery was repaired using only native tissue. As the annulus was small, right ventricular outflow tract reconstruction was done with an autologous pericardial patch.

Postoperative recovery was uneventful. Prior to hospital discharge, an echocardiogram revealed good repair of the aneurysm and a gradient of 33 mmHg across the pulmonary valve.

Histopathological examination of the excised sac showed focal fibrosis, myxoid degeneration and loss of elastic tissue in the media at places (Fig. 4).

**Discussion**

Aneurysms of the main pulmonary artery are rare and may be idiopathic. However, several underlying diseases have been reported in the literature such as tricuspid valve disease in intravenous drug addicts, congenital heart disease with intracardiac shunting, vascular abnormalities...
such as arteritis, pulmonary artery hypertension. In our case, there was no evidence of arteritis, fungal or bacterial infection in the material examined.

The various histologic findings that have been reported include fragmentation or decrease of elastic fibers in the media, medial degeneration, increase of collagen fibers and decrease of smooth muscle cells. However, some authors have reported a normal histology. There are controversies regarding the treatment of pulmonary artery aneurysms and no specific guidelines exist regarding indications for surgical treatment. Some authors suggest conservative treatment if there is no intracardiac shunt or significant pulmonary hypertension because in such patients the course of the disease is relatively benign and uncomplicated. However, progressive enlargement of the pulmonary trunk aneurysm in the absence of an intracardiac shunt and pulmonary hypertension has been demonstrated. The relationship between the rate of aneurysmal enlargement and the level of pulmonary artery pressure is unclear. In our opinion, if the patient has an acceptable operative risk, surgical repair should be recommended.

Several surgical techniques have been employed to repair pulmonary trunk aneurysms: aneurysmorrhaphy, pulmonary allograft replacement, and replacement by the combined use of a stentless bioprosthesis and a Dacron prosthesis. If the lesion is peripherally located, embolization of the aneurysm with steel coils or detachable balloons has been reported.

The current case demonstrates that surgical repair of pulmonary artery aneurysm is feasible with a low operative risk. Serial, noninvasive, postoperative follow-up is recommended.

Conclusions: Pulmonary artery aneurysm is a rare disease, mostly idiopathic in nature, though it can be associated with pulmonary stenosis, as in the present case. Repair of the pulmonary artery with concomitant pulmonary valvotomy and infundibular resection has yielded good results, although long-term follow-up is needed.

References
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Radiofrequency (RF) ablation for the slow pathway in patients with atrioventricular nodal re-entry tachycardia (AVNRT) is performed via the femoral route. We report the case of a patient in whom the ablation procedure had to be performed via the subclavian route since both the iliac veins were chronically occluded.

Case Report

An 80-year-old woman was referred to us with frequent episodes of paroxysmal supraventricular tachycardia over the past 20 years. Initial treatment with verapamil and then amiodarone had both failed to prevent the recurrence of tachycardia. The frequency of her episodes had been steadily increasing. Of late, she had been having almost daily episodes, which needed intravenous diltiazem for termination. There was no history of angina or syncope. She also had long-standing diabetes mellitus which was well controlled with sulfonylureas. She had sustained a fracture of the right femur neck 7 years ago. She had minimal pedal edema which was controlled by wearing stockings and elevating her feet during sleep.

Clinical examination revealed that she was otherwise healthy and able to perform all routine activities independently. The resting ECG was normal. The ECG taken during tachycardia was suggestive of slow–fast AVNRT, as evidenced by an "r" wave in lead V1. Routine biochemistry, which included serum albumin, was normal. Two-dimensional echocardiography was unremarkable.

Electrophysiologic study was performed under local anesthesia. After introducing a sheath into the right femoral vein, it was found that neither the electrode catheter nor a hydrophilic guidewire could be advanced into the inferior vena cava. Contrast injection (Fig. 1a) showed a chronic occlusion of the right common iliac vein with
Collateralization. A sheath was then introduced into the left femoral vein; again, the guidewire could not be passed into the inferior vena cava. Contrast injection (Fig. 1b) showed an occlusion of the left common iliac vein with collateralization.

![Fig. 1b. Left femoral vein angiogram. The left common iliac vein is completely occluded with opacification of the paravertebral collateral venous channels.](image1)

We decided to attempt RF ablation via the subclavian route. Subclavian vein punctures were difficult to achieve. Two sheaths were introduced into the right subclavian vein. A deflectable 6 F decapolar catheter (Cordis) was negotiated into the coronary sinus and a 7 F medium curve thermocouple RF ablation catheter (Cordis) was positioned in the region of the bundle of His (Fig. 2). Both the catheters could be positioned with difficulty. The tachycardia could be easily initiated with atrial extrastimuli and was confirmed to be AVNRT. The ablation catheter was positioned in the posterior region of the triangle of Koch. Radiofrequency energy was unsuccessful in ablating the slow pathway in this region. Hence, the catheter was flexed upwards and positioned in the midseptal region (Figs 3a and b). The AV ratio was less than 0.5 and the “A” was fractionated in this area. Radiofrequency energy achieved a peak temperature of 51°C and successfully eliminated the slow pathway. Following ablation, there was no AV nodal echo despite isoprenaline. The patient has had no recurrences of tachycardia at follow-up after 2 months.

![Fig. 2. The lower catheter is positioned in the coronary sinus, while the ablation catheter is situated in the region of the bundle of His, LAO view.](image2)

**Discussion**

The incidence of an inadvertent AV block during slow pathway ablation for AVNRT is less than 1%. The femoral route has been used in all major studies for positioning the ablation catheter for this purpose, as this route allows easy maneuverability and stable positioning. Moreover, the operator finds it convenient to observe the fluoroscopy screen and the electrograms simultaneously when this route is employed. There are isolated reports of the subclavian route being used for this purpose.

In our patient we had no choice. The question was which subclavian vein to access. Though the left subclavian route is easier for entering the coronary sinus, this approach would have made it very cumbersome to observe the fluoroscopy screen and electrograms simultaneously when this route is employed. We went in via the right subclavian vein. The minimum necessary catheters were introduced, since subclavian access was difficult and we did not want to risk thrombosis of the vein.
We used a medium curve RF ablation catheter. A medium or even a large curve is preferred for the ablation catheter when using the subclavian route, as a small curve is likely to be inadequate for maintaining a stable flexed position in the right atrial cavity. The difficulty encountered in obtaining stable catheter positions was anticipated. Our case suggests an alternative route when the preferred femoral route is not feasible.

**Acknowledgments**

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**References**

Tetralogy of Fallot in Monozygotic Twins

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A pair of monozygotic twins having tetralogy of Fallot is reported for the first time in the Indian literature. This case report will help in further enriching the existing data on genetic hypothesis of congenital heart defects.

(Indian Heart J 2002; 54: 83–85)

Key Words: Tetralogy of Fallot, Congenital heart defects, Monozygotic twins

Tetralogy of Fallot (ToF) was originally described by Nicholas Steno in 1673. In 1888, Fallot described a group of patients with infundibular pulmonary stenosis, ventricular septal defect, overriding of the aorta and right ventricular hypertrophy. Tetralogy of Fallot has been reported to occur in 2.6 to 9.6 cases per 10,000 births. It is the commonest cardiac anomaly causing cyanosis after infancy and is responsible for 4%–6% of all congenital heart defects.

Twins have a special place in human genetics because they are useful in comparing the effect of genes and the environment. We present a rare manifestation of ToF in a pair of monozygotic twins. To the best of our knowledge, this has previously not been reported in the Indian literature.

Case Report

A pair of 7-year-old monozygotic twin sisters were admitted to our hospital with complaints of easy fatiguability, growth failure and cyanosis. They had been having cyanotic spells since infancy. A family pedigree was obtained which did not document congenital heart disease (CHD) in any of the other family members.

Physical examination revealed proportionate short stature, cyanosis, clubbing and normal jugular venous pulse (Fig. 1). They had phenotypically identical characteristics and the same blood group. Thus the determination of zygosity was done by comparing the physical characteristics and blood group, which is a fairly reliable and cost-effective alternative to blood genetic studies. There was no facial dysmorphism or skeletal abnormality. The cardiac impulse was right ventricular in nature. Auscultation revealed a systolic murmur (grade 5/6 in the third and fourth left intercostal spaces) and a single second heart sound. The packed cell volume was 74% in both children. The chest X-ray was similar in the sisters and showed a boot-shaped heart with pulmonary oligemia. Electrocardiogram showed a sinus rhythm, normal P waves with a PR interval of 0.12 s and a QRS axis of +100. There were tall R waves in V1 and absent Q waves in the left precordial leads with right ventricular hypertrophy. Two-dimensional echocardiography and Doppler studies revealed a large subaortic ventricular septal defect (VSD) (measuring 14 mm in twin A and 12.5 mm in twin B), 50% aortic override, right ventricular outflow obstruction, and right ventricular hypertrophy in both the sisters (Fig. 2). They were both diagnosed to have isolated ToF. They were thus concordant in their manifestation of CHD.

Discussion

In most types of CHD, genetic influences cannot be quantified but examination of experimental and clinical data has contributed to an understanding of their importance. The influence of genetic factors can be studied in three different scenarios: (i) isolated CHD; (ii) syndromes with abnormal chromosomes such as trisomies/Turner; and (iii) hereditary disease with normal chromosomes as in Marfan’s syndrome, Ellis van Creveld syndrome, etc. The study of individual pedigree in the third scenario shows a dominant or recessive pattern of inheritance, which suggests that an abnormal gene or group of genes is responsible. This pair of twins reported by us represents the first scenario of isolated CHD.

The risk of CHD in the general population is between 0.5 and 0.7 per 100 live-births, which increases to 1%–4% if there is already one affected child in the family and to
5%-8% if there are 2 affected siblings.9,10 Data from previous studies on the frequency of first cousin marriages, i.e. consanguinity with autosomal recessive inheritance, have suggested that a recessive gene may be a factor in these CHDs (situs inversus, secundum ASD, PDA, VSD and possibly pulmonary venous stenosis and ToF).8

Twins have a special place in human genetics because they help in comparing the effects of genes and the environment.11 A common genetic predisposition or environmental exposure may cause CHD in twins/triplets.11 Studies have shown that CHDs are present more frequently in monozygotic twins as compared to dizygotic ones, which is an evidence of the influence of genetic factors.12

This case report helps in enriching the existing data and adding to the extensive literature on the genetic hypothesis of CHD. A review of four series of randomly ascertained twins with CHD showed concordance in only 1 of 41 monozygotic sets of twins, thus challenging the genetic contribution to the etiology of CHD.12 A study by Nora et al.12 combined the results of their own study and nine previous studies. This combined data showed that 25% of monozygotic twins were concordant for CHD as compared to only 4.9% of dizygotic twins.12 These findings and the present case report strongly indicate that genetic factors have a significant role. Pitt13 has hypothesized a dominant gene with low penetrance as a mechanism of inheritance, which did not follow the classical Mendelian rules.

Environmental factors such as infections (rubella, coxsackie B), use of teratogenic drugs, and exposure to radiation in the first trimester are important in the etiology of CHD because of lack of 100% concordance in monozygotic twins.14 Genetic and environmental factors act together and have both been postulated in the genesis of CHD.8 This dual concept is the multifactorial or polygenic etiology of CHD.12

The recurrence risk of CHD for children of a patient with ToF is 2.5%-8.3% and in siblings it is 2%.15 Boon et al.3 have placed ToF in the category of disorders of probable but complex genetic etiology on account of familial aggregation without a clear-cut hereditary pattern. Fallot's tetralogy in twins, triplets, in families and even three subsequent generations has been reported.3,11,12 Pitt13 reported 8 families, each of which had 2 members with ToF. In the study of monozygotic twins by Nora et al.12 1 set was concordant for ToF. Furhmann9 reported a family in which 3 siblings had ToF and 2 families in which 2 siblings had ToF. Friedberg6 reported the occurrence of ToF with a right aortic arch in 3 successive generations. In 1991, ToF was reported in triplet siblings.11

Prospective genetic counseling in isolated CHD entails communication of the risk of recurrence. A meticulous pedigree should be obtained and documented to determine any other relatives affected with a CHD. Fetal echocardiography beginning at the 16th week of gestation can be offered to families with increased genetic risk (affected parents or siblings). These parents can be counseled regarding the specific cardiac anomaly and...
current medical or surgical management options. Fetal chromosomal analysis to determine the possibility of an associated syndromewith chromosomal abnormality such as Down syndrome may be warranted. Avoidance of consanguineous, late marriages, treatment of maternal viral infection, and immunization programmes before pregnancy or therapeutic abortions can mitigate the incidence of CHD.16

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References
Cardiotoxicity due to antineoplastic agents such as doxorubicin, daunorubicin, cyclophosphamide, vincristin, vinblastin, cisplatin and busulfan is well known. However, 5-fluorouracil-induced cardiotoxicity is yet to be widely recognized by cardiologists. We report a patient who developed 5-fluorouracil-induced cardiotoxicity syndrome. (Indian Heart J 2002; 54: 86–87)

**Key Words:** Cardiotoxicity, 5-fluorouracil, Dilated cardiomyopathy

A wide variety of antineoplastic drugs can induce cardiac manifestations such as arrhythmias, ST–T wave changes and heart failure. 5-fluorouracil (5-FU) is being recognized as a drug with cardiotoxic potential. We report the case of a patient in whom exposure to 5-FU resulted in a reversible myocardial infarction (MI) pattern in the electrocardiogram (ECG) and reversible left ventricular (LV) dysfunction.

**Case Report**

A 33-year-old man was diagnosed to have squamous cell carcinoma of the mouth in August 2000 and was on treatment with split-course radiotherapy and chemotherapy. On 23 December 2000 and 1 March 2001, he received an injection of 20 mg mitomycin. From 15 March till 12 April 2001 he received 500 mg 5-FU daily as an i.v. bolus. On the next day, he developed rapid onset dyspnea (NYHA class III) which progressed to class IV in an hour. There was no history of chest pain, palpitation, syncope and his effort tolerance had been normal till the previous day. He was a heavy smoker and had never consumed alcohol. He came to hospital a day later despite marked difficulty in breathing. When he was received in our ICU, he was found to be in a state of cardiogenic shock. His heart rate was 130 beats/min, systolic BP was 85 mmHg and his limbs were cold and clammy. Cardiac auscultation revealed normal S1 and S2, a left ventricular third heart sound and no murmurs. There were coarse rales extending up to the apices of both lungs.

An ECG taken in the emergency room (Fig. 1) revealed sinus tachycardia and acute extensive anterior and inferior myocardial infarction (MI) pattern characterized by marked ST elevation. An ECG taken in the ICU a few minutes later (Fig. 2) revealed sinus tachycardia, partial left bundle branch block (LBBB) and minimal ST–T wave changes. Serial estimation of serum glutamic oxaloacetic acid transaminase (SGOT) did not show any rise in the levels. A bedside echocardiogram was performed using a Vingmed

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CFM 725 system with a 3.25 mHz transducer. It revealed mild dilatation of the LV (LVed 52 mm; LVes 47 mm), normal wall thickness (9 mm) and global hypokinesia of the LV with an ejection fraction of 25%. There was no mitral regurgitation or thrombus. Right ventricular (RV) function was normal. He was managed with dopamine infusion at a dose of 10–15 µg/kg/min and after the BP improved, it was substituted with dobutamine infusion at a dose of 10 µg/kg/min. He also received parenteral frusemide, hydrocortisone, oral digoxin, carnitine and antioxidants. Within 3 days of admission, he was relieved of his symptoms and echocardiogram revealed normal LV function. He was subsequently given oral digoxin, frusemide and enalapril.

Discussion

Though the ECG taken in the emergency room was typical of anterior wall MI, a dilated cardiomyopathy picture on echocardiography and rapid resolution of the ST segment in the ECG raised the suspicion that these phenomena could be due to the chemotherapeutic agents. Normalization of LV function within 3 days (confirmed by echocardiography) supported the diagnosis.

Though mitomycin is also implicated in cardiotoxicity, he did not receive the drug in adequate dosages and for a long enough duration. Radiation-induced cardiotoxicity was unlikely because there was no chest exposure to radiation. Moreover, just prior to admission he had received 5-FU. Cardiotoxicity due to 5-FU is known to occur in 1%–2% of patients receiving the drug. The incidence is higher (4%–6%) in those with pre-existing heart disease and in those who receive higher doses (6%–7%). Robben et al. had analyzed the syndrome of cardiotoxicity due to 5-FU. Of 135 patients described to have had this phenomenon, angina was encountered in 89%, ST–T wave changes of ischemia on ECG in 75%, echocardiographically documented LV dysfunction in 24% (in one-fourth of them, the LV dysfunction reverted to normal), MI by clinical means and ECG in 10%, cardiac arrhythmias in 15% and death in 10%. In some patients, therapeutic re-challenge was attempted and on 90% of occasions, the syndrome was reproduced. Cardiotoxicity due to 5-FU is suspected to be mediated by coronary vasospasm (explaining the occurrence of angina and MI and rapid normalization of the ST segment) and free radical damage to the myocardium. Management consists of discontinuation of the drug, conventional measures for cardiac failure and nitrates. Calcium-channel blockers could have a role if the LV function is normal. Antioxidants also have a potential role in the prevention and management of the condition.

In conclusion, chemotherapeutic drug-induced dilated cardiomyopathy (DCM) is one of the few forms of reversible DCM, the others being alcoholic DCM, peripartum DCM, DCM due to deficiency of selenium, hypocalcemia, hypophosphatemia, hyperthyroidism and tachycardio-myopathy. This case report emphasizes the need for prompt cessation of therapy once cardiac manifestations occur. Routine periodic echocardiographic evaluation during 5-FU therapy may not be of value because cumulative toxicity is unlikely to occur with this agent, in contrast to other drugs such as doxorubicin. The majority of adverse events occur during the first cycle of 5-FU.

References

Expression and Functional Activity of Receptor-C<sub>k</sub> in Mononuclear Cells of a Homozygous Hypercholesterolemic Family

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The study was addressed to explore the expression and functional activity of a novel cholesterol-specific cell surface receptor-C<sub>k</sub> in a typical homozygous familial hypercholesterolemic family. Functional activity of receptor-C<sub>k</sub> was characterized by its ability to downregulate Bcl-2 gene expression through a 47 kDa factor having an affinity for the sterol-regulatory element in the promoter region of this gene. The result of such a study revealed normal expression and functional activity of receptor-C<sub>k</sub> accompanied by a lack of Apolipoprotein B-specific low-density lipoprotein receptor gene expression in the mononuclear cells derived from these patients. On the basis of these results, it is tempting to speculate that receptor-C<sub>k</sub> may be involved in the maintenance of cellular cholesterol homeostasis observed in homozygous familial hypercholesterolemic patients. (Indian Heart J 2002; 54: 88–90)

Key Words: Hypercholesterolemia, Cholesterol homeostasis, Myocardial infarction

Case Report

The history of the patient’s family revealed that his elder brothers (who were also suffering from familial hypercholesterolemia) died due to premature myocardial infarction whereas his sisters were leading a normal life. The patient (a 17-year-old male) displayed subcutaneous
studies have identified these cholesterol sensors designated as receptor-C₃ for extracellular cholesterol¹ and LXRα for intracellular oxysterols.¹² LXRα has been shown to regulate the transcription of the SREBP gene¹³ and receptor-C₃-dependent signaling has been shown to regulate various genes.¹ Bcl-2 gene expression is downregulated by receptor-C₃ cleavage of 125 kDa SREBP resulting in the generation of a 47 kDa transcription factor having an affinity for the SRE sequence in the promoter region of this gene.¹ Hence the absence of Bcl-2 expression accompanied by the presence of a 47 kDa SREBP factor observed in cells derived from normal subjects, the patient and his parents indicates that at least one copy of the receptor-C₃ gene is functional in these subjects (Fig. 1). However, the presence of both Bcl-2 gene expression as well as a 47 kDa factor in the patient’s mother signifies that the receptor-C₃ gene may be mutated in her (Fig. 1B M). Further, as compared to normal, there was increased expression of receptor-C₃ as well as an increased amount of 47 kDa SREBP in cells derived from the father and mother of the patient (Fig. 1B F,M).

**Discussion**

Cells from higher animals face the complex problem of not only sensing extracellular cholesterol but also the intracellular oxysterol pool that arises as a result of either uptake through passive diffusion of Apo B/E-specific LDL receptor or oxidation of cholesterol within cells.¹⁰,¹¹ Recent
receptor-C\(_k\) gene product in the cells of those with HFH is responsible for the maintenance of normal cholesterol homeostasis in these cells.

References
Transient Complete Heart Block Complicating Acute Rheumatic Fever

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First-degree heart block is a common electrocardiographic manifestation of acute rheumatic fever and is included in Jones' diagnostic criteria. Other electrocardiographic changes such as sinus tachycardia, bundle branch blocks, nonspecific ST–T wave changes, atrial and ventricular premature complexes have been reported with variable frequency. However, complete heart block is an exceptionally rare manifestation of acute rheumatic fever. We report the clinical course of a 16-year-old boy with acute rheumatic fever who had prolonged P–R interval in the electrocardiogram on admission which subsequently progressed to complete heart block. The patient regained normal sinus rhythm within a few minutes without any pharmacologic or electrical intervention. (Indian Heart J 2002; 54: 91–92)

Key Words: Complete heart block, Jones’ criteria, Rheumatic fever

Rheumatic fever (RF) is a clinical syndrome that follows group A streptococcal infection of the pharynx as a delayed nonsuppurative sequel. In 1944, T Duckett Jones first proposed the diagnostic criteria for acute RF which were later modified by the American Heart Association. RF is characterized by varying involvement of the heart, joints, central nervous system, skin and subcutaneous tissues. Its clinical spectrum includes migratory polyarthritis, carditis, Sydenham’s chorea, subcutaneous nodules and erythema marginatum as major manifestations, and fever, arthralgias, C-reactive protein, increased ESR and prolonged P–R interval as minor manifestations. Whereas second-degree AV block has been reported in the literature, complete heart block (CHB) is an exceptionally rare manifestation of acute RF.

Case Report

A 16-year-old student was admitted to the Government Medical College Hospital, Srinagar for evaluation of migratory polyarthritis of one week duration. He complained of symptoms suggestive of upper respiratory tract infection for about 10 days before the onset of joint pains. His investigations on admission revealed a normal hemogram except for an increased ESR (38 mm/h) (Westergren). Antistreptolysin-O (ASO) titer was 310 Todd units/ml, and throat culture was positive for group A β-hemolytic streptococci. Routine biochemical investigations, chest X-ray, two-dimensional and Doppler echocardiography were normal. His electrocardiogram (ECG) on admission showed a P–R interval of 0.28 (Fig. 1a). However, on the third day of hospitalization, he developed syncope. A portable ECG revealed CHB (Fig. 1b). He was subsequently shifted to the intensive care unit and put on a monitor. Within a few minutes, he reverted to normal sinus rhythm with a normal P–R interval (Fig. 1c). Subsequently, his ECGs did not show any abnormality till he was discharged from the hospital.

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Fig. 1. ECG showing a. normal sinus rhythm with prolonged P–R interval; b. complete heart block; c. normal sinus rhythm with normal P–R interval.
The patient was administered a single intramuscular injection of benzathine penicillin G 1.2 million units and aspirin 6 g per day in 4-hourly divided doses. His joint pains subsided, ESR normalized and he was discharged with the advice to take aspirin 4 g for a further 6 weeks. His ECG on the last outpatient follow-up was normal.

Discussion

Even though the twentieth century has witnessed a tremendous decline in the incidence of RF and rheumatic heart disease (RHD) in the industrialized nations, in many developing countries this disease still accounts for 10%–35% of all cardiac admissions. In India, there are more than one million patients with RHD and the annual incidence of RF is approximately 50 000.

Though RF is a multisystem disease, its primary target is the heart with valvular disease dominating the clinical picture. In rheumatic carditis, persistent sinus tachycardia that does not resolve during sleep is very common as is a prolonged P–R interval. The incidence of prolonged P–R interval in acute RF varies from 10% to 84%. A recent study described ECG changes in 232 patients with RF and showed AV conduction abnormality in 74 patients. Of these 74 patients, 64 had a prolonged P–R interval, 6 had transient AV block and 4 had transient episodes of AV dissociation. It is believed that AV conduction delay including AV dissociation is a manifestation of rheumatic carditis; however, its lack of correlation with clinical carditis and its response to atropine support the suggestion that it could be a nonspecific finding. Bundle branch blocks are rare, but transient CHB causing Stokes–Adams attacks have been reported. Thus, it is common to find a prolonged P–R interval in acute RF. However, it is neither diagnostic of carditis nor does it correlate with the ultimate development of chronic RHD. In the event of recurrence, though carditis is rare for patients who do not have it initially—it is crucial that RF patients be optimally protected from streptococcal infection by continuous antimicrobial prophylaxis.

References

The Potential for Vaccine Development Against Rheumatic Fever

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Group A streptococcus (GAS) is a human pathogen capable of causing a wide range of clinical manifestations: from localized infections such as pharyngitis and pyoderma to more serious invasive infections such as necrotizing fasciitis, sepsis and the toxic shock syndrome. Infection with Streptococcus pyogenes can also lead to the development of severe sequelae such as acute rheumatic fever (ARF), rheumatic heart disease (RHD) and acute post-streptococcal glomerulonephritis.

A cuterhematic fever is an inflammatory disease which seems to be mediated by autoimmune mechanisms activated by a group A streptococcal infection. Clinical manifestations of ARF such as polyarthritis with fever occur a few weeks after a pharyngeal infection by GAS. The most serious clinical manifestation is RHD which develops in many cases with ARF. Although the link between GAS infection and the development of RHD was reported as early as 1889 by Cheadle and is now universally accepted, the precise pathogenesis of ARF and RHD is not fully understood. Autoimmune processes involving molecular mimicry between streptococci and the human heart have been implicated in the pathogenesis of RHD.

A worldwide resurgence of GAS infections and their autoimmune sequelae have been observed in recent years, emphasizing the urgent need for more effective preventive strategies against streptococcal infections. In this review we discuss the current status of vaccine development against GAS infection, and the advantages and disadvantages of different candidates for vaccine.

Incidence of ARF and RHD
The epidemiology of ARF varies between countries. In developing countries, ARF is endemic and remains one of the major causes of cardiovascular disease. The incidence of ARF has declined in industrialized countries since the 1950s with an annual incidence of 0.5 cases per 100,000 children of school age. Although the frequency of the disease was very high at the beginning of the 20th century (100–200 cases per 100,000 individuals in the USA in 1900), the incidence has fallen progressively since the late 1920s. The introduction of antibiotics in the 1940s demonstrated that penicillin treatment for streptococcal pharyngitis has a preventive effect against ARF; however, the occurrence of the disease had already been declining since the beginning of the 20th century. Despite optimal antibiotic therapy and improvement in the standard of living resulting from industrialization, which seem to have contributed to the fall in the incidence of ARF, the disease has not been completely abolished and recent outbreaks have been reported in the USA. The fact that the aboriginal population of the northern territory of Australia exhibited the highest rates of RHD in the world might suggest a genetic predisposition of the host towards its development.

Etiology of ARF
A cuterhematic fever is an autoimmune sequelae of GAS infection which occurs in approximately 3% of GAS-infected patients aged between 5 and 15 years. Although several organs are affected during episodes of ARF, the heart is the most severely and critically damaged. Chronic RHD affects mainly the valves which can become so highly deteriorated that the only possibility of survival for the patient is surgical valve replacement. Although the pathogenic mechanisms leading to heart damage in ARF are not well understood, the presence of heart-reactive antibodies in the serum of patients with RHD and the deposition of such antibodies in the myocardium have emphasized the importance of humoral immunity. More recent work suggests that cell-mediated immunity within the heart is responsible for the resulting cardiac damage. Antigenic mimicry or cross-reactivity between GAS antigens and cardiac autoantigens may initiate the autoimmune response resulting in cardiovascular damage. Many studies have tried to identify cross-reactive cardiac antigens and the corresponding streptococcal antigens however, the exact nature of the autoimmune response...
associated with RHD remains unclear. Both host and microbial factors have been shown to influence the development of autoimmune sequelae following a GAS infection. Several studies have focused unsuccessfully on the identification of host genetic markers for predisposition to develop RHD. An increased frequency of specific HLA class II haplotypes has been observed among RHD patients but only in particular locations.

Regarding the influence of bacterial factors on RHD, studies performed by Kaplan et al. demonstrated that injection of cell wall extracts into rabbits immunized the animals and allowed them to develop antibodies which bound to myocardial tissue from patients who had died from carditis. Streptococcal M protein has long been recognized as the major determinant of virulence of S. pyogenes. M protein contains immunological determinants similar to several host autoantigens including myosin, tropomyosin, vimentin, keratin and laminin. Serological classification of GAS into specific types is based on the type of M protein. Although 93 different M protein types have now been identified, only a single type is expressed by each strain. It has been shown that particular serotypes are more frequently associated with pharyngitis, invasive GAS infection or ARF. In particular, the M5 serotype of S. pyogenes has been associated with outbreaks of ARF. However, there are geographic variations among rheumatogenic GAS strains. An example of this variation is the M18 type which has been found in the USA but not in the UK. In addition, certain serotypes appear for a period of time then subsequently disappear and are substituted by new serotypes. M proteins share epitopes with human heart tissue including cardiac myosin and sarcolemmal membrane proteins. Antibodies against the M protein can cross-react with heart tissue and induce heart valve damage due to inflammatory reaction. A recent study has shown a high rate of groups C and G streptococcus carriage in a particular population, raising the question of the involvement of these streptococcal strains in the development of ARF.

Strategies for the Prevention of ARF

The most extensively used strategy for the prevention of ARF has been the administration of penicillin. Oral penicillin V has been used for many years for the treatment of tonsillopharyngitis without changes in the susceptibility of GAS to the antibiotic during this period. The preventive effects of administration of injected penicillin against RHD were demonstrated in studies performed on the armed forces personnel of the USA. Secondary prophylaxis with penicillin is, however, not only expensive but has not been very effective in controlling ARF because of poor compliance.

The major challenge for the prevention of ARF is the development of an active vaccine against GAS infection. Progress towards the development of such a vaccine has been made in recent years and several potential streptococcal candidate antigens have already been identified. Much work has been focused on the M protein, the major virulence factor of S. pyogenes. Due to its antiphagocytic capabilities, its ability to bind human plasma proteins and to block the deposition of C3b onto the bacterial surface, it has been suggested that M protein plays an important role in the ability of S. pyogenes to evade the host immune mechanisms. Antibodies elicited against M protein are opsonic and have been shown to be protective in animal models of GAS infection. However, a major limitation of an M protein-based vaccine is that anti-M protein antibodies are also cross-reactive with heart tissue. In this regard, many of the tissue cross-reactive epitopes have been identified and the use of only non-cross-reacting protective epitopes from the M protein has been proposed. An additional problem related to M protein-based vaccine is that immunity against M protein is largely strain-specific and more than one hundred different M types have already been identified in addition to a number of M nontypeable clinical isolates. Structural and functional analyses have revealed that the amino-terminal nonrepeated regions of M protein contain determinants of type-specificity, whereas epitopes on the highly conserved carboxy-terminal region are common to different serotypes (Fig. 1). Based on this information, vaccine prototypes containing C-repeat peptides have been shown to be protective in a mouse model of streptococcal infection. Multivalent M protein vaccine prototypes containing a variable number of peptides from the M protein constitute a different approach for an M protein-based vaccine which has been tested in animal models with encouraging results. The first M protein multivalent vaccine designed was a tetravalent hybrid protein which included fragments of M24, M5, M6 and M19 serotypes. This vaccine elicited significant levels of opsonic, noncross-reacting antibodies against the different M epitopes in immunized rabbits. Further multivalent vaccines were developed using the same
approach but including a higher number of M antigenic determinants. A major limitation of this construct was that the strength of the immune response generated against each epitope was dependent on its size and location within the hybrid protein. These vaccine prototypes are currently undergoing optimization.

An alternative approach to the development of an anti-GAS vaccine is based on the use of streptococcal antigens critical for the infection process. Group A streptococcus is an extracellular pathogen; therefore, bacterial attachment to the mucosal surface constitutes a prerequisite for successful bacterial colonization. Several bacterial constituents have been demonstrated to mediate bacterial adhesion to eukaryotic cells including lipoteichoic acid and surface proteins able to bind components of the extracellular matrix, e.g. fibronectin, vitronectin among others. Impairment of bacterial colonization might constitute an effective strategy to prevent onset of infection and the subsequent development of disease. In this regard, new vaccine prototypes have been proposed using highly conserved virulence determinants such as fibronectin-binding proteins which are involved in bacterial attachment to host epithelial cells. The fibronectin-binding protein I (SfbI or protein F) from S. pyogenes is a major surface adhesin. The SfbI protein contains an aromatic domain, a proline-rich repeats region and fibronectin-binding domains (Fig. 2).

SfbI protein mediates bacterial attachment and internalization into epithelial cells via fibronectin (Fig. 3). Intranasal immunization of mice with SfbI protein has been shown to elicit a protective immune response against bacterial challenge with homologous and heterologous strains of S. pyogenes (Fig. 4). The part of the protein involved in protection has been identified in the fibronectin-binding domain. The advantages of an SfbI-based vaccine are multiple. SfbI protein is expressed by more than 70% of clinical isolates independently of their serotype, geographic location or clinical manifestation and its fibronectin-binding domain is highly conserved. An additional advantage is the lack of cross-reactivity between immunity elicited against SfbI protein and the human heart. SfbI protein vaccine prototypes are soon going for phase I trial.

A second fibronectin-binding protein of S. pyogenes, FBP54, has been tested in protective studies using an animal model with promising results. The gene FBP54 is present in all clinical isolates and is highly conserved among the different M serotypes.

Another bacterial antigen proposed as a candidate for vaccine is the streptococcal C5a peptidase, an important virulence factor expressed by approximately 40 different serotypes of GAS. This peptidase specifically inactivates C5a and, therefore, impairs its ability to attract PMNs to the focus of infection. Intranasal immunization with purified C5a peptidase evoked systemic and mucosal immune response able to reduce the level of bacterial colonization in a mouse model of streptococcal infection.

Extracellular cysteine protease derived from streptococcal pyrogenic exotoxin B plays an important role in bacterial pathogenicity. Extracellular cysteine protease is expressed in a large number of clinical isolates, and...
passive and active immunization with this protein resulted in enhanced survival times of mice after challenge with virulent S. pyogenes.\textsuperscript{71,72}

**Perspectives**

A major limitation of the study of immunopathology of RHD has been the lack of suitable animal models. The development of a “humanized” animal model of RHD which closely parallels the human disease would facilitate the disclosure of the different steps involved in the pathogenesis of rheumatic carditis. Transgenic mice can be engineered to express appropriate human HLA-DR and also cross-reacting human antigen in their heart tissue. This “humanized” animal model for RHD would be an ideal tool to explore the specific immune effector mechanisms involved in causing ongoing cardiac damage during RF. This animal model will be essential for understanding how immune effector cells are targeted at the heart, how these cells are activated, and if their effector functions are antigen specific. In addition, identification of the streptococcal proteins involved in the development of the autoimmune process leading to RHD may offer new strategies for improved control measures against this inflammatory process by treating affected patients with nonpathogenic competitor peptides cross-reactive to self-determinants in an antagonist fashion.

**Conclusions**

Decline in the incidence of RHD in endemic areas can be achieved by adopting a prophylactic approach. Although antibiotic treatment of tonsillopharyngitis has proved to be effective in reducing the incidence of RHD in industrialized countries, the development of an efficient vaccine would be the most effective strategy to prevent the development of RHD in developing areas. This vaccine should be capable of being globally applicable to all geographic locations, and should be able to protect against the existing strains as well as against potentially emerging streptococcal serotypes. Despite the great expectations for the development of such a vaccine, much work needs to be done to find more suitable antigens which might fulfill these requirements.

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Prevention of Heart Disease in India in the 21st Century: Need for a Concerted Effort

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Among the many health predictions for the new millennium, the most alarming is that of cardiovascular disease (CVD)—heart disease and stroke—topping the list for death and disability. While there are undoubted regional differences between the developed countries and other economies, the predictions for India by 2015 show a steady increase since 1985. The projected rate per 100,000 for all "circulatory diseases" was 145 males, 126 females; for 2000, 253 males and 204 females and for 2015, 295 males and 239 females, which is higher than that for other causes such as cancer.

Burden of CVD (Heart Disease and Stroke)

Global burden: It has been estimated that in AD 2001, 17 million people died of CVD of all types. The most important causes were ischemic heart disease (IHD), hypertension and rheumatic heart disease (RHD).

Ischemic heart disease: In 1998, 12.4 million died of heart attack and stroke (heart attack 7.3 million; stroke 5.1 million); of these, 78% were in the low- and middle-income countries. The high-income countries had lower death rates because of better preventive and treatment programs.

Hypertension: There were 600 million hypertensives in the world at risk for heart attack, stroke and cardiac failure; 180 million in the high-income and 420 in the low- and middle-income countries.

Rheumatic heart disease: There were 12 million young adults and children with RHD requiring secondary prophylaxis of whom 8 million were of schoolgoing age, mostly in low- and middle-income countries.

Burden in India

Coronary heart disease

Mortality statistics: Specific mortality data ideal for making comparisons with other countries are not available in India. This is due to inadequate and inappropriate death certification, and multiple concurrent causes of death. The annual surveys conducted by the Registrar General of India cover about 0.5% of rural deaths in India. The subjects covered under "circulatory diseases" include anemia, among others. Stroke, RHD and hypertension are not included. The figures published by the World Health Organization (WHO), drawn mainly from this source and for what they are worth, show a much higher prevalence in India than in many other developing countries.

Population surveys: Population-based surveys, with all their attendant pitfalls in sampling design, sample size standardization and measurement errors, remain the most important source of information today. Old surveys pointed to a low incidence of IHD, 1%-4%, whereas recent surveys show a figure of nearly 10% (96.7/1000). There are great regional variations.

Hospital statistics: These are obviously biased data and form the reason for the present impression of an "epidemic of IHD in India". Data from Christian Medical College (CMC), Vellore and All India Institute of Medical Sciences, New Delhi (AIIMS) over a period of 30 years show a decline in admission for RHD and an increase in admission for CAD. Cardiac institutions have sprung up in many metropolitan cities. Departments of cardiology and cardiac surgery have been upgraded in many hospitals, especially private. Intensive coronary care units (ICCUs) have sprung up in small towns and there has been an increase in cardiac surgery of all types.

In 1980, coronary artery bypass grafting (CABG) accounted for less than 10% of all cardiac surgeries. Today, it accounts for more than 60%. Every year 25,000 coronary bypass operations and 12,000 percutaneous transluminal coronary angioplasties (PTCA) are carried out. In 1999, a total of 6607 valve replacements were done mostly for RHD and 6750 surgeries for congenital cardiac defects. Out of 42,000 open heart operations done in 1999, only 11,450 were performed in government hospitals.

Even though the number of open heart surgeries performed (42 operations per million) is small as compared to 1700 per million in the USA, it provides a clue to the enormous increase in the availability of this facility in India.
Clinical impression alone suggests that there has been phenomenal increase in IHD throughout India. The reasons, as in other developing countries, are obvious. Increase in life expectancy (from 41 in 1961 to 63 in 2001), smoking, a western-style diet (with increase in saturated fat, salt, calories and less intake of fiber) and decreased physical activity resulting in obesity are all responsible. Urbanization is on the increase and is responsible for many of these changes in lifestyle.

Risk factors—old and new: The traditional risk factors such as smoking, high blood pressure, high serum cholesterol level and diabetes are applicable to the majority of cases in India.\(^3\) The emerging risk factors—abdominal obesity, high triglycerides, insulin resistance, the so-called metabolic syndrome, elevated homocysteine levels, fibrinogen factors, etc.—need not be invoked to explain the present high incidence of heart attacks as they are yet to be proven as being causative in this era of evidence-based medicine. Control of the traditional risk factors should suffice in any preventive program.

The Barker hypothesis: Besides the traditional and newer risk factors, the reason for the present high prevalence has been attributed to the Barker hypothesis which suggests poor maternal nutrition with impaired fetal growth results in low birth-weight, short birth length and small head circumference. These adverse influences program the development of adaptive metabolic and physiologic responses with an increased risk of glucose intolerance, hypertension, dyslipidemia and adult CVD.\(^7\) This scenario is not difficult to envisage in India, especially with increased survival of these infants due to better child care.

Burden of hypertension: Since 1942, there have been several small and large population-based studies on hypertension. A recent publication found no less than 34 references. A meta-analysis showed an increase in the prevalence of hypertension over the years, especially of systolic levels, more in urban than in rural areas.\(^8\) Recent studies using the criterion of 140/90 mmHg as the cut-off point for hypertension have shown a prevalence of 10%–30.9% in urban areas, while earlier reports since 1950 showed a prevalence of 1%–3%. The reason for the increasing trend has been attributed to the same factors as those for CAD.\(^8\)

Hypertension appears to be the most important risk factor for the development of CAD throughout India. In a study in Delhi involving 8000 subjects, the most important risk factor for CAD was hypertension in over 50% of subjects, young and old, followed by smoking and diabetes.\(^8\) This has also been seen at AIIMS, New Delhi and CMC, Vellore.\(^8\)

Burden of RHD: Although in the twenty-first century RHD has been eradicated in western countries, in India and other developing countries it continues to cause a high mortality among children and young adults. The present prevalence data are from school surveys (the most important source for the prevalence of RHD).

A prevalence of RHD of 3.9/1000 in the last school study in primary schoolchildren 6–10 years of age is unacceptably high. Further proof of the continuing large reservoir of RHD cases is the large number of patients in their teens and twenties coming in for the (relatively) new modality of balloon mitral valvotomy. Pediatric clinics in large hospitals from various parts of India have reported several cases with acute manifestations of RHD such as carditis, chorea, nodules and polyarthritis.\(^10,11\)

Role of Treatment versus Prevention

It is now being accepted that part of the decline in mortality from heart disease in the West is due to better treatment, both medical (ICCU, drugs, PTCA) and surgical.\(^12,13\) Treatment facilities for heart disease need to go hand-in-hand with preventive measures.

Cost of medical care; facilities for diagnosis and treatment: In India, the lack of facilities for diagnosis and treatment, and unaffordable cost of medical care add to the huge existing burden of heart disease. There are about 35 well-equipped centers for modern diagnosis and treatment mostly in the six metropolitan cities, grossly inadequate for a vast country with an immense population such as India. Surgical care is even less adequate. It has been stated that in the developing countries of Asia, 25 cardiac surgeries per million population are carried out as against 1000 in the USA, 569 in Europe and 786 in Australia.\(^14\) The cost of surgery is forbidding and most patients have to do without it. Medical insurance is still in its infancy in India.

Agencies Involved in Prevention

Cardiac societies and foundations: In industrialized countries, societies and foundations such as the World Heart Federation (WHF) and WHO have been most active. Observance of World Heart Day since \(2000\) (the last Sunday in September every year), World Health Day (7 April) and World Non-Smoking Day (31 May) has increased awareness and the seeking of medical help. In India, the concept of a World Heart Day is slowly gaining acceptance. Apart from the big cities, it was celebrated in 2001 in Assam, Kerala and Uttar Pradesh. Statements by
the American Heart Association (AHA)/American College of Cardiology (ACC), National Heart, Lung and Blood Institute, British Heart Foundation, Heart Foundation of Australia and New Zealand, the European Society of Cardiology and the European Heart Network have been very effective in reaching out to the public through the media. There are several conference statements available such as the Vancouver, Singapore, Barcelona and Kyoto declarations. A conference on preventive cardiology is organized by WHF every 4 years, which attracts huge participation (the last one was held in Kyoto in May 2001).

**Government:** This is the single most important agency in developing countries where other agencies such as NGOs and specialist societies often do not exist. However, governments are usually very bureaucratic, slow and ineffective. For the past 10 years the Cardiological Society of India (CSI) and All India Heart Foundation (AIHF) have been knocking at the doors of the Government of India for a hearing and a policy statement on heart disease. Governments, especially in the developing countries, can do a lot by way of legislation against the use of tobacco and alcohol, and for labeling of processed foods to declare their fat and sodium content. In India, we have not even made a start on tobacco despite the recent ban on smoking in public places and other measures by the Supreme Court. In the case of RHD, the technology for control is available through primary health centers (PHCs) and school health services. The government must have the political will to eradicate the disease by proper transfer of technology to the states. The Government of India has failed to provide an impetus to eradicate RHD as it mostly affects the poor.

**Prevention strategies**

Three types of prevention are advocated by WHO: primordial, primary and secondary. Prevention may be population-based or target high-risk groups. In some types of heart disease (e.g. RHD), secondary prevention is the most practical. In the case of CAD and hypertension, scientists now recommend primordial prevention (prevention of appearance of risk factors) as primary prevention, i.e. control of risk factors has been done in many interventional studies in Europe and the USA with only partial response. Secondary prevention recommended for IHD has also had many pitfalls as shown in the EUROASPIRE study.16

**Methods of prevention:** Much of the knowledge accrued on preventing heart disease became available over the past 20 years. In the 1960s, the pioneering work by Dr Ancel Keys in the Seven Countries Study set the ball rolling. In simplistic terms, it focuses on diet (low in saturated fat and salt, high in fiber and antioxidants), weight control, moderation in consumption of alcohol, abstinence from smoking and increased physical activity and periodic check-ups to monitor the levels of blood glucose and serum cholesterol, as well as blood pressure. This program incidentally helps to control many of the other degenerative diseases such as osteoporosis, certain types of cancers and arthritis, besides coronary heart disease and hypertension.

**Rheumatic heart disease:** Prevention of RHD has been tried in several countries for many years. Secondary prevention has remained the most practical method followed by primary prevention. Recently, an RF vaccine has become a distinct possibility. Efforts are under way for the use of this vaccine in India. It will go a long way in preventing disability among children due to cardiac disease.9,10

**Suggested solutions for India:** As the situation calls for urgent action, I suggest the following, keeping in mind the present information technology (IT) explosion and the availability of the Internet and its ramifications. This method is being tried successfully elsewhere17 and India has the infrastructure in good measure to make such a method possible.

The CSI and AIHF should together shoulder the task of prevention on a large scale like the ACC/AHA and similar bodies in the UK, Australia and Canada. The AIHF is doing its bit in a small way. The CSI has many regional chapters but no population outreach. Although the AIHF is an all-India body including laymen and doctors as representatives, it has no regional chapters. Such chapters combining the AIHF and CSI could be created for joint action. The following programs are suggested:

1. Public health education aimed at patients, the general public and healthcare providers. The AIHF is already active in this regard. Promotion through pamphlets, videos and TV as well as radio talk shows in English and regional languages could be strengthened by the regional chapters.
2. Population outreach by holding heart camps in rural and urban areas to create awareness about heart disease and its prevention by nonpharmacological means such as diet, smoking, exercise, yoga and meditation, etc.
3. In the Indian context, special attention should be paid to three areas—tobacco, hypertension and lipids and diabetes. Emphasis should be placed on low-tech...
methods such as lifestyle changes (diet, exercise, weight control, no smoking, restricted alcohol) and the use of inexpensive drugs (β-blockers and diuretics) rather than ACE inhibitors and statins, which are expensive. However, it is expected that some of the latter may become inexpensive once their patents expire.13

4. Training of paramedical personnel (nurses and health workers of all types) and general practitioners in the techniques of blood pressure measurement and simple remedies.

5. Strengthening diagnostic and curative services throughout India must go hand-in-hand with preventive measures. This has to be done by the government and private sector on a corporate or cooperative basis by small communities, keeping in mind the need to cut both medical and surgical costs for diagnosis and treatment.

6. Research:
   a. A MONICA-type project to observe trends in the incidence of the disease. Cross-sectional studies on prevalence must continue in each state of the country which must be uniform and well designed by the Indian Council of Medical Research (ICMR).
   b. Operational research at the regional level for feasibility studies at both village and urban levels.

References

2. WHO CVD Strategy 2001-2002
10. Padmavati S. Rheumatic fever and rheumatic heart disease in India at the turn of the century. Indian Heart J 2001; 53: 35–37
17. Lown B. Cardiology at the crossroads: challenges for India and lessons from the West. Indian Heart J 2001; 53: 38–43
Prevalence of Coronary Artery Disease in India

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Vijaya Hospital, Chennai

Studies on the prevalence of coronary artery disease (CAD) in India reveal some disturbing trends (Fig. 1).1–6 Figure 1 shows the data from selected references of work done exclusively in India. No report or study done on Indians living outside the country has been included. Figure 1 represents published data on community-based prevalence studies covering a 40-year period and involving different authors/workers and regions. The instruments used, namely the Rose Angina questionnaire as well as the Minnesota ECG code, have indeed served the profession well and have been used by most workers in the field for conducting community-based studies. The age groups studied by each group were different, as shown in Fig. 1. The graph confirms the current opinion that the actual prevalence of CAD is zooming in a linear if not exponential fashion; it increased from 4% in 1960 to 11% in 2001. In more meaningful terms, from every 25th individual in 1960, to every 9th in 2001 can be confidently suspected of having CAD. Should we stop at that or should we ask ourselves more questions?

The questions that come up include:

1. Is this the real picture?
2. Is there external validity in all these reports?
3. Have the available instruments of enquiry, referred to earlier, been used effectively?
4. The importance of endothelial dysfunction in the development of atherosclerotic vascular disease as well as the knowledge that deterioration in endothelial function starts after the age of 30 years7 is well known. Since clinically manifest disease presents at an even later age, how will a community-based study including individuals below the age of 35 years affect the end results? The total prevalence would be underestimated, though not the age-specific prevalence, which is negligible below 40 years of age.
5. It is likely that future studies or reports on prevalence will yield new data, giving rise to the same questions listed here with all the results being accepted and attributed to “diversity” or “regional disparities”.

Considering the fact that at all levels of health care—primary, secondary and tertiary cardiac care—more cases of CAD are being handled, it is time to move on from prevalence studies to incidence studies of CAD, which may be more relevant. These studies should be well designed and well documented. Both aspects—available prevalence data as well as future incidence studies—will reiterate greater emphasis on steps directed at prevention and control of modifiable risk factors as well as a future coronary event or clinical manifestation. The situation calls for the involvement of all health workers.

References


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Fig. 1. The prevalence of CAD in India.
Burden of Rheumatic and Congenital Heart Disease in India: Lowest Estimate Based on the 2001 Census

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Departments of Cardiology and Cardiothoracic Surgery, Postgraduate Institute of Medical Education and Research, Chandigarh

After Roget's thesaurus equates “burden” with “load” and “responsibility”. This article discusses the load of rheumatic heart disease (RHD) and congenital heart disease (CHD) in India, and also the responsibilities of cardiologists, cardiothoracic surgeons and health planners to deal with this load with the available resources.

Each newborn is a responsibility of the immediate family, the society and finally, the nation. During a lifetime and even during the months prior to birth, any individual may develop heart disease, or acquire a lifestyle pattern or environment that fast-tracks him/her to develop heart disease. It is important for primary care physicians, specialists working in tertiary care centers and health planners to know the extent of the total cardiovascular disease burden. In the Indian context, this not only includes ischemic heart disease (IHD) but a significant number of cases of CHD and RHD as well. The literature tends to discuss only IHD and omits the significant burden of RHD and CHD. The latter two diseases contribute significantly to the total burden, and require adequate manpower, resources and facilities for the care of suffering patients. Recent reports suggest that about two-thirds of in-hospital cardiac patients have RHD and CHD, and one-third have IHD. Thus, the emphasis of this article is limited to RHD and CHD.

Data Sources
Health statistics in India, as in any other developing country, are not easily available and when available, lack precision and accuracy. Therefore, multiple sources of information were used and cross validation of analytical studies was carried out to arrive at a figure. For the denominator, the data from the 1991 and 2001 Censuses were used. To calculate the lowest estimate of burden of RHD and CHD, we used the following sources for data, in descending order of reliability:

1. National Census Data 2001 (available online at http://www.censusindia.net)
2. Epidemiological data from articles published in peer-reviewed, indexed journals
3. Autopsy data from tertiary care institutes of India
4. Data from specific registries and monitored clinics, including the rural Raipurtri registry and pediatric cardiology clinic. Data from the central registration department of Nehru Hospital affiliated to the Postgraduate Institute of Medical Education and Research (PGIMER), Chandigarh, India*
5. Data from company records of medical equipment manufacturing units — utilization of equipment reflects the service provided.

2001 Census Data
Table 1 shows the total population, crude birth rate and percentage distribution of the population of various age groups in relevance to the article. At a crude birth rate of 27.2/1000, the total annual live-births would be 27.93 million. This figure does not include either spontaneous abortions or stillbirths, which are associated with significantly higher proportions of serious heart defects than live-births. Among the latter, approximately 80% survive the first year and three-fourth survive the first 15 years of life. Population at risk is defined as a proportion of the population which is at maximum risk of suffering from the disease, where a sufficient number of point

*Hospital morbidity and mortality statistics published by the Department of Biostatics, PGIMER annually details lists of patients examined and their diagnoses established in various clinics, including the Pediatric Cardiology Clinic, Adult Cardiac Clinic, and Cardio-Obstetric Clinic. For mortality statistics, it maintains a proforma filled as per international guidelines, which not only includes immediate cause, but also antecedent causes leading to the terminal event.

Correspondence: Dr Anil Grover, Department of Cardiology, PGIMER, Chandigarh 160 012. e-mail: anilgrover444@hotmail.com
prevalence studies have been conducted and a longitudinal follow-up is available in the literature. Additionally, the natural history of the disease on the life expectancy of a patient was considered. For the purpose of calculation of the lowest estimate of CHD, the age group of 0–15 years was taken to be at risk and for RHD, 5–40 years was taken as the population at risk.

### Congenital Heart Disease

Congenital heart disease is the most common birth defect and affects a large number of children. Research directed at the cause and “ultimately” possible prevention is an essential component of any agenda to reduce premature death and morbidity due to cardiovascular disease. The incidence of CHD in various countries and different ethnic groups is about the same. The incidence of CHD in infancy varies from 4 to 12/1000 live-births in various community- and hospital-based studies (Tables 2 and 3).6–12 It is a fact that hospital-based studies estimate a higher prevalence as compared to community-based studies. Considering the lowest estimate of 4/1000 live-births, approximately 112,000 infants with CHD are added every year to the total pool.

The number of cases of CHD recognized in the first year of life is only about two-thirds the number of cases recognized in a population of children followed up till their teens.6 Thus, an additional 37,000 CHD cases are diagnosed during childhood. Every year, about 121,000 children with CHD reach the age of 15 years. Of these, one-third would require long-term follow-up in adult life. These figures predict the need for adult follow-up of CHD of over 425 extra cases per 100,000 live-births each year.24,25 The number of adult CHD patients is substantial in India because of a lack of health awareness, poverty and inadequate health manpower and facilities.

About 45% of CHD cases require some form of intervention or surgery during childhood.11 Thus, every year, nearly 50,000 children require surgery or care at an advanced infant cardiac center. However, in our country every child who needs surgery does not get operated. Taking the number of pediatric oxygenators used as an indirect measure of pediatric cardiac surgeries performed for children below 1 year of age, the number for India is <1000 for the year 1999.23

### Rheumatic Heart Disease

India is in the phase of “epidemiological transition”. On the one hand, there is a substantial burden due to RHD, infection and malnutrition and, on the other hand, there are a vast number of cases of IHD, obesity and diabetes which represent the degenerative and man-made diseases.1 The prevalence of RHD has declined in the West but continues to be an important cause of cardiovascular morbidity and mortality in India. The prevalence of RHD varies from 1.0 to 5.4/1000 schoolchildren (Table 4).

### Table 1. Relevant census data

<table>
<thead>
<tr>
<th>Data</th>
<th>1991</th>
<th>2001</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total population (in millions)</td>
<td>846</td>
<td>1027</td>
</tr>
<tr>
<td>Crude birth rate (per 1000 population)</td>
<td>30.0</td>
<td>27.2</td>
</tr>
<tr>
<td>% population &lt;15 years of age</td>
<td>37.3</td>
<td>34.3</td>
</tr>
<tr>
<td>% population 5–15 years of age</td>
<td>25.1</td>
<td>23.6</td>
</tr>
<tr>
<td>% population 5–40 years of age</td>
<td>64.9</td>
<td>65.2</td>
</tr>
</tbody>
</table>

## Table 2. Congenital heart disease in defined live-birth population

<table>
<thead>
<tr>
<th>Author</th>
<th>Community/ hospital-based</th>
<th>Total infants</th>
<th>CHD (n)</th>
<th>CHD/1000 live-births</th>
</tr>
</thead>
<tbody>
<tr>
<td>Khalil et al.3</td>
<td>Hospital</td>
<td>10,964</td>
<td>43</td>
<td>3.9</td>
</tr>
<tr>
<td>Wren et al.6</td>
<td>Community</td>
<td>377,310</td>
<td>1942</td>
<td>5.2</td>
</tr>
<tr>
<td>Subramanyan et al.1</td>
<td>Hospital</td>
<td>139,707</td>
<td>992</td>
<td>7.1</td>
</tr>
<tr>
<td>Samanek et al.8</td>
<td>Community</td>
<td>816,569</td>
<td>5030</td>
<td>6.16</td>
</tr>
<tr>
<td>Roy et al.8</td>
<td>Hospital</td>
<td>-</td>
<td>-</td>
<td>8.0</td>
</tr>
<tr>
<td>Robida et al.12</td>
<td>Hospital</td>
<td>49,887</td>
<td>610</td>
<td>12.23</td>
</tr>
<tr>
<td>Fixler et al.21</td>
<td>Community</td>
<td>379,561</td>
<td>2509</td>
<td>6.6</td>
</tr>
<tr>
<td>Bilir et al.12</td>
<td>Hospital</td>
<td>-</td>
<td>-</td>
<td>11.5</td>
</tr>
</tbody>
</table>

India is in the phase of “epidemiological transition”. On the one hand, there is a substantial burden due to RHD, infection and malnutrition and, on the other hand, there are a vast number of cases of IHD, obesity and diabetes which represent the degenerative and man-made diseases.1 The prevalence of RHD has declined in the West but continues to be an important cause of cardiovascular morbidity and mortality in India. The prevalence of RHD varies from 1.0 to 5.4/1000 schoolchildren (Table 4).

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feature of both public health and clinical importance. Juvenile RHD is a more severe and rapidly progressive disease. It is associated with significant mitral stenosis, organic tricuspid valve disease, severe pulmonary artery hypertension and congestive heart failure.26–28 It is the commonest heart disease associated with pregnancy and is found in about 1% of pregnant women.29 The most common and dominant valvular lesion is mitral stenosis (72%),29 which leads to significant maternal and fetal morbidity and mortality.30 These patients require either balloon mitral valvuloplasty or surgical mitral commissurotomy. Both procedures are available at limited centers in India.

Valvular surgery in India is performed mostly for RHD. During 1999, a total of 6607 valve replacements were done.23 Of these, 4640 were mitral valve replacements, 1967 aortic valve replacements, and 642 repair/replacement of other valves. These operations cover only a fraction of the very large number of patients who need them. The high cost of prosthetic valves and inadequate facilities for operative management of these patients are hindrances to valve replacement surgery. Valve replacement surgery costs approximately 10 times the average annual income of a person. There is a need to set up an agency to provide heart valves at subsidized cost to these poor patients and lend support to programs aimed at eradicating RHD from India.

## Conclusions

At present, prevention is an established and cost-effective strategy for RHD. Dissemination of education can assimilate this into routine health care practice. For CHD, early detection and awareness of known antenatal risk factors can probably reduce the incidence. Genetic and general counseling for all adolescent heart diseases (e.g., RF and infective endocarditis prophylaxis) as well as advice about the appropriate timing of surgery is a must. More emphasis on the establishment of adolescent heart disease clinics by trained specialists can significantly reduce morbidity. Advances in biogenetics (such as the RF vaccine) will probably end these diseases in this millennium.

## References


### Table 3. Estimated number of patients with congenital and rheumatic heart disease in India

<table>
<thead>
<tr>
<th>Disease</th>
<th>Prevalence rate (%)</th>
<th>Age at risk (age group)</th>
<th>Population at risk (in million)</th>
<th>Number of patients (in million)</th>
<th>Estimated annual new patients added</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHD</td>
<td>0.4</td>
<td>&lt;15 years</td>
<td>354</td>
<td>1.41</td>
<td>121 000</td>
</tr>
<tr>
<td>RHD</td>
<td>0.21</td>
<td>5–40 years</td>
<td>670</td>
<td>1.4</td>
<td>50 000</td>
</tr>
<tr>
<td>CHD and RHD</td>
<td>-</td>
<td>-</td>
<td>1027</td>
<td>2.81</td>
<td>171 000</td>
</tr>
</tbody>
</table>

CHD: congenital heart disease; RHD: rheumatic heart disease

### Table 4. Rheumatic fever/rheumatic heart disease status in India

<table>
<thead>
<tr>
<th>Authors</th>
<th>Place</th>
<th>Year</th>
<th>Age (years)</th>
<th>Population studied</th>
<th>RHD prevalence (per 1000)</th>
<th>RF incidence (per 1000/year)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICMR</td>
<td>Ballabgarh</td>
<td>1982–1990</td>
<td>5–15</td>
<td>22 729</td>
<td>1.0</td>
<td>-</td>
</tr>
<tr>
<td>ICMR</td>
<td>Varanasi</td>
<td>1982–1990</td>
<td>5–15</td>
<td>12 190</td>
<td>5.4</td>
<td>-</td>
</tr>
<tr>
<td>ICMR</td>
<td>Vellore</td>
<td>1982–1990</td>
<td>5–15</td>
<td>13 509</td>
<td>2.9</td>
<td>-</td>
</tr>
<tr>
<td>Padmavati</td>
<td>Delhi (urban)</td>
<td>1984–1994</td>
<td>5–10</td>
<td>40 000</td>
<td>3.9</td>
<td>0.384</td>
</tr>
<tr>
<td>Grover</td>
<td>Raipurani</td>
<td>1988–1991</td>
<td>5–15</td>
<td>31 200</td>
<td>2.1</td>
<td>0.54</td>
</tr>
<tr>
<td>Avasthi</td>
<td>Ludhiana</td>
<td>1987</td>
<td>6–16</td>
<td>6005</td>
<td>1.3</td>
<td>0.70</td>
</tr>
<tr>
<td>Patel</td>
<td>Anand</td>
<td>1986</td>
<td>8–18</td>
<td>11 346</td>
<td>2.03</td>
<td>0.176</td>
</tr>
<tr>
<td>Lalchandani</td>
<td>Kanpur</td>
<td>2000</td>
<td>7–15</td>
<td>3963</td>
<td>4.54</td>
<td>0.75</td>
</tr>
</tbody>
</table>

RF: rheumatic fever; RHD: rheumatic heart disease
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A four-year-old girl presented to our hospital for evaluation of a murmur which was detected on routine check-up by her family physician. On examination, there was a grade 3/6 continuous murmur with diastolic accentuation in the lower left sternal border. The heart sounds were normal. The chest X-ray and ECG were unremarkable. She underwent two-dimensional echocardiography (2-DE) and color Doppler study, which suggested coronary arteriovenous fistula (CAF) to the right atrium (Figs 1–4).

Krause was the first to describe congenital coronary

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**Coronary Arterial Fistula to the Right Atrium**

V Jacob Jose, Bobby John

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**Fig. 1.** Two-dimensional echocardiographic picture in a short axis view at the level of the aorta showing the pulmonary valve at 2 o'clock position. At 10 o'clock position a dilated right coronary artery origin is seen. Just below that traversing to the right atrium, a tract can also be seen.

**Fig. 2.** Color Doppler imaging of the same frame showing blood flow into the right coronary artery from the aorta and mosaic color pattern of blood entry into the right atrium.

**Fig. 3.** Two-dimensional echocardiographic picture in a subcostal view in which the right atrium is seen in the upper part of the picture and a tract can be seen which opens into it.

**Fig. 4.** Color Doppler imaging of the same frame showing the blood tracking through the fistulous tract of the coronary artery fistula to the right atrium.
arteriovenous fistula in 1865. More than 90% of CAF drain into the right side of the heart. Approximately half of the fistulae arise from the right coronary artery, less than half from the left coronary artery and 5% from both. The most frequent site of drainage is the right ventricle (41%), followed by the right atrium (26%) and pulmonary artery (17%). The majority of patients with CAF are asymptomatic. They may present with myocardial ischemia that is believed to result from coronary steal and rarely coronary spasm. Endocarditis has been associated with CAF. It may also present as congestive heart failure in the elderly. Ventricular tachycardia has also been reported. Noninvasive diagnosis of CAF has been suggested by 2-DE alone in 50% of cases and Doppler further improves the rate of detection to 92%. The treatment modalities for CAF include surgical ligation, Symbas procedure and coil embolization.

References

Letters to the Editor

Indian Heart J 2002; 54: 110-111

Lipoprotein (a) and Lipid Levels in Young Patients with Myocardial Infarction and their First-Degree Relatives

We read with interest the above-mentioned article by Isser et al.1 and would like to offer the following comments and suggestions.

1. The demographic profile shown in the study of young patients aged <45 years with myocardial infarction (MI) documents the male:female ratio of 50:0. The incidence of MI in young females is much lower than that in males due to hormonal protection during the fertile period, but it is still not expected to be zero. Previous studies in young patients with MI have shown a male:female ratio varying from 4:1 to 20.6:1 (Table 1).2-4 The studies carried out in east Delhi in 1997 and 2000 by Dwivedi et al. have documented a male:female ratio of 4.5:12 and 4:1,4 respectively. In contrast to previous studies, the male:female ratio of 50:0 in this study needs to be looked into for the cause and effect of the said variance.

2. The demographic profile of India for 2001 showed that the overall male:female ratio is 1000:933, i.e. 1.07:1.4 Isser et al.3 in the above-mentioned study have reported a male:female ratio of 2.3:1, i.e. 1000:437 among first-degree relatives (all relatives, both healthy and diseased). The values seem to be intriguing. Till date, we have not come across such a low incidence of females in the Indian population.

3. The prevalence of smoking is lower in this study. It needs to be clarified whether the patients taking tobacco orally or other modes (e.g. gutka) were included. In eastern Uttar Pradesh and Bihar, the oral intake of tobacco is far more common.

4. The prevalence of hypertension is reported to be lower in Lucknow in comparison to Delhi, while a higher prevalence of diabetes has been reported in this study. Hypertension and diabetes usually go hand-in-hand in various areas and communities of India. The prevalence of hypertension and diabetes together is greater in the urban population in comparison to a rural population.

Table 1. Risk factors in young patients with myocardial infarction

<table>
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<tr>
<td></td>
<td>Dwivedi et al.2</td>
<td>Swach et al.3</td>
<td>Dwivedi et al.4</td>
<td>Isser et al.1</td>
</tr>
<tr>
<td>Male:female ratio</td>
<td>4:1</td>
<td>4:1</td>
<td>4:1</td>
<td>50:0</td>
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<tr>
<td>Smoking</td>
<td>59.1</td>
<td>87.6</td>
<td>61.42</td>
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<td>Hypertension</td>
<td>57.6</td>
<td>10.7</td>
<td>44.2</td>
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<td>Diabetes mellitus</td>
<td>12.1</td>
<td>1.5</td>
<td>7.14</td>
<td>14.0</td>
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<td>Family history of CAD</td>
<td>23.7</td>
<td>9.2</td>
<td>18.8</td>
<td>24.0</td>
</tr>
</tbody>
</table>

All figures are in percentages except the male and female ratio

CAD: coronary artery disease

Lipoprotein (a) and lipid levels in young patients with myocardial infarction and their first-degree relatives. Indian Heart J 2001; 53: 463-466


5. Registrar General and Census Commissioner of India, Census of India 2001 (website)

S Giri and S Dwivedi
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Reply

Giri et al. have basically inquired about male-to-female ratio in young patients suffering from myocardial infarction (MI). They themselves note that MI in young females is much lower. In fact, I hate to make a diagnosis of MI in a female less than 45 years of age because whenever I suspected MI, I found that their coronary arteries were normal. Our study had only 50 patients over a small period of time and, therefore, it is not surprising to find no female patients less than 45 years of age suffering from MI. The demographic profile should not be relied upon when the number of patients is small and the criteria for making the diagnosis should include an angiographically proven record. Similarly, the prevalence of smoking, hypertension and diabetes is also shown in the data of 50 patients. It should not be interpreted for prevalence, in view of the small number of patients. Hypertension and diabetes usually go hand-in-hand, as suggested by them, but many times this may not be the case, that is, we may find only one of the two. Our study aimed to identify lipoprotein (a) abnormalities in MI patients and in their relatives, and demographic observation in such a small number does not require scientific proof.

VK Puri
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Lucknow

Reference

1. Isser HS, Puri VK, Narain VS, Saran RK, Dwivedi SK, Singh S. Lipoprotein (a) and lipid levels in young patients with myocardial infarction and their first-degree relatives. Indian Heart J 2001; 53: 463-466


5. Registrar General and Census Commissioner of India, Census of India 2001 (website)
Final Report on Tobacco Risks from a Case-Control Study

I read with great interest the paper by Prem Pais et al. If the intention of the paper is to convey an antismoking message then the message is well delivered. However, as a scientific paper it leaves a lot to be desired.

In the first place, the authors are confused as to what they are talking about. Is it acute myocardial infarction (AMI), ischemic heart disease (IHD) or coronary artery disease (CAD)? This is not just about semantics. The distinctions are very important in a paper published in a leading cardiology journal. In the background information they state: “In India tobacco is smoked as both cigarettes and beedies. No studies have evaluated their importance as risk factors for IHD among the Indian population. The present study explores the importance of smoking either cigarettes or beedies as risk factors for myocardial infarction.” Further, their introduction starts with “Smoking is a modifiable risk factor that can lend itself to a population-based strategy of primary or primordial prevention. Such strategies are the most practical ways to control the projected epidemic of IHD. In this paper, we present detailed information about the risks of AMI associated with smoking either beedies or cigarettes among Indians in South India.” Their conclusion reads thus: “The present study reports the results of a case-control study of 600 subjects and clearly demonstrates the importance of smoking either beedies or cigarettes as a risk factor for AMI in urban Indians in India. Tobacco smoking also interacts with other risk factors for IHD further increasing their risk. It is a modifiable risk factor for IHD and one in which cessation has been shown to reduce the risk.”

If they are using AMI as a representative of the spectrum of entities coming under the general term IHD (or do they mean CAD?), then this study is grossly inadequate. Among the controls, no stress testing was done to detect “non-infarct” IHD. Hence the assumption that these persons were free of “IHD” would not be tenable. Also, smoking can cause AMI in patients with normal coronary arteries. In such cases do they consider that AMI represents “IHD”?

This paper is a sententious statistical work. It reaffirms the fact that AMI is common in smokers. The distinctive information here is about beedies. So far, so good. The implied extrapolation and references to “IHD” are unwarranted. Such inferences are non sequitur to the body of the study.

References


George Thomas
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Reply

We thank Dr George Thomas for the interest with which he read our article. We wish we could thank him for his criticism which is far from constructive. Does he feel that acute myocardial infarction is not a manifestation of ischemic heart disease (IHD)? If so, we beg to differ. We are aware that IHD has different manifestations. We feel our article clearly states that our study was on acute myocardial infarction (AMI). The title itself states this. The conclusion of the abstract states: “Smoking >10 cigarettes or beedies/day carries an independent four-fold increased risk of acute myocardial infarction.” The section from the conclusion to the main article quoted by Dr Thomas is also clear in stating that beedi smoking is an important risk factor for AMI. Tobacco smoking has been shown by numerous studies to interact with risk factors such as lipids, known to be risk factors for IHD including MI. As regards the criticism about not conducting stress tests in all controls, it is not practical to do such tests in epidemiological studies and most such studies even in developed countries have not used stress testing on controls. We, therefore, fail to understand the rationale behind Dr Thomas acerbic comments.

References

1. Prem Pais, Michael P Fay, Salim Yusuf. Increased risk of acute myocardial infarction with beedi and cigarette smoking in Indians: final report on tobacco risks from a case-control study. Indian Heart J 2001; 53: 731–735

Prem Pais
Department of Medicine
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Prevalence of Coronary Artery Disease and its Relationship to Lipids in a Selected Population in South India (CUPS No. 5)

V Mohan et al. J Am Coll Cardiol 2001; 38: 682-687

Summary

Several recent reports have shown that migrant Indians have a higher prevalence of coronary artery disease (CAD) than indigenous populations, and an epidemic of CAD has been predicted in India as well. The Chennai Urban Population Study (CUPS No. 5) was designed to assess the prevalence of CAD in urban Chennai and its relation with risk factors, especially lipids. The subjects included 1262 individuals >20 years of age, who underwent evaluation for diabetes, hypertension, obesity, lipids and CAD, using standard diagnostic criteria. CAD (for prevalence purposes) was diagnosed on the basis of an abnormal 12-lead ECG (Minnesota codes), medical records and drug treatment for CAD (aspirin or nitrates). The overall prevalence of CAD was 11.0%. The age-standardized prevalence rate of overall Q wave abnormalities among men was 2.1% while in women it was 1.3%. However, documented MI or the presence of ST changes or Q waves on a 12-lead ECG were used for defining CAD for analysis of risk factors. Documented CAD was associated with older age, body mass index (BMI), waist circumference, waist-hip ratio, systolic and diastolic blood pressure and hypertension on univariate analysis. There was a highly significant linear correlation between CAD and serum cholesterol levels from \(<4.0\) mmol/L to \(>7.0\) mmol/L \((p<0.001)\), LDL-cholesterol \(<3.0\) to \(>5.0\) mmol/L and triglyceride (TG) levels \(<1.0\) mmol/L to \(>3.0\) mmol/L \((p=0.002)\). CAD was also more prevalent in those with impaired glucose tolerance (14.9%) and diabetes mellitus (21.4%) compared to those with normal glucose tolerance (9.1%). On multiple regression analysis, only age and LDL-cholesterol had a significant association with CAD.

Comments

The overall prevalence of CAD (though including nonspecific T wave changes) was 11%, which is similar to the 7%-17% prevalence in migrant Indians. This reflects a 10-fold increase in the prevalence of CAD in urban Indians over the past 40 years. Most traditional risk factors had a significant association with CAD, with the exception of HDL-cholesterol and smoking. This is probably because of the low sample size. Though there was no direct relation with HDL, it was confirmed that HDL levels are lower in Indians as has been seen in earlier studies also. This could be responsible for the increased risk despite the relatively modest elevation of LDL levels. Further, elevation in TG levels did not correlate with CAD on multiple regression analysis, which has earlier been found to have a strong association in studies in migrant Indians. Our data are supported by findings from the Multiple Risk Factor Intervention Trial (MRFIT) and 3 other recent studies, showing no significant correlation of TG levels over and above serum cholesterol levels. Other risk factors like lipoprotein (a) and homocysteine levels were not checked in this study. Another interesting finding is the relatively low waist circumference (80.2 cm) and BMI (24.0) found in even those with CAD.

Study limitations included the small sample size and the methods used to diagnose CAD. ECG abnormalities included T wave changes, which are nonspecific. Further, these were more commonly found in females, who are often known to have nonspecific T wave abnormalities. Mortality records were not checked, which could have provided a more complete picture. The use of antihypertensive drugs could have confounded the correlation of hypertension with CAD, which is otherwise well established. Another risk factor that is well established but found to be insignificant in this study is smoking. All these are probably due to the small sample size and case selection from only one city. The same investigators are planning to conduct a larger study (>50 000 individuals), which should give a better idea about the actual prevalence of CAD and its relationship with various risk factors.

However, the findings of this study highlight the dramatic rise in CAD events over the past two decades owing to the change in lifestyle, and is now approaching the prevalence of CAD in migrant Indians. Urgent steps in lifestyle modification need to be adopted to control these risk factors and bring this epidemic of CAD under control.
Summary

The Valsartan Heart Failure Trial (Val-HeFT) is a multicentric, randomized, placebo-controlled, double-blind, parallel-group trial designed to evaluate the long-term effects of the addition of an angiotensin-receptor blocker (ARB) to standard therapy for heart failure. In this trial, 5010 patients with heart failure with a documented left ventricular ejection fraction (LVEF) of less than 40%, who were in NYHA class II–IV, were randomized to receive either 160 mg of valsartan or placebo twice daily. The primary outcome measures were mortality and a combined endpoint of mortality and morbidity. Morbidity in this study was defined as resuscitated cardiac arrest, hospitalization for heart failure or treatment with intravenous inotropes or vasodilators for more than four hours. Patients were followed up for a mean of 23 months.

At two years, there was no significant difference in mortality between the patients who received valsartan (19.7%) and those who received placebo (19.4%). There was, however, a significant 13.2% reduction in the combined end-point in the group treated with valsartan (p=0.009). This was largely because of the 24% lower hospitalizations in the valsartan group (13.8% v 18.2%, p<0.001). Treatment with valsartan also resulted in significant improvement in NYHA class, ejection fraction, signs and symptoms of heart failure and quality of life. The occurrence of the primary end-points was also studied in the sub-groups defined post-hoc according to baseline treatment with angiotensin-converting enzyme (ACE) inhibitors or beta-blockers. At the time of randomization, 93% of patients were receiving ACE inhibitors and 35% were on beta-blockers. Although the addition of valsartan had a favorable effect in patients receiving neither or one of these types of drugs, there was a significant adverse effect on mortality in the subgroup of patients who were already on both ACE inhibitors and beta-blockers. Valsartan therapy was well tolerated requiring withdrawal in only 9.9% in treatment group versus 7.2% in placebo group.

Comments

It is believed that ARBs might circumvent the problem of incomplete suppression of the renin–angiotensin–aldosterone system by ACE inhibitors alone. They have also been shown to reduce the incidence of bradykinin-related adverse effects (cough and angioedema) associated with ACE inhibitors. The initial studies using ARBs were designed primarily to determine if they were better tolerated than ACE inhibitors. The unexpected reduction in all-cause mortality detected in the ELITE study, however, triggered the initiation of a series of trials, which were designed to detect differences in mortality. Val-HeFT is the largest trial evaluating the influence of ARBs on mortality in patients with heart failure. The study found that the addition of valsartan at a dose of 160 mg twice a day to a standard treatment regime for heart failure did not result in any survival benefit. There was a 3.3% absolute reduction in the combined end-point, which was largely driven by the 4.4% absolute reduction in the rate of hospitalization for heart failure (number needed to treat to prevent the occurrence of the combined end-point: 30). This benefit is much smaller in magnitude compared to that produced by the addition of beta-blockers, particularly in the absence of any survival benefit. In this context, it is pertinent to note that only about 35% of the patients in the standard treatment group were receiving beta-blockers and only about 5% were on spironolactone, both of which have unequivocally been shown to reduce mortality in heart failure. Of much more concern is the increase in mortality observed when valsartan was given to patients already on ACE inhibitors and beta-blockers—the current standard of care. Whether this represents a true interaction or is due to chance will only be known once the results of the ongoing ARB trials become available. It therefore appears that patients with CHF would be better off if we aimed at giving beta-blockers and spironolactone to the majority. Further, patients who are already on beta-blockers for heart failure should not be prescribed ARBs till (and if) the safety of this group of drugs is established in this setting in the ongoing trials.
Randomized Trial of a Perindopril-Based Blood Pressure-Lowering Regimen Among 6105 Individuals with Previous Stroke or Transient Ischemic Attack


Summary

The Perindopril Protection against Recurrent Stroke Study (PROGRESS) was designed to determine the effects of a blood pressure-lowering regimen of perindopril in patients with a history of stroke or transient ischemic attack (TIA). It was a prospective, randomized, double-blind, multicentric study, which recruited 6105 individuals with a history of stroke or TIA from both eastern and western populations. The patients were both hypertensive and normotensive and were enrolled early or late after their qualifying cerebrovascular event, whether ischemic or hemorrhagic in origin; thus a wide spectrum of patients were included. Active treatment consisted of a flexible regimen based on perindopril (4 mg daily) with the addition of the diuretic indapamide at the discretion of the treating physician, but specified at the onset of the study. The primary end-point was total stroke (fatal or nonfatal), whereas secondary end-points were total major vascular events (nonfatal stroke, nonfatal myocardial infarction (MI) or death due to any vascular cause), total and cause-specific death, and hospital admissions. Baseline characteristics were similar in both the groups. On follow-up of over 3.9 years, active treatment reduced the blood pressure by 9/4 mmHg. This blood pressure reduction translated into a relative risk reduction of 28% (95% CI: 17–38, p<0.001) in the stroke rate [307 strokes (10%) in the active treatment group as compared to 420 (14%) in the placebo group]. Active treatment also reduced the risk of total major vascular events by 26% (95% CI: 17–38, p<0.0001) in the stroke rate [307 strokes (10%) in the active treatment group as compared to the placebo group]. Active treatment also reduced the risk of total major vascular events by 26% (95% CI: 16–34), nonfatal MI by 38% and death from coronary artery disease by 6%. These reductions were consistent irrespective of the hypertensive status of the patients or type of stroke. There were fewer hospital admissions in the treated group but no significant difference in total deaths or deaths from vascular or nonvascular causes. Combination therapy with perindopril and indapamide led to an even greater reduction in the blood pressure (12.3/5 mmHg) and stroke risk (43%, 95% CI: 30–54). Although single-drug therapy with perindopril was able to reduce the blood pressure (4.9/2.8 mmHg), it was unable to reduce the risk of stroke (only 5% reduction, 95% CI: 19–23). Overall, the drugs (perindopril and indapamide) were well tolerated. There were only 2% more withdrawals from active drugs compared to placebo over a mean follow-up of 3.9 years. The main reasons for discontinuation in the active arm as compared to the placebo arm were cough (2.7% v. 0.4%) and hypotension (2.1% v. 0.9%). The authors concluded that perindopril and indapamide therapy should be routinely considered for patients with a history of stroke or TIA irrespective of the baseline blood pressure.

Comments

As of date, diuretics and beta-blockers are considered first-line agents in the management of hypertension, despite their unfavorable effects on glucose tolerance and lipid profile. This is due to the fact that they are not only able to reduce the risk of cardiovascular and cerebrovascular events but also actually decrease mortality. Other antihypertensive agents have not shown any reduction in mortality, probably because of the small sample size of their study populations. Recently, a lot of interest has been generated regarding the use of angiotensin-converting enzyme (ACE) inhibitors following the publication of the HOPE trial results, which showed a marked reduction in coronary events and progression of renal disease with ramipril therapy. It also showed a large reduction in the risk of stroke. However, the HOPE trial was not primarily designed to study the effect on stroke. Currently, management of thrombotic stroke involves antiplatelet therapy, anticoagulants, carotid endarterectomy and antihypertensives, wherever applicable. However, no treatment has yet been proven useful in reducing the risk of stroke among patients with a history of cerebral hemorrhage. In the present study, the PROGRESS collaborators have shown that over and above the usual medications used in these patients, therapy with perindopril and indapamide was effective in reducing the risk of stroke and other vascular and coronary events irrespective of ethnicity, duration of stroke, type of stroke and blood pressure levels. The effects on reduction of stroke and coronary events were similar to that shown by ramipril in the HOPE study. Perindopril therapy was found to be safe with good compliance. However, the therapy failed to show any mortality benefits (either total mortality or mortality related to vascular complications). Therefore, therapy with perindopril and perhaps other ACE inhibitors along with the diuretic indapamide should be routinely instituted in patients with a history of stroke or TIA.
Summary
The effect of chelation therapy using the EDTA protocol on exercise and quality of life parameters in patients with stable coronary artery disease were studied in this randomized, double-blind, placebo-controlled trial. The study enrolled 84 subjects with coronary artery disease (proven by angiography or a documented myocardial infarction) and stable angina while receiving optimal medical therapy. All the patients had a positive treadmill test performed prior to enrolment in the study. Patients were randomized to receive either chelation therapy (weight-adjusted EDTA infusion at a dose of 40 mg/kg) or placebo infusions for 3 hours per treatment, twice weekly for 15 weeks and once a month for an additional 3 months. Patients in both groups were also given high-dose oral multivitamin therapy. Both the groups were able to significantly increase their exercise time to ischemia on the treadmill at the 27th week after initiation of drug/placebo (54 s, 95% CI: 23–84 s; p<0.001 in the placebo group and 63 s, 95% CI: 29–95 s, p<0.001 in the chelation therapy group). The difference was, however, not statistically significant between the EDTA chelation therapy and placebo groups (9 s; 95% CI: 36–53 s; p=0.69). Exercise capacity and quality of life scores improved by a similar degree in both the groups. One patient receiving EDTA had a transient increase in serum creatinine. Based on these results, the authors concluded that there is no evidence to support a beneficial effect of chelation therapy using EDTA in patients with stable coronary artery disease and a positive exercise treadmill test.

Comments
End-stage ischemic coronary and peripheral vascular disease is difficult to treat. In general, these patients are refractory to conventional drug therapy and not amenable to either angioplasty or surgery. Therefore, many of these patients continue to seek alternative therapy, even without definite scientific proof. Chelation therapy, a programme of repeated intravenous administration of EDTA together with vitamin supplementation, has also been promoted as an effective alternative treatment. EDTA is an amino acid complex with high affinity for divalent or trivalent cations. Intravenous infusions of EDTA may help chelate lead, iron, copper and calcium, implicated in the complex pathogenesis of an atheromatous plaque. Pathophysiological mechanisms proposed for its beneficial effect also include a free radical scavenging function, inhibition of lipid oxidation, reduction of total body iron stores, cell membranestabilization, arterial dilatation and prostacyclin production. Several anecdotal case reports and small uncontrolled trials have shown favorable results. However, none of the randomized controlled trials conducted in those with ischemic peripheral vascular disease have shown favorable results. There is even less evidence for the use of this therapy in coronary artery disease. Despite this fact, more than 500 000 patients are treated with this therapy every year and, till date, over 6 million chelation treatments have been delivered in the USA alone. Randomized clinical trials that have produced negative results have been criticized for several methodological errors, insufficient numbers and confounding variables. For instance, many studies were not truly blinded, patient compliance to lifestyle modification, particular cessation of smoking, was not very good, patients were given oral iron therapy (which binds to EDTA) in some studies. More importantly, in many of the earlier studies, magnesium, manganese, zinc, copper, pyridoxine and many other essential nutrients which are removed by EDTA, were not replaced. On the other hand, in one of the positive studies of chelation therapy, the beneficial effect was suspected to be due to intravenous multivitamin therapy given to the chelation therapy group only. The present study, which has taken into account all of these confounding variables, conclusively shows that the use of chelation therapy to increase ischemic threshold and to improve the quality of life is of no benefit in patients with stable coronary artery disease.