Primary Pulmonary Hypertension—An Update

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Primary pulmonary hypertension (PPH) is a mysterious, fascinating but serious disorder. In many parts of the world, the therapeutic options for patients with PPH have been severely limited in the absence of prostacyclins, and physicians often have “a benign neglect” for the disease. However, tremendous progress has been made in the understanding and the treatment of PPH in the past decade or so.

In this review, we briefly recapitulate the salient aspects of the mechanisms and management of PPH.

Pathobiology of PPH

The histopathology of PPH is not unique. In the 1998 World Health Organization (WHO) symposium, several disorders causing pulmonary arterial hypertension (PAH) were grouped under category I based on similar morphology and therapeutic approaches. These include PPH, PAH secondary to congenital shunt lesions, connective tissue disorders, portal hypertension, drug-induced PAH and human immunodeficiency virus (HIV)-related PAH.1

The pathological alterations in PPH are widespread and involve endothelium, smooth muscle cells, connective tissue matrix and adventitia mainly of the precapillary pulmonary arterioles of size 400–1000 µm.2 The concept of PPH as a disease of vasoconstriction has been replaced by a disease of growth dysregulation resulting in proliferative and obliterator changes in the pulmonary vasculature. In the pathogenesis of PPH, vasoconstriction (or lack of vasodilatory influences), growth promoting substances (or lack of apoptotic stimuli), hemodynamic stress, in situ thrombosis and inflammation may initiate or perpetuate the injury and result in the full-blown pathoanatomy of PPH that finally leads to right ventricular hypertrophy and failure.3 The remarkable finding that endothelial cell proliferation in the plexogenic arteriopathy of PPH (but not in the secondary forms of PAH) is a monoclonal expansion akin to tumorlets emphasizes the importance of dysregulated growth as a primary abnormality.4 The discovery of mutations in the BMPR-2 (bone morphogenetic protein receptor-2) genes in a number of patients with familial PPH is highly significant.5 Similar mutations have been found in nearly 26% of sporadic PPH as well.6 These genes code for the transforming growth factor-β (TGF-β) receptor that eventually, through cascades of specific regulatory signals, controls cell differentiation and proliferation/apoptosis. However, everyone with these mutations does not develop PPH. Clearly, much more remains to be understood regarding the manner by which BMPR-2 mutations induce the disease. Further, the realization that established changes of PPH can sometimes regress has provided impetus to explore the mechanisms of regression.7 In experimental settings, the pathological changes of PAH, induced by monocrotaline alkaloid in rats, completely disappeared by serine elastase inhibitors.8 The serine elastase may be produced from dysfunctional endothelium or smooth muscle cells and these may initiate changes in the connective tissue matrix leading to smooth muscle cell proliferation and fibrosis.7 Significantly, the pathological changes also regressed following hemodynamic unloading (by transplanting the diseased lung into a healthy rat).9 This observation underscores the importance of hemodynamic stress perpetuating the damage and nature’s healing abilities. The occurrence of PPH in a minority of patients using appetite-suppressant drugs10 (that inhibit serotonin uptake), and the observation of PPH in a rare platelet storage disorder11 focussed attention on serotonergic transport system abnormalities in the pathogenesis of PPH, perhaps working through voltage-gated potassium channels. Similarly, abnormalities in the hemostatic system, endothelin and other mediators of inflammation, and a host of other mechanisms are under intense scrutiny for their involvement in the pathogenesis of PPH.1 These discoveries have offered newer insights into the mysteries of PPH, but much remains to be understood.

Treatment of PPH

General measures: Advise regarding diet, exercise, avoiding infection and thromboembolism, anesthesia, pregnancy, air travel, etc. need special and individualized attention.

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Diet: A diet rich in L-arginine may lead to nitric oxide (NO) synthesis, but this has not been adequately studied. In a small study, supplementation of L-arginine for 1 week improved hemodynamics and exercise capacity in patients with PAH.12

Supplemental oxygen: Routine home oxygen therapy for patients with PPH is not recommended. Supplemental oxygen may be useful during episodes of acute hypoxia, e.g. infection. Some patients may have a nocturnal dip in oxygen saturation without hypoventilation;13 such patients may benefit from oxygen therapy. During air travel, a mild degree of hypoxia occurs which is well tolerated by most people, but may cause additional hypoxic pulmonary vasoconstriction in PPH patients and may require in-flight supplemental oxygen.14

Contraception: The risks of currently available low-estrogen contraceptive pills are much lower than those previously reported. These drugs may be used (if other methods of contraception are not feasible), rather than risk an unwarranted pregnancy in a patient with PPH.

Inotropic support: For short-term acute intervention, dobutamine or milrinone is preferred. The role of digoxin, used routinely in patients with heart failure and is probably beneficial. Diuretics need to be judiciously used as the hypertrophied right ventricle is markedly preload dependent.

Anticoagulation: The evidence that anticoagulants are beneficial in patients with PPH is not large,16,17 but the physiologic rationale is strong. Thrombi in the lungs were seen in nearly half of the patients dying from PPH.16 The survival rates at 3 years in patients using anticoagulation were 49% compared to 21% in controls in a retrospective analysis,16 and were 47% compared to 31% in a small prospective study.17 There is no unanimity regarding the optimal degree of anticoagulation. An INR of 1.5–2 is recommended by many,1 but perhaps an INR of about 2–2.5 appears more reasonable.14 In patients with a past history of mild hemoptysis, an INR of 1.5–2 may be appropriate, but patients with a history of life-threatening hemoptysis cannot be anticoagulated. There are no studies evaluating the efficacy of antiplatelet therapy in PPH even though platelets have a role in the pathogenesis of PPH.

Calcium-Channel blockers

Despite years of recommendations, calcium-channel blockers (CCB) are often not optimally utilized. Only 20% of adults17 and up to 40% of children18 may respond to vasodilator therapy with high-dose CCB. Unfortunately, the responders cannot be identified by the duration or severity of symptoms or other resting hemodynamic variables, but must be identified by acute hemodynamic drug testing (as showing >20% decline both in pulmonary vascular resistance and mean pulmonary artery pressure with the intervention). Empirical therapy in nonresponders is not only futile, but may also be life-threatening. And half-hearted therapy in responders may possibly deny them the only chance of halting the progression of the disease by employing the full dose of CCB.17,18 Acute drug testing with CCB has resulted in adverse reactions including death in a number of nonresponders, and should be abandoned.19 Alternatively, NO inhalation (10–40 ppm with a face mask for 7–10 min) has been found to be safe and predictive of response to long-term, high-dose CCB therapy. Nitric oxide testing had 90% sensitivity and 100% specificity in identifying the responders in small studies.19 Intravenous adenosine20 (50–500 µg/kg/min) and inhaled iloprost21 (17 ng aerosolized iloprost) have also been used for acute vasodilatory response. A marked fall in mean pulmonary artery pressure (>50%) with acute vasodilatory testing indicates a good prognosis. Such patients have a very low mortality with long-term CCB and may be cured with these drugs.17 Other patients may lose reactivity with time. Whether the responders are a different subset of PPH patients, or merely represent an early stage of the disease has not been adequately understood. High doses of CCB (up to 240 mg nifedipine, 900 mg of diltiazem) have been utilized. More recently, up to 40 mg amlodipine has also been used.22 Amlodipine may be preferred as it also has antiproliferative effects and fewer negative inotropic effects. Our own preliminary observation favors the use of amlodipine over nifedipine;23 however, larger studies are required.

Prostacyclins

Continuous intravenous prostacyclin I₂ (epoprostenol) infusion by an indwelling catheter and a venous pump has been widely discussed. Its use improves symptoms, hemodynamics and mortality.24 Long-term benefits are seen even when there are no acute hemodynamic effects (nonresponders). The mechanisms of favorable influence relate to the vasodilatory, platelet antiaggregatory and antiproliferative properties of prostacyclins, and possibly also due to a host of other effects such as endothelin clearance and positive inotropic effects. The estimates of 1-, 2-, and 3-year survival rates for patients treated with epoprostenol were 87%–93%, 72%–76%, 62%–65%.
respectively, compared to 77.4%, 51.6% and 40.6% in a similar group of conventionally treated patients in the NIH registry data.\textsuperscript{24} The benefits were higher in sicker patients. Currently, epoprostenol is considered for patients in NYHA class III or IV despite maximal conventional treatment, as the treatment is expensive (US$ 60 000/year), cumbersome and is associated with adverse effects. Epoprostenol doses were reported to range from 0.5 to 270 ng/kg/min, but 22–45 ng/kg/min appears optimum.\textsuperscript{25} The problems of venous thrombosis, sepsis, acute decompensation following the cessation of therapy and drug tolerance requiring increasing dosages underlie the need for simpler methods of delivery or alternative modes of treatment. Unfortunately, this treatment is not available in India, but in the next few years continuous epoprostenol infusion would be of historic interest only, as stable analogs are being developed that can be used by subcutaneous, inhalation, or oral routes.

**Subcutaneous treprostinil:** A stable analog of prostacyclin, treprostinil (UT-15) is available for subcutaneous infusion by a minipump, akin to the one used for insulin. In view of serious central venous catheter-related problems, subcutaneous infusion is preferred. Transition from epoprostenol to treprostinil therapy is reported in some cases.\textsuperscript{26} However, comparative data on efficacy are not available. In a large, placebo-controlled trial involving 470 patients with PAH,\textsuperscript{27} modest improvement in 6-min walk test (±17 m) and in hemodynamics was seen at 3 months. There was no mortality benefit during the short study period. Patients receiving >13.8 ng/kg/min had greater improvement in exercise performance. Local site pain was common (85%), but rarely necessitated drug withdrawal (8%).\textsuperscript{27}

**Iloprost**

Iloprost, a stable carbacyclin analog of PGI\textsubscript{2}, is available for intravenous or aerosolized administration. The experience with intravenous use is limited and similar to epoprostenol. Inhaled iloprost is a potent pulmonary vasodilator that improves cardiac output and exercise capacity.\textsuperscript{21,28,29} In an acute study of 35 patients with PPH, nebulized iloprost led to significant reduction in mean PA pressures (–8.3 mmHg) and pulmonary vascular resistance (–477 dynes/sec/cm).\textsuperscript{31} This was similar to the effect of intravenous prostacyclins but with fewer side-effects. Inhaled iloprost appeared superior to inhaled NO (40 ppm) in reducing pulmonary vascular resistance.\textsuperscript{31} A European, multicentric, randomized, placebo-controlled trial of 203 NYHA class III and IV patients with PAH (AIR study) showed that there was improvement in functional class in 17% of patients receiving iloprost compared to 4% in the placebo group.\textsuperscript{30} The 6-min walk test distance improved by 57 m in patients with PPH. Some other studies have been less encouraging.\textsuperscript{31} Longer-term data are awaited. The main drawback, however, is that inhalations are required 6–12 times daily, significantly restricting the quality of life. More recently, the combination of inhaled iloprost with phosphodiesterase (PDE) inhibitors has been shown to improve efficacy and prolong the effects of the drug.\textsuperscript{32}

**Oral Beraprost**

An orally active prostacyclin was eagerly awaited. Beraprost sodium is one such stable analog currently available in Japan and Germany for the treatment of PPH. The drug is well tolerated and is associated with minor side-effects. The dose is gradually increased from 20 µg (three to four times) and the usual required dose is 80 µg four times daily. A mortality benefit was reported in an uncontrolled study.\textsuperscript{33} Two recently concluded placebo-controlled trials showed clinical benefits after 12 weeks of therapy.\textsuperscript{34,35} In the larger trial involving 130 patients with PAH and in NYHA class II or III, symptomatic improvement in dyspnea and improvement in the 6-min walk test (+25 m) were seen in the treated patients. On the basis of current experience, beraprost should be used in relatively stable patients with NYHA functional class II or early class III status.\textsuperscript{35}

It needs to be emphasized that comparative studies among these prostacyclins or different modes of administration are not available. Mortality benefits with the newer agents are yet to be ascertained. The decision in individual patient is guided by many clinical factors, for example, oral beraprost and subcutaneous treprostinil may take several weeks for clinical response as the dose is built up. Inhaled iloprost may be a preferred agent in NYHA class IV patients, but may not always be effective. Epoprostenol is still the gold standard of therapy for PPH.

**Inhaled Nitric Oxide**

Nitric oxide (NO) leads to systemic and pulmonary vasodilatation through cGMP-mediated pathways.\textsuperscript{16} Inhaled NO has selective pulmonary effects and is remarkably safe as an acute pulmonary vasodilator.\textsuperscript{19} Inhaled NO has been successfully used in postoperative pulmonary hypertensive crisis and in persistent pulmonary hypertension of newborns.\textsuperscript{17} Long-term inhaled NO therapy for PPH has rarely been reported.\textsuperscript{38} In an uncontrolled pilot study, inhaled NO was used with nasal
cannulae and a gas pulsing device. Improvement in cardiac output and PA pressures was seen in 3 out of 5 patients over 12 weeks. One patient has continued NO over 5 years with near normalization of pulmonary hemodynamics.\(^{17}\) Yet, inhaled NO is not widely used. The sophisticated delivery system it needs is not usually available. Moreover, physiologic considerations indicate that NO is a double-edged sword. Higher concentrations of NO generate highly reactive toxic metabolites that may worsen or perpetuate vascular damage.\(^{36}\) As such, the efficacy of long-term inhaled NO therapy in PPH needs to be established.

**Endothelin Receptor Antagonists**

Endothelin, a vasoconstrictor and a pro-proliferative polypeptide, is implicated in the pathogenesis of a number of experimental PAH, and also in PPH in humans.\(^{19}\) Increased endothelin 1 expression and increased endothelin production in the lungs have been found in PPH patients. Accordingly, endothelin receptor antagonists have been evaluated in the treatment of PPH. The nonselective endothelin antagonist bosentan, which inhibits ET\(_A\) and ET\(_B\) receptors, can be orally administered and causes pulmonary and systemic vasodilatation. Recently, two placebo-controlled trials using bosentan in PAH have been completed.\(^{40,41}\) In the larger trial involving 213 patients of either PPH or PAH with connective tissue disease and in NYHA class III, bosentan was used for 4 months.\(^{41}\) The 6-min walk distance improved in treated patients (+44 m) compared to those given placebo. Functional class, dyspnea and time to clinical worsening also improved. The optimal dose was found to be 125 mg twice daily. Hepatic enzyme elevation was seen in 14% of patients, especially with the higher dose. Anemia was rarely seen. Based on these results, the FDA has approved bosentan for the treatment of PPH. It appears that bosentan would be used as a first-line therapy in class II or early class III patients as it is orally effective. Longer-term results are awaited. The selective ET\(_A\) receptor blocker, sitaxsentan has been also shown to be beneficial in a small trial, but fatal acute hepatitis was reported in one patient.\(^{42}\)

**Phosphodiesterase Inhibitors**

Phosphodiesterases (PDEs) are responsible for the tissue levels of the cyclic nucleotides cAMP and cGMP. The vasodilatory effects of prostacyclins and NO are mediated via cAMP and cGMP, respectively.\(^{41}\) Consequently, PDE inhibition may potentiate the effects of prostacyclins and NO. There are at least 11 isoymes of PDE with different affinities and tissue selectivities in mammals. PDE-3 and -4 are involved in the breakdown of cAMP metabolism, and PDE-5 for cGMP, but cross-talk between cAMP and cGMP metabolism occurs. Thus inhibitors of PDE-3 and -4 prolonged the effects of nebulized PGI\(_2\) in experimental models.\(^{44}\) Perhaps the most interesting has been the remarkable success of selective PDE-5 inhibitors such as sildenafil in the treatment of PAH.\(^{45-49}\)

PDE-5 is abundant in the lungs and in the corpora cavernosa, the PDE-5 inhibitor sildenafil has been shown to prolong the effect of iloprost\(^{42}\) and attenuate NO withdrawal.\(^{46}\) Anecdotal case reports\(^{45,47}\) and small series\(^{48,49}\) have reported the salutary effects of sildenafil on symptoms and exercise performance, which are comparable to those of the prostacyclins. The drug has been well tolerated without significant side-effects. Concerns about retinal toxicity (the retina contains PDE-6) remain. Situations causing increased NO levels (e.g. sepsis) may also pose problems. The terminal half-life of sildenafil is 3–4 h, and the dose used has been varying but 75–150 mg daily appears reasonable. However, controlled trials or longer-term mortality data are not yet available. Other PDE inhibitors with selective pulmonary effects are being searched.

**Balloon Atrial Septostomy**

Balloon atrial septostomy is helpful in patients of PPH with recurrent syncope or moderate right heart failure despite treatment.\(^{50}\) The mechanisms by which favorable effects occur are not completely clear, but relate to increased cardiac output (especially during exercise), decreased systemic venous congestion and improved coronary perfusion to the right ventricle. It is recommended that the procedure should be done at centers experienced in treating patients with severe PAH. Further, the septostomy should not be done in patients with a right atrial mean pressure >20 mmHg, pulmonary vascular resistance >55 Wood units, or impending death.\(^{50}\) The procedure-related mortality is substantial but recent advances in the ability to perforate the septum safely with a radiofrequency catheter may reduce the risks. In parts of the world where prostacyclins are not available, balloon atrial septostomy should be utilized more often.\(^{51}\)

**Lung Transplantation**

Lung transplantation for PPH is the last resort. Fortunately, the need for it has decreased following prostacyclin therapy, and the need should further reduce with advances in
medical therapy. The results of lung transplantation for PPH are sobering. The 1- and 3-year survival rates of transplantation for PPH are 65% and 55%, respectively. The results of single-lung, double-lung or heart–lung transplantation have been similar. Follow-up care is tedious and resource-intensive, marked by frequent infections and rejection episodes. Even so, transplant recipients feel that the efforts are worthwhile. No case of lung transplantation for PPH has yet been published from India. Partial-lobe transplant from live-related donors may improve the results further and may be guided by gene testing.

Further, the concept of hemodynamic unloading causing regression of pulmonary hypertensive changes (akin to the Batista II procedure) awaits appropriate testing. The results of single-lung, double-lung or heart–lung transplantation have been similar. Follow-up care is tedious and resource-intensive, marked by frequent infections and rejection episodes. Even so, transplant recipients feel that the efforts are worthwhile. No case of lung transplantation for PPH has yet been published from India. Partial-lobes transplant from live-related donors may improve the results further and may be guided by gene testing.

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Further, the concept of hemodynamic unloading causing regression of pulmonary hypertensive changes (akin to the Batista II procedure)54 awaits appropriate human application in PPH.

**Miscellaneous**

Progress on several fronts has opened up new vistas of research and treatment. Several other forms of therapy are being explored in experimental and human PAH. Serine elastase inhibitor, thromboxane synthesis inhibitors, adrenomedullins (a vasodilatory peptide), potassium-channel openers, inhalational heparins, are only some of the examples of ongoing research. Several paradigms of gene therapy are being explored in experimental PAH, even though it may be a while before these become clinically feasible. In a nutshell, this is a very exciting time for those involved with the management of patients with PAH.60

**References**


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Renal Artery Stenosis: Diagnosis and Management

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Renal artery stenosis (RAS) may lead to hypertension, fluid retention, progressive renal failure and flash pulmonary edema. Although due to isolated fibromuscular dysplasia (FMD) in a few young patients, atherosclerosis is the major cause of this disease and affects predominantly older patients. In this older group, atherosclerotic renovascular disease (ARVD) is only one element of a multisystem disease and patients usually present with established coronary, peripheral and cerebral vascular disease. The improved survival of these patients, together with the increasing indications for angiotensin-converting enzyme (ACE) inhibitors [or angiotensin II receptor blockers (ARB)] which may adversely affect renal function in RAS, has focused efforts on optimizing the diagnosis and management of patients with ARVD. The purpose of this review is to discuss current clinical practice in the diagnosis and management of RAS.

Fibromuscular Dysplasia

Clinical features: Fibromuscular dysplasia is more common in females less than 40 years of age, although it has been reported from infancy to old age. Clinical features include the presence of an abdominal bruit and the loss of a nocturnal dip in the 24-hour blood pressure record, which is suggestive of secondary hypertension. The diagnosis should be considered and excluded in any young person presenting with severe hypertension in the absence of a family history, in whom treatment of an underlying RAS may cure the hypertension. Fibromuscular dysplasia should be excluded in young persons presenting with carotid artery dissection or occlusion.

The natural history of FMD is variable and not necessarily benign. Although Pohl and Novick reported disease progression in 33% of 66 patients with FMD, no stenosis progressed to complete occlusion and there was no clear association with renal atrophy. However, Goncharenko et al. reported 42 patients (50% male) with angiographic evidence of progressive disease followed up for 4–136 months. In this study, 25% of affected arteries developed total occlusion and 62% of affected kidneys atrophied (>0.5 cm reduction in renal length). Generally FMD affects the mid- or distal (rather than proximal) renal artery and may be associated with branch stenoses (Fig. 1). However, in contrast to ARVD, the renal microcirculation is normal and therefore progressive renal atrophy is due to hemodynamically significant proximal arterial stenosis which needs to exceed 75%–80%. The presenting features of FMD and ARVD are given in Table 1.

Table 1. Presenting features of FMD and ARVD

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<th>FMD</th>
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<td>Early onset of severe hypertension with loss of diurnal variation</td>
<td>Hypertension</td>
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<td>Deterioration of renal function</td>
<td>Rise in creatinine following introduction of ACE inhibitor or ARB</td>
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<td>“Flash” pulmonary edema</td>
<td>Progressive renal failure</td>
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<td>Proteinuria</td>
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Pathogenesis of hypertension in unilateral and bilateral RAS: In unilateral disease, perfusion of the stenosed kidney is reduced, leading to activation of the renin–angiotensin–aldosterone (R–A–S) system. Angiotensin II-dependent hypertension results in a pressure natriuresis and suppressed R–A–S activity in the contralateral kidney. In bilateral disease, there is bilateral activation of renal R–A–S with volume expansion, which ultimately leads to feedback inhibition of R–A–S. Thus, plasma renin activity (PRA) should be increased in unilateral disease but normal or reduced in bilateral disease. In routine clinical practice, diagnostic renal vein sampling for PRA is of limited value.

Pathology: Eighty-five percent of cases of FMD are due to medial fibroplasia which tends to affect females, with the remainder due to periarterial or intimal fibroplasia. Other than an association with cigarette smoking, the pathogenesis remains uncertain but mural ischemia may result from functional defects in the vasa vasorum, possibly in association with developmental renal malposition.

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Atherosclerotic Renovascular Disease

Clinical features: Atherosclerotic RAS (ARAS) should be suspected in patients with resistant hypertension, renal asymmetry, unexplained acute (“flash”) pulmonary edema, a rise in creatinine (and very rarely acute renal failure) following the introduction of an ACE inhibitor or ARB. However, ARVD may also present with progressive renal insufficiency, proteinuria and even nephrotic syndrome. The risk factors for ARVD include age, female gender, smoking and those diseases which predispose to systemic atherosclerosis including hypertension, diabetes mellitus and hypercholesterolemia. Significant ARVD with stenosis exceeding 50% is present in 35% of elderly patients with heart failure, 20%–35% of patients with aorto-iliac disease, 15%–40% of patients with peripheral vascular disease and 5%–20% of patients with coronary artery disease.7 Atherosclerotic renovascular disease is bilateral in about one-third of cases and usually involves the proximal ostial renal artery with contiguous aortic plaques (Fig. 2).

Clinical features include a wide arterial pulse pressure, which reflects loss of arterial compliance; bruits over the renal and other major arteries; absent or weak popliteal and pedal pulses; and a reduced ankle–brachial pressure index.

Flash pulmonary edema usually occurs in association with acute hypertension, possibly with salt and water retention, and in the absence of an acute coronary event, although most patients have ischemic heart disease.7

Proteinuria and frank nephrotic syndrome due to biopsy-proven focal and segmental glomerulosclerosis can be the presenting complaint in ARVD.5,9 The pathogenesis is not known but may involve embolization of cholesterol crystals, platelet thrombi and other debris into the glomerular microcirculation.

Pathology: Although ARVD is progressive, only 3%–16% of stenoses progress to complete occlusion, as seen in longitudinal studies. Renal atrophy is present in 20% of kidneys with a stenosis which exceeds 60% and progressive stenosis is associated with progressive atrophy; however, atrophy may also develop in the absence of increasing stenosis. In 85 patients with ARAS who underwent repeated angiography, Schreiber et al.10 reported progression of stenosis in only 44% of kidneys, whereas renal atrophy (defined as reduction in renal length exceeding 1.5 cm) affected 70%. Three subsequent studies provide more evidence of this dissociation between progressive stenosis and renal atrophy.11–13 These data imply that progressive parenchymal injury and renal dysfunction is not solely due to the hemodynamic consequences of stenosis.

Depending on their stability, the surface of atherosclerotic plaques are a site for thrombogenesis and a source for platelet and cholesterol emboli which may obliterate the distal microcirculation and cause tissue injury. This would explain the electron beam computerized tomography findings of diminished renal cortical blood flow in ARAS compared to FMD14 and duplex Doppler findings of bilateral abnormal renal hemodynamics in patients with unilateral ARAS.15 Further support comes from a study by Farmer et al.16 who used isotopic glomerular filtration rate (GFR) and DMSA renography to calculate individual kidney function in patients with angiographically proven ARAS. They demonstrated a significant correlation between the degree of stenosis and GFR. However, in patients with ARVD but with a stenosis demonstrated in only one kidney, there was no difference in GFR between the stenosed and nonstenosed kidneys. These studies reinforce the importance of intrarenal vascular and parenchymal disease, as well as the hemodynamic consequences of proximal RAS in the etiology of renal dysfunction in ARVD.

Takayasu’s Arteritis and Giant Cell Arteritis

Takayasu’s arteritis affects the aorta and its distal major branches. It is typically a disease of young females (10–20 years old) and is more common in Asia than in Europe. In contrast, giant cell arteritis (GCA) tends to involve the carotid artery branches of northern Europeans >50 years of age. Both conditions feature acute inflammation and subsequent fibrosis which leads to stenoses including aortic coarctation, aneurysmal dilatation and distal ischemia. Although both conditions can affect the renal vasculature, this is more common with Takayasu’s arteritis17 and can lead to severe renovascular hypertension and renal failure. Initial therapy is steroid immunosuppression which may require to be supplemented with cytotoxic therapy. Severe renovascular hypertension which cannot be controlled medically may respond to angioplasty or bypass surgery.

Antiphospholipid Syndrome

Antiphospholipid antibodies, either isolated (i.e. primary antiphospholipid syndrome) or occurring in the context of an autoimmune disease such as systemic lupus erythematosus (SLE), are associated with both arterial and venous thromboses. Histologically, there is bland intimal proliferation without evidence of vasculitis. There are a number of reports of renal artery stenosis in patients with
both primary and secondary disease. This may reflect a focal inflammatory process or an underlying predisposition to premature atherosclerosis, possibly due to a cross-reaction between antiphospholipid antibodies and oxidized low-density lipoproteins. Medical management includes treatment of the underlying disease and anticoagulation with aspirin and/or warfarin.

Transplant Renal Artery Stenosis
Renal artery stenosis may complicate renal transplantation and is a potentially curable cause of hypertension and graft dysfunction. The pathogenesis may involve atherosclerosis, an anastomotic stricture due to fibrous tissue and chronic rejection as well as kinking of the vessels leading to a functional stenosis. The incidence of stenosis is lower when an end-to-side anastomosis is formed between the donor aortic patch surrounding the renal artery origin and the recipient’s external iliac artery.

Investigation of Renal Artery Stenosis
Ultrasound and duplex Doppler: Renal asymmetry may suggest the diagnosis of RAS and reflects renal atrophy. The use of duplex Doppler increases the sensitivity of the diagnosis of stenoses which exceeds 50%. However, this test requires substantial experience and may still be unsuccessful in 20% of patients.

Captopril renography: This is a functional test which provides evidence that the GFR is angiotensin II-dependent. This may be due to significant RAS or to volume depletion, and careful patient preparation with adequate hydration is crucial to the success of this test. In a positive test, the pre-administration of oral captopril 25–50 mg delays uptake of the tracer, reduces peak uptake, prolongs parenchymal transit and slows excretion as well as affects divided function in unilateral disease. The sensitivity and specificity of this test is high in patients with renovascular hypertension. This test can also be used to predict the likelihood of benefit from intervention which is of particular importance in patients with FMD. However, the value of this test in patients with significantly impaired renal function is less clear, and there is no evidence that a positive test can be used to predict a beneficial outcome from intervention in terms of preservation of renal function. This test is widely used by clinicians to convince themselves of the safety of ACE inhibitors or ARB in an individual patient. It actually provides little additional information than a check plasma creatinine level 3–5 days after introduction of the drug.

Magnetic resonance angiography (MRA): Contrast-enhanced (gadolinium) MRA is becoming the gold standard for investigation of RAS and has virtually superseded contrast radiography with its attendant risks of contrast nephropathy and precipitation of the cholesterol emboli syndrome. Future developments will hopefully speed up the examination, reduce the claustrophobia and allow the test to provide both anatomical and functional information. There are already data to support its superiority over duplex Doppler in uremic patients with ARAS. Currently, MRA is used as a second-line test either after a positive or a negative screening test (5%–10% false negatives) when the index of clinical suspicion is high. As availability increases, it is likely that MRA will become the screening test of choice.

Renal arteriography: The role of contrast radiography with aortography and selective renal artery cannulation is being redefined. The diagnostic and prognostic information available from captopril renography and the increasing availability of MRA have reduced the use of renal arteriography as a diagnostic test, except in kidneys with intrarenal branch artery stenoses and those with complex anatomy, including multiple accessory arteries. However, this test is usually performed in patients prior to angioplasty or other intervention.

Management of Renal Artery Stenosis
Fibromuscular dysplasia: In patients with FMD, the RAS tends to be post-ostial and highly amenable to percutaneous transluminal angioplasty (PTRA). Although PTRA may completely relieve the stenosis and cure hypertension in FMD, most patients still require some antihypertensive medication, and up to 25% of patients will have restenosis after one year. The outcome with PTRA plus stenting may turn out to be better and in patients with complex stenoses, surgical intervention may be more appropriate. Patients with RAS due to FMD tend to be younger and optimum medical management of their hypertension is essential to minimize their lifetime cardiovascular risk.

Atherosclerotic Renal Artery Stenosis/ Atherosclerotic Renovascular Disease
Medical management: Management should focus on control of hypertension, management of hyperlipidemia, use of antiplatelet agents such as aspirin, cessation of smoking, and lifestyle modification including reduced dietary intake of salt and increased exercise.
**Hypertension** is usually present in patients with a significant burden of systemic atherosclerosis with characteristically wide pulse pressure and isolated systolic hypertension. The management of hypertension in ARAS may be difficult, with excessive treatment worsening renal function. There are no specific drug recommendations but regimens usually include β-blockers, calcium antagonists and diuretics (to overcome fluid retention). There are interesting data which suggest that ACE inhibitors are safe and effective in patients with ARAS; however, these drugs should be started at low doses and the renal function tested after 3–5 days, and then again after subsequent dose increments.

**Dyslipidemia** is usually present in patients with ARVD but the degree of hypercholesterolemia does not predict progression of ARAS. Although there is no specific evidence of benefit in ARVD, evidence of clear benefit in other atherosclerotic syndromes (e.g., coronary artery disease) suggests that lipid-lowering drugs should be prescribed. Statins may be particularly beneficial due to their anti-inflammatory action and capacity to stabilize unstable atherosclerotic plaques and thereby reduce embolization into the distal microcirculation.

**Revascularization:** In recent years, there has been great enthusiasm for open surgery and, more recently, interventional radiological techniques (angioplasty with or without stent deployment) in the management of ARAS. However, the real role of these interventions remains uncertain as the data which compare the benefits from intervention with optimum medical management are inadequate. Assessing the suitability of a kidney for intervention requires ultrasound measurement of length (bipolar length should exceed 8 cm) and a measure of function such as simultaneous 51Cr-EDTA GFR and 99mTc-DMSA renograms to assess divided function and allow the calculation of the single kidney GFR. In kidneys in which acute tubular necrosis has supervened (perhaps following the use of an ACE inhibitor), a renal biopsy may help to discriminate between reversible and irreversible parenchymal damage.

**Surgical procedures** range from endarterectomy to bypass and their evaluation is beyond the scope of this brief review. However, available outcome data emphasize the importance of case selection focusing on the patient’s age and systemic burden of atherosclerosis.

**Angioplasty** (PTRA) appears to improve renal function in less than 50% of cases with ARAS. Poor renal function at the time of intervention predicts poor outcome at 12 months which suggests a failure to significantly affect the underlying pathological process.

**PTRA plus stent deployment** (PTRAS) may offer a better outcome than PTRA alone. However, data from prospective randomized studies are absent (although data from the current ASTRAL trial may be available in due course) and, in reality, the increasing use of PTRAS has been driven by technological development rather than evidence-based clinical benefit.

**Conclusions**

Renal artery stenosis should be excluded in young patients presenting with hypertension, and in older patients with resistant hypertension, acute renal dysfunction induced by ACE inhibitors or ARBs and unexplained episodes of “flash” pulmonary edema. Improved access to noninvasive imaging will undoubtedly result in the diagnosis of more cases of RAS, and some rationalization in terms of the management of these patients is necessary. In FMD, positive captopril renography supports intervention although hypertension is unlikely to be cured. In ARAS, the indications for and benefits from intervention are less clear but probably include improved blood pressure control and prevention of “flash” pulmonary edema in patients with a hemodynamically significant stenosis. The evidence that intervention protects against progressive renal insufficiency is not strong and, in all cases, medical management should focus on conventional goals with effective treatment of hypertension, lowering of cholesterol and use of antiplatelet agents.

**References**

Original Article

Racial Variation in Risk Factors and Occurrence of Acute Myocardial Infarction: Comparison Between Arab and South Asian Men in Kuwait

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Background: There are little data available on the rates of occurrence, risk factors and mortality due to acute myocardial infarction among the various ethnic groups living in Middle-East countries. Therefore, we did a study to compare Arabs and South Asians living in Kuwait.

Methods and Results: The data for this retrospective study were collected from the computerized database of the Coronary Care Unit at the Mubarak Al-Kabeer Hospital (a 476-bed teaching hospital) and the 1997–2000 Census data for the State of Kuwait. Arab and South Asian men above 25 years admitted between September 1997 and August 2000 with a diagnosis of acute myocardial infarction were included in the study. A total of 866 Arabs and 277 South Asian men were admitted. The rate of admission for the entire patient population was two-fold higher among Arabs as compared with South Asians (6.7/1000 population and 3.3/1000, respectively). Diabetes mellitus was present in 453 Arabs (52.3%) and 109 South Asians (39.4%) (p≤0.001) of those >25 years of age. Hypertension was recorded in 247 Arabs (28.5%) and 57 South Asians (20.6%) (p≤0.01). Among patients <55 years of age (454 Arabs and 226 South Asians), the rate of admission was 4.0/1000 in Arabs and 3.5/1000 in South Asians (not significant). Hypertension was present in 97 Arabs (21.3%) and 43 South Asians (19%) (not significant). Diabetes mellitus was present in 202 Arabs (44.5%) and 80 South Asians (35.4%) (p≤0.05). Smoking was recorded in 353 Arabs (77.8%) and 160 South Asians (70.8%) (not significant). Hypercholesterolemia was present in 182 (40.1%) and 88 (39%), respectively (not significant). While in hospital, 11 Arabs and 9 South Asians died (not significant).

Conclusions: Among men >55 and <75 years of age. Arabs had a higher rate of admission with acute myocardial infarction compared with men of South Asian origin. The incidence of diabetes and hypertension was significantly higher among Arabs in this age group. In younger patients (<55 years), the rate of acute myocardial infarction was not different between the two groups; however, diabetes was present more often among Arabs. The smoking rate is very high in both groups and is an important risk factor for both Arab and South Asian men living in the Middle East. (Indian Heart J 2002; 54: 266–270)

Key Words: Coronary heart disease, Epidemiology, Risk factors

Although the incidence of coronary artery disease (CAD) has been declining in western industrialized countries, it has been increasing in developing countries. Several studies from industrialized countries have identified the classic risk factors for CAD and their relation to case fatality. Attempts to modify these risk factors in the population may have contributed to the decline in the mortality due to CAD in these countries. The degree to which these risk factors contribute to disease causation among the population in developing countries is open to question.

Several studies have assessed racial differences in the rates of CAD and prognosis after acute myocardial infarction (AMI). African Americans had significantly less mortality from CAD than White men, whereas Mexican Americans had a higher mortality than non-Hispanic Whites. In several countries, South Asian immigrants have been shown to have an unusually high incidence of and mortality from CAD when compared to the other ethnic groups in their country of adoption. CAD has been reported as a leading cause of mortality.
The population in the Middle East differs in ethnic, cultural and geographic backgrounds. There are little comparative data available about the rates of occurrence, risk factors and mortality due to CAD among the various ethnic groups living in the Middle-East countries. Therefore, we studied the rate of occurrence, distribution of various risk factors and clinical outcomes of CAD among Arabs and South Asians living in Kuwait.

**Methods**

The data for this retrospective study were collected from the computerized database of the Coronary Care Unit (CCU) at the Mubarak Al-Kabeer Hospital and the 1997–2000 Census data for the Hawally Governorate, State of Kuwait. Mubarak Al-Kabeer Hospital is a 476-bed teaching hospital that provides service to almost 450,000 residents in the Hawally Governorate. All patients with AMI were admitted to our CCU. Arab and South Asian men above 25 years of age admitted to the CCU between September 1997 and August 2000 with a diagnosis of AMI, who were discharged from or died in the hospital, were included in the study. The diagnosis of AMI was based on any two of the following three criteria: ischemic type of chest pain; diagnostic serial ECG changes (ST and non-ST segment elevation) and twofold rise in the total creatine kinase (CK) level with MB fraction contributing to at least 6% of the total CK level. Patients were eligible for thrombolysis if they presented within 12 hours and had an acute ST segment elevation (>0.1 mV in two or more limb leads, or >0.2 mV in two or more contiguous precordial leads) or new left bundle branch block (LBBB) on the admission ECG.

The variables analyzed from the database included detailed information on demographics, medical history, risk factors, cardiac enzymes, admission and discharge diagnosis, and in-hospital mortality. Patients were categorized as Arabs (Kuwaitis and others of Arab origin) and South Asians (SA). The latter included Indians, Pakistanis, Bangladeshis and Sri Lankans. For patients who had been admitted more than once, data were analyzed from the first CCU admission with a diagnosis of AMI. Hypercholesterolemia was said to be present if the patient was either known to have hypercholesterolemia on treatment or had a fasting total cholesterol level >5.5 mmol/L (212 mg/dl) within 24 hours of admission. Diabetes mellitus was recorded if the patient was a known diabetic on treatment or had a fasting blood sugar >7.0 mmol/L (126 mg/dl) during the present hospital admission. Hypertension was said to be present if the patient had a known history of hypertension. Smoking was said to be present if the patient had smoked one or more cigarettes in the past 3 months.

**Statistical analysis:** Crude and age-adjusted rates of admission for AMI among men of different age groups were computed for Arabs and SA separately. Variation in the levels of risk factors between SA and Arab as well as between survivors and nonsurvivors within each racial group were assessed using tests of proportion; Z test in case of comparing proportion or t tests for the comparison of two means. The age-adjusted standardized AMI admission rate for SA was calculated with the age-specific AMI admission rate of Arab men as the reference population. The differences were considered significant on a two-tailed p<0.005. Analyses were carried out using the SPSS program.

**Results**

**Relative rate of myocardial infarction:** During the 1997–2000 Census, there were 129,780 Arabs and 84,541 SA (aggregate average per year) in the Hawally Governorate. During the above period, a total of 1,420 Arabs were admitted to the CCU with a diagnosis of acute coronary syndrome (ACS), of whom 866 (61%) were admitted for AMI. A total of 360 SA were admitted with a diagnosis of ACS, of whom 277 (77%) were admitted for AMI. The crude rate of admission for AMI was two-fold higher among Arabs as compared with SA (6.67/1000 population for Arabs and 3.27/1000 for SA). The age-specific rates of AMI in each ethnic group are given in Table 1. The admission rate for AMI was higher among Arabs only in those between 55 and 75 years of age. In men <55 years of age, the rate of admission for AMI was 4.0/1000 population for Arabs and 2.8/1000 for SA [not significant (ns)]. The age-adjusted standardized AMI admission rate for SA >25 years was 0.729, when age-specific AMI admission rate for Arabs was used as the reference population. The age-adjusted standardized AMI rate for SA >25 years and <75 years and >25 years and <55 years was 0.732 and 0.855, respectively.

**Risk factors and in-hospital mortality:** The risk factor profile and in-hospital mortality for the entire patient population is shown in Table 2. Of the risk factors, hypertension and diabetes mellitus was significantly higher in Arabs as compared to SA. As the Arabs were significantly older and there was no difference in the rate of admission in the younger age group, we compared the risk factor profile and in-hospital mortality for patients <55 years of age (Table 3). This age group had 454 Arabs and 226 SA;
the mean age at presentation was 45.8±6.3 years for Arabs and 45.6±5.7 years for SA (ns). Diabetes mellitus was the only risk factor which was significantly higher (p<0.05) in Arabs as compared to SA. The in-hospital mortality was 2.4% among Arabs and 4.0% among SA (ns).

**Risk factors and other variables among survivors and nonsurvivors:** To determine whether there were differential influences on outcome between the two groups, survivors were compared with nonsurvivors (Table 4). Among the Arabs, nonsurvivors were significantly older than survivors. However, there was no significant difference for any risk factors between survivors and nonsurvivors amongst Arabs or SA. Among Arabs and SA, there was no difference between survivors and nonsurvivors for history of previous MI or peak CK levels.

**Discussion**

This is the first study from Kuwait on AMI, comparing the racial differences between Arabs and SA. These data indicate that there is a higher admission rate for AMI among men of Arab origin >55 years and <75 years of age compared to SA living in Kuwait. Diabetes and hypertension were also significantly higher among Arabs.

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**Table 1. Rate of acute myocardial infarction by age group among the two ethnic groups (>25 years of age)**

<table>
<thead>
<tr>
<th>Age group (years)</th>
<th>Arab population</th>
<th>SA population</th>
<th>Number of AMI in Arabs</th>
<th>Number of AMI in SA</th>
<th>AMI rate in Arabs/1000</th>
<th>AMI rate in SA/1000</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>26–29</td>
<td>18 607</td>
<td>14 646</td>
<td>3</td>
<td>0</td>
<td>0.16</td>
<td>0</td>
<td>ns</td>
</tr>
<tr>
<td>30–34</td>
<td>27 110</td>
<td>21 463</td>
<td>17</td>
<td>10</td>
<td>0.63</td>
<td>0.47</td>
<td>ns</td>
</tr>
<tr>
<td>35–39</td>
<td>24 057</td>
<td>17 069</td>
<td>62</td>
<td>36</td>
<td>2.58</td>
<td>2.11</td>
<td>ns</td>
</tr>
<tr>
<td>40–44</td>
<td>19 955</td>
<td>13 487</td>
<td>77</td>
<td>57</td>
<td>3.86</td>
<td>4.23</td>
<td>ns</td>
</tr>
<tr>
<td>45–49</td>
<td>14 560</td>
<td>8479</td>
<td>139</td>
<td>73</td>
<td>9.55</td>
<td>8.61</td>
<td>ns</td>
</tr>
<tr>
<td>50–54</td>
<td>10 401</td>
<td>3769</td>
<td>156</td>
<td>50</td>
<td>15.00</td>
<td>13.2</td>
<td>ns</td>
</tr>
<tr>
<td>55–59</td>
<td>6885</td>
<td>3407</td>
<td>138</td>
<td>28</td>
<td>20.04</td>
<td>8.21</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>60–64</td>
<td>4259</td>
<td>1469</td>
<td>111</td>
<td>12</td>
<td>26.06</td>
<td>8.17</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>65–69</td>
<td>2060</td>
<td>536</td>
<td>71</td>
<td>7</td>
<td>34.47</td>
<td>13.05</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>70–74</td>
<td>1039</td>
<td>164</td>
<td>49</td>
<td>3</td>
<td>47.15</td>
<td>18.29</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>75+</td>
<td>8477</td>
<td>32</td>
<td>43</td>
<td>1</td>
<td>50.75</td>
<td>19.23</td>
<td>ns</td>
</tr>
</tbody>
</table>

Values are mean±SD; in parentheses are percentages
AMI: acute myocardial infarction; ns: not significant

---

**Table 2. Comparison of demographics and risk factors between Arabs and South Asians >25 years of age admitted to the CCU with a diagnosis of AMI**

<table>
<thead>
<tr>
<th></th>
<th>Arabs n=866</th>
<th>South Asians n=277</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>54.4±11.5</td>
<td>47.5±8.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypertension</td>
<td>247 (28.5)</td>
<td>57 (20.6)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>453 (52.3)</td>
<td>109 (39.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Smoking</td>
<td>549 (63.3)</td>
<td>184 (66.4)</td>
<td>ns</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>355 (41.0)</td>
<td>110 (40.0)</td>
<td>ns</td>
</tr>
<tr>
<td>In-hospital mortality</td>
<td>53 (6.1)</td>
<td>12 (4.3)</td>
<td>ns</td>
</tr>
</tbody>
</table>

Values are mean±SD; in parentheses are percentages
AMI: acute myocardial infarction; ns: not significant

---

**Table 3. Comparison of demographics and risk factors between Arabs and South Asians >25 and <55 years of age admitted with a diagnosis of AMI**

<table>
<thead>
<tr>
<th></th>
<th>Arabs n=454</th>
<th>South Asians n=226</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>45.80±6.3</td>
<td>45.62±5.7</td>
<td>ns</td>
</tr>
<tr>
<td>Hypertension</td>
<td>97 (21.3)</td>
<td>43 (19.0)</td>
<td>ns</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>202 (44.5)</td>
<td>80 (35.4)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Smoking</td>
<td>353 (77.8)</td>
<td>160 (70.8)</td>
<td>ns</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>182 (40.1)</td>
<td>88 (39.0)</td>
<td>ns</td>
</tr>
<tr>
<td>In-hospital mortality</td>
<td>11 (2.4)</td>
<td>9 (4.0)</td>
<td>ns</td>
</tr>
</tbody>
</table>

Values are mean±SD; in parentheses are percentages
AMI: acute myocardial infarction; ns: not significant

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**Table 4. Comparison of risk factors and other variables between survivors and nonsurvivors of AMI among Arabs and South Asians <55 years of age**

<table>
<thead>
<tr>
<th></th>
<th>Arabs n=443</th>
<th>South Asians n=217</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>45.7±6.3</td>
<td>50.2±4.1*</td>
<td>44.6±5.6</td>
</tr>
<tr>
<td>Hypertension</td>
<td>93 (21)</td>
<td>4 (16)</td>
<td>42 (19)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>196 (44)</td>
<td>65 (55)</td>
<td>77 (35)</td>
</tr>
<tr>
<td>Smoking</td>
<td>147 (78)</td>
<td>6 (55)</td>
<td>153 (71)</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>178 (40)</td>
<td>4 (36)</td>
<td>89 (41)</td>
</tr>
<tr>
<td>Previous MI</td>
<td>60 (14)</td>
<td>3 (27)</td>
<td>25 (12)</td>
</tr>
<tr>
<td>Peak CK level</td>
<td>2225±2209</td>
<td>2416±2001</td>
<td>2656±2597</td>
</tr>
</tbody>
</table>

*p<0.05

Values in parentheses are percentages
AMI: acute myocardial infarction; CK: creatine kinase
in this age group. In younger patients (<55 years), the rate of AMI was not different between the two groups; however, that of diabetes mellitus was higher among Arabs. The rate of smoking in our study was very high in both the Arabs and SA population.

Our observation is slightly different from that of other countries, where SA were found to have a higher rate of AMI compared with the native population. Studies from the United Kingdom and Trinidad have shown a two- to four-fold greater incidence of AMI among SA compared with the native population. Indian immigrants to the United Kingdom have also been shown to have a higher rate of risk factors for coronary heart disease (CHD) compared to their siblings living in India. In the United States, hospitalization and prevalence rates of CAD among SA were reported to be three to four times higher than that in other populations. In our study, the mean age of Arabs is higher than that of SA. This is mainly because SA constitute the main workforce in Kuwait, and tend to return to their homeland on retirement. This difference in the population characteristics may explain some of the observed differences between the two groups in those admitted with AMI. The study was confined to men as there were few women patients in the SA group. This is because of the fact that among the SA population living in Kuwait, the number of women is small.

Among the major risk factors for CAD, Arabs had a significantly higher prevalence of diabetes mellitus. The prevalence of diabetes mellitus among the young Arab men in our study (44.3%) is also much higher than that reported for CAD patients from other studies. In the OASIS registry, among patients with non-ST segment elevation acute coronary syndrome (ACS), the overall prevalence of diabetes mellitus was 21% with the highest reported among patients from the USA (30%). Among patients in the US National Registry of Myocardial Infarction, the average prevalence of diabetes mellitus was 25%. The Arab patient population in our study consisted mainly of Kuwaiti nationals and a higher rate of diabetes in this population has been reported before. In a population-based cross-sectional study in Kuwait, the overall prevalence of type 2 diabetes mellitus among Kuwaiti adults >20 years of age was reported to be 14.8%.

The rate of smoking, though not different between the two groups, is higher than that reported in the literature. In the OASIS registry, the rate of smoking was 22% with the highest in Brazil (27%). In the National Registry of Myocardial Infarction, the rate of smoking was 29%. In a recent survey from Kuwait, the overall prevalence of smoking was 34.4% in men and 1.9% in women. While the prevalence of smoking has been reported to be decreasing in the West, smoking rates are generally believed to be increasing in Kuwait, especially among the young.

Among Arabs, nonsurvivors were significantly older which may explain the higher risk of the patients who died in this group. In SA the age or rates of any of the risk factors were not different among nonsurvivors compared to survivors. It appears that major risk factors do not have a significant impact on in-hospital mortality in either group.

Limitations: This study has some limitations. Firstly, the characteristics of the admitted patients do not apply to the general population and any conclusions derived from the patient sample may not be applicable to the general population. Secondly, the number of deaths in both the groups was too small to make comparisons between survivors and nonsurvivors. Thirdly, though we believe that almost all patients from the Hawally Governorate were admitted to the Mubarak hospital, some may have been admitted to other hospitals and hence the calculations of incidence may not be exact. In Kuwait, patients are allowed to visit only the hospital in their area of residence, and to the best of our knowledge almost all patients living in the Hawally Governorate were admitted to the Mubarak hospital. Lastly, SA, being the main workforce in Kuwait, tend to return to their homeland on retirement. This may result in a more healthy and young SA population living in Kuwait. Comparison between this population and the Arab population may explain some of the observed differences between the two groups. However, the Arab population also consists of expatriates and many of them tend to return to their country of origin on retirement. Larger epidemiological studies are required to confirm the findings mentioned in our study.

In conclusion, Arab men between 55 and 75 years of age had a higher risk/rate of admission with AMI compared to SA which could be explained by the higher rate of diabetes mellitus and hypertension in this group. Among Arab men <55 years of age, the admission rate for AMI was not different from that of SA. The rate of diabetes mellitus was higher among Arab men, even in the younger age group. Though people of SA origin have been thought to be at a higher risk for AMI, this study shows that Arab men >55 and <75 years of age are at a higher risk. Therefore, careful attention should be focused on this high-risk group to address future preventive and treatment strategies for CAD. The rate of smoking is alarmingly high in both the groups and may be an important risk factor in both Arabs and SA. As our study was based only on hospital
admission for AMI and has limitations, further prospective epidemiological studies are required to explore the findings of our study.

Acknowledgment

We acknowledge the help of Dr Mumtaz Shukkur with the statistical calculations.

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1. Cardiovascular disease mortality in the developing countries. World Health Stat Q 1993; 46: 89–150
Congenital Coronary Anomalies of Origin and Distribution in Adults: A Coronary Arteriographic Study

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Background: Coronary anomalies should be recognized to avoid problems during coronary intervention and cardiac surgery.

Methods and Results: We retrospectively reviewed 7400 coronary angiograms to find out the pattern and incidence of coronary anomalies of origin and distribution. We excluded patients with congenital heart diseases, coronary artery fistulae and patients with separate origin of the conus artery, and found 34 cases (0.46%) (22 males), mean age 50.7±12 years with coronary anomalies. Six cases underwent angiography prior to valve replacement and the rest were part of the evaluation for atherosclerotic coronary artery disease. The most common anomaly was separate origins of the left anterior descending coronary artery and left circumflex coronary artery [n=12 (35.3%)]. The next most common anomalies were origins of the right coronary artery from the left coronary sinus [n=7 (20.6%)] and left circumflex artery from the right sinus [n=6 (20%)]. A single coronary artery was seen in 3 cases (8.8%) which included one case of postmyocardial infarction ventricular septal rupture with triple-vessel disease, and another with two small coronary fistulae. One case each of the following coronary anomalies was found: (i) double right coronary artery, (ii) left anterior descending coronary artery from the right coronary sinus, (iii) all three coronary arteries originating separately from the right sinus, and (iv) left main coronary artery from the right sinus. Of these 34 patients, 11 (32.4%) had significant atherosclerotic disease in the anomalous vessel.

Conclusions: The incidence of primary coronary anomaly seems to be less than that in earlier reports, but the pattern of anomalies appears to be similar. (Indian Heart J 2002; 54: 271–275)

Key Words: Coronary anomalies, Coronary angiography, Coronary artery disease

The incidence of primary congenital coronary anomalies varies from 0.95% to 2% in the adult population undergoing coronary angiogram (CAG). Some of the anomalies are hemodynamically significant leading to abnormal myocardial perfusion. The hemodynamically insignificant group consists mainly of anomalies of abnormal aortic origin or distribution. Many of the anomalies are silent and are discovered as incidental findings during CAG or autopsy. Unrecognized coronary anomalies may lead to errors in diagnosis and problems during or after surgery. Geographical variation in the frequency of these anomalies is known. There are only few reports from India on this aspect. We report the data on coronary anomalies from our adult patient population undergoing CAG.

Methods

We retrospectively reviewed the angiogram reports of all adult patients (>18 years) who underwent CAG in the past 20 years (1980–2000) in our institute. The angiograms of those patients who had an abnormal coronary anatomy were reviewed by two experienced angiographers and a consensus was reached if there was a difference of opinion. Patients with congenital heart disease including bicuspid aortic valves, coronary artery fistulae (CAF), high “take off” of coronary arteries and separate origin of the conus artery from the right aortic sinus were excluded. Patients were categorized as having significant coronary artery disease.
(CAD), if they had more than 50% narrowing of intraluminal diameter.

Results

Out of the 7400 CAGs done during that period, 34 patients (0.46%) were found to have the anomalies of coronary origin and distribution described earlier. Out of these, 22 patients were male (70.96%) and 12 were female. The age range was 23–72 years (mean age 50.7±12 years). Of the 22 male patients, 6 underwent CAGs prior to valve replacement [all 6 had rheumatic heart disease (mitral valve disease in 5 and aortic disease in 1)]. The remaining CAGs were done to evaluate chest pain to detect or rule out atherosclerotic CAD. Table 1 shows the distribution of different coronary anomalies in the patient population.

Table 1. Incidence of coronary anomalies in the study population (n=7400)

<table>
<thead>
<tr>
<th>Serial no.</th>
<th>Coronary anomaly</th>
<th>Number of patients</th>
<th>Incidence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Separate origins of LAD and LCx</td>
<td>12</td>
<td>35.29</td>
</tr>
<tr>
<td>2.</td>
<td>RCA from LCS</td>
<td>7</td>
<td>20.58</td>
</tr>
<tr>
<td>3.</td>
<td>LCx from RCS</td>
<td>6</td>
<td>17.64</td>
</tr>
<tr>
<td>4.</td>
<td>Single coronary artery</td>
<td>3</td>
<td>8.82</td>
</tr>
<tr>
<td>5.</td>
<td>RCA from the posterior sinus</td>
<td>2</td>
<td>5.8</td>
</tr>
<tr>
<td>6.</td>
<td>LMCA from RCS</td>
<td>1</td>
<td>2.94</td>
</tr>
<tr>
<td>7.</td>
<td>Double RCA</td>
<td>1</td>
<td>2.94</td>
</tr>
<tr>
<td>8.</td>
<td>LAD, LCx, RCA from RCS</td>
<td>1</td>
<td>2.94</td>
</tr>
<tr>
<td>9.</td>
<td>LAD from RCS</td>
<td>1</td>
<td>2.94</td>
</tr>
<tr>
<td>TOTAL</td>
<td></td>
<td>34/7200</td>
<td>0.46</td>
</tr>
</tbody>
</table>

LAD: left anterior descending coronary artery; LCx: left circumflex coronary artery; RCA: right coronary artery; RCS: right coronary sinus; LMCA: left main coronary artery

Separate origins of LAD and LCx from the left coronary sinus: This was the most common anomaly we came across in 12 of the 34 patients (35.3%). Only those cases which required separate cannulation to engage the respective ostia were included. It was ensured that the angiographic appearance was not a result of a superselective injection secondary to an inadvertent deep engagement of the catheter or catheter-induced left main stem spasm. We found the left anterior oblique (LAO) caudal projection to be most useful in identifying this anomaly as it differentiates separate origins of the left circumflex coronary artery (LCx) and left anterior descending coronary artery (LAD) from a short left main stem.

RCA from LCS: The next common anomaly was origin of the right coronary artery (RCA) from the left coronary sinus (LCS), n=7 (20.6%). In this anomaly, the RCA originated from an orifice located anterior to the left main coronary ostium in the left sinus and passed between the aorta and pulmonary artery before reaching the right atrioventricular (AV) groove. These anomalous vessels were difficult to cannulate and in most cases the cannulation was done with left-sided Amplatz catheters (Fig. 1). The final distribution was normal in all cases and the left coronary artery system was also normal.

LCx from the right coronary sinus/RCA: This anomaly was seen in 6 patients (17.6%). In 4 patients, the LCx originated from the right coronary sinus (RCS) and in 2 patients it originated from the RCA (Fig. 2). The initial course was retro-aortic in all cases. Peripheral distribution of the LCx was normal in all the patients. In all the cases, the LAD originated from the left sinus and had a normal distribution.

Single coronary artery: A single coronary artery (SCA) was seen in 3 patients (8.8%). Of the 3 patients, 2 were females and 1 was a male. The SCA was typed according to the Lipton classification. All patients had L-II A type of SCA. The male patient was a case of postmyocardial infarction (MI) ventricular septal rupture who had triple-vessel CAD (Fig. 3). The other 2 patients had no significant coronary lesions, but 1 patient had two small coronary AV fistulae arising from the LCx and draining in to the left atrium which we have already reported.
RCA from the posterior sinus: In 2 cases (5.8%), the RCA originated from the posterior sinus of Valsalva. The coronaries were difficult to cannulate with right Judkin’s catheters and both of them were cannulated with left-sided Amplatz catheters.

Double right coronary artery: Two separately originating RCAs, coursing down the right AV groove were seen in a 52-year-old woman who underwent CAG prior to mitral valve replacement. The superior RCA, after the origin of the conus artery and two right ventricular (RV) branches, descended beyond the acute margin of the heart and terminated as the posterior descending coronary artery (PDA). The inferior RCA, after giving off one small RV branch ended at the crux, as the PDA and a small posterolateral branch. Both RCAs and the left coronary artery system were free from any disease.

LAD from the right coronary sinus: In 1 patient, the LAD originated from the RCS. The anomalous LAD coursed anterior to the RV outflow tract and had a normal peripheral distribution. The LCx in that patient arose from the LCS and had a normal distribution pattern.

LMCA and RCA from the right sinus: One patient had the left main coronary artery (LMCA) arising from the right aortic sinus. The distribution pattern of the vessels was normal (Fig. 4). He had a 40% lesion in the LCx, 80% lesion in the RCA and a normal LAD. He underwent balloon angioplasty and stenting to the RCA and is on follow-up.

LAD, LCx and RCA arising separately from the RCS: In 1 patient the LAD, LCx and RCA originated separately from the right sinus. The distribution of the vessels was normal.

Atherosclerotic disease in anomalous coronaries: Of these 34 patients, 11 had significant atherosclerotic disease in the anomalous vessel. Of the 12 patients with separate origins of the LAD and LCx, 4 had severe disease in the LAD and 2 had disease in the LCx. One patient among them underwent percutaneous transluminal angioplasty to the LAD. Two patients in whom the RCA originated from the left sinus had lesions in the RCA. One patient with a single coronary artery had disease in all the three vessels. One patient who had a LCx arising from the RCA had 60% lesion in the RCA; other vessels were normal. The patient with a
Discussion

Angiographic recognition of anomalies of coronary origin and distribution is important for appropriate diagnosis and management of patients with atherosclerotic CAD and in those undergoing open heart surgery. Failure to identify these anomalies can lead to inaccurate and prolonged procedures which can result in catastrophic complications.

There are many reports describing these anomalies, both from India and abroad. The largest series is by Yamanaka et al.1 where he analyzed 126 595 angiograms and found 1686 patients with anomalous coronaries, an incidence of 1.6%. The incidence in our series is only 0.46%, but we have excluded ALCAPA, CAF and separate origin of the conus artery from the right sinus of Valsalva. In one report from northern India the incidence was 0.95%, (including CAF) and in the series by Topaz et al.8 the incidence was 0.61%.

The most common anomaly in our series was separate origin of the LCx and LAD (35.3%). Yamanaka et al.1 found that 30.4% of the anomalies was contributed to by separate origins of the LCx and LAD. This anomaly usually causes no hemodynamic impairment and is generally considered to be benign. In the series by Topaz et al.8 among 20 332 adult patients, 83 (0.4%) were found to have separate origins of the LAD and LCx (left main coronary artery absent). They found an increased incidence of left coronary dominance, a higher (6%) than usual (0.5%–1.5%) incidence of myocardial bridging but similar incidence of atherosclerotic CAD compared to patients whose left main artery is intact. We did not find increased incidence of myocardial bridging or left coronary dominance in our patients with this anomaly.

Occasionally this anomaly is not recognized at the time of CAG. The LAD or LCx may be misinterpreted as totally obstructed or congenitally absent, which may lead to an error in clinical management. The appearance of an avascular area in the distribution of the left coronary (a pseudo “no perfusion” sign) should raise the possibility of an anomalous origin of the circumflex or LAD either from the left or right sinus.8

The next commonly encountered anomaly was an RCA arising from the right aortic sinus had a 40% lesion in the LCx. 80% lesion in the RCA and normal LAD.

The next common anomaly which we encountered was anomalous LCx (LCx from the RCS/RCA) which was seen in 17.60% of patients. This is in concurrence with studies by Yamanaka et al., Topaz et al.8 and Garg et al.4 This anomaly should be suspected when injections into the LCA reveal an unusually long nonbranching proximal segment and a nonperfused lateral wall. If the angiographer assumes the vessel is occluded or congenitally absent, it will lead to mismanagement. The cardiac surgeon should be informed about this anomaly in order to avoid accidental compression of the vessel during valve replacement. In the absence of atherosclerosis this anomaly is considered benign.1

The RCA arising from the posterior sinus was found in 6% of our patients with coronary anomalies. However, an incidence of 20% was reported in a study among patients basically of Hispanic origin having coronary anomalies.8 An Indian study showed that this anomaly was present in 10% of all patients with coronary anomalies.4 Yamanaka et al.1 demonstrated an incidence of only 0.24% of all anomalies.

We came across 3 cases of SCA in our patient population. SCA is typied using the Lipton classification scheme.7 All three of our patients had L-II A type of single coronary artery (i.e. SCA arising from left sinus, RCA arising from LMCA and coursing anteriorly across the right ventricular outflow tract to the right AV groove, LAD and LCx running their usual course). We have reported elsewhere the association of SCA with coronary arteriovenous fistulae.15 There were 56 cases of SCA among 126 595 patients who underwent CAGs in the study by Yamanaka et al.1 The most common type was L-I followed by R-II and L-II in the above mentioned study. No cases of SCA were found in the study by Garg et al.4

Three cases of double RCAs are reported in the literature including one by us.11-13 In one of the previous reports of double RCA,13 the patient had a single coronary ostium, confirmed at surgery, but our case had two separate ostia. The branching pattern and distribution of the RCA in both the cases described above were similar.11,13

Origin of the LAD from the right aortic sinus is a rare anomaly which we came across in one patient; in the series by Topaz et al.8 the incidence was 5/80 cases, 38/1461 in the series by Yamanaka et al.1 and 1/35 in the series by Garg et al.4

We came across one case of the LMCA originating from the right aortic sinus. Twenty-two cases were described by Yamanaka et al.1 and five anatomical subtypes have been described—“anterior”, “between”, “septal”, “posterior”, and “combined”. The septal type is the most common and is considered benign, and the “between” type is a potentially
serious but rare anomaly. Our patient had the septal type of the anomaly.

We encountered one rare anomaly in which all three major coronary arteries arose separately from the right sinus with separate ostia. Such an anomaly has been reported by Fineschi et al.10

It is reported that anomalous coronaries are more prone to atherosclerosis.14 Coronary atherosclerosis of the anomalous arteries was found in 32% of patients in our series, while the overall incidence of atherosclerotic disease in this cohort was 58%. Thus anomalous coronaries do not appear to be associated with an increased risk of coronary atherosclerosis in this small group of patients. A greater degree of atherosclerotic involvement of the proximal anomalous LCx (LCx from RCA/RCS) is reported and is suggested to be due to its retro-aortic course.14 However none of our patients with an LCx from the RCS/RCA had atherosclerosis. The same finding is reported by Garg et al.4 and Topaz et al.8

Only 2 out of the 6 patients had atherosclerotic involvement of an anomalous RCA from the right sinus. This is in concurrence with the reports of Topaz et al.8 and Wilkins et al.14 who also found that there is no predisposition for atherosclerotic involvement of an anomalous RCA.

As the number of patients is small, this issue of atherosclerotic involvement in anomalous vessels has to be clarified in studies involving a larger number of patients with anomalous coronaries.

Recognition of these coronary anomalies are needed to ensure accurate angiographic interpretation and is important for patients undergoing cardiac surgery to selectively perfuse these vessels during cardiopulmonary bypass. Surgical problems may follow if the surgeon unwittingly incises an anomalous vessel. During valve replacement surgery, failure to identify these anomalies can lead to the ostium of the vessel being inadvertently obstructed or the anomalous vessel getting compressed by the valvar prosthesis.

The incidence of primary coronary anomalies in this series seems to be less compared to earlier reports, but the pattern of anomalies appears to be similar.

References
10. Fineschi M, Del Sordo M, Leosco D, Casini S, Bravi A. A rare anatomic variation of the anomalous origin of all three major coronary arteries from the right sinus of Valsalva. Ital J Cardiol 1998; 28: 564–566
Background: The renewed interest in mitral valve replacement with a pulmonary autograft encouraged us to perform this procedure in selected patients.

Methods and Results: From August 2000 to February 2002, 10 patients between 30 and 52 years of age with calcific mitral valvular disease underwent the Ross II procedure. Patients were either in New York Heart Association functional class III (7/10) or IV (3/10). Transthoracic echocardiography was done in all the patients to confirm the diagnosis. A pulmonary autograft was used to replace the diseased mitral valve. Intraoperative transesophageal echocardiography confirmed normal functioning of the autograft. There were 2 early deaths. The 8 survivors are in New York Heart Association functional class I with excellent autograft and homograft function at a follow-up of 2–20 months (mean 9 months).

Conclusions: This procedure is a viable option for mitral valve replacement in patients with calcific mitral valve disease. However, the procedure is technically demanding and requires a valve bank. (Indian Heart J 2002; 54: 276–278)

Key Words: Pulmonary autograft, Mitral valve disease, Ross procedure

Mitral valve disease of rheumatic origin remains a major indication for mitral valve replacement (MVR). Reparative techniques are preferred, but a severely calcified valve needs to be replaced. The choice of valve in such a patient is essentially limited to a prosthetic or bioprosthetic one. Yacoub et al. in 1969 reported homograft replacement of the mitral valve. In 1967, Ross reported the use of a pulmonary autograft in the mitral position in 2 patients but interest in the procedure waned with the development of newer prosthetic valves and better preservation techniques for bioprosthetic valves. Interest in the procedure was rekindled with the report of Kabbani and associates who expanded on their initial experience with a later report.

We reported on our technique for this procedure in an earlier publication. The early results are presented here.

Methods

From August 2000 through February 2002, 10 patients underwent the Ross II procedure. There were 6 males and 4 females, and their ages ranged from 30 to 52 years (mean 41.2 years). The indication for the procedure was isolated calcific mitral valve disease (stenosis and/or incompetence). Patients with associated tricuspid valve disease or those who had undergone closed mitral valvotomy in the past were not considered suitable for the procedure, as the presence of pericardial adhesions between the pulmonary artery and left atrial appendage make harvesting of the autograft hazardous.

Severe rheumatic mitral stenosis with a mitral valve area (MVA) <1.0 cm² (on transthoracic echocardiography) was present in 9 of the 10 patients; one patient had an MVA of 1.2 cm². Mitral valve calcification was seen on fluoroscopy in all except one patient. Moderate mitral regurgitation was present in 3 of the 10 patients. Additional valvular lesions that did not warrant any surgical intervention (trivial aortic regurgitation) were present in 2 patients.

Cardiac catheterization was performed in 6 of the 10 patients to rule out associated coronary artery disease. These patients were >40 years of age and all showed moderate-to-severe pulmonary arterial (mean 62 mmHg) and pulmonary venous hypertension (mean pulmonary capillary wedge pressure 35.2 mmHg). Seven of the 10 patients were in preoperative New York Heart Association (NYHA) functional class III and the remaining were in class IV. Four of the 10 were in atrial fibrillation.
Surgical technique: A median sternotomy and vertical pericardiotomy was performed in all the patients. The pulmonary artery was dissected and looped. Moderately hypothermic (28°C) cardiopulmonary bypass (CPB) was established and cold antegrade cardioplegia and topical cooling was used for myocardial preservation. After a left atriotomy, the LA thrombus, if present, was removed and the mitral valve excised with preservation of both anterior and posterior chordae and subvalvular apparatus in all the patients by Miki’s technique. The pulmonary autograft was harvested and sutured in the mitral position as described in our earlier publication. Competence of the autograft was checked by filling the left ventricle with saline. The LA was closed and the right ventricular outflow tract was reconstructed using an appropriate-sized cryopreserved pulmonary homograft from our own valve bank. Immediate postoperative transesophageal echocardiography was performed before decannulation in all the patients to confirm that the autograft and homograft were functioning satisfactorily.

Results
All patients survived the operation. The CPB time varied between 119 and 180 min (mean 144.3 min) and aortic cross-clamp times varied between 63 and 150 min (mean 115.6 min).

One patient was re-explored due to excessive bleeding. There were 2 early deaths. One patient developed acute pulmonary edema on the third postoperative day. On re-exploration, it was found that the proximal sutures had given way—these were successfully repaired. However, the patient developed irreversible myocardial failure and died. The second patient had a largely uneventful postoperative period. She developed sudden intractable ventricular tachyarrhythmia on the tenth postoperative day and died while in hospital.

On an average, patients were discharged on the sixth postoperative day (range 5–11 days). Of the 8 patients, 2 remained in atrial fibrillation postoperatively. A minor wound complication developed in 1 patient.

Follow-up ranged from 2 to 20 months (mean 9 months). All patients were in NYHA class I. All patients who were in sinus rhythm preoperatively have remained so while 2 continue to be in atrial fibrillation. Transthoracic echocardiography revealed good autograft function in all with mild mitral regurgitation in 1 patient. The measured valve area was >2.2 cm² in all the patients (mean 2.8 cm²). There was no significant transvalvular gradient in any patient. The function of the pulmonary homograft was normal with no regurgitation or gradient in any patient. Left ventricular function was normal in all of them.

Discussion
In India, mitral valve disease remains a major problem requiring valve replacement. The use of prosthetic valves is limited by the necessity of lifelong anticoagulation. Also, frequent and expensive tests are not easy in a country with limited resources and where patient compliance remains uncertain. Bioprosthetic valves are not suitable in these patients.

We believe that the use of a pulmonary autograft in the mitral position is a viable option in patients with isolated calcific rheumatic valve disease. Kabbani et al. reported excellent early to medium-term results of the procedure. The pulmonary autograft provides the largest valve area in the mitral position as compared to any other currently available valve substitute.

We expect that once the technical aspects of the procedure are refined the results will improve. Our technique is slightly different from that reported by Kabbani et al. We do not use a conduit for the autograft; instead, we use a supporting teflon felt stent which has some potential advantages in permitting autograft growth.

One remaining issue is that of potential homograft degeneration in the pulmonary position. The excellent results reported for the Ross procedure (pulmonary autograft in the aortic position) with the right-sided low pressure circuit led us to believe that homograft degeneration is less likely. The long-term results should therefore be good.

It is important to realize that there are certain limitations associated with this procedure. It is probably not suitable for young patients with rheumatic heart disease (age <35 years). Our experience with the Ross procedure (pulmonary autograft in aortic position) in this subgroup of patients has been disappointing due to accelerated autograft degeneration. We therefore do not recommend this procedure in young (age <35 years) rheumatic patients. In addition, this procedure requires the development of a tissue valve bank and reasonable experience in mitral valve surgery. The operation is technically demanding and an appropriate-sized homograft is a prerequisite.
References

Minimally Invasive Mitral Valve Surgery

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Department of Cardiovascular Surgery, Department of Anaesthesiology, Department of Cardiology, Escorts Heart Institute and Research Centre, New Delhi

Background: To reduce surgical trauma and the drawbacks associated with sternotomy, we performed robotically controlled, video-assisted mitral valve surgery, using either the port-access or the transthoracic clamp technique.

Methods and Results: Between September 1997 and September 2000, 221 patients (78 males, 143 females) underwent mitral valve surgery through a small right minithoracotomy using the port-access endovascular cardiopulmonary bypass system. Mitral valve exposure was facilitated with an endoscope attached to a voice-controlled robotic arm (AESOP 3000) allowing stabilization and voice-activated camera positioning. Twenty-six patients underwent mitral valve repair and 195 had valve replacement. In 197 patients, mitral valve surgery was the primary operation, while 24 were redo cases. Skin-to-skin mean operating time was 3.5±1.2 hours and aortic cross-clamp time was 58±16 min, mean intensive care unit stay was 22±7 hours and hospital stay 6.4±1.2 days. There was no re-exploration for bleeding. There was no late death or re-operation on mean follow-up of 16.4±12.2 months. Patients showed improvement in their NYHA functional class from 2.6±0.5 to 1.4±0.8 postoperatively. Outcomes were compared with those of our previous 220 patients who underwent mitral valve surgery with the median sternotomy approach.

Conclusions: The use of video and robotic assistance in port-access mitral valve surgery not only minimizes the length of the incision, but also gives full visualization of the entire mitral valve apparatus. This approach provides comparable results with the sternotomy approach, as well as marked advantages of reduced intensive care unit stay, lower blood transfusion requirement, better cosmesis and earlier hospital discharge. (Indian Heart J 2002; 54: 279–283)

Key Words: Port access, Video-assisted surgery, Mitral valve disease
maintaining the same level of safety and favorable results as that of conventional surgery.

Methods

Between September 1997 and September 2000, 221 patients underwent mitral valve surgery by a minimally invasive approach through a right anterolateral minithoracotomy at the fourth intercostal space. The video-assisted approach was used in 120 patients while in 101 surgery was carried out under direct vision. There were 78 males and 143 females (mean age 36.4±10.5 years). As shown in Table 1, most of the patients had rheumatic valvular pathology, while 33 had degenerative mitral valve pathology. Seventy-four patients had involvement of the tricuspid valve along with mitral valve disease; of these, 15 required tricuspid valve repair as well as mitral valve surgery.

Table 1. Patient characteristics and parameters of cardiac function

<table>
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<th>Variable</th>
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<td>Total no. of cases</td>
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<tr>
<td>Male/female ratio</td>
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<tr>
<td>Mean age (years)</td>
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<td>NYHA functional class</td>
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<tr>
<td>Class III</td>
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<td>Rheumatic</td>
<td>188</td>
</tr>
<tr>
<td>Degenerative</td>
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</tr>
<tr>
<td>Predominant mitral insufficiency</td>
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</tr>
<tr>
<td>Predominant mitral stenosis</td>
<td>77</td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
<td>45±7</td>
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<tr>
<td>Tricuspid regurgitation</td>
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<td>Severe</td>
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<tr>
<td>Mild-to-moderate</td>
<td>62</td>
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<tr>
<td>Redo cases</td>
<td>24</td>
</tr>
</tbody>
</table>

NYHA: New York Heart Association

Table 1. Patient characteristics and parameters of cardiac function

To achieve the potential benefit of minimally invasive mitral valve surgery, the following modifications of the conventional operative technique were applied: (i) minithoracotomy; (ii) femoral bypass; (iii) centrifugal pump-assisted venous return; (iv) endoaortic balloon or direct transthoracic aortic clamp occlusion; (v) endoscope and voice-controlled robotic arm for videoscopic mitral valve exposure; and (vi) use of specially designed instruments for this surgery.

Surgery: Patients were placed in the supine position with the right side of the chest slightly elevated. Standard anesthetic techniques were used. The right or left femoral artery and vein were surgically exposed through a 3–4 cm incision parallel to the inguinal skin fold. After systemic heparinization, a 21 F, Y-shaped arterial return cannula (Heart Port, Inc, Redwood City, CA) or 21 F straight cannula (DLP Inc, Grand Rapids, MI) was inserted into the femoral artery, depending on whether an endoaortic or transthoracic occlusion clamp was being used. A 28 F venous return cannula (Heart Port, Inc, Redwood City, CA) was placed in the femoral vein and advanced to the right atrium and then to the superior vena cava under transesophageal echocardiographic (TEE) guidance. A conventional cardiopulmonary bypass system with a roller pump and membrane oxygenator was used. In addition, a centrifugal pump (Sarns Inc., Ann Arbor, MI) was placed in the venous line to enhance venous drainage.

Simultaneously a 5–8 cm long incision was made anterolaterally over the fourth intercostal space on the right side. The pericardium was opened 3 cm above and parallel to the right phrenic nerve to expose the roof of the left atrium. Exposure was enhanced by placing stay sutures on the pericardium which were fixed to the chest wall. Cardiopulmonary bypass was instituted with a temperature drift, without active cooling or warming, until the aortic cross-clamp was in place. Before inserting the endoaortic clamp (EAC), the aorta was examined by TEE for atheromatous plaques and thrombi to avoid cerebral embolization with retrograde perfusion. Advancement of the guidewire could be visualized from the descending aorta to the aortic valve by TEE. Placement of the EAC (1 cm above the level of the sinotubular junction) was controlled by fluoroscopy (Sieremobil 2000, Siemens, Erlangen Germany) and multiplane TEE (Sonos 5500 Hewlett Packard, Inc., Andover, MA). The EAC balloon was inflated to endoluminally block the ascending aorta while the heart was vented through the distal lumen of the EAC in the aortic root. After clamping, the EAC balloon pressure was continuously measured and maintained between 250 and 340 mmHg. In case the balloon pressure fell below 250 mmHg, the balloon was further inflated. Warm blood cardioplegic solution was delivered antegrade through the lumen while maintaining the aortic root pressure between 50 and 70 mmHg.

The EAC was used in the initial 38 patients, but now our preference is the transthoracic sliding-rod aortic clamp (Scanlan International Inc., Minneapolis, MN) which was used in 163 cases in the present series. This clamp is passed through the third intercostal space at the midclavicular line...
through a 3 mm port. For delivery of antegrade cardioplegia, the DLP cardioplegia catheter (DLP Inc., Grand Rapids, MI) was used; the DLP catheter was also used for aortic root suction during de-airing. After cardiac arrest was established, the left atrium was opened and the mitral valve exposed by a specially designed atrial retractor (Heart port Inc., Redwood City, CA) inserted parasternally through another 3 mm port at the fifth or sixth intercostal space. Mitral valve repair or replacement was performed under direct vision with the use of a specially designed instrument (Heart port Inc., Redwood City, CA). After completion of the procedure, the left atrial vent was positioned across the mitral valve and the left atrial incision was closed.

In patients requiring tricuspid valve repair along with mitral valve surgery, the venous drainage cannula was withdrawn to the inferior vena cava after completion of mitral valve surgery and the right atrium was opened while the pump sucker was sucking out blood returning from the superior vena cava. The tricuspid valve was exposed with an in situ mitral retractor and the repair was completed. After completion of tricuspid valve repair the right atrium was closed and the venous drainage cannula pushed back to the right atrium. Air was removed by inflating the lungs and simultaneous reduction of venous drainage with the patient placed in the Trendelenburg position. Air in the aorta was removed by suction through the distal lumen of the EAC or cardioplegia catheter (depending on which was in place). The EAC was deflated and the catheter left in place for further venting until de-airing was complete. If necessary, defibrillation was performed using external defibrillation pads. A temporary pacing wire was placed in the right ventricular epicardium before the aortic cross-clamp was removed. After appropriate reperfusion, the arterial and venous cannulas were removed and the femoral vessels repaired. The chest wound was closed after inserting a drainage tube into the pleural space.

**Follow-up:** Postoperative follow-up was carried out at 3 months and 6 months, followed by an annual check-up with serial echocardiography. Preoperative, operative and postoperative data were prospectively collected and stored in a prescribed form and database.

**Results**

**Surgical technique:** In all our patients, the mitral valve was easily accessible through the right anterolateral minithoracotomy. The average length of the incision was 6.8±1.8 cm (range 5–8 cm). Conversion to sternotomy was not required.

In 22 patients, the mitral valve was repaired by a combination of techniques including commissurotomy, sliding plasty and annuloplasty with a Carpentier Edwards ring. Successful repair was achieved in all the patients as demonstrated by intraoperative TEE. In the repair group, 1 patient had an atrial septal defect which was closed by a pericardial patch. In 3 patients with severe tricuspid regurgitation the tricuspid valve was repaired along with the mitral valve.

In 178 patients who underwent mitral valve replacement, preservation of the posterior mitral leaflet was possible in 153. In the remaining 25 patients, the posterior leaflet was heavily calcified and could not be preserved. In the replacement group, 4 patients also underwent closure of atrial septal defects with a pericardial patch. In 1 patient, post-mitral valve replacement, a paravalvular leak was closed with a Dacron Patch (Table 2). In the replacement group, tricuspid valve repair was performed in 12 cases.

**Table 2. Operative procedures**

<table>
<thead>
<tr>
<th>Variable</th>
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<tbody>
<tr>
<td>MVR</td>
<td>178</td>
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<tr>
<td>MVR+TV repair</td>
<td>12</td>
</tr>
<tr>
<td>MV repair+ASD closure</td>
<td>1</td>
</tr>
<tr>
<td>MVR+ASD closure</td>
<td>4</td>
</tr>
<tr>
<td>MV+TV repair</td>
<td>3</td>
</tr>
<tr>
<td>MV repair</td>
<td>22</td>
</tr>
<tr>
<td>Post-MVR paravalvular leak closure</td>
<td>1</td>
</tr>
</tbody>
</table>

ASD: atrial septal defect; MV: mitral valve; MVR: mitral valve replacement; TV: tricuspid valve

We prefer to use the Starr Edwards mitral valve prosthesis (Baxter Health Care Corp, Edwards CVS Division, Irvine, CA) as management of anticoagulation is easier. The mean duration of skin-to-skin operating time and cross-clamp time was 3.5±1.2 hours and 58±16 min, respectively.

**Transthoracic sliding-rod aortic cross-clamping:**
There were no aortic clamp-related injuries and no incidence of aortic dissection.

**Postoperative course and complications:** The mean duration of intensive care and hospital stay was 22±7 hours and 6.4±1.2 days, respectively. Median postoperative blood loss was 332±104 ml (Table 3). Four patients developed lymphorrhea from the groin wounds requiring surgical intervention, in the form of ligation of cut-open lymphatics. One patient developed left hemiparesis on postoperative day 1 after extubation, which fully recovered on postoperative day 3. Three patients had chest wound
complications. There was one death on postoperative day 12 due to massive upper gastrointestinal bleeding (Table 4). This was an 85-year-old male patient operated on for degenerative mitral regurgitation with Carpentier Edwards’ bioprosthesis.

Table 3. Perioperative variables (n=221)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Operative time (hours)</td>
<td>3.5±1.2</td>
</tr>
<tr>
<td>Aortic cross-clamp time (min)</td>
<td>58±16</td>
</tr>
<tr>
<td>ICU stay (hours)</td>
<td>22±7</td>
</tr>
<tr>
<td>Hospital stay (days)</td>
<td>6.4±1.2</td>
</tr>
<tr>
<td>Postoperative blood loss (ml)</td>
<td>332±104</td>
</tr>
</tbody>
</table>

ICU: intensive care unit

Table 4. Postoperative complications

<table>
<thead>
<tr>
<th>Variable</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transient neurological deficit</td>
<td>1 (0.45)</td>
</tr>
<tr>
<td>Lymphorrhea from groin wound</td>
<td>4 (1.8)</td>
</tr>
<tr>
<td>Chest wound complications</td>
<td>3 (1.35)</td>
</tr>
<tr>
<td>In-hospital mortality</td>
<td>1 (0.45)</td>
</tr>
</tbody>
</table>

Values in parentheses are percentages

Surgical efficacy and follow-up results: The mean follow-up time was 16.4±12.2 months (Table 5). There were no late deaths or re-operations during this period.

At discharge after mitral valve repair, all patients had normal mitral valve function with no or trivial regurgitation. All implanted valves were functioning normally as shown by postoperative echocardiographic studies. None of the patients had paravalvular leakage. One patient developed vegetations of subacute bacterial endocarditis on the prosthetic valve. At the mean follow-up of 16.4±12.2 months, NYHA functional class had improved by one class in all except 5 patients. These were the patients who had long-standing mitral regurgitation with high pulmonary artery pressure.

Table 6 compares the results of the video-assisted port-access approach with the median sternotomy approach. The patient population in the minimally invasive group was younger with a mean age of 36.4±10.5 years. The average cardiopulmonary bypass time was slightly longer with the minimally invasive approach (126±41 min) as compared to the sternotomy approach (120±38 min). The average hospital stay was less in the minimally invasive approach group (6.4±1.2 days). The hospital mortality was 3.5% for the sternotomy and 0.4% for the minimally invasive approach. At 1 year, residual mitral insufficiency was similar between the sternotomy and minimally invasive approach groups (0.80±0.3 v. 0.6±0.7). Improvement in the NYHA functional class at 1 year was also comparable for the sternotomy (1.5±0.5) and (1.4±0.8) minimally invasive approach groups.

Table 6. Comparison of sternotomy with video-assisted port-access technique (n=221)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Sternotomy</th>
<th>Video-assisted port access</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (years)</td>
<td>41.8±14.8</td>
<td>36.4±10.5</td>
</tr>
<tr>
<td>Operative time (hours)</td>
<td>3.1±1.4</td>
<td>3.5±1.2</td>
</tr>
<tr>
<td>Aortic cross-clamp time (min)</td>
<td>51.7±17</td>
<td>58±16</td>
</tr>
<tr>
<td>CPB time (min)</td>
<td>120±38</td>
<td>126±41</td>
</tr>
<tr>
<td>ICU stay (hours)</td>
<td>23±5</td>
<td>22±7</td>
</tr>
<tr>
<td>Hospital stay (days)</td>
<td>8±2</td>
<td>6.4±1.2</td>
</tr>
<tr>
<td>Postoperative blood loss (ml)</td>
<td>440±92</td>
<td>332±104</td>
</tr>
<tr>
<td>Hospital mortality (%)</td>
<td>3.5</td>
<td>0.45</td>
</tr>
<tr>
<td>Residual mitral insufficiency at 1 year</td>
<td>0.8±0.3</td>
<td>0.6±0.7</td>
</tr>
</tbody>
</table>

CPB: cardiopulmonary bypass; ICU: intensive care unit, NYHA: New York Heart Association

Discussion

Right anterolateral minithoracotomy for minimally invasive mitral valve surgery is appropriate because the incision gives a direct view of the left atrium with minimal discomfort. Nearly two-thirds of our patients were young women; and this incision gives a good cosmesis as it is hidden below the breast.
Using a video- and voice-controlled robotic arm (AESOP 3000) it was possible to minimize the length of the incision and obtain good visualization of the entire mitral apparatus. We now routinely use the transthoracic aortic clamp in place of the EAC, because this technique is safe and requires few additional resources or disposable supplies. The transthoracic-clamp technique reduces the time of surgery, facilitates complete aortic cross-clamping, provides good myocardial protection via antegrade cardioplegia and minimizes cost. The EAC provides similar intraluminal aortic occlusion and antegrade cardioplegia, but is expensive. In our series there was no aortic dissection with the use of EAC as reported by Mohr et al. This may be because of the younger age of our patients. There were no complications related to femoral artery cannulation as reported by Mohr et al. and Aklog et al. because of the same reason.

In our series, 24 patients were redo cases. Five patients had undergone aortic valve replacement, 8 coronary bypass grafting and 10 closed mitral commissurotomy. One patient had a paravalvular leak in whom we had replaced the mitral valve 1 year ago. In all redo cases except previous closed mitral commissurotomies, the EAC was used as it avoids the excessive dissection needed to clear the aorta for external clamping. Right minithoracotomy offers an excellent approach to the mitral valve in patients who have had previous cardiac surgery through a median sternotomy.

In the present series, the median blood loss was only 400 ml and there was no re-exploration for bleeding. There was only one hospital mortality (0.45%). Other authors have reported similar hospital mortality of 1.1%, 3.7% and even zero percent. Mohr et al. reported a mortality rate of 9% in their initial experience with the port-access approach. Their initial experience was complicated with significant morbidity, including acute retrograde aortic dissections in 2 out of 51 patients. In our present series, the mean age of our patient population was younger and hence no aortic dissections or difficulty in femoral artery cannulation was encountered. Besides the minimally invasive approach group patients were referred for surgery at an earlier symptomatic point in the course of their disease. On mean follow-up of 16.4±12.2 months, there was no late death or re-operation.

The excellent early echocardiographic results attest to the safety and efficacy of this approach, similar to those of conventional surgery. However, the minimally invasive technique required slightly longer operating time, which is attributed to the additional technical maneuvers to enhance exposure and proper de-airing under TEE control.

In conclusion, our results of minimally invasive mitral valve surgery suggest that the procedure is safe and benefits the patient, through reduced ICU stay, lower blood transfusion requirement, less postoperative discomfort, better cosmesis and earlier hospital discharge.

**Acknowledgment:** We thank Mrs Preeti Saxena for her secretarial assistance.

**Reference**

Prospective epidemiological studies have identified several independent coronary risk factors including smoking, dyslipidemia, hypertension and diabetes mellitus (DM). A risk of myocardial infarction was found to be directly related to the concentration of total cholesterol and LDL-cholesterol and inversely related to HDL-cholesterol. A long-term predictive value of elevated C-reactive protein (CRP) levels was found in patients with documented coronary artery disease (CAD) and angina and in individuals with multiple risk factors. Moreover, in the Physicians’ Health Study, among low-risk individuals, CRP levels within the normal range were linearly related to the incidence of myocardial infarction over a follow-up period of 8 years.
Alternative markers of CAD risk are needed because standard cardiovascular risk factors incompletely predict incidental CAD events. CRP, a serologic marker of inflammation, has also been associated with the risk of development of coronary heart disease (CHD). It is possible that CRP is predictive for CHD risk either through a correlation with CAD extent (a disease marker) or as an indicator of inflammation that leads to atherothrombotic events such as plaque rupture (a process marker). Defining the relationships between CRP and disease markers (such as CAD extent assessed by coronary angiography) will enhance our understanding of whether inflammatory markers such as CRP would be complementary or redundant when combined with clinical risk prediction with other risk markers. To investigate further whether CRP is predictive for CHD risk either through a correlation with CAD extent (a disease marker) or as an indicator of inflammation that leads to atherothrombotic events such as plaque rupture (a process marker). Defining the relationships between CRP and disease markers (such as CAD extent assessed by coronary angiography) will enhance our understanding of whether inflammatory markers such as CRP would be complementary or redundant when combined with clinical risk prediction with other risk markers.

To investigate further whether CRP is predictive for CHD risk either through a correlation with CAD extent (a disease marker) or as an indicator of inflammation that leads to atherothrombotic events such as plaque rupture (a process marker). Defining the relationships between CRP and disease markers (such as CAD extent assessed by coronary angiography) will enhance our understanding of whether inflammatory markers such as CRP would be complementary or redundant when combined with clinical risk prediction with other risk markers.

**Methods**

**Patient population:** We carried out a cross-sectional study for which 100 patients referred for coronary angiography were allocated. Written informed consent was obtained from all study subjects by which they authorized angiography. Thus, the purpose of this analysis was to explore the relationships between CRP and the extent and severity of CAD assessed by coronary angiography.

**Variables assessed:** The medical record of each patient was reviewed and each patient was interviewed to determine the presence of risk factors for atherosclerotic cardiovascular disease. Coronary arteriography studies were performed according to the technique of Judkins after a 12-hour fasting period. Two experienced cardiologists blinded for clinical and laboratory data reviewed the cinefilms. Angiographic severity of CAD was defined by the addition of three-vessel score systems (minimum score 0; maximum score 27). Cardiac markers included (i) vessel score: 0–3 points; 1 point for each of the three main coronary arteries with a diameter stenosis. (ii) Segment score: 0–3 points; each coronary artery was divided into three segments. (iii) Stenosis score: 0–3 points; 0, 1, 2, 3 points for no, less than 50%, 50% to 75% and more than 75% diameter stenosis, respectively. CAD was defined by the presence of stenosis of at least one epicardial coronary vessel of any degree.

Fasting venous blood samples were obtained between 8:00 a.m. and 10:00 a.m. in plain tubes and in tubes containing EDTA or buffered citrate. The plasma was separated by centrifugation (2000 g for 20 min) within 1 h. Laboratory testing was done immediately after blood sampling. Plasma lipoprotein cholesterol concentrations were measured according to the procedures of the Lipid Research Clinics. Glucose, total cholesterol and LDL-cholesterol were measured with standard laboratory equipment (Hitachi, Roche, Germany). High-sensitivity CRP (hsCRP) was assayed by rate nephelometry (Behring NA latex CRP; Behring, Germany). The median normal value for CRP is 0.7 mg/L, and the analytical variability was 5.2%.

Measures of CRP were expressed in the model as quintiles. The lowest group was used as the reference category in all the analyses. The cut-off points used were: first quintile—serum CRP less than 3 mg/L; second quintile—serum CRP ranging from >3 to 6 mg/L; third quintile—serum CRP ranging from >6 to 9 mg/L; fourth quintile—serum CRP ranging from >9 to 12 mg/L; fifth quintile—serum CRP >12 mg/L. Patients' characteristics including the mean values for age and other selected variables are shown in Table 1. The estimates of the relative risk of CHD according to the quintile of serum CRP are shown in Fig. 1.

**Statistical analysis:** All the data are reported as median and mean±SD, if not otherwise specified. To have an 80% chance of detecting a significant (at the two-sided 5% level) 45% difference between the groups in the CRP levels, 33 subjects in each group were required (99 total). Tests of the significance of trends across categories of CRP were conducted in the model by treating the quintiles as ordered categories scaled to the median for each quintile. Statistical analysis was performed using the ANOVA, or Mann–Whitney rank–sum test, where appropriate, in case of continuous variables between different groups. The power of the Mann–Whitney rank–sum test was confirmed (calculated to be >85%) by the use of formulae provided by Noether. In case of dichotomous or categorical variables, the Chi-square test was used. Step-wise logistic regression was performed to assess the ability to use a subject's serum CRP concentrations to determine the probability of his or
her having CAD while other predictor variables were simultaneously considered. Statistical significance was considered as rejection of the null hypothesis with >95% confidence (p values <0.05 were considered significant).

Results

Estimates of the relative risk of CHD for the third quintile of serum CRP as compared with the first quintile were 1.79 (95% confidence interval: 1.23–2.39). Serum CRP levels were 3.54 (±7.07) mg/L, 11.41 (±13.5) mg/L and 5.66 (±8.32) mg/L in groups A, B and C, respectively and represented an independent risk factor for the presence of CAD assessed by coronary angiography (p<0.01).

Moreover, the presence of angiographic CAD was associated with patient age (p=0.048), male sex (p<0.01), high LDL-cholesterol levels (p=0.02), low HDL-cholesterol levels (p=0.02), high plasma fibrinogen levels (p<0.01) and high fasting total homocysteine levels (p=0.04).

Discussion

Postulated mechanisms for the association between CRP and the development of CHD include a possible relationship to the extent of coronary atherosclerosis (a disease marker) or the extent of inflammation within the atherosclerosis present (a process marker). In this cross-sectional study of patients referred for coronary angiography, we compared serum CRP levels to the presence and extent of CAD assessed by coronary angiography.

The principal finding of this study is a relationship between CRP and CAD, suggesting that the relationship

<table>
<thead>
<tr>
<th>Table 1. Sample characteristics of patients</th>
</tr>
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<tbody>
<tr>
<td>No overt CAD (group A)</td>
</tr>
<tr>
<td>-------------------------</td>
</tr>
<tr>
<td>Age (mean; range)</td>
</tr>
<tr>
<td>Gender (male %)</td>
</tr>
<tr>
<td>History of hypertension (%)</td>
</tr>
<tr>
<td>History of myocardial infarction (%) (&gt; 2weeks)</td>
</tr>
<tr>
<td>Diabetes mellitus (%)</td>
</tr>
<tr>
<td>Current smoker (%)</td>
</tr>
<tr>
<td>Stable angina (%)</td>
</tr>
<tr>
<td>Angina class (CCS)</td>
</tr>
<tr>
<td>I (%)</td>
</tr>
<tr>
<td>II (%)</td>
</tr>
<tr>
<td>III (%)</td>
</tr>
<tr>
<td>Unstable angina (%)</td>
</tr>
<tr>
<td>De novo (%)</td>
</tr>
<tr>
<td>Crescendo (%)</td>
</tr>
<tr>
<td>Post MI (%)</td>
</tr>
<tr>
<td>Serum ferritin (ng/ml)</td>
</tr>
<tr>
<td>Transferrin saturation (%)</td>
</tr>
<tr>
<td>Serum iron (µg/dl)</td>
</tr>
<tr>
<td>Fasting glucose (mg/dl)</td>
</tr>
<tr>
<td>Total cholesterol (mg/dl)</td>
</tr>
<tr>
<td>LDL-cholesterol (mg/dl)</td>
</tr>
<tr>
<td>HDL-cholesterol (mg/dl)</td>
</tr>
<tr>
<td>Total homocysteine (µmol/L)</td>
</tr>
<tr>
<td>Erythrocyte sedimentation rate (mm/h)</td>
</tr>
<tr>
<td>HbA1c (%)</td>
</tr>
<tr>
<td>Plasma fibrinogen (g/L)</td>
</tr>
<tr>
<td>Serum free thyroxine (ng/dl)</td>
</tr>
<tr>
<td>Plasma lipoprotein(a) (mg/dl)</td>
</tr>
<tr>
<td>Serum CRP (mg/L)</td>
</tr>
</tbody>
</table>

Values as mean ± standard deviation (SD) when not otherwise specified.
CAD: coronary artery disease; CCS: Canadian Cardiovascular Society; MI: myocardial infarction.
To convert the values of serum iron to micromoles per liter multiply by 0.1791; and to convert the values of serum total cholesterol to millimoles per liter multiply by 0.02586.
between hsCRP and CHD events could be both the result of an active inflammatory process and a “passive” marker of the presence and extent of atherosclerosis. Several lines of evidence suggest a role for CRP in predicting the presence or absence of atherosclerosis. First, CRP is related to standard cardiac risk factors and has been identified within atheroma, particularly co-localized with foam cells. Second, inflammation is an essential component in the development of atherosclerosis. Studies in genetically modified mice lacking macrophage colony-stimulating factor, interleukin-8, or monocyte chemotactic protein-1, or with impaired leucocyte signaling have demonstrated the inhibition of atherosclerosis. Such data have contributed to our basic understanding of the importance of inflammation in atherogenesis. However, the relevance of different levels of “subclinical” inflammation on the extent of development of atherosclerosis within populations of immunocompetent humans is unclear. In contrast, the strong association of inflammatory markers with atherothrombotic coronary events in humans provides clinical evidence, supporting basic data on the role of inflammation in promoting coronary plaque instability and thrombotic potential. In previous reports, CRP has been more consistently identified within atheromatous and potentially vulnerable plaques compared with fibrous plaques.

Our data support previous findings that CRP levels are elevated in patients with clinical CAD frequently identified by angiography. Moreover, our findings in patients referred for coronary angiography are consistent with data from studies showing that CRP levels do not show a linear correlation with the extent and severity of CAD on angiography.

Limitations: Our study has certain limitations. First, it is a cross-sectional study of patients referred for coronary angiography. Such a study design cannot establish causality. It can only establish an association. Hence, any conclusion derived from such a study must be considered preliminary and hypothesis-generating rather than hypothesis-proving.

Second, the finding that 40% of patients had no or minimal CAD reflects liberal selection criteria for coronary angiography. Thus, a particular group of patients with noncardiac chest pain has been included in this study. Therefore, this series and the results could be diluted by less rigorous referral and selection criteria for coronary angiography.

Third, including all patients with a score of 8 or more in the “severe CAD” group could have reduced the weightage of patients with single or multiple subtotal or total coronary artery occlusions that could be reflected by much higher CRP levels. Nevertheless, we defined these criteria for selection to a particular group because of sample size (”severe” group n=27). Introduction of further subgroups with very small numbers could invalidate the results.

On the other hand, group 1 comprises subjects that range from no to subclinical CAD. This could introduce error but reflects clinical reality and does not invalidate data, as coronary angiography (generally considered as a “gold standard” for invasive evaluation of the coronary arteries) has limited sensitivity for detection of subclinical CAD. Other diagnostic tools such as intravascular ultrasound (IVUS) could enhance diagnostic accuracy, but are not widely used in clinical practice.

Moreover, variability in commercial assays may limit the external validity of these data.

Conclusions: This study demonstrated that CRP is significantly related to the presence of coronary atherosclerosis as assessed by angiography. It suggests that serologic inflammatory markers are principally a measure of both the atheroinflammatory disease process and an index of the presence of coronary atherosclerotic plaques. The independent prognostic utility of quantifying systemic inflammation suggests that CRP and other inflammatory molecules as disease and process markers of atherosclerosis may be excellent tools in CHD prediction. This hypothesis requires direct confirmation in prospective clinical trials.

In contrast, these data suggest that CRP is not associated with severity of CAD in patients referred for coronary angiography.

References
C-Reactive Protein and Coronary Atherosclerosis


Autologous Right Atrial Patch for Closure of Atrial Septal Defect

Arkalgud Sampath Kumar, Shiv Kumar Choudhary, Ruma Ray, Sachin Talwar, Rajnish Juneja
Cardiothoracic Sciences Centre, All India Institute of Medical Sciences, New Delhi

Variations in the size and morphology of atrial septal defects (ASD) often necessitate the use of a patch for surgical closure. Prosthetic patches are associated with infrequent but definite problems. As an alternative, we used a right atrial free-wall patch in 12 patients, 7–54 years of age.

**Methods and Results:** The presence of a large secundum atrial septal defect (n=2), associated mitral valve regurgitation (n=7), primum atrial septal defect (n=2) and sinus venosus defect (n=1) necessitated the use of a patch. The mitral valve was repaired in 9 patients (including 2 with a primum defect). One patient with a primum defect who was in congestive heart failure preoperatively died after 3 weeks due to refractory ventricular fibrillation. The remaining patients were discharged 5 to 7 days post procedure. No flow was detected across the septal patch on predischarge echocardiography. One patient underwent reoperation for failed mitral valve repair one month postprocedure. At reoperation, the patch was found to be intact with normal texture and without any suture dehiscence. Histopathological examination of the explanted patch revealed viable endothelium and subendothelial muscle on both surfaces of the patch. Follow-up ranged from 6 to 36 months. Echocardiography performed after 6 to 32 months post procedure showed an intact patch with no residual defect. All the patients are in sinus rhythm. Holter monitoring performed in 6 patients was normal in all of them. Electrophysiological study was performed in 2 patients using a mapping catheter 4 and 6 months post-procedure, respectively, and recorded normal atrial potentials from the site of the patch.

**Conclusions:** The use of an autologous free right atrial wall as a patch for atrial septal defect closure is a viable option. *(Indian Heart J 2002; 54: 289–291)*

**Key Words:** Atrial septal defect, Pericardial patch, Cardiopulmonary bypass

**Background:** Prosthetic or pericardial patches used for the closure of atrial septal defects are associated with infrequent but definite problems. As an alternative, we used a right atrial free-wall patch in 12 patients, 7–54 years of age.

**Methods**
From July 1998 through March 2001, 12 patients (8 females), 7–54 years of age (median 22 years) underwent closure of ASD with an atrial patch in our institution. The diagnosis was secundum ASD in 9 patients, primum ASD in 2, and sinus venosus ASD in 1. Both the patients with primum ASD and 7 of those with secundum ASD had associated moderate-to-severe mitral regurgitation. Dyspnea on exertion was the presenting complaint in all while 2 patients had frank congestive heart failure. Preoperatively, 3 patients were in atrial fibrillation while the remaining were in normal sinus rhythm.

A right anterolateral thoracotomy was used in 7 patients while a mid-sternotomy approach was adopted in the remaining. Normothermic cardiopulmonary bypass was established with aortic and bicaval cannulation. The superior vena cava was cannulated through the right atrial appendage except in the patient with sinus venosus ASD in

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whom the superior vena cava was cannulated directly. The
inferior vena cava was cannulated through the body of the
right atrium. Antegrade, hyperkalemic, cold blood
cardioplegia and topical ice slush were used for myocardial
preservation. The right atrium was opened by an oblique
atriotomy incision parallel to and 1 cm away from the
atrioventricular groove. The regurgitant mitral valve was
repaired (n=9). The presence of a large secundum ASD
(almost common atrium) in 7, primum ASD in 2 and sinus venous
defect in 1 necessitated patch closure of the ASD. An
appropriately sized patch of the free right atrial wall was
obtained from the inferolateral flap of the atriotomy
incision, care being taken not to incise the crista terminals.
The patch was sutured in place with 5-0 polypropylene
sutures, with the trabeculated endocardial surface towards
the left atrium. The right atrial incision was sutured directly
without the need for a patch. The patient was weaned away
from bypass in the usual fashion.

Transesophageal echocardiography (TEE) was
performed to assess mitral valve function. Before discharge
from the hospital, transthoracic echocardiography was also
performed in all the patients to assess the status of the septal
patch. After discharge from the hospital, the patients were
followed up in the outpatient department. All the patients
underwent serial transthoracic/transesophageal
echocardiographic evaluation after 1 month, 6 months and
then at yearly intervals after the procedure. Five patients
underwent 24-hour ambulatory Holter monitoring after
an interval of 4 to 12 months post procedure. Two patients
underwent electrophysiological study using a mapping
catheter at an interval of 4 and 6 months post procedure,
respectively.

Results

All the patient survived the operation. One 30-year-old
patient, who had severe cardiomegaly and had undergone
mitral valve repair and primum ASD closure, developed
resistant ventricular fibrillation and died 3 weeks after
surgery. The remaining patients were discharged after
5–7 days. No flow was detected across the septal patch on
predischarge echocardiography.

In the case of a 45-year-old female, the mitral valve
repair failed and she had to be reoperated after one month.
At reoperation, the patch was found to be intact with
normal texture and no suture dehiscence was seen. Histopathological examination revealed an intact
endocardial lining. The original endocardial lining and the
epicardium (the neo-endocardium after implantation)
could not be differentiated. The subendocardial
myocardium was histologically viable as seen beneath both
the aspects of the implanted patch. The central core of
myocytes underwent coagulative necrosis with a loss of
nuclear detail (Fig. 1). The necrotic zone appeared bland,
as there was no infiltration by inflammatory cells including
macrophages. Immunohistochemical stain for desmin
showed preservation of immunoreactivity within the
subendocardial myocytes, signifying viability. The central
necrotic muscle appeared unstained (Fig. 2).

Follow-up ranged from 6 to 36 months and was 100%. All
the patients were asymptomatic. Echocardiographic
examination performed after 6–32 months revealed an
intact patch with no residual defect. The echo density of
the patch was similar to that of the rest of the interatrial
septum. Even after 32 months of follow-up, the
echocardiographic texture of the patch had not altered. One
The patient had mild mitral regurgitation. All the patients were in sinus rhythm. Holter monitoring in 5 patients revealed normal sinus rhythm in all of them. Only one patient, a 54-year-old female who underwent secundum ASD closure and mitral valve repair, showed occasional atrial ectopics. Electrophysiological study carried out in 2 patients using a mapping catheter after 4 and 6 months, respectively, recorded normal atrial potentials from the site of the patch.

Discussion

The choice of a patch for surgical closure of an ASD generally depends on the surgeon and institutional practice. It also depends on the morphology of the ASD and age of the patient. We have used synthetic and pericardial patches (fresh and treated with 0.625% gluteraldehyde). However, some problems remained, such as patch dehiscence, aneurysm formation, residual defect, shrinkage and hemolysis. Thrombosis and embolic complications have also been reported in the literature.1–3 We used the free atrial wall to avoid these problems as it is autologous, easy to handle, elastic and has a smooth lining on both sides. Because the right atrium is dilated in an ASD, removing a small part of the wall does not cause any problems and it can be obtained in all patients with an ASD. The right atrial incision can be closed directly without a patch.

Although it is difficult to demonstrate the contractile function, in 2 of the 11 patients electrical activity in the patch was similar to that in the rest of the atrium. This observation indicates a viable (living) patch and can only be ascertained by this method without explanting the patch. The patch explanted one month postoperatively showed viable endothelium and subendothelial muscle on both sides of the patch. This suggests that the patch remains viable and functional. Compared to all other patch materials, the free right atrial wall provides a nonthrombogenic surface on both sides, an important advantage in this situation.

To conclude, the use of autologous free right wall as a patch for closure of ASD is a viable option. Early results are satisfactory. However, longer follow-up may demonstrate the true advantages of a living autologous patch for ASD closure.

References

Unusual ST–T Changes in Ebstein’s Anomaly With Occlusion of a Nondominant Coronary Artery

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We present a case report of a patient of Ebstein’s anomaly presenting with unusual ECG changes during acute coronary syndrome. The patient had undergone radiofrequency ablation of right posteroseptal accessory pathway. Two years later, he presented with acute chest pain. His ECG revealed ST elevation of 6–7 mm in leads III, aVF, V₃₃, V₁₋₄ with atrioventricular dissociation. He was thrombolysed for the same. He subsequently underwent an angiogram for continuing angina. His angiogram showed a nondominant right coronary artery with a 95% stenosis. The left circumflex artery was dominant but without any stenosis. The left anterior descending artery was also normal. Angioplasty and stenting were done for the right coronary artery lesion and the patient did well on follow-up. The ST segment elevation in the anterior precordial leads resulting from occlusion of a nondominant right coronary artery is unusual. The possible reason for this is the isolated right ventricular infarction in the absence of any left ventricular infarction. Thus the electrical current of injury resulting from the right ventricular infarction was unopposed by any counterbalancing current of injury from the inferior surface of the left ventricle. (Indian Heart J 2002; 54: 292–294)

Key Words: Ebstein’s anomaly, Pre-excitation, Myocardial infarction

Ebstein’s anomaly is a congenital heart disease with a prevalence of 0.5%. In 20%–30% cases, there is an associated Wolff–Parkinson–White syndrome. No particular mention is made in the literature of electrocardiographic (ECG) changes, if these patients were to develop coronary artery disease. This case report describes the unusual features seen on surface electrocardiogram (ECG) in a patient with Ebstein’s anomaly who developed acute myocardial infarction (MI).

Case Report

A 32-year-old male had multiple hospital admissions with a history of dyspnea on effort and recurrent palpitations since the age of 5 years. Clinical examination at the time of first admission revealed a pulse rate of 80 beats/min and blood pressure of 120/80 mmHg. Cardiovascular examination revealed the apex to be in the sixth intercostal space, a grade I parasternal heave, widely split S₁, wide and variable split S₂, and right ventricular (RV) S₃ and S₄. A harsh grade 4/6 murmur was heard at the left sternal border which did not increase with inspiration. A chest X-ray (PA view) revealed a CT ratio of 68%, right atrial (RA) enlargement and normal pulmonary blood flow. His echocardiogram revealed a displaced septal leaflet of the tricuspid valve (3.6 cm), RA enlargement, an intact atrial septum and severe tricuspid regurgitation with a right ventricular (RV) systolic pressure of 32 mmHg. There were no regional wall motion abnormalities of the right or left ventricle. The global left ventricular ejection fraction (LVEF) was 60%. His ECG showed pre-excitation which was consistent with a right posteroseptal accessory pathway (Fig. 1a). For this, the patient underwent an electrophysiological study and successful radiofrequency ablation of the accessory pathway was done (Fig. 1b). The subsequent hospital stay of the patient was uneventful and he did not experience any recurrence on follow-up.

He presented again to the hospital after 2 years with complaints of acute retrosternal chest pain and sweating. The ECG revealed ST segment elevation of 6–7 mm in leads III, aVF, V₃₃, V₁₋₄ (Fig. 2) with atrioventricular (AV) dissociation. He was diagnosed to have inferior, RV and anterior infarction and thrombolysed with streptokinase 15 lakh units. Subsequently, he recovered sinus rhythm and was discharged after 7 days. However, he continued to have
angina and dyspnea on effort (class III) and was taken up for coronary angiography after 2 months. The coronary angiogram revealed normal left main, left anterior descending (LAD) and a dominant left circumflex artery (Fig. 3). The right coronary artery (RCA) was nondominant with large RV branches and had a 95% type B, 12 mm long stenosis in the proximal segment (Fig. 4). The LV angiogram revealed no regional wall motion abnormality and an ejection fraction of 60%. The patient subsequently underwent stenting of the RCA. Following angioplasty, the patient has been free from angina on follow-up of more than 1 year.

**Discussion**

Ebstein’s anomaly is a congenital heart disease with a prevalence of 0.5%. The right-sided accessory pathways (posteroseptal, posterolateral) are well-known associations in 20%–30% of these patients. This patient population experiences arrhythmias: paroxysmal supraventricular tachycardia, atrial flutter and atrial fibrillation. However,
not much is mentioned in the literature about ECG manifestations of coronary artery disease or acute MI in these patients.

The point of interest in this case report is the occurrence of ST segment elevation in the anterior precordial leads associated with disease of a nondominant RCA. ST segment elevation in the anterior precordial leads in the setting of an acute inferior wall MI may present an unusual ECG presentation of right ventricular MI. In a report by Mafrici et al., 3 patients with inferior MI had ST segment elevation in the left precordial leads. Coronary angiography revealed proximal RCA occlusion and percutaneous transluminal coronary angioplasty (PTCA) was successfully done in 2 patients. Tan et al. reported an isolated case of right ventricular MI with massive ST segment elevation in the precordial leads resembling anterior MI; here also angiography revealed single-vessel disease involving the RCA.

Porter et al. reported a case of isolated RV infarction with minimal ST segment elevation in the left precordial leads and accompanying ST elevation in the inferior leads. Angiography revealed single-vessel disease involving the RCA which was small and nondominant. In our patient also, a nondominant RCA resulted in anterior precordial ST segment elevation. This might have been accentuated by the distorted anatomy resulting from Ebstein’s anomaly. From a review of the literature, it is apparent that extensive anterior wall ST segment elevation can occur due to occlusion of the RCA. This is more likely to occur when the RCA is large but nondominant and in hearts with a distorted anatomy. The possible reason for this is the isolated RV infarction in the absence of any LV infarction. Thus, the electrical current of injury resulting from RV infarction is unopposed by any counterbalancing current of injury from the inferior surface of the LV.

Our patient was a young male in whom smoking was the only risk factor. This raises the doubt as to whether the stenosis in the RCA was atherosclerotic or due to some mechanism related to his previous radiofrequency catheter ablation. Among the possible mechanisms for radiofrequency-related coronary injury, spasm is postulated to be the most common, especially if the radiofrequency energy is delivered within the coronary sinus, because of its proximity to the epicardial surface of the heart. Inadvertent delivery of an intracoronary radiofrequency current can also result in acute or subacute coronary occlusion. Thrombus formation at the site of radiofrequency ablation with embolization into coronary circulation is a possible mechanism but has never been reported. Alternatively, the coronary artery could be directly traumatized by the ablation catheter during attempts to cross the aortic valve with subsequent intimal dissection and thrombus formation.

In our patient, none of these mechanisms are likely as the radiofrequency ablation was done on the right heart chambers and its application was spatially and temporally remote from the site where stenosis in the RCA was seen. In conclusion, this patient with Ebstein’s anomaly had atherosclerotic occlusion of a nondominant RCA, which manifested as extensive ST–T changes in the inferior and anterior precordial leads. The possibility of occlusion of a nondominant RCA should be considered in patients presenting with ST elevation of both inferior and anterior leads.

References
Primary chylous effusion of the pericardium is a rare entity of obscure etiology.1–4 We describe a 2-month-old infant with a massive chylopericardium which was successfully treated with surgical ligation of the thoracic duct and creation of a posterior pericardial window.

Case Report
A 2-month-old, 6 kg male infant had a history of cough and tachypnea of 3 weeks’ duration. Clinical examination revealed a well-grown infant with no obvious facial dysmorphism and bilateral congenital talipes equinovarus. He had a resting heart rate of 140 beats/min, blood pressure of 90/60 mmHg and a respiratory rate of 56/min. Cardiac examination revealed a prominent third heart sound. Chest X-ray showed massive cardiac enlargement. The echocardiogram confirmed massive circumferential pericardial effusion (maximum diameter 2 cm) and revealed no structural abnormality in the heart. There was evidence of right atrial and right ventricular diastolic collapse.

A diagnostic pericardiocentesis revealed milky white fluid. Analysis showed a total cholesterol level of 110 mg/dl, triglycerides 1021 mg/dl, HDL cholesterol 0.7 mg/dl, LDL cholesterol 15 mg/dl and VLDL cholesterol 204 mg/dl. The protein content was 4.5 g/dl with albumin 3.9 g/dl. The amylase level in the fluid was 1410 IU/L. Microscopy revealed abundant mature lymphocytes with a few smudge cells and occasional mesothelial cells. Culture from the fluid was sterile after 48 hours. The blood counts, serum lipids and liver function tests were within normal limits. A CT scan of the thorax revealed a massive pericardial effusion along with thymic enlargement; the effusion had a water density of 5–12 HU. No other abnormality was identified in the thorax or the mediastinum.

One hundred fifty milliliters of fluid was aspirated from the pericardium and an echocardiogram confirmed complete removal. A pigtail catheter was inserted in the pericardium for continuous drainage as there was rapid re-accumulation to the original size overnight. The infant was then taken up for a surgical procedure. Via a left posterolateral thoracotomy in the fifth intercostal space, the thoracic duct was identified between the inferior vena cava anteriorly and the esophagus posteriorly (just above the diaphragm) and ligated. In addition, a posterior pericardial window was created. The postoperative period was uneventful and the pre-discharge chest X-ray and echocardiogram showed no pericardial or pleural effusion. The infant was symptom-free and thriving at 6 months’ follow-up, and the echocardiogram revealed no residual pericardial effusion.

Discussion
Surgical trauma is the commonest cause of chylopericardium. Other causes include radiation, mediastinal lymphangiomas, tuberculosis or lymphomas which press on the thoracic duct.1,5–7 Thoracic duct obstruction with failure of adequate collateral drainage results in the reflux of chyle through the lymphatics draining the pericardium. When no cause is identified, the condition is called primary or idiopathic chylopericardium.8,9 To date, only four cases have been...
reported in infants.\textsuperscript{1,4,9,10} Current treatment includes dietary medium chain triglycerides, continuous pericardial drainage, pericardiectomy and thoracic duct ligation.\textsuperscript{1,4,7,8,9,10} The age at presentation of primary chylopericardium ranges from the newborn to the second decade.\textsuperscript{1,11,12} Although there are reports of spontaneous recovery following repeated pericardiocentesis, aggressive evaluation and management is recommended because cardiac tamponade is a potential complication.\textsuperscript{1,1,5,8} Nonsurgical management involves institution of steroid therapy and a diet of medium chain triglycerides.\textsuperscript{1,5,8,9} This was not considered in the present case because of the rapid accumulation of fluid after initial drainage and practical difficulties with instituting a specialized diet in a breast-fed infant. We, therefore, chose to ligate the thoracic duct and create a pericardial window. The lymphatic communication to the pericardium has been successfully demonstrated in older patients by lymphangiography and radionuclide scanning. These modalities are useful in demonstrating the fistulous connections between the thoracic duct and the pleura or pericardium. However, it is technically difficult to accomplish this in infants, especially by lymphangiography. The information from these tests is useful for the resection and ligation of fistulae. Unlike in chylothorax, chylopericardium usually does not result from visible leakage from the thoracic duct and therefore operative attempts at duct visualization are not considered essential. Mass ligation or ligation and resection of the thoracic duct can correct the condition.\textsuperscript{1,11}

To summarize, primary chyloous pericardial effusion in an infant is a rare condition that can be successfully treated through thoracic duct ligation and creation of a posterior pericardial window.

References
Sildenafil in the Management of Primary Pulmonary Hypertension

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Primary pulmonary hypertension is a rare disorder of unknown etiology with a poor prognosis. There is no cure, and drug therapy is effective in only a few patients. Calcium-channel antagonists and anticoagulants are the mainstay of therapy. Prostacyclin therapy leads to significant clinical improvement but its use is restricted due to high cost and complex drug delivery systems. Sildenafil is a selective vasodilator and has been shown to be effective in decreasing pulmonary vascular resistance in animal models of pulmonary hypertension. We report the use of sildenafil in two patients of primary pulmonary hypertension who were refractory to conventional drug therapy.

Key Words: Primary pulmonary artery hypertension, Sildenafil, Beraprost

Case Reports

Case no. 1: A 30-year-old woman presented one year ago with dyspnea on exertion, lower extremity edema, dry cough and a history of occasional chest pain 2 months after her first delivery. She had no history of diet suppressant drug use or collagen vascular disease, and was HIV negative. Her electrocardiogram (ECG) showed sinus tachycardia and right ventricular enlargement while the chest X-ray showed cardiomegaly with a prominent pulmonary conus. An echocardiogram revealed dilated right-sided chambers. The estimated systolic pulmonary artery pressure was 80 mmHg and the left ventricle showed normal size and function. Pulmonary embolism as a cause was ruled out with a normal ventilation-perfusion lung scan and lower limb Doppler study. Pulmonary function tests, including diffusion capacity, were normal. The patient underwent cardiac catheterization. Relevant data are depicted in Table 1.

The patient was started on conventional therapy with calcium-channel blockers (amlodipine), warfarin, digoxin and diuretics. She was started on amlodipine 2.5 mg once a day, which was gradually increased to 15 mg twice a day. She initially responded with an increase in functional capacity; however, this improvement was short-lived and she gradually worsened to New York Heart Association (NYHA) functional class IV. At this stage, beraprost, an oral

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sildenafil in the management of patients with PPH from India.

Primary pulmonary hypertension (PPH) is a progressive disorder of unknown etiology characterized by elevated pulmonary artery pressure and pulmonary vascular resistance. It carries a poor prognosis and if untreated, life expectancy is less than one year. Only a few patients who respond to calcium-channel antagonists and anticoagulation may have a better prognosis. Continuous infusion of prostacyclin also reduces mortality due to PPH but catheter infections, systemic effects and tachyphylaxis limit the application of systemic prostacyclin. Treatment with inhaled iloprost and oral beraprost (prostacyclin analogues) have been shown to improve exercise tolerance in some patients. However, treatment with infusion, inhaled or oral prostaglandins is hampered by very high costs.

Sildenafil citrate is a selective vasodilator that enhances and prolongs the action of cyclic guanosine monophosphate (cGMP). In animal models of acute pulmonary hypertension, sildenafil decreased pulmonary artery pressures in a dose-dependent manner. There are few reports of the beneficial effects of sildenafil on PPH in humans. We report our experience with the use of sildenafil in 2 patients with severe PPH. In the first patient, the oral prostacyclin analogue (beraprost) was also used. This constitutes the first report of using beraprost and
prostaglycin analogue was added (10 µg q.i.d.) and the dose was gradually increased every two weeks to the maximum tolerated daily dose of 240 µg. There was no improvement in her clinical condition even after 2 months of therapy. Based on some recent reports on the use of sildenafil in the treatment of PPH, therapy with sildenafil 25 mg thrice a day was started and the dose stepped up gradually to 100 mg four times a day. The patient tolerated this dose of sildenafil. Amlodipine was gradually tapered off, while beraprost was continued. A marked improvement was noted within 2 weeks’ time and she showed progressive improvement over the next 1 month, being able to complete the 6 min walk test. At 5 months follow-up with a combination of beraprost (240 µg/day) and sildenafil (400 mg/day), echocardiography showed a pulmonary artery pressure of 44 mmHg. The patient is in NYHA functional class II and has resumed work.

Case no. 2: The second patient is a 33-year-old female with complaints of progressive dyspnea on effort for 2 years. She also had an increasing degree of fatigue with some heaviness of the chest on exertion. She denied any history of exposure to toxic chemicals, intake of weight loss medications or history suggestive of collagen vascular pathology. ECG revealed right axis deviation with right ventricular hypertrophy while the chest X-ray was normal. Pulmonary function tests and ventilation–perfusion scan were also normal. Transthoracic and transesophageal echocardiography demonstrated evidence of severe pulmonary hypertension (estimated right ventricular systolic pressure of 130 mmHg), with significant dilatation of the right side of the heart and a severe reduction in right ventricular systolic function. The structure and function of the left side of the heart were normal. There was no evidence of any intracardiac shunt. The patient subsequently had a right and left heart catheterization (Table 1) which showed severe pulmonary hypertension with a pulmonary vascular resistance of 25.92 Wood units. There was no evidence of a shunt lesion. On this basis, pulmonary hypertension was diagnosed and treated with a full dose of oral calcium-channel antagonists (amlodipine) and anticoagulants. Amlodipine was given in a dose of 15 mg twice a day. On repeat cardiac catheterization after 6 weeks of therapy, there was no improvement in the pulmonary artery pressure or pulmonary vascular resistance. The patient gradually worsened and had to be admitted with severe right heart failure and hypoxemia. As a last resort, oral sildenafil in a dose of 25 mg thrice a day was started. The patient tolerated this dose and showed remarkable improvement in her symptoms. Over the next week, the dose was gradually increased to 100 mg thrice a day and the patient showed substantial clinical improvement. Over a follow-up of 3 months, the dosage of sildenafil was increased to 100 mg four times a day and, the patient could complete 410 m on a 6 min walk test. Echocardiography showed a

<table>
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<tr>
<th>Case no. 1</th>
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<tr>
<td><strong>Pressure (mmHg)</strong></td>
<td><strong>Pressure (mmHg)</strong></td>
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<td>RA (mean 14)</td>
<td>RA (mean 5)</td>
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<td>RV 60/16</td>
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<td>PA 55/26 (mean 36)</td>
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<td>LV 100/8</td>
<td>LV 130/12</td>
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<td>AO 96/68 (mean 77)</td>
<td>AO 130/70 (mean 90)</td>
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<td>CO 3.1 L/min</td>
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<td>CI 2.0 L/min/m²</td>
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<td>PVR 8.7 Wood units</td>
<td>PVR 25.92 Wood units</td>
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<td>SVR 20.32 Wood units</td>
<td>SVR 31.48 Wood units</td>
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<td>PVR/SVR 0.43</td>
<td>PVR/SVR 0.82</td>
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<td>LV angiogram: normal</td>
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RA: right atrium; RV: right ventricle; PA: pulmonary artery; PCWP: pulmonary capillary wedge pressure; LV: left ventricle; AO: aorta; CO: cardiac output; CI: cardiac index; PVR: pulmonary vascular resistance; SVR: systemic vascular resistance
remarkable reduction in the estimated RV systolic pressure from 130 mmHg to 68 mmHg.

Discussion

Primary pulmonary hypertension is a progressive disease for which there is no cure. It mainly affects young women and carries a poor prognosis. Patients often present with severe exercise limitation, and pharmacological intervention with vasodilator therapy is directed towards reduction of the raised pulmonary artery pressure.

Calcium-channel antagonists are the mainstay of therapy but only a small number of patients respond. Continuous infusion of prostacyclin has also been shown to reduce mortality. However, application of systemic prostacyclin is limited by catheter infection, systemic hypotension, tachyphylaxis, and a lack of selectivity for the pulmonary vasculature. Therefore, despite some advances, the available therapies are limited by poor efficacy, a complex drug delivery system or very high costs. There is thus a need for treatment which achieves a sustained decrease in pulmonary artery pressure and pulmonary vascular resistance without these shortcomings.

Beraprost is a chemically stable and orally active prostacyclin analogue. An open-labeled, uncontrolled, dosing study of beraprost demonstrated significant improvement in cardiopulmonary hemodynamics and NYHA functional class in 34 patients. A follow-up study confirmed the sustained beneficial effects of this drug. A large, multicentric phase III trial, evaluating the effect of beraprost on disease progression in patients with pulmonary hypertension, is currently under way and will help to answer questions regarding its utility and feasibility. However, in the first case reported here, no adequate response to beraprost was observed when it was given alone.

Sildenafil citrate is a selective and potent inhibitor of cGMP-specific phosphodiesterase (PDE 5). It has been demonstrated in vitro that sildenafil, as a specific inhibitor of PDE 5, leads to smooth muscle relaxation via a nitric oxide-dependent increase of cGMP. Inhibition of PDE 5—found in high concentration in lung tissue—by sildenafil might reduce pulmonary vascular pressures by this pathway. To test this hypothesis, Weimann et al. studied the role of sildenafil on pulmonary artery pressures in pulmonary hypertensive lambs and found a dose-related decrease of pulmonary arterial pressures after the administration of oral sildenafil. This finding was further supported by Atz et al. who found that the use of sildenafil prevented rebound pulmonary hypertension in infants on withdrawal of nitric oxide treatment. However, there are only anecdotal reports of the beneficial effects of sildenafil in humans with PPH. Abrams et al. found it to be useful in a 4-year-old girl with childhood PPH. Recently, Prasad et al. observed a reduction of pulmonary artery pressure and improvement of exercise capacity in a young man with PPH who had received sildenafil for 3 months. Wilkens et al. studied the acute effects of inhaled iloprost (a prostacyclin analogue) plus oral sildenafil in 5 patients with PPH. They found significant and durable reduction in the mean pulmonary artery pressure and pulmonary vascular resistance with the use of sildenafil alone, and further improvement after inhalation of iloprost.

Besides oral sildenafil, studies are under way regarding the use of inhaled or intravenous sildenafil. Recently, Ichinose et al. reported the beneficial effects of inhaled sildenafil in an experimental lamb model with acute pulmonary hypertension. A phase II, open-label study on the acute effects of intravenous sildenafil in patients with pulmonary artery hypertension is also in progress in Europe.

In the 2 patients with PPH whom we studied, there was significant clinical improvement with sildenafil, despite the failure of conventional medical management. Therefore, we recommend that the role of sildenafil in PPH be further evaluated.

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Aortoarteritis involves narrowing or obliteration of the major arteries and branches of the aorta resulting in the terminology "pulseless disease". Tuberculosis, syphilis, rheumatic fever, systemic lupus erythematosus (SLE) and other autoimmune diseases have been implicated in its etiology. So far, 20 cases of aortitis syndrome coexisting with SLE have been described, of which 3 had associated antiphospholipid antibody syndrome (aPLS). To our knowledge, this is the fourth case of this rare association with certain unique features such as aortic regurgitation, coronary artery disease and pulmonary artery hypertension.

**Case Report**

The patient, a 41-year-old woman, presented with unstable angina of five days' duration in May 2000. In 1988, she was evaluated for asynchronous pulses and hypertension. Angiography revealed marked narrowing of the right subclavian artery with poststenotic dilatation, complete occlusion of the left subclavian artery with subclavian steal syndrome (Fig. 1), an irregularly outlined thoracic aorta and normal renal arteries. Antinuclear antibodies (ANA) were positive. A diagnosis of Takayasu’s arteritis type III was made and the patient discharged on antihypertensive therapy. In 1990, the patient developed Raynaud’s phenomenon. Her Mantoux test was positive (22 mm). She took steroids and antitubercular treatment for 1 year. In October 1996, she had an anterior wall myocardial infarction (not thrombolyzed). Angiography at our hospital revealed a 99% stenosis of the left anterior descending (LAD) artery which was subjected to angioplasty (Fig. 2). The patient also had grade 2/4 aortic regurgitation (AR) and her pulmonary pressure was 64/36 mmHg (Fig. 3).

**Key Words:** Aortoarteritis, Systemic lupus erythematosus, Antiphospholipid antibody syndrome
April 2000, the patient had abdominal pain associated with 15–20 episodes of melena over 2 days which required blood transfusions. Upper gastrointestinal endoscopy revealed mild gastric and duodenal erosion.

The patient also had (i) progressive thinning of the fingers since childhood with shedding of the nails and swelling of the terminal phalanges of the 4th and 5th digits of the left hand; (ii) unexplained high-grade fever with arthralgias for 1 month at the age of 15 years; (iii) five recurrent abortions in the third month of pregnancy (1983–87); and (iv) had no family history of similar complaints.

Examination revealed marked pallor. All the peripheral pulses were felt but the left brachial and radial pulses were reduced in intensity and asynchronous as compared to the right. Pulsations were present in the right supraclavicular region and the carotids were bounding. Bruits were heard over both the carotids, supraclavicular (right more than left), epigastric and right axillary regions. Pistol shot sounds were heard over the femoral arteries. The blood pressure (BP) in the supine position in the right arm was 140/70 mmHg, left arm 110/70 mmHg and both the legs 200/80 mmHg. Cardiac examination revealed a hyperdynamic apex in the 5th and 6th intercostal spaces in the midclavicular line; grade III parasternal heave; loud P2, grade 3/6 systolic murmur in the aortic, pulmonary and mitral regions; and grade 2/6 early diastolic murmur in the aortic region audible on hand grip. The liver and spleen were enlarged 2 cm below the costal margin.

Investigations revealed a hemoglobin (Hb) level of 7.2 g% with microcytic hypochromic anemia, TLC 6300/cmm, ESR 61 mm in the first hour (Wintrobe), platelet count 32 000/cmm, blood urea 77.3 mg%, creatinine 1.4 mg%, 24-hour urinary protein 1×2g/L, negative Coombs’ test and VDRL, positive ANA—diffuse pattern, strongly positive double-stranded DNA (dsDNA) 50 units (normal range 0–5.2), raised IgG anticardiolipin antibodies 18.8 units (normal range 0–12), raised APTT 73 s (control 28.4 s), strongly positive lupus anticoagulant. Lipid profile revealed a serum cholesterol level of 136 mg/dl, HDL 28 mg/dl, triglycerides 95 mg/dl, VLDL 19 mg/dl and LDL 89 mg/dl.

Electrocardiogram (ECG) revealed old anterior wall infarction changes with 1.5 mm ST–segment depression in the lateral leads. Chest X-ray and cardiac enzymes were normal. Echocardiography revealed thickening of the aortic cusps, moderate-to-severe AR, hypokinesia of the distal septum and anterior wall, an ejection fraction (EF) of 40%, pulmonary artery pressure of 50/24 mmHg and left subclavian steal syndrome (Fig. 2). Pulmonary tests revealed mild restrictive defect. The patient declined to give consent for angiography, kidney and skin biopsies.

The patient was given packed cell transfusions, stepped-up antianginal therapy, ACE inhibitors (ramipril) and oral steroids (prednisolone). Her Hb rose to 11.2 g%, platelet count to 96 000/cmm, APTT 39.3 s (test) [23.4 s (control) and 36.4 s (mixing test and control plasma)]. The angina subsided and the patient left on request on June 14, 2000.
Discussion

Five out of 6 American College of Rheumatology criteria supporting a diagnosis of aortoarteritis were met which included (i) age of onset <40 years; (ii) decreased left brachial artery pulse; (iii) blood pressure difference of >10 mmHg between the two arms; (iv) bruit over the subclavian artery and abdominal aorta; and (v) arteriographic abnormalities. Aortic regurgitation, pulmonary artery hypertension and myocardial infarction are uncommon but serious manifestations of aortoarteritis.1–3 Four of the American College of Rheumatology criteria supporting a diagnosis of SLE were met with which included: (i) hematological disorders—thrombocytopenia (<1 lakh), anemia; (ii) renal disorder—24-hour urinary protein 1 g/L; (iii) immunological disorder—strongly positive dsDNA; (iv) strongly positive ANA.

Associated aPLS was suggested by the history of recurrent fetal loss, findings of thrombocytopenia, thrombosis as evidenced by unstable angina and myocardial infarction, presence of lupus anticoagulant, raised APTT and raised anticardiolipin antibodies.7 Raynaud’s phenomenon and pulmonary artery hypertension can occur in both SLE and aortoarteritis. The episodes of melena could be explained by erosive gastritis or vasculitis.

SLE commonly causes thrombosis of the small and peripheral vessels; lesions of the aorta are rare but have been described.7,8 The incidence of cardiovascular involvement in SLE increases with associated aPLS.7 These cases usually have low cholesterol and HDL levels,10 as in our case. In one major study comprising 93 cases, 3 cases had proximal LAD occlusion and 1 had vasculitis and severe aortic regurgitation (similar to our case), though valvular thickening, vegetations and pericardial involvement were more common.9

It has been proposed that large vessel thrombosis occurs in SLE secondary to aPLS due to the presence of lupus anticoagulant and may mimic obstructive vasculopathy as seen in aortoarteritis.9 Aortitis syndrome involves mononuclear infiltration, granulomatous change and fibrosis in the media with intimal thickening and obliterative aortitis of the large vessels. Immune mechanisms (mainly cell-mediated immunity) probably play a major role.2,3 Tuberculosis has also been implicated.1–3 In fact, our case had a Mantoux test reaction of 22 mm and was placed on antitubercular treatment, though no other evidence of tuberculosis could be found. Endothelial injury may be mediated by immune complexes or vasculitis due to SLE.1,2,7 The thrombosis associated with hypercoagulable states may involve the vasa vasora of the major vessels and may mimic the vascular changes of aortoarteritis.4,8 Thus hypercoagulable states may also have a possible role in the pathogenesis and progression of aortoarteritis.

References
Left Ventricle Dynamics During Pulsus Alternans: Insights From Tissue Velocity Imaging

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A 34-year-old female patient with idiopathic dilated cardiomyopathy presented with hemodynamic pulsus alternans. Mitral annular tissue Doppler velocities showed reciprocal beat-to-beat alterations during systolic ejection and diastolic filling periods. Tissue velocity waves were unaltered during the isovolumic relaxation and contraction periods. (Indian Heart J 2002; 54: 304-305)

Key Words: Pulsus alternans, Dilated cardiomyopathy, Tissue Doppler echocardiography

Pulsus alternans or mechanical alternans is a term used to describe the phenomenon of alternate strong and weak ventricular contractions in the presence of an unaltered heart rate and QRS complex. There has been a prolonged debate about the mechanism of pulsus alternans. In this report, we present our observations on the myocardial dynamics of hemodynamic alternans as observed on tissue velocity imaging.

Case Report

A 34-year-old female patient with idiopathic dilated cardiomyopathy was detected to have pulsus alternans on clinical follow-up. Her echocardiogram showed a dilated left ventricle with global hypokinesia and an ejection fraction of 30% (Fig. 1). Pulsed Doppler at the left ventricular outflow tract confirmed hemodynamic pulsus alternans (Fig. 2). There was mild mitral regurgitation due to dilatation of the mitral valve annulus. Pulse Doppler at mitral inflow showed a restrictive filling pattern (E/A=3.2, deceleration time 102 ms) without any beat-to-beat variation. There was mild tricuspid regurgitation and the estimated right ventricular systolic pressure was 55 mmHg. Tissue velocity imaging was performed on the Vingmed System Five (General Electronics). A 10 mm sample gate was placed at the lateral and septal corners of the mitral annulus and tissue velocities were obtained in apnea. The Nyquist limits were set at -20 and +20 cm/s. Peak velocities and wave duration during isovolumic contraction time (IVCT), systolic ejection period (SEP), isovolumic relaxation time (IVRT), early left ventricular filling (E') and late left ventricular filling (A') were recorded. The left ventricular shortening (SEP) wave and relaxation waves were reciprocal beat-to-beat changes during systolic ejection and diastolic filling periods.

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Fig. 1. Apical 4-chamber view of the patient with idiopathic dilated cardiomyopathy showing a dilated left ventricle.

Fig. 2. Pulse Doppler tracing at the left ventricular outflow showing the presence of alternating small- and large-stroke volume confirming hemodynamic pulsus alternans. Note the ECG tracing below which a normal sinus rhythm is seen (R-R= sinus cycle length).
(E' and A') showed reciprocal alteration in duration and velocities (Fig. 3). Lengthening of the diastolic filling period (DFP) was associated with lower E' and A' velocities. The duration of the systolic ejection wave (S₂) of the next beat varied reciprocally, being shorter in duration with a longer diastolic filling period and vice versa. The peak velocities during either period also had a reciprocal relation to the duration of the wave. A longer wave duration was associated with higher velocity and vice versa. The isovolumic contraction and relaxation (IVC and IVR) waves were unaltered in their velocities and duration. These reciprocal variations in systolic and diastolic waves were not associated with any significant beat-to-beat alterations in the sinus cycle length (R–R) on ECG.

Discussion

Tissue Doppler imaging is a relatively new technique for evaluating regional and global myocardial function and it provides a quantitative estimate of the myocardial fiber dynamics during the entire cardiac cycle. Regional shortening and relaxation waves during ejection, diastolic filling, IVC and IVR can be independently and accurately estimated. To the best of our knowledge, the myocardial shortening and lengthening velocities have not been described earlier in a patient with hemodynamic alternans. This case highlights that pulsus alternans is associated with a reciprocal beat-to-beat alteration in the duration and peak velocities of waves during the systolic ejection and diastolic filling periods. Myocardial contraction and relaxation dynamics are, however, unaltered in the IVC and IVR periods.

The existing literature regarding the genesis of pulsus alternans is not clear as to whether alternans results from alteration in ventricular filling or an intrinsic abnormality in contractility of all or a portion of the muscle fiber. The current evidence is more in favor of an alteration in the contractile state as a causative process. It has been shown that an altered calcium cycling and restitution process are the prime causes of alternating forces with consequent hemodynamic alternans. However, our observations suggest that contractility and relaxation are unaltered during the IVC and IVR periods, which are relatively load-independent periods of myocardial contraction and relaxation. It has been shown earlier that the weaker beat in pulsus alternans is associated with shorter end-diastolic fiber length, due to preceding small end-systolic volume. Afterload reduction and sympathetic stimulation has also been shown to reverse this phenomenon. These findings and our observations suggest that the defect at the sarcomere level is predominantly an abnormality in the myocardium which reduces the ability to handle load changes. This reduction in contractility reserve and myocardial compliance results in an inability to rapidly compensate for volume changes. The alternating small and large stroke volumes therefore reverberate for a long time resulting in pulsus alternans.

References

Interventional Therapy for Multiple Cardiac Defects

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We describe a patient with a rare combination of coronary artery disease and congenital heart disease. The patient underwent successful complex and multivessel coronary angioplasty, balloon pulmonary valvuloplasty by the Inoue balloon and transcatheter closure of an atrial septal defect in a staged manner. It is technically feasible and safe to perform multiple interventions as an alternative to open heart surgery. (Indian Heart J 2002; 54: 306–308)

Key Words: Angioplasty, Valvuloplasty, Transcatheter atrial septal defect closure

Since its introduction in 1977, percutaneous transluminal coronary angioplasty (PTCA) has increasingly been applied to patients with complex lesions and multivessel disease.1–3 Similarly, balloon pulmonary valvuloplasty (BPV) as originally described by Kan et al.,4 is now considered the treatment of choice for valvular pulmonic stenosis (PS) with excellent short- and long-term results.5–7 In selected patients, atrial septal defect (ASD) of the fossa ovalis type can be successfully closed percutaneously with device implantation.8

We report the simultaneous presence of significant multivessel coronary artery disease and secundum ASD with severe valvular PS and bidirectional shunting. The patient was successfully treated with percutaneous multivessel revascularization, dilatation of the pulmonary valve by an Inoue balloon and closure of the ASD with the Amplatzer septal occluder, performed in two stages.

Case Report

A 65-year-old male presented with a past history of cardiac murmur since early childhood, exertional breathlessness (New York Heart Association [NYHA] functional class II) for 15 years, effort angina (Canadian Cardiovascular Society class III) for 6 months and 1 episode of syncope about 3 weeks prior to presentation. Risk factors for coronary artery disease included essential hypertension and diabetes mellitus. The treadmill test was strongly positive for reversible ischemia. Cardiac catheterization and angiography done at the age of 47 years revealed moderate valvular PS with a peak systolic gradient (PSG) across the pulmonary valve of 52–54 mmHg, following which the patient was advised medical follow-up. Echocardiography (transthoracic and transesophageal) done at the time of admission revealed a mildly dilated right atrium (RA), normal-sized and hypertrophied right ventricle (RV) with adequate contractility and severe valvular PS (PSG 90–96 mmHg); in addition, a secundum ASD (12 mm in size) with bidirectional flow and good size upper and lower rims of septal tissue was also detected.

Diagnostic cardiac catheterization and angiography confirmed the presence of severe and calcific valvular PS (PSG 82–85 mmHg) and a small secundum ASD with bidirectional shunting (right-to-left and left-to-right shunts being 0.2 and 0.3 L/min/m², respectively; systemic arterial saturation 90.7%) (Fig. 1). Coronary angiography showed a totally (100%) occluded left anterior descending (LAD) artery in its mid-segment with adequate retrograde filling through collaterals and evidence of distal diffuse disease; 90% ostial narrowing of a large first diagonal (D1) branch of the LAD; 95% stenosis of a large first obtuse marginal (OM) branch before its bifurcation into 2 moderate-sized divisions which showed multiple wall irregularities (Fig. 2); 75% eccentric stenosis of a dominant right coronary artery (RCA) in its proximal and middle segments with a large right ventricular branch arising from the diseased segment; and 75% stenosis in the proximal portion of a large posterior descending artery (PDA) with wall irregularities in its mid- and distal segments. Treatment options, including open heart surgery versus percutaneous means (multivessel angioplasty, BPV and transcatheter ASD closure), were discussed with the patient and his relatives and the merits and demerits of each treatment option.
explained to them. They opted for the nonsurgical method which was carried out in two stages. An informed written consent was obtained prior to each procedure.

In the first stage, BPV and multivessel angioplasty were planned. The pulmonary valve was dilated using an Inoue balloon (Fig. 3). The pulmonary annulus as measured on right ventricular angiogram was 22 mm. A 26 mm Inoue balloon over a 0.032" exchange guidewire was used to cross the stenosed and calcific pulmonary valve. The latter was then serially dilated with balloon sizes of 22, 24, 26 and 27 mm. After dilatation with the 27 mm balloon, the PSG was only 8–10 mmHg at the valvular level. At this stage, the Inoue balloon was withdrawn. In the same sitting, multivessel coronary angioplasty was performed. The ostial D1 and proximal OM1 lesions were opened by rotational atherectomy and adjunctive balloon angioplasty. Elective stenting of the RCA lesion was planned. A 4.0 mm Bx Velocity stent (Cordis Europa N.V., the Netherlands) was successfully deployed across the lesion in the RCA while the lesion in the proximal segment of the PDA was dilated with a 2.5 mm balloon. Check angiography revealed good opening of all lesions without any residual stenosis or angiographic complication. Hemodynamic study performed at the end of the procedure revealed a 9% step-up in oxygen saturation from the superior vena cava to the RA. The patient was intensively monitored after the procedure. As a routine, sheaths were removed the same day followed by twice daily injections of low-molecular-weight heparin for three days. In accordance with our protocol for stenting, aspirin and clopidogrel were prescribed.

Four days later, the patient was taken up for transcatheter closure of the ASD. The stretched diameter of the secundum ASD was 17 mm. Accordingly, the ASD was plugged with a 20 mm Amplatzer septal occluder. Transesophageal echocardiographic examination performed immediately after the procedure did not reveal any residual interatrial shunting. The patient’s overall
hospital stay was uneventful and he was discharged three days after the second procedure.

At the first follow-up visit, which was approximately three months after discharge, the patient was asymptomatic (NYHA functional class I) with marked improvement in exertional dyspnea and angina. There was no clinical cyanosis; oxygen saturation as measured by a pulse oximeter was 96%. Transthoracic echocardiography revealed a normal-sized RA and RV; the Amplatzer device was in position with no residual interatrial shunt and the PSG across the pulmonary valve was 15 mmHg. As per the patient’s wish he was not subjected to stress testing.

**Discussion**

We had performed BPV and transcatheter ASD closure earlier in four patients who presented with gradually progressive exertional breathlessness (NYHA functional class II–III). Echocardiography, cardiac catheterization and angiography had revealed a small secundum ASD with severe valvular PS and bidirectional shunting in these patients. Pulmonary valve dilatation by the Inoue balloon and ASD closure with a “buttoned” double-disc device were performed with excellent results. Others have also reported the feasibility of performing simultaneous balloon dilatation of the pulmonary valve and transcatheter ASD closure.

In the patient reported here, we were justified in performing multiple interventions because: (i) the LAD artery was diffusely diseased and nongraftable; (ii) the OM artery had a longish segment lesion just before its bifurcation into 2 moderate-sized branches, the latter having wall irregularities and it being technically difficult to place grafts; (iii) balloon valvuloplasty is the treatment of choice for valvular PS; (iv) device closure of small secundum defects with good upper and lower rims of septal tissue has a fairly high success rate; (v) surgery carried a somewhat higher risk because of associated chronic obstructive airway disease; and (vi) lastly, but not the least, the patient himself was afraid of open heart surgery and was looking for a less traumatic and invasive method, especially in patients who are at high surgical risk because of age or associated extracardiac diseases, or for those who refuse surgery. The only disadvantage of such interventional therapy, especially in a country like India is the higher cost compared to open heart surgery.

**References**

Neurovascular Rescue for Embolic Stroke Following Atrial Septal Defect Closure

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Strokes following cardiac surgery occur in about 5% of patients. Intra-arterial thrombolysis is a good option in such a setting where intravenous thrombolysis is contraindicated, and when in-hospital strokes are detected well within the window for treatment and the chances of complete reperfusion are maximum. On postoperative day 4 after atrial septal defect correction, a 34-year-old woman with paroxysmal atrial fibrillation developed left middle cerebral artery stroke causing severe neurological deficits. Intra-arterial thrombolysis with urokinase led to remarkable recovery. (Indian Heart J 2002; 54: 309–311)

Key Words: Embolic stroke, Intra-arterial thrombolysis, Paroxysmal atrial fibrillation

Perioperative cerebrovascular accidents following cardiac and noncardiac surgery can be either hemorrhagic or nonhemorrhagic. The incidence of stroke among patients who undergo general surgery is estimated to be about 2.9%. As many as 5% of patients undergoing coronary artery bypass grafting are afflicted with a stroke. Nonhemorrhagic stroke following cardiac surgery can occur as a result of destabilization of a pre-existing obstructive cerebrovascular plaque or embolism of atheromatous or thrombotic material from the cardiovascular source. Dislodgment of pre-existing or newly formed thrombi arising from the cardiac chambers, prosthetic materials, suture lines or from the aorta can occur either during surgery or subsequently. Atrial fibrillation, a common cause for embolic stroke, is an extremely common arrhythmia following cardiac surgery and appears most frequently on postoperative day 2 or 3.

Treatment of cerebrovascular ischemic events following surgery is very difficult. During the early postoperative period, systemic thrombolysis is associated with the risk of bleeding from the surgical sites. Intra-arterial thrombolysis uses a lower dose and local delivery of the lytic agent, and accomplishes clot-specific lysis of an occlusive thrombus with limited systemic plasminogen activation and is a viable therapeutic option for treating postoperative stroke.

Although several centers have started using intra-arterial thrombolysis for treating stroke, the reported experience in a probable embolic stroke following cardiac surgery is limited. In this report we present the case of a 34-year-old woman who developed stroke on postoperative day 4 following surgical correction of an atrial septal defect (ASD) and underwent intra-arterial thrombolysis followed by remarkable functional recovery.

Case Report

A 34-year-old woman was operated for correction of ASD. Following the surgery, the patient had recurrent supraventricular arrhythmias (paroxysmal atrial fibrillation). On postoperative day 4 while undergoing chest physiotherapy she suddenly developed right hemiplegia (motor power grade zero on the Medical Research Council scale) with global aphasia (NIH stroke scale score of 23). A left middle cerebral artery territory stroke was suspected. The patient was taken up for magnetic resonance imaging (MRI) of the brain, which showed fresh ischemia in the left insular cortex, temporal and parietal lobules and corona radiata, manifested as a bright signal on diffusion-weighted images (Fig. 1). The FLAIR, T-2W and T-1W images did not show any abnormalities. Magnetic resonance angiogram of the cerebral vessels showed complete occlusion of the left middle cerebral artery immediately distal to its origin (M1 segment).

A transthoracic echocardiogram showed an intact IAS patch. No thrombus was noted in the left atrium. The patient’s neurological condition precluded a transesophageal echocardiography (TEE).
The patient was taken up for cerebral angiogram. A carotid angiogram was performed through the right femoral access using a 7 F JRs 5 guide catheter. The left internal carotid angiogram showed a complete cut-off of the left M1 segment of the middle cerebral artery (TIMI 0) (Fig. 2). A 3 F Tracker catheter was placed in the internal carotid artery over a 0.018" coronary guidewire at the site of bifurcation of the internal carotid artery.

Thrombolysis was performed by intra-arterial urokinase 50,000 units bolus followed by 100,000 units hourly as infusion for 4 hours. Intra-arterial thrombolysis was started within 5 hours of the onset of the stroke. No attempt was made to mechanically dislodge the clot. Post-procedure, heparin was administered as an infusion at a dose of 1000 units per hour to keep the aPTT twice that of the control. Within about 4 hours of initiation of therapy, the patient started regaining power on the hemiplegic side, attaining grade 4 power (MRC) in the lower limb and more than grade 3 power in the upper limb. Global aphasia improved to moderate motor aphasia. The patient could walk without support the next day (NIH stroke scale score of 6).

The patient did not develop any hemorrhagic complications at the surgical site. Angiogram taken post-procedure showed complete recanalization of the previously occluded left middle cerebral artery (TIMI 3) (Fig. 3).

From the second day of thrombolysis, the patient was maintained on anticoagulation to keep the INR around 2–2.5. At discharge, the patient was in the same neurological status of NIHSS score 6 and a modified Rankin disability scale of 2 (slight disability, unable to carry out some previous activity, but able to look after own affairs without assistance). At 3 months follow-up, the patient was in the same modified Rankin scale.

Discussion

The cerebral circulation absorbs 10%–15% of the cardiac output. Carotid artery blood flow accounts for
approximately 90% of the total cerebral blood flow. The most common sites of cardiac emboli are the main trunk and branches of the middle cerebral artery.\(^5\)

The effects of a major vessel territory stroke because of embolism following cardiac surgery is very devastating for a young patient, considering the fact that the patient did not have any neurological problems prior to the surgery. Hence the prevention and treatment of such an event is very important.

As postoperative strokes occur in the hospital setting, they are easily recognized within the window of opportunity for thrombolytic treatment. But major surgery within 14 days is considered an absolute contraindication for intravenous thrombolysis as outlined in the American Heart Association guidelines for stroke thrombolysis.\(^9\)

Previous studies have proven the efficacy of intra-arterial thrombolysis as an alternative approach to intravenous thrombolysis in acute ischemic stroke.\(^10\) Treatment by local delivery of the thrombolytic agent is well suited in the immediate postoperative period. Such an approach uses small doses of the thrombolytic agent at the site of arterial occlusion, limiting the systemic exposure of this therapy to the surgical bed.\(^11\) Several small studies have been reported which have shown the efficacy\(^5,7\) and safety\(^6\) of intra-arterial thrombolysis in the postoperative setting.

Our patient developed stroke most probably related to the paroxysmal atrial fibrillation she had following the surgery. Thrombus formation and dislodgement from the ASD patch or suture line is a less likely cause.

Magnetic resonance imaging in our patient did not show any abnormality in the T-1W or T-2W images, but the diffusion-weighted imaging picked up early signs of infarct. Studies have shown that diffusion-weighted images consistently show an increased signal as early as 2 to 3 minutes after the onset of severe ischemia which is not picked up by conventional T1 and T2 sequences.\(^12\)

Various centers have used different agents for intra-arterial thrombolysis. There is no demonstrated superiority of tPA or urokinase for local intra-arterial thrombolysis in acute stroke.\(^5\) Our choice of thrombolytic agent was based on the availability and lower cost of urokinase. Although tPA is more clot specific than urokinase, it has a similar effect on postsurgical hemostatic plugs.

Though intra-arterial thrombolysis is a good option for postoperative stroke, it has a number of drawbacks. The major disadvantage is the need for 24-hour availability of angiographic facilities and trained personnel.

Post-procedure, heparin was given similar to the PROACT II recommendation.\(^4\) Though our patient did not have bleeding at the surgical site, asymptomatic intracranial hemorrhage cannot be excluded for certain, as we did not repeat the neuroimaging. Repeat neuroimaging, especially a diffusion-weighted and a perfusion-weighted MRI scan, would have helped us to objectivize the improvement in the jeopardized critically perfused brain tissue.

Local intra-arterial thrombolysis seems to be a good treatment option in patients who develop stroke in a postoperative cardiac surgery setting and in whom the essential inclusion and exclusion criteria are satisfied, in places where the facility is available. Large randomized trials are needed to validate the wider application of this method.

References

Management of Atrial Fibrillation with Reference to Valvular Heart Disease

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Atrial fibrillation (AF) is the most common sustained cardiac rhythm disturbance encountered in clinical practice, with an overall prevalence of 0.4%. Most of the epidemiologic data about AF (largely nonvalvular) is from the Framingham Heart study, a prospective study of 5200 patients. The incidence increases rapidly with age, from 2.3% between the ages of 40 and 60 years to 5.9% in people over 65 years of age. The pattern of increased incidence with age is slightly higher in men than in women. The presence of congestive heart failure, hypertensive heart disease, diabetes mellitus, mitral and tricuspid valve disease, hyperthyroidism, and pericardial disease is associated with a marked increase in the incidence of AF. In parts of the world with a high prevalence of rheumatic heart disease (as in western countries in the past), heart valve disease is the most common cause for the occurrence of AF, especially in patients below the age of 50 years. The guidelines for the treatment of AF in valvular disease are not well defined due to lack of large, multicenter studies. However, based on single-center studies in patients with valvular disease and the results of large multicenter studies involving patients with AF of nonvalvular etiology, some recommendations can be made.

The most frequently diseased valve in patients with AF and valvular heart disease is the mitral valve. In a large surgical series, AF has been found in 40% of cases with mitral stenosis and 25% of cases with mitral regurgitation, but in only 1% of patients with aortic stenosis. Diker et al. found AF in 29% of patients with isolated mitral stenosis, 16% with isolated mitral regurgitation, 52% in combined mitral stenosis and regurgitation but in only 1% of patients with aortic valvular disease (Table 1). In a study involving 385 patients with AF undergoing cardiac catheterization, 36% had mitral regurgitation, 34% mitral stenosis, 21% hypertensive heart disease and 19% coronary artery disease.

Table 1. Incidence of atrial fibrillation in valvular heart disease (n=1110)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Number of patients</th>
<th>% with atrial fibrillation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mitral stenosis</td>
<td>250</td>
<td>29</td>
</tr>
<tr>
<td>Mitral regurgitation</td>
<td>74</td>
<td>16</td>
</tr>
<tr>
<td>Aortic regurgitation</td>
<td>24</td>
<td>0</td>
</tr>
<tr>
<td>Aortic stenosis</td>
<td>20</td>
<td>1</td>
</tr>
<tr>
<td>Mitral stenosis+mitral regurgitation</td>
<td>274</td>
<td>52</td>
</tr>
<tr>
<td>Mitral stenosis+tricuspid regurgitation</td>
<td>42</td>
<td>64</td>
</tr>
<tr>
<td>Mitral stenosis+aortic regurgitation</td>
<td>144</td>
<td>70</td>
</tr>
<tr>
<td>Mitral stenosis+aortic regurgitation</td>
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<td>4</td>
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<tr>
<td>Mitral stenosis+mitral and tricuspid regurgitation</td>
<td>78</td>
<td>11</td>
</tr>
<tr>
<td>Mitral stenosis+mitral and tricuspid regurgitation</td>
<td>36</td>
<td>21</td>
</tr>
<tr>
<td>Mitral stenosis+aortic regurgitation</td>
<td>23</td>
<td>16</td>
</tr>
<tr>
<td>Other</td>
<td>35</td>
<td>46</td>
</tr>
</tbody>
</table>

Adapted from Diker et al.

Pathophysiology

The underlying pathophysiologic mechanism leading to AF is not well understood. There are apparent differences in the pathological findings in patients with valvular and nonvalvular AF. Occurrence of AF has been consistently related to the size of the left atrium. Univariate analysis in one study revealed that the incidence of AF was 3% when the left atrial diameter was <4.0 cm but increased to 54% if the left atrial diameter was >4.0 cm, thus explaining the highest incidence in patients with mitral valve disease, which leads to maximum left atrial enlargement. Mitral valve disease causes an elevation of left atrial pressure resulting in left atrial hypertrophy and dilatation, a precedent of AF. Besides left atrial enlargement, other echocardiographic findings that have been associated with an increased risk of the development of AF include increased left ventricular wall thickness and reduced left ventricular shortening fraction.

A large postmortem study on patients with AF with associated organic heart disease showed diversity of histologic abnormalities diffusely involving both the right and left atria. It is postulated that fibrosis and degeneration of the atrial myocardium in valvular heart disease, especially of rheumatic etiology, disturbs impulse
propagation in the atria and leads to AF. Atrial fibrosis probably contributes to persistent AF after valvuloplasty or valve replacement/repair. In patients with valvular disease, AF also occurs more frequently with mitral valve calcification and prolapse, and following valve replacement surgery. The higher incidence of pathological changes reported with valvular heart disease and AF could be because the atria in these patients are more easily accessible for examination at the time of valve surgery as compared to patients with nonvalvular AF. A study involving endomyocardial atrial septal biopsies in patients with nonvalvular AF reported histologic changes in 75% of patients; 66% had changes consistent with myocarditis. Based on the findings of inflammation, it is tempting to speculate on the role of inflammation in the development of AF. Recent studies have shown elevated levels of C-reactive protein in patients with paroxysmal as well as persistent AF. Levels of C-reactive protein correlated with AF burden.

Clinical Course

The natural history of nonvalvular AF is extremely variable. In a large number of these patients, AF remains paroxysmal or intermittent for a prolonged period, becoming chronic or persistent in a few. On the other hand, although the initial course of AF in valvular heart disease may be paroxysmal, it almost invariably progresses to chronic AF. Symptoms are related to the irregular heart beat, rapid ventricular rate, development of heart failure and atrial stasis leading to thrombus formation with a potential for thromboembolism. Both heart failure and thromboembolic complications are related to the duration of AF and occur more often in AF associated with valvular heart disease. Management in these patients is aimed at either control of ventricular rate without attempting to restore sinus rhythm, or restoration of sinus rhythm with concomitant aggressive therapy to maintain it. As embolic complications are the major cause of morbidity, chronic anticoagulant therapy is important in all patients with AF and enlarged atria when sinus rhythm cannot be restored. Treatment of the underlying valvular abnormality, e.g. mitral or tricuspid valve replacement/repair in severe regurgitant lesions, or valvuloplasty in predominant mitral stenosis, should be considered. However, in patients with enlarged and dysfunctional atria, despite correction of the underlying valvular lesion, AF often persists.

This article briefly reviews the current management of AF in patients with valvular disease in comparison with those having nonvalvular AF. The guidelines for antiarrhythmic and antithrombotic therapies and the role of newer nonpharmacologic modalities for the management of AF are briefly reviewed. Management Considerations

Treatment of AF has one or more of the following aims: (i) correction of the underlying cause; (ii) control of ventricular rate; (iii) restoration of sinus rhythm; (iv) maintenance of sinus rhythm; and (v) reduction of stroke risk.

Table 2. Management of atrial fibrillation in patients with valvular heart disease

1. Control of ventricular rate
   (a) Treatment of reversible factors
      —valvular lesion (valvuloplasty or surgery)*
      —heart failure
      —rheumatic activity
      —pulmonary embolism
      —chest infection
   (b) Drugs to block the AV node
      —digoxin
      —beta-blockers
      —calcium-channel blockers
   (c) Nonpharmacologic measures
      —atrioventricular nodal ablation
2. Restoration of sinus rhythm
   —correction of valvular lesion*
   —chemical cardioversion (new agents ibutilide and dofetilide)
   —external cardioversion (biphasic shock highly successful)
   —internal cardioversion (rarely needed)
3. Maintenance of sinus rhythm
   —correction of valvular lesion*
   —antiarrhythmic drugs
   —surgical maze procedure
   —catheter ablation (linear lesions and pulmonary vein isolation)
4. Prevention of embolic complications
   —heparin
   —warfarin (INR 1.5–4)*
   —aspirin
   —correction of valvular lesion*
   —left atrial appendage resection
   (recurrent embol despite anticoagulation or when anticoagulation cannot be given)

*applicable to patients with valvular heart disease
INR: international normalized ratio

1. Correction of underlying etiology: In patients with nonvalvular AF, it is usually not possible to identify or correct factors responsible for initiation of the arrhythmia. Thyrotoxicosis, pulmonary disorders and caffeine and alcohol intake are potentially reversible causes that are responsible for a small proportion of episodes. On the contrary, the onset of AF in patients with valvular heart disease is often the first indication of deterioration of the valvular and/or left ventricular function, rise in pulmonary pressure or onset of heart failure. Atrial fibrillation in valvular disease might also be a result of nonvalvular factors such as pulmonary disease, thyrotoxicosis or...
pericardial effusion. Treatment of heart failure (with diuretic therapy, digoxin and converting-enzyme inhibitors), or treatment of acute or acute exacerbation of chronic pulmonary conditions (chronic obstructive lung disease or pulmonary emboli) is often sufficient for termination of recent AF. The onset of AF in patients with mitral regurgitation is considered to be an indication of significant left ventricular dysfunction, especially when the left ventricular cavity is not apparently dilated, and thus mitral valve replacement/repair may be indicated. In mitral stenosis, it denotes a moderate rise in left atrial pressure related to significant reduction in valve area, indicating the need for mitral valvuloplasty or valve replacement/repair. Despite correction of the valvular lesion, AF not infrequently persists and this is probably related to fibrotic changes in the atrial myocardium. It is, at present, difficult to predict the chronicity of AF of recent onset in either nonvalvular or valvular AF, but the former is more likely to be permanent, as a correctable factor is usually not identifiable.  

2. Control of ventricular rate: Control of ventricular rate is one of the main goals of the treatment of patients with all forms of AF when sinus rhythm cannot be restored immediately. In a computer model of AF, Rawles demonstrated that with an increase in heart rate of up to 140 beats/min, the cardiac output progressively increases. With further increase in ventricular rate, it begins to decline. Williamson et al. demonstrated that control of ventricular rate with AV nodal ablation and implantation of a rate-responsive permanent pacemaker significantly reduced maximal ventricular rates during exercise from 180±39 to 126±24 beats/min and led to improvement in both left ventricular function and exercise capacity. In patients with an ejection fraction of less than 50%, AV nodal ablation and implantation of pacemaker was associated with a decrease in end-systolic and end-diastolic cavity dimensions, reduction in left atrial size and a significant improvement in left ventricular ejection fraction. The ventricular rate during AF is determined by the properties of the AV node (and any accessory pathway conducting anterogradely). A resting heart rate of less than 90 beats/min is optimal, provided it can increase adequately with exercise. Exercise testing in patients with AF often reveals an inappropriate rapid ventricular rate response during the initial stages of exercise, unlike the linear heart rate response to increasing work levels seen in normal sinus rhythm. Digitalis, a long-standing drug of choice for the control of ventricular rate in AF, is very often ineffective during exercise because its electrophysiologic action is mediated through augmentation of vagal tone on the AV node. Vagal tone is at its minimum during exercise, as increase in heart rate during exercise is mediated by increased sympathetic activity. Beta-blockers such as propranolol, metoprolol and atenolol, as well as negative chronotropic calcium-channel blockers such as verapamil and diltiazem are effective agents for ventricular rate control with a low incidence of adverse effects. The addition of beta-blockers or calcium-channel blockers to patients on maintenance digoxin reduces resting and exercise heart rate and improves exercise capacity. Excessive bradycardia is rare, although the outcome of a digoxin–beta-blocker combination therapy may depend on the type of beta-blocker used. Studies have shown that combining digoxin with a beta-blocker that has intrinsic sympathomimetic activity keeps peak ventricular rates down while minimizing the effects of these drugs when heart rates are lowest, as is usually seen during the night. During the acute stage, intravenous digoxin may also be effective in controlling the ventricular rate but it has a delayed onset of action when compared to intravenous diltiazem. In patients with chronic AF and hemodynamically significant valvular lesions, ventricular rate is more easily controlled following correction of valvular lesions. Catheter ablation of the AV junction and implantation of a rate-responsive ventricular permanent pacemaker should be considered in drug-refractory patients or patients who cannot take beta-blockers and calcium-channel blockers. This is often the case in patients with valvular heart disease (more so mitral regurgitation) who have impaired left ventricular function that precludes therapy with beta-blockers and calcium-channel blockers. Rate control remains the mainstay for the management of patients who present initially with AF. The long-term benefits of aggressive attempts at maintaining sinus rhythm as compared to controlling ventricular rate in AF are still not established. The AFFIRM trial, a study comparing 300 patients with nonvalvular AF, randomized patients to either rate control or rhythm control with mortality as the primary end-point. The preliminary results have been recently released and although mortality in the two groups was not significantly different, there was a trend towards lower mortality in the rate control arm of the study. The incidence of stroke was also similar. The German Pharmacological Intervention in Atrial Fibrillation (PIAF) study randomized patients with persistent AF to rate control with diltiazem or amiodarone or cardioversion. Although the number of patients in sinus rhythm was significantly higher in the cardioversion group and exercise duration was significantly better in those maintaining sinus rhythm, the quality of life did not differ.
3. **Restoration of sinus rhythm:** The purpose of cardioversion is to improve atrial contraction, restore AV synchrony and control the ventricular response more effectively, thereby preventing the development of cardiomyopathy. Maintaining sinus rhythm has also been associated with immediate and long-term improvement of systemic hemodynamics. Cardioversion to sinus rhythm in both valvular and nonvalvular AF may be achieved by chemical means or electrical cardioversion. Chemical agents are less effective if the arrhythmia is of >48 h duration. Agents of Vaughan Williams classes IA, IC or III are effective. Success rates in the range of 60% have been reported with flecainide, propafenone and amiodarone. The efficacy of new rapidly acting class III agents such as intravenous ibutilide and intravenous or oral dofetilide appears to be promising. They are most effective in atrial flutter and fibrillation of recent onset. These drugs have a 3%–5% incidence of ventricular proarrhythmia, more so with impaired left ventricular function. Short-term amiodarone with or without electrical cardioversion has been shown to be effective in the restoration of sinus rhythm in chronic AF after mitral valve surgery. Treatment with beta-blockers has also been consistently shown to reduce the incidence of postoperative AF in patients undergoing coronary bypass and valvular heart surgery. Prophylactic use of oral amiodarone and sotalol has been shown to prevent AF immediately following cardiac surgery.

Transthoracic direct current counter-shock performed under short-acting general anesthesia is a standard method for termination of AF. Less than 5% of patients who successfully undergo cardioversion to sinus rhythm require more than 200 J. Van Gelder et al. showed that shorter duration of AF and younger age were predictors of a high success rate. Complications from direct current shock include ventricular fibrillation if the shock is improperly synchronized to the QRS complex. The incidence of ventricular fibrillation is increased by the presence of hypokalemia, a serum digoxin level above the therapeutic range or a prolongation of the QTc interval due to antiarrhythmic therapy. The use of defibrillators that deliver biphasic shocks has led to higher success rates of cardioversion. As lower energy is needed, the risk of complications is probably lower. In patients resistant to external cardioversion and antiarrhythmic therapy, Levy et al. reported high success rates (70%) using high-energy (200–300 J) shocks delivered from a catheter within the atrial cavity. Internal cardioversion using low-energy (around 4 J) shocks delivered between coiled defibrillation electrodes in the right atrium and coronary sinus is equally effective and can be performed without anesthesia. However, with the availability of biphasic external defibrillators, internal cardioversion is hardly ever needed. The role of an automatic implantable cardioverter–defibrillator for acute conversion of recurrent AF is still not well defined.

Prior to restoration of sinus rhythm, AF of 48 h duration, in the absence of other risk factors for thromboembolism (e.g. left ventricular dysfunction and left atrial enlargement), does not require anticoagulation. Atrial fibrillation that has been present for more than 48 hours requires anticoagulation for 3 weeks before and for 4 weeks following cardioversion to minimize thromboembolic complications. However, it is prudent to start anticoagulation for patients presenting with AF associated with significant valvular heart disease irrespective of the duration of arrhythmia, as these patients may have pre-existing atrial stasis from mitral valve disease. It is assumed that poorly adherent clots formed in the atrium are likely to be dislodged by cardioversion. The estimated time for organization of the newly formed clot is approximately 2 weeks. Therefore, anticoagulation during this time would allow organization and adherence of existing clots and prevent the formation of new clots. It has been shown that recovery of normal atrial mechanical function, despite restoration of sinus rhythm, can take 4 weeks necessitating continued anticoagulation following cardioversion for at least 4 weeks.

4. **Maintenance of sinus rhythm:** It is difficult to predict the risk of recurrence of AF after the first episode. In the presence of “mild” structural heart disease or a treatable precipitating etiology, it is reasonable to monitor the patient without therapy. A duration of AF of <48 h, alone or in combination with left atrial diameter ≤45 mm in nonvalvular AF, has been found to be the best predictor for long-term maintenance of sinus rhythm. In a multivariate analysis, low precardioversion functional class and presence of atrial flutter rather than AF were shown to be associated with longer arrhythmia-free periods, while the presence of significant valvular lesions was associated with shorter arrhythmia-free episodes. An abnormal signal-averaged electrocardiogram of the P wave with prolonged duration has been suggested to be a predictor of early recurrence and conversion of paroxysmal AF to chronic AF.

Van Gelder et al. reported continuance of sinus rhythm in up to 40% of patients at 12 months on maintenance antiarrhythmic therapy. The results are much lower without treatment with antiarrhythmic drugs, though the risks of such therapy must be balanced against the potential benefits of maintaining sinus rhythm. The risk of recurrent AF can be reduced with quinidine, disopyramide,
procainamide, flecainide, propafenone, amiodarone and sotalol. Quinidine, which was widely used in the past, reduces the risk of recurrent AF to around 50% at 1 year, compared with about 25% in the control population. However, its significant potential for cardiac and extracardiac side-effects and increased mortality has resulted in the use of newer agents such as sotalol, propafenone and flecainide. Although class IC agents are more effective than class IA drugs, encainide and flecainide have been shown to increase mortality in patients with previous myocardial infarction and low left ventricular ejection fraction in the Cardiac Arrhythmia Suppression Trial. Although no controlled studies are available, in patients without coronary artery disease and good left ventricular function, class IC agents when compared with class IA drugs are significantly more effective and have a significantly less pro-arrhythmic potential. Amiodarone may be effective where other agents have failed, but it is less effective if the atrial diameter is >60 mm. Amiodarone and dofetilide have established safety and efficacy in patients with heart failure—a group of patients that is particularly susceptible to the ventricular proarrhythmic effects of antiarrhythmic drugs. The recommendations of the ACC/AHA/ESC Guidelines on the management of patients with nonvalvular AF are that in the presence of coronary artery disease, beta-blockers are the drugs of first choice, and in patients with hypertension, propafenone and flecainide are reasonable choices; however, if marked LVH is present, amiodarone becomes the drug of choice. In a patient with the WPW syndrome, AF may constitute a medical emergency requiring DC cardioversion; in case the patient is hemodynamically stable the drugs of choice—class IC agents are significantly more effective and have a significantly less pro-arrhythmic potential. Amiodarone may be effective where other agents have failed, but it is less effective if the atrial diameter is >60 mm. Amiodarone and dofetilide have established safety and efficacy in patients with heart failure—a group of patients that is particularly susceptible to the ventricular proarrhythmic effects of antiarrhythmic drugs. The recommendations of the ACC/AHA/ESC Guidelines on the management of patients with nonvalvular AF are that in the presence of coronary artery disease, beta-blockers are the drugs of first choice, and in patients with hypertension, propafenone and flecainide are reasonable choices; however, if marked LVH is present, amiodarone becomes the drug of choice. In a patient with the WPW syndrome, AF may constitute a medical emergency requiring DC cardioversion; in case the patient is hemodynamically stable the drugs of choice are intravenous procainamide or ibutilide. Preliminary results from AFFIRM have shown that amiodarone has a higher efficacy as compared with other drugs in maintaining sinus rhythm. 

Limited data are available about how long antiarrhythmic therapy should be given after sinus rhythm has been restored. Some of these issues will be addressed after further analysis of data from AFFIRM. In patients with a low risk of recurrence, therapy can be discontinued after a few months. It is advisable to continue long-term antiarrhythmic therapy for those with multiple previous episodes of AF, significant clinical deterioration when in AF, when a valvular lesion cannot be corrected and those in AF despite correction of the valve lesion (e.g. postmitral valve repair, replacement or valvuloplasty). 

Multiple nonpharmacologic interventions have been tried for the maintenance of sinus rhythm in patients with frequent paroxysmal or chronic AF. Dual-site atrial pacing has been shown to increase the duration of arrhythmia-free intervals in patients with nonvalvular AF. Surgical treatment of AF has been shown to be effective in maintaining sinus rhythm. The “maze procedure” developed by Cox and colleagues has been found to be effective in nonvalvular AF. It is used as a last resort in symptomatic patients. Kosakai et al. reported the use of a modified maze procedure in 62 patients with chronic AF undergoing mitral valve surgery. Atrial rhythm and atrial function was restored in 84% of their patients. On long-term follow-up, there was improvement in the atrial contractile function. Seventy-one percent of the patients in whom sinus rhythm was restored had effective atrial contraction as demonstrated by transmitral blood flow. The authors suggested that the maze procedure is safe and effective and should therefore be considered for patients with chronic AF undergoing mitral valve surgery. A similar study by Sie et al. in which a modified radiofrequency maze procedure was used concurrently with cardiac surgery (mitral valve surgery in 108 of 122 patients), showed that such a hybrid approach was successful in eliminating AF and restoring atrial transport function. Multiple approaches for catheter ablation of AF are under clinical investigation, and although preliminary results are encouraging, indications, safety and long-term success are still not well-defined. A relatively recent study by Nair et al. in patients with AF and rheumatic heart disease has shown that in a large number of these patients, the arrhythmia is a relatively organized rhythm with earliest atrial activity near the os of the coronary sinus. 

Catheter ablation in this area was successful in restoring sinus rhythm in most of these patients. In patients who have recurrent AF triggered by atrial premature beats, AF is considered to be focal. Pulmonary vein isolation by a circumsferential lesion around the os of all four pulmonary veins has shown a success rate of 60%–70%. It is increasingly being used in patients with nonvalvular AF. Pulmonary vein isolation has been shown to have limited success in “persistent” AF, which is usually the arrhythmia that patients with valvular heart disease have. It can be postulated that, after correction of the valvular lesion, patients who continue to have AF with features of focal/paroxysmal AF are likely to benefit from pulmonary vein isolation.

5. Reduction in stroke risk: Atrial fibrillation is responsible for more than 85% of systemic thromboembolism from the heart. In patients over the age of 65 years, AF causes more than one-third of all strokes. The risk of embolic stroke in patients with AF is related to age, history of previous thromboembolic event, presence of mitral valve disease, congestive heart failure, enlarged left atrium, previous MI, hypertension and left atrial thrombus on tranesophageal echocardiography.
When associated with mitral valve disease, AF has the highest stroke risk—about seventeen times greater than in unaffected controls. In comparison, in patients with nonvalvular heart disease, the risk is increased five-fold. Stroke in patients with AF is associated with 70% increase in mortality and markedly poor neurological and functional outcomes. The recurrence rate in the first year after the initial stroke varies between 13% and 32%. Lifetime recurrence rates, especially for patients with AF associated with mitral valve disease, may be as high as 30%–75%. The rate of recurrent strokes appears to be similar with chronic and paroxysmal AF.

Transesophageal echocardiography is an efficient method for detecting left atrial thrombi in patients with AF and thus assessing the risk of embolic stroke in both valvular and nonvalvular AF. In patients with valvular heart disease, transesophageal echocardiography has a positive predictive value of 100%, negative predictive value of 98.9% and diagnostic accuracy of 99.1% (or specificity 100%; sensitivity 93.3%). By transesophageal echocardiography, Hwang et al. demonstrated that 20% of patients with mitral stenosis had left atrial thrombi; interestingly, in this study none of the patients with mitral regurgitation had left atrial thrombi. More importantly, 28 of the 30 patients (93%) with atrial thrombi were in AF, demonstrating the contribution of rhythm disturbance to the left atrial thrombus. Most thrombi were found to be located in the left atrial appendage. Jordan et al. in an autopsy series of 51 patients with mitral stenosis and left atrial thrombi, found 42% of the thrombi to be limited to the left atrial appendage, and 82% to the left side of the heart. In patients with mitral valve disease, in addition to the left atrial appendage, thrombi form in the body of the left atrium. This is in contrast to nonvalvular AF in which thrombi form predominantly (90%) in the left atrial appendage. It has been suggested that obliteration of the left atrial appendage may be considered in patients with nonvalvular AF deemed ineligible for long-term warfarin therapy.

Transesophageal echocardiographic studies have shown that the presence of significant mitral regurgitation, as compared to mitral stenosis, is associated with a lower incidence of spontaneous echo contrast in the left atrium and thus lower risk of thrombi and embolization. In a surgical clinicopathologic study, in patients with AF, the prevalence of left atrial clot with predominant mitral regurgitation was 8.3% in comparison with 54% in patients with predominant mitral stenosis (p<0.0001). In sinus rhythm, the prevalence of left atrial clot was 0% in predominant mitral regurgitation and 14.3% in patients with mitral stenosis (p<0.001). None of the patients with AF and severe mitral regurgitation had left atrial clot. Thus, it can be recommended that prophylactic anticoagulation is not needed when mitral regurgitation is severe or when the patient is in sinus rhythm. Prophylactic anticoagulation should be used for patients with predominant mitral stenosis if they are in AF, as this is a very high-risk group for thromboembolic complications. The use and timing of anticoagulation for patients with mitral stenosis in sinus rhythm is still debatable. In an effort to anticipate the onset of AF, some advocate anticoagulation based on valve area, others when medical therapies are initiated, and still others begin warfarin immediately, when the diagnosis of mitral stenosis is made. In mitral stenosis, successful balloon valvuloplasty results in resolution of echo contrast and decrease in thromboembolic risk. Correction of the valvular lesion thus results in decreased thromboembolic risk and should be undertaken whenever feasible.

Use of oral anticoagulation in patients with nonvalvular AF significantly reduces the incidence of stroke. Five recent randomized trials examined warfarin use for primary prevention of stroke in AF. Taken together, warfarin use [international normalized ratio (INR) range 1.8–4.2] reduced the frequency of all strokes by 68%, with an absolute annual reduction of 3.1%. Bleeding risk was less than 1% per year. In patients with nonvalvular AF and no other risk factors, the use of anticoagulation is debatable. There is little doubt that in patients with AF and valvular heart disease, the risk–benefit ratio is strongly in favor of anticoagulation. In the absence of contraindications, all patients with AF associated with valvular heart disease should be considered for anticoagulation. There are no dose-ranging trials to guide anticoagulant therapy in patients with AF and valvular heart disease. Based on trials in nonvalvular AF, some suggestions can be made. The Copenhagen Atrial Fibrillation Aspirin and Anticoagulation study (AFASAK), a prospective, randomized trial of patients with nonvalvular AF, demonstrated the beneficial effects of warfarin (INR: 2.8–4.2). This study also showed that aspirin at a dose of 75 mg per day did not have any significant effect in altering the risk of thromboembolic events. The Stroke Prevention in Atrial Fibrillation (SPAF) trial showed that both aspirin at a dose of 325 mg per day and warfarin (INR: 2–3.5) effectively reduced stroke rates in patients with nonvalvular AF. A separate subgroup analysis performed showed no significant effect of aspirin on the rate of embolic events in patients >75 years of age. Data from larger, multicenter studies in patients with prosthetic heart valves show that a target INR of 2.5–3.5 results in an acceptable balance of reduction in risk of thromboembolic and bleeding complications. Patients who suffer hemorrhagic complications should receive lower-intensity
anticoagulation (INR about 2.0). The usual regimen is to start warfarin at a daily dose of 5 mg and to monitor the prothrombin time (PT). A higher starting dose is no longer recommended. Subsequent daily doses are adjusted until the PT stabilizes in the therapeutic range. An INR of 2.5–3.5 (PT of 2.5–3.5 times of control value can be alternatively used) is considered to be therapeutic. In patients who have previously had an embolic complication, an INR of 3–4.5 should be the target. For patients who have thromboembolic episodes on therapeutic doses of warfarin, aspirin is used in addition.

The overall risk of bleeding from anticoagulant therapy (with an INR of 2.5–3.5) requiring medical intervention is about 1.0% per year for the aspirin group and 1.3% for the warfarin group, as compared to 1.0% per year for the control group.68 Hemorrhagic complications in anticoagulated patients are most commonly gastrointestinal, genitourinary, vaginal, respiratory, retroperitoneal and intracranial. The major management issue in most patients with AF is the relative risk versus the benefit of anticoagulation. The European Atrial Fibrillation trial study group found the optimal intensity of anticoagulation to lie between an INR of 2.0 and 3.9.66 The rate of thromboembolic events was lowest at INRs ranging from 2.0 to 3.9 and most major bleeding complications occurred with treatment at an INR of 5.0 or above.67 Thus it is generally agreed that in patients with valvular heart disease and AF, INR should be maintained in the range of 3–3.5 which results in an optimal risk-benefit ratio.68

Conclusions
Atrial fibrillation, though considered a relatively benign arrhythmia, is a challenge to physicians because of the associated complications. A rational approach to management depends on the symptoms, severity and presence or absence of heart failure and embolic risk versus the risk from pharmacologic, interventional and anticoagulant therapies. In patients with valvular heart disease, paroxysmal and chronic AF have a similar risk of thromboembolic complications. Although therapy for nonvalvular AF is extensively investigated and well defined, correct management of AF in valvular heart disease is less well defined. Correction of the valvular lesion, if possible, and adequate anticoagulation are primary goals for the management of AF in valvular heart disease. Maintenance of sinus rhythm is a secondary goal. The radiofrequency maze procedure percutaneously or during surgery for valvular lesions might prove useful in maintaining sinus rhythm even in patients with large atria. It should be stressed that optimal anticoagulation is imperative in significantly reducing morbidity and mortality caused by embolic complications.

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Isolated Left Ventricular Noncompaction in an Adult

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A 21-year-old woman presented with a history of dyspnea on exertion since early childhood. She had worsened to NYHA functional class III with dyspnea and palpitations for the past 1 year. On examination, there was evidence of cardiomegaly with a prominent left ventricular third heart sound. Chest X-ray also revealed cardiac enlargement with pulmonary venous hypertension. A diagnosis of dilated cardiomyopathy was made and the patient underwent echocardiography which demonstrated a dilated left ventricle with global hypokinesia. The wall of the left ventricle appeared double layered with excessive trabeculations. There were deep recesses in the ventricular wall adjoining the main ventricular cavity (Fig. 1a and 1b). Left ventricular ejection fraction was calculated to be 22%.

The patient was started on decongestive therapy, vasodilators and beta-blockers, and improved to NYHA functional class II. Subsequently, she underwent a pregnancy during which she again deteriorated to NYHA functional class III. Although the delivery was uneventful, her functional status did not improve. She was admitted twice for heart failure and died of progressive ventricular dysfunction nine months after delivery.

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Isolated ventricular noncompaction (IVNC) is a rare disorder of endomycardial morphogenesis. It is characterized by prominent trabeculations with deep intertrabecular recesses and impaired ventricular systolic function in the absence of associated congenital heart disease.1,2 The disorder is believed to occur because of intrauterine arrest of compaction of the loose interwoven mesh of myocardial fibers normally seen during development.2 Genetic mutations have been identified as a possible cause of IVNC.3

Most patients with IVNC present with congestive heart failure, and the diagnosis is made by echocardiography. The presence of a two-layered myocardial wall structure with a thin epicardial compacted zone and a thickened endocardial noncompacted zone with deep recesses filled with blood from the ventricular cavity is characteristic. A ratio of noncompacted to compacted myocardium of two or more is diagnostic of IVNC.5

IVNC is associated with a poor prognosis.3 Mortality is nearly 40% at 5 years.5 Fifty percent of these deaths are sudden (due to ventricular arrhythmia). Heart failure is the second most common cause of death. One-fourth of patients die or require heart transplantation due to refractory heart failure. Systemic thromboembolic events are common in adults with IVNC. Coronary microcirculatory dysfunction has been shown to be associated with this condition.5
There are no specific modalities of treatment for IVNC. Systemic anticoagulation is routinely advocated because of the high incidence of thromboembolic events. Prophylactic implantation of a cardioverter-defibrillator and heart transplantation are viable options for prolonging life.

References


Pollution, Cytokines and Atherosclerosis: An Indian Perspective

Atmospheric air pollution has been observed to be associated with progression of atherosclerosis in experimental animals and increased cardiovascular morbidity and mortality in humans as observed in the developed countries. Several large cities in India are severely polluted, including New Delhi, which is one of the 10 most polluted cities in the world. In a recent study in New Delhi, levels of carbon monoxide (CO), nitrogen oxides (NOx), sulphur dioxide (SO2) and total suspended particulates calculated on the 24-hour averaged recordings for the years 1997–1998 were markedly high (except SO2) as compared to the Ambient Air Quality standards in the US. The averaged background CO concentrations were 19.39 µg/m³, nearly four times that recorded in eastern USA (500 µg/m³). Emissions from automobiles predominantly contributed to the CO and NOx levels. Further, the particulate matter <10 µm (PM10) constituting the predominant thoracic particulate matter was high; coarse (>2.1–10 µ) 68.3±17 µg/m³ and fine (<2.1 µ) 71.3±15 µg/m³. The mean PM10 is 200 µg/m³ in India, three times the levels observed in the most polluted areas of the USA, and is contributed by vehicular emissions, industrial emissions and soil re-suspension. The Indian Supreme Court has ordered substitution of petrol in heavy vehicles with compressed natural gas, and restrained culprit industrial units in an effort to decrease atmospheric pollution. Unfortunately, little has changed despite the judicial measures, heightened media exposure, social activism, and widespread public concern.

Except one, no study has addressed this issue in relation to coronary heart disease (CHD) in India. Pande et al. conducted a study of emergency room visits to the All India Institute of Medical Sciences (AIIMS), New Delhi, situated close to one of the heavily polluted traffic intersections in the city. The authors correlated the data of the respiratory and cardiovascular acute events in the emergency room to the daily levels of various pollutants. The ambient levels of pollution exceeded the standards set by air quality standards for most of the days, particularly in winters, over the two-year period of the study. At the same time, presentation with acute coronary events to the emergency room increased by 24.3% on account of higher than acceptable levels of pollutants. Other significant contributory respiratory pollutants in the Indian population are the high prevalence of cigarette and bidi (indigenous cigarettes made of tobacco leaves) smoking (mostly males) and indoor pollution due to wood, coal and kerosene-based cooking systems (seen mostly in females). Although smoking is equally common in urban and rural areas, indoor air pollution is more prevalent in urban slums, semi-urban and rural areas. The data on indoor air pollution are particularly striking: 24-hour concentrations of PM10 exceeded 2000 µg/m³, and attained even higher levels during the actual cooking period. Additionally, emissions from the house are likely to pollute the surrounding areas, particularly so in densely populated areas, such as urban slums.

Increased levels of soluble intercellular adhesion molecule-1 (sICAM-1), a marker for endothelial activation, was recently recorded by our group among people of the low socio-economic strata living in urban slums and healthy resident medical students of AIIMS, New Delhi. Of particular note, the urban slum area studied by our group is located 1 km away from the medical institution where Pande et al. conducted their study and close to two of the busiest traffic intersections in the city—it is presumably exposed to a similar level of pollution. Furthermore, the medical students recruited as controls resided in the same institution. Interestingly, nearly 25%–35% of the subjects, including apparently healthy medical students having no evidence of infection, had high levels of sICAM-1, and there was no difference in the levels of sICAM-1 between the two groups. The same population of the urban slums was recently reported to have a high prevalence of several metabolic disorders and coronary risk factors. We proposed that one of the reasons for the high levels of sICAM-1 in the study could be the persistent exposure of the population sample to high levels of pollution. People residing in slums are additionally exposed to indoor pollution.

It is now clearly known that sICAM-1 promotes leucocyte adhesion to the vascular endothelium, thus contributing to the formation of foam cells. sICAM-1 is found located specifically in atherosclerotic vascular lesions and high levels are reported in patients with CHD. Short-term exposure to particulate diesel exhaust fume in healthy human volunteers upregulates sICAM-1 in the bronchial tissues. According to Suwa et al., induction of acute and chronic coronary events could be initiated by the cytokines released by alveolar macrophages in response to particulate matter phagocytosed in the lungs. In line with their arguments and consistent with the experimental data, it is not altogether unreasonable to postulate that a high level of atmospheric pollution is an important cause of endothelial dysfunction and pulmonary macrophage activation. It can potentially contribute to CHD and the metabolic syndrome by elaboration of cytokines (e.g. sICAM-1, interleukin-6, etc.) conducive to the development of atherosclerosis.
of atherosclerosis. The scenario is realistic for Asian Indians residing in major Indian cities and exposed to high levels of atmospheric pollution, as well as for those exposed to indoor pollution.

The data, though limited, should be viewed with concern, particularly so in view of the increasing incidence of CHD in India. Epidemiological transition in India has brought forth demographic transition, adverse changes in the physical activity profile and nutrition, and adult-life adverse effects of adverse in utero and early life events—all prime factors for atherosclerosis. According to a series of studies done by our group, people residing in urban slums appear to be particularly prone to developing CHD due to the presence of conventional coronary risk factors (obesity, hyperlipidemia, diabetes, smoking, insulin resistance, newer coronary risk factors (homocysteine), imbalanced nutrition (high intake of saturated fat, low intake of monounsaturated fat, fiber and vitamin E, and low ratio of n-6/n-3), and endothelial dysfunction (high levels of sICAM-1).

The current estimates indicate doubling of cardiovascular disease-attributable mortality in the years 1985–2015, putting India as a leading global contributor of CHD morbidity and mortality. Already, men residing in New Delhi have a four times higher prevalence rate of CHD as compared to men in Framingham, MA, USA. The evidence suggests that high levels of pollution in many Indian cities may also be considered as a coronary risk factor. A recent tentative estimate of annual health effects of indoor air pollution exposure suggests that it may be responsible for 54,000–200,000 deaths, 0.49–1.8 lost life years, and 0.55–2.1 disability-adjusted life years due to CHD, even as the data on outdoor air pollution are lacking. Thus cardiovascular effects of outdoor air pollution should form an important research question in future epidemiological studies in India.

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5-Fluorouracil-Associated Cardiotoxicity

I read the brief report “5-Fluorouracil-Induced Cardiotoxicity” by Shanmugasundaram et al. Over the past few years, there have been occasional reports of 5-fluorouracil-associated cardiotoxicity (5-FUAC) manifesting as myocardial ischemia. 5-FUAC was first recorded during multiple drug therapy. Since then, approximately 135 proven cases have been described. The risk of 5-FUAC increases with combination chemotherapy, radiotherapy and pre-existing cardiac pathology.

Because of the paucity of experimental studies and increasing reports of the cardiotoxicity of various antineoplastic drugs, we for the first time in India, conducted an original experimental research on 5-FU and cyclophosphamide-induced cardiotoxicity on albino rat hearts to investigate its mechanism. The proposed mechanism for 5-FUAC was described. We observed multiple myocardial interstitial hemorrhages, multiple areas of minimal to mild myofiber necrosis and associated inflammatory reaction, dilatation of some of the superficial vessels with disruption of the endothelium and extravasation of blood. Keeping these findings in view we hypothesize that the prime toxic effects of 5-FU on the endothelium result in its damage and disruption, leading to extravasation of blood containing 5-FU. The leaked 5-FU caused toxicity to the cardiac muscles with resultant myonecrosis and inflammatory reaction. It is important to remember that 5-FU is more toxic to the endothelial cells than cardiac muscles. We also observed ischemic changes in the ECGs of albino rats treated with 5-FU.

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Reply

I have gone through the suggestions given by Kumar S et al. regarding the postulated mechanisms of 5-fluorouracil-associated cardiotoxicity (5-FUAC). While appreciating their experimental study conducted on rats, I have to point out that the ECG changes of acute ST elevation anterior wall myocardial infarction cannot return to normal in a few hours and LV dysfunction cannot normalize in few days unless vasospasm is implicated. In my opinion, vasospasm also plays a significant, probably initial, role in 5-FUAC. The endothelial damage, vascular disruption and myocardial damage are probably responsible for delayed and more permanent changes.

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Graded Balloon Atrial Septostomy in Severe Pulmonary Hypertension

I disagree with the approach and argument that creating an atrial septal defect (ASD) helps patients with primary pulmonary hypertension (PPH).1

Increase in right atrial pressure in PPH is due to right ventricular dysfunction. Right ventricular failure cannot be relieved by creating an ASD. The logical way of relieving right ventricular failure would be creating a ventricular septal defect (VSD) or a patent ductus arteriosus (PDA). Patients with Eisenmenger physiology with a right-to-left shunt through a VSD or PDA differ from those with an ASD in having a normal heart size and absence of right ventricular failure. On the other hand, Eisenmenger physiology in ASD is associated with cardiomegaly and right ventricular failure.

Physiologically creating an ASD in PPH with right ventricular failure results in a right-to-left shunt at the atrial level and an increase in the cardiac output due to the amount of unoxygenated right-to-left shunt. However, the failing right ventricle does not benefit and the pulmonary blood flow decreases by the amount of blood shunting right-to-left through the ASD.

Is an improved unsaturated systemic flow resulting from the created ASD at the cost of decreased pulmonary blood flow better for the patient? Can it increase life expectancy? The patient and the physician might be deceived into complacency by the absence of hepatomegaly and a better appetite but physical activity will get restricted due to decreased pulmonary blood flow and less oxygenated blood reaching the systemic circulation.

Reference


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Reply

I thank Dr Tandon for his comments on the issue of creating an atrial septal defect (ASD) in patients with primary pulmonary hypertension (PPH). I agree that creating a ventricular septal defect or a patent ductus may be an even better idea but since these procedures are not clinically feasible, an ASD is preferred.

After reviewing the world experience of creating an ASD, the expert committee on PPH recommended the procedure for patients with recurrent syncope, or right ventricular failure despite maximal medical therapy.1 The clinical benefits of ASD in these patients are well documented by now. The beneficial influence on mortality is probable, though not established. Obviously, ASD per se cannot retard the progression of this ominous disease but several lines of evidence attest to the beneficial effects of an ASD. Historical evidence,2 experimental evidence in dogs,3 and several clinical series (reviewed in the article)4 argue in favor of the procedure.

However, the mechanism(s) of benefit have not been well studied. Improvement in cardiac output (especially during exercise), decrease in right ventricular wall stress, improved right ventricular perfusion, alteration in septal geometry, neurohumoral consequences, or other unknown factors may be operative. Progressive improvement in right ventricle function following septostomy was demonstrated in one small study.5 In fact, in the parts of the world where prostacyclins are not available, balloon atrial septostomy for PPH should be considered more frequently, and earlier in the course of the disease.

References


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Randomized Trial of a Distal Embolic Protection Device During Percutaneous Intervention of Saphenous Vein Aorto-Coronary Bypass Grafts


Summary

The Saphenous vein graft Angioplasty Free of Embolic Randomized (SAFER) trial was designed to evaluate the usefulness of the GuardWire distal protection device in conjunction with saphenous vein graft stenting. Eight hundred and one patients were randomized to either the distal protection device group (n=406) or control group (n=395). The baseline characteristics were matched in the two groups. Symptomatic patients with evidence of myocardial ischemia resulting from saphenous vein graft stenosis of more than 50% located in the midportion of the graft with a reference diameter between 3 and 6 mm, were included in the study. Patients with recent myocardial infarction, significantly impaired left ventricular dysfunction (EF <25%), impaired renal function (creatinine >2.5 mg%) and those in whom the use of an atherectomy device was planned were excluded from the study. Percutaneous coronary intervention (PCI) was carried out by the standard procedure. In patients assigned to the distal protection device arm, the 014” hollow core GuardWire was advanced beyond the lesion and the GuardWire balloon occlusion device (appropriately inflated with dilute radiographic contrast) was used to block the antegrade flow in the graft. The lumen of the GuardWire was then sealed. After a stenting procedure, a 5 F aspiration catheter (Export) was advanced over the GuardWire just proximal to the occlusion balloon and 20–40 ml of blood was vigorously aspirated. Subsequently, the distal occlusion balloon was deflated to restore antegrade flow. Use of a platelet glycoprotein IIb/IIIa receptor antagonist was left to the discretion of the operator (used in 61%) and standard post-stent therapy was instituted. The primary end-point was a composite of death, myocardial infarction, emergency bypass, or target lesion revascularization by 30 days. In the GuardWire arm, success was achieved in 90.1% of cases. Technical failure was due to inability to deliver the GuardWire (5.4%), inability to achieve/sustain occlusion of antegrade flow (3.2%) and inability to aspirate 20 ml of blood before deflation of the balloon (1.2%). The median GuardWire occlusion time was 388 s. There was a 42% relative reduction in the primary end-point (16.5% in the control group and 9.6% in the embolic protection device group, p<0.005), significant reduction in peri-procedure myocardial infarction (14.7% v. 8.6%, p=0.008) and in no-reflow phenomenon (9% v. 3%, p=0.02). The benefit with the distal protection device was observed irrespective of the use of glycoprotein IIb/IIIa receptor antagonists.

Comments

Percutaneous transluminal coronary angioplasty (PTCA) of saphenous vein grafts is different from that in native vessels, not only because it is technically more demanding but also because it is associated with more complications such as abrupt closure, distal embolization and coronary perforation. In native-vessel PTCA, coronary artery embolization is a rare complication occurring in <0.2% cases. On the other hand, in PTCA of vein grafts, coronary artery embolization is much more common, occurring in 3%–7% of cases. Embolization is even more common in patients undergoing directional atherectomy (up to 14%). Furthermore, coronary embolization is associated with much worse in-hospital and 12-month outcomes, with mortality as high as over 3%. Conventionally, the frequency of this complication has been minimized by careful selection of patients, avoiding diffusely diseased vein grafts, thrombotic and eccentric lesions. In this context, the concept of a distal embolic protection device is a significant technological advancement towards amelioration of this major problem in vein graft stenting. Distal protection devices act by mopping up the thrombotic and atheromatous debris and thus overcome this problem of slow-flow/no-reflow in the distal vessels. The SAFER trial is the first major randomized, multicentric trial addressing this issue. This trial clearly demonstrates the importance of distal embolization in causing major adverse cardiac events and the value of a distal embolization protection device in preventing these complications. Use of a distal protection device in these patients was associated with a lower rate of no-reflow phenomenon (one-third of the control group) and this translated into a marked reduction in mortality (57%), myocardial infarction (42%), need for CABG and major adverse cardiac events (42%). The benefits were apparent in all subsets of patients and occurred irrespective of the use of glycoprotein IIb/IIIa receptor antagonists. However, although adverse events were reduced with the usage of distal embolization protection devices, they were still higher than those encountered during PTCA of a native artery, suggesting an ongoing technical challenge in the ability to achieve complete distal protection.
Efficacy and Safety of Ezetimibe Co-Administered With Atorvastatin or Simvastatin in Patients With Homozygous Familial Hypercholesterolemia

Summary
In this multicentric, double-blind, parallel-group study, 50 patients with a diagnosis of homozygous familial hypercholesterolemia (HOFN) were randomized to one of three treatment arms: atorvastatin or simvastatin 40 mg/day; or Ezetimibe 10 mg/day plus atorvastatin or simvastatin 80 mg/day for 12 weeks. Adults or children (at least 12 years old or body weight ≥40 kg) with HOFN were included in the study. The diagnosis of HOFN was established either by genetic tests or by clinical criteria. The presence of 2 mutated alleles at the LDL-receptor locus was essential for genetic diagnosis; clinical diagnosis was made by a history of LDL-cholesterol >220 mg/dl while receiving maximally tolerated lipid-lowering therapy with <15% response; LDL-cholesterol above the 90th percentile in ≥2 first-degree relatives; and the presence of tendinous xanthomas and/or manifestations of premature coronary heart disease or corneal arcus. Patients with significant liver disease, renal disease, coronary syndromes, advanced CHF, or ongoing treatment with fibric acid derivatives were excluded from the study. LDL apheresis was permitted when necessary. The primary efficacy variable was the mean percentage change in LDL-cholesterol from baseline. Baseline characteristics, including the need for LDL apheresis, were matched in both the high-dose statin and Ezetimibe groups. After 12 weeks, co-administration of Ezetimibe with statin was highly effective in reducing LDL-cholesterol as compared to statin alone (–20.7% vs. –6.7%, p=0.007). The LDL-lowering effect of co-administration was apparent as early as 2 weeks after initiation and persisted throughout the 12-week study period. The LDL-cholesterol lowering effect of Ezetimibe plus statin was consistent among all subgroups studied. There was a similar reduction in total cholesterol in the Ezetimibe treatment arm but there was no significant difference in mean HDL-cholesterol, triglycerides, apolipoprotein B or -A1 concentrations.

Comments
Familial hypercholesterolemia is one of the commonest genetic disorders in humans, with a prevalence as high as 1 in 72 individuals reported in some communities. The defect affects the metabolism of LDL-cholesterol that leads to a pathologic accumulation of cholesterol and atherosclerosis. Homozygous familial hypercholesterolemia is a particularly malignant variety of this disorder leading to extremely high levels of serum cholesterol. The disease is particularly resistant to conventional therapy and culminates in premature atherosclerotic disease and even mortality. At present, LDL apheresis is the only effective treatment available, but this therapy is associated with several problems. Not only does it provide only a temporary relief, but is also associated with episodes of hypotension and is expensive. In this context, Ezetimibe, a new class of cholesterol absorption inhibitor, is a useful addition to the therapeutic armamentarium. It potently inhibits dietary and biliary cholesterol absorption at the brush border of the intestine without affecting the absorption of triglycerides or fat-soluble vitamins. Importantly, not only does this drug lead to approximately 20% reduction in LDL-cholesterol but its effects are additive over and above the effect of statins. The efficacy and low toxicity of this hypolipidemic agent have been borne out by this multicenter, randomized, double-blind study of Ezetimibe carried out in homozygous familial hypercholesterolemic subjects. In this study, addition of Ezetimibe led to an additional 20% reduction in both LDL- and total cholesterol without any additional side-effects. However, the study had several limitations. First, it studied only the short-term (12-week) effect of the drug. Second, some patients continued to be on LDL apheresis and they were not randomized or stratified based on this important variable. Finally, whether this 20% reduction in LDL-cholesterol translated into a clinical benefit is not known.
Impact of Clinical Syndrome Acuity on the Differential Response to Glycoprotein IIb/IIIa Inhibitors in Patients Undergoing Coronary Stenting


Summary

In this prospective, multicenter, randomized trial, the impact of acuity of development of a coronary syndrome was correlated with differential response to abciximab versus tirofiban therapy in patients undergoing elective coronary stent implantation. Four thousand eight hundred and nine patients were randomized in a double-blind, double-dummy design to either tirofiban (10 μg/kg intravenous bolus followed by an infusion of 0.15 μg/kg/min for up to 24 hours) or abciximab (0.25 μg/kg bolus followed by an infusion of 0.125 μg/kg/min for 12 hours). All patients received a standard dose of aspirin and a loading dose of clopidogrel (300 mg) prior to the procedure and these drugs were continued thereafter. Clinical follow-up was performed at 30 days and 6 months. The presenting clinical syndrome was acute coronary syndrome (ACS) in the majority (3025 patients); the rest had stable coronary syndrome (1784 patients). The baseline characteristics of patients with ACS were different as compared to non-ACS patients. There were more females, current smokers and more patients who had a history of antecedent angina, prior myocardial infarction (MI) and left ventricular (LV) dysfunction. Lesions of ACS were also more often thrombotic and located in the bypass grafts. These patients had an overall higher rate of mortality. MI and target vessels revascularization (TVR) at 30 days and 6 months. However, baseline characteristics in both the tirofiban and abciximab groups were matched. Overall procedural outcome was also similar in both the groups. However, in patients with ACS, the use of abciximab led to a reduction of peri procedural infarctions both at 30 days (5.8% vs. 8.4%; p=0.004) and 6 months (7.2% vs. 9.8%; p=0.013). Composite of death and MI at 30 days was greater in patients presenting with non-Q MI (6.9% vs. 11.7%; p=0.02) as compared to those presenting with unstable angina. However, total mortality and the need for TVR were similar in both the groups at 30 days and 6 months. In non-ACS patients, although the occurrence of MI and mortality was similar in both the abciximab and tirofiban groups, TVR was required less frequently in the tirofiban-assigned non-ACS group (5.8% vs. 8.4%; p=0.58). Although bleeding complications were similar in both the groups, the incidence of thrombocytopenia was higher in the abciximab group in both the ACS and non-ACS settings.

Comments

The efficacy of glycoprotein (Gp) IIb/IIIa antagonists in the prevention of complications associated with percutaneous coronary intervention (PCI) is well documented. These drugs act by occupying Gp IIb/IIIa receptors on the platelet surface, preventing fibrinogen binding and thereby preventing platelet aggregation. Experimental and clinical studies have suggested that occupancy of >80% of the receptor population results in a potent antithrombotic effect, unaffected by other thrombotic mechanisms, as it acts at the final common pathway. However, recently the differential effects of various Gp IIb/IIIa inhibitors at different receptors have been recognized. Abciximab is a Fab fragment of a humanized murine antibody having a strong affinity for receptors and a relatively long half-life, so that receptor occupancy persists for weeks. Furthermore, abciximab is not specific for the Gp IIb/IIIa receptor and also inhibits the vitronectin receptor (alpha v beta 3) on endothelial cells and the MAC-1 receptor on leucocytes. Eptifibatide is a cyclic heptapeptide that contains the KGD (Lys-Gly-Asp) sequence, whereas tirofiban and lamifiban are nonapeptide mimetics of the complementary RGD sequence of fibrinogen. These small molecules are highly specific for Gp IIb/IIIa receptors but they have no effect on vitronectin receptors. They also have a shorter half-life of up to 8 hours. Moreover, different Gp IIb/IIIa antagonists bind to different sites on the receptor and result in somewhat different binding properties that may modify their platelet effects and may paradoxically even activate the receptors. However, up till now no head-to-head comparison between these drugs was available. The TARGET trial has, for the first time, attempted to identify a separate niche for abciximab and tirofiban in the setting of PCI. It has shown that abciximab is more useful in acute situations (ACS), particularly in recent MI. Conversely, tirofiban was found more useful in stable non-ACS situations. During ACS, there is upregulation of Gp IIb/IIIa receptors. Thus, any therapy which provides an early and marked platelet inhibition is likely to be more useful. Abciximab, because of its action on a variety of receptors besides Gp IIb/IIIa, some plaque-stabilizing effects beyond the antithrombotic one and rapidity of action, is more useful in this context. The greater efficacy of tirofiban in non-ACS situations is, however, surprising and requires closer investigation. Another interesting finding noted in this study is a dissociation between periprocedural myonecrosis and 6-month mortality. Thus although periprocedural myonecrosis was lesser in the abciximab group, it did not translate into any mortality advantage over those in the tirofiban group. Finally, the study has several limitations. Serum troponin levels were not measured and the degree of platelet inhibition achieved was not quantified; therefore, whether abciximab and tirofiban achieved equipotent platelet inhibition is not known. Nevertheless, the TARGET trial is very important as it clarifies the role of two important potent platelet inhibitors in the context of PCI, particularly in view of their differing costs.
Efficacy and Safety of Intravenous Levosimendan Compared with Dobutamine in Severe Low-Output Heart Failure (The LIDO Study): a Randomized Double-Blind Trial


Summary

In this prospective, multicenter, randomized trial conducted in 11 European countries, the safety and efficacy of intravenous (IV) levosimendan was compared with IV dobutamine. Two hundred and three patients with severe low-output failure with left ventricular dysfunction (EF < 35%), cardiac index < 2.5 L/min and pulmonary capillary wedge pressure (PCWP) > 15 mmHg, requiring IV inotropic therapy were enrolled in this double-blind, double-dummy, parallel-group trial and randomized to receive either IV levosimendan (n=103) or IV dobutamine (n=100) for 24 hours. Young patients (< 21 years of age), women of child-bearing age, patients with a structural cause for heart failure [restrictive and hypertrophic cardiomyopathy, valvular heart disease, active coronary artery disease (CAD), ongoing arrhythmias], shock (SBP < 85 mmHg), renal, hepatic or pulmonary failure, cardiac tamponade and sepsis were excluded from the present study. The use of other inotropic agents such as β-adrenergic agonists, IV vasodilators, IV milrinone, etc. was curtailed and other cardiovascular drugs such as digoxin, diuretics and angiotensin-converting enzyme inhibitors (ACE-I) were also excluded from the present study. The treatment with levosimendan was started with a loading dose of 24 mg/kg over 10 min followed by IV infusion at the rate of 0.1 mg/kg/min. Dobutamine was initiated as a continuous infusion at a rate of 5 mg/kg/min. If an adequate response was not achieved after 2 hours, the rate of infusion was doubled every 2 hours until the effect was achieved or a dose-limiting event occurred. Adequate response was achieved in 28% of patients on levosimendan and 15% of those on dobutamine (95% CI: 1.1–3.3, p=0.022). The levels of serum creatinine and markers of liver dysfunction declined in the levosimendan group as compared to the dobutamine group, probably reflecting better perfusion. Improvement in dyspnea (68% vs. 59%) and fatigue (63% vs. 47%) was also more pronounced in the levosimendan group. Although it was statistically insignificant, β-blockers attenuated the effect of dobutamine on cardiac index and PCWP but not in levosimendan treated patients. Finally, termination of the infusion led to a rapid loss of efficacy (within 6 hours) of dobutamine but not of levosimendan. There was a higher mortality in the dobutamine group compared to the levosimendan group, both at 31 days (17% vs. 81%; CI: 0.018–1.00; p=0.049) and 180 days (38% vs. 26%, CI: 0.34–0.95; p=0.029). Overall, the safety profile of the two drugs was similar (47% of levosimendan patients and 42% of dobutamine patients had some adverse effects, but serious adverse effects were rare in both the groups (< 5%)). Three patients in the dobutamine group died during infusion but none during levosimendan infusion. Coronary events were commoner in the dobutamine group (7% vs. 0%, p=0.013); rate and rhythm disturbances were also commoner. (13% vs. 4%; p=0.023), but headache and migraine were less common (5% vs. 14% p=0.052). Overall, IV levosimendan was not only more efficacious but also safer than IV dobutamine, and, more importantly, it provided a survival advantage in patients with severe, low-output heart failure.

Comments

As of date, intravenous inotropic therapy for worsening congestive heart failure (CHF) leads certainly to short-term stabilization and improvement in symptoms but, in the long-term, actually increases mortality. This has aptly been brought out in the PROMISE trial. Even IV dobutamine, while very effective for acute stabilization, may actually contribute to increased mortality. Increased risk with these inotropes may be due to irreversible catecholamine-induced damage to a proportion of cardiac myocytes leading to increased risk of death. On the one hand, levosimendan, which is a long-acting calcium sensitizer, does not increase myocardial oxygen requirement. On the other hand, due to a predominant vasodilatory effect, it improves myocardial perfusion. At the molecular level, it does not increase the intracellular concentration of cyclic AMP and calcium ions and has an antistunning effect. Finally, it has no proarrhythmic effect. In the present LIDO study, the use of IV levosimendan was associated with a greater increase in cardiac output and more pronounced decrease in PCWP and systemic vascular resistance as compared to dobutamine, which contributed to its greater clinical efficacy. Furthermore, levosimendan was well tolerated and had fewer adverse cardiac events vis-à-vis dobutamine. The most important message from this study was that IV levosimendan offered a survival advantage of more than 30% over a 6-month period in these very sick patients as compared to IV dobutamine. Another interesting outcome of this study is that unlike dobutamine, the effects of IV levosimendan are not attenuated with concomitant use of β-blockers. The usefulness of β-blockers in the management of CHF is well established. However, the study had several limitations. The sample size was small, as yet the exact dose and duration of infusion has not been established and, finally, its usefulness in patients of cardiogenic shock was not evaluated.
**Calendar of Conferences**

**August 31–September 4, 2002, XXIV Congress of the European Society of Cardiology, Berlin, Germany**
Contact: European Society of Cardiology (ECOR), B.P. 174, Sophia Antipolis, Cedex F-06903, France
Fax: 33 4 9244 7601

Contact: The Course Directors, 55 East, 59th Street, 6th Floor, New York, NY 10022–1112, USA
Fax: 1212 434 6386
e-mail: info@crf.org

**September 28–29, 2002, The 4th Annual Conference of the Cardiological Society of India – NE Chapter, Imphal, Manipur, India**
Contact: Dr Kala Singh, Organizing Secretary, Cardiovacular and Thoracic Unit, Regional Institute of Medical Sciences, Imphal 795004
Fax: 0385 310625

**October 6–11, 2002, The XVth Lancefield International Symposium on Streptococci and Streptococcal Diseases, Goa, India**
Contact: Professor KK Talwar, Department of Cardiology, All India Institute of Medical Sciences, Ansari Nagar, New Delhi 110029, India
Fax: 91 11 6862663
e-mail: kktalwar@hotmail.com

**October 19–20, 2002, 2nd Annual Conference of the Indian College of Interventional Cardiology, Mumbai**
Contact: Professor Lekha Pathak, Hemdil, 5th Floor, Above Grand Living, Linking Road, Santa Cruz (W), Mumbai
Fax: 91 22 649 4996

**November 17–20, 2002, 75th Annual Session, American Heart Association, Chicago, Illinois, USA**
Contact: American Heart Association, 7320 Greenville Avenue, Dallas, TX 75231, USA
Fax: 1 214 373 3406

**December 1–4, 2002, 54th Annual Conference of the Cardiological Society of India, Kochi, Kerala**
Contact: Dr Rajan Joseph Manjuran, Hotel BTH Sarovaram, Kochi Bypass, Maradu, Kochi
Telefax: 0484 304494
e-mail: mail@csi2002.info
Website: www.csi2002.info

**January 12–14, 2003, International Conference on Chest Diseases and Allied Sciences, Delhi**
Contact: Dr VK Vijayan, Director, V.P. Chest Institute, University of Delhi, P.O. Box No. 2101, Delhi 110007, India,
Telefax : +91-11-7667420;
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**February 7–9, 2003, 8th Annual Conference of the Indian Academy of Echocardiography, Hyderabad, India**
Contact: Dr AV Anjaneyulu, Organizing Secretary, D. No.: 6-3-248/1, Care Hospital, Road No. 1, Banjara Hills, Hyderabad 500034, Andhra Pradesh
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Contact: Dr SB Gupta, Organizing Secretary, ISECON-2003, Head, Department of Medicine and Cardiology, Central Railway Headquarters Hospital, Byculla, Mumbai 400027
Fax: 91 22 265 1044
e-mail: sbgupta@vsnl.net

**June 25–28, 2003, 14th Asian Pacific Congress of Cardiology (APCC), Singapore, Singapore**
Contact: Dr Michael Lim, Chairman, 14th APCC, The Secretariat, 302, Orchard Road # 16-04, Tong Building, Singapore 238862, Republic of Singapore
Fax: 65 836 0436
e-mail: enquirv@14apcc.com

**December 4–7, 2003, 55th Annual Conference of the Cardiological Society of India, Kolkata**
Contact: Dr Asok Kumar Kar, Organizing Secretary, Indian Heart House, P-60, CIT Road, Scheme VIIIM, Kankurgachi, Kolkata 700 054
Fax: 033 355 6308
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