Takayasu’s Arteritis Revisited

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Takayasu’s arteritis has remained an enigma since it was first described one century ago. It is “an idiopathic inflammatory disease of the large elastic arteries occurring in the young and resulting in occlusive or ectatic changes mainly in the aorta and its immediate branches as well as the pulmonary artery and its branches”. The exact cause is not known, though some studies suggest that it is an autoimmune response to an unknown antigen. Over the past two decades, better modalities for diagnosis of the disease have evolved. These help in defining the extent of arterial involvement by the disease. The diagnosis of disease activity, though difficult, is important as this is the stage when proper treatment may prevent the development of obstructive lesions. Newer techniques of imaging may help in this goal. Management has improved with the availability of better immunosuppressive agents, and effective techniques of arterial angioplasty and surgical revascularization. The current focus of research is on newer developments which have taken place with regard to etiology, diagnosis of disease activity and management aspects.

Etiopathogenesis

One century has passed since the first description of Takayasu’s arteritis (TA) but we are no closer to the exact etiopathogenesis of the disease. Clinical associations and some similarities with end-stage aortic disease in the past suggested various etiologies such as syphilis, nematode infestation, malignancy, giant cell arteritis, rheumatic fever and congenital vascular anomalies. Subsequent reports, however, have effectively ruled these out as etiological factors for TA.

Several workers from India and Japan have suggested hypersensitivity to Mycobacterium tuberculosis as a possible factor in the pathogenesis. The Japanese were the first to suggest a role for tuberculosis at a time when it was widely prevalent in Japan. Lupi-Herrera et al. found evidence of previous tuberculosis in 48% of their Japanese patients, while the Indian series by Sen et al. reported the presence of tuberculosis in 71% of their patients. Pantell and Goodman reviewed the literature from 1961 to 1981 and found that the tuberculin test was positive in 73.3% – 100% of cases and active tuberculosis was present in 0.26% – 4.2% of the cases. They concluded that the likelihood of tuberculin positivity and actiutuberculosis was higher in TA patients.

The epidemiological link of TA and tuberculosis led to a search for markers of enhanced cellular and humoral immune responses to tubercular antigens. Immunohistochemical studies of aortic tissues samples from patients with TA have shown that the infiltrating cells mainly consisted of gamma delta T lymphocytes, natural killer cells, macrophages, cytotoxic T lymphocytes and T helper cells, thereby suggesting a cell-mediated immune response, though it is still not clear as to what the trigger for this immuneresponse is. A 65 kDa heat shock protein (HSP) is a major immunogenic component of M. tuberculosis and expression of HSP has been shown to be strongly induced in the aortic tissue. This may enhance the cytotoxicity of the infiltrating lymphocytes. It is possible that TA is caused by a humoral/cell-mediated immune response after the human host is exposed to bacterial HSP (HSP kDa). The antibodies generated after exposure to the bacterial HSP 65 may cross-react with the human homologue of HSP 65, which is expressed on the surface of stressed endothelial cells. This interaction with the endothelial HSP may initiate an immune response responsible for the subsequent lesion.

Aggarwal et al. reported a heightened response to tubercular antigens, especially the 65 kDa HSP. They found that patients with TA had elevated levels of IgG, IgM and IgA antibodies to sonicated M. tuberculosis extract and also its recombinant 65 kDa HSP. They concluded that elevated antibodies to tubercular antigens, especially in 65 kDa HSP, suggested a role for M. tuberculosis in the pathogenesis of TA. Sagar et al. tested the blast transformation to various antigens in patients with TA. Purified human aortic antigen caused a significant blast transformation, suggesting a role for autoimmunity. Purified protein derivative (PPD) evoked a variable response, thereby implying that while autoimmunity may have a role, the antigen might not be M. tuberculosis. Direct involvement of the aorta by M. tuberculosis appears unlikely, as tubercular aortitis lesions are discrete with localized aneurysm formation, and are usually nonobstructive. Granulomas due to tuberculosis are caseating in nature while in TA they are proliferative without caseation.

All the data regarding the link to tuberculosis have been...
generated from countries where tuberculosis was also highly prevalent at that time. While India still has a high prevalence of tuberculosis and TA, the Japanese continue to report substantial incidence of TA, though that of tuberculosis has gone down. Thus, it can be seen that while there seems to be an association with M. tuberculosis, the evidence regarding causation is not very strong.

An autoimmune mechanism was first suggested in 1962 by Judge, who suggested that TA could be due to an immune reaction against elastin, based on his findings of high levels of gammaglobulins, raised ESR, leucocytosis, arthralgia and high titers of anti-aorta antibodies. The association with connective tissue diseases such as systemic lupus erythematosus and Still's disease, and autoimmune endocrine disorders such as diabetes and thyrotoxicosis also suggested a role for autoimmunity. A study of peripheral lymphocytes showed an increased CD4/CD8 ratio and increased B lymphocytes. These suggest defective T-cell regulation, pointing towards a role for cell-mediated immunity. Histological studies from the affected aorta have shown infiltration with gamma delta T lymphocytes, natural killer cells, macrophages, cytotoxic T lymphocytes and T helper cells. The production of immunoregulatory cytokines, blast transformation of peripheral lymphocytes challenged with aorta extract and the demonstration of CD8 lymphocytes all suggest that cell-mediated immunity may play a role. Anti-aorta antibodies have also been found by a number of Japanese workers, which were localized in the outer part of the media and adventitia. In a recent study, anti-aorta antibodies were reported using ELISA and these titers decreased on using collagenases, suggesting a role for collagen as the antigenic stimulant for autoimmunity. However, it is worth pointing out that the authors did not use electroimmunotransference to confirm their ELISA findings. As the data reported are not consistent in all studies, the current opinion is that while cell-mediated immunity may have a role in the etiopathogenesis, humoral autoimmune mechanisms do not seem to be important.

There are some reports of TA occurring in family members, which point to a genetic origin. Sixteen families with familial TA have been reported from Japan. It has also been reported in monozygotic twin sisters and in male siblings sharing the same HLA haplotypes. As autoimmunity has also been implicated in the pathogenesis of TA, a number of studies have explored the association between human immune response genes (HLA genes) and TA. An association of HLA-B5 or its molecular subtypes has been reported from Japan, Korea and India, but not so extensively from Mexico or North America. Studies done by Mehra et al. in 104 Indian patients suggest a strong association of the disease with HLA-B5 as well as its two serological subtypes, B51 and B52. Japanese studies have shown that TA is associated with HLA-B52 and -DR2. DNA analysis has shown that HLA-B*52, -B39, HLA-DR B1*1502, -DQ*0601 and DPB1*0901 show a positive association. Disease manifestations have also shown a link to the HLA type. In HLA-B52-positive patients, aortic regurgitation, ischemic heart disease and pulmonary infarction are much more common. Renal artery stenosis occurs more frequently in HLA-B39-positive patients. HLA molecules bind antigenic peptides and present them to T lymphocytes, and this may have a role in the induction of various autoimmune mechanisms. The above studies have clearly shown an association of some HLA subtypes with TA. It is believed that the HLA molecules either directly have a role in the pathogenesis of TA or they are in linkage disequilibrium with some unknown genes which are involved in the pathogenesis of TA.

Since TA affects predominantly females of the reproductive age group, the role of sex hormones has also been studied. Urinary estrogens measured during the follicular phase were elevated in 16 of 20 TA patients, compared with 11 healthy controls. It was also found that estradiol and progesterone, but not testosterone, enhance leucocyte adhesion to endothelial cells in the presence of tumor necrosis factor.

To summarize, the pathogenesis of TA probably starts with a genetically predisposed individual with perhaps a specific hormonal milieu, followed by exposure to an unidentified antigen (which may or may not be tuberculosis) leading to an immune response that targets the large vessels.

**Assessment of Disease Activity**

The evaluation of disease activity in patients with TA is a challenge. It was initially believed that the disease had three phases: a pre-inflammatory or systemic phase, followed by vascular inflammation, and ending in a "burnt-out" fibrotic, stenotic phase. However, this is too simplistic a sequence. The absence of systemic clinical features does not exclude ongoing vascular inflammation nor does the presence of ischemic symptoms always suggest active inflammation. As many as 44% of clinically inactive patients were found to have active vasculitis when tissue samples were taken from vessels at surgery performed for obstructive lesions. Angiography is the gold standard for detecting the extent of disease but it cannot diagnose disease activity.

The ability to measure disease activity in TA is limited by the absence of any definite laboratory test for this purpose. The presence of constitutional symptoms along with raised levels of acute-phase reactants have usually been used to diagnose disease activity. The gold standard for the determination of active vasculitis is histopathological examination of the involved arteries, which is not usually
possible unless the patient is going for surgery. In 50% of patients, the onset of disease is heralded by constitutional symptoms such as fever, anorexia, arthralgia, signs and symptoms of local limb ischemia, hypertension and raised ESR; in the other 50%, there is no history suggestive of an acute phase and these patients present with advanced obstructive lesions. Fever is present in 20%–42.5% and acute phase and these patients present with advanced symptoms of local limb ischemia, hypertension and raised ESR; in the other 50%, there is no history suggestive of active disease. However, ESR has not been found to be reliable, as 30% of clinically active patients have a normal ESR and 44% of quiescent patients have an elevated ESR.

The National Institutes of Health (NIH) have arbitrarily defined active disease as new onset or worsening of at least two of the following four features: (i) signs and symptoms of vascular inflammation or ischemia (claudication, decreased or absent pulses or blood pressure in the extremities, bruises or carotidynia); (ii) elevated ESR; (iii) angiographic abnormalities; and (iv) systemic symptoms not attributable to another disease, e.g. fever, polyarthralgia, polymyalgia.

Data from NIH are available from surgical biopsy specimens obtained from the origin and insertion of vascular bypass grafts. In these patients, in whom surgery was done at the time of presumed remission according to the NIH criteria, histopathological evidence of vasculitis was found in 44% of nine specimens. In another study, histological evidence of vasculitis was found in 42% of 33 patients thought to have inactive disease. The NIH data also showed that among patients believed to be in clinical remission, 61% had new lesions on angiographic studies. Fifty-six percent of patients thought to be in clinical remission had an elevated ESR. Thus the NIH experience showed that in about half of their patients, clinical parameters and non-specific acute-phase reactants were inadequate measures of disease activity and therefore not reliable enough for therapeutic decisions. As these markers cannot predict disease progression, research needs to focus on more perceptive and accurate markers of disease activity and progression.

Attempts have been made to detect disease activity by using serum markers such as acute-phase reactants and other modulators of inflammation, including cytokines. The International Network for the Study of the Systemic Vasculitides (INSSYS) recruited 29 patients with TA and 26 healthy controls. A activity assessment was based on the Birmingham Vasculitis Activity Scores. Serological tests were done, which included ESR, C-reactive protein (CRP), tissue factor, von Willebrand factor, thrombomodulin, tissue plasminogen activator, ICAM-1, VCA M-1, E selectin and PECAM-1. None of the markers could reliably distinguish between healthy volunteers and patients with active TA. In a study of cytokines, it was found that all patients with TA studied during an active phase of the disease, had increased serum concentration of IL-6, which paralleled disease activity to the extent that its serum concentrations were comparable to those of control subjects when patients were studied during remission. The concentration of another cytokine, RANTES, was also higher than normal in the serum of all patients with active TA.

Noninvasive radiological techniques aimed at detecting arterial involvement are being evaluated. High-resolution B-mode ultrasonography is useful in showing obstructive involvement of the blood vessels, and can also detect intimal-media thickening in the absence of obstructive lesions, which may be a sign of active disease. One study demonstrated circumferential thickening of the common carotid arteries in 19 of 23 TA patients, while angiography revealed stenotic lesions in only 13 of these patients. The characteristic finding was circumferential arterial wall thickening of one or both common carotid arteries in the form of macaroni-like, diffusely thickened intima-media complex. As ultrasonography cannot pick up pulmonary or coronary involvement, magnetic resonance imaging (MRI) and computerized tomography (CT) have also been evaluated as diagnostic techniques. In the early stages of the disease, subtle inflammatory wall thickening may be the only abnormality and MRI may pick up concentric wall thickening of the vessels. T2-weighted images may show bright signals of edema in and around the inflamed vessel. Contrast-enhanced MRI, showing enhanced vessel walls even in the chronic stage, may suggest activity.

Intravenous ultrasound (IVUS) studies of the aorta have shown thickening and altered echogenicity of the media, adventitia and peri-arterial tissues. This was seen even in some portions of the aorta, which looked normal on angiography. The above-mentioned serum markers and imaging techniques have shown some promise in assessing disease activity but they are mainly based on small series of patients and, as yet, none of them can be considered a reliable test for detecting disease activity. Endomyocardial biopsy (EMB) has shown a high incidence of myocarditis (26 of 92 patients) and these patients had a higher incidence of heart failure. Eight of eleven patients with clinically active disease had myocarditis. The presence of myocarditis may thus be an indicator of activity.

To summarize, assessment of activity in TA remains a problem. Reliance is still on clinical criteria, as none of the serological markers have been found to be useful in either the diagnosis or exclusion of activity. Newer techniques which include serological markers such as cytokines, ultrasonography, MRI, IVUS and EMB may prove useful for the assessment of disease activity in the future.
Management of Takayasu's Arteritis

Management is based mainly on the symptomatology and the immune basis of the disease. Obstructive lesions need to be tackled by revascularization techniques such as angioplasty and surgery, while active disease needs to be treated with immunosuppressive agents.

Angioplasty along with stent implantation is fairly successful for discrete aortic lesions, with low rates of restenosis (0%-19%). Renal angioplasty is also highly successful (95%) and helps in the control of hypertension. Stent-supported angioplasty has also been useful for subclavian and carotid artery obstructions with good success rates (86%)[33] and moderate rates of restenosis. These modalities are useful if the lesions are discrete.

Surgery was the mainstay for treatment of obstruction before the advent of balloon angioplasty. It remains the option when the lesions are diffuse and not suitable for angioplasty or in patients with aneurysms. The surgical options include bypass of the obstructed segment, resection with an interposition graft, endarterectomy, excision of aneurysms and aortic valve replacement. Surgery provides symptomatic relief and good long-term results have been reported. In the chronic obstructive stage, treatment by percutaneous angioplasty or surgical bypass are the viable options, but both are limited by the fact that the disease is progressive and often multifocal.

Management of active TA: Ideally, the disease needs to be picked up in the active phase so that immunosuppressive therapy can be started. Glucocorticoids are the mainstay of therapy for active TA and success rates of 20%-100% have been reported. Ishikawa[35] reported a series of 118 patients treated with adjunctive azathioprine, cyclophosphamide, or mercaptopurine and the response was good in 29%, fair in 33% and ineffective in 29%.[36]

The NIH has also reported their experience.[37,38] The treatment protocol followed by NIH included steroids in doses of 1 mg/kg body weight, up to a maximum of 60 mg/day, for 1–3 months, and then tapered to an alternate-day schedule during the next 4–8 weeks if the disease became inactive. If the disease continued to remain inactive, steroids were further tapered and discontinued over a period of 6–12 months. If steroid tapering was unsuccessful, or relapse of disease occurred, the patients were put on daily cyclophosphamide (2 mg/kg) or weekly methotrexate (0.15–0.3 mg/kg) therapy. Sixty patients were included in the NIH studies and observed over 3–5 years. Forty-eight patients had active disease and were put on steroids. Sixty percent achieved remission with steroids alone. Those not in remission and those with relapse were put on cytotoxic therapy. Forty percent of these achieved sustained remissions. Twenty-three percent of patients never achieved drug-free remissions and 45% with remission had at least one relapse. One-fourth of patients had no significant level of disability, 26% had partial disability, while 47% had significant disability.

Concerns about the long-term toxicity of cyclophosphamide have led to the emergence of methotrexate as an alternative therapy. In a study of 18 steroid-resistant or relapsed TA patients, weekly methotrexate (mean dose 17 mg, range 10–25 mg) was given for a mean period of 14.4 months.[38] Treatment initially consisted of methotrexate 0.3 mg/kg/week, not exceeding 15 mg/week. The dose was then gradually increased by 2.5 mg every 1–2 weeks, up to a maximum of 25 mg/week. This steroid–methotrexate regimen led to remission in 81% of patients but was followed by a relapse in 54%. Half the patients who had a relapse were re-induced into remission using the same protocol. Fifty percent had sustained remissions for a period of 18 months. Twenty-five percent had sustained remissions for one year and 20% of patients experienced progressive disease in spite of methotrexate. Pneumocystis carinii pneumonia occurred in one patient, elevated enzymes in 28%, nausea in 22% and stomatitis in 6%. Mycophenolate mofetil is a new immunosuppressive agent which has been used recently for active TA in 3 patients.[39]

Conclusions

Takayasu's arteritis continues to be an enigma one century after its first description. The exact etiology is unknown. It is believed to occur in a genetically predisposed individual due to autoimmune responses to an as yet unknown stimulus. Several modifications have been suggested in the criteria for diagnosis as well as classification of the disease, keeping in mind the varied spectrum of disease manifestation worldwide. Detection of active disease remains
a challenge, as the current surrogate markers of disease activity are inadequate. Newer techniques such as ultrasound and MRI seem promising. Immunosuppressive therapy is the mainstay of medical therapy during the active stage of the disease, while surgery and percutaneous angioplasty provide relief in patients with obstructive lesions.

References
36. Ito I. Medical treatment of Takayasu arteritis: Heart Vessels Suppl 1992; 7: 133–137
Congenital Long Q-T Syndromes in Children

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Congenital long Q-T syndromes (LQTS) form an infrequent but serious group of disorders of myocardial repolarization, characterized by a prolonged corrected Q-T interval (QTc) in the electrocardiogram (ECG) associated with ventricular arrhythmia, seizures and/or sudden death. Current estimates from the United States suggest that 3000–4000 children and young adults are affected and 1 in 10 000 persons is a gene carrier. Several case series have also been reported from developing countries. Children account for about 50% of probands and 40%–50% affected family members are enrolled in the International LQTS Registry. This review summarizes the current understanding of the pathogenesis and molecular genetics, and outlines the management of congenital LQTS.

Genetic Basis and Inheritance

Long Q-T syndromes are the result of a defect in the proteins encoding cardiac ion channels (or channel subunits) that form the basis of cardiac excitability. Two syndromes have been described in relation to LQTS. Of these, the Romano-Ward syndrome is more frequent but less severe and does not affect hearing. It is usually transmitted as an autosomal dominant gene with low penetrance, although recently autosomal recessive transmission has also been described. Noncardiac abnormalities such as diabetes mellitus, asthma and syndactyly may be occasionally associated. Five genes—KVLQT1 (LQT1), HERG (LQT2), SCN5A (LQT3), KCNE1 (LQT5) and KCNE2 (LQT6)—have been implicated in this syndrome (Table 1). Among 262 unrelated patients with LQTS, KVLQT1 (42%) and HERG (45%) accounted for 87% of all identified mutations. Missense mutations were the most common (72%), followed by frameshift mutations (10%), in-frame deletions (6%), nonsense mutations (6%) and splice-site mutations (6%). Most mutations resided in the intracellular (52%) and transmembrane (30%) domains.

LQT1 is characterized by early onset of symptoms, exercise or stress-induced events and broad-based or normal-looking T waves on ECG. Bifid T waves on ECG or Holter recordings may point towards LQT2. Exercise-triggered events are less common in LQT2. Those with LQT3 have fewer symptoms, but these occur more often during sleep and are associated with a high likelihood of sudden death. Late onset or asymmetrical peaked T waves are characteristic of LQT3. Bradycardia and exercise-induced Q-T shortening are also more common in LQT3. The risk of cardiac events is highest between 5 and 15 years of age in LQT1 and between 10 and 15 years in LQT2, whereas in LQT3 cardiac events are infrequent below the age of 10 years.

Jervell and Lange-Nielsen syndrome is associated with congenital sensorineural deafness and shows autosomal recessive transmission. Homozygous mutations of KVLQT1 (JLN1) and KCNE1 (JLN2) underlie this syndrome, which account for only 1% of all LQTS. Deafness is attributed to dysfunction of potassium channels that exist in the stria vascularis of the inner ear.

Many antiarrhythmic drugs are known to prolong the Q-T interval and provoke ventricular tachycardia (VT). Similar Q-T prolongation can also be caused by noncardiac drugs like antihistamines (terfenadine, astemizole), imidazole antifungals, macrolide antibiotics, fluoroquinolones, antimalarials (mefloquin), tricyclic antidepressants, neuroleptics, and prokinetic agents (cisapride and domperidone). The common mechanism for such an effect is the blockade of the delayed rectifier Ikr potassium channel. Drug-induced Q-T prolongation has also been associated with (but not yet formally linked to) inherited defects in the cardiac potassium channels. It is tempting to speculate that Q-T interval screening before drug prescription and/or genetic screening could prevent drug-related torsade de pointes. Also, Brugada syndrome, characterized by S-T segment elevation in leads V1 to V3, with or without right bundle branch block and ventricular fibrillation (VF), has been linked to a close SCN5A mutation.
Table 1. Details of genetic defects identified in patients with long Q–T syndromes

<table>
<thead>
<tr>
<th>LQTS type</th>
<th>Gene</th>
<th>Genetic locus</th>
<th>Defective channel</th>
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<tbody>
<tr>
<td>LQT1∗/JLN1†</td>
<td>KCNQ1 (KVLQT1)</td>
<td>11p15.5</td>
<td>Potassium channel (I(_{\text{KS}}))</td>
</tr>
<tr>
<td>LQT2*</td>
<td>HERG</td>
<td>7q35-36</td>
<td>Potassium channel (I(_{\text{Kr}}))</td>
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<tr>
<td>LQT3*</td>
<td>SCN5A</td>
<td>3p21-24</td>
<td>Sodium channel (I(_{\text{Na}}))</td>
</tr>
<tr>
<td>LQT4*</td>
<td>Not known</td>
<td>4q25-27</td>
<td>Not known</td>
</tr>
<tr>
<td>LQT5*/JLN2†</td>
<td>KCNE1 (minK)</td>
<td>21q22.1-22.2</td>
<td>Potassium channel (I(_{\text{KS}}))</td>
</tr>
<tr>
<td>LQT6*</td>
<td>KCNE2 (MiRP1)</td>
<td>21q22.1-22.2</td>
<td>Potassium channel (I(_{\text{Kr}}))</td>
</tr>
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</table>

∗Romano-Ward syndrome, when heterozygous; †Jervell and Lange-Nielsen syndrome when homozygous; I\(_{\text{KS}}\): channel mediating the slowly activating delayed rectifier potassium current; I\(_{\text{Kr}}\): channel mediating the rapidly activating delayed rectifier potassium current; minK: beta subunit which coassembles with KCNQ1 to form functional I\(_{\text{KS}}\) current; MiRP1: beta subunit which coassembles with HERG to form functional I\(_{\text{Kr}}\) current

Alternate mechanism to explain the pathophysiology: The autonomic imbalance hypothesis states that a lower than normal right cardiac sympathetic activity accompanied by reflex hyperactivity of the left cardiac sympathetic system causes an unbalanced regional adrenergic input to the ventricular myocardium. This in turn could lead to a cascade of electrophysiologic and biochemical alterations including ionic disturbances, that sensitize the heart to catecholamines. Experimental ablation of the right stellate ganglion or electrical stimulation of the left ganglion in animals can produce some features of LQTS, and therapeutic block, denervation or ablation of the left stellate ganglion improves symptoms in patients resistant to beta-blocker therapy.

Electrophysiologic Abnormality

Q–T lengthening reflects a prolongation of the ventricular action potential and the prolonged repolarization predisposes to polymorphic ventricular tachycardia. This is brought about either by a reduction in the net outward current and/or by an enhancement of inward currents during phase 2 and 3 (plateau and late phases) of the action potential. The prolongation of action potential duration generates deformities, known as after-depolarizations in these two phases.

Prolonged recovery from electrical excitation contributes to increased dispersion of refractoriness. Consequently, the wave of excitation may pursue a distinctive pathway around a focal point in the myocardium with increased likelihood that early after-depolarization-induced extrasystoles will trigger re-entry and VT or VF. Episodes of arrhythmia are preceded by irregularity of the heart rate referred to as “short–long–short” sequence, i.e. an initial short coupling interval of premature beat, subsequent long compensatory pause, and another short coupling interval of premature beat followed by an episode of torsade de pointes (Fig. 1). Calcium loading due to the first short cycle(s) of the short–long–short series favors the emergence of early after-depolarizations (and triggered activity). The majority of such episodes produce short, self-limited bursts of torsade de pointes. At times, however, the arrhythmia lasts longer and becomes clinically significant. The mid-myocardial cells (M cells) are directly implicated in the genesis of Q–T interval prolongation and related T–U wave abnormalities as well as in the origin of VT, as these cells are the last to repolarize and mark the end of the T wave. M cells have a weaker, slowly activating component of the delayed rectifier current and increased late sodium current, either of which may be abnormal in LQTS. The inhomogeneity in recovery of excitability is critical for development of arrhythmia, and the catecholamine surge induced by precipitating stress factors may aid expression of this heterogeneity.

![Fig. 1. Holter recording showing a “short–long–short” sequence of R–R intervals preceding the onset of torsade de pointes. Following two sinus beats a premature ventricular complex (*) generates a long postextrasystolic pause. The pause is followed by a sinus complex with marked postextrasystolic Q–T changes (arrow head) from which a short burst of torsade originates. This, in turn, results in a new pause. The sinus complex that follows this pause demonstrates giant and bizarre T–U waves (arrow), from which a longer burst of torsade originates. (From Viskin30 with permission)](image-url)
manifest in the preteen to teenage years. These are often induced by exercise (56%), especially swimming, intense emotional upset like anger or fright (47%), sudden awakening from sleep (19%), or auditory stimuli like the ringing of an alarm clock or telephone, or the sound of thunder (8%). Both fatal and nonfatal cardiac events have been observed more frequently in adolescents. Hormonal changes, psychological lability of the adolescent and possible maturation of the autonomic nervous system associated with puberty could contribute to this increased risk. A definite male preponderance in the risk of cardiac events has been documented in children <15 years, as against the female preponderance noted in adults. Factors implicated include greater physical activity in boys and potential differences in autonomic reaction to triggering events. About one-third of affected patients are asymptomatic. The syndrome is usually associated with a structurally normal heart. Physical findings are generally unremarkable.

LQTS should be considered in patients with syncope or seizures who give a history of sudden deaths in other family members. Abrupt onset-abrupt offset syncopal events are more suggestive of LQTS than gradual onset-gradual offset syncope (as with hypoglycemia and vasovagal reaction) or abrupt onset-gradual offset syncope (primary seizures). Often the arrhythmia is never documented due to its transient nature and the diagnosis is made by inference (Table 2).

**Table 2. Diagnostic criteria for long Q-T syndromes**

<table>
<thead>
<tr>
<th>Criteria 1993 LQTS</th>
<th>Diagnostic criteria</th>
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<tr>
<td>a) ECG findings: QTc &gt;480 ms (3 points); 460–470 ms (2 points); 450 ms in males (1 point); torsade de pointes (2 points); T wave alternans (1 point); notched T wave in 3 leads (1 point); low heart rate &lt;2nd percentile for age (0.5 point)</td>
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<tr>
<td>b) Clinical features: syncope with stress (2 points); syncope without stress (1 point); congenital deafness (0.5 point)</td>
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<tr>
<td>c) Family history: definite LQTS (1 point); unexplained sudden death at &lt;30 years of age among immediate family members (0.5 point)</td>
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Score ≤1 point—low probability; 2-3 points—intermediate probability; ≥4 points—high probability

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(a) Corrected QT interval (QTc) > 0.44 s* OR
(b) Family history of LQTS plus unexplained syncope, seizure or cardiac arrest associated with typical inciting event such as exercise or emotion even if QTc is normal

* In the absence of medications or disorders known to affect these ECG features

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Fig. 2. An approach to patients presenting with symptoms suggestive of long Q-T syndrome.* Where clinical suspicion is strong, additional 24-hour ambulatory ECG and/or exercise stress test is desirable even if the routine ECG shows normal corrected Q-T interval.

**Fig. 2. An approach to patients presenting with symptoms suggestive of long Q-T syndrome.** Where clinical suspicion is strong, additional 24-hour ambulatory ECG and/or exercise stress test is desirable even if the routine ECG shows normal corrected Q-T interval.
prolongation of QTc, it is necessary to perform another 12-lead ECG, a 24-hour ambulatory ECG and/or a treadmill exercise test before making the diagnosis.

ECG in LQTS may also show abnormal T wave configurations like wide-based slowly generated T waves, biphasic or bifid T waves, notched T waves, low amplitude humps on the descending limb of the T wave, indistinct termination of T waves due to U waves (T–U complex), alternate positive and negative T waves (T alternans)\(^\text{11,37}\) (Fig. 3). Other abnormalities may include bradycardia, second-degree atrioventricular block, multifocal premature ventricular contractions, monomorphic VT and polymorphic VT (torsade de pointes).\(^\text{26,27}\)

**Treatment**

Systematic data on therapy for LQTS exclusively in children are scarce. Most published studies have included adolescents and children also. As in adults, beta-adrenoceptor blockers form the cornerstone of therapy and reduce or even eliminate symptoms in 75%–80% of patients.\(^\text{44}\) The Q–T interval generally remains prolonged, although recent reports suggest a significant reduction in QTc in patients who respond well to therapy.\(^\text{44}\) Propranolol is the most widely used beta-blocker, but others like atenolol, metoprolol and nadolol requiring less frequent dosing are equally effective.\(^\text{44}\) Moderate doses are preferred, as higher doses do not give additional benefit, and may even lead to dangerous bradycardia. Genotypes LQT1 and LQT2 respond better to beta-blockers.\(^\text{45,46}\) The efficacy of therapy can be assessed clinically by freedom from symptoms and absence of arrhythmia on 24-hour ambulatory ECG. A blunted heart rate response to treadmill exercise (exercise heart rate achieved <130/min) may indicate adequate beta-blockade.\(^\text{25}\) Patients who become asymptomatic with beta-blocker therapy should continue treatment indefinitely. Those in whom the QTc normalizes over time\(^\text{47}\) and who remain free from symptoms for several years may slowly taper off and ultimately discontinue the medication.

Patients should avoid vigorous exercise (especially swimming), competitive sports and other forms of acute adrenergic arousal, including exposure to significant emotional or auditory stimuli. Eliminating alarm clocks,
the need for additional implantation of a pacemaker. Profound bradycardia or long sinus pauses may indicate genetic heterogeneity. Patients with documented pause-short-long-short sequences) and decrease repolarization phenomena that atrioventricular (AV) block can develop even at physiological atrial pacing rates. Given the potential for developing functional second-degree AV block, ventricular or dual-chamber pacing in high-risk patients. However, many patients with LQTS have such long repolarization phenomena that atrioventricular (AV) block can develop even at physiological atrial pacing rates. Given the potential for developing functional second-degree AV block, ventricular or dual-chamber pacing is generally recommended. Initial pacing rates of 70–80 bpm are used, with faster pacing rates should recurrent syncope develop.

Surgical options in resistant patients include left stellectomy, left cervicothoracic sympathectomy or high thoracic left sympathectomy. These procedures have been tried in children with subsidence of symptoms in 55% and shortening of QTc in 11%. The beneficial effect could be explained by a reduction in the release of norepinephrine in localized areas of the ventricle. The possibility of an important role for an alpha-adrenergic mechanism in the genesis of arrhythmia in these patients is supported by the efficacy of sympathetic denervation in patients who continue to have syncope despite adequate beta-adrenergic blockade. The shortening of QTc following surgery could also contribute by modifying the electrophysiological parameters involved in arrhythmogenesis. Recent studies emphasize the role of an implantable cardioverter-defibrillator in patients who are persistently symptomatic. Children, especially adolescents with a prior aborted cardiac arrest and those who show poor compliance to medical therapy, are potential candidates. Suitably sized implantable cardioverter-defibrillators for use in infants and young children are now available, and with the expansion of facilities for implantation and regular follow-up, these may soon gain popularity. The high cost of the device, need for periodic replacement due to short battery life, unpleasant awareness of the electric shock, and the need for life-long instrumentation remain some of the major hurdles to be overcome. The long-term benefits of these devices also need to be evaluated. Some newer devices combine pacemaker function with cardioverter-defibrillator capabilities.

Antiarrhythmic drugs other than beta-blockers are generally contraindicated in patients with LQTS. However, those with the LQT3 genotype with severe symptomatology may benefit from mexiletine, a class IB antiarrhythmic agent, which does not prolong the resting membrane potential, duration of action potential or the Q–T interval on the surface ECG. Potassium supplementation with spironolactone in LQT1 and LQT2 patients is also under trial. Other options, mostly experimental, include use of alpha-adrenergic blockers, calcium-channel blockers, pentoxifylline and nicorandil.

Prognosis

The affected genes, along with the genetic background of the patient, determine the clinical severity of the disease and the outcome. A significant proportion of children with LQTS die suddenly without prior medical assessment and thus the mortality profile and prognostic indicators are biased. With the introduction of beta-blocker therapy, mortality has been reduced from 60%–70% to 3%–5%. The need for life-long instrumentation remain some of the major hurdles to be overcome. The long-term benefits of these devices also need to be evaluated. Some newer devices combine pacemaker function with cardioverter-defibrillator capabilities.
A longer duration of QTc (>0.54 s) and a higher basal heart rate have been identified as indicators of poor prognosis.\textsuperscript{27} Other suggested poor prognostic indicators include young age at onset of symptoms, strong family history of life-threatening events, documented repetitive ventricular arrhythmia, labile T waves especially T wave alternans and notched T waves, slow baseline heart rate, sudden increases in heart rate and AV block in the neonatal period.\textsuperscript{43,59} Deaths can occur even while on therapy. In one series, among patients who experienced sudden death, 40% were receiving propranolol, 10% were receiving another beta-blocker and 20% had received a pacemaker.\textsuperscript{26} Caution should be exercised in the presence of bradycardia or AV block.\textsuperscript{27,30} Asymptomatic patients with prolonged QTc from families with frequent lethal cardiac events are at high risk. However, there is no evidence that treatment is effective in preventing these deaths. LQT1 patients respond better to beta-blockers and hence survive longer.\textsuperscript{40} LQT3 has the worst outcome.\textsuperscript{45} As age advances, the severity of symptoms and even the degree of Q–T prolongation tends to decrease. In some families with LQTS, the QTc normalizes in males after puberty.\textsuperscript{47} Elderly patients who are asymptomatic with borderline QTc generally do not require therapy.

In summary, LQTS is clinically and genetically a heterogeneous group of disorders of ventricular repolarization. The affected genes in any patient can lead to a wide spectrum of clinical outcomes. Important issues confronting researchers include the development of cheap and effective tools for diagnosis, as well as prevention and risk stratification. An understanding of the mechanisms and genetics responsible for LQTS is expected to enable presymptomatic diagnosis, allow genotype-phenotype studies and ultimately lead to the development of gene-specific therapy.

References

The need for reoperation in patients with coronary artery disease is increasing. The incidence of redo coronary artery bypass grafting (CABG) is approximately 3% at 5 years, 11% at 10 years and 17% at 12 years. An increase from 1.9% in 1980 to 7.0% in 1990 has been indicated by the Society of Thoracic Surgeons National Database. The technical obstacles in redo CABG are difficulty in re-entry, potential for cardiac and conduit injury during dissection, limited availability of conduits, management of patent grafts and myocardial protection. To reduce morbidity and mortality, various adaptations in surgical technique have evolved. These include minimal dissection, routine femoral cannulation and administration of antegrade and retrograde cardioplegia.

The advent of minimally invasive techniques to perform CABG without cardiopulmonary bypass (OPCAB) may be particularly useful in redo CABG. This serves as an alternative method of “myocardial protection” as well as reduces the inherent risks of cardiopulmonary bypass (CPB). Patients with diffuse atherosclerosis of the ascending aorta may benefit from OPCAB as this technique reduces the risk of atheromatous embolization during aortic cannulation.

We review our experience of redo CABG (with and without CPB) and compare the clinical outcome and early mortality between the two procedures.

Methods

From January 1995 to December 2001, 350 patients underwent redo CABG. One hundred and fifty-six patients

BEATING HEART VERSUS CONVENTIONAL REOPERATIVE CORONARY ARTERY BYPASS SURGERY

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Escorts Heart Institute and Research Centre, New Delhi

Background: The incidence of reoperative coronary artery bypass grafting is increasing with an increase in the number of patients undergoing coronary artery bypass surgery. The clinical outcome of redo coronary artery bypass grafting without cardiopulmonary bypass and conventional coronary artery bypass grafting using cardiopulmonary bypass are different.

Methods and Results: We compared clinical parameters in patients who underwent off-pump (n=156) versus on-pump (n=194) redo coronary artery bypass grafting performed between January 1995 and December 2001 in our institute, to determine if off-pump surgery has improved the surgical outcome of redo coronary artery bypass grafting and emerged as an ideal technique. Patients who underwent on-pump redo surgery required more postoperative blood transfusion (86.53% on-pump v. 12.82% off-pump, p=0.001), prolonged ventilatory support (>24 hours) (16.49% on-pump v. 7.7% off-pump, p=0.021) and higher inotropic support (23.71% on-pump v. 10.89% off-pump, p=0.003). On-pump redo coronary artery bypass grafting was also associated with a prolonged stay in the intensive care unit (40±6.2 hours on-pump v. 20±4.1 hours off-pump, p=0.001) and longer hospital stay (9±4.2 days on-pump v. 5±3.4 days off-pump, p=0.001). In-hospital mortality was higher in on-pump patients than in off-pump ones (7.7% v. 3.2%); however, this was not statistically significant (p=0.114).

Conclusions: Off-pump redo coronary artery bypass grafting is a safe method of myocardial revascularization with lower operative morbidity and mortality, less requirement of blood products and early hospital discharge, compared with conventional on-pump redo coronary artery bypass grafting. (Indian Heart J 2002; 54: 159–163)

Key Words: Coronary artery bypass grafting, Coronary artery disease, Reoperation
underwent redo OPCAB (Group A) while 194 patients underwent redo conventional on-pump CABG (conventional coronary artery bypass surgery [CCAB]; Group B). Group A consisted of 141 male and 15 female patients (mean age 60.18±6.11 years). Group B consisted of 175 male and 19 female patients (mean age 59.32±6.14 years) (p=0.193). Mean left ventricular ejection fraction was 42%±6.8% in group A and 43%±6.6% in group B (p=0.165). Fifty-seven patients in group A and 86 patients in group B had unstable angina for which emergency redo CABG was done (p=0.172); 70 patients (44.9%) had prior myocardial infarction (MI) and 11 patients (7.05%) were in congestive heart failure in group A. In group B, 96 patients (49.5%) had previous MI while 9 patients (4.6%) had congestive heart failure at the time of surgery (p=0.452 and p=0.463, respectively). Twenty-five patients (16.02%) in group A and 41 patients (21.1%) in group B had critical left main coronary artery disease but were stable at the time of induction (p=0.282). Patient-related data including risk factors are summarized in Table 1. All preoperative parameters in groups A and B were comparable.

**Technique:** All the surgeries were performed by senior surgeons having adequate experience and expertise in all techniques of redo surgery. Various approaches were used for redo CABG in both the groups. In group A, the routine mid-sternotomy approach was used in 112 patients, 37 patients underwent left anterior mini-thoracotomy, 6 patients left posterolateral thoracotomy and the combined approach was used in 1 patient. All 194 patients in group B underwent redo CABG via a mid-sternotomy approach. All patients were monitored hemodynamically with radial arterial, central venous and pulmonary arterial catheters, as well as by transesophageal echocardiography.

One hundred and ninety-four patients (group B) underwent redo CCAB. Median sternotomy was carefully performed with an oscillating saw. After dissecting the heart away from the sternum, the aorta and right atrium were exposed, starting at the diaphragmatic surface of the heart to enable early cannulation in case of any cardiac decompensation. Native graft manipulation was strictly avoided. Both antegrade and, wherever possible, retrograde hypothermic blood cardioplegia was given. Moderate systemic hypothermia was used during CPB.

All proximal anastomoses were done on cross-clamp with retrograde reperfusion of warm blood. One hundred and twelve patients underwent redo OPCAB via the mid-sternotomy approach. Sternal entry and adhesiolysis were similar to those for redo CCAB. Systemic heparinization with 2 mg/kg body weight of heparin was done in all off-pump cases. In patients who required a graft to the left anterior descending artery (LAD) alone, the left internal mammary artery (LIMA), if not used during the primary surgery, was grafted by the minimally invasive direct coronary bypass (MIDCAB) technique via an incision in the fourth or fifth intercostal space. The techniques for these approaches have been described in detail earlier.4–6 In 3 patients the LAD was not graftable, hence the LIMA was used to bypass the intermedius branch via a median sternotomy on beating heart. In another patient, the LIMA was grafted on beating heart on a previously exposed, starting at the diaphragmatic surface of the heart to enable early cannulation in case of any cardiac decompensation. Native graft manipulation was strictly avoided. Both antegrade and, wherever possible, retrograde hypothermic blood cardioplegia was given. Moderate systemic hypothermia was used during CPB.

Four patients in group A with blocked reversed SVGs to the circumflex territory underwent hybrid percutaneous transluminal coronary angioplasty (PTCA) to the obtuse marginal (OM) branches 5 days after redo CABG. Systemic heparinization with 2 mg/kg body weight of heparin was done in all off-pump cases. In patients who required a graft to the left anterior descending artery (LAD) alone, the left internal mammary artery (LIMA), if not used during the primary surgery, was grafted by the minimally invasive direct coronary bypass (MIDCAB) technique via an incision in the fourth or fifth intercostal space. The techniques for these approaches have been described in detail earlier.4–6 In 3 patients the LAD was not graftable, hence the LIMA was used to bypass the intermedius branch via a median sternotomy on beating heart. In another patient, the LIMA was grafted on beating heart on a previously placed saphenous vein graft (SVG) to an LAD that was blocked proximally but patent distally; the distal LAD was small and intramyocardial.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group A OPCAB (n=156)</th>
<th>Group B CCAB (n=194)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male/female</td>
<td>141/15 (90.4)</td>
<td>175/19 (90.2)</td>
</tr>
<tr>
<td>Mean age (years)</td>
<td>60.18±6.11</td>
<td>59.32±6.14</td>
</tr>
<tr>
<td>Unstable angina</td>
<td>57 (36.53)</td>
<td>86 (44.32)</td>
</tr>
<tr>
<td>CHF</td>
<td>11 (7.05)</td>
<td>9 (4.6)</td>
</tr>
<tr>
<td>PVD</td>
<td>9 (5.76)</td>
<td>6 (3.09)</td>
</tr>
<tr>
<td>Aortic atheroma</td>
<td>13 (8.33)</td>
<td>14 (7.21)</td>
</tr>
<tr>
<td>SVD</td>
<td>2 (1.3)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>DVD</td>
<td>26 (16.7)</td>
<td>33 (17.0)</td>
</tr>
<tr>
<td>TVD</td>
<td>128 (82.05)</td>
<td>161 (83.0)</td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
<td>42±6.8</td>
<td>43±6.6</td>
</tr>
<tr>
<td>Emergency CABG</td>
<td>57 (36.53)</td>
<td>86 (44.32)</td>
</tr>
<tr>
<td>IABP</td>
<td>12 (7.71)</td>
<td>17 (8.8)</td>
</tr>
<tr>
<td>Previous myocardial infarction</td>
<td>70 (44.9)</td>
<td>96 (49.5)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>50 (32.0)</td>
<td>61 (31.4)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>78 (50)</td>
<td>104 (53.60)</td>
</tr>
<tr>
<td>History of CVA</td>
<td>5 (3.2)</td>
<td>4 (2.06)</td>
</tr>
<tr>
<td>Left main disease</td>
<td>25 (16.02)</td>
<td>41 (21.1%)</td>
</tr>
</tbody>
</table>

Values in parentheses are percentages.

CHF: congestive heart failure; PVD: peripheral vascular disease; SVD: single-vessel disease; DVD: double-vessel disease; TVD: triple-vessel disease; CABG: coronary artery bypass grafting; IABP: intra-aortic balloon pump; CVA: cerebrovascular accident; OPCAB: off-pump coronary artery bypass surgery; CCAB: conventional coronary artery bypass surgery
We reviewed intraoperative LIMA graft patency by Doppler flow measurement in all patients who underwent the MIDCAB procedure. Postoperative course in the intensive care unit and during hospital stay was compared in both groups.

### Table 2. Conduits and number of grafts used in redo CABG

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group A (n=156)</th>
<th>Group B (n=194)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average no. of grafts/patient</td>
<td>1.67±0.76</td>
<td>2.50±0.66</td>
</tr>
<tr>
<td>LIMA</td>
<td>124 (79.48)</td>
<td>147 (75.8)</td>
</tr>
<tr>
<td>RA</td>
<td>113 (72.43)</td>
<td>139 (71.64)</td>
</tr>
<tr>
<td>RSVG</td>
<td>137 (87.82)</td>
<td>173 (89.17)</td>
</tr>
<tr>
<td>RGEA</td>
<td>2 (1.3)</td>
<td>1 (0.5)</td>
</tr>
<tr>
<td>TMLR</td>
<td>4 (2.6)</td>
<td>-</td>
</tr>
<tr>
<td>Hybrid PTCA</td>
<td>4 (2.6)</td>
<td>-</td>
</tr>
<tr>
<td>CABG × 1 graft</td>
<td>86 (55.1)</td>
<td>16 (8.2)</td>
</tr>
<tr>
<td>CABG × 2 grafts</td>
<td>40 (25.6)</td>
<td>74 (38.14)</td>
</tr>
<tr>
<td>CABG × 3 grafts</td>
<td>26 (16.67)</td>
<td>95 (49.0)</td>
</tr>
<tr>
<td>CABG × 4 grafts</td>
<td>4 (2.6)</td>
<td>9 (4.6)</td>
</tr>
</tbody>
</table>

Values in parentheses are percentages

Types and number of grafts in each group:
- LIMA: left internal mammary artery
- RA: radial artery
- RSVG: reverse saphenous vein graft
- RGEA: right gastroepiploic artery
- TMLR: transmyocardial laser revascularization
- PTCA: percutaneous transluminal coronary angioplasty
- CABG: coronary artery bypass grafting

### Statistical analysis

Data are reported as mean ± standard deviation. The Chi-square or Fisher exact tests were used to compare categorical variables. Unpaired Student’s t test was used for continuous variables between the groups. A p value of <0.05 was accepted as significant. Variables that were not normally distributed were compared using the Mann–Whitney test.

### Results

Over the years, we noted an increase in the number of redo patients operated off-pump (Table 3). There were 5 hospital deaths (3.2%) in group A and 15 deaths (7.7%) in group B (p=0.114). Three patients in group A died after the MIDCAB procedure. They were in congestive heart failure and were put on an intra-aortic balloon pump (IABP) preoperatively. Of these, 1 patient underwent surgery after failed PTCA to a diseased LAD–vein graft. Two patients had acute MI with post-MI angina; they were put on IABP and taken up for surgery. Both these patients had low cardiac output and intractable ventricular arrhythmias postoperatively and died on the first and second postoperative day, respectively.

Of the 15 hospital deaths in group B, 8 patients were taken up for emergency redo CABG due to unstable angina refractory to medical management. All of them had a low ejection fraction (EF 35%–45%) and were on IABP at the time of induction. Postoperatively, they all had intractable ventricular arrhythmias with severe ventricular dysfunction. Three patients with an EF <35% and high pulmonary artery (PA) pressures could not be weaned away from CPB. Four patients with preoperative ventricular dysfunction had persistent postoperative low cardiac output requiring high inotropic support. They were on IABP support and could not be weaned away from the ventilator. They died within a week of redo CABG due to low cardiac output and multi-organ failure. Conversion of technique from OPCAB to CCAB was done in 7 patients. The reason in all these cases was dense pericardial adhesions with patent LIMA to LAD grafts for which it was decided to continue adequate lateral wall adhesiolysis for grafting the ramus intermedius (2 patients) and OMs (3 patients) on CPB. In 2 patients with an EF of 30%–35%, conversion from OPCAB to CCAB was done due to unstable hemodynamics while proceeding with right coronary artery anastomosis. Ventricular tachyarrhythmias were observed in 14 patients while doing distal anastomosis in the off-pump group. These were managed successfully with a bolus of intravenous lignocaine.

As shown in Table 1, there were 57 (36.53%) emergency redo CABGs in group A vs. 86 (44.32%) in group B (p=0.172). These were the patients who developed unstable angina refractory to medical management. Twelve patients (7.71%) in group A and 17 patients (8.8%) in group B required preoperative IABP support (p=0.868). In 3 patients in group A and 2 patients in group B, IABP was inserted immediately after anesthetic induction, for high PA pressure and low EF (EF ≤30%). The postoperative characteristics of the patients are summarized in Table 4. Seven patients (4.48%) from group A and 14 patients (7.21%) from group B had perioperative MI based on raised
Inferior walls and tolerated the procedure well.

Coronary angiography was done on the fifth
Doppler revealed adequate diastolic flow, this being a
adhesions from the previous operation. In all our patients
manipulation of patent grafts and mobilization of
hemodynamic instability while grafting the RCA.
Surgery; CCAB: conventional redo coronary artery bypass surgery; OPCAB: off-pump redo coronary artery bypass surgery

Table 4. Postoperative characteristics

<table>
<thead>
<tr>
<th></th>
<th>Group A</th>
<th>Group B</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OPCAB</td>
<td>CCAB</td>
<td></td>
</tr>
<tr>
<td>Mortality</td>
<td>5 (3.2)</td>
<td>15 (7.7)</td>
<td>0.114 (ns)</td>
</tr>
<tr>
<td>Ventricular arrhythmia</td>
<td>4</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>Severe LV dysfunction</td>
<td>1</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>+ multishystem organ failure</td>
<td>Corebrovascular accident</td>
<td>0</td>
<td>2 (1.3)</td>
</tr>
<tr>
<td>Perioperative MI</td>
<td>7 (4.8)</td>
<td>14 (7.21)</td>
<td>0.399 (ns)</td>
</tr>
<tr>
<td>Reoperation for bleeding</td>
<td>3 (1.9)</td>
<td>7 (3.60)</td>
<td>0.522 (ns)</td>
</tr>
<tr>
<td>Patient requiring Tx</td>
<td>20 (12.82)</td>
<td>168 (86.59)</td>
<td>0.001</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>5 (3.20)</td>
<td>14 (7.21)</td>
<td>0.159 (ns)</td>
</tr>
<tr>
<td>Prolonged ventilator (&gt;24 hours)</td>
<td>12 (7.7)</td>
<td>32 (16.49)</td>
<td>0.021</td>
</tr>
<tr>
<td>Postop inotropic support</td>
<td>17 (10.89)</td>
<td>46 (23.71)</td>
<td>0.003</td>
</tr>
<tr>
<td>ICU stay (hours)</td>
<td>20±4.1</td>
<td>40±6.2</td>
<td>0.001</td>
</tr>
<tr>
<td>Hospital stay (days)</td>
<td>5±3.4</td>
<td>9±4.2</td>
<td>0.001</td>
</tr>
</tbody>
</table>

All variables are expressed as numbers and percentages. Values in parentheses are
LV: left ventricular; MI: myocardial infarction; Tx: transfusion; ICU: intensive care unit; ns: not statistically significant; OPCAB: off-pump redo coronary artery bypass surgery; CCAB: conventional redo coronary artery bypass surgery

of our study (Table 4). Off-pump redo CABG aims at providing a safe surgical technique, depending on the need of an individual patient so as to reduce the high mortality and morbidity associated with all redo CABGs.7–9

Even in the presence of improved perfusion techniques, the potential hemodynamic and cerebral hazards of CPB remain, more so in cases of redo CABG where one expects prolonged pump time.10,11 In this study, we found that OPCAB had lower rates of morbidity and mortality as compared to CCAB. Although the mortality rates are not statistically significant, low mortality in the large number of patients who underwent redo CABG is encouraging. Specifically, off-pump redo CABG was associated with less need for intraoperative and postoperative blood transfusion, as also documented by others.10,12,13

 Patients undergoing on-pump redo CABG had an almost 3-fold increased incidence of prolonged ventilatory support and a significant increase in postoperative inotropic support. There is a higher incidence of atrial fibrillation in CCAB patients,10,12,14,15 as seen in our study as well. This can be attributed to systemic hypothermia, atrial manipulation and greater surgical trauma as compared to off-pump cases.

Increased cardiac trauma and myocardial injury as seen with raised troponin-T and CPK levels can be associated with a defective adaptive response of the heart muscle to this surgical stress and prolonged aortic cross-clamping.16,17 Reports of reduced cytokinase response and myocardial injury have also been noted with off-pump redo CABG.18

Off-pump redo CABG has significantly shortened hospital stay, thus reducing hospital resources and health care costs. Studies have shown the use of CPB as an independent predictor of prolonged hospital stay.12,19,20

Coronary angiography was done on the fifth postoperative day in 25 patients in group A and 15 patients in group B. In all these cases, patency of the redo grafts was confirmed. Four of these patients from group A underwent a simultaneous hybrid PTCA with check angiography for occluded primary OM vein grafts. Four patients had MIDCAB and TM LR to the posterolateral and inferior walls and tolerated the procedure well.

Discussion

As the surgical trend is universally towards minimally invasive techniques, we too observed an increase in the number of off-pump redo CABG surgeries during the course
approach for selected patients. The mortality in our study is comparable with that reported in various other series.\textsuperscript{12,24,25}

In summary, the introduction of off-pump CABG in clinical practice extends the various benefits of coronary revascularization to a group of patients otherwise considered at high risk for redo surgery. Although the technical quality of anastomosis governing the early outcome of the procedure has been excellent, the feasibility and durability of this approach will be dictated by long-term patency data. With the advent of more sophisticated but simplified myocardial stabilizers and with increasing surgical expertise, the proportion of patients undergoing off-pump CABG with its favorable results is likely to increase further, thus determining the ultimate outcome of redo CABG surgery.

Acknowledgment

We thank Mr Vinod Thapliyal for secretarial assistance.

References

Graded Balloon Atrial Septostomy in Severe Pulmonary Hypertension

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Background: The prognosis of patients with severe primary pulmonary hypertension is poor. The role of balloon atrial septostomy as a palliative procedure in these patients is not well defined. We retrospectively analyzed our data regarding the safety, clinical outcome and survival benefit of graded balloon atrial septostomy in patients with severe pulmonary hypertension.

Methods and Results: Eleven patients (7 males), aged 6 to 30 years (mean age 16.2 ± 8.9 years), with severe pulmonary artery hypertension (mean pulmonary artery pressure of 76 ± 16.9 mmHg) and refractory congestive heart failure and/or recurrent syncope underwent balloon atrial septostomy. Graded balloon dilatation under echocardiographic guidance and arterial oxygen saturation monitoring was done in all the patients. Procedure-related mortality was 18.2%. Significant acute hemodynamic improvement was seen in the survivors (pre-balloon atrial septostomy cardiac index 1.88 ± 0.48 L/min/m²; post-balloon atrial septostomy cardiac index 2.18 ± 0.37 L/min/m², p < 0.009). Patients were followed up for a mean period of 20.3 months after the procedure (range: 3 months–5 years). There was functional improvement and increased exercise tolerance in all the patients for a mean follow-up period of 14.6 months (NYHA functional class 3.62 ± 0.69 to 2 ± 0.50). The estimated probability of survival in this cohort at 1 year was only 48%; but 7 of 8 patients (87%) who survived the procedure were alive at 1 year.

Conclusion: We conclude that balloon atrial septostomy improves clinical status, hemodynamic variables and possibly also improves survival in selected patients with severe pulmonary artery hypertension. It remains a definite palliative option for refractory primary pulmonary hypertension. However, the procedure-related risks are high in very sick patients and, therefore, balloon atrial septostomy may be advocated early in the course of the disease. (Indian Heart J 2002; 54: 164–169)

Key Words: Balloon dilatation, Atrial septostomy, Primary pulmonary hypertension

Primary pulmonary hypertension (PPH) is characterized by progressive elevation of pulmonary artery pressure (PAP), which eventually leads to right ventricular failure and death. The prognosis of PPH remains poor and patients with severe right heart failure generally survive less than 6 months.1,2 In spite of vasodilator therapy, long-term infusion of prostacyclin and lung transplantation, the treatment of PPH remains a serious challenge. Vasodilator therapy is effective in only 25%–30% of the patients and the benefits of prostacyclin infusion and lung transplantation are limited by nonavailability, clinical difficulties and the costs involved.3–5

Patients with Eisenmenger’s syndrome have a better prognosis than patients with pulmonary hypertension without a cardiac shunt.6,7 Similarly, patients with PPH and a right-to-left shunt through an interatrial communication have a better survival than those without it.6,9 An interatrial communication may preserve systemic output and thereby improve symptoms and survival. This suggests that creating an interatrial communication in patients with severe pulmonary arterial hypertension (PAH) may be beneficial. Based on these considerations, a palliative blade-balloon atrial septostomy was first performed by Rich et al.10 in 1983. Subsequently, a few series of patients treated by balloon atrial septostomy (BAS) have been described.11–17 However, the reported data are not large and results are not uniform. Clinical experience with this modality of treatment is evolving. Accordingly, we retrospectively analyzed our data regarding the safety, clinical outcome and survival benefit of graded BAS in patients with severe PAH.
Methods

Patient population: Between May 1995 and October 2001, we performed BAS in 11 patients with severe PAH (7 males and 4 females; mean age 16.2±8.9 years; age range 6–30 years). Their clinical characteristics are shown in Table 1. All except one patient were in congestive heart failure (CHF) and 7 of them were in NYHA functional class IV. Three patients had recurrent syncope. The duration of symptoms ranged from 6 to 24 months prior to the septostomy. Seven patients had severe PPH and the remaining 4 had severe PAH following surgical repair of atrial or ventricular septal defect earlier in childhood. Two of the 11 patients were admitted to the intensive care unit for refractory CHF and were receiving inotropic support prior to septostomy. All the patients were on diuretics and digoxin. Only 5 patients tolerated vasodilator therapy. Three patients were receiving oral anticoagulants that were stopped prior to the procedure. Bleeding and coagulation parameters were checked in all the patients.

Baseline hemodynamics: Baseline hemodynamic data are shown in Table 2. All the patients had severe pulmonary hypertension with a mean PAP of 76±17 mmHg and mean right atrial pressure (RAP) of 19±5.8 mmHg. Baseline hemodynamic data suggest that the patients were very sick with a high total pulmonary resistance index (TPRI) of 43±16 (Wood units/m²) and low cardiac index (CI) of 1.88±0.48 L/min/m². The procedure was performed because of the presence of severe pulmonary hypertension with right ventricular (RV) dysfunction and CHF, or for recurrent syncope unresponsive to medical therapy.

All the patients underwent routine clinical evaluation including a complete history, physical examination, laboratory evaluation and noninvasive studies with electrocardiogram (ECG), chest X-ray and two-dimensional echocardiograms. Table 1 provides follow-up status and comments on patients. Additional comments are provided in the text.
echocardiography. Balloon atrial septostomy was done by the standard procedure. Briefly, right heart catheterization was performed and pulmonary artery angiogram was done in two views to mark the silhouette of the left atrium (LA) using nonionic contrast. Arterial pressure was monitored. A pigtail catheter lodged in the aortic sinus was helpful in localizing the site of puncture. Under fluoroscopic and echocardiographic guidance, the atrial septum was traversed with a Brockenbrough needle, which was then used to advance a Mullin’s sheath into the LA. Balloon atrial septostomy was performed using a valvuloplasty balloon (Smash, Mansfield or Tyshak) and serial dilatations were performed with balloon diameter ranging from 4 to 15 mm. Hemodynamic parameters and oxygen saturation were monitored throughout the procedure. Cardiac output was determined according to the Fick’s principle using assumed oxygen consumption. The final size of the defect was considered adequate if either the atrial septal defect (ASD) measured 5 mm on echocardiogram or the systemic arterial saturation was less than 80%. All the patients were monitored in the intensive care unit for 24 hours.

All the survivors were followed up clinically and noninvasively with chest X-ray, ECG and transthoracic echocardiography at regular intervals.

Statistical analysis: Comparisons between baseline and post-procedural data were made using the Wilcoxon signed rank test for paired data. Significance was defined as a two-tailed p value <0.05.

Table 2: Hemodynamic data

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Pre-balloon atrial septostomy</th>
<th>Post-balloon atrial septostomy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>mRAP (mmHg)</td>
<td>mRAP (mmHg)</td>
</tr>
<tr>
<td>1</td>
<td>22</td>
<td>63</td>
</tr>
<tr>
<td>2</td>
<td>15</td>
<td>103</td>
</tr>
<tr>
<td>3</td>
<td>26</td>
<td>86</td>
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<td>4</td>
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<td>105</td>
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<tr>
<td>5</td>
<td>6</td>
<td>61</td>
</tr>
<tr>
<td>6</td>
<td>22</td>
<td>50</td>
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<tr>
<td>7</td>
<td>18</td>
<td>70</td>
</tr>
<tr>
<td>8</td>
<td>16</td>
<td>80</td>
</tr>
<tr>
<td>9</td>
<td>26</td>
<td>80</td>
</tr>
<tr>
<td>10</td>
<td>15</td>
<td>70</td>
</tr>
<tr>
<td>11</td>
<td>20</td>
<td>70</td>
</tr>
</tbody>
</table>

Mean: 19 | 76 | 10 | 95 | 93 | 1.88 | 43 |
SD: 5.8 | 17 | 2.9 | 8.3 | 4.8 | 0.48 | 16 |

mRAP: mean right atrial pressure; mRAP: mean pulmonary artery pressure; mLAP: mean left atrial pressure; mSAP: mean systemic arterial pressure; SaO₂: systemic oxygen saturation; CI: cardiac index; TPRI: total pulmonary vascular resistance index; SD: standard deviation

*Procedural mortality

Results

Mortality: Two patients died within 24 hours of the procedure (patient no. 4 and 7). Patient no. 4 had a mean PAP of 105 mmHg with TPRI of 75 Wood units/m² and RAP of 22 mmHg. She had cardiac tamponade and could not be resuscitated. Patient no. 7 had a mean PAP of 70 mmHg with TPRI of 26 Wood units/m². He underwent successful septostomy but had ST segment elevation in the inferior leads after the procedure and died within 4 hours of the procedure, probably because of coronary embolism.

One more patient (patient no. 2) died 3 days after the procedure after a bout of severe hemoptysis. He had a mean PAP of 103 mmHg and TPRI of 57 Wood units/m².

Acute hemodynamic improvement: The remaining 8 patients had significant hemodynamic improvement after the procedure (Table 2). Cardiac output increased significantly after the procedure (1.88 ± 0.48 to 2.18 ± 0.37 L/min/m², p < 0.009). The mean arterial saturation decreased significantly after the procedure (93 ± 4.8% to 82 ± 6.6%, p < 0.009). The mean RAP (19 ± 5.8 to 16 ± 6.5 mmHg, p < 0.01), and mean PAP (76 ± 17 to 70 ± 14 mmHg, p < 0.02) also reduced after BAS.

Follow-up results: Follow-up results are shown in Table 1. Patients were followed up for a mean period of 20.3 months after the procedure (range 3 months–5 years). There was functional improvement and increased exercise tolerance in all the patients after a mean follow-up period of 14.6
months (NYHA functional class 3.62±0.69 to 2±0.50). None of the patients had syncope during this period. Two patients subsequently deteriorated and one died after 5 years of follow-up (patient no. 1). The other patient (patient no. 10) also improved for 1 year but deteriorated afterwards, and his ASD sealed off. Tricuspid regurgitation was reduced by one grade in five patients during follow-up. All the patients continued to have clinical and echocardiographic evidence of severe PAH.

The septostomy was sealed off in three patients at 3 months, 1 year and 2 years of follow-up, respectively. One patient deteriorated markedly (patient no. 10 referred to above). The subsequent follow-up data in the other two patients are limited.

Survival: We calculated the probability of survival of the eight remaining patients at 1 and 2 years using the equation developed from the National Institute of Health Primary Pulmonary Hypertension Registry data.²

$$P(t) = H(t)^{a+b+c}$$

where $$P(t)$$ indicates the patient's chance of survival, “x” is mean PAP, “y” is mean RAP, “z” is CI, (t) = 1, 2 or 3 years after the diagnosis and $$H(t) = [0.88 - 0.14t + 0.01t^2]$$. Using this formula, the predicted probability of survival for the patients at 1 year and 2 years was 0.48 and 0.32, respectively. In this study, the survival rate was 100% at 1-year follow-up but more than 1-year follow-up data were available for only 3 of 8 patients.

### Table 3. Balloon atrial septostomy: Published data

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of pts</th>
<th>Age range (years)</th>
<th>NYHA Class/pts</th>
<th>mRAP (mmHg)</th>
<th>mRAP (mmHg)</th>
<th>PVRI (Wood units/m²)</th>
<th>CI (L/min/m²)</th>
<th>CI (L/min/m²)</th>
<th>SaO₂ %</th>
<th>Procedural mortality</th>
<th>Follow-up duration (months)</th>
<th>Survived (no. of pts)</th>
<th>Patients improved (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nihill et al.¹¹</td>
<td>14</td>
<td>0.4–50</td>
<td>NA</td>
<td>11.8</td>
<td>68.4</td>
<td>NA</td>
<td>2.04</td>
<td>2.78</td>
<td>79</td>
<td>2</td>
<td>11–96</td>
<td>9</td>
<td>64 (90)</td>
</tr>
<tr>
<td>Kerstein et al.¹²</td>
<td>15</td>
<td>7–39</td>
<td>III/7 IV/28</td>
<td>11.2</td>
<td>69.6</td>
<td>NA</td>
<td>2.2</td>
<td>2.6</td>
<td>89</td>
<td>2</td>
<td>2–45</td>
<td>13</td>
<td>73 (57)</td>
</tr>
<tr>
<td>Rich et al.¹³</td>
<td>6</td>
<td>22–55</td>
<td>III/2 IV/4</td>
<td>17</td>
<td>67</td>
<td>NA</td>
<td>1.7</td>
<td>2.69</td>
<td>78</td>
<td>2</td>
<td>40</td>
<td>3</td>
<td>50 (75)</td>
</tr>
<tr>
<td>Sandoval et al.¹⁴¹⁵</td>
<td>22–51</td>
<td>III/4 IV/10</td>
<td>10.5</td>
<td>66</td>
<td>33</td>
<td>2.2</td>
<td>3</td>
<td>83</td>
<td>1</td>
<td>2–36</td>
<td>13</td>
<td>13 (86)</td>
<td></td>
</tr>
<tr>
<td>Rothman et al.¹³</td>
<td>12</td>
<td>13–56</td>
<td>III and IV/12</td>
<td>23</td>
<td>NA</td>
<td>46</td>
<td>1.7</td>
<td>2.1</td>
<td>85</td>
<td>2</td>
<td>2–14</td>
<td>6</td>
<td>50 (75)</td>
</tr>
<tr>
<td>Present study</td>
<td>11</td>
<td>6–30</td>
<td>III/3 IV/7 II/1</td>
<td>19</td>
<td>76</td>
<td>43¹</td>
<td>1.8</td>
<td>2.1</td>
<td>82</td>
<td>2</td>
<td>3–60</td>
<td>7</td>
<td>8 (72)</td>
</tr>
</tbody>
</table>

NYHA: New York Heart Association; m RAP: mean right atrial pressure; m PAP: mean pulmonary artery pressure; PVRI: pulmonary vascular resistance index; SaO₂: systemic oxygen saturation; pts: patients; NA: data not available; mon: months; CI: Cardiac index, tTPRI: total pulmonary vascular resistance

*One patient died after 5 years

**Discussion**

Prognosis of patients with severe PAH is poor. A relatively better survival has been described in patients with PPH who have an interatrial communication.⁶ An interatrial communication in patients with severe PAH causes systemic arterial desaturation but improves oxygen transport. The signs and symptoms of right heart failure may improve as the RA is able to decompress, and syncope can be averted as the cardiac output may be better preserved during exertion.

Studies have reported that BAS results in significant clinical and hemodynamic improvement and shows a trend towards improved survival in selected patients with severe PPH who had recurrent syncope and/or right heart failure (Table 3).¹¹-¹⁵ Our study showed that BAS resulted in significant clinical and hemodynamic improvement in patients with severe PAH. Three patients who had recurrent syncope did not have further syncopal episodes after BAS, and 6 of the 7 patients who were in CHF improved clinically (Table 1). Functional improvement continued during a mean follow-up of 14.6 months. Whether BAS can improve survival is not very clear. It appears from our experience that BAS probably alters the natural course of the disease favorably. The predicted probability of survival in the study group at 1 year was only 48%, whereas 7 of the 8 patients followed up for 1 year were alive.
The procedural mortality of BAS in these patients has been high. Rich et al. reported 50% mortality associated with BAS in very sick patients (mean RAP 17 mmHg, CI 1.7 L/min/m²). Mortality has also been reported in relatively stable patients (Table 3).11,12,14 Our patients were sicker (mean RAP of 19±5.8 mmHg, CI 1.88±0.47 L/min/m²) compared to previously reported studies. All three deaths were during the initial study period, probably due to the learning curve. Based on the collective experience in the literature, the 1998 World Symposium on Primary Pulmonary Hypertension published guidelines for performing BAS. According to these guidelines, BAS should not be performed in patients with impending death and severe right ventricular failure.18 Predictors of procedure-related death include a mean RAP of more than 20 mmHg, a PVRI of 55 Wood units/m², and a predicted 1-year survival of less than 40%.

Some technical considerations are important. The anatomy of the interatrial septum may be altered due to a grossly enlarged RA and a very small LA. Thus, selecting an appropriate puncture site is important. A pulmonary angiogram (done with a nonionic contrast medium) is useful in selecting the puncture site. Graded balloon dilatation and monitoring of arterial saturation after each dilatation is important to avoid a precipitous fall in saturation with a large right-to-left shunt. Blood transfusion before the BAS should be considered to provide an optimal hemoglobin level matching the saturation levels after the procedure. Transthoracic echocardiographic monitoring during the procedure also helps in sizing the defect.

Three of our patients had a sealed septostomy during follow-up. In the series by Sandoval et al. 4 of the 15 patients had spontaneous closure of an ASD on follow-up of 2–36 months. In other studies, spontaneous closure has not been reported. It appears that blade-balloon atrial septostomy may be associated with less spontaneous closure of an ASD compared to BAS alone. However, graded balloon dilatation can be better controlled and may be safer. The balloons are widely available and the procedure is easy to repeat if the ASD becomes smaller.

Significant advances have been made in the management of patients with severe PAH. Prostaglandin inhalers, oral prostaglandins and endothelin antagonists like bosentan and darusentan have shown clinical benefit in PPH. However, they are still in the evolving stage and not easily available. Thus BAS may be an important palliative measure for these patients. Perhaps it should be done earlier in the course of the disease. Recent advances like intracardiac echocardiography and the use of a radiofrequency ablation catheter to create an ASD would further reduce the risk of the procedure.

Conclusions: The result of this uncontrolled retrospective study suggests that BAS improves the clinical status, hemodynamic variables and possibly also improves survival in selected patients with severe PAH. It remains a definite palliative option for refractory PPH. However, the procedure-related risks are high in very sick patients and therefore BAS may be advocated early in the course of the disease.

References
15. Rothman A, Beltran D, Kriett JM, Smith C, Wolf P, Jamieson SW. Graded balloon dilatation atrial septostomy as a bridge to
transplantation in primary pulmonary hypertension. Am Heart J 1993; 125:1763-1766
Efficacy of Terminalia arjuna in Chronic Stable Angina: A Double-Blind, Placebo-Controlled, Crossover Study Comparing Terminalia arjuna with Isosorbide Mononitrate

Anil Bharani, Arunangshu Ganguli, LK Mathur, Yogendra Jamra, PG Raman
Departments of Medicine, Cardiology and Biostatistics, MGM Medical College and MY Hospital, Indore

Background: Terminalia arjuna, an Indian medicinal plant, has been reported to have beneficial effects in patients with ischemic heart disease in a number of small, open studies. The need for a double-blind, randomized, placebo-controlled study with adequate sample size has long been felt. The bark extract (IPC-53) contains acids (arjunic acid, terminic acid), glycosides (arjunetin arjunosides I-IV), strong antioxidants (flavones, tannins, oligomeric proanthocyanidins), minerals, etc. and exhibits antifailure and anti-ischemic properties.

Methods and Results: Fifty-eight males with chronic stable angina (NYHA class II-III) with evidence of provable ischemia on treadmill exercise test received Terminalia arjuna (500 mg 8 hourly), isosorbide mononitrate (40 mg/daily) or a matching placebo for one week each, separated by a wash-out period of at least three days in a randomized, double-blind, crossover design. They underwent clinical, biochemical and treadmill exercise evaluation at the end of each therapy which were compared during the three therapy periods. Terminalia arjuna therapy was associated with significant decrease in the frequency of angina and need for isosorbide dinitrate (5.69±6.91 mg/week v. 18.22±9.29 mg/week during placebo therapy, p<0.005). The treadmill exercise test parameters improved significantly during therapy with Terminalia arjuna compared to those with placebo. The total duration of exercise increased (6.14±2.51 min v. 4.76±2.38 min, p<0.005), maximal ST depression during the longest equivalent stages of submaximal exercise decreased (1.41±0.55 mm v. 2.21±0.56 mm, p<0.005), time to recovery decreased (6.49±2.37 min v. 9.27±3.39 min, p<0.005) and higher double products were achieved (25.75±4.81×10^3 v. 23.11±4.83×10^3, p<0.005) during Terminalia arjuna therapy. Similar improvements in clinical and treadmill exercise test parameters were observed with isosorbide mononitrate compared to placebo therapy. No significant differences were observed in clinical or treadmill exercise test parameters when Terminalia arjuna and isosorbide mononitrate therapies were compared. No significant untoward effects were reported during Terminalia arjuna therapy.

Conclusions: Terminalia arjuna bark extract, 500 mg 8 hourly, given to patients with stable angina with provable ischemia on treadmill exercise, led to improvement in clinical and treadmill exercise parameters as compared to placebo therapy. These benefits were similar to those observed with isosorbide mononitrate (40 mg/day) therapy and the extract was well tolerated. Limitations of this study include applicability of the results to only men with chronic stable angina but not necessarily to women, as they were not studied. (Indian Heart J 2002; 54: 170-175)

Key Words: Coronary artery disease, Stable angina pectoris, Terminalia arjuna

Terminalia arjuna, an Indian medicinal plant, is known to be beneficial for the treatment of heart ailments since 500 BC.1,2 Used as a bark extract, Terminalia arjuna has been known to produce significant improvement in patients with chronic refractory heart failure.3 Recently, its antianginal properties have received renewed attention.4,5

The phytochemistry of Terminalia arjuna was extensively worked up and recently reviewed.6 The various constituents of the dried bark extract (IPC-53) include acids such as arjunic acid, gallic acid, ellagic acid, arjunin and terminic

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acid, glycosides such as arjunetin, arjunosides I–IV, the flavone arjunolone, tannins, oligomeric proanthocyanidins (OPCs), coloring matter, essential oils and minerals such as calcium, magnesium, zinc and copper.

The present study was undertaken to evaluate the anti-ischemic properties of Terminalia arjuna in patients with stable angina vis-à-vis the present gold standard of nitrate therapy7 using clinical and treadmill exercise test parameters.

Methods

Fifty-eight males aged 38–70 years (mean 51.68±9.12 years) with chronic stable angina (NYHA class II–III) and evidence of provokable myocardial ischemia on a treadmill exercise test were studied in a randomized, double-blind, placebo-controlled, crossover design. The protocol was approved by the institutional committee and all participants gave informed consent. During the trial period, patients continued prescribed drugs except beta-blockers and ISDN tablets consumed during the week were noted. They were provided with precounted tablets of isosorbide dinitrate (ISDN) for use during episodes of angina.

Exclusion criteria: Patients with acute myocardial infarction, unstable angina or severe effort angina (NYHA class IV), heart failure, chronic hepatic or renal diseases, neurological or orthopedic conditions posing difficulty in exercise performance, neuropsychiatric illness, malignancy and AIDS were excluded. Unconsenting patients, drug addicts and those with nitrate intolerance were also excluded. Females were not included in the study because of the high prevalence of false-positive results on treadmill exercise testing.

Patients underwent a thorough clinical evaluation and routine laboratory work-up; a 16-lead electrocardiogram (ECG), chest X-ray and echocardiography were performed to obtain baseline data. Special attention was given to the lifestyle and daily routine of the patients and clinical details of angina were noted, i.e. number and duration of episodes, extent of physical effort which precipitates angina and the number of ISDN tablets consumed weekly. Patients were encouraged to continue their normal lifestyle and immediately report any episode of prolonged or worsening angina to the investigators.

Patients were randomly provided one week’s medication in three bottles marked morning, afternoon and evening containing either Terminalia arjuna 500 mg, or matching placebo in all of them, or ISMN 20 mg in the morning and afternoon, and a placebo in the evening dose bottle. This ensured that they received either Terminalia arjuna 1500 mg/day, ISMN 40 mg/day in eccentric dosage or a matching placebo for one week, each separated by at least a 3-day wash-out period in a crossover design. At the end of each therapy period, a clinical, biochemical and treadmill exercise test evaluation was carried out for every patient. The number of episodes of angina and ISDN tablets consumed during the week were noted.

Treadmill exercise procedure: Treadmill exercise testing was done on a Marquette or Uni-inst treadmill system using the Bruce protocol. Caffeine and smoking were avoided on the day of exercise testing which was performed 2 hours after the morning dose of the study drug or placebo, but at the same time of the day. Patients were asked to exercise until they would normally stop to rest, until 2.5 mm ST segment depression was reached, or until the test was terminated at the discretion of the supervising physician.

The ST segment levels were measured 80 ms after the J point by the computer, which was manually rechecked. The measurements used to compare the two exercise tests were the total exercise time, ST depression during the longest equivalent stages of submaximal exercise, time to recovery and maximal double product (systolic blood pressure × heart rate) achieved. The ST depression during different tests was compared using the leads with the greatest amount of ST depression and not necessarily the matching leads. The ST segment depression at the longest equivalent submaximal exercise was defined as the longest submaximal time completed during different periods of therapy.

Possible untoward effects related to the administered drugs were noted after each period of therapy. The drug code was opened at the end of the study. The number of episodes of angina and ISDN consumed, treadmill exercise test parameters and possible side-effects of the drugs were compared during therapy with Terminalia arjuna and ISMN.

Statistical analysis: Statistical analysis was carried out using the Student’s paired t test for the differences observed in clinical and treadmill exercise parameters during various periods of therapy.

Preparation of the Terminalia arjuna extract: The bark was crushed to a coarse powder, 20–40 mesh size, and then repeatedly extracted with 90% v/v alcohol at boiling temperature till complete exhaustion. This was followed by extraction with water at 70°C for 2 hours. Both alcoholic and aqueous extracts were concentrated separately at 55–60°C and vacuum extracted to a syrup.
consistency. After uniform mixing, further drying was carried out at 60°C under vacuum conditions. The dried material was powdered to a mesh size of 80–100 and capsulated.

Results

Baseline clinical characteristics: Of the 61 patients enrolled with chronic stable angina, 58 completed the study. Three patients underwent a myocardial revascularization procedure before completion of the study protocol and hence were not included in the analysis. The age, class of angina, associated diseases and drug therapy that the patients received are shown in Table 1. They had normal left ventricular function (LVEF on echocardiography 58.66%±8.22%).

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>58, males</td>
</tr>
<tr>
<td>Age</td>
<td>38–70 years (mean 51.68±9.12 years)</td>
</tr>
<tr>
<td>Angina</td>
<td></td>
</tr>
<tr>
<td>NYHA class II</td>
<td>35</td>
</tr>
<tr>
<td>NYHA class III</td>
<td>23</td>
</tr>
<tr>
<td>Previous myocardial infarction*</td>
<td>18</td>
</tr>
<tr>
<td>Associated diseases</td>
<td></td>
</tr>
<tr>
<td>i Hypertension</td>
<td>12</td>
</tr>
<tr>
<td>ii Diabetes mellitus</td>
<td>3</td>
</tr>
<tr>
<td>iii Dyslipidemia</td>
<td>22</td>
</tr>
<tr>
<td>Drugs</td>
<td></td>
</tr>
<tr>
<td>Statins</td>
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<td>Amlodipine</td>
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<td>Ramipril</td>
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<td>Enalapril</td>
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<tr>
<td>Oral hypoglycemic agents</td>
<td>3</td>
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<tr>
<td>Aspirin</td>
<td>18</td>
</tr>
<tr>
<td>Beta-blockers **</td>
<td>58</td>
</tr>
<tr>
<td>Isosorbide mononitrate**</td>
<td>58</td>
</tr>
</tbody>
</table>

*Diagnosed with conventional clinical, electrocardiographic and echocardiographic criteria

**Discontinued during the study

Angina and nitrate use: Of the 58 patients, 35 were in NYHA functional class II and the remaining in class III at entry. This improved by at least one class in 27 and 31 patients during Terminalia arjuna and ISMN therapy respectively, but in none on placebo (Table 2). Fifty-six patients experienced improved effort tolerance with relief in angina and decreased need for ISDN while on Terminalia arjuna (5.69±6.91 mg/week) or ISMN (5.53±6.84 mg/week) as compared to placebo therapy (18.22±9.29 mg/week), which was statistically significant.

Effect on clinical and laboratory parameters: There were no appreciable differences regarding resting heart rate, systolic and diastolic blood pressure and findings on systemic examination during the three treatment periods compared to baseline values. Similarly, laboratory parameters such as blood sugar, creatinine, serum sodium, serum potassium and lipid profile did not show any significant differences during the various treatment periods. Patients with diabetes had no change in their glycemic control.

Treadmill exercise test parameters (Table 2)

Duration of exercise: There was a significant improvement in the duration of exercise in all except 2 patients during Terminalia arjuna (6.14±2.51 min) and ISMN (6.45±2.75 min) therapy as compared to placebo therapy (4.76±2.38 min).

Maximal ST depression: Maximal ST depression at the longest equivalent submaximal exercise showed a favorable change during Terminalia arjuna (1.41±0.55 mm) and ISMN (1.38±0.55 mm) therapy as compared to placebo (2.21±0.56 mm). The decrease in magnitude of ST segment depression with Terminalia arjuna therapy as compared to placebo was statistically highly significant. However, no significant difference was found when the magnitude of ST segment depression between Terminalia arjuna and ISMN therapy was compared.

Recovery time: There was early normalization of ST segment abnormalities induced by treadmill exercise during Terminalia arjuna (6.49±2.37 min) and ISMN (6.76±2.76 min) therapy compared to placebo (9.27±3.30 min), which was statistically significant. The differences in recovery time were not significant when Terminalia arjuna and ISMN therapy were compared.

Blood pressure × peak heart rate: Terminalia arjuna and ISMN therapy were associated with significantly higher double products achieved at peak exercise compared to placebo (25.75±4.81×10³ and 25.94±4.81×10³ during Terminalia arjuna and ISMN therapy, respectively, v. 23.11±4.83×10³ during placebo). Double products achieved during Terminalia arjuna and ISMN therapy were statistically not different.

Associated diseases and effect of therapy: The beneficial effects of Terminalia arjuna on clinical and treadmill test parameters among patients with diabetes, dyslipidemia, hypertension and previous myocardial infarction were similar to those seen in patients without
Untoward effects: The possible untoward symptoms reported by the patients during various therapy periods (Table 3) were mild and needed no specific treatment. There was no mortality or morbidity during the study period in our patient population.

Discussion

Terminalia arjuna has been reported to have beneficial effects in patients with ischemic heart disease. However, the available studies on Terminalia arjuna in ischemic heart disease have a number of limitations related to the sample size and evaluation methods. We felt the need for a critical evaluation of the anti-ischemic efficacy of this traditional remedy in a well-designed, scientific study which might open up new vistas for future research in this field.

We used the conventional clinical and treadmill exercise test parameters with certain modifications in a double-blind, placebo-controlled, crossover design to assess the effects of Terminalia arjuna in patients with stable angina and compared it with the gold standard nitrate therapy. The value of the treadmill exercise test for the objective measurement of treatment effects in patients with ischemic heart disease is limited by random error in the measurement of ST depression and may be biased by regression of the mean or by the decision of the physician to terminate the test. To overcome these difficulties and improve the sensitivity and specificity of the treadmill exercise test for assessment of treatment effect, it has been suggested that use be made of maximal ST depression at the longest equivalent submaximal exercise, maximal rate

Table 2. Clinical and treadmill exercise parameters

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Baseline</th>
<th>Placebo</th>
<th>T. arjuna</th>
<th>ISMN</th>
<th>Analysis of differences between therapies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angina NYHA class (no. of patients)</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>t</td>
</tr>
<tr>
<td>I</td>
<td>0</td>
<td>0</td>
<td>20</td>
<td>24</td>
<td>3 v. 2</td>
</tr>
<tr>
<td>II</td>
<td>35</td>
<td>35</td>
<td>22</td>
<td>18</td>
<td>4 v. 2</td>
</tr>
<tr>
<td>III</td>
<td>23</td>
<td>23</td>
<td>16</td>
<td>16</td>
<td>3 v. 4</td>
</tr>
<tr>
<td>Isosorbide dinitrate use (mg/week)</td>
<td>20.25±9.11</td>
<td>18.22±9.29</td>
<td>5.69±6.91</td>
<td>5.53±6.84</td>
<td>3 v. 2</td>
</tr>
<tr>
<td>Exercise duration (min)</td>
<td>4.74±2.34</td>
<td>4.76±2.38</td>
<td>6.14±2.51</td>
<td>6.45±2.75</td>
<td>4 v. 2</td>
</tr>
<tr>
<td>Maximal ST depression (mm)</td>
<td>2.21±0.56</td>
<td>2.21±0.56</td>
<td>1.41±0.55</td>
<td>1.38±0.55</td>
<td>3 v. 4</td>
</tr>
<tr>
<td>Recovery time (min)</td>
<td>9.01±3.40</td>
<td>9.27±3.39</td>
<td>6.49±2.37</td>
<td>6.76±2.76</td>
<td>3 v. 2</td>
</tr>
<tr>
<td>Double product (heart rate × SBP) (10^3)</td>
<td>22.46±4.48</td>
<td>23.11±4.83</td>
<td>25.75±4.81</td>
<td>25.94±4.81</td>
<td>3 v. 2</td>
</tr>
</tbody>
</table>

ns: not significant

Table 3. Side-effects of the study drugs

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>T. arjuna</th>
<th>ISMN</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>2</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>Constipation</td>
<td>4</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>Abdominal discomfort</td>
<td>2</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Bodyache</td>
<td>3</td>
<td>2</td>
<td>2</td>
</tr>
</tbody>
</table>

p=ns
of increase in ST depression and considering the leads with the greatest ST depression in each test without lead matching to avoid bias due to regression to the mean.10

Accordingly, we used the maximal ST depression at the longest equivalent submaximal exercise during each test without lead matching, and total exercise duration for assessing the effects of Terminalia arjuna, ISMN and placebo therapies in each patient. This offered us more sensitivity and accuracy with a moderate sample size. Further, treadmill exercise on the computerized system involves computerized averaging which may rarely induce errors related to ST segment shifts which were taken care of by recording the raw rhythms whenever found necessary during the test.11 The reporting of angina episodes may have had a subjective bias, but the amount of ISDN (mg) consumed during the week is expected to be more objective and informative regarding the clinical effect of the therapy.

Terminalia arjuna therapy caused a decrease in the need to use ISDN and improved effort tolerance in 56/58 (96%) patients, with improvement of at least one NYHA class in over half the patients. The treadmill exercise test parameters, i.e. maximal ST depression at the longest equivalent submaximal exercise, total exercise duration, time to recovery and double product reached showed significant improvement in the majority of patients during Terminalia arjuna therapy compared to placebo and were comparable to the benefits seen with nitrate therapy. The anti-ischemic effect of Terminalia arjuna in our patient population was impressive and statistically significant as compared to placebo.

The sensitivity and specificity of exercise-induced ST depression for coronary artery disease are less in women than in men.12 We did not include women in this drug evaluation study to avoid any possible confounding effect of sex on our treadmill test results. Thus, our results are applicable only to males with coronary artery disease, which is an important limitation of this study. However, since Terminalia arjuna has beneficial effects similar to those observed with ISMN, it should also be as useful in women, but this needs confirmation.

Terminalia arjuna was well tolerated without any major untoward effects during the study period. This was similar to observations made by other workers.3,4,5 Dwivedi et al.4 reported significant improvement in frequency of angina, decrease in nitroglycerine consumption and improvement in treadmill test criteria in a small group of patients with stable angina on Terminalia arjuna monotherapy. This study was uncontrolled and did not give details of various exercise test parameters. They reported a small decrease in systolic blood pressure with no effect on diastolic blood pressure.

In another study,9 adjuvant Terminalia arjuna therapy given to 12 patients with post-myocardial infarction angina caused decreased frequency of angina, decreased left ventricular mass and improved left ventricular ejection fraction compared to another 12 patients who received conventional anti-anginal therapy for 12 weeks. However, they did not use any objective measures to assess myocardial ischemia. In two other small studies,8,9 Terminalia arjuna therapy led to decreased angina frequency and improvement in treadmill test performance. Unlike our study, the published studies on Terminalia arjuna have obvious limitations as they fail to mention procedural details, chosen end-points, lead selection for comparison and whether or not maximal ST depression at the longest equivalent submaximal exercise was used. Our observations are in concordance with the prevailing folk belief and with the published studies supporting the usefulness of Terminalia arjuna in ischemic heart disease.4,5,8,9

In animal experiments, intravenous administration of Terminalia arjuna extract leads to dose-dependent decrease in blood pressure and heart rate which was thought to be centrally mediated.13 There was enhancement of aortic prostaglandin E₂-like activity following isoproterenol-induced ischemia in rabbits pretreated with Terminalia arjuna. This was associated with increase in the threshold for myocardial ischemia and ventricular arrhythmia.14 The drug is known to have no significant effect on heart rate, blood pressure and cardiac output in healthy volunteers but causes an increase in cardiac output and blood pressure and a decrease in heart rate in patients with a failing heart.15,16

However, very little is known about the precise mechanism of the beneficial effects and relation of the various components of this complex plant to the clinical effects reported in various studies. It is likely that the potent antioxidant properties of its constituents (flavonoids, tannins and OPCs) play a role in improving the endothelial functions of diseased coronary arteries.

We believe that there is a strong need for further evaluation of Terminalia arjuna in molecular biology, and animal and human experiments in order to find answers to some of these questions. Our study results have opened up a new direction for future large-scale, multicentre, clinical research to find an alternative and inexpensive drug therapy for patients with ischemic heart disease.

References
Bharani et al. Terminalia arjuna in Stable Angina

15. Colabawalla HM. An evaluation of the cardiotonic and other properties of Terminalia arjuna. Indian Heart J 1951; 3: 205–230
Management of Cardiomyopathy Resulting from Incessant Supraventricular Tachycardia in Infants and Children

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Background: Radiofrequency ablation is considered to be the treatment of choice in patients with ventricular dysfunction related to incessant supraventricular tachycardia. However, reservations regarding its use in infants and children prompted us to try alternative strategies for this group.

Methods and Results: Eight children (age range: 1 day to 10 years) were diagnosed to have tachycardia-related ventricular dysfunction in the past 6 years. They presented with symptoms of palpitation, dyspnea and/or generalized swelling over the body of 3 months to 2 years duration. The cardiothoracic ratio at presentation was 64% (52%–70%) and ejection fraction was 22.2% (15%–45%). In 7 patients tachycardia was diagnosed to be ectopic atrial and in 1 it was permanent junctional reciprocating tachycardia. Six of these children were managed with intravenous/oral amiodarone in combination with digoxin (3) and/or propranolol (2). In one child addition of amiodarone to digoxin and propranolol led to polymorphic ventricular tachycardia, and amiodarone was withdrawn. Only one child underwent radiofrequency ablation as the first choice because regular follow-up was not possible due to logistic reasons. Sinus rhythm with normalization of ventricular function was achieved in 6 of the 7 children treated medically. One child continued to have frequent episodes of tachycardia and underwent successful radiofrequency ablation of a high right atrial ectopic focus. Two out of the 6 patients on amiodarone could be managed with only digoxin and propranolol after their ventricular function had returned to normal. A third patient relapsed on stopping amiodarone and underwent successful radiofrequency ablation of a left atrial ectopic tachycardia.

Conclusions: Short-term amiodarone in combination with digoxin/propranolol is a safe and effective treatment strategy for infants/children with tachycardiomyopathy. Control of tachycardia is achieved in the majority, leading to recovery of ventricular function. This approach may avoid unnecessary ablations in children or at least postpone it till the procedure would be safer. (Indian Heart J 2002; 54: 176-180)

Key Words: Cardiomyopathy, Supraventricular tachycardia, Radiofrequency ablation

Radiofrequency ablation (RFA) has revolutionized the management of tachyarrhythmias in the past decade. With increasing experience, electrophysiologists now target some arrhythmias even in infants and young children, if indicated.\(^{1,2}\) Tachycardia-related ventricular dysfunction or tachycardiomyopathy in children is one such indication in which RFA is resorted to at an early age or as a first choice.\(^{3,4}\) Few reports exist of successful medical therapy in this setting,\(^5,6\) even though it is well appreciated that simple control of ventricular rate is enough to improve myocardial function.\(^7,8\) Given the natural history of arrhythmias in infants and children and the unknown long-term effects of RFA on growing hearts,\(^9\) a conservative approach may be more prudent. Possible reservations against use of drug therapy in this setting may be related to (i) low success rates with drugs such as digoxin and beta-blockers, as most of these patients have an ectopic atrial focus; (ii) the need for complete control of the tachyarrhythmia that may be more difficult with drugs; and (iii) lack of knowledge regarding the proarrhythmic risk of more effective class Ic drugs such as flecainide and propafenone.\(^{10}\) Amiodarone may provide a viable short-term alternative, whereas safer long-term alternatives could begin after recovery of ventricular function. Spontaneous disappearance of symptoms may occur in some of these children. This study aimed to assess the efficacy and safety of a relatively conservative strategy using short-term amiodarone in combination with digoxin and/or propranolol. Radiofrequency ablation was done only if medical therapy had failed or was anticipated to cause problems on long-term use.
Methods and Results

Between 1996 and 2001, all children admitted at our institute with a diagnosis of supraventricular tachycardia-related ventricular dysfunction were treated according to a standard protocol. The tachycardia mechanism was established based on standard electrocardiographic criteria and its response to intravenous adenosine, if needed. Treatment was initiated with intravenous/oral amiodarone along with oral digoxin, if necessary. Propranolol was added later, if required. ECG was continuously monitored till tachycardia was terminated and did not recur for a further 48 hours. A preliminary echocardiographic diagnosis of tachycardiomypathy was made during the tachycardia itself but ventricular function was also estimated in sinus rhythm following tachycardia termination. After tachycardia control, patients were followed up in the outpatient department with regular ECG monitoring and periodic estimation of ejection fraction (EF) by echocardiography. Biochemical tests were carried out at regular intervals to monitor organ toxicity of amiodarone. Amiodarone was stopped and a combination of digoxin and propranolol was given after left ventricular EF had recovered to more than 50% and the child had no arrhythmia for a few months, as estimated from the history and Holter recordings. RFA was done if the child continued to have tachycardia despite combination therapy, could not be taken off amiodarone or a regular follow-up was not possible.

Eight children (age range: 1 day to 10 years, median 2.5 years) were diagnosed to have tachycardia-related ventricular dysfunction in the past 6 years. Six of these 8 patients presented with palpitation, 3 had dyspnea and 2 had generalized edema because of congestive heart failure. These symptoms were present for a period ranging from 3 months to 2 years. Three of these children were being treated elsewhere as dilated cardiomyopathy while in the only child with a structural heart defect (tetralogy of Fallot) the heart failure had not been considered significant. The mean cardiothoracic ratio on X-ray chest at presentation was 64% (52%–70%) and echocardiographic mean left ventricular EF was 22.2% (15%–45%). Tachycardia was diagnosed to be ectopic atrial in 7 and permanent junctional reciprocating in one. Six children were managed with intravenous/oral amiodarone in combination with digoxin (3) and/or propranolol (2). In one child (patient no. 8), treatment was initiated with digoxin and propranolol and later addition of amiodarone led to recurrent short bursts of polymorphic ventricular tachycardia and amiodarone was withdrawn. These episodes were difficult to explain as the serum digoxin and serum K+ levels were normal and QTc was within normal limits on ECG. Digoxin doses were routinely kept at 50% of maintenance in all patients on amiodarone. The eighth child (patient no. 2) underwent RFA as the first choice because a regular follow-up was not possible due to logistic reasons. This child had a septal left atrial focus which was successfully ablated.

Sinus rhythm with normalization of ventricular function was achieved in 6 of 7 (85.7%) children treated medically. One child (patient no. 1) continued to have frequent episodes of tachycardia and underwent successful RFA of a high right atrial ectopic focus (Figs. 1and 2). On follow-up two out of the remaining (patients no. 4 and 6) 5 patients on amiodarone could be managed with only digoxin and propranolol after recovery of their ventricular function. A third child (patient no. 3) relapsed on stopping amiodarone and had successful RFA of a left atrial ectopic focus. The child with tetralogy of Fallot had surgical correction after recovery of his ventricular function but has been lost to follow-up.
follow-up since then. One child (patient no. 5) continues to be on amiodarone for the third year owing to relatively slow resolution of ventricular dysfunction and suboptimal follow-up.

Improvement in EF was noted as early as 10 days and time to near normalization (EF >50%) varied from 2 months to more than 2 years (Fig. 3). The neonate had the most rapid recovery, with EF increasing from 45% to 60% in less than 2 months. However, such comparisons may not be possible due to baseline differences in EF. Two of the three patients who underwent RFA had the procedure done only recently and therefore it is not possible to compare the time course of recovery of ventricular function in these two subsets in our study.

Discussion

Tachycardiomyopathy is a rare condition in which incessant supraventricular/ventricular tachycardia leads to worsening of myocardial function which is partially or completely reversible after normalization of the heart rate.11–13 This relationship was described for the first time in 1949 by Philips and Levine in patients with atrial fibrillation and reversible heart failure.14 Animal studies show that this condition is associated with reduction in myocyte attachment to the basement membrane resulting in decreased performance and scarring of the mechanical pump.15,17 Response to beta-adrenergic stimulation is blunted, probably due to reduced beta-adrenergic receptor density.18–20 Furthermore, a primary defect in isolated myocyte contractile function associated with blunted responsiveness to extracellular calcium and alterations in cytoarchitecture have also been shown.21–23 Spinale et al.24 found a 50% reduction in myocardial blood flow per gram of tissue at rest and decrease in endocardial/epicardial flow ratio. Clinical studies reveal a reduced EF, increased end-systolic and end-diastolic volumes11 and increased end-diastolic25 and pulmonary artery pressures.26 Myocardial biopsy samples demonstrate reduced total creatinine and phosphocreatinine, leading to the speculation that depletion of high-energy phosphates due to myocardial ischemia is responsible for the depressed myocardial function.27

The diagnosis should be suspected when, on evaluation, tachycardia is felt to be out of proportion to the heart failure in a child with dilated cardiomyopathy (DCM).28 In most of our patients this diagnosis had not been suspected at referral. An abnormal P wave axis points to the tachycardia as not being of sinus origin. Non-variation of heart rate indicates lack of effect of the autonomic nervous system and points to an ectopic origin. Vagal maneuvers and/or intravenous adenosine can be useful in confirming the diagnosis of an atrial tachycardia by eliciting an AV block. Thus, a high index of suspicion derived from the history and clinical features remains the only available tool to diagnose a tachycardiomyopathy in a patient.28

Given the natural history of arrhythmias in children and also the unknown effects of RFA in infants and children, we treated them with an alternative strategy of medical management, choosing to ablate only if required. The efficacy of medical therapy is proved by the success in treating the tachycardia and subsequent normalization of ventricular function. The time course of recovery of ventricular function after successful RFA is well defined with complete recovery in 3–6 months; rarely, patients may take several years to recover.3,29 Our medically managed patients showed similar ventricular function recovery times, thus proving that drugs could provide effective control of the arrhythmia. We were able to take some of these patients off amiodarone, thereby avoiding its serious long-term effects. Even though amiodarone has been considered to be relatively safe in the pediatric population,30 its long-term use should be avoided except in cases of complex arrhythmias. The fact that some of these patients with incessant tachycardias have been stable only on digoxin/propranolol or its combination could suggest that the tachycardia focus has stopped by itself as is known to occur in children.

![Fig. 3. Graph showing time course of recovery of left ventricular ejection fraction (EF) for individual patients (10 months follow-up shown in the graph). Only 5 patients are shown in the figure as others underwent radiofrequency ablation. The X axis shows time in months.](image)
Radiofrequency ablation was carried out successfully in 3 patients with ectopic atrial tachycardia. One of them had to have 3 ablation sessions, as the tachycardia was highly susceptible to sleep. Small amounts of sedation led to sinus rhythm and isoprenaline also did not help. This made mapping difficult and the use of more sophisticated systems such as CARTO even more difficult. These systems need the patient to be lying still for hours to create the map and are often done under heavy sedation which could render the tachycardia noninducible. Thus, a conservative policy towards ablation would avoid unnecessary interventions in these children.

The choice of drug for control of tachycardia remains debatable. Class Ic drugs such as flecainide and propafenone are known to be highly effective in controlling most of the supraventricular tachycardias (SVTs) and are safe in the setting of a normal heart. But can these be defined as normal hearts? Is ventricular dysfunction a contraindication to their use in the absence of ischemia? Do ventricular dilatation and dysfunction by themselves not lead to increased wall stress and ischemia? Sotalol is also useful in a variety of supraventricular arrhythmias but torsades does occur even in normal hearts and the drug needs more careful monitoring, which is difficult in patients from remote areas with poor knowledge of adverse effects. Furthermore, none of these three drugs is easily available in India. Fishberger et al.29 had reported a large series of 33 patients, with ventricular dysfunction in 21. Flecainide was used in 7 patients out of whom 4 patients had a fractional shortening (FS) Z score of <−3, propafenone in 1 who had an FS Z score of −6.3 and sotalol in 3 patients, 2 of whom had an FS Z score of <−5. No significant morbidity was found in these cases. We chose amiodarone because of its efficacy, low cost and safety profile in the setting of ventricular dysfunction.31

None of the patients had any serious side-effects except for polymorphic ventricular tachycardia in one. The etiology of this tachycardia is not clear but it did not recur after stopping amiodarone. The digoxin level was normal but the possibility of amiodarone-digoxin interaction leading to digoxin toxicity cannot be excluded, even though digoxin doses were routinely reduced to 50% of maintenance in all patients on amiodarone.

Our data are limited by the small number of cases and the lack of a prospective randomized design between ablation and drug therapy. Furthermore, other drugs such as flecainide, and sotalol were not used because they are expensive and difficult to obtain. Hence, the comparative efficacy/safety of these drugs remains unclear.

**Conclusions:** This small observational study suggests that tachycardiomyopathy in children need not be considered an absolute indication for RFA. Medical therapy can successfully control the tachycardia in over half of these patients. Amiodarone is useful in the initial phase and can be substituted with safer drugs once ventricular function has normalized.

### Table 1. Patient characteristics, treatment received and outcome

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age</th>
<th>Weight (kg)</th>
<th>EF (%)</th>
<th>Treatment</th>
<th>RFA</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>6 years</td>
<td>15</td>
<td>15</td>
<td>A, D, P</td>
<td></td>
<td>Right atrial focus, Drugs unsuccessful</td>
</tr>
<tr>
<td>2</td>
<td>10 years</td>
<td>26</td>
<td>20</td>
<td>D, P</td>
<td></td>
<td>Left atrial focus, RFA first choice</td>
</tr>
<tr>
<td>3</td>
<td>8 years</td>
<td>16</td>
<td>15</td>
<td>A, D</td>
<td></td>
<td>Left atrial focus, Recurrence on stopping amiodarone</td>
</tr>
<tr>
<td>4</td>
<td>7 years</td>
<td>16</td>
<td>20</td>
<td>A</td>
<td></td>
<td>Off amiodarone</td>
</tr>
<tr>
<td>5</td>
<td>2.5 years</td>
<td>10</td>
<td>20</td>
<td>A</td>
<td></td>
<td>Off amiodarone</td>
</tr>
<tr>
<td>6</td>
<td>1 day</td>
<td>3.5</td>
<td>45</td>
<td>A, D, P</td>
<td></td>
<td>TOF (lost to follow-up)</td>
</tr>
<tr>
<td>7</td>
<td>5 months</td>
<td>5.5</td>
<td>20</td>
<td>A</td>
<td></td>
<td>PMVT on amiodarone</td>
</tr>
<tr>
<td>8</td>
<td>13 months</td>
<td>8.6</td>
<td>20</td>
<td>D, P</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

A: amiodarone; D: digoxin; P: propranolol; TOF: tetralogy of Fallot; PMVT: polymorphic ventricular tachycardia

### References

8. Fukumoto Y, Urabe Y, Shimokawa H, Chishaki-Suyama A,


Background: The incidence of bacteremia induced by transesophageal echocardiography is controversial in the Indian population. This study aimed to find out the occurrence of bacteremia following transesophageal echocardiography.

Methods and Results: Between February 2000 and January 2001, 47 patients (26 males and 21 females) were enrolled for the study. Their ages ranged from 13 to 61 years (mean: 35±11.4 years). Patients with prosthetic valves, suspected infective endocarditis and those on antibiotics were excluded. For each procedure, two sets of blood cultures were obtained immediately before and after the procedure. For each blood culture, 10 ml of blood was evenly inoculated into brain-heart infusion broth and biphasic infusion medium and incubated for 7 days. Transesophageal echocardiography was carried out under oropharyngeal anesthesia (xylocaine gel and spray). Two blood cultures taken before the procedure were positive and excluded from the final analysis. Of the remaining 45 patients whose preprocedure blood cultures were sterile, 6 samples (13.3%) were positive after the procedure—diphtheroids in 3, micrococci in 2 and aerobic spore formers in 1.

Conclusions: This study demonstrates that the incidence of bacteremia related to transesophageal echocardiography is not insignificant, as reported in previous studies. Though routine antibiotic prophylaxis before transesophageal echocardiography is not advocated, it should be recommended in high-risk patients such as those with prosthetic valves, multivalvular involvement or those with a past history of infective endocarditis.

Key Words: Transesophageal echocardiography, Bacteremia, Infective endocarditis

Original Article

Transesophageal echocardiography (TEE) provides better structural and functional details of the heart and thoracic aorta as compared to transthoracic echocardiography (TTE). TEE is superior to TTE in detecting thrombi, vegetations and assessing malfunctioning prosthetic valves.1-3 It is, however, more invasive than TTE, with the potential for mucosal trauma to the gingiva, pharynx and esophagus. As patients who undergo TEE generally have a high prevalence of hemodynamically significant valvular lesions, the risk of bacterial endocarditis and the need for antimicrobial prophylaxis is a matter of concern. The current American Heart Association guidelines for antimicrobial prophylaxis do not recommend routine administration of antimicrobials prior to diagnostic endoscopy.4 Previous studies that addressed the issue of bacteremia during TEE have shown varying results.5-7 Moreover, the incidence of bacteremia induced by TEE is controversial in the Indian population. The present study aimed to find out the occurrence of bacteremia following TEE.

Methods

Between February 2000 and January 2001, 47 patients scheduled for TEE were enrolled for the study. Patients with prosthetic valves, suspected infective endocarditis and those who were on antimicrobial therapy were excluded.

The Hewlett-Packard Sonos 5500-echocardiography system equipped with an Omniplanetransesophageal probe was used for the study. The probe was sterilized by immersing it in 2% glutaraldehyde solution for a minimum of 40 min. Before the procedure, it was thoroughly washed in running water and scrubbed to remove any organic matter.
Patients were asked to abstain from food and water for at least 4 hours before the procedure. Informed consent was obtained from all the patients. Oropharyngeal anesthesia was achieved using 10% lignocaine spray and 15 ml of viscous lidocaine hydrochloride gel. No sedatives were given prior to the procedure. The patients were placed in the left lateral decubitus position. Intubation of the esophagus was done by the no-digital method in which the probe is introduced in the patient's mouth and swallow-assisted examination is performed while gently pushing the probe. Intubation was achieved in a single attempt in all the patients. The mean procedural time was 9.35±5.01 min.

Two sets of blood cultures were obtained from each patient after thorough cleaning of the forearm skin using povidone-iodine and a spirit swab. Blood cultures were obtained immediately before and 15 min after the procedure from separate venepuncture sites. Each time, 10 ml of venous blood was obtained and aliquots of 5 ml were inoculated into brain–heart infusion broth (BHIB) and biphasic infusion medium (BPIM). Blood cultures were incubated at 37°C and inspected for turbidity for a total of 7 days. After 24 hours, if turbidity was noted, subcultures were done on blood agar, chocolate agar and MacConkey's agar. If no turbidity was seen, the cultures were incubated for a total of 7 days till final subcultures were done. Bacterial growth was identified using Gram stain and colony characteristics and biochemical reactions.

Results

A total of 47 patients, 26 males (55%) and 21 females (45%), were included in the study. The indications for TEE were assessment of valvular lesions in 22 (46%), intracardiac shunts in 12 (25%), intracardiac mass in 1 (2%), investigation for cardiac source of emboli in 3 (6%) and inadequate TTE study in 1 (2%).

Two blood cultures taken before TEE were positive for bacteremia and these patients were excluded from the study. Of the remaining 45 patients whose preprocedure blood cultures were sterile, growth was noted in 6 (13.3%) postprocedure samples. The organisms cultured included diphtheroids in 3, micrococi in 2 and aerobic spore formers in 1. All these organisms are normal commensals of the mouth. The characteristics of patients whose blood cultures were positive are shown in Table 1.

Discussion

The incidence of transient bacteremia after esophagogastroscopy has been documented in about 4%–8% of cultures and the incidence increases if interventions are performed. The technique of esophageal intubation with the TEE probe is similar to that of esophagogastroscopy. Once in the esophagus, maneuvering the probe to optimize the images may injure the mucosa.

Studies on the incidence of bacteremia during TEE have been controversial. The reported incidence ranges from 2% to 17%. Chandrasekaran et al. reported that all cultures in their series of 85 patients were negative except those of 2 patients with pre-existing bacteremia. A few other studies that addressed the issue of bacteremia following TEE have concluded that antibiotic prophylaxis may not be warranted prior to the procedure.6–11 Our findings show that 6 of 45 patients (13%) had bacteremia after the procedure. This observation is in agreement with that of Gorge et al., who prospectively studied 24 patients with two blood cultures obtained simultaneously 6–12 min after beginning TEE and found 4 patients (17%) with positive blood cultures. Although in all 4 patients both blood cultures were positive for microorganisms, in only 1 patient was the same organism (coagulase-negative streptococci) recovered from both cultures. Isolation of multiple organisms in the same patient raises the possibility of contamination of the samples.

In the present study, only one sample was taken following the procedure and isolation of organisms in a single sample may suggest contamination. Though contamination can be a problem despite the use of proper techniques, isolation of organisms in 13% of patients cannot be ignored as being due to contamination. Moreover, diphtheroids, which were reported to cause early prosthetic valve endocarditis, were isolated in 3 out of 6 samples. Although the number of patients in our study is small, bacteremia following TEE does not seem to be uncommon.

Limitations: Our study population was small and we collected only one blood sample within 15 min after the procedure. We expected the likelihood of bacteremia would
be highest in the early phase because of microinjuries. Isolation of the same organism in multiple samples collected from the same patient would have strengthened the possibility of true bacteremia. However, multiple venepunctures are impractical and multiple sampling through an indwelling needle or catheter would facilitate contamination. We did not collect throat swabs from the patients prior to TEE. The isolation of a similar organism in the throat swab and blood sample would have aided in confirming true bacteremia.

Conclusions: Bacteremia following TEE was not insignificant in our study group. Though routine antibiotic prophylaxis before TEE is not advocated, it should be recommended in high-risk patients such as those with prosthetic valves, multivalvular involvement or those with a past history of infective endocarditis.

References

Coronary Angiography Using 4 French Catheters with Power Injection: A Randomized Comparison with 6 French Catheters

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Background: Coronary angiography using 4 F catheters may reduce access-site complications and enable early ambulation, although earlier studies suggested that the quality of images may be an issue of concern.

Methods and Results: To ascertain the quality of angiographic images and safety of early ambulation, 500 patients were randomized to coronary angiography with either 4 F or 6 F catheters. Procedural characteristics, angiographic quality scores and results of ambulation were analyzed in the two groups. Patients in the 4 F group were mobilized at 2 hours post-procedure while those in the 6 F group were ambulated at 6 hours. There was no procedure-related complication in either group. The procedure was successfully completed in 250 of 252 patients randomized to the 4 F group. In two patients in the 4 F group, sheaths were upgraded to 6 F to complete the procedure, as difficulty was encountered in hooking the coronary ostium with a 4 F Judkin’s catheter. Coronary angiographic quality scores in these two groups were comparable. Angiographic scores for the 4 F and 6 F groups for the left coronary artery averaged 4.45±0.5 and 4.58±0.3 (p>0.1), respectively. The right coronary artery scores averaged 4.30±0.4 and 4.35±0.2 (p>0.1) in the 4 F and 6 F groups. Angiographic scores for the left ventricular angiogram averaged 4.22±0.1 and 4.44±0.3 (p>0.1) in the 4 F and 6 F groups, respectively. None of the angiograms were assigned a score of <3.0 (not diagnostic). The total contrast volume consumed in the two groups was also equivalent. There were no groin-related complications in the 4 F group although these patients were ambulated 2 hours after the procedure.

Conclusions: Coronary angiography performed with a 4 F catheter is a safe and reliable procedure. The quality of image obtained with a 4 F catheter is equivalent to that obtained with a 6 F catheter. Early ambulation at 2 hours is feasible without compromising safety. (Indian Heart J 2002; 54: 184-188)

Key Words: Coronary angiography, 4 French catheters, Coronary artery disease
Injection-assisted coronary angiography would result in equivalent or superior angiographic studies compared with 6 F catheters, and permit early ambulation safely with fewer access-site complications.

**Methods**

From May to October 2001, 500 patients subjected to diagnostic left heart catheterization and coronary arteriography were included in the study. Of these, 252 were randomly allocated to coronary angiography with 4 F diagnostic coronary catheters. The procedure was performed by experienced cardiologists. The indications for angiography included chronic stable angina, unstable angina pectoris and post-infarction patients with a positive stress test. Patients were excluded if they had acute myocardial infarction, severe concomitant valvular heart disease, marked hemodynamic instability and those who had undergone a prior coronary artery bypass surgery. In the remaining 248 patients, coronary angiograms were performed using 6 F diagnostic coronary catheters.

Four French Quick Care Infiniti catheters (Cordis, Miami, FL) were used for the study and the results were compared with coronary angiograms performed with 6 F catheters. These 4 F Infiniti catheters have an internal luminal diameter of 0.042". Femoral artery puncture was done with an 18-gauge puncture needle and catheterization was performed according to the Seldinger technique. We did not give a scalpel nick in the groin prior to sheath insertion. Systemic heparinization was not done in any of the patients, although heparinized saline was used for periodic flushing of the sheath and catheters. Left and right diagnostic Judkin’s catheters (4 F) and 4 F pigtail catheters were used. Multiple angled views of the left and right coronary arteries were taken. For the left coronary system, 6–8 ml of contrast was injected with the help of an Angiomet injector at a flow rate of 3 ml/s at 650 psi. To visualize the right coronary system, 3–5 ml of contrast was used at the same flow rates. Coronary angiograms in the 6 F group were performed by the hand injection technique. Left ventricular (LV) angiography was performed in RAO 30° view using 30–40 ml of contrast at a flow rate of 12 ml/s and pressure of 650 psi. The contrast agent used was Omnipaque 350 (Nycomed Amersham, Bucks, UK) warmed to 37 °C.

Procedural details noted during angiography included catheter performance, total procedural and fluoroscopy time, number of catheters used, need for a switch to a 6 F catheter and total volume of contrast used. Sheaths were removed at the end of the procedure and the groin was compressed manually to achieve complete hemostasis. Time to achieve total hemostasis was also recorded. Patients catheterized with 4 F catheters were ambulated at 2 hours in the absence of complications, while those catheterized with 6 F catheters were mobilized at 6 hours. Before discharge, the patients were observed in the ward for an hour after mobilization. Groin complications at ambulation and on subsequent outpatient follow-up were recorded. The first follow-up was done on the day after the coronary angiogram when the groin was re-inspected and any bruising or local hematoma was noted.

Coronary angiograms were recorded on a CD-ROM and an experienced observer performed quantitative angiographic grading in a blinded manner. The first four images of the left coronary artery, the first two images of the right coronary artery and LV images were graded on a scale of 1–5 (1=poor, 3=marginal diagnostic, 5=optimal). The angiographic score for each artery was calculated for an individual patient and mean scores were determined for each artery in the study population.

**Statistical Analysis**. Results are expressed with their mean and standard deviation. Statistical significance was assessed by the unpaired Student’s t test. A p value of <0.05 was accepted as statistically significant.

**Results**

Five hundred patients were included in the study, of whom 252 underwent coronary angiography with 4 F catheters. There were no significant differences in the baseline characteristics between the two groups of patients (Table 1). No statistically significant differences were recorded in the number of patients with single-, two- or three-vessel disease in either group.

The procedure was successfully completed in 250 of the

**Table 1. Patient and angiographic characteristics**

<table>
<thead>
<tr>
<th>Clinical variable</th>
<th>4 French</th>
<th>6 French</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>252</td>
<td>248</td>
</tr>
<tr>
<td>Age (years)</td>
<td>50±16</td>
<td>52±15</td>
</tr>
<tr>
<td>Males (%)</td>
<td>176 (69.8)</td>
<td>188 (75.8)</td>
</tr>
<tr>
<td>Chronic stable angina (%)</td>
<td>158 (62.6)</td>
<td>152 (61.2)</td>
</tr>
<tr>
<td>Unstable angina (%)</td>
<td>38 (15.1)</td>
<td>36 (14.5)</td>
</tr>
<tr>
<td>Post-infarction with positive TMT (%)</td>
<td>36 (14.2)</td>
<td>37 (14.9)</td>
</tr>
<tr>
<td>Non-Q wave MI (%)</td>
<td>15 (5.9)</td>
<td>17 (6.8)</td>
</tr>
<tr>
<td>Atypical chest pain</td>
<td>5 (1.9)</td>
<td>6 (2.4)</td>
</tr>
<tr>
<td>Normal coronary arteries (%)</td>
<td>28 (11.1)</td>
<td>25 (10.1)</td>
</tr>
<tr>
<td>1-vessel disease (%)</td>
<td>141 (55.9)</td>
<td>136 (54.8)</td>
</tr>
<tr>
<td>2-vessel disease (%)</td>
<td>46 (18.2)</td>
<td>47 (18.9)</td>
</tr>
<tr>
<td>3-vessel disease (%)</td>
<td>37 (14.7)</td>
<td>40 (16.1)</td>
</tr>
<tr>
<td>Left main disease (%)</td>
<td>13 (5.1)</td>
<td>16 (6.4)</td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
<td>38±4</td>
<td>36±3</td>
</tr>
</tbody>
</table>

MI: myocardial infarction; TMT: treadmill test.
252 patients. In 2 patients, difficulty was encountered in engaging the coronary ostium (left and right coronary ostium in one case each) and 6 F catheters were used to complete the procedure. In both these patients, the coronary ostia were finally hooked with 6 F left Amplatz catheters (4 F left Amplatz catheters were not available with us at the time of conducting the study). Besides these two cases, the operators did not report any technical difficulty in performing the procedure with 4 F catheters. The total fluoroscopic time was 182±80 s for the 4 F group and 170±75 s for the 6 F group, p>0.1 (Table 2). There was no significant difference in the volume of contrast required in patients catheterized with 4 F versus 6 F catheters (95±15 ml in the 4 F group v. 90±13 ml in the 6 F group). The time needed to achieve complete hemostasis at the arterial access-site was significantly shorter in patients catheterized with 4 F catheters.

Angiographic scores for 4 F and 6 F catheters are shown in Table 3. There was no statistically significant difference in the quality of angiographic images between the two groups. None of the images in either group was assigned a score of less than 3.0 (nondiagnostic). The scores for the left coronary system with 4 F catheters were 4.45±0.5 and with 6 F catheters they were 4.58±0.3, p>0.1. For the right coronary artery, the scores with 4 F catheters were 4.3±0.4, and with 6 F catheters they were 4.35±0.2, p>0.1. LV angiograms were scored as 4.22±0.1 using 4 F catheters and 4.44±0.3 with 6 F catheters, p>0.1.

Table 2. Procedural results

<table>
<thead>
<tr>
<th>Procedure time</th>
<th>4 French (n=252)</th>
<th>6 French (n=248)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluoroscopic time</td>
<td>182±80 s</td>
<td>170±75 s</td>
<td>&gt;0.1</td>
</tr>
<tr>
<td>Contrast volume</td>
<td>95±15 ml</td>
<td>90±13 ml</td>
<td>&gt;0.1</td>
</tr>
</tbody>
</table>

No major hematomas were seen in either the 4 F or 6 F groups. Time to achieve complete hemostasis was significantly shorter in patients catheterized with 4 F catheters. The median time to complete hemostasis in the 4 F group was 6.2 min v. 10.5 min in the 6 F group (p<0.01). All patients in the 4 F group were successfully ambulated at 2 hours. No complications were recorded on subsequent follow-up in the outpatient clinic. Patients catheterized with 4 F catheters reported significantly less local discomfort after the procedure, as compared to the 6 F group.

Discussion

Diagnostic cardiac catheterization is now performed as an outpatient procedure in a large number of patients who have stable clinical characteristics. The number of patients who need this diagnostic study is steadily increasing. Early ambulation following catheterization can reduce hospital stay, allowing optimal utilization of hospital resources. This is possible by using smaller 5 F and 4 F diagnostic catheters. Safety of early ambulation using 5 F and 4 F catheters has been demonstrated in earlier studies.6,7 However, the quality of images and technical limitations have been a cause for concern during coronary angiography with these catheters using manual injection.6,7,8 This was a prospective, single-center trial done to evaluate the angiographic quality and safety of early ambulation using 4 F catheters.

The angiographic quality of left coronary, right coronary, and LV angiograms was comparable to those with 6 F catheters. Importantly, none of the angiograms was nondiagnostic. The results are consistent with those observed in earlier studies6,7,9 which have reported similar findings. Khoukaz et al.9 randomized 101 patients to coronary angiography with either 4 F or 6 F catheters. In the 4 F group, coronary injections were performed using a power injection device with default settings of 10 ml at 3 ml/s for the left coronary and 6 ml at 3 ml/s for the right coronary system. The angiographic scores for the left coronary system were 4.73±0.6 in the 4 F group and 4.78±0.65 in the 6 F group (p=0.28). The scores for the right coronary artery were 4.98±0.13 in the 4 F and 4.97±0.16 in the 6 F group (p=0.48). Chahoud et al.10 reported similar results with angiographic scores of 4.7±0.6 for the left coronary artery and 4.88±0.1 for the right coronary artery with a power injection technique. A larger, multicenter, prospective, randomized trial conducted in the UK also demonstrated that coronary angiograms performed with 4 F catheters were of adequate angiographic quality, although the angiographic scores of the left anterior descending artery were lower in the 4 F group.11 The angiographic scores for the right coronary artery and LV angiogram were comparable between the two groups. Similar results were reported by Danzi et al.12 in another large study, in which 400 patients were randomized to coronary angiography with either 4 F or 6 F catheters. The investigators demonstrated that the radiographic resolution of images was adequate for clinical decision-making. However, they felt that the angiographic
quality of images was inferior to that with 6 F catheters. This discrepancy is because this group used the hand-injection technique to opacify the coronary system. It is our observation also that hand injection produces suboptimal images and can at best be used for the right coronary artery. Power injections produce a much better image, similar to that obtained with 6 F catheters.

The angiographic quality of LV angiograms were also similar in the two groups. Khoukaz et al.\(^9\) had reported an inferior quality of LV angiographic images with 4 F catheters. The total quantity of contrast used in 4 F group ranged from 10 to 54 ml compared with 30 to 45 ml (average 37±4 ml) for the 6 F group. This variation in injection volume in the 4 F group was because the operator had the discretion of stopping the injection if it appeared that opacification of the left ventricle was adequate. However, when these angiograms were analyzed later by an independent observer, they were assigned lower scores. We did not find any statistically significant difference in the quality of LV angiograms between the two groups in our study, because a fixed preset volume (30–40 ml of contrast) was used and the LV injection was not operator controlled. Other studies\(^9,11\) have also demonstrated that the quality of LV angiograms are adequate and similar in both groups.

We did not find any groin-related complications in either of the two groups, although patients in the 4 F group were mobilized at 2 hours. Similar results have been reported by other observers.\(^9,11\) In the study by Khoukaz et al.,\(^9\) all patients (including those who had undergone angiography with 6 F catheters) were ambulated at an average of 91±19 min after the procedure without any access-site complications. They reported only one hematoma each in the 4 F and 6 F groups, respectively. We did not encounter any significant hematomas in either of the two groups of patients despite early ambulation of patients in the 4 F group. However, as we did not ambulate patients who had undergone angiography with 6 F catheters at 120 min, the ambulation times and related complications may not be comparable. Some authors have mobilized patients even earlier after angiography and demonstrated its safety. In a study involving 410 patients of whom 205 were catheterized with 4 F catheters, Todd et al.\(^11\) demonstrated significantly lower incidence of groin hematoma/bruising in the 4 F group despite mobilization 1 hour after angiography. This greatly reduces the invasiveness of the procedure as the patient is not bed-bound for a prolonged period.

The radial route for performing coronary angiograms is a potentially suitable alternative to the femoral approach. This approach has been shown to be technically feasible if performed with the help of long radial sheaths and is associated with a shorter hospitalization time.\(^13\) However, it is associated with a learning curve, as most operators are more familiar with the femoral approach. Also, it is not free from complications and even in experienced hands, it is associated with a procedural failure rate of 5%–10%.\(^13,14\)

Early ambulation at 2 hours can be safely accomplished as the patient are exposed to more radiation is also an issue with the radial route, although this can be partially circumvented by placing the arm by the side of the patient after the arterial puncture is done. The advantage of these small-bore catheters is that early ambulation is possible and most operators would be more comfortable performing coronary angiograms from the femoral route.

Conclusions: Coronary angiography performed with a 4 F catheter is technically feasible and is associated with negligible groin complications. The power injection technique produces images of similar quality to that obtained with 6 F catheters without any untoward effects. Early ambulation at 2 hours can be safely accomplished with 4 F catheters.

References

results of a multicenter trial. J Am Coll Cardiol 1990; 15:1475-1483
Brief Report

Bioptome-Assisted Coil Occlusion of Coronary Artery Fistula

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We describe a novel technique that allows controlled and precise delivery of single or multiple coils simultaneously for occlusion of a coronary artery fistula using a bioptome passed via a long sheath positioned at the distal end of the fistula. The fistula was balloon occluded distal to the take-off of the native branches before, during and after coil delivery in two patients. (Indian Heart J 2002; 54: 189-192)

Key Words: Coronary artery fistula, Transcatheter intervention, Congenital heart disease

Coronary artery fistula is uncommon but remains the most frequent hemodynamically significant congenital coronary artery anomaly. A large fistula requires closure to prevent complications such as myocardial ischemia resulting from coronary steal, congestive heart failure, endocarditis and potential aneurysmal dilatation and rupture. Successful transcatheter closure of a coronary artery fistula has been reported using Gianturco coils, detachable balloons, polyvinyl alcohol foam and occlusive devices. Bioptome-assisted delivery has been used recently to improve control during coil deployment for patent arterial ducts. We have previously described a technique of bioptome-assisted simultaneous delivery of multiple coils for closure of large patent arterial ducts. This report describes the application of a similar technique for closure of a large coronary artery fistula in two patients.

Case Report

Case 1: A 19-year-old asymptomatic woman was referred to our center for evaluation of a loud (grade 4/6), continuous murmur. The resting electrocardiogram (ECG) showed prominent left ventricular forces and chest X-ray was within normal limits. On echocardiography, a fistula was seen arising from a dilated right coronary artery (RCA) and draining into the right ventricle (RV) beneath the posterior leaflet of the tricuspid valve. A previous attempt at transcatheter closure using the conventional technique of distal delivery of Gianturco coils had failed because of repeated embolization of the coils into the pulmonary artery. Under conscious sedation, both the femoral arteries (8 F and 6 F sheaths) and the right femoral vein (8 F sheath) were cannulated and the patient was heparinized (100 units/kg). Pulmonary artery pressures were normal and the ratio of pulmonary-to-systemic blood flow was 2:1. Selective coronary angiography revealed a dilated RCA (8 mm) and a coronary fistula originating distally and opening into the RV below the tricuspid valve (Fig. 1a). The origins of the posterior descending artery and the posterolateral

Fig. 1a. An injection in the LAO view made via the right coronary catheter (JR 4) shows the dilated right coronary artery (RCA) with the balloon catheter inflated distal to the origin of the posterolateral ventricular (PLV) and posterior descending (PD) branches of the RCA. An exchange length wire has been passed into the pulmonary artery (PA).
ventricular branches of the RCA were close to the origin of the fistula at the crux of the heart (Fig. 1a).

A 5 F Judkin’s right coronary catheter was advanced into the fistula. A guidewire (Terumo, Japan) was advanced out of the distal end of the fistula into the pulmonary artery. The right coronary catheter was then advanced over this wire. A 0.038" exchange guidewire (260 cm, Cook) was passed through this catheter into the pulmonary artery and then snared using a 10 mm Amplatzer gooseneck snare (Microvena Corp., MN, USA). The exchange wire was exteriorized out of the femoral vein forming an arteriovenous wire loop. An 8 F long sheath (Arrow Flex, Arrow Inc., PA, USA) with the dilator was advanced over the exchange wire from the femoral vein and positioned within the right ventricular mouth of the fistula after which the dilator was removed (Fig. 1b). A 7 F balloon wedge catheter (Arrow Inc.) was passed via the femoral artery over the exchange wire and advanced into the RCA beyond the take-off of all its native branches and inflated. A 5 F, right Judkin’s catheter (JR 4) passed via the left femoral artery was used for angiography to delineate the native branches of the distal RCA. Temporary balloon occlusion of the fistula allowed satisfactory visualization of the native branches of the RCA (Fig. 1a). Contrast injections via the long sheath were made in two orthogonal views which showed the fistula to be 12 mm long and its mouth, where it opened into the RV, to be 6 mm in diameter (Fig. 1b).

Two 8 mm × 8 cm, 0.052" Gianturco coils (Cook Inc., Bloomington, IN, USA) were selected and prepared using the technique previously described by us.10 A small part of the proximal end of the coils was pushed out of the delivery tubes, and the round ball at the proximal end stretched out for a small distance and intertwined (Fig. 1c). A 5.2 F, 120 cm long bioptome (Cook Inc.) was passed via a 7 F short introducer sheath. One of the balls was held by the bioptome and the coils were drawn into the short sheath. With the short sheath serving as an introducer, the coils were introduced into the 8 F long sheath and deployed into the fistula. The balloon wedge catheter was kept inflated for 10 min to enable faster clot formation and prevent coil migration. With the bioptome still holding the coil, the balloon wedge catheter was deflated. An angiogram of the RCA was performed to ensure patency of the native branches. There was a small amount of residual flow across the fistula.

After ensuring that the coils remained stable, the jaws of the bioptome were opened to release the coil. Repeat contrast injection with the 5 F RCA catheter showed further reduction in the flow with a stable position of the coil mass (Fig. 1d). Echocardiography performed the next day showed a small residual flow. There were no ECG changes. No residual flow across the fistula was demonstrable by color Doppler at three months. The patient remains well after one year of follow-up and ECGs and ventricular function are normal.

**Case 2:** An 11-month-old infant with a large coronary arteriovenous fistula presented with failure to thrive (weight 6.5 kg). Physical examination revealed a grade 4/6 continuous murmur heard at the left lower sternal border. On chest X-ray, there was cardiomegaly and plethoric lung fields while the ECG showed a left ventricle volume overload...
pattern. Echocardiography showed a large coronary fistula arising from the left main coronary artery (LMCA) and draining into the right atrium (RA) close to the opening of the superior vena cava (SVC).

Cardiac catheterization revealed normal pulmonary artery pressures with a pulmonary-to-systemic blood flow ratio of 1.7:1. On aortography and selective coronary angiography, a dilated LMCA and a large coronary fistula directly arising from the distal LMCA was seen draining into the RA below the SVC-RA junction. It was 3.8 cm long; the initial portion was tubular and had two saccular dilatations towards the RA end, each measuring 10 mm. The narrow end of the fistulous opening into the RA measured 3 mm. A 5 F balloon wedge catheter was floated into the fistula and a 0.018" exchange guidewire (260 cm, Cook) was passed through this catheter and the fistula into the RV, and advanced into the main pulmonary artery. The wire was then snared from the pulmonary artery and the exchange wire exteriorized out of the femoral vein. A 6 F long sheath (Balkin Contralateral Sheath, Cook) with the dilator was advanced over the exchange wire into the RA end of the fistula. The remainder of the procedure was essentially identical to that in Case 1. In this patient, however, a single 8 mm x 8 cm, 0.052" coil (Cook) was delivered using a 3.2 F, 60 cm long bioptome (Cook). Three additional coils (0.052", 8 mm x 8 cm) were delivered through the sheath using the same technique. The balloon wedge catheter was kept inflated for 10 min as in the first case. Contrast injection through it showed minimal flow and a very stable position of the coil mass. Echocardiography performed in the catheterization laboratory after the procedure showed a small residual flow. There were no ECG changes. The patient is well five months after the procedure and awaits a follow-up echocardiogram.

Discussion

Transcatheter closure of congenital coronary artery fistula has been described in many reports using a variety of techniques and devices including Gianturco coils. The requirements for satisfactory coil closure of a coronary artery fistula include the ability to safely cannulate the branch of the coronary artery which supplies the fistula, and a relatively narrow and ideally single communication into the cardiac chamber or vessel. The choice of device and technique is determined by the cost, familiarity of the operator with the different approaches and the anatomic characteristics of the fistula. The concerns with using unassisted Gianturco coils are that limited control may result in coil positions that compromise native coronary blood flow resulting in ischemia and embolization out of the distal end of the fistula. Large coronary arterial fistulas are typically considered unsuitable for coil closure and occlusive devices have been used for them. Both our patients had large fistulas, which may have merited the consideration of occlusive devices.

The Amplatzer duct occluder has been successfully used to close large, high-flow fistula that drain into the RV or RA in small children, but economic considerations precluded this option in both our patients. Even with the use of four coils as in Case 2, the total cost of the procedure is substantially less as compared to using the Amplatzer device.

Coil occlusion of a large fistula may be associated with significant problems, with embolization rates as high as 23%. Perry et al. reported successful transcatheter closure of coronary artery fistula using various techniques in 9 patients, including Gianturco coils in 6. Two coils migrated, one of which was retrieved.

In Case 1, the fistula arose close to the origin of the posterior descending and posterolateral ventricular branches of the RCA. These features necessitated that the coils be released near the right ventricular mouth of the fistula beyond the origin of the distal branches. Bioptome-assisted coil occlusion helped us overcome many of the potential difficulties of coil closure and ensured precise delivery at the desired site. The technique described here allows more than one coil to be deployed simultaneously (as was done in Case 1), and also allows retrieval and repositioning of all the coils if the initial position is not satisfactory.

Balloon occlusion of a coronary arterial fistula allows better visualization of the native branches by eliminating
distal run-off through the fistula (Fig. 1a). The combined strategy of bioptome-aided coil delivery along with balloon occlusion has the potential of closing large fistulas which would otherwise require occlusive devices or surgical operation. In addition to improved visualization of the native branches, balloon occlusion allows better control of the coil delivery process by eliminating flow at the distal end of the fistula. We kept the balloon inflated after coil deployment to allow clot formation.

Conclusions: This report demonstrates the feasibility of using bioptome-assisted coil delivery for closure of large coronary arterial fistulas. This method is a less expensive alternative to occlusive devices for large coronary fistulas that are not suited for closure by coil delivery. Balloon occlusion of the fistula allows better definition of the coronary anatomy and eliminates flow during and after coil deployment.

References


Familial Primary Pulmonary Hypertension

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Primary pulmonary hypertension is a rare disease affecting mostly females. We report a family where 2 of the 3 male children born to consanguineous parents had severe pulmonary hypertension of unexplained cause. The occurrence of overtly manifest primary pulmonary hypertension is rare in males, especially at an early age. (Indian Heart J 2002; 54: 193–195)

Key Words: Congenital heart disease, Pulmonary hypertension, Consanguinity

Of the 3 male children born to consanguineous parents, 2 presented with early onset of severe pulmonary hypertension of unexplained cause. This unusual variety of primary pulmonary hypertension (PPH), which is transmitted as an autosomal dominant trait, is presented for the rarity of overt presentation.

Case Report

A 10-year-old male child (SA) weighing 20 kg was found to have a heart murmur 2 years ago when he was evaluated for failure to thrive. He had dyspnea on effort—NYHA class II—for the past 3 years with no history of syncope, palpitation, chest pain or hemoptysis. He had no history of frequent respiratory infections in childhood. He was the second child of 3 offsprings born to consanguineous parents at full term by lower segment cesarean section. His weight at birth was 2.25 kg. Mental and motor development were normal. Physical examination revealed an undernourished child with a pulse rate of 96/min and BP of 100/60 mmHg. The jugular venous pulse (JVP) was normal; the apical impulse was of normal character in the fourth left intercostal space in the midclavicular line and parasternal heave was present. S1 was normal, S2 was loud and single, there was a pulmonary ejection click, and a grade 2/6 ejection murmur along the upper left sternal border. The lungs and abdomen were normal. Oxygen saturation by pulse oximetry was 97%. An electrocardiogram (ECG) revealed sinus rhythm, right axis deviation and right ventricular hypertrophy (RVH) with strain. Chest X-ray revealed mild cardiomegaly and features of pulmonary arterial hypertension (PAH).

Echocardiogram (Fig. 1) revealed enlargement of the right atrium (RA) and right ventricle (RV), intact septae, RV hypertrophy with preserved RV function, dilated pulmonary arteries, absent “a” waves and mid-systolic notching of the pulmonary valve on M-mode echocardiography, mild tricuspid regurgitation (TR) on color Doppler with a calculated RV systolic pressure of 140 mmHg. MRI scan revealed dilated pulmonary arteries (PA), dilated RA and RV with intact septae. The patient developed severe acute right ventricular failure with hypotension following a febrile illness, to which he succumbed.

The younger brother of the child discussed above (IK), aged 6 years, also presented with recurrent respiratory
infections from birth till 1 year of age and failure to thrive. He is the last of the 3 siblings born to consanguineous parents and had been delivered by cesarean section. He was treated for aspiration pneumonia in the immediate neonatal period. He never had dyspnea or syncope. Physical examination revealed mild central cyanosis, a pulse rate of 90/min, BP 110/90 mmHg, a normal S1, loud P2, pulmonary ejection click and no murmur. Pulse oximetry revealed an O2 saturation of 89%. The ECG showed sinus rhythm, right axis deviation and R VH with strain. Chest X-ray revealed mild cardiomegaly and features of pulmonary arterial hypertension. Echocardiogram (Fig. 2) revealed RA and RV enlargement, R V hypertrophy with dysfunction, mild TR (calculated R V systolic pressure of 120 mmHg) and right-to-left shunt across a patent foramen ovale. Cardiac catheterization revealed an O2 saturation of 89% at the RA, 100% at the left upper pulmonary vein; 90% at the left atrium (LA), 65% at the RV, 60% at the left pulmonary artery (LPA) and 86% at the femoral artery. The mean RA pressure was 12 mmHg, mean LA pressure 10 mmHg, RV pressure 115/10 mmHg, PA pressure 108/74 (mean 48) mmHg. The aortic pressure was 92/62 (mean 44) mmHg. The pulmonary vascular resistance (PVR) was 40 Wood units.

Both parents and the other sibling (male) are healthy with normal ECG, chest X-ray and echocardiogram. No other member in the family (traced back by history to two previous generations) had cardiac illness or sudden death. However, no specific search for involvement of relatives of probands was made for these patients.

**Discussion**

Primary pulmonary hypertension, characterized by obstruction of precapillary pulmonary arteries due to proliferation of endothelial and smooth muscle cells and vascular remodeling, is a rare disease affecting mostly females. The mean age at presentation is 36±15 years. Clinically overt familial PPH occurs in approximately 6% of cases of PPH. Inheritance is autosomal dominant with incomplete penetrance. The clinical, pathologic and demographic features, and prognosis of patients with familial PPH are said to be similar to those of sporadic PPH. This case report features a younger age of onset. Vertical transmission has been demonstrated to occur in as many as five generations in one family and is probably indicative of a single dominant gene. The locus of a gene linked to familial PPH has been identified on chromosome 2q31-q33. The low penetrance of this confers about 10%-20% likelihood of development of the disease.

It has also been found that asymptomatic carriers of the PPH gene with normal resting PA pressure manifest exercise-induced elevation—a surrogate marker for familial transmission of susceptibility of the pulmonary vasculature to an exogenous trigger. Stress Doppler echocardiography during supine bicycle exercise and genetic linkage analysis were performed on 52 members of 2 families with PPH. There were 4 patients of PPH; 14 members with normal resting PA pressure (23±4 mmHg) manifested an abnormal rise (56±11 mmHg). All these 14 members, but only 2 out of the rest of the asymptomatic family members showing normal response to exercise, manifested linkage to chromosome 2q31-q32.

Familial PPH is linked to the 3-cM region on chromosome 2q33 (locus PPH1). One of the genes, bone morphogenetic protein receptor-2 (BMPR2) gene, shows mutations leading to a defective bone morphogenetic protein-signaling pathway. BMP signaling may occur through both the "Smad" and nitrogen-activated protein kinase cascades, and both are inhibited by Smad6, which can be induced by vascular shear stress. Either (i) the reduced apoptotic signals from the BMP pathway caused by mutations in the BMPR2 gene or other molecules in the signaling cascades, or (ii) shear stress via Smad6, possibly after an initial nidus of vascular injury, might underlie many forms of PPH, including those associated with HIV or appetite-suppressant drugs. Abnormal fibrinolysis has been identified in one instance of familial PPH.

It has been observed that in familial PPH, more females had the PPH1 gene and more females with the gene developed the disease. This condition has also been described in family members born with hemoglobinopathies (the PPH
gene may be located near the gene responsible for beta globulin or the in situ thrombosis due to abnormal hemoglobin might have caused PAH) and in a family with familial platelet storage pool disease.

In conclusion, this report stresses the rarity of overtly manifest PPH. Occurrence in males and earlier age of onset are contrary to what has been commonly observed and described.

**References**


Brief Report

Left Ventricular Thrombi in the Presence of Normal Left Ventricular Function

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We report two cases of left ventricular thrombi identified by routine echocardiography in the presence of normal ventricular function to highlight the rarity and clinical significance of this condition. A 14-year-old boy, positive for anticardiolipin and antinuclear antibodies, was found to have a left ventricular thrombus. A 30-year-old male, who presented with a transient ischemic attack, was found to have hypereosinophilic syndrome and a mobile left ventricular thrombus. The thrombi disappeared in both patients after a few days of anticoagulant therapy without symptoms of embolization. (Indian Heart J 2002; 54: 196-198)

Key Words: Thrombus, Anticardiolipin antibody, Echocardiography

Left ventricular (LV) thrombi in the presence of normal ventricular function are uncommon. We report two cases of LV thrombi in the presence of normal LV function identified by echocardiography, to highlight the rarity of this entity and its clinical significance.

Case Report

Case 1: A 14-year-old boy was admitted with a 6-day history of fever, maculopapular rashes all over the body and arthralgia. He had received a course of crystalline penicillin from a local hospital. Blood counts were normal except for a borderline platelet count of 1.5 lac/cmm. The erythrocyte sedimentation rate (ESR) was persistently elevated (> 100 mm in the first hour). All cultures were negative. Tests for double-stranded DNA and anticardiolipin antibody were positive. Echocardiogram showed a mobile mass measuring 16×18 mm in size and normal LV contractility. He was started on oral anticoagulants preceded by heparin. Echocardiogram repeated on day 4 of admission showed that the mass had disappeared. The patient did not have any features of embolization. He was put on steroids and improved. He is asymptomatic after a 2-year follow-up.

Case 2: A 30-year-old male was admitted with a transient ischemic attack (left hemiparesis). Echocardiogram showed endocardial thickening and a mobile LV mass 10×20 mm in size (Fig. 1). His differential blood count revealed 62% eosinophils with an absolute eosinophil count of 2800/cmm. He showed no evidence of parasitic, allergic or neoplastic illnesses. The ESR was 45 mm in the first hour. Antinuclear antibody (ANA), anticardiolipin antibody and VDRL tests were negative. He was put on oral anticoagulants preceded by heparin and oral steroids. Echocardiogram repeated on day 3 of admission showed that the mass had disappeared. At 6-month follow-up, his eosinophil count was normal and repeat echocardiogram showed regression of the endocardial thickening. He has no residual neurological deficits.

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Fig. 1. Echocardiogram showing echogenic mass suggestive of thrombus in the apex of the left ventricle (arrows).
Discussion

Left ventricular thrombi usually occur in the presence of impaired LV function such as dilated cardiomyopathy, LV aneurysm and following a myocardial infarction. Normal LV contractility is a major factor in preventing the formation of thrombus because of the churning effect. Rarely, other causes which produce a thrombogenic milieu such as antiphospholipid antibody syndrome (APS) and protein C deficiency can lead to LV thrombus formation. Other conditions such as cardiac trauma, Salmonella septicartitis, myeloproliferative disorders and eosinophilic endocarditis can give rise to LV thrombi. Reports of LV thrombi occurring without any obvious heart disease are also mentioned in the literature.

Intracavitary echodense masses in the LV are considered to be thrombotic in nature. Full dissolution of the masses indicate that they are likely to be thrombotic. The size of the thrombus is likely to be more than the size measured on echocardiography, as only the central core is echogenic and can be measured.

The antiphospholipid syndrome (APS) is characterized by arterial and venous thrombosis. Four types of antiphospholipid antibodies (aPL) have been described—lupus anti-coagulant, antiphospholipid antibodies, anti-beta-2 glycoprotein-1 antibodies and false-positive serological test for syphilis.

Anticardiolipin antibody-associated thrombosis syndromemay exhibit both arterial and venous thrombosis, whereas in lupus anti-coagulant-associated syndrome, venous thrombosis predominates. The diagnostic criteria for APS includes at least one criteria each from clinical and serological categories and a positive aPL. Our patient satisfied the criteria for APS, and double-stranded DNA was positive. This may, therefore, be APS secondary to systemic lupus erythematosus.

Treatment of APS is aimed at neutralization or elimination of aPL. Steroids, immunosuppression, plasma exchange and immunoglobulins have been tried. Low-dose aspirin is recommended to prevent thrombotic events.

Idiopathic hypereosinophilic syndrome is an entity where there is elevation in the number of eosinophils with tissue toxicity manifesting as multisystem involvement. The tissue damage is produced by a major basic protein, eosinophil cationic protein, eosinophil peroxidase and eosinophil-derived neurotoxin present in the eosinophils.

A major cause of the morbidity and mortality due to this syndrome is the associated cardiac involvement. Typical cardiac findings include endocardial fibrosis and mural thrombus, which is most frequent in the apices of both ventricles. Valvular involvement is reported and cavity obliteration is seen in the later stages of the disease. The thrombus may extend up to the inflow tract of the atrioventricular valves, impede normal leaflet function and produce valvular regurgitation.

Hypereosinophilic syndrome is usually treated with steroids which give good remission rates. In patients who do not respond, immunosuppressives such as hydroxyurea and vincristine are the most commonly used drugs. Our patient also responded well to steroids with regression of endocardial thickening and reduction in eosinophil count.

In both the above cases, the thrombi disappeared after 3-4 days of anticoagulant therapy. Though early dissolution of thrombus has been reported, it is more likely that fragments of the thrombci had embolized downstream without any clinical consequences.

These two cases highlight the fact that routine echocardiography should be done in patients who have thrombotic tendencies and in young patients presenting with stroke.

References

6. Ommen Sr, Seward JB, Tajik AJ. Clinical and echocardiographic features of hypereosinophilic syndromes. Am J Cardiol 2006; 88: 110–113
7. Vagans SA, Fox KR, Kitchen JG 3rd. Left ventricular thrombus in
the absence of detectable heart disease. Chest 1989; 96: 426-427
Thromboembolism: A Rare Complication of Cardiac Hydatidosis

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A cardiac hydatid cyst is rare. We report a case of cardiac hydatid cyst localized in the atria which was diagnosed by two-dimensional echocardiography following a thromboembolic stroke. Surgical resection of the cyst was performed and histopathologic examination confirmed the diagnosis. (Indian Heart J 2002; 54: 199-201)

Key Words: Cardiac hydatidosis, Thromboembolism, Echocardiography

Hydatidosis caused by larval forms of the dog tapeworm Echinococcus granulosus rarely involves the heart. The reported incidence ranges from 0.5% to 2%. We report a case of cardiac hydatidosis associated with intracardiac thrombus formation and systemic thromboembolism that was successfully excised surgically.

Case Report
A 13-year-old boy presented with sudden onset of right-sided hemiparesis. There was no history of preceding fever, headache or head trauma. He was conscious and afebrile. Examination of the cardiovascular system revealed an ejection systolic murmur (grade 3/6) along the left sternal border. The resting electrocardiogram (ECG) showed normal sinus rhythm with left atrial enlargement, a QRS axis of +90° and incomplete right bundle branch block. Chest X-ray showed a dense retrocardiac shadow in the region of the left atrium and a cardiothoracic ratio of 55%. The lung fields were clear. Blood biochemistry results were within normal limits. Three blood cultures taken within one hour were normal. A transthoracic echocardiogram in the parasternal long-axis view showed a large, well defined, round, cystic mass with a central echolucent area and large, echo-dense mass (suggestive of a thrombus or vegetation) on its outer surface that prolapsed during diastole through the mitral orifice into the left ventricle (Fig. 1a). The apical four-chamber and modified parasternal short-axis views showed the cyst extending from the left to the right atrium across the interatrial septum, producing an hour-glass type of narrowing. Daughter cysts were seen within the main large cyst (Fig. 1b). All the valves were normal. No other cysts were seen in the heart. A spiral CT scan of the chest corroborated the echocardiographic findings and showed a thin-walled, bilobed, cystic mass 7 x 4 cm, predominantly in the right atrium extending across the interatrial septum into the left atrium (Figs. 2a, 2b). There was no evidence of pulmonary involvement. A coronary angiogram showed normal coronary arteries. A CT scan of the head showed an ischemic infarct in the left basal ganglia. There was no evidence of hydatidosis of the central nervous system. A CT scan of the abdomen revealed a 6 x 5 cm rounded mass in the liver with thin, internal septations. The other abdominal organs were normal. As the indirect haemagglutination test was negative for hydatidosis, the diagnosis was established on the basis of the imaging studies.

The patient was started on albendazole and enucleation of the cardiac cyst was planned. Six weeks later, the patient was taken up for enucleation of the cardiac cyst under cardiopulmonary bypass via a median sternotomy. Care was taken to avoid rupturing the cyst by using an angled-tip venous cannula. On opening the right atrium, a large cyst was seen extending into the left atrium across the interatrial septum (Fig. 3). Hypertonic saline was injected into the cyst to sterilize it. The left atrium was then opened and the cyst completely enucleated. It had a thrombus on its external surface. The interatrial septum was repaired using a pericardial patch.

The postoperative period was uneventful and the patient was discharged on postoperative day 10. At follow-up after 4 weeks, a repeat echocardiogram showed no evidence of an intracardiac cyst and neurological examination showed near-normal power on the right side. Histopathological examination confirmed the diagnosis of hydatid cyst.

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Hydatidosis in humans (intermediate host) occurs when the eggs of *Echinococcus granulosus* from canine (definitive host) faeces are accidentally swallowed. Onchosphere larvae hatch in the duodenum and are carried to the liver through blood vessels or lymphatics. About 65% are trapped in the liver (first filter); the remaining pass through it. Of these, 25% are trapped in the lungs (second filter) and less than 10% reach various organs through the systemic circulation. Only about 0.5%–2% of hydatid cysts are found in the heart.³ Hydatid cyst of the heart is rare because contraction of the heart provides natural resistance to the presence of viable cysts.³ The heart is usually involved due to contamination from the systemic, coronary or pulmonary circulations, or direct extension from neighboring structures.³ A hydatid cyst of the heart is predominantly found in the following locations: left ventricle (75%), right ventricle (18%) and interventricular septum (7%).⁴ Cysts in the pericardium, right atrium,⁵ and left atrium⁶ are extremely rare and the clinical picture depends on the location, size and integrity of the cysts. The majority of patients with cardiac hydatidosis are asymptomatic. Chest pain is usually the most common complaint, probably due
also been reported.9,10 Sudden death may occur, the reported simulating mitral, tricuspid and aortic valvular disease have result of compression by the cyst.8 Large cystic masses have also been reported.12 Emboli are usually composed of cerebral embolism of ruptured left-sided cysts caused by intracerebral embolism of cardiac hydatidosis.9,10 Our patient had a combination of two rare entities—firstly, localization of the cyst in the atria and secondly, cerebral embolism secondary to a thrombus formed on the surface of the unruptured cyst.

Two-dimensional echocardiography is the best diagnostic procedure for demonstration of cardiac hydatid cysts.14 On echocardiography, a unilocular cyst with well-defined margins and internal trabeculations corresponding to daughter cysts is diagnostic of an echinococcal cyst.15 CT scan shows the anatomic extent of the mass and its relation to cardiac and extracardiac structures. Coronary angiogram helps in excluding coronary involvement, often totally missed on echocardiographic examination.

No effective chemotherapy is known against larval infection. It is generally accepted that treatment of cardiac hydatidosis is surgical because of the fear of sudden death. In our patient, because of the high risk of repeat systemic thromboembolism as well as that of rupture, the cyst was surgically removed after sterilizing its contents, with due care taken to avoid spillage.

References

Phasic narrowing of the coronary arteries on angiography is a well-known entity in both children and adults and has been described in relation to all epicardial arteries. There is a high incidence of myocardial bridges in hypertrophic cardiomyopathy. We report the case of a 6-year-old girl with hypertrophic obstructive cardiomyopathy who had extrinsic obstruction of the left main and right coronary arteries. (Indian Heart J 2002; 54:202–205)

Key Words: Myocardial bridge, Coronary artery disease, Hypertrophic cardiomyopathy

Myocardial bridge (MB) is described as the systolic compression of an epicardial coronary arterial segment by the overlying myocardium. It is frequently found in patients with hypertrophic obstructive cardiomyopathy (HOCM). Bridging is associated with increased septal hypertrophy, a high ratio of interventricular septum to posterior wall thickness, and a higher left ventricular outflow tract (LVOT) gradient. Myocardial bridge most commonly involves the left anterior descending (LAD) artery although it has been described in other epicardial vessels. It is rare to have an MB of the left main coronary artery (LMCA).

Case Report

A 6-year-old girl presented with a history of transient episodes of giddiness. There was no history of chest pain, breathlessness on exertion or loss of consciousness. There was no family history of sudden cardiac death or heart disease. She had clinical features of Noonan’s syndrome—short stature, webbing of the neck, low-set ears and hypertelorism. On examination, she was of average build and weighed 17 kg. Her systemic blood pressure was 108/66 mmHg in the right upper limb. She had a grade 3/6 mid-systolic murmur at the left sternal base that increased on standing from a squatting position and by the Valsalva maneuver. Chest X-ray showed a cardiothoracic ratio of 60% with mild pulmonary venous congestion, and the ECG showed a normal sinus rhythm, normal axis with biventricular hypertrophy, PR interval 0.12 s, and QTc 0.43s (normal for age and sex). On echocardiography, she was found to have HOCM with an LVOT gradient of 50 mmHg and a right ventricular outflow tract (RVOT) gradient of 140 mmHg with biventricular hypertrophy. Systolic anterior motion of the mitral valve was seen. The ratio of the interventricular septum to left ventricular posterior wall thickness during diastole was 1.3. On echocardiography, the anatomy of the coronary arteries was abnormal. The right coronary artery (RCA) had a discrete tight narrowing at its origin and the LMCA appeared to have a dynamic obstruction with acceleration of color Doppler flow. Cardiac catheterization and angiography were done under sedation with access through the right femoral vein and right femoral artery. Arterial oxygen saturation was 100% and there was no step-up of oxygen at any level. Angiography showed systolic compression of the proximal part of the LMCA and ostial stenosis of the RCA (Figs 1, 2 and 3). Other branches of the coronary arteries were normal. Pressure study showed a gradient of 86 mmHg across the RVOT (right ventricle 128/14 mmHg, pulmonary artery 42/29 mmHg) and a gradient of 30 mmHg across the LVOT (left ventricle 116/15 mmHg, ascending aorta 86/55 mmHg).

As the patient had significant LVOT and RVOT gradients and severe narrowing of the coronary arteries, it was decided that she should undergo surgical repair. Transatrial excision of the right-sided septal hypertrophy and deroofing of the membrane over the coronary arteries (enlargement of the ostia of the RCA and LMCA with bovine pericardium) were done. Resection of the LVOT was not done as the LVOT gradient was not significant.
The postoperative course was uneventful. Postoperative echocardiography showed no evidence of obstruction in either the LMCA or RCA. The LVOT and RVOT gradients were 25 mmHg and 30 mmHg, respectively. Angiography showed well-opened coronary ostia with good antegrade flow and no residual stenosis (Figs 4–8). A pressure study showed no significant gradients across the outflow tracts (RV 42/10, RVOT 32/8, PA 25/8, LV 102/15, ascending aorta 90/45 mmHg). The child was discharged on postoperative day 10.

Discussion

Myocardial bridge was first reported by Geiringer in 1951 and was angiographically demonstrated by Portsmann in 1960. It is defined as an anatomical entity in which a segment of the epicardial coronary artery becomes engulfed by myocardial fibers. Angiographically, it is described as any degree of systolic narrowing of a coronary artery observed in at least one angiographic projection. The
clinical manifestation of MB is due to the result of a reduction in the myocardial blood flow not only during systole but persisting throughout or a major part of the diastole leading to ischemia. The ischemia may be more during strenuous physical activity which may even precipitate malignant ventricular arrhythmias. The incidence of MB ranges from 1% to 10% of coronary angiograms. In an autopsy study, the incidence ranged from 15% to 86%. There is a high incidence of MB in patients with HOCM and it can be documented in up to 50% of cases. Myocardial bridges, at multiple sites has also been reported, which usually has a poor prognosis. The commonest site of MB is the LAD; other arteries are rarely involved. Our case is a rare example simulating MB in the LMCA and RCA in a case of HOCM. There is no documented literature available regarding an MB in the LMCA. The exact mechanism by which an MB occurs in the LMCA is not clear, but intraoperatively we found that there was a thick membrane over the origins of the LMCA and RCA, which was resected during surgery. Since we did not carry out histopathologic examination of the membrane, we cannot state whether it was a membrane or a muscle band. On
Fig. 8. Postoperative right coronary artery angiogram in the left anterior oblique view with cranial angulation (55°, 20°) shows a well-opened right coronary artery ostium.

After postoperative angiography, the opened vessels could be clearly seen. It may be debatable to label this child as having an MB as there was a thick membrane over the coronary arteries. The diagnosis of MB was made on angiography alone. As the LMCA and RCA do not lie over the ventricles, it is questionable whether MB can occur at these sites. Hypertrophy of the muscles in patients with HOCM may be responsible for producing thick muscle bands over the origins of the LMCA and RCA.

Sudden cardiac death (SCD) can be one of the presentations of HOCM. The incidence ranges from 4% to 6% and mainly affects young and often asymptomatic patients. Myocardial bridge is an important predisposing factor for SCD in HOCM. Other risk factors of SCD in HOCM patients include nonsustained ventricular tachycardia and a strong family history of SCD.

If the vessel obstruction leads to myocardial ischemia, MB may require interventional therapy. However, this is rare as myocardial perfusion occurs mainly during diastole. It is recommended that in patients with HOCM, resection of an MB should be done even in the presence of atypical symptoms due to the poor prognosis associated with this condition. Surgical unroofing of an MB may reduce the chances of SCD.

Our patient did not have any symptoms other than mild giddiness. However, since she had HOCM and suspected to have an MB in the main coronary arteries, surgical resection of the bridging myocardial tissue was considered to be the best option.

As patients with HOCM have a high incidence of MB, they should be screened for coronary abnormalities and, if these are detected, such patients should be managed by appropriate intervention.

References
Reduction of Pacemaker-Induced Pectoral Muscle Stimulation Using an Insulating Patch

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An 82-year-old female patient was admitted for replacement of her pulse generator battery which had reached an end-of-life situation. The old unipolar leads were retained. Pectoral muscle stimulation began shortly after implantation. Though complete abolition of muscle stimulation was not achieved, an insulating patch placed between the muscle and the pacemaker can reduced stimulation. (Indian Heart J 2002; 54: 206–207)

Key Words: Muscle stimulation, Insulation patch, Pacemaker

Implantable pulse generators have been the preferred method of treatment for various forms of bradycardia since the 1950s. In the US alone, over 300,000 pacemakers were shipped in 1999, representing a growth rate of 30% over the previous year. Many patients undergo procedures to replace pacemaker units that have reached end-of-life (EOL) situations. Physicians sometimes face challenges while adapting older technologies to current models after several generations have been developed since the initial implant. This article discusses one instance of this dilemma in which muscle stimulation was caused by a retained unipolar lead and a replacement pulse generator.

Case Report

An 82-year-old woman was admitted for change of her pulse generator battery which had reached an EOL situation. The original pulse generator had been implanted in 1984 for the treatment of complete heart block. The patient was implanted with a Spectrax SXT 8423 unipolar pacemaker (Medtronic, Minneapolis, MN) and a Medtronic Target Tip 4011-58 tined ventricular transvenous lead with a 5 mm connector block. Venous access was via the left subclavian vein with the pacemaker pocket in the left infraclavicular area. This pulse generator battery was replaced in 1995 with a Medtronic 8941 unipolar pacemaker due to battery depletion. The original lead was retained.

In August 2000, the second pulse generator was replaced. The patient was very frail and had very little subcutaneous fat in the pectoral area. Considering the frail condition of the patient, the risk of pneumothorax and other potential complications, the implanting surgeon decided to retain the original Target Tip lead. The lead was still functional though the impedance was 385 Ω based on a measured current at 2.6 mA. The generator paced and sensed well with a pulse width of 0.5 ms and threshold at 1.0 V amplitude. The upper and lower rates were set at 120 ppm and 60 ppm, respectively, in the VVIR mode. The sensitivity for measuring intrinsic R waves was set at 2.8 mV.

Muscle stimulation of the left anterior chest wall began shortly after implantation, 4–5 cm from the midline. The output voltage could not be lowered sufficiently to abolish stimulation as well as achieve pacing efficacy. Increasing the pulse width was also not efficacious. A 2x safety margin was followed since the patient was completely pacemaker-dependent.

The replacement pulse generator did not have a nonconductive paralene coating on one surface, which contributed to the pacing of the muscle. A 3" square mesh of Gore-Tex (WL Gore & Associates, Flagstaff, AZ) was placed over the chest wall under the pacemaker battery. The patch was sutured to the pectoral muscle fascia using several interrupted 3-0 GI silk sutures. The pacemaker can was placed over this and sutured to the chest wall with a 2-0 silk suture through the mesh. This reduced stimulation of the muscle but did not completely abolish it.

After hemostasis and irrigation with sterile saline solution, the pocket was closed normally. The patient tolerated the procedure well.
Discussion

This case represents a method for adapting an uncoated pulse generator to a retained unipolar lead. Generally, a unipolar system consists of an electrode tip which stimulates the heart (cathode) and the pacemaker can that serves as the reference (anode). A bipolar stimulating device has the cathode and anode at the stimulating tip in the form of a ring, as shown in Fig. 1. Because the unipolar system uses the pacemaker can as a common anode, the can itself is typically coated with a nonconductive paralene coating which serves as insulation. Traditionally, unipolar pulse generator systems are manufactured with the paralene coating but are generally not used with bipolar systems. In this instance, the Gore-Tex patch served as the insulating material.

Insulation of the can was preferred over using a new lead because of the extremely frail condition of the patient and the increased risk of pneumothorax. If a new lead system is considered, the old lead is usually left in place because of potential complications. A new lead could have been inserted from the opposite side; however, this was not considered to be a good option because of the frailty of the patient.

The solution in this case did not lead to a complete abolition of pectoral muscle stimulation. However, the patient did not complain of discomfort or pain after the surgery. Since the pacemaker was efficacious for the treatment of complete heart block, the patient was in better condition after the implantation than before. This case demonstrates the possible need for device designers to reinvestigate the use of the paralene coating for this type of condition. An alternative may include the use of a Parsonnet pouch (Bard, Covington, GA), a polyester boot which fits over the pacemaker and prevents pulse generator migration and extrusion, and may provide some insulation.

Other possible causes of pectoral muscle stimulation that have been reported in the literature include defective coating, insulation defects, superfast recharge pulse, spontaneous rotation, lead dislodgement, or break in lead insulation.

References

An unusual form of hypertrophic cardiomyopathy (HCM) localized to the left ventricular (LV) apex was first described in Japan in 1976. Apical HCM is distinctly uncommon in other parts of the world and probably constitutes 1%–2% of those with HCM. In Japan this apical variant of HCM constitutes about 25% of patients with HCM.

Takayasu’s arteritis is a nonatherosclerotic, nonspecific inflammatory disease of the aorta with or without involvement of its branches producing occlusion/narrowing or aneurysm formation. The majority of cases of Takayasu’s arteritis are reported from Japan, South-east Asia and Africa.

We present an interesting report of a patient who had Takayasu’s arteritis and apical hypertrophic cardiomyopathy. To the best of our knowledge, the association of both entities in the same patient has not been reported till date.

**Case Report**

A 36-year-old male patient was referred to our institute with complaints of claudication of both limbs and breathlessness on exertion (New York Heart Association [NYHA] functional class II). He was detected to have moderate systemic hypertension one year back and is a non-smoker and not a known diabetic. There was no family history of similar symptoms.

Physical examination revealed absent arterial pulses in the right carotid artery, right upper limb and both the lower limbs. Blood pressure in the left upper limb was 160/99 mmHg. Cardiovascular examination revealed a heaving apical impulse in the left 5th intercostal space in the midclavicular line. The first and second heart sounds were normal and a prominent fourth heart sound was heard. An ejection systolic murmur of grade 2/6 was heard at the apex.

Biochemical parameters showed elevated blood urea (78 mg%) and creatinine (2.4 mg%). The erythrocyte sedimentation rate was 12 mm in the first hour and the C-reactive protein was <6 mg/L. The other hematological parameters were also within the normal range. Chest X-ray showed a cardiothoracic ratio of 60% and an LV contour of the cardiac apex. Electrocardiogram (ECG) showed sinus rhythm with QRS axis of +60° and absent septal Q waves. Increased QRS voltage was noted in leads V1–V6, ranging from 30 to 38 mm. Giant negative T waves were noted in leads V3–V6 measuring 6–12 mm in depth (Fig. 1).

Transthoracic echocardiogram showed a grossly thickened LV apical myocardium with obliteration of the apical portion of the LV cavity (Fig. 2). The LV apical thickness was 23 mm while septal and posterobasal thickness were 10 and 11 mm, respectively. There was no systolic anterior motion of the anterior mitral leaflet or mitral regurgitation. On Doppler evaluation of mitral inflow velocities, the ratio between early diastolic flow (E) and atrial systolic flow (A) was less than 1. Transesophageal echocardiographic examination clearly delineated the gross LV apical myocardial hypertrophy giving it the classical appearance of “ace of spades” (Fig. 3).

The patient underwent cardiac catheterization through the left brachial arterial approach. The pulmonary arterial
pressure was 30/12 mmHg, mean pulmonary capillary wedge pressure was 20 mmHg, LV pressure at the mid-cavitary and outflow tract was 166/32 mmHg and the central aortic pressure was 166/99 mmHg. There was no gradient in the LV mid-cavitary or outflow tract.

Coronary angiogram revealed normal coronary arteries. An aortic arch angiogram showed total obliteration of the right brachiocephalic trunk with mild diffuse narrowing of the left subclavian and common carotid arteries (Fig. 4). Abdominal aortogram showed a diseased renal segment of the aorta with total occlusion of the infrarenal segment.

Fig. 1. Twelve-lead electrocardiogram showing increased QRS voltage with giant negative T waves in the chest leads.

Fig. 2. Two-dimensional apical four-chamber transthoracic echocardiogram demonstrating LV apical hypertrophy (arrows). LA: left atrium; LV: left ventricle; RA: right atrium; RV: right ventricle.

Fig. 3. Transesophageal echocardiogram in vertical axis showing grossly thickened LV apex (arrows) with classical "ace of spades" appearance of LV. LV: left ventricular; LA: left atrium

Fig. 4. Aortic arch angiogram in anteroposterior view showing totally occluded right brachiocephalic trunk (arrow), diseased left common carotid and left subclavian arteries.

The inferior mesenteric artery was enlarged, stenosed at its origin and gave rise to a prominent artery of Drummond. The left renal artery showed diffuse severe stenosis with a thread-like appearance while the right renal artery had mild disease at its origin (Fig. 5). Due to the high LV end-diastolic pressure (LVEDP) and to limit the contrast load in view of elevated renal parameters, an LV angiogram was omitted.

The patient is being managed conservatively in view of the extensive vascular involvement due to Takayasu’s arteritis and deranged renal function.

Discussion

In Takayasu’s arteritis, the myocardium can be affected secondary to systemic hypertension or involvement of the coronary arteries, valves or pulmonary arteries. Primary
involvement of the myocardium in the form of myocarditis and dilated or congestive cardiomyopathy has been reported in different series. Concentric LV hypertrophy can occur secondary to systemic hypertension in these patients, but apical HCM has not been noted in any of the published series of this entity. We feel that the apical HCM in this patient is unrelated to the coexisting aortoarteritis.

Systemic hypertension in patients with apical HCM has been noted in different series. However, systemic hypertension is unlikely to be a significant etiological factor in the development of localized apical hypertrophy in these patients.

The ECG findings are the most characteristic in patients with apical HCM. The most conspicuous findings are high QRS voltage with absence of septal Q waves as well as extremely deep inverted T waves in the precordial leads, especially in leads V₆ and V₇, where the apical segment potentials are most clearly reflected. Our patient's ECG depicted all these classic features.

The distinctive LV appearance of "ace of spades" on left ventriculography has been used to confirm the diagnosis of apical HCM. However, echocardiography is being increasingly used for the diagnosis of this condition. Transesophageal echocardiography is found to be more sensitive in detecting LV apical hypertrophy than transthoracic echocardiography, as it provides high-resolution images of all segments of the LV, particularly the apex. Recently, intravenous contrast echocardiography, which improves delineation of the endocardial border, has been proposed as the technique of choice for the diagnosis of apical HCM where conventional echocardiography fails to detect it.

Echocardiographic assessment consistently shows normal or hyperdynamic left ventricular systolic function in patients with apical HCM. However, diastolic function is abnormal with slow early ventricular filling associated with increased dependence on atrial contraction and late diastolic filling. This may lead to left atrial dilatation and atrial fibrillation.

However, the patient being discussed is unique in having a severe form of aortoarteritis along with apical HCM. The diastolic LV dysfunction secondary to apical HCM may further worsen due to the increased afterload caused by diffuse involvement of the aortic arch and descending thoracic aorta, and systemic hypertension due to Takayasu's arteritis. Diastolic dysfunction with grossly elevated LVEDP might well be responsible for the complaint of dyspnea on exertion in our patient.

Besides management of systemic hypertension and its complications, steroids and immunosuppressive agents such as methotrexate and cyclophosphamide are used to suppress disease activity. Surgical bypass or percutaneous transluminal angioplasty procedures are being carried out with varying success for occlusive arterial lesions. Our patient had fibrotic occlusive arterial disease with no clinical or hematological evidence of active disease. In view of the extensive vascular involvement along with deranged renal function, the patient is being managed conservatively.

References
Drug-Eluting Stents in the Treatment of Atherosclerotic Coronary Heart Disease

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In the past decade, coronary stenting has become the most commonly employed technique for percutaneous treatment of atherosclerotic heart disease and currently accounts for more than 75% of all procedures performed worldwide. However, although stenting was demonstrated to effectively reduce the rate of restenosis when compared to balloon dilatation, in-stent restenosis remains the major late-term limitation of this technique. Occurring in 15%–35% of cases, it frequently presents a challenging clinical problem, with a high recurrence rate in its most complex forms, regardless of recent developments in coronary brachytherapy. Therefore, there is a need for effective prophylactic as well as therapeutic strategies to treat in-stent restenosis.

Pathophysiology of Restenosis
In-stent restenosis is considered to be the result of neointimal hyperplasia alone, which is mainly due to intima-derived smooth muscle cells and extracellular proteoglycan matrix. Several cellular and molecular events have been identified to occur sequentially after the vascular injury caused by stent implantation. Shortly after the procedure, fibrin deposition, platelet activation and thrombus formation take place. The process also involves acute inflammatory cells, granulation tissue formation and the local release of a large number of substances, including chemotactic and growth factors, and oxygen-derived free radicals, which trigger a complex array of events that modulate matrix production and cellular migration and proliferation, ultimately leading to neointima formation. Recently, neointimal tissue was demonstrated to have a peculiar gene expression profile, distinct from control specimens of nonrestenotic arterial segments.

Prophylaxis for Restenosis
Multiple systemically administered drugs with different pharmacological properties (e.g. antiplatelet, antithrombotic, anti-inflammatory and antiproliferative) have been tested in humans. Almost all such substances have proven ineffective for the prevention of in-stent restenosis. Troglitazone, which was associated with neointimal reduction in a recent small study, was the exception. However, systemic administration may limit the efficacy of the treatment due to the localized nature of the restenotic process. Instead, local administration of anti-restenotic drugs seems to be an attractive approach that may potentially reduce the many limitations of systemic treatment.

The strategy of local drug administration utilizing the stent itself as the delivery platform has some theoretical advantages. Since the drug and stent are delivered as a complex, its action begins at the time of vessel injury, and additional interventions or manipulations are not needed. However, the metal structure of the stent does not allow easy drug binding and delivery. Although in some reports the tested drug was directly adjoined to the stent (e.g. by dipping the stent in an active solution), a more effective delivery vehicle was needed. Strict pharmacologic and mechanical requirements must be fulfilled to guarantee drug release in a predictable and controlled fashion over a time period. In earlier studies, polymers have shown conflicting results in the experimental setting, with some provoking severe tissue response. However, at present these problems have been controlled and safe delivery vehicles for drug-eluting systems are available. This review focuses on the results of recently published clinical trials and currently ongoing studies of drug-eluting stent systems.

Drug-Eluting Stents
Due to the similarities between neointimal growth and some aspects of tissue reparation and tumoral biology, antiproliferative and antitumoral drugs seem to be the logical choices. The agents currently tested with stents have been accepted for clinical use in cancer treatment and post-transplantation immunosuppression.
**Actinomycin-D**: Actinomycin-D (C62H86N12O16; Cosmegen®) is an antibiotic used for its antiproliferative properties in the treatment of various malignant neoplasms and has been marketed worldwide for almost 40 years. Actinomycin-D is a protein synthesis inhibitor at the transcriptional level that blocks cellular proliferation by forming a stable complex with double-stranded DNA (via deoxyguanosine residues), thus blocking DNA-directed RNA synthesis.

Currently, there are no published data regarding the use of actinomycin-D for the treatment of coronary artery disease and/or restenosis. The Phase 1, randomized clinical trial “ACTinomycin eluting stent Improves Outcomes by reducing Neointimal Hyperplasia” (ACTION) was started in June 2001 to evaluate the safety and performance of the Multi-link tetra™-D stent system. A total of 360 patients were randomized to 3 arms and received: (i) a high-dose actinomycin-D coated stent (10 µg/cm² of metal surface area), (ii) a low-dose actinomycin-D coated stent (2.5 µg/cm² of metal surface area) or (iii) a non-coated stent. Inclusion criteria were treatment of de novo lesions in native coronary arteries with a vessel caliber of 3.0–4.0 mm. Six-month angiographic follow-up was expected to be completed in June 2002 and the 12-month clinical follow-up was expected to be completed by the end of 2002. However, in March 2002, this study was interrupted prematurely by the safety committee due to a higher incidence of restenosis in patients treated with the actinomycin-D-eluting stent. The US pivotal study, the OPEN trial, plans to randomize patients to either control or coated stents. The dose of actinomycin-D to be used will be determined by the 6-month results from the two drug-treated groups of the ACTION trial. The primary end-point of OPEN will be target vessel revascularization (TVR) at 9 months.

**Paclitaxel**: Paclitaxel (Taxol®) is an antitumoral drug naturally extracted from the bark of the Pacific yew Taxus brevifolia. Its antineoplastic properties are mainly related to a unique effect on the microtubular function. Microtubules are formed by polymers of tubulin in a dynamic equilibrium of alpha and beta subunits, and their principal function is the formation of the mitotic spindle during cellular division. Furthermore, microtubules help to maintain the cell shape, and are intimately related to the functions of intracellular transport, signaling, protein secretion and motility. Paclitaxel induces abnormal polymerization of tubulin, forming stable dysfunctional microtubules and thereby disrupting these cellular processes that rely on prompt depolymerization of the microtubules. Thus, paclitaxel is an antiproliferative agent that blocks the mitotic cycle at the metaphase/anaphase transition. The taxol derivative QP2 (7-hexanoyltaxol) has similar properties and has also been tested for the prevention of restenosis.

In experimental models of restenosis, local administration of paclitaxel led to significant neointimal reduction, with a clear dose-dependent effect. However, although associated with more pronounced neointimal inhibition, exposure to higher doses was shown to eliminate direct contact between stent struts and the medial wall, implying an enlargement of the vessel wall relative to the stent, even though no aneurysmal dilatation was observed.

Several clinical trials utilizing paclitaxel-eluting stents (or its derivative QP2) have been already published or are currently being conducted. The Taxus Trial family is a series of studies utilizing the NIR or Express stents coated with paclitaxel (Boston Scientific/Scimed Corp., Maple Grove, Minn). The already concluded Taxus-I trial is a safety study that randomized 61 patients with de novo lesions for implantation of NIR bare stents or NIR Conformer stents eluting paclitaxel in a slow-release formulation (1.0 µg/mm²). At 6 months, there were no major events in the active treatment group versus 6.7% of cumulative events in the bare stent group of patients (p=0.24). The restenosis rate was 0% in the taxol group versus 10.3% in the bare NIR group (p=0.11). No edge effect was observed. Taxus-II is an efficacy study that enrolled 532 patients with de novo short lesions. Sequential slow and moderate paclitaxel-releasing NIR Conformer stents were tested, the primary objective being volumetric intravascular ultrasound (IVUS) findings. Final results are expected at the end of 2002. Taxus-III is a feasibility study that enrolled 30 patients with in-stent restenosis treated with NIR Conformer stents in a slow-release formulation. The primary objective is major adverse cardiac events (MACE) at 30 days.

The EvalUation of paclitaxel Eluting Stents (ELUTES) trial was a double-blind, efficacy study that evaluated paclitaxel-coated V-Flex™ stents (Cook Inc, Bloomington, IN) in 190 patients with de novo lesions. No polymeric vehicle was utilized and the drug was directly applied to the stents. Bare and coated stents in 4 doses (from 0.2 µg/mm² to 2.7 µg/mm²) were compared and a dose-dependent effect was observed at a 6-month angiographic evaluation. Percent diameter stenosis ranged from 34% for the bare stent, to 33%, 26%, 23% and 14% for ascending dose densities of the paclitaxel-coated stents. The restenosis rate was 21% in the group treated with bare stents and 3% in the group receiving the 2.7 µg/mm² stent (p=0.055). The
percent stenosis was 34% in the control group and 14% in the high-dose group (p<0.01). However, event-free survival at 6 months was not different between the two groups. No late thrombosis was reported.24 The A Sian Paclitaxel-Eluting Stent Clinical Trial (ASPECT) included 177 patients with de novo lesions submitted to implantation of Supra G™ stent (Cook Inc, Bloomington, IN) and randomized to no-drug or to paclitaxel at two different doses (low-dose density: 1.3 mcg/mm² and high-dose density: 3.1 mcg/mm²). No additional vehicle was used and the active drug was directly bound to the stent. A significant reduction of in-stent neointimal hyperplasia was observed in both the active treatment groups, with a more pronounced effect in the high-dose group of patients. Binary restenosis was observed in 27%, 12% and 4% in the groups with bare low-dose and high-dose stents, respectively (p<0.001).27 Additionally, the Paclitaxel-eluting stENT for CYtostatic Prevention of Restenosis (PatenCy) pilot study is now enrolling 50 patients who will be randomized to two arms to study the effects of the 3 µg/mm² paclitaxel-coated Logic stent (Cook Inc, Bloomington, IN) versus controls.

The taxol derivative QP2 was evaluated in some clinical trials. In a pilot study, the QuaDS-QP2 stent (Quanam Medical Corp) was evaluated by serial IVUS analyses (immediately after intervention and at follow-up at 8.3 months) in 15 native coronary lesions. The stent was prepared with multiple polymer sleeves that slowly release QP2. At follow-up, only mild neointimal proliferation was observed, with a mean neointimal area within the stent of 1.2±1.3 mm².23 In another series, the QuaDS-QP2 stent containing up to 4000 µg of QP2 was implanted in 32 patients. Among these, 13 patients underwent follow-up angiographic and IVUS studies (11.2 months; range 6–15 months) and no significant proliferation was observed within the stents. A total of two re-interventions have been required in the 32-patient study group, and both relate to either new disease or to distal, small-vessel disease beyond the stent.28 Based on the results of this pilot study, the controlled, randomized trial SCORE was conducted in western Europe. In this study, 266 patients were randomized to receive a QuaDS-QP2 stent or a bare stent. However, this trial was stopped by the safety committee because of an excessive adverse event rate in the QuaDS-QP2 stent group of 13% at 30 days, with a subacute stent thrombosis rate of 8%. These complications have been credited to the polymer sleeves of the stents.29 Late stent thrombosis was seen in a patient submitted to QuaDS-QP2 stent implantation. Angiography at 6 months showed complete absence of intimal hyperplasia and ticlopidine was discontinued. The patient was admitted with thrombotic stent occlusion after 15 days.30

Rapamycin: Rapamycin (Sirolimus; Rapamune®), produced by Streptomyces hygroscopicus, is a macrolide antibiotic with a potent immunosuppressive action. It was approved by the US Food and Drug Administration in September 1999 for use in renal transplant recipients. Rapamycin blocks cell cycle progression at the G1 to S transition, thereby inhibiting cellular proliferation. Its action is mediated by binding to an intracellular receptor, the FK506 binding protein (FKBP12). The complex rapamycin–FKBP12 then inhibits the activity of a specific kinase named mammalian target of rapamycin (mTOR), which prevents mitogen-induced downregulation of p27Kip1 by an unknown mechanism.31,32 Additionally, evidence derived from experiments with p27Kip1 knockout mice suggested that inhibition of smooth muscle cell proliferation by rapamycin–FKBP12 may also operate in a subset of cells via a pathway that is independent of p27Kip1.31 Human neointimal tissue extracted during atherectomy exhibited a peculiar upregulation of FKBP12 at the mRNA and protein levels, indicating a niche for rapamycin action in coronary restenosis.11 Accordingly, systemic and local administration of rapamycin in porcine models of restenosis were reported to be associated with a significant reduction of neointimal hyperplasia.33,34

The First In Man sirolimus-coated stent implantation (FIM) study was a registry of 45 patients with de novo lesions submitted to implantation of Bx Velocity™ stents (Johnson & Johnson—Cordis® unit) coated with sirolimus.35 Two different formulations of stents were utilized. A fast-release preparation permitted total drug elimination by 15 days and a slow-release preparation maintained drug delivery for >28 days. The total dosage of sirolimus was not different between the two formulations (140 µg/cm²), which differed according to the polymer coating. Thirty patients were treated in São Paulo, Brazil (15 patients with fast-release and 15 patients with slow-release stents) and were submitted to angiographic and volumetric IVUS evaluation at 4 and 12 months. Fifteen patients were treated in Rotterdam, the Netherlands (all with the slow-release stent) and were submitted to angiographic and IVUS control at 6 months. In the latest evaluation available (either at 6 months or at 12 months), there was no restenosis and in-stent neointimal hyperplasia, as analyzed by ultrasound, was negligible (~2% of volume obstruction). No edge effect was observed in the segment proximal and distal to the stent.36,37

The RA Ndomized study with the sirolimus-coated Bx VE Locity™ balloon-expandable stent in the treatment of
patients with de novo native coronary artery lesions (RAVEL) was a multicenter, prospective, randomized, double-blind trial that compared the outcome of 238 patients with de novo lesions submitted to implantation of either bare stents or drug-eluting stents. At 6 months, the restenosis rate in the drug-treated group was zero, the loss in minimal luminal diameter was zero and there was no target lesion re-intervention. Event-free survival at 6 months was 96.7% for the sirolimus group and 72.9% for the bare stent group (p<0.001). The SIRIUS trial is an ongoing study conducted in the US that randomized 1100 patients with focal de novo native coronary arterial lesions to treatment with rapamycin-coated or baremetal Bx Velocity™ balloon-expandable stents. The primary end-points of the SIRIUS trial are target vessel failure (death, myocardial infarction, target lesion revascularization) at 9 months. In addition, secondary end-points are core laboratory analysis of angiographic and IVUS data to determine treatment effects on neointimal hyperplasia and in-stent restenosis. Preliminary results of the first 400 patients included in the trial were presented in the Paris Course on Revascularization 2002 (Leon M, Moses J, EuroPCR, May 2002). For these patients, repeat revascularization at 9 months was 4.1% in the sirolimus-eluting stent arm versus 16.7% in the bare stent cohort (p<0.001). In-stent restenosis at 8 months was 2% and 31% in the sirolimus and non-coated stents, respectively (p<0.001). Final results are expected by the end of 2002.

**Limitations**

Although the principle of stent implantation is well established and most of the applied drugs and polymers have been used in clinical practice for a long time, there is little experimental and only preliminary clinical knowledge of the acute and long-term effects of drug-eluting stents in the coronary arteries. Several theoretical concerns and open questions remain to be addressed in the future. The pharmacokinetics of local intracoronary drug delivery by eluting stents probably obeys very specific mechanisms that may be influenced not only by drug composition and concentration, but also by factors such as stent design and homogeneity of strut placement. Therefore, each drug-polymers–stent complex may present a peculiar profile of interaction with the vessel wall and plaque at the treated segment.

Histologic findings compatible with incomplete healing have been observed in animal studies with paclitaxel. However, no cases of late stent thrombosis (which could be related to inadequate re-endothelialization) was observed in the RAVEL trial, which used a relatively short, combined antiplatelet treatment regimen for only 2 months.

**Conclusions**

Drug-eluting stents are very promising. The drastic reduction (or even abolition) of in-stent restenosis may prove to be a solution for an unresolved issue that affects thousands of patients each year. Depending on the results of ongoing and future studies, broadening of the current practice of coronary stenting may be expected, with more liberal indications in those at high risk of restenosis.

The impressive results of local drug administration using stents as the delivery platform open up a new area of investigation. The role of other agents with potential benefits (e.g. statins, adenovirus-mediated arterial gene transfer, tyrosine kinase inhibitors, L-arginine, abciximab, angiopeptin, r-PEG-hirudin and iloprost) as well as biodegradable stents may be tested in the future.

**References**

Lemos et al. Drug-Eluting Stents

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Loop the loop

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A 3-year-old child who underwent surgery for a moderate-sized, sub-aortic ventricular septal defect developed complete atrioventricular (AV) block postoperatively. The child was monitored for 12 days after surgery in the cardiac care unit (CCU) with a back-up temporary pacemaker, following which a VVIR permanent pacemaker was implanted.

A tined lead (Medtronic) was advanced to the right ventricle. As the patient was a child, an attempt was made to put a loop in the right atrium, to allow for growth. However, despite repeated attempts, an atrial loop of the lead could not be made because of a very large right ventricle. The loop was finally made in the dilated right ventricular outflow tract (RVOT).

An additional loop in the ventricular pacing lead has been proposed as a means of extending the longevity of endocardial pacing systems in children who require ventricular pacing. An atrial loop is commonly used in the majority of centers.\(^1\) Rare sites used are the RVOT and inferior vena cava.

In our case, the loop could not be positioned inside the atrium due to marked dilatation of the RVOT. Ventricular tachyarrhythmias remain a problem for those with an RVOT loop.\(^2\) However, there were no lead-induced ventricular tachyarrhythmias till the last follow-up in this child.

References


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Fig. 1. Permanent pacemaker lead in the right ventricle with a loop in the right ventricular outflow tract.
Letters to the Editor

Clopidogrel and Cardiac Surgery

We read with interest the excellent review article on clopidogrel by Orford et al.1 The platelet-rich intracoronary thrombus is central to the pathogenesis of acute myocardial infarction, unstable angina, acute coronary syndromes and the majority of the complications of percutaneous coronary interventions (PCI) and stent implantation. The use of dual antiplatelet therapy with aspirin and clopidogrel in such patients is of proven benefit. However, what is disturbing is the trend of administering clopidogrel routinely to all patients admitted for a coronary angiogram in anticipation of a PCI—a distressingly universal phenomenon.2 The problem occurs when such a patient is found to be unsuitable for PCI and needs an early coronary artery bypass grafting (CABG). Clopidogrel selectively interferes with ADP-induced platelet aggregation. It takes 3–5 days for the effect of clopidogrel to wear off.3 Thus, the surgeon is faced with the dilemma of delaying surgery and risking an adverse cardiac event due to coronary thrombosis in the interim, or performing CABG with the knowledge that there will be more bleeding and more blood products, especially platelets, will be required and patients may end up getting fewer internal mammary artery grafts than otherwise indicated. The two conflicting goals pose an ever-increasing challenge as new, more effective agents are added to the armamentarium of the interventional cardiologist in his quest for the holy grail of a 100% safe PCI.

Cardiac surgeons are always wary of putting patients at risk of preventable postoperative bleeding, mediastinal tamponade, blood product usage with its attendant risks and repeat surgery for re-exploration. All surgeons know that assessing postoperative bleeding for potential technical causes in the setting of a profound hemostatic defect can be frustrating, dangerous and costly. In one report on surgery following abciximab administration, patients were exposed to 131 donors at a cost of (Australian) $23,500 for blood transfusion alone.4 Blankenship et al.5 described increased bleeding during surgical intervention in abciximab-treated patients in the EPIC trial and a 1–4-day increase in the length of hospital stay. The same has been reported in other series also6,7 and with clopidogrel in the discussion forum of the Society of Thoracic Surgeons (http://www.ctsnet.org/forum/17/0/2528). Our protocol for managing patients who have been on clopidogrel prior to surgery is based on the Group Recommendations8 for cardiac surgery in patients treated with abciximab:

1. Delaying surgery for 3–5 days if the patient is relatively stable. This obviously has to be balanced against the severity and instability of the coronary artery disease.
2. If the patient is stable but the lesion is critical—the patient is put on heparin till the effect of clopidogrel wears off.
3. No “prophylactic” preoperative transfusion of any blood product
4. Full dose of heparin on cardiopulmonary bypass
5. Use of off-pump technique9 wherever feasible
6. Platelet transfusion only after administration of protamine
7. Adequate postoperative drainage of the mediastinum
8. Judicious re-exploration.

Surgeons have survived and thrived by adapting to changes in the field of cardiology and have effectively adapted to deal with new pharmacotherapy in order to maximize benefit to patient and minimize morbidity and mortality due to excesses of risk of bleeding. However, it does behoove the cardiologist to exercise prudence in the routine administration of clopidogrel. It is equally important for the surgeon to appreciate the clinical benefits of antiplatelet therapy and the concern of the interventionist, as it is for the cardiologist to understand the substantial risks associated with surgical bleeding. It is only a mutual understanding of these issues that will allow for optimal choice of antiplatelet therapy in patients with ischemic heart disease admitted for a coronary angiogram.

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Letters to the Editor

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Reply

We appreciate the comments of Bedi et al. about the risk of bleeding in patients on dual antiplatelet therapy undergoing surgery. This increased risk of bleeding poses a problem for cardiologists struggling to identify the most appropriate treatment for patients with an acute coronary syndrome who may need cardiac surgery, and for cardiac surgeons who operate on such patients. The risk of reoperation for bleeding is at least 50% greater in patients who have taken clopidogrel at any time in the prior five days, and may be as much as five times greater, or more, in patients receiving a thienopyridine at the time of surgery.1–3 The findings of the Clopidogrel in Unstable angina to prevent Recurrent Events (CURE) and the PCI-CURE trials define the challenge, since the results of CURE, a large, randomized, placebo-controlled trial and PCI-CURE, an analysis of the subset of patients in CURE who underwent PCI, suggest that all patients presenting with an acute coronary syndrome without ST segment elevation should receive early dual antiplatelet therapy, perhaps even prior to diagnostic angiography.4–5 However, there was a 50% increase in the risk of major or life-threatening bleeding in patients enrolled in the CURE trial who received clopidogrel within the five days prior to surgery (9.6% v. 6.3%; relative risk, 1.53; p=0.06). This poses a particular problem for medical centers like ours, in which angiography is invariably performed early after admission for an acute coronary syndrome and patients are routinely sent for surgery within a day or two of angiography. A reasonable approach might be to withhold early clopidogrel treatment (prior to diagnostic angiography) if there is a high likelihood of “surgical” anatomy and if the prevailing treatment strategy is the immediate or early referral of such patients for definitive surgical revascularization. This group of patients might include all patients who have undergone prior angiography and are known to have multivessel disease or moderate left main coronary artery stenosis, patients with a remote history of prior coronary artery bypass grafting, multiple prior myocardial infarctions, diabetes mellitus, chronic renal insufficiency, or concomitant peripheral or cerebrovascular disease, all of which greatly increase the likelihood for need of coronary bypass surgery among patients with an acute coronary syndrome. However, such an approach will exclude many patients who might receive benefit from the early use of clopidogrel, and will not identify a small number of patients who might also require emergent or urgent cardiac surgery. We wholeheartedly agree with the sentiments of Bedi et al. that “only a mutual understanding of these issues will allow for optimal choice of antiplatelet therapy in patients with ischemic heart disease admitted for a coronary angiogram”.

References


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Quantitative determinations of cardiac troponin T (cTnT) in the blood have been found to have excellent prognostic value in acute ischemic syndromes. We evaluated the usefulness of a rapid qualitative bedside test for cTnT in unstable angina (UA). One hundred consecutive patients, 40–65 years of age, who were hospitalized for UA diagnosed as per the criteria and classification proposed by Eugene Braunwald, were registered for the study after informed consent and after ruling out acute myocardial infarction (MI). Patients with post-MI (2 weeks) angina, valvular heart disease, cardiomyopathy, arrhythmias, pericardial disease, renal failure or recent (2 weeks) surgery or cardiac intervention were excluded. All the patients were given standard medical treatment. A standard 12-lead ECG was taken on admission and subsequently whenever indicated. The patients were followed during hospitalization and afterwards for a total period of one month. Presence of cTnT in the blood was detected on the day of admission as soon as feasible using “Troponin T Sensitive Rapid Test” which is a commercially available, qualitative immunological test kit (cat no. 1621904, Boehringer, Mannheim, Germany). The test was conducted as per the details provided in the application sheet of the manufacturer.

Patients with positive and negative cTnT tests were comparable with respect to baseline clinical characteristics and risk factor profile. Angina at rest, congestive cardiac failure (CCF), and ECG abnormalities were found more often in patients with a positive cTnT test than in those with a negative test (p<0.001). The clinical course during the first week of hospitalization was related to the presence of detectable cTnT in the blood. The difference was especially significant with respect to the occurrence of nonfatal MI (p<0.001), CCF (p<0.01) and recurrent angina with or without ST–T changes (p<0.05). Fourteen patients with a positive cTnT test had one or more complications as compared to only two patients in the cTnT-negative group (p<0.005); out of these, 5 patients in the positive group and 1 patient in the negative group needed coronary intervention (coronary angioplasty or bypass surgery) in the first week (p>0.025). Two patients in the positive cTnT test group were readmitted in the second week after discharge and died of cardiogenic shock related to acute MI. No death was encountered in the troponin-negative group. At the end of the one-month of follow-up, significant differences were noted in the clinical outcomes and cardiac event rates between the cTnT-positive and -negative groups (nonfatal MI: 5 v. 1, p<0.025; CCF: 4 v. 0, p<0.01; recurrent angina: 9 v. 5, p<0.025; any complication: 15 v. 6, p<0.001; coronary intervention: 7 v. 2, p<0.01).

The Troponin T Sensitive Rapid Test used has a positive threshold value of 0.1 ng/ml. At this discrimination level, a positive test on admission identified patients with UA who had other adverse prognostic factors also (rest angina, CCF, ST–T changes). Further, both the one-week and one-month event rates were significantly higher in the subgroup of patients with detectable cTnT in the blood on admission. These results are in agreement with previous observations about quantitative cTnT testing in acute ischemic syndromes with similar cut-off values for cTnT. We conclude that if acute MI is ruled out, a single qualitative test for cTnT at the time of admission that can be rapidly performed at the bedside is a useful adjunct in the risk stratification of UA. Such a point-of-care testing for cTnT could be a cost-effective strategy with respect to large, heterogenous groups of patients with chest pain, especially in areas of the world with limited availability of resources.

References


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Is Hypertrophic Obstructive Cardiomyopathy Really Different in Elderly Patients? A Case of Typical HOCM Detected in a 94-Year-Old Female

Hypertrophic obstructive cardiomyopathy (HOCM) in the elderly is considered to have different clinical and morphologic features compared to those seen in the young.1 Features in the elderly, in contrast to findings in younger patients are: mild degree of left ventricular and septal hypertrophy, reversed septal curvature and an ovoid-shaped cavity with posterior excursion of the septum being the major contributor to outflow tract obstruction.2,3

We report a case of typical HOCM diagnosed in a 94-year-old female who presented with a history of effort dyspnea, angina and syncope of one-year duration. On examination, she was tachypneic, pulse 120 beats/min regular; blood pressure 150/90 mmHg and bilateral chest crepitations. Her Hb was 8.3 g/dl and serum biochemistry was normal. Cardiovascular examination revealed mild cardiomegaly with palpable apical S4, S1 was soft and S2 normally split with A2 louder than P2. An apical pansystolic murmur grade 4/6 radiating to the axilla and an ejection systolic murmur grade 3/6 along the left upper sternal border, which increased on standing, was audible. ECG showed sinus rhythm, left atrial enlargement and left ventricular hypertrophy with ST–T wave changes and no Q waves. Echocardiography revealed systolic anterior motion (SAM) of the anterior mitral leaflet, a small crescentic left ventricular cavity, gross asymmetric septal hypertrophy (ASH) (35 mm v. 20 mm posterior wall, ratio 1.75) with abnormal echo texture, mild right ventricular hypertrophy, enlarged left (32 mm) and right atra and heavy mitral annular calcification. Doppler evaluation showed moderate mitral regurgitation, mild tricuspid regurgitation, a resting left ventricular outflow tract gradient of 35 mmHg, estimated systolic pulmonary artery pressure of 51 mmHg and abnormal mitral inflow pattern favoring impaired left ventricular relaxation (E > A).

Our patient had severe ASH which is rare in elderly patients with HOCM. The SAM, rather than posterior excursion of the septum, was a major contributor to the outflow tract obstruction. Mitral annular calcification contributed to the mitral regurgitation. A search of the literature in English revealed the oldest described patient with HOCM to be a 92-year-old person.4 At 94 years of age, our patient perhaps is the oldest known case of HOCM with severe hypertrophy of the interventricular septum, which is thought to be incompatible with such longevity.

References

2. Lewis JF, Maron BJ. Clinical and morphologic expression of hypertrophic cardiomyopathy in patients > or = 65 years of age. Am J Cardiol 1994; 73: 1105–1111

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**Losartan Intervention For End-point Reduction in Hypertension Study (LIFE): a Randomized Trial Against Atenolol**


**Summary**

The best documented therapy for reduction of cardiovascular morbidity and mortality in patients with hypertension are beta-blockers and diuretics. The LIFE study was a double-masked, randomized, parallel group trial conducted in 9193 individuals with essential hypertension (age 55–80 years, sitting blood pressure [BP] 160–200/95–115 mmHg). It aimed to check if angiotensin receptor blockers (ARBs) reduce left ventricular hypertrophy (LVH) and cardiovascular mortality beyond BP reduction with atenolol. The essential inclusion criterion, apart from BP level, was ECG evidence of LVH (by Cornell product or Sokolow Lyon criteria). The exclusion criteria were secondary hypertension, MI or stroke within 6 months, angina needing beta- or calcium-channel blockers heart failure or LVEF <40%. After starting with 50 mg atenolol or losartan the dose could be increased and, if needed, hydrochlorthiazide followed by other drugs could be added. After a mean follow-up of 4.8 years (minimum 4 years), there were similar reductions in BP (30.2±18.5/10.1 mmHg in the losartan group vs. 29.1±19.2/10.1 mmHg in the atenolol group). The primary composite end-point of death, MI and stroke occurred significantly less often in the losartan group (23.8 vs. 27.9/1000 patient-years, RR 0.87, p=0.021). This was mainly due to a reduction in the rate of stroke (10.8 vs. 14.5/1000 patient-years, p=0.001), while cardiovascular mortality (9.2 v. 10.6/1000 patient-years) and MI (9.2 v. 8.7/1000 patient-years) did not reduce significantly. There was also no difference in total mortality, need for PTCA/CABG, hospital admissions, or resuscitated cardiac arrest. The incidence of new-onset diabetes was also lower in the losartan group (13.0 v. 17.4/1000 patient-years, p=0.001). There was also a significantly greater reduction of LVH in the losartan group by both criteria (p<0.001). The incidence of drug-related adverse effects was lower with losartan (p=0.001).

**Comments**

Beta-blockers and diuretics have long been the cornerstone of therapy for hypertension due to the vast experience and documented mortality and morbidity reduction with these drugs. Other groups of antihypertensives (calcium antagonists, ACE inhibitors, alpha-blockers and vasodilators) have similar efficacy with fewer adverse effects but do not have similarly reported large data for benefit (till the recent PROGRESS study with perindopril). The LIFE study compared losartan, an ARB which has the lowest reported incidence of side-effects, with atenolol in subjects with moderate-to-severe hypertension and LVH. Despite similar large reductions in BP in both the groups, the losartan group had a 13% reduction in the composite end-point versus atenolol, which was largely due to a 25% lower incidence of stroke. The incidences of death and MI were similar, which have thus far been the strongest points in favor of beta-blockers. Further, even though regression of LVH occurred in both groups, it was greater with losartan. This was expected, as it is a specific antagonist of angiotensin-II, which is known to be associated in the pathophysiology of LVH. As this greater reduction in LVH goes with the lower composite end-point, this may confirm the additional implication of LVH on prognosis, underlining the role of therapy tailored to reduce it further by greater reduction in BP. Of note, the incidence of new-onset diabetes was 25% lower (probably due to a beneficial effect on insulin resistance), which is known to be worsened with beta-blockers. As expected, adverse effects as well as withdrawals were also lower with losartan.

These are substantial benefits favoring losartan, which has thus far been only a second-line drug for treatment of hypertension and congestive heart failure. It provides effective BP control, with no increase in cardiac events or mortality and with acceptable side-effects and additional beneficial effects in reducing LVH and diabetes. The benefits could also be due to specific effects of losartan or result from increased protection against the detrimental effects of angiotensin II. This study might help in modifying future guidelines for BP control, making ARBs first-line antihypertensive drugs.
Comparison of Angioplasty with Stenting, With or Without Abciximab, in Acute Myocardial Infarction


Summary
This multicenter trial involving 2082 patients with acute myocardial infarction (AMI) using a 2-by-2 factorial design randomized patients to undergo percutaneous transluminal coronary angioplasty (PTCA) alone, PTCA plus abciximab therapy, stenting alone or stenting plus abciximab therapy. Symptomatic patients of AMI (duration of chest pain at least 30 min but less than 12 hours) with either characteristic ECG changes or high-grade angiographic stentosis and associated abnormalities in regional wall motion were included. Patients with cardiogenic shock, vein graft occlusion or symptoms for more than 12 hours were excluded from the present study. Before undergoing catheterization, patients received a full dose of aspirin, 500 mg ticlopidine/300 mg clopidogrel orally, bolus of 5000 U heparin and beta-blocker intravenously. Based on angiographic criteria, patients were excluded if medical management seemed appropriate, if multivessel angioplasty was required or if the angiographic lesion was unsuitable for stenting. The choice of stent was Multilink or Multilink duet (Guidant, Santa Clara, Calif). In the patients randomized to receive abciximab, it was administered as a bolus in a dose of 0.25 mg/kg body weight at the time of the procedure, followed by a 12-hour infusion at a rate of 0.125 µg/kg/min. Patients who received stents were given 250 mg of ticlopidine bd/75 mg of clopidogrel daily for 4 weeks. Out of 2681 patients enrolled at 76 centers in 9 countries, 77.7% (2082) could be randomized in the present study. TIMI grade 3 flow was achieved in 95% of patients, irrespective of their randomization group. Overall, 16% of patients in the PTCA-only group crossed over to the stenting group and 10% of patients in the no-abciximab group actually received abciximab due to “no reflow” phenomenon. At six months, the primary end-point—a composite of death, reinfarction, disabling stroke, and target-vessel revascularization (TVR)—occurred in 20% of patients in the PTCA group, 16.5% in PTCA plus abciximab, 11.5% in stenting alone and 10.2% in stenting plus abciximab group (p<0.001). However, the difference in the primary end-point was due entirely to the difference in TVR, maximum in the plain angioplasty group (15.7%) and minimum in the stenting and abciximab group (5.2%) (p<0.001). The rate of restenosis (22.2% v. 40.8%) and reocclusion of the infarct-related artery (5.7% v. 11.3%) was lower in the stented patients as compared to those who underwent plain balloon angioplasty (p=0.01), irrespective of abciximab use.

Comments
The superiority of primary angioplasty over conventional thrombolysis is now well established. However, the use of stents in this situation has been controversial. While stenting reduces the problems of restenosis and acute thrombosis which have continued to be a bane of angioplasty, some studies have shown poorer results with stenting as compared with plain old balloon angioplasty (POBA) in this setting. For instance, in the Stent-PAMI trial, although stenting reduced rates of ischemia and restenosis, the intermediate-term results and late mortality were actually higher with stenting as compared to POBA. Even when compared with conventional thrombolysis, Le May et al. have shown that, while the composite end-point of death, reinfarction, stroke and repeat TVR at 6 months was lower, mortality was actually higher (though statistically not significant) in the stent group. One possible reason could be the frequent occurrence of slow/no reflow phenomenon in the stented group, attributable probably to extrusion of the thrombus through the stent struts, followed by its distal embolization. Indeed, the ADMIRAL trial demonstrated that administration of abciximab along with stenting improves coronary patency and clinical outcome up to at least 6 months, especially if abciximab is delivered early (prior to the procedure). Better results in recent trials could also be ascribed to improved stent design or greater operator experience. In this context, the CADILLAC trial clarifies many of these issues. It has shown that at experienced centers and with the use of newer-generation stents, a strategy of stent implantation is clearly superior to that of POBA (irrespective of the use of abciximab) for achieving revascularization in a wide range of patients with AMI. The major limitation of this study was that abciximab was not administered before catheterization (in the casualty or CCU) and therefore its efficacy could have been limited.
Effect of Nicorandil on Coronary Events in Patients with Stable Angina: The Impact of Nicorandil in Angina (IONA) Randomized Trial

Summary
In this randomized, double-blind trial, 5126 patients with stable angina from 226 centers in the UK were enrolled with the view to find out whether nicorandil could reduce the frequency of coronary events. The patients were men > 45 years, or women > 55 years of age, with recently diagnosed stable angina and clearly established coronary artery disease (CAD) (history of myocardial infarction [MI], coronary bypass surgery, positive angiography or a documented positive exercise test). In addition, there had to be one of the following high-risk features: left ventricular hypertrophy (LVH) on ECG, left ventricular (LV) ejection fraction <45%, end-diastolic dimension (EDD) of more than 55 mm on echocardiography, type 1 or type 2 diabetes mellitus, hypertension or documented evidence of peripheral vascular disease. Exclusion criteria were unstable CAD, long-standing symptoms or use of sulphonyl urea (which inhibits opening of the K⁺ channels). Patients were randomly assigned to nicorandil 10 mg twice daily for 2 weeks and 20 mg twice daily thereafter. Patients were followed up for at least 1 year and up to 3 years, irrespective of whether or not they had withdrawn from the study medication. The primary composite end-point was death due to coronary heart disease (CHD), nonfatal MI or unplanned hospital admission for cardiac chest pain. The secondary end-point was the combined outcome of CHD death or nonfatal MI. Other outcomes evaluated were all-cause mortality, all cardiovascular events and acute coronary syndromes (ACS).

While the patients were high-risk, stable CAD patients, most of them had only mild angina (nearly 90% were Canadian Cardiovascular Society Functional [CCSF] class I or II). Nearly 90% of them were on aspirin and nitrates but less than 60% received beta-blockers, calcium-channel blockers and statins, and less than 30% of patients were on ACE inhibitors. After a mean follow-up of 1.6 years, the combined end-point of CHD death, nonfatal MI or unplanned hospital admission was decreased in the nicorandil group (13.1% v. 15.5%, p=0.014), but the difference was almost entirely due to the difference in hospital admission rate. The rate of ACS (6.1% v. 7.6%, p=0.028) and all cardiovascular events (14.7% v. 17%, p=0.027) were also lower in the nicorandil group as compared to the placebo group. There was a similar number of cerebrovascular (CVS) and non-CVS deaths in the two groups. There was no significant improvement in anginal class with the use of nicorandil. Overall, the rates of serious adverse events were similar in both the groups, although gastrointestinal events were commoner in the nicorandil group (7.5% v. 5.2%). At the end of the study, withdrawals were higher in the nicorandil group (39.1% v. 31.6%), mostly due to headache.

Comments
The aims of management of any manifestation of CAD are two-fold—improvement of symptoms and reduction of cardiovascular events and mortality. In patients with stable angina where vasodilators and nitrates are very effective in reducing symptoms, none of them have shown any evidence of reduction in event rate or mortality in large, randomized controlled trials. Several studies have shown secondary prevention with beta-blockers in acute MI and chronic heart failure, and several small studies have shown possible benefit in outcome even in patients with stable angina. However, this benefit has not been proven in large, randomized controlled trials till date. On the other hand, although aspirin, ACE inhibitors and statins have a definite role in secondary prevention in patients with stable angina, they have very little role in symptom amelioration. In this context, nicorandil, which has a dual mode of action, may have an effect on both these outcomes. By its nitrate-like action it can dilate the epicardial coronary arteries and systemic veins, reducing both pre- and afterload and thus reducing symptoms. By its ability to open both sarcolemmal and mitochondrial K⁺ channels, it can induce preconditioning and act as a myocardial cytoprotective agent. Indeed, in the present study, nicorandil could significantly reduce the combined end-point of CHD death, nonfatal MI and unplanned hospital admissions, with improvement seen in all the individual components, but mostly in reduced hospital admission. In addition, nicorandil was also conclusively shown to reduce occurrence of ACS and CVS events. However, this study has several limitations. It enrolled patients with recently diagnosed stable angina but otherwise high-risk CAD patients which may cater to only a narrow spectrum of the total population of stable angina patients. Nicorandil did not show any significant improvement in class of angina, probably because the patients were mildly symptomatic anyway (nearly 90% had class I or II angina). Finally, in this study, patients were not optimally controlled on drugs known to improve cardiovascular outcomes such as ACE inhibitors and statins, and not all patients were receiving aspirin or other antiplatelet therapy.
Bosentan Therapy for Pulmonary Arterial Hypertension: Bosentan Randomized Trial of Endothelin Antagonist Therapy (BREATHE-I) Study

**Summary**

In this randomized, double-blind, placebo-controlled trial conducted in 27 centers in Europe, North America, Israel and Australia, the effect of bosentan, an orally administered dual endothelin-receptor antagonist, was investigated in patients with pulmonary arterial hypertension. Inclusion criteria were: (i) markedly symptomatic patients (WHO class III or IV) with severe pulmonary arterial hypertension (primary pulmonary hypertension [PPH] or secondary to connective tissue disease) refractory to therapy with anticoagulant drugs, vasodilators, diuretics, cardiac glycosides or supplemental oxygen; (ii) baseline six-minute walking distance between 150 and 450 m; (iii) resting mean pulmonary artery pressure >25 mmHg; (iv) pulmonary capillary wedge pressure <15 mmHg; and (v) pulmonary vascular resistance >240 dynes sec/cm⁵. Patients who had recently (within 1 month) changed drugs and those who had used epoprostenol within the past 3 months were excluded. Patients receiving glyburide or cyclosporine were also excluded. In all, 213 patients were randomized to receive placebo or 62.5 mg of bosentan twice daily for 4 weeks, followed by 125 or 250 mg of bosentan twice daily for 12 weeks. The primary end-point of the study was the change (from baseline to week 16) in exercise capacity as assessed by a six-minute walk test. Secondary end-points included a change in Borg dyspnea index, WHO functional class and time from randomization to clinical worsening (defined as death, lung transplantation, hospitalization for pulmonary hypertension, lack of clinical improvement or worsening leading to discontinuation, need for epoprostenol therapy or septal septostomy).

The baseline characteristics were well matched in the two groups. Nearly 80% of the patients were female and the majority (70%) of patients had PPH. About half the patients were receiving calcium-channel blockers and nearly one-third required supplemental oxygen. Most patients were in WHO class III and some were in class IV.

The mean duration of treatment was approximately 125 days. At the end of the study, the six-minute walk test revealed that walk distance (a parameter for exercise capacity) had improved by 44 m in the bosentan group as compared to the placebo group (95% CI: 21–67, p<0.001). The improvement was more pronounced in the 250 mg dose group (54 m vs. 35 m, respectively), but the difference was not statistically significant. On subgroup analysis, improvement in the bosentan-treated group occurred irrespective of sex, cause of disease, associated congenital heart defect, time from diagnosis, baseline walk test performance, and baseline hemodynamic measurements. Interestingly, although similar overall benefit occurred in patients with both PPH and scleroderma, improvement in those with PPH occurred primarily by improving exercise capacity as compared to placebo, whereas in the scleroderma group, benefit occurred by prevention of deterioration in exercise capacity. Bosentan also improved the Borg dyspnea index and WHO functional class, and increased the time to clinical worsening. The most common adverse effect in the bosentan group was abnormal hepatic function (especially in 250 mg dose group). Bosentan therapy did not alter the heart rate and blood pressure.

**Comments**

Patients with severe pulmonary hypertension, particularly PPH have high morbidity and mortality. Small reports had suggested that beta-agonists, alpha-blockers and hydralazine were effective, however, the benefits could not be confirmed in larger studies over a long-term period. Only calcium-channel blockers could cause a sustained reduction in pulmonary vascular resistance, but this effect could be observed in only 20%–25%. Recently, intravenous epoprostenol (prostacyclin) has not only been found to improve functional capacity but also improve survival in these patients. This drug appears to act by increasing c-AMP levels. However, not only is this drug expensive but continuous intravenous infusion is technically demanding and it does have undesirable side-effects. Prostacyclin analogues given by continuous subcutaneous infusion, orally or by intermittent aerosol have shown promising results but require larger trials to confirm their usefulness. Other vasodilators, such as inhaled nitric oxide and oral sildenafil are also useful but their exact niche in the therapeutic armamentarium is yet to be established. Oral arginine and citrulline, which act by releasing nitric oxide, may also be useful. Endothelin-1 is a potent endogenous peptide active on endothelin A and B receptors. Activation of the endothelin A receptor causes vasoconstriction and smooth muscle cell growth, whereas that of endothelin B receptors causes vasodilation. Bosentan acts on both receptors but its predominant effect is pulmonary vasodilation. In the present study, bosentan has shown small but significant improvement in exercise capacity and functional class. The ideal dose seems to be 125 mg (250 mg is equally efficacious but produces more side-effects). However, this study is limited in many aspects. The number was too small to show any effect on mortality. A short-term vasodilator testing was not performed as a part of the study, therefore it is not known whether patients improved with bosentan therapy. Finally, endothelin levels were not measured, therefore any correlation between these levels and clinical effect could not be established.
Calendar of Conferences

June 19–22, 2002, A World Congress in Cardiac Electrophysiology, Nice, France
Contact: Dr Jacques Mugica, Cardiostim 12 rue Pasteur, Saint-Cloud 92210, France
Fax: 33 1 4602 0509
e-mail: cardiostim@wanadoo.fr

July 17–21, 2002, 14th ASEAN Congress of Cardiology, Kuala Lumpur, Malaysia
Contact: Dr David KL Quek, Chairman, Organizing Committee, c/o Letter Box 1502, 15th Floor, Menara Merais, 1 Jalan 19/3 Petaling Jaya 46300, Selangor, Malaysia
Fax: 60 3757 8363

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 Cardiological Society of India – NE Chapter, Imphal, Manipur, India
Contact: Dr Kala Singh, Organizing Secretary, Cardiovascular and Thoracic Unit, Regional Institute of Medical Sciences, Imphal – 795004
Fax: (0385) 310625

October 19–20, 2002, 2nd Annual Conference of the Indian College of Interventional Cardiology, Mumbai, India
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

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
Fax: 040 6625003
e-mail: anjan.anne@yahoo.com

Contact: Dr SB Gupta, Organizing Secretary, ISECON-2003
Head, Department of Medicine and Cardiology Central Railway Headquarters Hospital Byculla, Mumbai 400027
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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
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