A remarkable paradigm shift is occurring in our understanding of organ regeneration that may have significant therapeutic implications. Conventionally, the heart is perceived as a terminally differentiated organ incapable of regeneration. It is thought that the myocytes respond to physiologic or pathologic stress only by hypertrophy, but not by increase in number. However, recent evidence suggests that adult myocytes may have the ability, albeit limited, to divide and increase in number under certain circumstances. This iconoclastic message has opened the doors for experimentation to increase myocyte number as a strategy to combat cardiac disorders. Simultaneously, experience is accumulating on several aspects of cell transplantation in animal experiments. Historically, various cell types including embryonic, fetal, and neonatal rodent and porcine cardiomyocytes, fetal smooth muscle cells, AT-1 tumor cardiomyocytes, adult and fetal human cardiomyocytes, adult atrial cells, and dermal fibroblasts have been used to augment declining myocyte function. More recently, the focus is on using autologous skeletal myoblasts and bone marrow (BM)-derived stem cells. In this editorial, we briefly review the nascent field of stem cell therapy in cardiac disease.

Stem Cells
Stem cells are primitive cells with extensive capacity for self-renewal and the ability to differentiate into multiple cell types. Until recently, adult stem cells were considered to have a "committed" fate such that they would replicate a selected or limited type of tissue. But a series of experiments have established that, under appropriate circumstances, adult stem cells are capable of transdifferentiation into various cell lines including cardiomyocytes, neurons, hepatocytes, epithelial cells, and pancreatic cells. The factors governing the differentiation of stem cells into a particular cell type are only beginning to be understood; of these, local milieu seems to be important. The ability of certain cells to regenerate into endothelium, smooth muscle cells and cardiomyocytes has raised hopes regarding myocardial regeneration, even though much remains to be learnt. The cells being evaluated for cell transplantation include fetal cardiomyocytes, embryonal stem cells, and adult autologous stem cells including BM-derived cells and skeletal myoblasts.

Fetal cardiomyocytes: The first cells used for cellular cardiomyoplasty were fetal cardiomyocytes. These cells appear to be an ideal replacement for lost cardiomyocytes, since they are capable of integration with the host myocardium by the formation of intercalated discs and gap junctions. Transplantation of fetal cardiomyocytes has been shown to improve cardiac function in animal models of myocardial infarction. Fetal cardiomyocyte transplantation limits infarct progression even when ultrastructural connection with the host myocardial cells could not be established. However, the major obstacles to further progress with fetal cardiomyocytes are their limited availability, possibility of rejection, and ethical issues. Besides, fetal cardiomyocytes are very ischemia-sensitive, and die in large numbers (up to 99%) upon engraftment.

Embryonal stem cells: Embryonal stem (ES) cells develop on day 5 of fertilization in humans as the inner cell mass. These cells are pluripotent, undifferentiated cells with an enormous capacity for proliferation and differentiation. Upon cultivation on appropriate feeder layers, ES cells are highly expandable, and aggregate to form embryoid bodies, which are capable of differentiating into a wide variety of specialized cells including cardiomyocytes. The cultured cardiomyocytes can be divided into 3 stages of differentiation: early (pacemaker-like, primary myocardial-like cells), intermediate, and terminal (atrial-, ventricular-, nodal-, His- and Purkinje-like cells), which could be differentiated on the basis of electrophysiologic, histochemical and morphologic properties. ES cells show the most promise for the large-scale production of cardiomyocytes. However, like fetal cells, the utility of ES cells is limited because of ethical considerations, difficulty

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animal models, even though little is known at present.

These myoblasts were capable of contraction upon exogenous stimulation, but it is not clear if these grafts contract coherently in vivo. Possibly, mechanical activation of stretch-activated ion channels, or direct transmembrane activation by a field effect resulting from activation of cardiac cells, may be responsible for triggering the action potential in transplanted myoblasts. It has been suggested that prevention of remodeling by a scaffolding effect could be the major mechanism by which myoblast transplantation exerts beneficial effects.

Human trial with myoblast transplantation has been reported. Specimens from a patient’s thigh muscle cells cultured in selective myogenic media for 2–3 weeks yielded a high number (average of 870 million cells) of viable CD56-positive myoblasts. These myoblasts were inoculated in areas of previous infarction, which had not been revascularized. Fourteen out of 22 such injected segments demonstrated new onset systolic thickening. Unfortunately, 4 of the 10 patients developed serious ventricular arrhythmia soon (11–22 days) after the implantation, and required implantable defibrillators. Possibly, disorganized myocardial architecture, difference in the activation kinetics of the ion channels between skeletal and cardiac muscle, or inflammatory responses against the dead myoblasts were responsible for this arrhythmogenesis. Further research is required to establish whether skeletal myoblast transplant therapy would become a clinically feasible option.

**Bone marrow stem cells:** The adult BM contains hematopoietic (1%–2%) and stromal (<0.05%) stem/progenitor cells. The blood-forming cells can be categorized into hematopoietic stem cells (HSC) capable of long-term, permanent reconstitution of the entire hematopoietic system, and progenitor cells capable of short-term (1–2 months) reconstitution. HSCs give rise to different lineages of cells, some of which (e.g. endothelial cells) have the capacity to differentiate into cardiomyocytes. BM stromal stem cells include adult mesenchymal stem cells (MSCs) and multipotent adult progenitor cells, both capable of multilineage differentiation. On culture, MSCs maintain an undifferentiated stable phenotype; these are induced to transdifferentiate into cardiomyocytes by 5-azacytidine, a DNA demethylating agent. Further research is required to establish whether skeletal myoblast transplant therapy would become a clinically feasible option.

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Lin– c-kit+ cells could generate cardiomyocytes, smooth muscle cells, and endothelial cells. The results of a phase-1 human study using AC133+ cells are in agreement with experimental studies showing the high angiogenic potential of the nonhematopoietic (CD34−) subpopulation of the BM, which is a constituent of AC133+ cells. Thus, AC133, CD34, Lin– and c-kit could be important markers that could identify more useful subpopulations of BM stem cells in terms of cardiac regeneration. This requires further validation.

**Stem Cell Mobilization**

BM stem cells are the central repository not only for hematopoietic cells, but possibly also for stem cells in other organs. It is interesting to note that intravenous injection of a single male BM stem cell in lethally irradiated adult mice populated many organs, suggesting the potential of stem cell migration to other organs. The proposed hypothesis of natural myocardial regeneration from BM stem cells suggests that BM stem cells could be continuously trafficking all tissues, or could be released from the BM following injury to an organ. Attempts are being made to augment this process.

Stem cell mobilization using granulocyte colony-stimulating factor (G-CSF) is routinely used in hematological practice. Cytokine-mobilized cells have been shown to regenerate myocardium with the formation of myocytes resembling fetal cardiomyocytes, capillaries and arterioles. Significantly, cytokine therapy in a mouse myocardial infarction (MI) model had resulted in improvement in ejection fraction, left ventricular (LV) end-diastolic pressure, and LV end-systolic pressure. Moreover, cytokine therapy resulted in significant survival benefit. Granulocyte-macrophage colony-stimulating factor (GM-CSF) is similar to G-CSF, but is less potent in stem cell mobilization. In a clinical trial of 21 patients of coronary artery disease (CAD) who were unsuitable for or refused coronary artery bypass grafting (CABG), GM-CSF (n=10) or placebo was given initially through the intracoronary route followed by the intravenous route daily for 2 weeks. GM-CSF therapy was associated with improved collateral flow at 2 weeks. However, clinically relevant parameters and the number/type of the BM cells mobilized were not analyzed in that study. Whether in vivo therapy can augment mobilization and effective "homing in" of stem cells remains to be established.

**The "Homing-in" Process**

The homing in of transplanted stem cells to the injured myocardium is the initial key event. The fate of the transplanted stem cells is not intrinsically pre-programmed, but is dependent on the milieu of engraftment. Ischemia or hypoxia could enhance the homing-in process because of increased vascular permeability, release of chemoattractive factors, and expression of adhesive molecules. Systemic and local factors could influence the homing-in of stem cells. For instance, vascular endothelial growth factor (VEGF) augments the mobilization of endothelial progenitor cells from the BM in patients with acute MI. Recent evidence suggests that expression of the VEGF receptor, especially VEGF receptor-2, on the stem cells is the point where they become committed to a vascular progenitor lineage. HSCs express a tyrosine kinase receptor named c-kit, and the migration of cells could be regulated by stem cell factor (SCF), the c-kit ligand, which is expressed on neonatal and fetal hearts, myocardial macrophages, and fibroblasts. Within hours following myocardial ischemia, matrix metalloproteinase-9 (MMP-9) mediated release of c-kit ligand has been shown to play a key role in the recruitment of BM cells. However, the cellular and molecular mechanisms of the engraftment and differentiation of stem cells are not well understood at present. Various other factors including, CXCR4 and its ligand stromal cell derived factor-1 (SDF-1), and G-CSF may be important.

**Clinical Studies**

A few clinical studies using adult autologous stem cells have been published (Table 1). Aspiration of the BM allows the isolation of a sufficient quantity of mononuclear stem cells in a few hours, the methodology of which is described elsewhere. A variety of techniques for isolation, number and type of cells, and different route of delivery were used. The initial studies attest to the feasibility and safety of the procedure. Overall, the results are encouraging. Improvements in perfusion, in contraction of the scarred segments, and in overall ejection fraction have been reported (Table 1). However, the trials reported until now are either observational or nonrandomized in nature, and involve small numbers of a highly selected population.

BM stem cell plasticity resides in CD34+ population. However, HSCs are not limited to the CD34+ cell population, and the role of CD34+ HSCs in hematopoietic reconstitution and regenerative biology is not clear. BM-derived CD34+ endothelial progenitor cells have been isolated from peripheral blood and the BM in humans. Lin– c-kit– cells, known to be devoid of stem cells, failed to regenerate cardiac cells upon transplantation, whereas Lin– c-kit+ cells could generate cardiomyocytes, smooth muscle cells, and endothelial cells. The hypothesis of natural myocardial regeneration from BM stem cell plasticity resides in CD34+ population, and the role of CD34– HSCs in hematopoietic reconstitution and regenerative biology is not clear. BM-derived CD34+ endothelial progenitor cells have been isolated from peripheral blood and the BM in humans. Lin– c-kit– cells, known to be devoid of stem cells, failed to regenerate cardiac cells upon transplantation, whereas Lin– c-kit+ cells could generate cardiomyocytes, smooth muscle cells, and endothelial cells. The results of a phase-1 human study using AC133+ cells are in agreement with experimental studies showing the high angiogenic potential of the nonhematopoietic (CD34−) subpopulation of the BM, which is a constituent of AC133+ cells. Thus, AC133, CD34, Lin– and c-kit could be important markers that could identify more useful subpopulations of BM stem cells in terms of cardiac regeneration. This requires further validation.
Phase II clinical trials using BM stem cells are under way, the results of which are eagerly awaited.

**Route of delivery:** Ideally, stem cells should be delivered in high concentrations to the area of interest in a targeted fashion, while preventing a spill-over to other organs. Intravenous, transcatheter (coronary-arterial or venous, transendocardial), and direct intramyocardial delivery at the time of surgery are being tried. Direct intramyocardial injection under vision is simple, but invasive, and can be done only in patients who are being operated. Intracoronary administration is simpler, practical, and is suited for the delivery of cells into a specific coronary territory. Access through the coronary sinus and great cardiac vein could also be obtained. Catheter-based transendocardial delivery using electroanatomic and contraction mapping has been tried in humans (NOGA system, Cordis). The scarred, normal, and viable ischemic myocardium could be mapped and selectively targeted by the injection catheter. Intravenous cell administration is the simplest method, but the delivery is not targeted. Only 3% of the cardiac output passes through the heart vasculature in a minute. The major concern is the possibility that the cells could home in to other organs, the consequences of which are presently unknown. The intravenous route could be valuable in instances such as acute ischemia, wherein target myocardial homing signals are more intense. Intracoronary and intravenous modes of delivery are not suitable for delivering larger cells such as skeletal myoblasts because of the propensity for embolization.

**Dosing:** Human adult myocardium is estimated to contain 4-5 billion cardiomyocytes, and a cell loss of 30%-40% in an infarct causes heart failure. Hence, the estimated deficiency is about 750 million to 1 billion cardiomyocytes. The optimal number of cells required for myocardial regeneration could vary, depending on the clinical situation, types of cell used, and whether the primary focus is on angiogenesis or myogenesis, with the latter requiring a larger number of cells. In experimental models, improvement in function is correlated with the number of myoblasts transplanted. However, little is known about the optimal dose in humans.

**Unresolved Issues**

A number of issues need to be resolved before the dream of stem cell transplantation to treat cardiac disease can be realized. The entire concept of stem cell plasticity has been questioned by some researchers. It is argued that homing in and integration of stem cells into target tissue cells results in cell-cell fusion, with the fused hybrid cells exhibiting a dual phenotype, and subsequent proliferation results from the hybrid cells rather than stem cell transdifferentiation. However, the available evidence of significant tissue regeneration following cell transplantation is unlikely to be explained on the basis of infrequently occurring cell-cell fusion.

A number of other issues remain to be addressed. The benefits of stem cell transplantation have to be validated in controlled clinical studies. The patient population that would derive clinical benefit and the optimal time of intervention has to be ascertained. Whether ischemic and

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**Table 1. Clinical trials of bone marrow cell transplantation***

<table>
<thead>
<tr>
<th>No.</th>
<th>Trial</th>
<th>Patients</th>
<th>Cells</th>
<th>No. of patients</th>
<th>Route</th>
<th>Follow-up</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Hamano et al.52</td>
<td>CABG candidates with post-MI scar</td>
<td>Mononuclear BMC</td>
<td>5</td>
<td>Intramyocardial injections</td>
<td>1 year</td>
<td>Perfusion improved in 3 patients</td>
</tr>
<tr>
<td>2</td>
<td>Assmus et al.51</td>
<td>Post-MI (mean 4.3 days)</td>
<td>Circulating (n=11) or BM-derived (n=9) progenitor cells</td>
<td>20</td>
<td>Intracoronary into IRA</td>
<td>3 months</td>
<td>RWMA ↓, perfusion, viability, and EF improved (51.6% →60.1%)</td>
</tr>
<tr>
<td>3</td>
<td>Strauer et al.51</td>
<td>Post-MI (5-9 days)</td>
<td>Mononuclear BMC</td>
<td>10 study v. 10 control</td>
<td>Intracoronary into IRA</td>
<td>3 months</td>
<td>Infarct size ↓, perfusion and function improved (EF 51% →53%)</td>
</tr>
<tr>
<td>4</td>
<td>Stamm et al.52</td>
<td>CABG candidates with post-MI scar</td>
<td>AC133+ BMC</td>
<td>6</td>
<td>Intramyocardial injections</td>
<td>3-9 months</td>
<td>Perfusion improved in 5 patients, EF improved in 4 patients</td>
</tr>
<tr>
<td>5</td>
<td>Perin et al.53</td>
<td>End-stage CAD</td>
<td>Mononuclear BMC</td>
<td>14 study v. 7 control</td>
<td>Transendocardial (NOGA)</td>
<td>4 months</td>
<td>EF improved (20% →29%), improvement in contraction of injected segment</td>
</tr>
</tbody>
</table>

*The studies are either observational or nonrandomized
CABG: coronary artery bypass grafting; MI: myocardial infarction; BMC: bone marrow cell; BM: bone marrow; IRA: infarct related artery; RWMA: regional wall motion abnormality; EF: ejection fraction; CAD: coronary artery disease
*p value nonsignificant
nonischemic forms of cardiac injury (e.g. dilated cardiomyopathy, hypertensive heart failure) would respond similarly to stem cell therapy is not known. Further, the ideal types of cells, the dose, and the route of delivery all need to be addressed. Noninvasive tracking of labeled stem cells is possible with magnetic resonance imaging\(^6\) that would clarify the fate of stem cells in vivo. In vivo therapy to mobilize stem cells and homing in to the areas of interest may be feasible in the future. Combining the concept of gene therapy with BM stem cell transplantation may augment the efficacy of stem cell therapy.\(^7\) Thus, cautious optimism regarding stem cell therapy seems warranted, but much hard work yet remains to be done.

**References**

Despite considerable progress in the management of congestive heart failure (CHF), it remains a major health problem worldwide. The incidence and prevalence of this disease continues to increase due to an aging population which, in part, is related to the use of new pharmacologic, i.e. thrombolytic therapy, angiotensin-converting enzyme inhibitors, beta-blockers, spironolactone, etc., and nonpharmacologic therapies.

However, despite these advances, the quality of life in patients with advanced heart failure remains poor, they are frequently hospitalized, and pump failure is a common cause of death. In addition, the cost involved in the management of this problem is enormous and continues to climb. Cardiac transplantation, the gold standard of treatment for advanced CHF, is restricted by the lack of available donors and other factors, such as cost, that exclude a significant segment of the population and allow cardiac transplantation for only 1% of the patients with significant heart failure. This number is even smaller in developing countries.

Patients with advanced heart failure frequently have conduction disturbances that may play a role in worsening cardiac systolic function: therefore, pacing techniques have been introduced in an attempt to improve cardiac function, functional capacity, and prognosis. This review details the current knowledge regarding the role of resynchronization therapy in patients with CHF.

Demographics of Congestive Heart Failure

An estimated 6–7 million people have CHF in the United States and Europe, and approximately 1 million patients are diagnosed with CHF every year. Worldwide, approximately 15 million people have CHF, ischemic idiopathic cardiomyopathies and Chagas’ disease are common causes of cardiomyopathy. CHF is a common cause of hospitalization: 2% of all hospital discharges carried a principal diagnosis of heart failure, and an additional 4% carried a secondary diagnosis of CHF. The annual incidence of CHF increases dramatically with age. For example, the incidence increased from 3 cases per 1000 in men 50–59 years of age to 27 cases per 1000 in men 80–89 years of age. Although advances in the treatment of CHF have had a favorable effect on overall mortality, death rates remain high. In patients with mild CHF (NYHA functional class II), the overall annual mortality is 5%–15%, with 50%–80% of deaths classified as sudden. In patients with class III CHF, mortality rises to 20%–50% and in patients with class IV CHF it often exceeds 50%. However, the proportion of sudden cardiac death (SCD) decreases to 20%–50% in patients with class III CHF, and 5%–30% in class IV CHF. The reduction in mortality in the Studies of Left Ventricular Dysfunction and in the Cooperative North Scandinavian Enalapril Survival Study trials was mostly a result of a reduction in the number of patients dying from progressive pump failure, whereas the incidence of SCD remained unaffected (Fig. 1).

Conduction Abnormalities in CHF

Prolongation of the PR interval and widening of the QRS complex are common findings in patients with CHF, present in a reported 20%–50% of these patients. The prevalence of these conduction disturbances depends upon the severity of CHF: functional NYHA class IV patients tend to have wider QRS complexes. In one study, 82% of patients had significant intraventricular conduction defects in the electrocardiogram (ECG) recorded within 60 days before death and, in 68% of these patients, the conduction abnormality was progressive. In another study, 29% of patients had complete left bundle branch block (LBBB) and 9% had a right bundle branch block (RBBB), which was associated with left axis deviation in two-thirds of these patients, indicating probable involvement of the left bundle branch. Overall, left axis deviation (>30 degrees) was seen in 65% of patients with CHF. Both prolongation of the PR interval and a wide QRS complex have been found to be independent predictors of mortality in various studies of patients with CHF. In the VEST Study, Gottipaty et al. evaluated 3654 ECGs in patients with CHF and dilated cardiomyopathy. The QRS duration was measured by blinded reviewers. The QRS duration was found to be an...
independent predictor of mortality as patients with a wide QRS (>200 ms) had a five times greater mortality risk than those with a narrow (<90 ms) QRS duration (Fig. 2). Resting ECG thus seems to be a powerful yet accessible marker of prognosis in patients with dilated cardiomyopathy and CHF.

**Prolongation of the PR interval:** In patients with CHF, PR interval prolongation may occur as a result of intraatrial or intra/infranodal conduction delay.12 Prolongation of the PR interval has several detrimental consequences: (i) decrease in ventricular filling time; (ii) diastolic atrioventricular (AV) valve regurgitation;13–15 and (iii) decreased pulse pressure and cardiac output.

The filling time is decreased because the prolonged PR interval delays the onset of ventricular systole and diastole; therefore, the closing and opening of the mitral and tricuspid valves is delayed and encroaches upon the next sinus beat. A decrease in filling time diminishes the left ventricular (LV) preload and increases the left atrial and pulmonary venous pressures. In addition, a long PR interval results in premature closure of the mitral valve when the valve closes as a result of the atrial contraction instead of the ventricular contraction. In these cases, delays of up to 100 ms between mitral valve closure and ventricular contraction have been described.14 These delays serve neither LV filling nor ejection. This is especially true in patients with CHF who have diastolic/relaxation abnormalities where LV inflow during early rapid filling is reduced and the time available for filling in late diastole becomes significant and may contribute to end-diastolic volume and stroke volume.

A nother adverse consequence of a prolonged AV interval is diastolic AV regurgitation, which was found in approximately 60% of patients with PR interval prolongation (mean PR interval 264 ms) and normal LV systolic function.13 Diastolic or presystolic mitral regurgitation occurs because of the development of a ventriculo-left atrial pressure gradient in late diastole induced by the atrial contraction. When the PR interval is normal or short, diastolic mitral regurgitation cannot be detected because tight closure of the AV valve is accomplished by rapid elevation of intraventricular pressure resulting from ventricular contraction. The pathophysiologic changes associated with prolonged PR interval, i.e. decreased preload associated with decreased filling time and abnormal timing of the atrial contraction, result in decreased stroke volume and pulse pressure (Fig. 3).

It should be stressed that, in patients with CHF and LBBB, long mechanical AV delay is present even in the setting of a normal PR interval.15 The LBBB delays LV ejection as a result of delayed ventricular depolarization. Consequently, there is also a mechanical delay between the left atrium and the LV. Therefore, a “nonphysiologic,” short electrical AV interval may be preferable.16,17
Von Bibra et al.\textsuperscript{14} noted that, in paced patients with AV intervals of 150 ms (or longer), mitral valve closure frequently occurs before ventricular systole. This was in contrast with narrow QRS complexes, where PR intervals of more than 200 ms were usually required for mitral valve closure to precede ventricular contraction. The difference between the interval required for atrial contraction to produce mitral closure resulted from the longer delay in the onset of LV systole in paced patients. The "functional" AV interval in paced patients lasts 80 ms longer than in patients with narrow QRS and similar PR interval. Therefore, they proposed that AV delays of 50–100 ms should be sufficient to maintain the normal intervals between atrial and ventricular contraction in paced patients.\textsuperscript{14} In addition, a short AV delay did not result in a premature cut-off of the atrial A wave by ventricular systole, due, in part, to a delay in ventricular contraction after the pacing spike. It has also been noted that, in some patients, there may be a delay between the atrial spike and atrial contraction, which may vary between 30 and 120 ms, and should be added to the AV delay.\textsuperscript{14,18} In a recent publication by Auricchio et al.,\textsuperscript{19} the optimal AV delay during acute biventricular (BiV) pacing was 120 ms, although considerable individual variation was seen.

In this context, Hochleitner’s 1990 study\textsuperscript{16} reported significant clinical improvement in 17 patients with sinus rhythm and severe CHF with average LVEF of 15% who received conventional dual-chamber pacemakers programmed to an AV delay of 100 ms. Remarkable clinical improvement was noted with increase in blood pressure and LVEF, and decreased heart size, heart rate, and LV dimensions. None of the patients were rehospitalized for CHF after pacemaker implantation. It was believed that shortening of the AV delay might have accounted for some of this dramatic clinical improvement. Multiple studies assessing the role and hemodynamic effects of dual-chamber pacing in patients with CHF followed Hochleitner’s publication. Shortening of the AV delay by pacing was found to improve cardiac hemodynamics in some,\textsuperscript{21,17} but not all, subsequent studies.\textsuperscript{15,17} Brecker et al.\textsuperscript{27} reported that dual-chamber pacing (i.e. DDD mode) with a short AV interval eliminated presystolic mitral regurgitation (also noted in patients with severe LV dysfunction and normal PR interval), doubled the ventricular filling time in some cases, and increased stroke volume and cardiac output. Nishimura et al.\textsuperscript{22} performed hemodynamic studies during DDD pacing at various AV delays in 15 patients with LVEF less than 19%. Four patients had LBBB, 1 had RBBB, and 2 were paced. In 8 patients with a PR interval of more than 200 ms, AV interval optimization resulted in improved cardiac output, LV end-diastolic pressure, LV filling times, and abolished mitral regurgitation. However, in the 7 patients with normal baseline PR interval, the cardiac output—decreased during pacing and filling time—did not change.\textsuperscript{22} Therefore, in this study, cardiac performance was improved by DDD pacing and short AV delay only in patients with long PR intervals, short LV filling time, and long duration of mitral regurgitation.

The above-mentioned favorable results, however, could not be reproduced in other studies.\textsuperscript{21,23} In a crossover, randomized study, Gold et al.\textsuperscript{21} compared temporary septal or outflow pacing with sinus rhythm in 13 patients with CHF. Overall, pacing did not significantly improve cardiac output or right heart hemodynamics, and a subgroup analysis revealed no influence of a pre-existing long PR interval on the outcome. In another study involving 12 patients with compensated CHF,\textsuperscript{20} short-paced AV delays of 100 ms significantly improved the LV filling time by 37 ms (p<0.01), but there was also a drop in cardiac output that was not significantly different from the control and, with an AV delay of 60 ms, stroke volume and cardiac indices declined. In another study,\textsuperscript{24} septal DDD right ventricular (RV) pacing significantly increased cardiac output compared to no pacing (4.9±8 L/min vs. 4.1±7 L/min, p=0.04), but the difference was not significant when a comparison was made with RV apical DDD pacing (4.4 L/min, p=NS).

Although shortening of the AV interval has not been consistently shown to improve hemodynamics when patients are studied in the supine position at rest, prolonged PR intervals could be more detrimental during physical activity, when the increase in heart rate will additionally.
shorten an already reduced ventricular filling time. Longer AV intervals have an increasingly greater negative influence on filling time as heart rate increases.\textsuperscript{14} For example, at an AV delay of 150 ms, the filling time was reduced by 60 ms and this reduction increased to 130 ms when the delay was 250 ms. In fact, at an AV delay of 250 ms, the filling time was close to zero if the cardiac cycle length was 405 ms.\textsuperscript{14} Several studies have challenged the role of short AV interval in improving exercise capacity.\textsuperscript{25} Some of these studies have concluded that different AV intervals do not affect the maximal exercise capacity, maximal oxygen uptake, and minute ventilation, and that the ability to increase the ventricular rate is the most important factor for maximal physical performance. These studies, however, have included only patients without structural heart disease with normal ventricular function, and these conclusions may not apply to patients with significant LV dysfunction.

**Intraventricular conduction delay:** During LBBB there is delayed activation of the lateral wall of the LV. Different studies have demonstrated the adverse hemodynamic effects of an LBBB. Decreases in $\frac{dP}{dt}$ (50% [Fig. 4]), cardiac output (20%), mean arterial pressure (30%), and LVEF have been reported in patients with LBBB even in the presence of normal LV function and EF.\textsuperscript{26-30} Grines et al.\textsuperscript{26} showed a depressed septal function in patients with LBBB compared with those with narrow QRS complexes. As a result of this decreased septal contribution, the global LVEF was significantly reduced in these patients (54\%±7\% vs. 62\%±5\%, p<0.005). These authors also noted significant interventricular dysynchrony, with the LV contraction occurring an average of 85 ms after the onset of the RV contraction. Other hemodynamic abnormalities resulting from LBBB are listed in Table 1.\textsuperscript{15,31} In a study with exercise radionuclide angiography, it was demonstrated that patients with rate-dependent LBBB do not exhibit the normal increase in LVEF typically seen during exercise in patients with a narrow QRS complex (Fig. 5).\textsuperscript{28}

### Table 1. Hemodynamic/mechanical changes due to LBBB

| Decreased septal contribution to global LVEF | Prolonged LV contraction, ejection, and relaxation | No increase in LVEF with exercise |
| RV contraction precedes LV by 85 ms | Filling of RV precedes that of LV by 110 ms | Late LV sites still depolarizing in early diastole |
| Septum displaced towards LV during RV contraction | Delayed aortic/mitral opening and closure | Worsening of volume and duration of mitral regurgitation |

LBBB: left bundle branch block; LV: left ventricular; LVEF: left ventricular ejection fraction; RV: right ventricular

In 50 patients with CHF and wide QRS complexes, Xiao et al.\textsuperscript{31} described a positive correlation between the QRS width and the duration of mitral regurgitation, LV contraction and relaxation times, and negative correlation with the peak rise in LV pressure. In addition, the prolongation of isovolumic contraction and relaxation times decreased the LV filling time to a critical value of 200 ms or less in patients with the longest QRS durations. The morphology of the QRS complex (typical RBBB or LBBB or nonspecific block) seemed to have no direct influence on the magnitude of the abnormalities in this population. Left axis deviation was associated with the longest QRS duration and more severe electromechanical abnormalities.

Curry et al.\textsuperscript{32} developed a technique with tagged magnetic resonance imaging to stain the LV to reveal the

![Fig. 4. Effect of intermittent LBBB on ventricular contractile function. An LBBB results in a decrease in systolic pressure, pulse pressure, and $\frac{dP}{dt}$. (Reprinted from Takeshita A, Basta LL, Kioschos JM, Effect of intermittent left bundle branch block on left ventricular performance, Am J Med, 1974; 56: 253. Copyright 1974, with permission from Excerpta Medica Inc.)](image)

![Fig. 5. Changes in left ventricular ejection fraction (LVEF) with exercise in patients with normal conduction and rate-dependent left bundle branch block (RDLBBB). An RDLBBB prevents the increase in LVEF that normally occurs during exercise. In the RDLBBB group there is an initial increase in LVEF, similar to the normal conduction group, followed by an abrupt drop in LVEF when the RDLBBB develops. (From Bramlet DA, Morris KG, Coleman RE. Effects of rate-dependent left bundle branch block on global and regional left ventricular function. Circulation 1983; 67: 1062. Reproduced with permission.)](image)
strain patterns. In the absence of an LBBB, ventricular contraction was synchronous with symmetric distribution of the strain pattern. However, in the presence of an LBBB, the authors found that distribution of wall strain was nonuniform during systole. The septum shortened first followed by stretching on the lateral wall; then the lateral wall shortened and stretched the septum. As the lateral wall was over-preloaded, the lateral wall was over-stretching the septum at the end of the contraction. Therefore, in the presence of an LBBB, the ventricle pumps ineffectively and there is nonuniform wall strain in the myocardium.

An LBBB may also facilitate and worsen systolic mitral regurgitation. The slow ventricular activation can magnify the mechanical asynchrony between different ventricular regions, in particular, between the septum (posterior papillary muscle) and the free wall (lateral papillary muscle), and also adversely influence the timing of force development in the lateral papillary muscle.15

Cardiac Resynchronization

In 1994, Cazeau et al.33 and Bakker et al.34 published the first case reports on the use of epicardial Biv pacing in patients with advanced CHF and a wide QRS complex. In 1998, Daubert et al.35 published the results of the first fully transvenous permanent Biv pacemaker.

In contrast to the inconsistent results seen with standard dual-chamber pacing for CHF, the results with Biv pacing and CHF with a wide QRS complex have been positive and fairly consistent. Approximately 75% of appropriate candidates improve their functional capacity, as discussed later. Approximately 10% of patients with CHF admitted to a primary care hospital were considered candidates for cardiac resynchronization therapy (CRT). This, however, may be an overestimation, as the study was based on a cutoff QRS duration of 120 ms. When a QRS complex of 150 ms was used, only half of these patients (i.e. 5%) were believed to be candidates for Biv pacing.36 The average age of the patients in this study was 79 years, considerably older than the mean age of 60–65 years of subjects enrolled in some Biv pacing studies,37 so the patient population may not reflect the same type of patients enrolled in other clinical trials.

Acute hemodynamic effects of resynchronization:

Several studies done on acute hemodynamics are depicted in Table 2. The first hemodynamic study with temporary epicardial Biv pacing was published by Foster et al.38 and included a series of 18 post-coronary bypass surgery patients with no conduction system disease. Atio-Biv pacing improved cardiac output and decreased systemic vascular resistance compared with atrial, atrio-RV, and atrio-LV pacing.38 Since then, multiple studies have assessed the hemodynamic effect of temporary Biv pacing (and sometimes LV pacing alone) in patients with CHF and a wide QRS complex, usually an LBBB.19,39–41 The end-points analyzed in these studies generally included the LV dp/dt, systolic blood pressure, and pulse pressure; parameters that acutely improved. It is not clear if improvement in acute hemodynamic parameters predicted improved clinical outcome.

Auricchio et al.19 studied 27 patients with severe LV dysfunction and wide QRS complexes (LVEF 21%±6%, and QRS duration 168±29 ms). They assessed the role of Biv pacing versus LV pacing alone (via the coronary sinus) and the corresponding optimal AV interval for maximal acute benefit. The dp/dt, arterial systolic pressure, and pulse pressure were significantly greater with Biv pacing compared with the results during RV pacing (p<0.01); and the LV pacing effects in dp/dt were greater than those seen during Biv pacing (p<0.01). In this study, the AV delay was a significant determinant of LV systolic parameters (Fig. 6), especially in patients with wider QRS complexes. However, the optimal AV delay varied widely among patients and often differed for pulse pressure and dp/dt. In this study, the 6 patients with narrower QRS complexes (<150 ms) had predominantly negative LV systolic changes with pacing.
Kass et al. 40 studied 18 patients with CHF (LVEF 19%±17%, QRS duration 157±36 ms). R V apical or midseptal pacing had negligible contractile or systolic effects. However, LV free wall pacing raised LV dp/dt by 23%±19% and pulse pressure by 18%±18% (p< 0.01). BiV pacing (with LV pacing via the coronary sinus) yielded less change than LV pacing: 12%±9% increase in dp/dt, p<0.05 compared to LV pacing.

Pressure–volume loops in 11 patients revealed increased stroke work and lower end-systolic volumes with LV pacing (Fig. 7). Importantly, the basal QRS duration positively correlated with the change in dp/dt (p=0.0005) (Fig. 8), although pacing was not associated with QRS narrowing. Similar to the study by Auricchio et al.,19 the AV delay had less influence on LV function than the pacing site (i.e. LV v. BiV), although the optimal AV interval averaged 125±49 ms.

In 27 patients studied by Blanc et al.,41 BiV and LV pacing resulted in significant increases in systolic blood pressure (p<0.03) and significantly lowered pulmonary capillary wedge pressure and v wave (p<0.01 and p<0.001, respectively) (Fig. 9). The results with LV pacing alone were similar to those obtained with BiV pacing. In contrast, RV apical or outflow tract pacing had no effect on these hemodynamic parameters. Saxon et al.43 reported that pressure by 6±4% (p<0.0005). Only a small trend was noted between improvement in dp/dt and QRS narrowing, and no relation between QRS change and pulse pressure changes. Patients with lower dp/dts had the greatest changes in this parameter, and no change in pulse pressure with LV pacing. LVEF was a weaker predictor of changes in dp/dt and pulse pressure with LV pacing. In this study, the greatest improvements with LV pacing (i.e. increase >25% in dp/dt, and increase >10% in pulse pressure) occurred in patients with baseline dp/dt <700 mm Hg/s and QRS >155 ms. The authors felt that this could be translated to a 40%–50% rise in cardiac output.42

In 27 patients studied by Blanc et al., BiV and LV pacing resulted in significant increases in systolic blood pressure (p<0.03) and significantly lowered pulmonary capillary wedge pressure and v wave (p<0.01 and p<0.001, respectively) (Fig. 9). The results with LV pacing alone were similar to those obtained with BiV pacing. In contrast, RV apical or outflow tract pacing had no effect on these hemodynamic parameters. Saxon et al.43 reported that...
echocardiographic LVEF improved with BiV pacing but not with other pacing modalities. In this study, BiV pacing restored the normal segmental LV contraction sequence when compared to baseline.

Therefore, the acute hemodynamic benefit was not associated with any significant QRS narrowing in these studies, although patients with the wider QRS tended to obtain the most benefit from BiV or LV pacing. Conversely, patients with narrower QRS complexes (i.e., <150 ms) had less or no hemodynamic improvement with these pacing modalities.

In addition, it was noted in these studies that hemodynamic improvement was immediate upon initiation of pacing, and the opposite was also true—the hemodynamics worsened rapidly after cessation of pacing (Fig. 10).
Cardiac resynchronization and myocardial performance: Although there are abundant data suggesting the clinical benefit of CRT, the mechanisms by which LV and BiV pacing improve myocardial performance are complex and not well understood (Table 3). Unrelated to BiV pacing, CRT can shorten the PR interval, which can provide hemodynamic benefits. Patients with wide QRS complexes exhibit interventricular and intraventricular dys synchrony. Interventricular dyssynchrony is an asymmetric RV or LV contraction pattern, whereas intraventricular dyssynchrony represents discontinuous progression of contraction between adjacent ventricular segments. The degree of interventricular dyssynchrony in a given patient is dependent upon the type of bundle branch block, the site(s) of block, and the degree of myocardial dysfunction. Kerwin et al. using scintigraphic studies, showed that BiV pacing improved interventricular dyssynchrony in 13 patients with CHF and wide QRS complexes who had implanted BiV pacemakers. The magnitude of this correction correlated with improvements in LVEF (r=0.69, p<0.01), which improved by 35%. These authors believed that pre-excitation of a critical mass of late contracting ventricular myocardium may shorten the delay in RV and LV emptying, and that simultaneous activation of the LV and RV may improve ventricular septal coordination. BiV pacing did not improve intraventricular dyssynchrony. In this study, patients with lesser degrees of interventricular dyssynchrony (QRS <120 ms) also demonstrated improved LVEF, which suggested that additional mechanisms may contribute to improved LVEF, irrespective of interventricular dyssynchrony.

Shortening of the QRS duration may be a marker of improved ventricular synchrony during BiV pacing. It would seem logical that better “electrical resynchronization” is achieved when the QRS duration shortens during BiV pacing, and this could translate into better LV mechanical performance. Shortening of the QRS duration with BiV pacing could then be an easy way to predict clinical improvement, or to identify the optimal pacing sites in the LV epicardial surface. However, this has not been consistently demonstrated. For example, during acute studies, hemodynamic improvement with BiV pacing occurred in the absence of QRS shortening. Acute hemodynamic improvement was also seen in patients with LV pacing alone, which often widens the QRS interval; some patients responded better to LV than to BiV pacing.

Alonso et al. initially reported, in a noncontrolled study of 26 patients with CHF and conduction abnormalities, that 73% of the patients showed improvement by BiV pacing. The only parameter that differed significantly between the responders and nonresponders was the QRS duration under BiV pacing. The responders had a significantly shorter QRS during BiV pacing than at baseline (154±17 ms vs. 179±22 ms, p<0.05) compared with the nonresponders (177±26 ms vs. 176±30 ms). In a follow-up study of 103 patients by the same investigators, the mortality was higher in patients whose QRS duration was not decreased by BiV pacing. However, in the Multisite Stimulation in Cardiomyopathy (MUSTIC) Study, no significant shortening was noted with BiV pacing (175±19 ms vs. 172±22 ms), in spite of significant clinical benefit. Other studies have also reported clinical improvement in the absence of QRS shortening during BiV pacing. Reuter et al. described 9 patients in whom the QRS duration prolonged during active BiV pacing (baseline QRS duration 158±57 ms vs. 188±38 ms during BiV pacing [p<0.02]). Seven of these 9 patients had clinical improvement during follow-up. It is not clear how the QRS would widen during BiV pacing, but this finding has also been reported by another group. In the latter study, however, patients with prolongation of the QRS during BiV pacing had no clinical improvement.

Myocardial oxygen consumption was found to significantly decrease with temporary BiV pacing despite increased LV contractility (Fig. 11). In contrast, the use of dobutamine in the same patients titrated to achieve a similar systolic blood pressure as during BiV pacing increased the LV contractility at the expense of significantly increasing myocardial oxygen consumption (Fig. 12). Other mechanisms such as decreased levels of norepinephrine and release of vasodilatory

Table 3. Potential mechanisms of cardiac resynchronization

<table>
<thead>
<tr>
<th>AV interval optimization/shorter AV delay</th>
<th>Biventricular pacing</th>
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<tbody>
<tr>
<td>Decreased diastolic AV valve regurgitation</td>
<td>Improves interventricular synchrony</td>
</tr>
<tr>
<td>Improved filling time</td>
<td>Synchronizes septal and LV free-wall contraction</td>
</tr>
<tr>
<td>Improved ventricular preload</td>
<td>Decreases mitral regurgitation</td>
</tr>
<tr>
<td>Decreased pulmonary venous pressure</td>
<td>Coordinates papillary muscle contraction?</td>
</tr>
<tr>
<td>Increased pulse pressure</td>
<td>Remodeling of LV geometry?</td>
</tr>
</tbody>
</table>

AV: atrioventricular; LBBB: left bundle branch block; LV: left ventricular
substances\textsuperscript{51} may also be involved in the improved cardiac function witnessed during BiV pacing.

As previously noted, LBBB may facilitate and worsen mitral regurgitation. BiV pacing may decrease mitral regurgitation by different mechanisms such as alteration of the geometry of the LV and resynchronization of papillary muscle control\textsuperscript{41} (Figs 13 and 14). Besides improving ventricular performance, BiV pacing may have antiarrhythmic properties. The frequency of ventricular arrhythmias on 24-hour Holter monitoring significantly decreased during BiV pacing compared to sham pacing (p<0.001) in 20 patients.\textsuperscript{52} In another study, active BiV pacing diminished the number of antitachycardia pacing episodes in 32 patients.\textsuperscript{53} These findings were not supported by other studies where BiV pacing did not affect the incidence nor the time to first recurrence of sustained ventricular tachycardia (VT) in patients with BiV pacing and implantable cardioverter defibrillators (ICD).\textsuperscript{54} The clinical importance of these findings remains unclear at the present time.

Fig. 11. LV and BiV pacing. (A), individual patient changes in mechanical and energetic parameters comparing baseline control (Con) with left free wall VDD pacing (LV pace) or with BiV pacing (BiV pace). In both instances, systolic function improved as myocardial oxygen consumption (MVO₂) declined. (B), summary data displaying percentage changes induced by LV free wall (top) or BiV stimulation (bottom). (From Nelson GS, Berger RD, Fetics BJ, Talbot M, Spirelli JC, Hare JM, et al. Left ventricular or biventricular pacing improves cardiac function at diminished energy cost in patients with dilated cardiomyopathy and left bundle-branch block. Circulation 2000; 102: 3056. Reproduced with permission.)

Fig. 12. Relationship between increase in dp/dt and myocardial oxygen consumption (MVO₂) during LV pacing versus dobutamine in the same patients. Although a similar increase in dp/dt is achieved with dobutamine, there is a significant increase in myocardial oxygen consumption, compared with LV pacing. (From Nelson GS, Berger RD, Fetics BJ, Talbot M, Spirelli JC, Hare JM, et al. Left ventricular or biventricular pacing improves cardiac function at diminished energy cost in patients with dilated cardiomyopathy and left bundle-branch block. Circulation 2000; 102: 3057. Reproduced with permission.)

Fig. 13. Significant mitral regurgitation with synchronization Off versus during BiV pacing.

In a recent study by Yu et al.,\textsuperscript{55} tissue Doppler echocardiographic evidence of reverse remodeling and improved synchronicity by simultaneously delaying regional contraction after BiV pacing therapy in heart failure was assessed in 25 patients with NYHA class III–IV. All patients had a QRS duration of less than 140 ms. Patients were assessed serially for up to 3 months after pacing and when pacing was withheld for 4 weeks. Tissue Doppler echocardiography was used to assess time to peak systolic function (Ts). There was significant improvement of EF, dp/dt, and myocardial performance index; decrease in mitral regurgitation, end-diastolic performance index (205±68 ml v. 168±67 ml, p<0.01) and end-systolic volume (162±54 ml v. 122±42 ml, p<0.01); and improved 6 min walk distance and quality-of-life score after pacing for 3 months. The mechanisms of benefits were defined as: (i) improved LV synchrony, as evident by homogeneous delay of Ts to a timing closest to the latest (usually the
lateral) segment abolishing the intersegmental difference in $T_s$ and decreasing the standard deviation of $T_s$ within the LV (37.7±10.9 ms vs. 29.3±8.3 ms, p<0.05) (Figs 15 and 16); (ii) improved interventricular synchrony; and (iii) shortened isovolumic contraction time (122±57 ms vs. 82±36 ms, p<0.05) but increased diastolic filling time. These benefits were pacing dependent because withholding the pacing resulted in the loss of these improvements.

Popovic et al.56 used tissue Doppler imaging (TDI) in a recent study to assess cardiac contractile function during resynchronization. A subgroup of 22 patients from the Multicenter InSync Randomized Clinical Evaluation (MIRACLE) study55 were analyzed using echocardiography and TID with pacing ON and OFF. The two-dimensional pulsed wave TDI was processed to construct strain maps of segments of the LV and RV. The study demonstrated that spatial and temporal heterogeneity of LV contraction decreased with CRT. The indices measured included the $te$ index (LV isovolumic contraction time=LV isovolumic

**Fig. 15.** Changes in the time to peak regional sustained systolic contraction ($T_s$) before (-) and after (?) BiV pacing. At baseline, there was marked regional variation in $T_s$ among the LV segments and between the left and right ventricles. The $T_s$ was earliest in the basal anteroseptal segment and latest in the basal lateral segment so that regional variation in $T_s$ was abolished. *p<0.05 vs. basal anteroseptal segment at baseline † p<0.05 when comparing the same segment before and after pacing therapy. (B): basal; M: mid; A: anterior; AS: anteroseptal; I: inferior; L, lateral; P: posterior; S: septal; RV: right ventricular. (From Yu CM, Chau E, Sanderson JE, Pan K, Tang M O, Fung WH, et al. Tissue Doppler echocardiographic evidence of reverse remodeling and improved synchronicity by simultaneously delaying regional contraction after biventricular pacing therapy in heart failure. Circulation 2002; 105: 442. Reproduced with permission.)

**Fig. 16.** Regional myocardial velocity curves obtained by tissue Doppler imaging at the basal septal and basal lateral segments. The two-dimensional pictures show movement of the myocardium toward the probe (during contraction) and away from the probe (during relaxation). (A) In a patient with left bundle branch block, there was delay in the onset and peak sustained systolic contraction ($S_{SM}$) in the lateral compared with the septal wall. Regional contraction and regional systole occurred in a haphazard manner in various segments as illustrated by the patchy areas (arrowheads). (B) After BiV pacing, there was a dramatic improvement in the synchronicity, as reflected by the overlapping of velocity curves in the basal septal and basal lateral segments and the homogeneous area in the two-dimensional picture. (C) Another patient with left bundle branch block had systolic paradoxical septal motion resulting in significant delay in peak $S_{SM}$ in the septal relative to the lateral wall (arrowheads). (D) After BiV pacing therapy, systolic synchronicity was achieved, as reflected by the superimposition of the myocardial velocity curves and the uniform area seen in the two-dimensional picture. (From Yu CM, Chau E, Sanderson JE, Fan K, Tang M O, Fung WH, et al. Tissue Doppler echocardiographic evidence of reverse remodeling and improved synchronicity by simultaneously delaying regional contraction after biventricular pacing therapy in heart failure. Circulation 2002; 105: 442. Reproduced with permission.)
relaxation/LV ejection time) and the 2 ratio (fraction of the cardiac cycle during which either LV ejection or filling occurs). The significance of these parameters lies in their ability to quantify the isovolumic (mechanically ineffective) portion of the cardiac cycle. A fall in tei index and rise in the 2 ratio will be consistent with improvement in ventricular mechanics.

**Clinical studies:** Several controlled and uncontrolled studies of CRT for the treatment of advanced CHF and wide QRS complexes have been published. In addition, there are multiple ongoing, randomized, controlled trials in the United States and Europe (Table 4).

The primary end-points of the BiV pacing studies include changes in 6 min walk distance, NYHA class, and the effect of CRT on quality of life as assessed by the Minnesota-Living-In-CHF score. Other end-points include VO2 during exercise testing, and LVEF. Total mortality is an end-point in some of the ongoing studies. The general inclusion and exclusion criteria for these trials are shown in Table 5.

The MUSTIC study enrolled patients with NYHA class III CHF, LVEF <35%, and QRS width more than 150 ms. It was a single-blind, crossover study with a 3-month treatment period comparing resynchronization therapy with control. All patients had devices implanted (92% success rate), with pacing leads in the RV and coronary sinus. Patients in sinus rhythm (67 patients, group 1) had an atrial lead placed as well. Patients in atrial fibrillation (AF) (64 patients, group 2), were recruited only if they had slow ventricular rate or AV junction ablation (discussed later). The study was powered to detect a 10% increase with 95% confidence intervals. Patients in sinus rhythm had a

### Table 4. Ongoing and completed clinical cardiac resynchronization trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Characteristics</th>
<th># Patients</th>
<th>Site</th>
<th>ICD arm</th>
</tr>
</thead>
<tbody>
<tr>
<td>MIRACLE</td>
<td>BiV pacing</td>
<td>300</td>
<td>US, C</td>
<td>No</td>
</tr>
<tr>
<td>MIRACLE ICD</td>
<td>BiV pacing + ICD indication</td>
<td>400</td>
<td>US, C</td>
<td>Yes</td>
</tr>
<tr>
<td>CONTAK-CD</td>
<td>BiV pacing + ICD indication</td>
<td>580</td>
<td>US</td>
<td>Yes</td>
</tr>
<tr>
<td>COMPANION</td>
<td>BiV pacing</td>
<td>2200</td>
<td>US</td>
<td>Yes (1/3 arms)</td>
</tr>
<tr>
<td>VECtor</td>
<td>BiV pacing (mortality study)</td>
<td>420</td>
<td>US, EUR, C</td>
<td>No</td>
</tr>
<tr>
<td>BELIEVE</td>
<td>BiV vs LV pacing with ICD indications (pilot)</td>
<td>75</td>
<td>I</td>
<td>Yes</td>
</tr>
<tr>
<td>INSYNC III</td>
<td>BiV pacing: asynchronous LV-RV</td>
<td>224</td>
<td>US, C,Eur</td>
<td>No</td>
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<tr>
<td>CARE-HF</td>
<td>BiV pacing (mortality study)</td>
<td>800</td>
<td>Eur</td>
<td>No</td>
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<tr>
<td>LV3P-CHF</td>
<td>LV versus RV pacing; CHF + indication brady pacing</td>
<td>NA</td>
<td>Worldwide</td>
<td>No</td>
</tr>
<tr>
<td>PAVE</td>
<td>AF: post-AV junction ablation</td>
<td>650</td>
<td>US, C</td>
<td>No</td>
</tr>
<tr>
<td>PATH-CHF II</td>
<td>Acute and chronic optimized LV, RV, BiV pacing; QRS ≤150 ms v. &gt;150 ms</td>
<td>64</td>
<td>Eur</td>
<td>If indicated</td>
</tr>
</tbody>
</table>

AF: atrial fibrillation; AV: atrioventricular; BiV: biventricular; C: Canada; CHF: congestive heart failure; Eur: Europe; ICD: implantable cardioverter defibrillator; I: Italy; LV: left ventricular; NA: not available; RV: right ventricular; US: United States

### Table 5. Criteria for cardiac resynchronization trials

<table>
<thead>
<tr>
<th>Inclusion criteria for CR trials</th>
<th>Exclusion criteria for CR trials</th>
</tr>
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<tbody>
<tr>
<td>Dilated cardiomyopathy (ischemic or idiopathic)</td>
<td>LVEF &gt;35%</td>
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<tr>
<td>LVEF 35% or less</td>
<td>Narrow QRS complex</td>
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<tr>
<td>Wide QRS complex: ≥120-150 ms</td>
<td>NYHA Functional class 1</td>
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<tr>
<td>CHF symptoms (most studies): NYHA class II or more</td>
<td>Indication or contraindication for pacing</td>
</tr>
<tr>
<td>Adequate CHF medical therapy</td>
<td>Recent myocardial infarction or revascularization</td>
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<tr>
<td>PR interval &gt;150 ms (some studies)</td>
<td>Acute myocarditis</td>
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<td></td>
<td>Unexplained syncope</td>
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<td></td>
<td>Hypertrophic cardiomyopathy</td>
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<tr>
<td></td>
<td>Other major health problems</td>
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<tr>
<td></td>
<td>(significant hepatic, renal)</td>
</tr>
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<td></td>
<td>Noncompliance</td>
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</table>

CHF: congestive heart failure; CR: cardiac resynchronization; LVEF: left ventricular ejection fraction; NYHA: New York Heart Association
significant increase in the 6 min walk distance, increase in peak exercise $O_2$ consumption, improvement in quality-of-life score, and significantly fewer hospitalizations (Figs 17 and 18). The optimal AV delay was 108±43 ms. More than 80% of patients preferred resynchronization to control ($p<0.001$). Mortality was low (4 patients) but usually occurred during the resynchronization period.

The MIRACLE study$^{55-59}$ was a prospective, randomized, double-blind, controlled trial of BiV pacing. The study included a total of 453 patients with CHF, an ejection fraction of 35% or less, and a QRS duration of 130 ms. Patients were randomly assigned to the CRT group (228 patients) or control group (225 patients) for six months, while conventional therapy for heart failure was maintained. The primary end-points were the NYHA functional class, quality of life and the distance walked in 6 min.

As compared with the control group, patients assigned to CRT experienced an improvement in the distance walked in 6 min (39 m vs. 10 m [$p=0.005$]), functional class ($p<0.001$), quality of life ($-18$ points vs. $-9$ points [$p=0.001$]) (Fig. 19), time on the treadmill during exercise testing (81 s vs. 19 s [$p=0.001$]) and ejection fraction (4.6% vs. -0.2% [$p<0.001$]). In addition, fewer patients in the group assigned to CRT required hospitalization than in the control group (8% vs. 15% [$p=0.05$]) (Fig. 20) or intravenous medications for treatment of heart failure (7% vs. 15% [$p<0.05$]). Implantation of the device was unsuccessful in 8% of the patients and was complicated by refractory hypotension, bradycardia or asystole in 4 patients (2 of whom died). There were 35 coronary sinus-related complications observed. Six of these complications (1%) involved coronary sinus dissection or perforation.
The median duration of the procedure was 2.7 hours (range 0.9–7.3 hours). After implantation, 20 patients required repositioning and 10 patients required replacement of the coronary sinus lead. Seven patients reported a pacemaker-related infection that required explantation. The results of this study thus indicated that CRT improved a broad range of parameters measuring cardiac function and clinical status in patients with moderate to severe heart failure and a prolonged QRS interval. Cardiac resynchronization also reduced the degree of ventricular dyssynchrony as evidenced by a shortened duration of the QRS interval. This was accomplished by an increase in the LVEF and a decrease in LV end-diastolic dimension and magnitude of mitral regurgitation.

The Pacing Therapies for Congestive Heart Failure (PATH-CHF) study was a European multicenter trial that started in 1995. It included an initial acute hemodynamic study to determine the most optimal pacing site and AV delay. Two right atrial (RA) leads and 1 RV lead were placed, followed by an epicardial LV screw-in lead. The 4 leads were connected to 2 different pacemaker generators to achieve AV and BiV pacing. This was then followed by either 1 month of pacing in the best univentricular mode, or 1 month of BiV pacing, randomly selected. The previously described end-points were assessed (6 min walk distance, NYHA class, quality-of-life score, and VO2). There were 42 patients with ischemic (n=13) or nonischemic (n=29) cardiomyopathies, with NYHA class of 3.1, and QRS duration of 175±32 ms. All end-points improved significantly during the month of pacing and declined during the month of no pacing, although the decline was not to pre-implant levels (Figs 21–23). Importantly, the benefit was maintained during the follow-up period.60 Whether the type of underlying heart disease has any influence on the clinical success of BiV has been assessed.

Fig. 20. Kaplan–Meier estimates of the time to death or hospitalization for worsening heart failure in the control and resynchronization groups. The risk of an event was 40% lower in the resynchronization group (95% confidence interval: 4%–63%; p=0.03). (From Abraham WT, Fisher WG, Smith AL, et al. Cardiac resynchronization in chronic heart failure N Eng J Med 2002; 346: 1853. Copyright 2002 Massachusetts Medical Society. All rights reserved.)

Fig. 21. In the PATH-CHF study, changes in the 6 min walk improved significantly during cardiac resynchronization, and declined during the month of no pacing, although they did not decline to pre-implant levels. (Adapted from Auricchio A, et al. for the PATH-CHF investigators, J Cardiac Fail, 1999; 5: 78. Copyright 1999 with permission from Elsevier Science.)

Fig. 22. In the PATH-CHF study, changes in the NYHA class improved significantly during cardiac resynchronization, and declined during the month of no pacing, although they did not decline to pre-implant levels. (Adapted from Auricchio A, et al. for the PATH-CHF investigators, J Cardiac Fail, 1999; 5: 78. Copyright 1999 with permission from Elsevier Science.)
by several studies. These studies have concluded that the response to BiV was similar, regardless of whether the cardiomyopathy was of ischemic or nonischemic etiology.\(^3\),\(^5\),\(^7\),\(^5\),\(^6\),\(^3\) Several uncontrolled, nonrandomized studies have also reported their experience with BiV pacing in CHF patients with widened QRS.\(^4\),\(^7\),\(^8\),\(^5\) Overall, the results are consistent, with improvement in clinical status, as evidenced by improved functional capacity and LVEF in about 75% of the patients.\(^4\),\(^6\) In one study, no clinical improvement was noted in patients with class IV CHF, poor functional capacity, and a markedly prolonged QRS.\(^6\) These findings were similar to those of a study by Leclercq et al.,\(^5\) where patients with advanced CHF did not improve and had high mortality due to pump failure.\(^5\)

**Hospitalizations for CHF:** Hospital care is a significant part of the economic burden of heart failure. Each year, approximately 35% of heart failure patients are admitted to the hospital.\(^2\) Therefore, considerable interest exists in determining the potential effect of CRT in reducing the hospitalization rate in this population. In the MUSTIC Study,\(^5\) the number of hospitalizations during the first crossover period was decreased during active treatment by two-thirds: 3 hospitalizations for CHF occurred during active pacing, as compared with 9 during inactive pacing (p<0.05). In an uncontrolled study of 16 patients,\(^5\) 13 patients were clinically improved by at least one functional class, and the 6 min walk distance improved from 375±83 m to 437±73 m. In this group of patients, the total number of heart failure-related hospital days was 183 the year before BiV pacing, compared with 39 the year after BiV pacing (p<0.01). Total heart failure hospitalizations also declined from 31 before BiV pacing to 7 after BiV pacing (p<0.01) (Fig. 24). Although these results were preliminary and involved a small number of patients, they were encouraging.

In the MIRACLE Study (Fig. 20), during the 6-month follow-up period, there were 50 hospitalizations for heart failure. Of these, 34 occurred in control patients remaining in hospital for a total of 363 days. In the resynchronization group there were 25 hospitalizations for heart failure in 18 patients, for a total of 83 days in hospital. The difference in frequency of hospitalizations between the two groups was significant (p=0.02).

**Resynchronization therapy and cardiac mortality:** The effect of CRT on cardiac mortality, particularly mortality from pump failure, is not clear at this point as published trials on their own have not been sufficiently powered to answer this question. However, total mortality is one of the end-points in several ongoing studies (i.e. Cardiac Resynchronization in Heart Failure [CARE-HF] Study and Ventricular Resynchronization Therapy Randomized Trial in Heart Failure Patients Without Pacing Indications [VECTOR] Study, Table 4). In the MUSTIC Study (58 randomized patients),\(^5\) mortality from pump failure was surprisingly low for this class III NYHA population; 1 patient died in heart failure during the no-pace mode, and 2 patients had SCD during active treatment. In an uncontrolled study of 50 patients with severe CHF treated with BiV pacemakers, mortality was 52% in patients with class IV CHF compared to 12.5% for patients with class...
III CHF during a 15-month follow-up period.\textsuperscript{58} The InSync trial,\textsuperscript{48} an uncontrolled, prospective study in which 68 patients with CHF had successful implantation of BiV devices, had a mortality rate of 16.6% at 6 months’ follow-up (compared with 5% in the MUSTIC Study).\textsuperscript{37} A preliminary study involving 511 patients (442 patients with an ICD with BiV pacing capabilities; 69 patients with conventional ICD) suggests that BiV pacing with ICD capabilities may impact survival favorably when compared to a group treated with ICD therapy alone.\textsuperscript{66} In the PATH-CHF study,\textsuperscript{60} it was felt that BiV pacing, combined with an ICD might have prevented 4 of 9 deaths (44%). In the MIRACLE Study, using intention-to-treat analysis, there were 16 deaths in the control group and 12 deaths in the resynchronization group (Fig. 20).

Four recent, randomized clinical trials of BiV pacing on 1634 patients evaluated the effectiveness of CRT in the prevention of death in patients with heart failure.\textsuperscript{67} Pooled data from these trials showed that CRT reduced death from progressive heart failure by 52% (Fig. 25) relative to controls (odds ratio: 0.49; 95% confidence interval: 0.25–0.95). Progressive heart failure mortality was 1.7% for CRT patients and 3.5% for controls. A trend was evident showing that CRT reduced all-cause mortality (odds ratio: 0.77; 95% confidence interval: 0.51–1.18). The trials failed to demonstrate that CRT had a statistically significant effect in preventing death in patients who were not in heart failure (odds ratio: 1.15; 95% confidence interval: 0.65–2.02). There was no evidence that CRT impacts mortality in patients with ventricular tachycardia and/or ventricular fibrillation.

**Cardiac resynchronization in CHF and AF:** The role of BiV pacing in patients with CHF and wide QRS has been studied mainly in patients with sinus rhythm, and a history of AF has been an exclusion criteria in some of the controlled studies (i.e. MIRACLE, COMPANION [Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure]). During acute testing, Blanc et al.\textsuperscript{41} reported improvement in hemodynamic parameters in 6 patients with AF and temporary BiV pacing. Other studies\textsuperscript{68} also suggest improvement of various degrees when patients with AF were paced with temporary BiV leads.

In the group II of the MUSTIC Study,\textsuperscript{69} patients with chronic AF and slow ventricular response who were referred for pacing were randomized to active BiV ventricular-based pacing (VVIR) or right ventricular VVIR pacing, both at 70 bpm. No difference in the 6 min walk distance, peak VO\textsubscript{2}, quality-of-life score, or frequency of hospitalizations was observed using an intention-to-treat analysis. With a secondary analysis of only those patients with properly functioning pacemakers, BiV pacing was associated with a 9% increase in the 6 min walk distance, a 12% increase in peak VO\textsubscript{2}, and an 11% improvement in quality-of-life score. In the (uncontrolled) Italian InSync study (n=190 patients),\textsuperscript{70} the presence of AF in 25 patients did not seem to adversely influence the role of BiV pacing in improving functional status. Other uncontrolled studies\textsuperscript{68,71} of patients with chronic AF showed similar results where AF did not preclude benefit from BiV pacing. However, in some of these studies,\textsuperscript{71} AV junction ablation was used to control the rate and to allow continuous BiV pacing. Therefore, the effect of BiV pacing may be confounded by the rate control and rhythm regularization effect of AV junction ablation (this in light of previous studies with single-site RV pacing that have shown improvement in LV function after AV junction ablation in patients with AF).\textsuperscript{72,73}

The role of BiV pacing in patients with LV dysfunction, wide QRS complex and chronic AF needs to be established in larger studies. Limited data suggest that BiV pacing may also benefit suitable patients with chronic AF. The PAVE (Left Ventricular-based Cardiac Stimulation Post-AV Node Ablation Evaluation) study (Table 4) is currently assessing the role of BiV pacing after AV junction ablation in a controlled fashion.

**Cardiac resynchronization in patients with RBBB and in other clinical settings:** Approximately 10% of patients with CHF have a widened QRS with an RBBB pattern on the surface ECG. RBBB is common in patients with Chagas’ disease and CHF.\textsuperscript{1} Patients with RBBB may
also have significant conduction delays in the left bundle branch, which may manifest as left or right QRS axis deviation. The QRS duration in 12 patients with CHF and RBBB was 187±29 ms, comparable with the QRS duration with an LBBB. Preliminary studies in a small number of patients suggest that patients with RBBB tend to benefit more from BiV and RV stimulation than LV pacing. Therefore, improvement in cardiac function in patients with a wide QRS may be related to whether the ventricle ipsilateral to the conduction defect is stimulated. BiV pacing may also be beneficial in patients with first-degree AV block and a narrow QRS complex, or in patients with standard indications for pacing (i.e. complete AV block) in the absence of CHF or wide QRS complexes. Conventional ventricular pacing would be anticipated to reduce systolic function and thereby offset benefits from improved chamber filling, whereas BiV pacing may better maintain electrical and mechanical synchrony in such cases. In patients with CHF and pre-existing pacemakers, upgrading from single- or dual-chamber to BiV pacing may also result in functional benefit, especially if the patient is pacemaker dependent. Whether this will enhance function beyond that obtained from single-site pacing remains to be determined.

Technical Aspects and Implanting Techniques

In patients undergoing implantation of a CRT device, a total of 3 leads are used (Figs 26 and 27). In addition to standard RV and RA leads (if in sinus rhythm), a lead is placed into a branch of the coronary sinus to achieve epicardial LV pacing. Figure 28 depicts the detailed anatomy of the coronary sinus. Currently, this is the preferred approach for BiV pacing in these patients. To enter the coronary sinus, the subclavian vein approach is used and a guiding catheter is advanced into the RA and then into the coronary sinus. As the cardiac vein anatomy differs in individual patients, with wide variation seen in location and size of the branches, a coronary sinus venogram can be obtained to provide a “road-map” for manipulation of the pacing lead into one of the branches of the coronary sinus (Fig. 29). The coronary sinus anatomy can also be visualized during the delayed phase of the coronary angiogram (Fig. 30). Once the target vein is identified in the venogram, a pacemaker lead is advanced through the guidewire into one of the branches of the coronary sinus overlying the epicardial LV surface. Anatomically, a suitable branch is present in more than 90% of the patients. Two different leads are currently available: an “over-the-wire” system, where a guidewire is first placed in the coronary sinus branch and the lead is then advanced over this wire; and the second system, where a lead with a stylet is placed into the coronary sinus branch. Both have been tested with satisfactory results. Placement of the LV lead is limited to
available sites that provide reasonable pacing and sensing parameters. The implant procedure can be difficult because RA enlargement, LV dilatation and rotation, and obstruction of the coronary ostium by a Thebesian valve can make entering the coronary sinus or cannulating one of its branches challenging. Coronary sinus stenosis has been reported in patients with prior coronary heart surgery, possibly related to manipulation of the coronary sinus during retrograde cardioplegia. In spite of these technical difficulties, the reported success for implantation has been fairly good. In a study of 54 patients undergoing attempted

BiV pacemaker implantation, successful implantation was achieved in 49 of the 54 patients (91%). Lead dislodgment occurred in 5 patients. LV pacing thresholds were satisfactory and stable during follow-up (1.3 V and 1.6 V at implant and at 3-month follow-up, respectively). No significant complications occurred. Implant time significantly decreased in the second set of patients from 120 min to 90 min, respectively; as expected, there is a learning curve. In the MUSTIC Study, the implant success rate was 92% with 80% of the leads implanted in a lateral position. Other methods to achieve BiV pacing include trans-septal atrial puncture for endocardial LV stimulation or epicardially, requiring thoracotomy. Although the risk of embolic complications and associated surgical morbidity have limited the widespread use of these techniques, epicardial lead placement is an alternative if implantation of conventional BiV systems is unsuccessful.

**Pacing site:** In acute hemodynamic studies by Auricchio et al., pacing the lateral LV wall resulted in better pulse pressure and dp/dt than pacing the anterior or apical LV sites (Fig. 32). The rationale may be that, in the presence of an LBBB, these are the latest areas of the LV to be activated, and pacing these sites will provide maximal resynchronization. It is possible that lack of benefit from BiV pacing may be related, at least in some patients, to the optimal site in the LV not being paced. Data from patients with implanted devices to address the ideal site are not available at this time.

Additional studies are also needed to determine the optimal pacing sites in patients with ischemic cardiomyopathies and regional wall motion abnormalities; for example, an akinetic posterolateral wall will not be the optimal site for LV pacing in these patients.
LV pacing: Although BiV pacing has been consistently superior to RV pacing, the acute hemodynamic studies by Kass et al. and Auricchio et al. showed that some patients exhibited more improvement in dp/dt during LV pacing alone as compared to BiV pacing. Perhaps to achieve optimal hemodynamics the goal may not be to resynchronize both ventricles, but instead to eliminate the effect of an LBBB in the heart because LV pacing causes an RBBB pattern. The BELIEVE (Bi-Versus Left Ventricular Pacing: an Italian Evaluation on Heart Failure Patients with Ventricular Arrhythmias) study is the first to assess in a randomized, controlled fashion the role of LV pacing alone. (Table 4). Blanc et al. reported similar improvement in subjective and almost all objective parameters using LV pacing alone (n=18 patients) and BiV pacing (n=15 patients) at 6-month follow-up.

Asynchronous biventricular pacing: It is interesting that cardiac function may improve additionally during BiV pacing if there is a delay between RV and LV stimulation compared with simultaneous electric stimulation of the RV and LV. Preliminary studies suggest that a 30 ms interventricular delay (LV activated first) maximizes the benefit. Until recently, BiV devices did not allow programming such delay, but an ongoing study (i.e. InSync III) is assessing the role of BiV pacing with programmed interventricular delay.

RV bifocal stimulation: Recently, Pachon et al. described a novel pacing technique in 39 patients with CHF and wide QRS complexes who had an indication for pacemaker insertion (AV block in majority). The mean NYHA class was 3.1±0.8. The RV was paced simultaneously with one lead inserted in the apex and another in the high septum by the RV outflow tract. The authors noted improved LVEF, cardiac output, QRS narrowing, decreased mitral regurgitation, and improved quality-of-life score during follow-up. This is an interesting concept that needs to be confirmed in patients without indication for pacemaker implantation. The main advantage of this system would be a simpler and less technically challenging implantation.

Combined use of biventricular pacemakers and ICDs: ICDs have been shown to improve prognosis in patients at high risk of SCD. The incidence of SCD is highest in the general adult population, but it is virtually impossible for interventions to be universally applied to every patient. It is clear that heart failure patients and those with ventricular dysfunction represent an intermediate subgroup with a high annual incidence of SCD (Fig. 33). Heart failure patients experience SCD at 6–9 times the rate of the general population. However, in patients with advanced CHF, ICDs may not decrease mortality but rather change the mode of death from sudden...
to progressive CHF (Table 6). Conversely, a device with combined ICD and BiV pacing capabilities may provide mortality and morbidity benefits to patient with CHF that ICDs alone cannot produce. This type of device has been investigated in several multicenter, randomized trials. These devices are being implanted in patients with CHF and wide QRS complexes who have standard indications for ICD implantation (i.e. sudden death survivor, syncope with inducible sustained VT, or inducible sustained VT in patients with ischemic cardiomyopathy and nonsustained VT). In other studies, these devices are also being implanted in the absence of conventional ICD indications other than severe LV dysfunction, to assess the mortality impact of the ICD in this patient population at high risk of sudden death.

Conclusions and Remaining Issues Related to Cardiac Resynchronization

Given the consistent results of controlled and uncontrolled studies demonstrating that BiV pacing can improve functional capacity in patients with CHF, this novel pacing technique is becoming another tool in the armamentarium for the treatment of patients with CHF with wide QRS complexes. A great deal of enthusiasm currently exists to further define the indications, advantages, shortcomings, and pathophysiology involved in the use of this technique.

In countries without cardiac transplant programs or in patients who are not candidates for transplant, BiV pacing may offer the last hope, beyond maximal pharmacologic therapy, to improve the quality of life. Even in patients listed for cardiac transplantation, BiV pacing may improve functional capacity, and, in some cases, delay the need for transplantation.88

Table 6. Sudden death by severity of heart failure symptoms

<table>
<thead>
<tr>
<th>NYHA functional class</th>
<th>Annual mortality (%)</th>
<th>Sudden death (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>II</td>
<td>5–15</td>
<td>50–80</td>
</tr>
<tr>
<td>III</td>
<td>20–50</td>
<td>30–50</td>
</tr>
<tr>
<td>IV</td>
<td>30–70</td>
<td>5–30</td>
</tr>
</tbody>
</table>


There is still a lot to learn about CRT, and many questions remain unanswered. Some of these questions include the role of BiV pacing in mortality related to pump failure, the possibility of slowing the progression of LV dysfunction or remodeling with BiV implantation earlier in the course of the disease, the economic effect of this type of treatment; how the best candidates for BiV pacing can be identified, and the ideal sites for LV pacing. Finally, technical improvements in lead design and the development of tools to facilitate easier cannulation of LV pacing will be required to allow widespread implementation of this technique.

Acknowledgments

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Coronary sinus stenosis in patients with congestive heart failure and previous heart surgery. J Am Coll Cardiol 2001; 37: 116A
Dilated cardiomyopathy (DCM) in children is a rare but serious disorder. The natural history of DCM in children has been studied for over 2 decades, but remains inadequately characterized. Previous hospital-based clinical studies of DCM in children reported a small number of cases, included a heterogeneous group of patients, and provided conflicting results, with mortality rates of pediatric DCM varying from 16% to 72%.1–13 More recently, systematic population-based registry data from some parts of the world have begun to provide important epidemiological information on DCM in children.14–16 However, to the best of our knowledge, there are no data regarding the prognosis of DCM in Indian children. With the availability of heart transplantation in India, such prognostic information is clearly required. In the absence of population-based surveys, we sought to characterize the prognosis of DCM in a relatively large number of children seen at a tertiary care hospital. To minimize the loss of information due to drop-outs, we limited our analysis to patients from a pre-specified geographic region.

**Background:** The aim of this study was to ascertain the clinical course and prognosis of dilated cardiomyopathy in Indian children.

**Methods and Results:** The records of 82 children with dilated cardiomyopathy (50 males), less than 12 years of age (mean age 2.9±3.07 years), were retrospectively reviewed. Clinical variables, laboratory parameters, and serial echocardiograms were analyzed. On a mean follow-up of 25.09 months (range 15 days–118 months), 9 out of 78 patients died (11.5%) (CI: 4.5%–18.5%). Mortality was 25% (6/24) in infants but the actuarial survival was 87% at 5 years in those diagnosed beyond infancy. Serial echocardiograms of 66 patients (80%) were available. Of these, 39 patients (59%) (CI: 47%–70%) improved, 12 (18%) (CI: 9%–27%) deteriorated or died, and 15 (23%) (CI: 13%–33%) remained unchanged during the follow-up. Among the prognostic variables, only age less than 1 year, higher cardiothoracic ratio, and a higher ratio of left ventricular diastolic dimension/posterior wall thickness was associated with a poor outcome on univariate analysis.

**Conclusions:** Dilated cardiomyopathy in children pursues a heterogeneous course with a high mortality in infants. A large number of children diagnosed beyond infancy improve or recover. Further characterization of prognostic variables is warranted. (Indian Heart J 2003; 55: 147–151)

**Key Words:** Dilated cardiomyopathy, Heart failure, Echocardiography

**Methods**

The medical records of all the children with a diagnosis of DCM seen at the cardiac clinic of the All India Institute of Medical Sciences, New Delhi from January 1992 to December 2001 were reviewed. In an attempt to maximize information in a representative group of patients, only children within a pre-specified geographic region were included. The specified region was defined as within 250 km of Delhi. Follow-up information on this group of patients was obtained from the outpatient records. The patients were contacted by letter or telephone whenever required or feasible.

The diagnosis of DCM was based on clinical examination and echocardiographic evidence of systolic ventricular dysfunction (fractional shortening <20%).14 All the patients fulfilled the criteria for the diagnosis of DCM according to the WHO/ISFC task force.17 Secondary causes of ventricular dysfunction, specifically, coronary artery abnormalities, Takayasu’s aortoarteritis, tachycardio-myopathy, and rheumatic heart disease, were carefully excluded in all the patients. Detailed clinical evaluation, routine laboratory tests, electrocardiogram (ECG), chest X-ray, and serial echocardiograms were available and analyzed for all the patients. The following
data were recorded for each patient: age, gender, the age of onset of symptoms, duration of symptoms, history suggestive of viral illness at the onset, family history of heart disease or of sudden death, New York Heart Association (NYHA) functional class, cardiothoracic ratio on chest X-ray, left ventricular hypertrophy (LVH) by age-dependent voltage criteria, and ST–T changes and arrhythmias on ECG. In addition, several echocardiographic variables, including left ventricular dimensions, ejection fraction, left atrial/aortic ratio (LA/AO), presence of mitral regurgitation, and left ventricular end-diastolic dimension/posterior wall (LVED/PW) thickness ratio were analyzed. Cardiac catheterization, endomyocardial biopsy, or other metabolic investigations were conducted in only a few cases based on clinical discretion.

The clinical course, treatment and outcomes were noted. Patients were grouped according to the outcome as improved or cured (group I), no change in clinical status (group II), and worsened or dead (group III). Patients with improved clinical status and an increase in the ejection fraction >5% were defined as improved (group I). Of these, patients with normalization of left ventricular dimensions and no clinical symptoms were labeled as cured. No change or ≤5% change in the ejection fraction was considered as unchanged (group II). Clinical worsening and/or decline in the ejection fraction >5% was classified as worsened (group III). Whenever a death was recorded, an attempt was made to ascertain the probable cause of death from records, letters or historic evidence. The time of death from the first presentation was noted.

Patients who had a follow-up of less than 3 months (unless dead) were classified as lost to follow-up.

Statistical analysis: For identifying the statistical significance of the difference among various categories of outcome, we applied one-way analysis of variance with post hoc analysis. For assessing the difference between infants and older children, we applied the Student’s t test for continuous variables and the Chi-square test for categorical variables. Survival analysis for the entire group, and according to age, was done by the Kaplan–Meier method with p value of <0.05 being taken as statistically significant. BMDP 7.0 statistical software was used for statistical analysis.

Results
One hundred forty-five children less than 12 years of age were diagnosed with DCM from January 1992 to December 2001 at our institution. Of these, 82 children were identified as residing in the pre-specified geographic region, and are the subjects of this study. Of these, 50 were males and 32 females. Their ages ranged from 1 month to 12 years (mean 2.9±3.07 years). The study group included 26 infants (31.7%).

Fifty-one patients were in NYHA class II and 31 (37.8%) had NYHA class III or IV symptoms at presentation. The baseline demographic data are shown in Table 1. These variables did not significantly differ from those of the patients (n=63) not included in this report, thus suggesting that the patient group from the specified region was a representative population of DCM as generally seen at our institution. A history suggestive of antecedent viral infection was found in 25 patients (30.5%) while family history of DCM was present in 3 patients (3.6%). LVH by voltage criteria was seen in 64 patients (78%) and 32 patients (39%) showed ST–T changes on ECG. Left bundle branch block, abnormal Q waves, and atrial flutter were seen in one patient each (1.2%). On chest X-ray, cardiomegaly was present in all the cases, and the mean cardiothoracic ratio was 66%±8.14%.

Table 1. DCM in children: baseline demographic variables (n=82)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean±SD</th>
</tr>
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<tbody>
<tr>
<td>Age (years)</td>
<td>2.9±3.07</td>
</tr>
<tr>
<td>Gender (M/F)</td>
<td>50/32</td>
</tr>
<tr>
<td>NYHA class III/IV (%)</td>
<td>38</td>
</tr>
<tr>
<td>History of antecedent viral fever (%)</td>
<td>30.5</td>
</tr>
<tr>
<td>Duration of illness at presentation (months)</td>
<td>5.8±12.12</td>
</tr>
<tr>
<td>Cardiothoracic ratio on X-ray (%)</td>
<td>66±8.14</td>
</tr>
<tr>
<td>Left ventricular hypertrophy on ECG</td>
<td>78%</td>
</tr>
<tr>
<td>ST–T changes</td>
<td>39%</td>
</tr>
<tr>
<td>LV ejection fraction</td>
<td>24.0±11.58</td>
</tr>
<tr>
<td>LVED/PW thickness ratio</td>
<td>8.61±2.51</td>
</tr>
</tbody>
</table>

DCM: dilated cardiomyopathy; LVED/PW: left ventricular end-diastolic dimension/posterior wall

Depressed left ventricular systolic function was seen in all the patients. The mean left ventricular ejection fraction (LVEF) was 24%±11.5%. An intracavitary thrombus was present in 2 of these 82 cases, which resolved with intravenous heparin therapy. The LA/AO ratio was 1.48±0.32 (range 0.89±2.47). Mitral regurgitation was seen in 45 patients (54.8%); it was trivial to mild in 35 (42%), moderate in 9 (11%) and severe in 1 patient (1.2%). The ratio of LVED/PW thickness, possibly an indirect marker of the relative adequacy of ventricular hypertrophic response, was 8.61±2.51 in the whole group. Cardiac catheterization was done in 8 patients and endomyocardial
biopsy in 3. Nonspecific changes consistent with DCM were seen in all 3 biopsies. There were no differences in the baseline variables in male compared to female children.

**Follow-up and outcome:** Clinical follow-up of more than 6 months was available in 78 patients (95.1%). The follow-up period ranged from 15 days to 118 months (mean 25.09±25.0 months).

**Survival analysis:** Nine patients died (11.5%) (95% CI: 4.5%–18.5%). All the deaths were considered to be due to heart failure. Death occurred within 15 days of presentation to up to 52 months later, but most (6/9) occurred within 6 months of presentation. Six of the 9 deaths occurred in those diagnosed in infancy. Thus, infants had a higher mortality (6/24 v. 3/54, p=0.009).

For the entire population, the actuarial survival was 76% at 118 months. The actuarial survival at 5 years was 59% in those diagnosed in infancy compared to 87% in children diagnosed beyond infancy (Fig. 1).

**Follow-up information:** Serial echocardiograms or some of the measured variables were not available in 16 of the 82 patients. These 16 patients were excluded from the analysis of prognostic variables.

Of the remaining 66 patients, 39 (59%) (95% CI: 47%–70%) improved (group I). Their LVEF improved from 23.9±11.7% to 49.8±12.3%. Eight of these 39 patients were considered “cured.” In 15/66 (23%), the condition remained unchanged (group II), while 12/66 (18%) worsened or died (group III). The further prognosis of group II patients is not clear but may be one of insidious deterioration or slow improvement.

**Predictors of outcome:** On univariate analysis, gender, symptom duration, NYHA class at presentation, history of antecedent viral infection, LVH or ST–T changes on ECG, resting LVEF or LA/AO ratio on echocardiogram did not predict the outcome. Only age at diagnosis, higher cardiothoracic ratio, and a higher ratio of LVED/PW thickness were associated with a poor outcome. The mean cardiothoracic ratio was 63.01±7.9% in those who improved compared to 69.6±8.4% in those with a poor outcome (p=0.03). Similarly, the LVED/PW thickness ratio was lower in those who improved (8.17±2.45 v. 11.02±4.1) (Table 2). This ratio may indirectly reflect a preserved ventricular mass, although the values found in both groups were much higher than normal (3.4–3.8).18 The change in ejection fraction (the difference in the ejection fraction in the last and first echocardiograms) was

![Fig. 1. Actuarial survival in infants and children >1 year of age.](image)

Table 2. Clinical and echocardiographic variables in different prognostic subgroups (n=66)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Improved n=39</th>
<th>No change n=15</th>
<th>Worsened/died n=12</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>2.83±2.92</td>
<td>2.11±2.03</td>
<td>1.72±2.4</td>
<td>ns</td>
</tr>
<tr>
<td>Antecedent viral fever (%)</td>
<td>43</td>
<td>26.6</td>
<td>25</td>
<td>ns</td>
</tr>
<tr>
<td>Males (%)</td>
<td>53.8</td>
<td>73.3</td>
<td>83.3</td>
<td>ns</td>
</tr>
<tr>
<td>CT ratio</td>
<td>63.1±7.9</td>
<td>68.3±9.4</td>
<td>69.6±8.4</td>
<td>0.03</td>
</tr>
<tr>
<td>LVH (%)</td>
<td>38.2±1.44</td>
<td>42.7±15.6</td>
<td>51.2±12.5</td>
<td>ns</td>
</tr>
<tr>
<td>ST–T changes (%)</td>
<td>50</td>
<td>46.6</td>
<td>33.3</td>
<td>ns</td>
</tr>
<tr>
<td>LA/AO ratio</td>
<td>1.46±0.32</td>
<td>1.5±0.3</td>
<td>1.5±0.17</td>
<td>ns</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>23.9±11.7</td>
<td>21.7±11.2</td>
<td>27.0±15.2</td>
<td>ns</td>
</tr>
<tr>
<td>LVED/PW thickness ratio</td>
<td>8.17±2.45</td>
<td>7.85±1.75</td>
<td>11.02±4.1</td>
<td>0.015</td>
</tr>
<tr>
<td>LVEF at last follow-up (%)</td>
<td>49.8±12.3</td>
<td>23.8±10.0</td>
<td>20.5±9.3</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

LVH: left ventricular hypertrophy; LA/AO: left atrial/aortic ratio; LVEF: left ventricular ejection fraction; LVED/PW: left ventricular end-diastolic dimension/posterior wall thickness ratio
higher in females (20.7%±16.2% v. 10.8%±18.0%, p=0.03), but overall, gender did not influence the prognosis. Due to the small absolute numbers of events and patients, a multivariate analysis of predictive variables was not done.

Discussion

This study provides data on the prognosis of Indian children with DCM treated with conventional management. The study sample from a specified geographic region appears representative of DCM as generally seen at a referral hospital. The mortality in infants was high (25%). In the present study, the overall mortality was found to be lower than that previously reported. On an intermediate term follow-up, nearly 60% of patients improved, 18% worsened and 23% remained the same.

Several studies in the past have addressed the issue of the natural history of DCM in children and the predictive variables influencing the clinical course of the disease. These variables include age, gender, race, cardiomegaly, LVEF, arrhythmia, history of antecedent viral infection, family history, and others, but have not yielded consistent results (Table 3). A small number of patients, varying duration of follow-up, heterogeneous disorders presenting as DCM, and lack of uniform therapy may be responsible for the variation in these reports. Further, changes in the therapy of DCM with time (secular trends) and referral biases, may underlie some of the discrepancies. The wider use of ACE inhibitors, and the early diagnosis of DCM due to widespread access to echocardiography seem to have improved the prognosis of DCM in recent times. Beta-blockers have rarely been used in children with DCM, but are expected to improve the prognosis further, and are being investigated in trials. Familial DCM has been reported in nearly 20% of patients reported from western countries, but we found a family history in only 3.5% of cases. This might have resulted from incomplete ascertainment or possibly familial DCM is relatively uncommon in Asians. A recent survey in Japan also found familial forms in 13.6% of all DCM patients.

Sudden death is reportedly rarer in children with DCM compared to adults, but has been well documented and occurs in children with relatively well preserved ventricular function. In the Australian registry data, sudden death at presentation was seen in 3.6% of children with DCM. We did not record any instance of sudden cardiac death in our patient group.

The patterns and prevalence of DCM may vary according to region, race and other factors. For example, a high incidence of lymphocytic myocarditis was seen in DCM in Australia and a high incidence of sudden death was found in an indigenous population in the same report. In our study, age at presentation, cardiothoracic ratio, and higher ratio of LVED/PW thickness were associated with a poorer prognosis. In contrast to our findings, better prognosis in infants compared to children beyond infancy was reported in some studies, while others reports found no prognostic relationship with age. Infants are expected to have higher regeneration capabilities, but probably suffer from severe disease. The ratio of LVED/PW thickness was also found to be a useful predictor by Carvalho et al.

Table 3. DCM in children: review of the literature

<table>
<thead>
<tr>
<th>Author</th>
<th>No. of patients</th>
<th>Follow-up duration: mean (range)</th>
<th>Mortality (%)</th>
<th>Variables associated with poor outcome (predictive variable)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Griffin et al. (1998)</td>
<td>32</td>
<td>48 months (0-14 years)</td>
<td>53</td>
<td>Age &gt;2 years at presentation, cardiomegaly, arrhythmia</td>
</tr>
<tr>
<td>Chen et al. (1990)</td>
<td>23</td>
<td>43 months (1 month-14 years)</td>
<td>48</td>
<td>Fractional shortening, EFE, familial DCM</td>
</tr>
<tr>
<td>Akagi et al. (1991)</td>
<td>25</td>
<td>15 months (1-7.8 years)</td>
<td>72</td>
<td>LVEF, CT ratio</td>
</tr>
<tr>
<td>Friedman et al. (1991)</td>
<td>63</td>
<td>48 months (0-10 years)</td>
<td>16</td>
<td>Persistent CHF, ST-T changes</td>
</tr>
<tr>
<td>Lewis et al. (1991)</td>
<td>81</td>
<td>42 months (0-15.5 years)</td>
<td>37</td>
<td>Complex ventricular arrhythmia, &gt;20 mmHg LVEDP</td>
</tr>
<tr>
<td>Burch et al. (1994)</td>
<td>63</td>
<td>19 months (10-13 years)</td>
<td>16</td>
<td>Age &gt;2 years at presentation</td>
</tr>
<tr>
<td>Matitiau et al. (1994)*</td>
<td>24</td>
<td>34 months (0-8 years)</td>
<td>29</td>
<td>LVEF, spherical LV shape (myocarditis)</td>
</tr>
<tr>
<td>Arola et al. (1998)</td>
<td>62</td>
<td>46 months (0-25 years)</td>
<td>50</td>
<td>CHF, EFE, infants, &gt;15 years of age</td>
</tr>
<tr>
<td>Venugopalan et al. (1998)</td>
<td>18</td>
<td>12 months (4-94 months)</td>
<td>19</td>
<td>None</td>
</tr>
<tr>
<td>Venugopalan et al. (2001)</td>
<td>39</td>
<td>36 months (1 day-15 years)</td>
<td>31</td>
<td>None</td>
</tr>
<tr>
<td>Present study</td>
<td>82</td>
<td>25 months (15 day-118 months)</td>
<td>11.5</td>
<td>Infants, CT ratio, LVED/PW thickness ratio</td>
</tr>
</tbody>
</table>

CT: cardiothoracic; CHF: congestive heart failure; EFE: endocardial fibroelastosis; LVEF: left ventricular ejection fraction; LVED/PW: left ventricular end-diastolic dimension/posterior wall; LVEDP: left ventricular end-diastolic pressure

* included only children <2 years of age
in a small study. This index is independent of the age of the patients,\textsuperscript{16} and indirectly reflects the relatively preserved left ventricular mass. Alternatively, the presence of tissue edema (reversible) may influence this measurement. This index suggests that measures to increase the left ventricular mass may influence the course of DCM favorably. Significantly, the treatment of children with myocardial growth factors, such as growth hormone, have been reported.\textsuperscript{12} Further characterization of the ventricular hypertrophic response may yield important prognostic information.

The time course of mortality or improvement has not been fully characterized. While the majority of deaths occurred within 6 months of presentation in this study, late attrition did occur. On the other hand, slow recovery with delayed complete normalization of ventricular function has also been reported.\textsuperscript{25}

**Limitations of the study:** This was a retrospective analysis, and hence suffers from all the limitations inherent in such a study. The longer term follow-up data were less than ideal, hence the values of actuarial survival are to be interpreted cautiously. Nevertheless, we believe the data reflect the general trends of DCM in Indian children.

In conclusion, children with DCM pursue a variable course. Diagnosis in infancy, larger cardiothoracic ratio, and a higher LVED/PW thickness ratio are associated with a poorer prognosis. More than half the patients diagnosed beyond infancy improve or recover. Further characterization of prognostic variables and an etiology-specific therapy are warranted.

**References**

Has the Prevalence of Rheumatic Fever/Rheumatic Heart Disease Really Changed? A Hospital-Based Study

SN Routray
Department of Cardiology, SCB Medical College, Cuttack

Background: Rheumatic fever and rheumatic heart disease still remain major public health problems. With a dramatic rise in the incidence of coronary artery disease cases, the focus of the physician seems to be shifting away from rheumatic fever and rheumatic heart disease. The aim of the present study was to assess the prevalence of rheumatic fever and rheumatic heart disease, and to ascertain if there was any decline in the prevalence of the disease. For the first time, data on the prevalence of rheumatic fever and rheumatic heart disease are reported from Orissa, an underdeveloped state in eastern India.

Methods and Results: We scrutinized the records of cardiac patients admitted to the medicine, pediatrics and cardiology wards of the SCB Medical College and Hospital, Cuttack from 1981 to 1990 and 1991 to 2000. During the period 1981–1990, out of 11,782 cardiac patients, 5,537 (46.9%) were suffering from rheumatic fever and rheumatic heart disease. During 1991–2000, out of 14,803 cardiac patients, 6,670 hospitalized patients (45%) were found to have rheumatic fever and rheumatic heart disease. During the first and second periods, the number of patients with rheumatic fever admitted was 1,079 (9.2%) and 1,330 (8.9%), respectively. The decline in the percentage of rheumatic fever cases was statistically not significant (p>0.05). During the two periods, the number of rheumatic heart disease patients admitted was 4,458 (37.8%) and 5,340 (36.1%), respectively. During both the periods studied, the decline in the percentage of rheumatic heart disease cases admitted was statistically not significant (p>0.05). We also compared rheumatic fever and rheumatic heart disease cases admitted during 1981–1985 with those admitted during 1996–2000. This analysis also did not show any demonstrable decline in the prevalence of the disease (2,692 [46.2%] v. 3,296 [44.4%], p>0.05).

Conclusions: Our results show that rheumatic fever and rheumatic heart disease cases constitute a significant percentage of the admissions of total cardiac cases to our hospital. Over the past 20 years, there is no significant decline in the percentage of rheumatic fever and rheumatic heart disease cases being admitted to a major government hospital.

Key Words: Rheumatic fever, Rheumatic heart disease, Hospital survey
insufficient hospital admission statistics can come in the way of exact interpretation of the data.

Data from the All India Institute of Medical Sciences (AIIMS), New Delhi demonstrated that the percentage of hospitalized RHD cases declined from 45.9% (1966-1970) to 32.5% (1981-1985).4 However, Sapru,5 who reviewed hospital-based data from across India, opined that the prevalence of RHD has not fallen, unlike the dramatic decline witnessed in developed countries.

The aim of this study was to assess the prevalence of RF and RHD by analyzing the hospital records of all cardiac patients admitted to our hospital during 1981-2000. We scrutinized records from 1981 onwards, since an echocardiography machine was installed at our institution in this year. Orissa, where this study was conducted, is one of the poorest states of India; 47.2% of the population of the state live below the poverty line in comparison to 6% in Punjab.6 Data concerning RF and RHD are being reported for the first time from Orissa.

**Methods**

The SCB Medical College and Hospital, Cuttack is a 1200-bed premier medical institution of Orissa. It caters to nearly one-third of the population of the state. In this retrospective study, the case records of all the patients admitted to the cardiology, medicine and pediatric wards during 1981-2000 were obtained from the medical records section of the hospital. The total number of cardiac patients admitted to these wards was then calculated. Among the cardiac patients, the number of patients suffering from acute RF and RHD was determined. A person was diagnosed to have acute RF, if he/she fulfilled the Jones criteria, as applicable at the time of admission (the Jones criteria have been revised in 1968, 1984, 1988 and 1992.). Only those cases of RHD were included in whom the diagnosis of the valvular lesion was confirmed by echocardiography. Cases in which the rheumatic etiology of the valvular lesion was uncertain were not taken into consideration. For example, aortic valvular disease was not considered to be rheumatic, unless there was a definite history of RF or there was concurrent involvement of the mitral valve (either clinically or by echocardiography). Patients with established RHD, who presented with acute RF and were admitted, were categorized under the heading of RF. This was done to avoid the overlapping of RHD cases, while enlisting cases suffering from RF/RHD. Care was also taken that the patients who were re-admitted were not enlisted repeatedly.

As these 2 periods (1981-1990 and 1991-2000) represented a continuum, we additionally analyzed and compared the cases of RF and RHD admitted during the periods 1981-1985 and 1996-2000, to determine whether there was any demonstrable decline in the prevalence of the disease between these two periods.

**Statistical analysis:** Statistical analysis was done using percentage analysis and the Chi-square test.

**Results**

During the period 1981-1990, 11 782 cardiac patients were admitted to our hospital, of whom 5537 (46.9%) were suffering from RF and RHD. From 1991-2000, 14 803 had cardiac disease, of whom 6670 (45%) had RF and RHD (Table 1).

Table 1 also shows the distribution of other cardiac diseases. There was no significant difference between the distribution of congenital heart disease and hypertensive heart disease during the two periods, while there was a statistically significant increase in cases hospitalized for CAD during 1991-2000 (p<0.05). There was a marginal decrease in the percentage of hospitalized RF cases during the second period, though it was not statistically significant (p>0.05).

During these two periods 4458 (37.8%) and 5340 cases (36.1%) of RHD, respectively, were admitted (Table 2). Again, there was a decrease in the percentage of RHD cases, which was, however, not statistically significant (p>0.05). Annual data of RF and RHD cases are presented in Tables 3 and 4. During 1981-1990, the percentage of RF and RHD cases ranged from 43.6% to 50.7%. During 1991-2000, the percentage of RF and RHD cases ranged from 42.8% to 47.6% of all cardiac cases, respectively.

**Table 1. Distribution of cardiac diseases in hospitalized patients**

<table>
<thead>
<tr>
<th>Diseases</th>
<th>1981-1990 n (%)</th>
<th>1991-2000 n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RF/RHD</td>
<td>5537 (46.9)</td>
<td>6670 (45)</td>
</tr>
<tr>
<td>CHD</td>
<td>1061 (9.1)</td>
<td>1184 (7.9)</td>
</tr>
<tr>
<td>CAD</td>
<td>2356 (19.9)</td>
<td>4143 (28.0)</td>
</tr>
<tr>
<td>PMD</td>
<td>1179 (10)</td>
<td>1628 (11.1)</td>
</tr>
<tr>
<td>Hypertensive heart disease</td>
<td>827 (7.2)</td>
<td>741 (5.1)</td>
</tr>
<tr>
<td>Pericardial disease</td>
<td>573 (4.8)</td>
<td>296 (1.9)</td>
</tr>
<tr>
<td>Others</td>
<td>243 (2.1)</td>
<td>141 (1)</td>
</tr>
<tr>
<td>Total</td>
<td>11 782</td>
<td>14 803</td>
</tr>
</tbody>
</table>

RF: rheumatic fever; RHD: rheumatic heart disease; CHD: congenital heart disease; CAD: coronary artery disease; PMD: primary myocardial disease
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Indian Heart J 2003; 55: 152–157

Table 2. Prevalence of RHD and RF over past 2 decades

<table>
<thead>
<tr>
<th>Decades</th>
<th>RHD and RF n (%)</th>
<th>RF n (%)</th>
<th>RHD n (%)</th>
<th>Total HD n</th>
</tr>
</thead>
<tbody>
<tr>
<td>1981–1990</td>
<td>5537 (46.9)</td>
<td>1079 (9.2)</td>
<td>4458 (37.8)</td>
<td>11782</td>
</tr>
<tr>
<td>1991–2000</td>
<td>6670 (45)</td>
<td>1330 (8.9)</td>
<td>5340 (36.1)</td>
<td>14803</td>
</tr>
<tr>
<td>Total</td>
<td>12 207</td>
<td>2409</td>
<td>9798</td>
<td>26 585</td>
</tr>
</tbody>
</table>

p > 0.05
RF: rheumatic fever; RHD: rheumatic heart disease; HD: heart disease

Table 3. Annual prevalence of hospitalized RF/RHD cases (1981–1990)

<table>
<thead>
<tr>
<th>Year</th>
<th>RF n (%)</th>
<th>RHD n (%)</th>
<th>RF and RHD n (%)</th>
<th>Total HD n</th>
</tr>
</thead>
<tbody>
<tr>
<td>1981</td>
<td>113 (9.6)</td>
<td>403 (34.37)</td>
<td>516 (43.9)</td>
<td>1173</td>
</tr>
<tr>
<td>1982</td>
<td>107 (8.9)</td>
<td>446 (37.2)</td>
<td>553 (46.1)</td>
<td>1198</td>
</tr>
<tr>
<td>1983</td>
<td>99 (9.2)</td>
<td>437 (40.5)</td>
<td>536 (49.7)</td>
<td>1080</td>
</tr>
<tr>
<td>1984</td>
<td>109 (9.1)</td>
<td>432 (36.0)</td>
<td>541 (45.1)</td>
<td>1201</td>
</tr>
<tr>
<td>1985</td>
<td>101 (8.6)</td>
<td>445 (37.8)</td>
<td>546 (46.2)</td>
<td>1181</td>
</tr>
<tr>
<td>1986</td>
<td>113 (9.7)</td>
<td>477 (41.0)</td>
<td>590 (50.7)</td>
<td>1163</td>
</tr>
<tr>
<td>1987</td>
<td>106 (8.9)</td>
<td>479 (40.2)</td>
<td>585 (49.1)</td>
<td>1192</td>
</tr>
<tr>
<td>1988</td>
<td>103 (9.1)</td>
<td>442 (39.1)</td>
<td>545 (48.2)</td>
<td>1130</td>
</tr>
<tr>
<td>1989</td>
<td>111 (9.3)</td>
<td>459 (38.6)</td>
<td>570 (47.9)</td>
<td>1189</td>
</tr>
<tr>
<td>1990</td>
<td>117 (9.2)</td>
<td>438 (34.4)</td>
<td>555 (43.6)</td>
<td>1275</td>
</tr>
</tbody>
</table>

RF: rheumatic fever; RHD: rheumatic heart disease; HD: heart disease

Table 4. Annual prevalence of hospitalized RF/RHD cases (1991–2000)

<table>
<thead>
<tr>
<th>Year</th>
<th>RF n (%)</th>
<th>RHD n (%)</th>
<th>RF and RHD n (%)</th>
<th>Total HD n</th>
</tr>
</thead>
<tbody>
<tr>
<td>1991</td>
<td>119 (8.6)</td>
<td>511 (36.9)</td>
<td>630 (45.5)</td>
<td>1383</td>
</tr>
<tr>
<td>1992</td>
<td>137 (9.4)</td>
<td>522 (36.0)</td>
<td>659 (45.4)</td>
<td>1451</td>
</tr>
<tr>
<td>1993</td>
<td>148 (9.8)</td>
<td>529 (35.1)</td>
<td>677 (44.9)</td>
<td>1506</td>
</tr>
<tr>
<td>1994</td>
<td>145 (9.8)</td>
<td>563 (37.9)</td>
<td>708 (47.6)</td>
<td>1487</td>
</tr>
<tr>
<td>1995</td>
<td>144 (9.2)</td>
<td>556 (35.7)</td>
<td>700 (44.9)</td>
<td>1557</td>
</tr>
<tr>
<td>1996</td>
<td>139 (8.8)</td>
<td>546 (34.7)</td>
<td>685 (43.5)</td>
<td>1573</td>
</tr>
<tr>
<td>1997</td>
<td>136 (8.9)</td>
<td>543 (38.3)</td>
<td>669 (47.2)</td>
<td>1417</td>
</tr>
<tr>
<td>1998</td>
<td>121 (8.3)</td>
<td>519 (35.5)</td>
<td>640 (43.8)</td>
<td>1461</td>
</tr>
<tr>
<td>1999</td>
<td>123 (8.4)</td>
<td>533 (36.5)</td>
<td>656 (42.8)</td>
<td>1459</td>
</tr>
<tr>
<td>2000</td>
<td>128 (8.3)</td>
<td>518 (34.3)</td>
<td>646 (42.8)</td>
<td>1509</td>
</tr>
</tbody>
</table>

RF: rheumatic fever; RHD: rheumatic heart disease; HD: heart disease


<table>
<thead>
<tr>
<th>Year</th>
<th>RF n (%)</th>
<th>RHD n (%)</th>
<th>RF and RHD n (%)</th>
<th>Total HD n</th>
</tr>
</thead>
<tbody>
<tr>
<td>1981–1985</td>
<td>529 (9.1)</td>
<td>2163 (37.1)</td>
<td>2692 (46.2)</td>
<td>5833</td>
</tr>
<tr>
<td>1996–2000</td>
<td>637 (8.6)</td>
<td>2659 (35.8)</td>
<td>3296 (44.4)</td>
<td>7419</td>
</tr>
<tr>
<td>Total</td>
<td>1166</td>
<td>4822</td>
<td>5988</td>
<td>13 252</td>
</tr>
</tbody>
</table>

p > 0.05
RF: rheumatic fever; RHD: rheumatic heart disease; HD: heart disease

Table 6. Five-yearly distribution of RF and RHD cases from 1981–2000

<table>
<thead>
<tr>
<th>Year</th>
<th>RF n (%)</th>
<th>RHD n (%)</th>
<th>RF and RHD n (%)</th>
<th>Total HD n</th>
</tr>
</thead>
<tbody>
<tr>
<td>1981–1985</td>
<td>529 (9.1)</td>
<td>2163 (37.1)</td>
<td>2692 (46.2)</td>
<td>5833</td>
</tr>
<tr>
<td>1986–1990</td>
<td>550 (9.2)</td>
<td>2295 (38.6)</td>
<td>2845 (47.8)</td>
<td>5949</td>
</tr>
<tr>
<td>1991–1995</td>
<td>693 (9.3)</td>
<td>2681 (36.3)</td>
<td>3374 (45.7)</td>
<td>7384</td>
</tr>
<tr>
<td>1996–2000</td>
<td>637 (8.6)</td>
<td>2659 (35.8)</td>
<td>3296 (44.4)</td>
<td>7419</td>
</tr>
<tr>
<td>Total</td>
<td>2409</td>
<td>9798</td>
<td>12 207</td>
<td>26 585</td>
</tr>
</tbody>
</table>

RF: rheumatic fever; RHD: rheumatic heart disease; HD: heart disease

Discussion

In developed countries, where RF and RHD cases have almost disappeared, many young physicians have never seen a case of RF/RHD. In contrast, developing countries continue to grapple with the disease. Moreover, because the disease affects the younger population, resulting in a considerable loss of manpower, awareness of the prevalence of the disease in the community is important.

Several sources, such as school and population surveys, autopsy analysis, and hospital admission data are available to give us an insight into the prevalence of the disease. While school surveys have been regarded as ideal, they suffer from a lack of standardized methodology, uncertain reproducibility of the diagnostic process, and lack of information about absentees. Moreover, in a poor and underdeveloped state such as Orissa, where the literacy rate...
Routray Has the Prevalence of RF/RHD Really Changed?

is only 63.3% in comparison with states like Maharastra (77.2%) and Tamil Nadu (73%), the school drop-out rate is also very high (42%). Hence, school surveys may not reflect the true picture of the prevalence of the disease.

For these reasons, we opted to go through the hospital records of the largest medical college and hospital of Orissa. We also tried to ascertain if there was a declining trend in the prevalence of RF/RHD. The span of this retrospective study was from 1981 to 2000.

In the present study, 46.9% of all cardiac patients had RF/RHD during the period 1981–1990. This declined slightly to 45% during the period 1991–2000. As the two periods were actually a continuum, we additionally analyzed and compared the RF/RHD cases hospitalized during the initial 5 years (1981–1985) of the first period and the cases admitted in the last 5 years (1996–2000) of the second period. Comparison between these 2 periods did not show a significant declining trend in the prevalence of RF/RHD (Fig.1).

Hospital admission data on RF/RHD are available from various hospitals across the country. These data can be broadly divided into those reported before and after 1960. Before the 1960, RF and RHD cases accounted for 26.6–50% of all admission cases. Agarwal analyzed hospitalized cases from 1966–1973 and reported 40.6% of the cases to be rheumatic in origin. Data from the Postgraduate Institute of Medical Education and Research (PGIMER), Chandigarh showed the prevalence of RHD to be 24.9% in 1978.

Regarding the trends in the prevalence of RF/RHD, All India Institute of Medical Sciences (AIIMS), New Delhi reported a declining trend with the prevalence of RF/RHD declining from 39.1% (1976–1980) to 32.5% (1981–1985). In a retrospective study, Krishnaswami et al. from Vellore reported a significant fall in the number of admissions of RHD (800/year to 500/year) and RF cases (85/year to zero) over a period of 30 years (1960–1989). In our series, the absolute number of hospitalized RHD cases actually increased from 4458/year during 1981–1990 to 5340/year during 1991–2000, though a marginal decline was noted when RHD cases were calculated as a percentage of the total cardiac cases admitted to the hospital (37.8%–36.1%) (Table 2). Similarly, RF cases also increased from 1079/year to 1330/year during the 2 periods. In the series from Postgraduate Institute of Medical

### Table 7. Characteristics of patients with rheumatic fever

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of cases</td>
<td>1079</td>
<td>1330</td>
</tr>
<tr>
<td>Male:female</td>
<td>809:270 (3.1)</td>
<td>1006:324 (3.1:1)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>9.1±2.8</td>
<td>10.7±3.2</td>
</tr>
<tr>
<td>Recurrent attacks</td>
<td>349 (32.3%)</td>
<td>379 (28.4%)</td>
</tr>
<tr>
<td>Underlying heart disease</td>
<td>309 (28.7%)</td>
<td>323 (24.3%)</td>
</tr>
<tr>
<td>Penicillin prophylaxis</td>
<td>3 (0.28%)</td>
<td>2 (0.15%)</td>
</tr>
<tr>
<td>Prophylaxis in recurrent cases</td>
<td>Nil</td>
<td>Nil</td>
</tr>
<tr>
<td>Fever</td>
<td>917 (84.9%)</td>
<td>1170 (87.9%)</td>
</tr>
<tr>
<td>Carditis</td>
<td>843 (78.1%)</td>
<td>1021 (76.6%)</td>
</tr>
<tr>
<td>Polycythemia</td>
<td>513 (47.5%)</td>
<td>589 (44.2%)</td>
</tr>
<tr>
<td>Polymyelalgia</td>
<td>442 (40.9%)</td>
<td>573 (43.1%)</td>
</tr>
<tr>
<td>Chorea</td>
<td>591 (54.7%)</td>
<td>699 (52.5%)</td>
</tr>
<tr>
<td>Subcutaneous nodules</td>
<td>143 (13.2%)</td>
<td>148 (11.1%)</td>
</tr>
<tr>
<td>Erythema marginatum</td>
<td>Nil</td>
<td>Nil</td>
</tr>
</tbody>
</table>

### Table 8. Characteristics of patients with rheumatic heart disease

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of cases</td>
<td>4458</td>
<td>5340</td>
</tr>
<tr>
<td>Male:female</td>
<td>3285:1173 (2.8:1)</td>
<td>3769:1571 (2.4:1)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>23.5±11.2</td>
<td>25±14.3</td>
</tr>
<tr>
<td>Penicillin prophylaxis</td>
<td>2147 (48.2%)</td>
<td>2933 (54.9%)</td>
</tr>
<tr>
<td>Past history of RF</td>
<td>1778 (39.8%)</td>
<td>2252 (42.2%)</td>
</tr>
<tr>
<td>MS</td>
<td>1572 (35.2%)</td>
<td>1853 (34.7%)</td>
</tr>
<tr>
<td>MR</td>
<td>436 (9.8%)</td>
<td>422 (7.9%)</td>
</tr>
<tr>
<td>MS+MR</td>
<td>655 (14.7%)</td>
<td>817 (15.3%)</td>
</tr>
<tr>
<td>Mitral +aortic valve disease</td>
<td>1126 (25.3%)</td>
<td>1425 (26.7%)</td>
</tr>
<tr>
<td>Aortic valve disease</td>
<td>136 (3.1%)</td>
<td>150 (2.8%)</td>
</tr>
<tr>
<td>MV+TV disease</td>
<td>531 (11.9%)</td>
<td>673 (12.6%)</td>
</tr>
<tr>
<td>Recurrent hospitalization</td>
<td>459 (10.3%)</td>
<td>433 (8.1%)</td>
</tr>
<tr>
<td>Deaths</td>
<td>499 (11.2%)</td>
<td>443 (8.3%)</td>
</tr>
</tbody>
</table>

RF: rheumatic fever; MS: mitral stenosis; MR: mitral regurgitation; MV+TV: mitral valve and tricuspid valve

is only 63.3% in comparison with states like Maharastra (77.2%) and Tamil Nadu (73%), the school drop-out rate is also very high (42%). Hence, school surveys may not reflect the true picture of the prevalence of the disease.

For these reasons, we opted to go through the hospital records of the largest medical college and hospital of Orissa. We also tried to ascertain if there was a declining trend in the prevalence of RF/RHD. The span of this retrospective study was from 1981 to 2000.

In the present study, 46.9% of all cardiac patients had RF/RHD during the period 1981–1990. This declined slightly to 45% during the period 1991–2000. As the two periods were actually a continuum, we additionally analyzed and compared the RF/RHD cases hospitalized during the initial 5 years (1981–1985) of the first period and the cases admitted in the last 5 years (1996–2000) of the second period. Comparison between these 2 periods did not show a significant declining trend in the prevalence of RF/RHD (Fig.1).
Education and Research (PGIMER), Chandigarh, the data did not show any declining trend, with the prevalence of RHD cases being 24.2% and 24.9% in 1973 and 1978, respectively.

As a part of the RHD registry for the Cardiological Society of India (CSI), Jose et al. collected data from several Indian hospitals regarding the number of patients admitted with a diagnosis of RHD during 1999–2000. The percentage of RHD cases admitted to the hospital ranged from 5%–26% during the said period (Fig. 2). Our data show that RF and RHD cases accounted for 45% of total cardiac cases even during the period 1991–2000. Jose et al. found the highest rate of RHD admission (26%) in a Government General Hospital of Chennai, whereas the lowest admission rate was noted in the metropolitan city of Mumbai (Nanavati Hospital, 6%). He concluded that the hospital admission rates of RHD cases varied depending upon the socio-economic status of the population to which they cater.

The SCB Medical College Hospital, Cuttack from which we collected our data, chiefly caters to the population of Orissa. In Orissa, annual infant mortality rate, an important index of socio-economic status, is as high as 97/1000 in comparison to 42/1000 reported from Tripura and 14/1000 from Kerala.

A disturbing trend seen from the present data, which could partly explain the lack of decline in the prevalence of RHD, was that as many as 51.8% (1981–1990) and 45.1% (1991–2000) of established RHD cases were not receiving regular penicillin prophylaxis. This fact is also responsible for the high rate of recurrent attacks of RF (32.3% and 28.4% in the first and second periods, respectively). Reddy et al. have repeatedly emphasized the role of penicillin prophylaxis in the prevention and control of RF/RHD.

Study limitations: We carried out a retrospective analysis of hospitalized cases of RF/RHD. Most of the studies that involve retrospective analysis of hospital data have severe limitations. One limitation of our study is that it was carried out in a government hospital, which is not representative of the population studied. Also, hospital-based data are poor estimates of the prevalence of disease, as admissions depend upon the severity of illness, availability of hospital beds, and the range of services provided by the hospital, as well as disease awareness among the population seeking help. However, over the years the trend can show a stable figure. There has been a significant change in the populations served by government hospitals over the years, with only poor patients seeking care in such hospitals. This can result in a skewed representation of poor patients in government hospitals. However, these limitations may not be applicable to Orissa, as due to lack of major private/corporate hospitals catering to cardiac patients, all classes of people come to the government hospitals. Although hospital data do not necessarily reflect the disease pattern in the community, they can at least throw some light on changes in the pattern of cardiovascular diseases over a period of time.

Conclusions: RF and RHD continue to be major public health problems. There is no significant decline in RF/RHD cases in India. In our series, the percentage of patients admitted with RF/RHD showed a marginal (nonsignificant) decline during 1991–2000. A sizable number of such patients are still being admitted to our hospital, thus indicating that RF and RHD remain important diseases in a government hospital. Factors responsible for the increased prevalence of RF and subsequent RHD, such as overcrowding, poverty, and illiteracy, are still rampant in Orissa. Because of our preoccupation with angiography, angioplasty, and CABG, diseases such as RF and RHD do not receive due attention. However, it is hoped that the important work started by the CSI in maintaining a national registry of RHD will help us to refocus our attention on the disease.

Fig. 2. Prevalence of rheumatic heart disease in hospitals from different parts of the country during 1999–2000. Our data have been included in the figure.

Hospitals — Nana: Nanavati Hospital, Mumbai; Apollo V: Apollo Hospitals, Vizag; Batra: Batra Hospital and Medical Research Centre, New Delhi; Apollo-Hyd: Apollo Hospitals, Hyderabad; SSKM: Sheth Sukhlal Karnani Memorial Hospital, Kolkata; AFMC: Armed Forces Medical College, Pune; SCT: Sri Chitra Tirunal Institute of Medical Sciences and Technology, Trivuranthapuram; Amrita: Amrita Institute of Medical Sciences, Kochi; Jayadeva: Sri Jayadeva Institute of Cardiology, Bangalore; MMC: Madras Medical College, Chennai; CMCH: Christian Medical College Hospital, Vellore; SCBMCH: SCB Medical College Hospital, Cuttack

Source: Registry of Cardiological Society of India, as quoted by Jose et al.
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Declining Prevalence of Rheumatic Heart Disease in Rural Schoolchildren in India: 2001–2002

V Jacob Jose, M Gomathi
Department of Cardiology, Christian Medical College and Hospital, Vellore and Primary Health Centre, Poigai, Vellore

Background: Rheumatic heart disease is still a major health problem in developing countries such as India and, for the health planners to allocate funds, the actual prevalence of the disease should be known. This study aimed to assess the prevalence of rheumatic heart disease in rural school children in India.

Methods and Results: A total of 2,298,829 children between 6 and 18 years of age were screened as part of a school health program. All children with a valvar heart disease detected by the screening doctor were referred to a tertiary care center for evaluation by a cardiologist. The presence of cardiac lesions was confirmed by color Doppler examination. All children with known congenital heart disease were excluded from this study. A total of 374 children were found to have heart disease. Of these, 157 children were found to have rheumatic heart disease, confirmed by echocardiogram. Thus, the current prevalence of rheumatic heart disease is 0.68 per 1000 children.

Conclusions: In the largest school survey conducted to date in India, we report the prevalence of rheumatic heart disease to be 0.68 per 1000 children. Our study suggests that there may have been a dramatic decline in the prevalence of rheumatic heart disease in India. (Indian Heart J 2003; 55: 158–160)

Key Words: Rheumatic heart disease, Epidemiology, Echocardiography

Table 1. Age distribution of children screened

<table>
<thead>
<tr>
<th>Age of children (years)</th>
<th>Boys (%)</th>
<th>Girls (%)</th>
<th>Total (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5.1–7.0</td>
<td>18 854  (16.06)</td>
<td>18 941  (16.84)</td>
<td>37 795 (16.44)</td>
</tr>
<tr>
<td>7.1–9.0</td>
<td>19 213  (16.36)</td>
<td>19 641  (17.46)</td>
<td>38 854 (16.90)</td>
</tr>
<tr>
<td>9.1–11.0</td>
<td>18 177  (15.49)</td>
<td>17 860  (15.88)</td>
<td>36 037 (15.68)</td>
</tr>
<tr>
<td>11.1–13.0</td>
<td>12 879  (10.97)</td>
<td>12 930  (11.49)</td>
<td>25 809 (11.23)</td>
</tr>
<tr>
<td>13.1–15.0</td>
<td>16 105  (13.72)</td>
<td>22 591  (20.09)</td>
<td>38 696 (16.84)</td>
</tr>
<tr>
<td>15.1–17.0</td>
<td>32 143  (27.38)</td>
<td>20 495  (18.22)</td>
<td>52 638 (22.90)</td>
</tr>
<tr>
<td>Total</td>
<td>117 371</td>
<td>112 458</td>
<td>2 298 29</td>
</tr>
</tbody>
</table>

Correspondence: Dr V Jacob Jose, Department of Cardiology, Christian Medical College and Hospital, Vellore 632004.
Results

Of the 229,829 subjects screened, 157 were documented to have RHD. Different types of valvular lesions were identified. The types of mitral valve involvement were: mitral valve prolapse (MVP) (seen in 57 children), MVP with mitral regurgitation (MR) (44), mitral stenosis (MS) (9), MS with MR (3), and MR (16). The types of aortic valve involvement were: aortic regurgitation (AR) (5), and aortic stenosis (AS) with AR (1). The types of mitral and aortic valve involvement were: MS and AR (8), MS with MR and AR (10), MS with MR and AS (1), and AR with AS and MR (3). MVP with MR was the commonest lesion. In addition, 56 other subjects were on prophylaxis for rheumatic fever (RF) based on clinical history; their echocardiograms revealed only MVP without MR.

As per our data, the prevalence of RHD in these school-going children was found to be 0.68 per 1000 children, the lowest reported so far.

Discussion

The reported prevalence of RHD varies from 1 to 5.4 per 1000 schoolchildren. From the comparison of published data on the prevalence of RHD in India, it is apparent that our study is the largest reported in the literature to date (Table 2). A study done recently in north India among 3963 children found the prevalence of RHD to be 4.54 per 1000. The lower prevalence found in our study may be due to the following reasons. First, all the children were screened by the doctors, and later examined by a cardiologist, and the diagnosis confirmed by echocardiogram. This would have eliminated a lot of children with innocent murmurs or those with CHD. Second, we screened a very large number of schoolchildren. This would have diluted any possible error due to a small sample size. According to best of our knowledge, this is the first time such a large population of schoolchildren has been screened, and their cardiac lesions documented by echocardiography. Our impression is that many children who were examined by us would have been labeled as RHD if not for the echocardiogram. In fact, many of them were on injection benzathine penicillin prophylaxis, based on the presence of a murmur. The third and most likely reason for the low estimate could be that there has been a real decline in the prevalence of RHD in India. This is possible because of the improved socio-economic status of the people, and the better healthcare delivery systems that are available now.

All the earlier studies were based only on auscultation findings. Hence, it is likely that many of these would have included children with CHD or innocent murmurs as having RHD. Hence, our study emphasizes the fact that echocardiographic examination should be included to identify valvular lesions in school surveys.

Limitations of the study: This study was done in the rural areas of the Vellore district in Tamil Nadu. It is likely that the results could be different if we included the municipal areas of the district as well. However, we wanted to cover only this area because these children, belonging to a lower socioeconomic status were under a nutritious noon meal program run by the government, and we wanted to evaluate the impact of the same in these children. Accordingly, our results cannot be generalized for India and we feel that many such studies need to be done in different parts of the country, to accurately find out the prevalence of RHD in India for this decade.

Conclusions: In one of the largest school surveys conducted so far in India, we found the prevalence of RHD in rural schoolchildren to be 0.68 per 1000. This is the lowest estimate reported so far, and we feel that this is due to a dramatic decline in the prevalence of RHD.

Acknowledgments

We are extremely thankful to the following persons for their overwhelming cooperation in conducting this study: AC

Table 2. Comparative data of rheumatic heart disease from India

<table>
<thead>
<tr>
<th>Author</th>
<th>Place</th>
<th>Year</th>
<th>Age (years)</th>
<th>Population studied</th>
<th>Prevalence (per 1000)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICMR2</td>
<td>Delhi</td>
<td>1982-1990</td>
<td>5-15</td>
<td>13 509</td>
<td>2.9</td>
</tr>
<tr>
<td>Padmavati3</td>
<td>Delhi (urban)</td>
<td>1984-1994</td>
<td>5-10</td>
<td>40 000</td>
<td>3.9</td>
</tr>
<tr>
<td>Grover et al.4</td>
<td>Raipurrani</td>
<td>1988-1991</td>
<td>5-15</td>
<td>31 200</td>
<td>2.1</td>
</tr>
<tr>
<td>Avasthi et al.5</td>
<td>Ludhiana</td>
<td>1987</td>
<td>6-16</td>
<td>6005</td>
<td>1.3</td>
</tr>
<tr>
<td>Patil et al.6</td>
<td>Anand</td>
<td>1986</td>
<td>8-18</td>
<td>11 346</td>
<td>2.03</td>
</tr>
<tr>
<td>Lalchandani et al.7</td>
<td>Kanpur</td>
<td>2000</td>
<td>7-15</td>
<td>3963</td>
<td>4.54</td>
</tr>
<tr>
<td>Present study</td>
<td>Vellore</td>
<td>2001-2002</td>
<td>5-18</td>
<td>2 29 829</td>
<td>0.68</td>
</tr>
</tbody>
</table>
Mohandoss, District Collector, Vellore, P Krishnamoorthy, Director of Public Health and Preventive Medicine, Chennai, K Kolandaswamy, Deputy Director of Health Services, Vellore, M Gowrishankar, Medical Officer, Primary Health Centre, Thimiri, KR Natarajan, Health Inspector, Office of the DDHS, Vellore.

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Long-Term Outcome of Patients Operated for Large Ventricular Septal Defects with Increased Pulmonary Vascular Resistance

Bhava RJ Kannan, S Sivasankaran, Jaganmohan A Tharakan, Thomas Titus, VK Ajith Kumar, Bimal Francis, KM Krishnamoorthy, S Harikrishnan, R Padmakumar, Krishnakumar Nair
Department of Cardiology, Sree Chitra Tirunal Institute of Medical Sciences and Technology, Thiruvananthapuram

Background: There is a paucity of data regarding the long-term outcome of patients operated for ventricular septal defect with severe pulmonary arterial hypertension and elevated pulmonary vascular resistance.

Methods and Results: We evaluated the long-term follow-up results of a selected cohort of patients with nonrestrictive ventricular septal defect and elevated pulmonary vascular resistance (>6 Wood units). Thirty-eight patients, median age 7.5 years (range 6 months–27 years), with nonrestrictive ventricular septal defect with severe pulmonary hypertension were operated between 1985 and 1996 at our institute. Preoperative pulmonary vascular resistance, ratio of pulmonary blood flow to systemic blood flow, and ratio of pulmonary vascular resistance to systemic vascular resistance were 7.63±1.8 Wood units, 1.9±0.48, and 0.41±0.12, respectively. The majority (68.4%) had perimembranous ventricular septal defect. Thirty patients (79%) had a good outcome and were asymptomatic at a mean follow-up of 8.7 years, with significant reduction in pulmonary artery pressures. Eight patients (21%) had a poor outcome, which included 5 immediate postoperative deaths, 1 late death and 2 surviving patients with persistent severe pulmonary arterial hypertension. There was no significant difference regarding hemodynamic parameters at baseline between those who had a good outcome and those who did not. Eleven patients with a preoperative pulmonary blood flow to systemic blood flow ratio of <2:1, who had a good outcome following surgery, underwent repeat catheterization at follow-up. There was a significant reduction in their mean pulmonary vascular resistance (8.03±1.4 v. 4.16±1.6 Wood units, p=0.001) and pulmonary vascular resistance to systemic vascular resistance ratio (0.41±0.12 v. 0.19±0.06, p=0.05).

Conclusions: The late results of surgery on this selected group of patients with nonrestrictive ventricular septal defect with high pulmonary vascular resistance are encouraging. Operative correction of the ventricular septal defect should be actively considered in all children presenting with nonrestrictive ventricular septal defect with a significant left-to-right shunt, despite moderately elevated pulmonary vascular resistance. Even among older patients with ventricular septal defect and moderately elevated pulmonary vascular resistance, there is a specific group that does well after operation. (Indian Heart J 2003; 55: 161-166)

Key Words: Congenital heart disease, Ventricular septal defect, Pulmonary hypertension
baseline characteristics, if any, that could predict the outcome in these patients.

**Methods**

**Study design and patient population:** This was a retrospective cohort study. Patients operated for nonrestrictive VSD with elevated PVR (≥6 Wood units) between 1985 and 1996 at our institute were included. Since uniform guidelines were not followed for selecting patients with VSD and elevated PVR for operative correction, this is not a consecutive series. Generally, patients with clinical cyanosis were not advised surgery. The decision to subject a patient to surgery was dependent on the judgment of the individual cardiologist and the cardiac surgeon, acceptance of risk by the patient’s family, logistics of scheduling, and financial considerations. Our primary aim was not to formulate the indications for surgery in VSD with elevated PVR but to determine the long-term results of surgery on this selected cohort of patients.

Catheterization reports were reviewed, and patients with VSD with a basal PVR of ≥6 Wood units were selected for the study. For children with a body surface area <1 m², PVR was indexed to the body surface area, and an indexed value (PVRI) of ≥6 was the criterion for inclusion in the study.

Patients with hemodynamically significant associated lesions (such as atrial septal defect, patent ductus arteriosus, and coarctation of the aorta) were excluded. Patients with major lung disease at the time of catheterization were also excluded from the study.

**Preoperative catheterization:** All the patients underwent catheterization studies preoperatively. Flow measurements were calculated using an assumed value for oxygen consumption as per the nomogram based on body surface area. All patients in this cohort had not undergone repeat flow and resistance measurements after receiving high oxygen flows for a period of ≥10 min.

**Surgery:** VSD closure was performed by the standard technique with cardiopulmonary bypass. Thirty-one patients (82%) underwent VSD closure transatrially while in 6 patients (18%) it was done using the transventricular approach.

**Follow-up:** Letters were sent to all the patients requesting a follow-up visit. Every effort was made to obtain the follow-up data. One patient could not be traced. However, he had come for a routine follow-up 1.5 years ago, and his clinical and echocardiographic records were available. Two patients responded only by reply letters while all the others presented for clinical evaluation to the hospital. A detailed evaluation of the status at follow-up was done, including electrocardiogram (ECG), chest X-ray, and echocardiogram for all the patients. Good outcome was defined as survival at follow-up with a substantial reduction in the pulmonary artery pressure. Poor outcome was defined as postoperative or late mortality or persistent severe pulmonary arterial hypertension (PAH).

Repeat catheterization studies were planned at follow-up for those with persistent PAH and those operated after the age of 2 years with a preoperative pulmonary blood flow to systemic blood flow ratio (Qp:Qs) of ≤2. Sixteen patients were eligible for repeat studies. Two of them were pregnant at the time of evaluation. Two patients refused to undergo repeat catheterization while another did not report on the day of catheterization. The remaining 11 patients were subjected to hemodynamic studies at follow-up.

**Statistical methods:** Statistical analysis was done with the software SPSS for Windows, release 6.1.3. Continuous variables were analyzed by the unpaired Student’s t test, independent variables were analyzed by nonparametric t test and categorical variables were analyzed using the Chi-square test. Results were expressed as mean ± standard deviation or median (range), depending on the sample distribution. A p value of ≤0.05 was considered significant. Serial changes were evaluated by the unpaired t test.

**Results**

Thirty-eight patients operated between 1985 and 1996 at our institute were studied. The mean follow-up period was 8.76 years (range 4.5–15 years).

**Baseline characteristics:** The median age at surgery was 7.5 years (range 6 months–27 years) and mean age at follow-up was 16.2±9.8 years. Nineteen patients (50%) were males. The commonest location of the VSD was at the perimembranous region, seen in 26 patients (68%). Thirty patients had a good outcome while 8 had a poor outcome. The mean age at surgery in patients with a poor outcome was significantly lower (4.1±2.9 v. 10.6±7.8 years, p<0.001). The mean basal systemic arterial saturation was 94% in both the groups, the lowest being 87% in the good outcome group and 91% in the poor outcome group. One patient with good outcome had Down syndrome. No other patient had any dysmorphic features suggestive of any syndromic form of septal defect.

**Preoperative hemodynamic data:** The details are given in Table 1. Pulmonary artery pressures were systemic or
near-systemic in all. The pulmonary-to-systemic systolic pressure ratio (Pp:Ps) was 0.92±0.09 in those who had a good outcome and 0.92±0.05 in those who had a poor outcome. There was no significant difference in PVR, systemic vascular resistance (SVR) or the ratio of PVR:SVR between the two groups.

After the basal study on room air, 21 patients (18 in the good outcome group and 3 in the poor outcome group) underwent repeat hemodynamic studies after the administration of oxygen. There was a significant reduction in PVR and PVR:SVR ratio following administration of oxygen, associated with an increase in the left-to-right shunt. The mean ratio of Qp:Qs at the basal state and after oxygen administration was 1.83±0.44 and 3.1±0.79, respectively (p<0.0001). The mean PVR at the basal state and after oxygen administration was 7.63±1.8 and 4.7±2.3 Wood units, respectively (p<0.001).

**Outcome**

**Surgical mortality:** Five out of 38 patients (13.1%) died in the postoperative period. The causes of death are described in Table 2. No episode of pulmonary hypertensive crisis was encountered. One child, operated at the age of 14 months with a basal PVR of 8.23 Wood units, died 6 months later at home. He had an apparently uneventful postoperative course. Details of the cause of death was not available.

**Persistent pulmonary artery hypertension:** Two patients (both females) were in NYHA functional class III with clinical and echocardiographic evidence of severe pulmonary hypertension. One of them was operated at the age of 8 years with a basal PVR of 8.2 Wood units. She was 16 years old at follow-up and refused a repeat catheterization study. Her right ventricular systolic pressure, as estimated by the tricuspid regurgitation jet on echocardiography, was 120 mmHg. The other patient, 14 years old at follow-up, who was operated at the age of 5 years with a basal PVR of 9.8 Wood units, was subjected to repeat catheterization studies. Her pulmonary artery pressure, PVR and PVR:SVR ratio were 120/60 mmHg, 24.5 Wood units and 0.59, respectively, at follow-up.

**Follow-up of patients with good outcome**

**Clinical data:** The follow-up period ranged from 4.5 to 15 years (mean 8.76 years). All the patients in this group were asymptomatic except for one who had a significant

---

**Table 1. Preoperative hemodynamic data**

<table>
<thead>
<tr>
<th>All patients</th>
<th>Good outcome group (range)</th>
<th>Poor outcome group (range)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>PA systolic (mmHg)</td>
<td>89.3±18.5</td>
<td>93.8±13.7</td>
<td>83.5±9.7</td>
</tr>
<tr>
<td>Ao systolic (mmHg)</td>
<td>97.0±21.1</td>
<td>102±15</td>
<td>90.3±12</td>
</tr>
<tr>
<td>Pp:Ps</td>
<td>0.9±0.04</td>
<td>0.92±0.01</td>
<td>0.92±0.0</td>
</tr>
<tr>
<td>Qp:Qs</td>
<td>1.83±0.4</td>
<td>1.98±0.4</td>
<td>1.83±0.3</td>
</tr>
<tr>
<td>PVR (Wood units)</td>
<td>7.63±1.8</td>
<td>7.83±1.6</td>
<td>7.36±1.3</td>
</tr>
<tr>
<td>SVR (Wood units)</td>
<td>20.1±7.3</td>
<td>21.2±7.3</td>
<td>17.5±4.8</td>
</tr>
<tr>
<td>PVR:SVR</td>
<td>0.41±0.1</td>
<td>0.41±0.1</td>
<td>0.44±1</td>
</tr>
</tbody>
</table>

All values are expressed as mean±SD

PA: pulmonary artery; Ao: aorta; PVR: pulmonary vascular resistance; SVR: systemic vascular resistance; Pp:Ps: ratio of pulmonary artery systolic pressure to systemic systolic pressure; Qp:Qs: ratio of pulmonary blood flow to systemic blood flow; PVR:SVR: ratio of pulmonary vascular resistance to systemic vascular resistance; ns: not statistically significant

**Table 2. Details of the patients with a poor outcome**

<table>
<thead>
<tr>
<th>No.</th>
<th>Age at surgery (years)</th>
<th>Basal PVR (Wood units)</th>
<th>Basal Qp:Qs</th>
<th>On oxygen PVR (Wood units)</th>
<th>On oxygen Qp:Qs</th>
<th>Status</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.8</td>
<td>6.1</td>
<td>2.3</td>
<td>*</td>
<td>*</td>
<td>Dead</td>
<td>Had large residual VSD, reoperated 20 days later, and could not be weaned away from cardiopulmonary bypass</td>
</tr>
<tr>
<td>2</td>
<td>1.2</td>
<td>6.5</td>
<td>2.2</td>
<td>*</td>
<td>*</td>
<td>Dead</td>
<td>Failure to wean away from cardiopulmonary bypass</td>
</tr>
<tr>
<td>3</td>
<td>7.0</td>
<td>6.4</td>
<td>1.7</td>
<td>*</td>
<td>*</td>
<td>Dead</td>
<td>Died on 11th postoperative day with arrhythmia and acute renal failure</td>
</tr>
<tr>
<td>4</td>
<td>7.0</td>
<td>6.6</td>
<td>2.1</td>
<td>*</td>
<td>*</td>
<td>Dead</td>
<td>Needed prolonged ventilation, died on 15th postoperative day due to sepsisemia</td>
</tr>
<tr>
<td>5</td>
<td>2.5</td>
<td>7.1</td>
<td>1.9</td>
<td>*</td>
<td>*</td>
<td>Dead</td>
<td>Died on 3rd postoperative day due to multiorgan failure</td>
</tr>
<tr>
<td>6</td>
<td>1.5</td>
<td>8.2</td>
<td>1.4</td>
<td>4.1</td>
<td>2.8</td>
<td>Dead</td>
<td>Sudden death at home 6 months after surgery</td>
</tr>
<tr>
<td>7</td>
<td>5.0</td>
<td>9.8</td>
<td>1.4</td>
<td>5.4</td>
<td>2.2</td>
<td>Alive</td>
<td>Persistent severe PAH with PVR of 24 Wood units at follow-up, in NYHA functional class III</td>
</tr>
<tr>
<td>8</td>
<td>8.0</td>
<td>8.2</td>
<td>1.8</td>
<td>3.4</td>
<td>3.0</td>
<td>Alive</td>
<td>Persistent severe PAH with RVSP 120 mmHg, in NYHA functional class III</td>
</tr>
</tbody>
</table>

PVR: pulmonary vascular resistance; PAH: pulmonary arterial hypertension Qp:Qs ratio of pulmonary blood flow to systemic blood flow; RVSP: right ventricular systolic pressure based on tricuspid regurgitation by echocardiography.

*Not done*
residual VSD and NYHA functional class II dyspnea on exertion. All of them were leading active lives, either reading at schools and universities or employed. Three of them had delivered children uneventfully, and two of them, a 22-year-old woman and a 30-year-old woman, were pregnant at the time of evaluation. Four patients (12.1%) had a residual VSD. Echocardiography revealed small residual defects of <4 mm in 3 of them with an interventricular gradient of >70 mmHg. The only patient who had dyspnea on exertion was found to have a 7 mm residual VSD with clinical evidence of significant left-to-right shunt. A repeat catheterization study revealed a Qp:Qs of 1.8:1; hence, redo surgery was done. The patient recovered uneventfully after reoperation.

Hemodynamic data at follow-up: The details are given in Tables 3 and 4. Repeat hemodynamic studies were performed in 11 patients who had a good outcome following surgery after the age of 2 years with a basal Qp:Qs of <2:1. PVR and PVR:SVR ratio showed a 50% reduction at follow-up compared to the preoperative status. PVR had decreased from 8.03±1.4 to 4.16±1.68 Wood units (p=0.001), and the PVR:SVR ratio had come down from a preoperative value of 0.41±0.12 to 0.19±0.06 (p=0.005). Even in the patient with significant residual VSD with a Qp:Qs of 1.8:1 at follow-up, postoperatively there was a reduction in PVR from 10.5 to 3.45 Wood units, and PVR:SVR ratio from 0.32 to 0.24. The pulmonary artery pressure and PVR was near normal in an 11-year-old child who was operated at the age of 3 years. His preoperative PVR of 6.2 Wood units had come down to 2.4 Wood units at follow-up.

Discussion

The development of PVD is a major problem in unoperated patients with nonrestrictive VSDs. Patients in developing countries commonly present at an older age with large VSDs and high PVR. There is a paucity of data regarding patients operated for VSDs with elevated PVR. Such data are unlikely to be available from western countries because most patients are operated early, before the development of elevated PVR. Surgery is justified for patients with elevated PVR if it can be demonstrated that the vascular changes regress, or at least remain static, at long-term follow-up.

Our study population consisted of 38 patients with moderate PVR with a mean PVR of 7.63±1.8 Wood units that was 42% of the SVR. The role of identifying the reactive component of PVR using pulmonary vasodilators is controversial.15-17 In our study, we found that most of the patients in both the groups responded favorably to oxygen administration with a reduction of PVR by >30%, and this was an important factor while considering surgery in patients with elevated PVR.
The long-term results are encouraging, with the majority showing a substantial reduction in PVR. Surgery at a young age was found to be the only significant risk factor for a poor outcome. Three of the younger patients died in the early postoperative period. We have not been able to clearly identify pulmonary hypertension as a cause of death in these 3 patients; also, we have not convincingly ruled out the influence of other causes such as sepsis. The preoperative Qp:Qs ratio, PVR or PVR:SVR ratio did not predict a poor outcome for the entire cohort of patients because these were similar in the group with a poor outcome and the group that had a good long-term outcome. It is known that the rate of progression of PVR varies unpredictably between patients. Even older children or adults with uncorrected VSD with low PVR fare well after surgery. Rapid progression of PVR and early establishment of PVD puts younger children at a higher risk for surgery compared to older children or adults with a similar elevation of PVR.

In our series, 11 patients were more than 12 years old, and 6 of them were more than 18 years old at the time of surgery in the group that had a favorable outcome.

Eight of the patients in our cohort had a poor outcome. Five of the 38 patients (13.1%) died in the early postoperative period. Two patients could not be weaned away from cardiopulmonary bypass (CPB), 1 died of low cardiac output syndrome and 2 deaths were related to arrhythmias and multiorgan failure. Mortality rates in this subset have been reported to range from 15% to 50%, depending on the degree of preoperative elevation of PVR. Three patients operated before the age of 2 years had normal or near-normal PVR at follow-up. In those with a moderate elevation of PVR (more than one-third of SVR), there was no change or slight increase in PVR postoperatively. Park et al. found a significant fall in the pulmonary artery pressure and Pp:Ps ratio in all the patients who survived the operation but they remained above normal. Haneda et al. found a similar reduction in the PVR at follow-up as we did.

Parameters such as baseline arterial saturation, basal PVR, basal Qp:Qs or response to oxygen could not clearly differentiate a good responder from a poor responder to surgery. Other important parameters such as cardiomegaly, apical diastolic rumble, increased pulmonary blood flow seen on chest X-ray, and left atrial and left ventricular volume overload by echocardiography were probably taken into consideration but not consistently documented. Hence, no guideline could be drawn based on the catheterization data alone.

Limitations: Our study has the drawback of being a retrospective study with a relatively small number of patients. Patients were selected for surgery without uniform guidelines and they do not represent consecutive patients. Thus, it was a selective cohort of patients with nonrestrictive VSD and severe PAH on whom surgery was done based on the physician’s preference, surgeon’s acceptance and the finances of the patients. Therefore, no conclusion can be drawn regarding the recommendation of cut-off points for surgery on such patients. Repeat hemodynamic studies were not performed in all the patients. However, noninvasive studies suggested a significant reduction in pulmonary pressure in those patients who were clinically well. An additional limitation includes the use of assumed oxygen consumption for calculation of PVR. There are also limited data on the reversibility of increased PVR in baseline catheterization studies, and the influence of oxygen was not studied in all the patients. Most of the patients were catheterized in the pre-nitric oxide era.
Conclusions: This study demonstrates encouraging long-term results in a selected cohort of patients, many of whom were relatively older, and underwent VSD closure in spite of an elevated PVR. Many of these patients can lead active lives. Although pulmonary artery pressures seldom return to normal, a substantial reduction in PVR can occur. This study was unable to identify any demographic or hemodynamic variable that predicted the persistently high PVR that occurs in a minority of patients. In spite of a high early postoperative mortality, VSD closure should be considered in older patients with VSD and increased pulmonary blood flow in spite of elevation in PVR.

Acknowledgment

We thank R Krishnakumar, Amrita Institute of Medical Sciences, Kochi, India, for his valuable comments and assistance in reviewing the manuscript.

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Incidence and Risk Factors of Asymptomatic First-Dose Hypotension With Angiotensin-Converting Enzyme Inhibitors in Chronic Heart Failure due to Systolic Dysfunction

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Departments of Cardiology, Sri Ramachandra Medical College and Research Institute, Chennai, and All India Institute of Medical Sciences, Ansari Nagar, New Delhi

Background: In practice, chronic heart failure is often not treated with angiotensin-converting enzyme inhibitors. One reason is the fear of first-dose hypotension. In the majority of patients, this condition is asymptomatic and the consequences are unexpected. Presently, little is known of its epidemiology.

Methods and Results: This was a prospective, 48-hour observational study of 160 patients with chronic heart failure due to systolic dysfunction, previously untreated with angiotensin-converting enzyme inhibitors, randomly drawn from the clinical practice of selected cardiologists across India. The primary outcome was a change in the mean arterial pressure during the first 24-hours after the first dose of an angiotensin-converting enzyme inhibitor. In 131/160 patients (81.9%) with no hypotensive symptoms, the incidence of first-dose hypotension (maximum 24-hour fall in mean arterial pressure greater than 10% from baseline) was 56/131 (42.7%). Pre-treatment diastolic pressure had a negative, independent association with 24-hour change in mean arterial pressure, accounting for 29% (R²=0.29, p<0.01) of its variability, and its predictive value was greater with pro-drug angiotensin-converting enzyme inhibitors. The incidence of first-dose hypotension increased from 1 patient (4.8%) at a pre-treatment diastolic pressure of 50–70 mmHg to 35 patients (42.7%) at 71–90 mmHg, p<0.01.

Conclusions: The incidence of first-dose hypotension with angiotensin-converting enzyme inhibitors in outpatients with chronic heart failure due to systolic dysfunction is high. Pre-treatment diastolic pressure is an independent risk factor, and its predictive value increases with pro-drug angiotensin-converting enzyme inhibitors. This could help physicians to anticipate asymptomatic first-dose hypotension and increase the utilization of these agents in heart failure. (Indian Heart J 2003; 55: 167-171)

Key Words: Hypotension, Heart failure, Angiotensin-converting enzyme inhibitor

In clinical practice, up to 40% of patients with chronic heart failure (CHF) do not receive angiotensin-converting enzyme inhibitors (ACEI), and are thus denied the benefits of these agents. It has been observed that a precipitous fall in blood pressure due to first-dose hypotension (FDH) with ACEI, leading to end-organ damage, such as myocardial ischemia, is an important reason for their underutilization, particularly among noncardiologist physicians. In the majority of patients, FDH is asymptomatic, and the adverse consequences are unexpected. This may partly explain the reluctance of physicians, who are often the first to diagnose and treat heart failure in the community, to prescribe ACEI. Although symptomatic FDH has been studied in CHF patients selected for clinical trials with ACEI, there is little information on the incidence, magnitude, and risk factors that may be associated with asymptomatic FDH. Such information could be useful to physicians in anticipating an asymptomatic hypertensive response when initiating ACEI treatment in CHF, and in identifying patients who may be at increased risk, leading to increased confidence in the utilization of these agents in everyday clinical practice.

In this multicenter, 48-hour, prospective, observational
study on outpatients with CHF due to systolic dysfunction, who had not previously received an ACEI, drawn from the practice of randomly selected cardiologists across India, we examined the epidemiology of asymptomatic FDH after the initiation of ACEI treatment in daily practice.

Methods

Selection of participants: The study protocol was approved by the institutional ethics committee on human research. In 1997, the Cardiological Society of India had 1839 members distributed in 157 cities (with a population of more than 1 million) across India. In a two-stage random sampling process, 8 of these cities (5%) were selected first. Subsequently, in each of these cities, a 2% random sample of all practising cardiologists identified 18 (out of 896) who were invited to participate.

Selection of patients: Each cardiologist included consecutive outpatients from his practice who, in his overall clinical judgment, had CHF due to systolic dysfunction, requiring treatment with an ACEI; were of any age or either sex; whose sitting systolic blood pressure was above 100 mmHg; and who had not previously received an ACEI. CHF due to diastolic dysfunction, valvular heart disease, and contraindications to ACEI were exclusion criteria.

Assessments and treatment: Selected outpatients gave written informed consent, and were hospitalized for the purpose of the study for an observation period of 24 hours to assess pre-treatment demographic, clinical, and hemodynamic characteristics (Table 1). They were required not to smoke or ingest caffeine during the study period. Blood pressure was measured using a standard mercury sphygmomanometer with the patient sitting for 5 min. The value recorded was the average of 3 readings, each separated by a 2 min interval. Heart rate and blood pressure were assessed at the 2nd, 6th, 12th, and 24th hour after admission. Patients then received a single starting dose of an ACEI. The choice of the ACEI and its dose was at the discretion of the individual cardiologists so as to reflect their usual practice. Following this, blood pressure, heart rate, symptoms of hypotension and its possible complications were assessed hourly for the first 6 hours, and at the 12th and 24th hour. Associated treatment for CHF, such as diuretics and digoxin, or for other diseases, such as diabetes and hypertension, was allowed, according to the judgment of the cardiologist.

Statistical analysis: The primary outcome was maximum change in mean arterial pressure (defined as diastolic blood pressure plus one-third difference between systolic and diastolic blood pressures) from baseline during the 24 hours after dosage with an ACEI. Sample size was calculated to obtain a mean change from baseline in the outcome variable of -12 mmHg (standard deviation [SD] 6) within a range ±1 mmHg (estimated)\(^4\) at 95% probability. Allowing for an additional 15% expected to have symptoms of hypotension, we calculated that 160 patients would be required.

After checking the data for basic assumptions, a multiple linear regression analysis was done by the backward elimination method (SPSS, version 7.5) for the primary outcome as the dependent variable, to select the variable or variables which best predicted the post-dose 24-hour variation of mean arterial pressure. Covariables considered in the model were age, duration of CHF, pre-treatment ejection fraction, diastolic blood pressure, systolic blood pressure, and ejection fraction.

Table 1. Baseline characteristics of patients with chronic heart failure due to systolic dysfunction who did not develop hypotensive symptoms in response to the first dose of an angiotensin-converting enzyme inhibitor

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>n=131</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>57.5±12.6</td>
</tr>
<tr>
<td>Male sex</td>
<td>90 (68.7)</td>
</tr>
<tr>
<td>Clinical characteristics</td>
<td></td>
</tr>
<tr>
<td>Chronic heart failure duration (months)</td>
<td>15.0±21.5</td>
</tr>
<tr>
<td>Ejection fraction (%)(^*)</td>
<td>35.3±9.24</td>
</tr>
<tr>
<td>Chronic heart failure class(^1)</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>3 (2.3)</td>
</tr>
<tr>
<td>2</td>
<td>30 (22.9)</td>
</tr>
<tr>
<td>3</td>
<td>30 (22.9)</td>
</tr>
<tr>
<td>4</td>
<td>68 (51.9)</td>
</tr>
<tr>
<td>Etiology</td>
<td></td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>92 (70.2)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>13 (9.9)</td>
</tr>
<tr>
<td>Dilated cardiomyopathy</td>
<td>26 (19.8)</td>
</tr>
<tr>
<td>Normal renal function</td>
<td>126 (96.2)</td>
</tr>
<tr>
<td>No symptoms of dehydration</td>
<td>131 (100.0)</td>
</tr>
<tr>
<td>Chronic heart failure treatment</td>
<td></td>
</tr>
<tr>
<td>Diuretics</td>
<td>131 (100.0)</td>
</tr>
<tr>
<td>Digoxin</td>
<td>85 (64.9)</td>
</tr>
<tr>
<td>Associated disease</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>37 (28.2)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>69 (52.7)</td>
</tr>
<tr>
<td>Hemodynamic characteristics</td>
<td></td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>126.9±21.7</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>83.2±11.0</td>
</tr>
<tr>
<td>Mean arterial pressure (mmHg)</td>
<td>97.8±13.7</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>99.7±15.8</td>
</tr>
</tbody>
</table>

Values are mean±standard deviation. All other values are number of patients followed in parentheses by the percentage of the group.
\(n=93\). Echocardiography facility was not available at some centers.
\(^*\) According to New York Heart Association classification.
pressure, and heart rate. Initially, all covariates were included. The least significant variable was then dropped from the model at each step until the final model included only the variables with a p value <0.05. The fit of the variables finally selected in the regression model to the data was assessed by displays of residuals, and cross-validated in different patient subgroups.

Asymptomatic FDH was defined as a maximum fall in the mean arterial pressure >10% relative to the pre-treatment level, in the absence of symptoms of hypotension. Its incidence in patients stratified in terms of the variable identified by regression analysis was compared and tested for significance by the Chi-square test. Significance was defined as a two-tailed p value <0.05.

Results

All 18 cardiologists selected by random sampling participated, and included 160 patients. The number (%) of patients who received a single dose of an ACEI (mean±SD) was 50 (31.2) enalapril (3.8±1.4 mg); 46 (28.8) captopril (12.2±6.3 mg); 25 (15.6) ramipril (1.6±0.6 mg); 25 (15.6) perindopril (1.8±1.1 mg); 8 (5.0) lisinopril (1.9±0.6 mg); and 6 (3.8) benazepril (4.4±1.3 mg). The baseline characteristics of patients who did not develop symptoms of hypotension at any time during the post-dose 24-hour period are shown in Table 1. Most were in their sixth decade, male, with New York Heart Association classification grades 3 and 4 chronic heart failure, due to coronary artery disease of about 15 months' duration. The average ejection fraction was 35%. The majority were well hydrated, had normal renal function, and were under treatment for CHF with salt restriction, diuretics, and digoxin. About half had diabetes and one-fourth had hypertension. Hemodynamic characteristics, such as blood pressure and heart rate, were normal.

Incidence of asymptomatic first-dose hypotension: Of the 160 patients, 131 (81.9%, 95% confidence interval [CI]: 75.9–87.9) did not develop symptoms of hypotension after the first dose of an ACEI. In these asymptomatic patients, the 24-hour incidence rate of FDH was 56/131 (42.7%, 95% CI: 34.2–51.2). The 24-hour maximum fall in mean arterial pressure was 10.2 mmHg (8.5–11.8 mmHg), in systolic pressure 15.3 mmHg (12.7–17.8 mmHg), in diastolic pressure 8.4 mmHg (7.0–9.9 mmHg) and in heart rate 10.9 beats/min (9.2–12.6 beats/min).

Factors associated with first-dose change in mean arterial pressure: Of the 131 patients with no symptoms of FDH, multiple linear regression analysis showed that pre-treatment diastolic pressure had the strongest association with post-dose maximum 24-hour change in mean arterial pressure. The association was independent, and persisted after controlling for the effect of age, duration of CHF, and pre-treatment ejection fraction, heart rate, and systolic blood pressure. As shown in Table 2, pre-treatment diastolic blood pressure accounted for 29% of the variability of post-dose maximum 24-hour change in mean arterial pressure (adjusted coefficient of determination $R^2$=0.29) in all the patients. The association is negative, highly significant, and not influenced by either sex or treatment with digoxin. However, the choice of ACEI appears to affect its predictive value. With pro-drug ACEI (enalapril, perindopril, ramipril, and benazepril), pre-treatment diastolic blood pressure accounts for a greater variability in post-dose maximum 24-hour change in mean arterial pressure ($R^2$=0.38 or 38%) than nonpro-drug ACEI (captopril and lisinopril, $R^2$=0.13 or 13%). The effect of individual ACEI, impaired renal function, dehydration, and absence of diuretic treatment on the predictive value of pre-treatment diastolic blood pressure was not assessed because of an insufficient number of patients (Table 1).

Incidence of asymptomatic first-dose hypotension related to pre-treatment diastolic blood pressure level: The number of asymptomatic patients (%, 95% CI) with FDH increased from 1 (4.8, 0–13.9) at a pre-treatment diastolic blood pressure of 50–70 mmHg to 35 (42.7, 32.9–53.4) at 71–90 mmHg, and to 20 (75, 56.5–93.5) at 91–110 mmHg. These differences in incidence were significant at p<0.01. The relative risk of asymptomatic FDH with a diastolic blood pressure >70 mmHg was 10.9, and absolute risk 46.1%.

Magnitude of hemodynamic response: The 24-hour maximum reduction in hemodynamic variables after a dose of an ACEI appeared to be normally distributed. Mean (95% CI) reduction in mean arterial pressure was 10.2 mmHg (8.5–11.8 mmHg), in systolic pressure 15.3 mmHg (12.7–17.8 mmHg), in diastolic pressure 8.4 mmHg (7.0–9.9 mmHg) and in heart rate 10.9 beats/min (9.2–12.6 beats/min).

The consequences of asymptomatic FDH were observed in 1 patient (0.75%) who developed renal failure (normal function at baseline) 24 hours after taking an ACEI, in association with a 29.7% drop in mean arterial pressure.

Discussion

The majority (>80%) of unselected CHF outpatients with systolic dysfunction in daily clinical practice, who received an ACEI for the first time, had no hypotensive symptoms within 24 hours of the first dose. While in such asymptomatic patients there is no formal definition of FDH, a fall in blood pressure of 20 mmHg systolic and 10 mmHg
diastolic or 13 mmHg mean arterial pressure compared to pre-treatment levels has been suggested.\textsuperscript{2} Based on this, we defined asymptomatic FDH as a maximum fall in mean arterial pressure of 10% or more, compared to the pre-treatment level, within 24 hours of dosage. The overall incidence of FDH of this magnitude in our sample suggests that a third to half of all patients with CHF due to systolic dysfunction and without hypotensive symptoms may be affected.

Of the 6 candidate risk factors of asymptomatic FDH (age, duration of CHF, and pre-treatment ejection fraction, heart rate, systolic and diastolic blood pressure) considered in the multiple linear regression analysis, pre-treatment diastolic blood pressure had a significant association with maximum 24-hour post-dose change in mean arterial pressure, accounting for about a third of its variability. The association was negative, independent, and persisted after controlling for the effect of the other five risk factors. Further, the association was not influenced by sex or the use of digoxin (Table 2). However, the predictive value of pre-treatment diastolic blood pressure was stronger with pro-drug than non-prodrug ACEI (Table 2). The incidence of asymptomatic FDH in patients stratified by levels of pre-treatment diastolic blood pressure increased 9- to 15-fold above 70 mmHg (Fig. 1). The distribution of the extent of post-dose fall in mean arterial pressure in our sample suggests that it is likely to be 8–12 mmHg.

Although frequent, there is little epidemiologic information on asymptomatic FDH due to ACEI. Symptomatic FDH has been studied in chronic heart failure patients selected for clinical trials of ACEI treatment and, under these conditions, its reported incidence is about 5%.\textsuperscript{5} In these studies, the suggested risk factors such as severity of CHF,\textsuperscript{6} elderly patients, and low pre-treatment blood pressure\textsuperscript{7} are not supported by our results in chronic heart failure patients with systolic dysfunction who have no symptoms of FDH.

A major problem in the treatment of CHF is that a majority of patients are denied the established benefits of ACEI at the level of noncardiologist physicians.\textsuperscript{1,2} In those who do receive these agents, symptomatic FDH may be the most frequent cause of discontinuation of treatment.\textsuperscript{2} Since asymptomatic FDH is about 6-fold more frequent, possible end-organ damage such as renal failure and myocardial ischemia, occurring unexpectedly and without warning, may be sufficiently common experience among physicians to discourage the use of ACEI, and partly explain the underutilization of this group of drugs. Furthermore, it is these noncardiologist physicians who are often the first to diagnose and treat CHF in the community.

Our study was conducted on unselected CHF patients with systolic dysfunction drawn from the clinical practice of randomly selected cardiologists distributed throughout India. These outpatients were hospitalized for the purpose of the study, and frequent hemodynamic assessment made for 24 hours before and after administration of an ACEI. The focus of the study was asymptomatic hypotension, and

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**Table 2. Effect of pre-treatment diastolic blood pressure on maximum 24-hour change in mean arterial pressure after the first dose of an angiotensin-converting enzyme inhibitor (simple linear regression)**

<table>
<thead>
<tr>
<th>Patient group</th>
<th>n</th>
<th>$R^2$</th>
<th>Beta $^\dagger$</th>
<th>t</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>131</td>
<td>0.29</td>
<td>-0.54</td>
<td>-7.3</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Male</td>
<td>89</td>
<td>0.29</td>
<td>-0.54</td>
<td>-6.0</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Female</td>
<td>42</td>
<td>0.28</td>
<td>-0.55</td>
<td>-4.1</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>With digoxin</td>
<td>57</td>
<td>0.29</td>
<td>-0.54</td>
<td>-4.7</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Without digoxin</td>
<td>74</td>
<td>0.30</td>
<td>-0.56</td>
<td>-5.7</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Pro-drug angiotensin-converting enzyme inhibitors$^1$</td>
<td>88</td>
<td>0.38</td>
<td>-0.62</td>
<td>-7.4</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Nonpro-drug angiotensin-converting enzyme inhibitors$^1$</td>
<td>43</td>
<td>0.13</td>
<td>-0.36</td>
<td>-2.5</td>
<td>&lt;0.02</td>
</tr>
</tbody>
</table>

$^\ast$adjusted coefficient of determination (indicates proportion of variability in mean arterial pressure due to diastolic blood pressure)

$^\dagger$standardized partial coefficient

$^1$enalapril, perindopril, ramipril, and benazepril

$^2$captopril and lisinopril

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![Fig. 1. Incidence of asymptomatic first-dose hypotension according to the pre-treatment level of diastolic blood pressure. Hypotension is defined as the maximum fall in 24 hours of mean arterial pressure greater than 10% from the pre-treatment level, after the first dose of an angiotensin-converting enzyme inhibitor, 95% confidence interval. *Differences in incidence are significant at $p<0.01$.](image)
the results reflect its incidence, magnitude, and possible risk factors in daily outpatient practice. We did not standardize either the ACEI or dosage, because our aim was to study the problem under usual practice conditions. In our sample, the average dose of all ACEI used was close to that recommended for initiating treatment in CHF. We could not assess the influence of individual ACEI on asymptomatic FDH because the number of patients receiving the newer agents was small. However, a broad comparison between pro- and nonpro-drug ACEI was made to assess their effect on the predictive value of pre-treatment diastolic blood pressure as a risk factor (Table 2). A few patients had renal impairment, dehydration, or were not treated with diuretics (Table 1), and these possible risk factors were not assessed. The usefulness of our results is that they indicate to physicians the frequency and magnitude of asymptomatic FDH that could be expected to occur in CHF outpatients with systolic dysfunction treated with an ACEI for the first time in daily practice. In the absence of dehydration and renal impairment, pre-treatment diastolic pressure is an independent inverse predictor of post-dose mean arterial pressure, and its predictive value increases when pro-drug ACEI are used; and the incidence of asymptomatic FDH increases several-fold when pre-treatment diastolic pressure is >70 mmHg. This could help in anticipating asymptomatic FDH, and increase the confidence in and utilization of ACEI, particularly among noncardiologist physicians, who are often the first to diagnose and treat CHF in the community.

Acknowledgments

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References

Percutaneous Stenting of Chronic Total Occlusion of Unprotected Left Main Coronary Artery

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Stenosis of the left main coronary artery (LMCA) is found in 3%–5% of patients undergoing coronary angiography. Total occlusion of the LMCA, defined as the complete absence of antegrade flow of contrast beyond the bifurcation of the LMCA, is rare. The rarity of this condition in an angiographic series may be due to the high mortality in this subgroup. Traditionally, coronary artery bypass graft surgery has been considered the treatment of choice for these patients. However, percutaneous revascularization is being increasingly performed in such patients. We report a patient with chronic total occlusion of the LMCA, who underwent successful elective percutaneous revascularization of the unprotected LMCA.

Case Report
A 40-year-old man presented with a history of angina on exertion (Canadian Cardiovascular Society class II) for the past 5 months. He had sustained an anterior wall myocardial infarction 7 months back, for which he had not received thrombolytic therapy. Coronary angiography revealed a left main stump with 100% occlusion of the LMCA before its bifurcation. No antegrade flow could be seen in the left coronary system beyond the distal LMCA from the left coronary injection (Fig. 1). The right coronary artery was essentially normal, and gave off grade III collaterals to the left system. The left anterior descending (LAD) and left circumflex (LCx) coronary arteries were filling retrogradely from the right coronary artery (RCA) till the bifurcation of the LMCA (Fig. 2). Left ventriculography showed apical and anterolateral hypokinesia with an ejection fraction of 40%.

The patient refused to undergo coronary artery bypass graft surgery but consented to the nonsurgical alternative of percutaneous transluminal coronary angioplasty (PTCA) and stenting. A week later, he was taken up for elective PTCA and stenting with intra-aortic balloon pump (IABP) standby. A bolus of injection abciximab (0.25 mg/kg body weight) was given prior to the procedure, followed by an infusion at the rate of 10 µg/min for 12 hours.
The stump of the LMCA was engaged with a 7 F guiding catheter (Cordis, The Netherlands). The lesion was then crossed with a 0.014" extra-support Choice PT wire (Boston Scientific/Scimed, France), and the wire was advanced into the LAD. A 20 mm/1.5 mm Maverick balloon (Boston Scientific/Scimed, France) was then placed across the LMCA to the proximal LAD lesion and inflated at 12 atm. After inflation, some antegrade flow was restored in the LMCA to the LAD. The LCx could also be faintly visualized. Another Choice PT wire was then passed from the LMCA to the LCx, and the LMCA to LCx lesion was dilated with a 20 mm/1.5 mm Maverick balloon at 12 atm. The LMCA to proximal LAD lesion was serially dilated with resterilized 15 mm/2 mm, 15 mm/2.5 mm and 15 mm/3 mm cutting balloons (Boston Scientific/Scimed, France) at 6 atm. A 20 mm/2 mm cutting balloon (the 15 mm/2 mm cutting balloon was damaged during use in the LAD) was taken across the lesion from the LMCA to the LCx with some difficulty, and dilated at 6 atm. Following this, the lesion was further dilated with a 20 mm/2.5 mm Maverick balloon at 12 atm. A check angiogram revealed 50% residual stenosis at the ostium of the LCx from the distal LMCA to proximal LAD. The proximal LCx was therefore stented with a 20 mm/2.75 mm Express stent (Boston Scientific/Scimed, France) from its ostium at a pressure of 15 atm. Then the LMCA to LAD lesion was stented with a 15 mm/3 mm JOMED stent (JOMED, Germany) at 14 atm followed by in-stent dilatation with an 11 mm/4 mm JOMED balloon (JOMED, Germany) at 15 atm. The final result was a normal-looking LMCA, LAD, and LCx arteries with restoration of TIMI III flow (Fig. 3). A right coronary injection after the procedure showed disappearance of the
collaterals in the left coronary system (Fig. 4). The patient was discharged after 72 hours, and at a clinical follow-up after 8 months, he is asymptomatic and has a negative exercise stress test.

**Discussion**

Chronic total occlusion of the LMCA is rare. The reported incidence of chronic total occlusion of the LMCA is between 0.06% and 0.1%. Conventionally, coronary artery bypass grafting has been considered to be the treatment of choice in patients with disease in the LMCA. However, with improvement in the techniques of PTCA, and the advent of stents and glycoprotein IIb/IIIa inhibitors, percutaneous revascularization of the unprotected LMCA is being increasingly performed. To date, the largest series on elective stenting of the unprotected LMCA has been reported by Silvestri et al. and Park et al. However, none of the patients in these series, comprising a total of 267 patients, had 100% occlusion of the LMCA. There are a few case reports in which acute total occlusion of the LMCA has been successfully revascularized percutaneously. To the best of our knowledge, this is the first case report in the literature, in which a chronic, totally occluded, unprotected LMCA was successfully revascularized percutaneously.

**References**

Multivessel Cutting Balloon Angioplasty in a Patient With Type III Nonspecific Aortoarteritis

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A 23-year-old female patient with type III nonspecific aortoarteritis (Takayasu’s arteritis) presented with multiple obstructive lesions and severe congestive heart failure. Large, cutting balloons 5–8 mm in diameter were used to dilate lesions in the abdominal aorta, both renal arteries, right common carotid artery, proximal left subclavian artery, and ostium of the left vertebral artery. Wide luminal expansion without residual stenosis, substantial dissection or need for adjunctive stenting was achieved at all six angioplasty sites. The use of cutting balloons appears suitable for treating obstructive lesions in aortoarteritis. (Indian Heart J 2003; 55: 175–177)

Key Words: Aortoarteritis, Cutting balloon, Takayasu’s arteritis

Angioplasty of obstructive lesions in nonspecific aortoarteritis (Takayasu’s arteritis) is often limited by the resistant and fibrotic nature of these lesions. A large number of these lesions fail to yield adequately during balloon dilatation, even at very high pressures. Residual stenosis, elastic recoil, dissection, and even rupture of the vessel adjacent to the lesion may occur. Also, optimal expansion of stents used to overcome elastic recoil and dissection may not be obtained. A suboptimal immediate angioplasty result is a major factor responsible for the persistence of symptoms and subsequent restenosis. Peripheral cutting balloons™ (Boston Scientific/Interventional Technologies, San Diego, CA) 5–8 mm in diameter have recently become commercially available, and are of appropriate size for most of the vessels involved in aortoarteritis. In this report, we describe the effectiveness of peripheral cutting balloons in treating multiple obstructive lesions in a severely symptomatic patient with type III aortoarteritis.

Case Report

A 23-year-old female patient with a 4-year history of recurrent dizziness, syncope, and blurring of vision. Over the past two years she developed progressive exertional dyspnea, leg fatigue, and pedal edema, leading on to orthopnea and paroxysmal nocturnal dyspnea. For the past two weeks she had low-grade fever, cough, and hemoptysis.

On examination, the patient was small built and emaciated (body weight 26 kg), tachypneic and orthopneic. There was tachycardia, dependent edema, and distension of the neck veins. The carotid and left upper limb pulses were absent, and both lower limb pulses were feeble. The erythrocyte sedimentation rate and C-reactive protein levels were elevated, and the sputum was positive for acid-fast bacilli. Chest X-ray (Fig. 1) showed cardiomegaly, left atrial enlargement, pulmonary venous congestion, and bilateral pleural effusion. Echocardiography revealed enlarged left heart chambers, global hypokinesia (left ventricular ejection fraction 35%), and moderate mitral and tricuspid regurgitation. Multidrug therapy for tuberculosis and anti-failure measures were instituted. The heart failure remained refractory to medical therapy and, two weeks later, the patient was subjected to angiography.

Angiography revealed features typical of type III aortoarteritis. There was severe narrowing of the upper abdominal aorta at the level of the celiac axis with a mean translesion gradient of 44 mmHg (pressure above 137/62, mean 86 mmHg; pressure below 56/35, mean 42 mmHg), and bilateral severe renal artery stenosis (Fig. 2A). A lateral aortogram showed that the celiac axis itself was occluded, the ostium of the superior mesenteric artery was mildly narrowed, and the inferior mesenteric artery was normal. Aortic arch angiography (Fig. 3A) showed occlusion of both the common carotid arteries with distal reformation at the level of the carotid bifurcation. The right subclavian artery was free of major disease. There was marked stenosis of the proximal left subclavian artery and ostium of the
left vertebral artery. The mid and distal left subclavian artery was occluded, and distally the left axillary artery was seen to opacity through collaterals.

Treatment of the patient's obstructive lesions was carried out in two sittings, after obtaining informed consent. In the first sitting, the abdominal aortic stenosis was dilated using cutting balloon 8 mm in diameter at 7 atm pressure. Expansion of the luminal diameter to that of the cutting balloon, without elastic recoil or dissection, was obtained (Fig. 2B). The mean translesion gradient was reduced to 4 mmHg (pressure above 116/58, mean 81 mmHg; pressure below 117/57, mean 77 mmHg). Next, each of the renal artery lesions was dilated using a 6 mm cutting balloon at 8 atm. Luminal expansion to a diameter larger than that of the normal vessel beyond the lesion was obtained bilaterally, without elastic recoil, and with minor nonflow limiting dissection. Following the procedure, the lower limb pulses became normally palpable, and the next day the systemic blood pressure fell markedly, necessitating saline infusion for several hours. The symptoms of paroxysmal nocturnal dyspnea and orthopnea resolved completely, and the general condition of the patient improved markedly.

Ten days later, the supra-aortic lesions were treated percutaneously using the femoral approach. The occlusion in the right common carotid artery was traversed using a 0.014" Shinobi Plus wire (Cordis, Miami Lakes, FL) and the lesion was dilated using a 5 mm cutting balloon introduced through an 8 F guiding catheter. An excellent result was obtained with no residual stenosis, smooth outline, and rapid flow (Fig. 3B). The distal left common carotid artery occlusion was similarly probed, but wire passage could only be obtained into the left external carotid artery. Hence, cutting balloon angioplasty was not performed at this location. The proximal left subclavian artery and ostial left vertebral artery lesions were dilated using the same 5 mm cutting balloon at 6–8 atm pressure. Wide luminal patency with no dissection was obtained at both sites (Fig. 3B). The

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**Fig. 1.** Chest X-ray in anteroposterior projection showing cardiomegaly, left atrial enlargement, pulmonary venous congestion and bilateral pleural effusion.

**Fig. 2.** (A) Baseline abdominal aortogram in anteroposterior projection. Arrow indicates severe abdominal aortic stenosis at the level of the occluded celiac axis. Severe bilateral renal artery stenosis is evident. (B) After cutting balloon angioplasty, wide luminal expansion without elastic recoil or significant dissection is seen at the site of the aortic and both renal lesions.

**Fig. 3.** (A) Baseline aortic arch angiogram in left anterior oblique projection. Arrows indicate location of bilateral common carotid artery occlusions. (B) After cutting balloon angioplasty in the right common carotid artery, proximal left subclavian artery and ostial left vertebral artery lesions, a wide lumen without elastic recoil or significant dissection is seen in these lesions.
Discussion

Obstructive lesions in aortoarteritis are produced by circumferential intimal thickness and transmural fibrous scarring, with minimal or no calcification.\(^9\) Resistance of such lesions to plain balloon dilatation is well known.\(^1\) Residual stenosis after angioplasty is an important determinant of restenosis, and is related to the resistance offered by the lesion to dilatation, and to elastic recoil. Stents are useful in reducing elastic recoil and in tackling down dissections, but they exacerbate intimal hyperplasia, which can lead to luminal occlusion, especially if the stent is not adequately expanded. The cutting balloon has several features that are appropriate for dilating resistance fibrotic lesions in aortoarteritis, and may overcome these problems. It constitutes a noncompliant balloon with four 10 mm long microsurgical blades 0.007” in height, mounted longitudinally on its outer surface. The blades initiate microincisions in the lesion, after which the shear force applied by balloon inflation propagates the microincisions in a controlled manner while the interincisional segments are spared damage.\(^9\) The microincisions disrupt the fibroelastic continuity of circumferential lesions, thereby minimizing elastic recoil.\(^10\) The result is that the lesion is more completely dilated at lower balloon pressure, with less trauma to the vessel wall, and less elastic recoil than can be achieved by plain balloon dilatation. These actions of the cutting balloon may be sufficient to provide an optimal outcome, as seen in all six lesions, treated using cutting balloons in our patient, and may obviate the need for a stent. If flow-limiting dissection does occur and a stent has to be deployed, the work already done on the lesion by the cutting balloon will ensure optimal stent expansion. Cutting balloons can thus minimize the problem of residual stenosis after angioplasty in aortoarteritis, which may translate to lower restenosis rates in the long term. Till recently, cutting balloons that were only 4 mm or less in diameter were available, and were redesigned for coronary applications. Now that cutting balloons 5–8 mm in diameter have become commercially available, larger vessels with resistant lesions can be treated.\(^1\) In our patient, outcomes superior to what we have observed with plain balloon angioplasty were obtained in all six lesions that were treated using large cutting balloons; a wide vessel lumen without substantial dissection was obtained at relatively low pressure, without the need for stenting. The use of a cutting balloon appears suitable for treating obstructive lesions in aortoarteritis.

References

The Modified Inoue Technique: A Simple Troubleshooting Approach to a Proximal Segment Tear of an Inoue Balloon

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A tear in the proximal segment of an Inoue balloon was encountered during the dilatation of a calcific mitral stenosis. As a troubleshooting measure, we modified the steps of the standard Inoue technique. The mitral valve was successfully dilated using the same Inoue balloon. (Indian Heart J 2003; 55: 178-179)

Key Words: Percutaneous transvenous mitral commissurotomy, Balloon rupture, Mitral stenosis

Case Report
A 35-year-old woman was referred for percutaneous transvenous mitral commissurotomy (PTMC) for rheumatic MS. On echocardiography, the mitral valve area was 0.7 cm². Both the anterior and posterior mitral leaflets had significant calcification (Wilkins’ MV score of 11/16),7 though both commissures were free of calcification. The patient had severe pulmonary hypertension (pulmonary artery pressure 105/65, mean 78 mmHg). She was taken up for PTMC using the standard technique.8 A 28 mm first-use, pre-checked Inoue balloon was used. The first dilatation was performed with a 24 mm balloon size. The transmitral gradient decreased to 20 mmHg from 30 mmHg, and it was decided to redilate with a 26 mm balloon size. After placing the balloon in the left ventricle, a contrast–saline mixture was injected into the balloon. However, the proximal segment of the balloon inflated first instead of the distal one. It was deflated immediately and parked deep in the left ventricular cavity so that it would not inflate in the chordae. We inflated the balloon to observe the inflation–deflation sequence. The proximal segment inflated first, followed by the distal, and the middle segment was the last to inflate (Fig. 1a and b). During deflation, the middle segment was the first to deflate followed by the proximal segment. As soon as the proximal segment deflated, the balloon was hitched against the MV (Fig. 1c) and rapidly inflated (Fig. 1d). This time the valve opened well with reduction of the transmitral gradient to 4 mmHg. This was an acceptable end-result, and the balloon was withdrawn. During in vitro testing, we found a 4 mm tear in the outer rubber layer of the proximal segment (Fig. 2) and a similar inflation–deflation sequence was observed.

Discussion
The Inoue balloon has a unique design. It has double-layered rubber walls that contain a network of synthetic nylon fibers, which give different compliance characteristics to its distal, proximal, and middle segments.8 The distal segment, being the most compliant, inflates first, followed by the proximal, and finally the middle.8 When the balloon is deflated, it is the middle segment that deflates first, followed by the proximal and, finally, the distal segment.8 In the present case, this unique mechanism failed due to the tear 4 mm in size, in the outer layer of the proximal segment of the balloon, which made the proximal segment more compliant than the distal. Therefore, during inflation, the proximal segment inflated first, followed by the distal and, lastly, the middle segment (Fig. 1a and b). This reversal of the normal inflation–deflation mechanics led us to suspect a tear in the proximal segment.2 Due to this altered compliance characteristic, when the balloon was deflated, the middle segment deflated first, followed by the proximal. Before the distal segment started deflating, the balloon was hitched against the MV and rapidly inflated.
Thus, by modifying the steps of the standard Inoue technique, we were successful in dilating the MV using the same balloon.

Though generally well tolerated, balloon rupture could be potentially hazardous, and might cause embolism and difficulty in retrieval. Balloon rupture could be due to accidental or intentional use of a high inflation pressure, asynchronous balloon inflation during double balloon valvuloplasty or oversizing of the balloon. Valve morphology also plays an important role. Calcified, nonyielding bioprosthetic valves are associated with a very high incidence (50%) of balloon rupture, as is defective balloon material. A higher than usual incidence (20%) is reported when balloons are reused. The stronger rubber nylon micromesh of the Inoue balloon is claimed to account for the lower incidence of balloon rupture during PTMC of noncalcified valves. In the present case, rigidity of the valve because of significant calcium deposits seems to be responsible for the tear, since maximum inflation pressure with the Inoue syringe does not exceed 2 bars and the recommended maximum balloon size was not exceeded. Also, we used a first-use balloon, which was prechecked in vitro. A similar tear in the outer layer of the distal segment is not as important, as it does not change the inflation–deflation sequence. Thus, it does not require any modification in the standard technique.

In conclusion, with the increasing use of PTMC in calcific MS, the incidence of tear of an Inoue balloon is likely to increase. Ideally, PTMC should be performed by changing over to the double-balloon technique or by using another Inoue balloon. However, this simple modification of the standard technique can be attempted to complete the procedure with the same balloon. This not only saves procedural and fluoroscopic time but also reduces the cost of the procedure.

References
Thoracoscopic Window for a Post-Coronary Artery Bypass Grafting Pericardial Effusion

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We report the case of a 60-year-old man presenting with a symptomatic, posteriorly loculated, pericardial effusion, and a concomitant pleural effusion a month after coronary artery bypass grafting. Following the initial insertion of an intercostal drain, he was treated by thoracoscopic creation of a pericardial window. His postoperative recovery was uneventful, and he remains well 6 months post-procedure. Creation of a thoracoscopic pericardial window is a safe and feasible option in the management of patients with loculated pericardial effusions. (Indian Heart J 2003; 55: 180-181)

Key Words: Pericardial effusion, Thoracoscopy, Pericardial window

Thoracoscopy has been used for the diagnosis of intrathoracic diseases for several years. This technique has found several therapeutic applications following advances in video camera technology; the treatment of pericardial effusion (PE) is one of them. We report a patient who underwent thoracoscopic drainage and creation of a pericardial window for a large pleuropericardial effusion that developed after coronary artery bypass grafting (CABG).

Case Report

A 60-year-old man underwent CABG with harvesting of the right and left internal mammary arteries, and concomitant aortic valve replacement via a median sternotomy. Postoperatively, oral anticoagulants were started. After a month, he presented with dyspnea and pedal edema. Examination revealed features suggestive of PE. A chest X-ray confirmed the diagnosis of a large PE (Fig. 1). Echocardiography demonstrated a PE with a depth of 10 cm and posterior loculation. The replaced aortic valve was functioning well. A drain was placed in the fifth intercostal space to evacuate the pleural fluid.

Under general anesthesia, thoracoscopic drainage was performed using a double-lumen endotracheal tube. The patient was placed in a left lateral decubitus position with the surgeon and cameraperson both standing to the left of the patient; the monitor was placed facing them on the opposite side. The primary port for introduction of the telescope was placed through the track of the intercostal drainage tube. Two other 5 mm ports were placed in the posterior axillary line on either side of the camera port. The pleural fluid was aspirated and adhesions in the pleural space were divided. The presence of fluid in the pericardial sac was confirmed by aspiration with a long needle, and an incision was made on the pericardium away from the vascularized pericardial fat. The serosanguineous fluid that gushed out was aspirated. A disc of pericardium measuring 5 cm across was excised to create a window (Fig. 2). At the end of the procedure, a 28 F drain was inserted in the pericardial cavity under vision. The postoperative course was uneventful with the patient requiring minimal analgesia. The drain was removed on the fifth day, and the patient discharged the following day. He remains well at follow-up 6 months later.

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Discussion

Although PE commonly develops following open heart surgery, it is clinically significant in 0.8%–6% of patients.1 The factors predisposing to the development of post-operative effusion include valve surgery, use of anticoagulants, coagulation disorders, excessive mediastinal drainage, post-pericardiotomy syndrome, and autoimmune reactions.2 Although the incidence of PE developing late after cardiac surgery is low, this results in a higher mortality than that associated with early effusions.3 Occurrence of PE months after CABG is also well known, and some of these persist for a few years.4

The optimal treatment of a postoperative PE remains controversial. The Mayo Clinic group has reported a high success rate with pericardiocentesis performed under echocardiographic guidance, and strongly recommend this approach over the use of a blind subxiphoid aspiration.2 Although a single pericardiocentesis may fail to resolve the problem, this method is often utilized to relieve the tamponade, and establishing hemodynamic stability in an acute setting. However, a posteriorly located or loculated PE, as was present in our patient, is less likely to respond to pericardiocentesis.5

Traditional surgical approaches described for treatment of postoperative PE include placement of a drainage tube via a subxiphoid incision, or creation of a pericardial window via a left anterior thoracotomy or median sternotomy. Each of these may be combined with a varying degree of pericardiectomy. Although simple and efficacious in urgently relieving the tamponade, the subxiphoid route provides restricted access, and is associated with a relapse rate of 3%–18%.5 A formal thoracotomy overcomes these shortcomings but is associated with a higher morbidity, more postoperative pain, and longer hospitalization. Moreover, a patient in whom a left internal mammary artery graft has been harvested, a thoracotomy is likely to entail difficult dissection through postoperative adhesions.

Thoracoscopy has been used for the treatment of PE and pericarditis due to various causes, including systemic lupus erythematosus,6 uremia,7 post-cardiac transplantation,8 and post-CABG.9 The thoracoscopic approach allows drainage of the PE and wide fenestration of the pericardium. Adequate and dependent drainage is a key factor in decreasing the incidence of recurrence and formation of intrapericardial adhesions. As thoracoscopy affords excellent visualization of the pericardium, accurate placement of an intra-pericardial drain is possible. The precise extent of pericardial fenestration required to prevent recurrence of the effusion is controversial, but depends on the etiology of the effusion. In our patient, a 5 cm pericardial window created anterior to the phrenic nerve satisfactorily decompressed the pericardium. Additional benefits of the thoracoscopic approach for patients include reduced postoperative pain, lower incidence of wound-related problems, shorter hospitalization, and faster recovery.

In conclusion, a patient with a large PE post-CABG can be successfully treated by the thoracoscopic creation of a pericardial window.

References

Cardiac Myxoma With Glandular Elements: A Histologic, Histochemical, and Immunohistochemical Evaluation

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Brief Report

Epithelial differentiation in cardiac myxoma is a rare phenomenon. Out of 104 surgically excised specimens, we studied 3 cases of cardiac myxoma with glandular differentiation. All the cases had well formed glands in addition to the myxoma cells lying in a myxoid background. Detailed histochemical and immunohistochemical studies suggest that the epithelial islands in cardiac myxoma show an enteric phenotype.

Key Words: Cardiac myxoma, Glandular differentiation, Immunohistochemistry

Case Report

During the past 25 years, we examined 104 cases of surgically excised cardiac myxomas, of which 3 cases revealed the presence of glandular elements on light microscopic evaluation of hematoxylin–eosin stained slides. The representative sections were stained with alcian blue–periodic acid Schiff (AB–PAS), mucicarmine (MC), and high iron diamine–alcian blue (HID–AB). Immunohistochemical stains for cytokeratin (CK), and carcinoembryonic antigen (CEA) on formaldehyde-fixed, paraffin-embedded sections were performed by the peroxidase–antiperoxidase method. A detailed light microscopic evaluation was done in all 3 cases.

Two of the 3 cases of cardiac myxoma with glandular elements were sporadic in nature, while the third had a familial background. All the myxomas were located in the left atrium. Light microscopic evaluation of the lesion showed two components. The predominant component was that of a classical myxoma with stellate or spindle-shaped “lepidic cells” or “myxoma cells” lying in a myxoid background. The cells had a moderate amount of eosinophilic cytoplasm, and were evenly distributed with occasional perivascular aggregates. The myxoid background additionally had focal hemorrhage, fibrin insudation and hemosiderin-laden macrophages. The glandular component was located predominantly at the base of the lesion. There were well-defined glandular spaces lined by a single layer of cuboidal to tall columnar cells with the presence of goblet cells at places (Fig. 1A). Some of these glands contained luminal mucin. There was no nuclear atypia, mitosis or necrosis. Occasionally, the epithelial cells showed an abrupt transition into myxoma cells.

The glandular epithelium was mucicarminophilic and showed strong positivity with PAS after diastase digestion. The cells were also positive with alcian blue (Fig. 1B). HID–AB stain imparted both blue and brown colours either in the same cell or in individual cells (Fig. 1C). Immunoperoxidase staining of the glandular structures showed diffuse positivity for cytokeratin. CEA was positive in some cells in all 3 cases (Fig. 1D). None of the myxoma cells in the background was positive for any of these stains.

Discussion

Glandular differentiation in cardiac myxoma is a rare feature, and is reported to occur in about 3% of cases.3,9 A few case reports have been published on the subject.4–9 with

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cells (peroxidase–antiperoxidase stain ×35). for carcinoembryonic antigen shows focal positivity (arrows) in the epithelial sarcomas.11 In the past, the histogenesis of cardiac myxoma such markers except mesotheliomas and synovial myxoma. Mesenchymal tumors usually lack expression of keeping with the epithelial differentiation in cardiac intestinal mucosa. The expression of keratin and CEA is in epithelium, while sulfomucins are expressed in the large mucin (AB positive) and sulfomucin (HID positive) components. The acid mucin comprised sialomucin was composed of both neutral (P AS positive) and acid mucin (AB positive). The intracellular mucin histologic patterns, suggests the gastrointestinal or enteric nature of the epithelium. The intracellular mucin was composed of both neutral (PAS positive) and acid mucin (AB positive). The acid mucin comprised sialomucin (AB positive) and sulfomucin (HID positive) components. Sialomucins are commonly seen in the small intestinal epithelium, while sulfomucins are expressed in the large intestinal mucosa. The expression of keratin and CEA is in keeping with the epithelial differentiation in cardiac myxoma. Mesenchymal tumors usually lack expression of such markers except mesotheliomas and synovial sarcomas.11 In the past, the histogenesis of cardiac myxoma was debatable as there was a controversy regarding its thrombogenic and neoplastic origins. Most authors now believe that cardiac myxoma is a neoplastic lesion derived from “embryonal rests”, and the presence of various mesenchymal cells, such as the “myxoma cells”, endothelial cells, smooth muscle cells, fibroblasts, myofibroblasts, and chondroid cells represents divergent differentiation.12 The presence of the epithelial element is an example of one spectrum of the multidirectional differentiation.

In the present study, the areas of glandular differentiation were seen predominantly at the base or the pedicle of the cardiac myxoma, a finding also noted by previous observers. Recognition of these epithelial islands is important as they can mimic metastasis from a carcinoma. This is especially pertinent in the rare cases of epithelial differentiation in cardiac myxoma with the presence of adenocarcinoma elsewhere,7 when a critical evaluation is required to exclude metastasis. In such cases, atypical cells with frequent mitosis are seen, including abnormal forms, and areas of necrosis may be present. Additionally, it lacks the presence of myxoma cells or lepidic cells in the background.

The histogenesis of glandular differentiation in cardiac myxoma is an enigma. As described in the literature, the glandular structures might represent entrapped foregut rests. Alternatively, these islands can be due to intracardiac endodermal heterotopia.6,14 It is also possible that the primitive mesoderm is multipotential, and hence can have divergent differentiation. The epithelial differentiation seems to be an expression of the multipotentiality of the progenitor cells in cardiac myxoma, and is enteric in nature.

Fig. 1. (A) Photomicrograph of the glandular component in a cardiac myxoma. The gland has an irregular contour and is lined by cuboidal to columnar cells (hematoxylin–eosin × 35). (B) Alcian blue-periodic acid Schiff stain shows the presence of acidic mucin (blue) in the glandular lining cells (alcian blue-periodic acid Schiff stain ×75). (C) High iron diamine–alcian blue stain reveals the presence of both sialomucin (blue) and sulfomucin (brown) in the epithelial cells (high iron diamine–alcian blue stain ×75). (D) Immunohistochemical stain for carcinoembryonic antigen shows focal positivity (arrows) in the epithelial cells (peroxidase-antiperoxidase stain ×35).

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Heart-Lung Transplantation in India: Initial Experience

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Heart-lung transplantation is a well accepted and standard form of therapy for the surgical management of patients with end-stage cardiopulmonary disorders. The first heart-lung transplant in India was performed at our institution on May 3, 1999 and, subsequently, 2 more patients have undergone this procedure. The initial experience is encouraging and heralds a new era of thoracic organ transplantation in India. (Indian Heart J 2003;55:185-187)

Key Words: Heart lung transplantation, Lung preservation, Immunosuppressive therapy

Heart-lung transplantation has come of age and is offered to patients with end-stage cardiopulmonary disorders.1,2 Single-lung transplantation and bilateral sequential lung transplantation are being performed more often in patients with isolated end-stage lung disorders to maximize the use of donor organs. However, heart-lung transplantation has its own advantages, such as the removal of all the diseased tissues, absence of ventilation/perfusion imbalance, and avoidance of cross-contamination from a remaining contralateral lung. We present a brief case history and management of the three heart-lung transplantations performed at our institute.

Case Report

Case 1: A 29-year-old female with severe primary pulmonary hypertension and severe right ventricular dysfunction was evaluated for heart-lung transplantation. She was suffering from acute exacerbation of breathlessness and was hospitalized frequently. She underwent successful heart-lung transplantation on May 3, 1999, the first of its kind in India. A 41-year-old male who had sustained intracerebral hemorrhage and was declared brain dead was the donor. The cold ischemic time was 2 hours and 30 min. The recipient was extubated on postoperative day 1 and convalesced well. The respiratory gases were adequate and the cardiac function was good, as shown by two-dimensional (2-D) echocardiography. However, she developed severe respiratory infection and expired on postoperative day 35.

Case 2: A 31-year-old man was offered heart-lung transplantation after being diagnosed to have ventricular septal defect with Eisenmenger syndrome. He was on regular medical follow-up and was taken up for heart-lung transplantation upon availability of the organs. Clinically, he was cyanosed, had clubbing of the fingers, and a loud S2. His hemoglobin was 21 g/dl and hematocrit 66%. Echocardiogram revealed a large muscular ventricular septal defect with mainly right-to-left shunt, volume and pressure overload of the right atrium and ventricle, with severe pulmonary artery hypertension. The donor heart-lung block was retrieved from a 40-year-old women who was pronounced brain dead after a road traffic accident. During surgery, the lungs of the recipient were found to be densely adherent to the pleural cavity. After excision of the diseased heart-lung block, the donor heart-lung block was sewn in place, starting with the tracheal anastomosis, followed by the right atrial suture line and the aortic suture line, respectively. The heart spontaneously picked up normal sinus rhythm. The cold ischemic time was 3 hours and 45 min. After a brief period of support, the patient was weaned away from cardiopulmonary bypass with minimal inotropic support. He was extubated the same evening, and his immediate postoperative course was uneventful. He was started on immuno suppressive therapy with azathioprine, cyclosporin, and steroids, as well as ganciclovir in view of the donor blood and recipient testing positive for cytomegalovirus (CMV). At 1-year follow-up, 2-D echocardiography showed good left ventricular function with an ejection fraction of 60%, and the pulmonary function test showed good results. However, he developed respiratory infection combined with an episode of rejection, and died due to multiorgan failure 14 months after transplantation.

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Case 3: A 34-year-old male with an atrial septal defect with severe pulmonary hypertension, severe right ventricular dysfunction, and Eisenmenger syndrome underwent heart-lung transplantation on 17 January 2002. A 28-year-old male with brain death due to a head injury sustained in a road traffic accident was the donor. Intraoperatively, the pulmonary arteries were extremely dilated and occluded with thrombotic material (Fig. 1). Explantation of the heart and lungs was difficult due to the dense vascular adhesions of the lung to the chest wall. Heart-lung transplantation was carried out successfully, and the hemodynamics, including blood gases, showed good results. However, he had massive bleeding in the postoperative period, and expired on postoperative day 1.

Preservation techniques: The aim is to minimize the effects of ischemia and reperfusion on the allograft, resulting in optimal function after transplantation. We used cold crystalloid cardioplegia for myocardial protection. The pneumoplegic solution used by us consists of an infusion of PGE-1 initially, followed by an infusion of lung perfusate—Wallwork blood-based solution. The composition of the lung perfusate is given in Table 1. All 3 donor organs were distant organ procurements, i.e., harvested from other hospitals in the city.

Discussion

The classical indications for heart-lung transplantation include Eisenmenger syndrome, primary pulmonary hypertension, cystic fibrosis, fibrosing alveolitis, emphysema, sarcoidosis, bronchiectasis, histiocytosis X, and pulmonary fibrosis. Currently, for the majority of these indications, heart-lung transplantation has given way to bilateral sequential lung transplantation. Thus, present-day indications for heart-lung transplantation are Eisenmenger syndrome with complex congenital anomalies, primary pulmonary hypertension with severe RV dysfunction, and proximal bronchiectasis, i.e., those involving the main-stem bronchi.

The rate-limiting factor in clinical heart-lung transplantation is the continuing and acute shortage of suitable donor organs. The problem is particularly acute in the case of heart-lung donors because of the propensity for neurogenic pulmonary edema, atelectasis, pneumonia and other pulmonary complications in brain-dead ventilated patients. Due to the strict criteria for accepting lungs for transplantation, only about 15% of cardiac donors are suitable for heart-lung transplantation.

Eurocollins solution is the most commonly used clinical lung preservative solution, and is of intracellular ion composition. The lung perfusate used by us is extracellular in composition, similar to the recently introduced low potassium-dextran solution. Struber et al. demonstrated an improvement in the perioperative mortality and morbidity rates by changing the preservation protocol from flush solution with Eurocollins to low potassium-dextran solution.

The immunosuppressive regimen differs from that in orthotopic heart transplantation, in that steroids are minimized to enhance tracheal healing. A typical regimen includes cyclosporin, azathioprine, and small doses of steroids. Currently, drugs with few side-effects, such as mycophenolate mofetil and tacrolimus, are preferred over cyclosporin and azathioprine.

The major causes of mortality in the long term are infection and the bronchiolitis obliterans syndrome. International data obtained from the Registry of the International Society for Heart and Lung Transplantation document a 1-year survival of approximately 60% and a 5-year survival of 40%–50%. The survival at 11 years is approximately 21%.

Conclusions: Heart-lung transplantation is an extremely effective treatment for combined end-stage cardiac and pulmonary disease.
pulmonary disease. Survival rates in excess of 70% after 1 year can be anticipated in healthy young patients. Donor shortage is the main limiting factor. In view of its efficacy, heart-lung transplantation should be offered to appropriate recipients who have no hope otherwise.

References
Telemedicine Links Between Developing and Developed Nations

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Telemedicine is defined as technologically facilitated remote consultation and diagnosis. Telemedicine systems are characterized by the type of information sent (such as clinical information, ultrasonographic images, or on-line percutaneous coronary angioplasty consultation) and by the means used to transmit this information (modem, local or wide area networks, Ethernet, or, more recently, synchronous optical network).

Generally, telemedicine is used in 2 types of situations: (i) when geographic and socio-economic factors prevent rapid transfer of information between patients and healthcare providers; and (ii) when the availability of vital information would help with diagnosis and treatment. The primary rationale for the development of a telemedicine system is to serve populations that have limited access to traditional, high-quality, diagnostic or therapeutic medical services. Telemedicine lends itself particularly well to specialties in which images are crucial to the diagnosis.

Teleradiology, a subcategory of telemedicine, is characterized by the transmission and display of diagnostic radiologic images. Previous applications include remote viewing of radiographs, computed tomographic (CT) images, and magnetic resonance (MR) images.

There has been long-standing interest in transmitting cardiac imaging records for reasons similar to those for radiologic applications: to facilitate the diagnosis of conditions and treatment of patients at other institutions, or to get another opinion of a feature found during an examination (Table 1). Extension of teleradiology to cardiac imaging applications, however, was severely limited because of the dynamic nature of ultrasonographic and radiographic images and the need to display those dynamic images in a faithful manner.

Amid rapid technologic changes, it is opportune to critically examine the current status of telemedicine. This review focuses on the technical requirements of telemedicine and on its national and international applications with an emphasis on its use for cardiovascular diseases.

Table 1. Applications of telemedicine

<table>
<thead>
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<th>Applications of telemedicine</th>
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<tr>
<td>Enhance quality of patient care by providing access to a second opinion</td>
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<tr>
<td>Respond to requests for specialty expertise from distant locations</td>
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<tr>
<td>Reduce unnecessary travel costs and inconvenience</td>
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<tr>
<td>Develop innovative ways to practise medicine</td>
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<tr>
<td>Provide a triage mechanism to determine which patients require referral</td>
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<tr>
<td>Enhance and preserve existing relationships with patients and referring physicians</td>
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</table>

Technical Requirements

Data acquisition and transfer: Initially, telemedicine relied on telephone lines to transmit data over long distances, and the transfer rates were limited by the capacity of the modulation/demodulation devices (modems). Recently, higher capacity broadband network connections have been used routinely between medical institutions. A broadband network differs from a baseband network in its ability to transmit multiple channels over a wire by using multiplexing techniques. Broadband transmission networks, although more expensive, reduce transfer times by a factor of approximately 50, making transfer of single images almost instantaneous. Data transfer rates measure the amount of digital information that can be transmitted through a channel per second. Table 2 highlights some of the applications and corresponding data transfer rates.

There are 2 methods of data transfer: (i) “store-and-forward;” and (ii) “real-time.” In the store-and-forward approach, a clinical imaging examination is performed and the result of the procedure is sent to another site for display, assessment, and storage of the examination record. The advantage of the store-and-forward technology is that it obviates the need for the consulting parties to be available simultaneously. The low bandwidth requirements also tend to make it less expensive. The store-and-forward format is especially suited to radiology and pathology, in which reports on the assessment of the image data are not required immediately. Many echocardiographic and coronary angiographic images can be sent to other institutions by the use of this technique. A much more
There are two types of compression methods to reduce the amount of data transfer: (i) reversible or “lossless compression,” in which the user has precisely the same image or data that were available initially; and (ii) irreversible or “lossy compression,” in which the resulting information is a close approximation but is not strictly identical to the original image. Although the lossy compression method results in greater reduction of data, vital information may be lost.

Recently, results were published from the American College of Cardiology and the European Society of Cardiology International Study of Angiographic Data Compression.6–8 The 3-phase study was an examination of the effect of different degrees of Joint Photographic Experts Group (JPEG) target lossy compression ratios on various coronary angiographic features. Images compressed at a ratio of 6:1 were equivalent to uncompressed images. However, at a compression ratio of 10:1, nearly 10% of the compressed images were degraded, and at 16:1, 55% were degraded. The results of these studies indicate that as the compression of images is increased, the ability to detect clinical features is impaired. Hence, the use of lossy compression by cardiac catheterization laboratories was discouraged.

**Applications of Telemedicine in Cardiology**

In cardiology, the simplest application of telemedicine is the transmission of electrocardiograms.6 The most important application in pediatric cardiology is the transmission of echocardiographic images for the diagnosis of congenital heart disease in the neonate; in this situation, early diagnosis and management may be crucial.10,11 The main benefit of a telemedicine link is the transmission of diagnostic images to a remote location before a decision is made to transfer the patient.

The largest study of telemedicine in a pediatric echocardiographic diagnosis and management included 500 echocardiographic studies of 364 patients during a period of 30 months.12 In the study, desktop videoconferencing over 3 Integrated Services Digital Networks (ISDN) was done at Children’s National Medical Center and George Washington University Medical Center, Washington, DC. The echocardiographic studies guided by pediatric cardiologists resulted in only 1 minor change to a diagnosis. The use of telemedicine had an immediate effect on 151 transmissions. The most common interventions in the 2 community hospitals were indomethacin therapy for patent ductus arteriosus (n=76), retraction of umbilical venous catheter from the left atrium (n=45), inotropic or

**Table 2. Data transfer rates of various applications**

<table>
<thead>
<tr>
<th>Application</th>
<th>Rate</th>
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<tbody>
<tr>
<td>Dial-up modem connection</td>
<td>1200–28 800 bits/s</td>
</tr>
<tr>
<td>T1 digital WAN</td>
<td>64 000 bits/s</td>
</tr>
<tr>
<td>Ethernet LAN</td>
<td>10–100 Mbits/s</td>
</tr>
<tr>
<td>T3 digital WAN link</td>
<td>44.184 Mbits/s</td>
</tr>
<tr>
<td>High-speed serial interface</td>
<td>52 Mbits/s</td>
</tr>
<tr>
<td>Fiber-distributed data interface</td>
<td>100 Mbits/s</td>
</tr>
<tr>
<td>High-performance parallel interface</td>
<td>800–1600 Mbits/s</td>
</tr>
<tr>
<td>SONET</td>
<td>51.9 Mbits-2.5 Gbits/s</td>
</tr>
<tr>
<td>Future SONET</td>
<td>13.2 Gbits/s</td>
</tr>
</tbody>
</table>

LAN: local area network; SONET: synchronous optical network; WAN: wide area network
decongestive therapy \( n=19 \), anticoagulation \( n=8 \), and prostaglandin infusion \( n=8 \). Nineteen patients were transported to tertiary centers because of a diagnosis made with telemedicine. Hence, the use of telemedicine improved patient care and prevented unnecessary transfers resulting from wrong diagnoses.

A similar experience with cineangiography was reported by Randolph et al.\(^1\) who used higher bandwidth for transmission of 161 neonatal echocardiograms in 133 patients from a primary care center in Grand Forks, North Dakota, to the Mayo Clinic in Rochester, Minnesota. All studies were thought to be diagnostic, and 59% resulted in a change in therapeutic management or follow-up. In another study, 54 telemedicine consultations were conducted on previously obtained cineangiograms from 38 patients with congenital heart disease; the dynamic display was helpful in 96 of 108 observations (89%).\(^1\)

The use of telemedicine in the catheterization laboratory is still relatively new, but there are 4 important areas of potential application for real-time catheterization data transfer: (i) physician training; (ii) clinical conferencing; (iii) support for clinical trials; and (iv) support for clinical procedures. Except for clinical conferencing, these applications require accurate replication of angiographic, echocardiographic, and intravascular sound data. This would require high-fidelity and higher bandwidth telecommunication systems. The present cost of such systems may preclude the routine use of telemedicine in cardiology.

Currently, conducting percutaneous coronary interventions (PCIs) at centers without on-site cardiac surgery is not recommended for simple or complex elective cases or for patients with acute non-ST-segment elevation myocardial infarction. For the treatment of patients who have acute ST-segment elevation myocardial infarction or new left bundle branch block on electrocardiography at hospitals without on-site cardiac surgery, the 2001 American College of Cardiology/American Heart Association guidelines\(^1\) recommend that primary PCI be restricted to institutions with the following characteristics: (i) more than 36 cases of primary PCI are performed annually; (ii) a proven plan exists for rapid access to a nearby surgical facility; (iii) PCI can be performed rapidly (balloon inflation within 90±30 min); and (iv) skilled operators at the institution regularly perform at least 75 PCI procedures annually. If those requirements are met for elective cases or patients with non-ST-segment elevation myocardial infarction, primary PCI at a site without on-site cardiac surgery is considered a class IIb indication.\(^1\)

The Mayo Clinic has been instrumental in developing a system of telemedicine for PCI (tele-PCI). In this program, Saint Mary’s Hospital (SMH) in Rochester, Minnesota, which has on-site surgical capability, provides real-time tele-PCI services to 2 community hospitals, approximately 100–135 km from SMH, which do not have an on-site cardiac surgical facility. Each of the 2 community hospitals has a fully equipped cardiac catheterization laboratory and a link to the main hospital by means of a dedicated fiberoptic T3 line. During angiography and PCI, the angiographic images, hemodynamic data, video images from the cardiac catheterization laboratory, intravascular ultrasonographic images, and sound are transmitted to SMH. This on-line image and data transfer allows on-line consultation between the person performing the PCI and the cardiology and cardiovascular surgical colleagues at SMH. In a study on elective and primary PCI for acute myocardial infarction at a community hospital that was linked to Mayo Clinic with telemedicine, it was demonstrated that elective low-risk and primary PCI can be safely and effectively performed without on-site cardiac surgical capabilities.\(^1\)

Approximately 500 PCIs (including 180 emergent angioplasties for acute myocardial infarction) have been performed at these centers with excellent outcomes (unpublished data). The results of PCI at the community hospitals compared favorably with results at SMH, and no patient was transferred to SMH for emergent coronary bypass surgery for failed PCI.

Telemedicine Applications Between Developed and Developing Nations

The World Health Organization and World Bank estimate that deaths attributable to cardiovascular disease have increased in parallel with the increasing population in India. Of all the deaths in India in 1990, approximately 25% were attributable to cardiovascular diseases, as compared with 10% from diarreal diseases, 13% from respiratory infections, and 8% from tuberculosis. In India, cardiovascular mortality is expected to increase in parallel with an increase in life expectancy resulting from increases in per capita income and declining infant mortality.

However, the health and financial resources in India and other developing countries are limited. In addition, many people in these countries have limited access to state-of-the-art healthcare facilities because resources are not equitably distributed for geographic or socio-economic reasons. Distribution of resources through the use of telemedicine would help transcend social, economic, and
geographic health barriers. So far, telemedicine applications in cardiology have been limited to facsimile transmission of electrocardiograms and interpretation of complex echocardiograms from pediatric patients. The transfer of images to a tertiary care center could provide a crucial diagnosis resulting in immediate transfer and treatment of the neonate or infant. The diagnosis may also result in avoiding unnecessary transfers. Thus, the utility of telemedicine is amply demonstrated in this field.

For developing countries especially, cost is an important consideration. Instead of real-time transmission of the images, a reasonable alternative is the use of store-and-forward technology. The images could be interpreted later by a pediatric cardiologist at a tertiary center and the diagnosis conveyed to the primary physician. However, with the store-and-forward technology, subjective interpretation of images may pose problems.

The application of telemedicine in PCI is relatively new, but the results of PCI performed at sites without on-site surgery are encouraging. The advantages of this system are that on-line guidance can be obtained for decision-making during a difficult case of coronary intervention, problem-solving for a complication during the procedure, and coordinating the transfer and surgical help for a patient who has an acute complication during the procedure. However, this system needs real-time transfer of images, and the prohibitive costs limit its application in developing countries. The store-and-forward method can be used with limited success under these circumstances. This technology is currently used by the Mayo Clinic (Figs 1–3). With the use of telemedicine links, second opinions are given in various clinical and radiologic situations (including echocardiography and coronary angiography). After diagnostic angiography, the images can be reviewed and treatment options discussed before a patient is transferred to another facility.

Cost: The bandwidth needed to transmit an angiogram rapidly and completely remains expensive. The cost of digital network transmission depends on the type of service required; namely, store-and-forward transmission is less costly than real-time transmission. The annual operating cost for the telemedicine system is approximately US$ 200 000. This is the main reason that such networks are rare. As with other networking applications, the user must choose between low cost and high speed. To reduce the size of the file being transmitted, various compression methods have been tested that might prove cost-effective. However, one must realize that compressed data at the review station may differ from the original and the image

Fig. 1. Example of data transfer and workstation links between Mayo Clinic and a hospital on another continent.

Fig. 2. Flowchart of the processing of a telemedicine consultation at Mayo Clinic.

Fig. 3. The telemedicine workflow process.
may be inferior in quality. Although compression algorithms should not be used if the transmission involves clinical decision-making, they may be useful in videoconferencing during seminars or during national or international cardiology meetings. Several questions remain unanswered: (i) Is tele-PCI cost-effective? (ii) What is the relative utility of tele-PCI as compared with conventional treatment? (iii) What are the cost-reimbursement issues?

Legal and confidentiality issues: Many telemedicine issues?remain unanswered: (i) Is tele-PCI cost-effective? (ii) What international cardiology meetings. Several questions videoconferencing during seminars or during national or clinical decision-making, they may be useful in algorithms should not be used if the transmission involves privacy concerns and realize that the legality of sharing this information without a patient’s knowledge or consent varies from state to state.

References
Brugada Syndrome

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A 23-year-old student from West Bengal presented with a history of recurrent episodes of syncope and palpitations of 5 months’ duration. Palpitations were predominantly nocturnal and present sometimes even at rest. An ECG taken earlier had shown coved ST elevation of >2 mm in V₁ and V₂ (resembling right bundle branch block [RBBB]) and a negative T wave with little or no isoelectric separation (Fig. 1). At the time of presentation the ECG showed runs of nonsustained ventricular tachycardia of left bundlebranch block (LBBB) morphology (Fig. 2). Echocardiographic evaluation was normal. Holter monitoring done for 24 hours, prior to coming to our institution, showed recurrent polymorphic nonsustained ventricular tachycardia.

A diagnosis of Brugada syndrome was made on the basis of Type 1 ST segment elevation (coved type) in more than one right precordial lead (V₁ - V₃) with a history of syncope and self-terminating ventricular tachycardia. The patient was advised to immediately have an automatic implantable cardioverter defibrillator (AICD) implanted. Due to financial constraints, he could not have this done. Till then, we have advised him to continue amiodarone. As per the current recommendations, AICD implantation is the treatment of choice for this subset of patients.

Brugada syndrome is a familial disease which shows an autosomal dominant mode of transmission. It is common in the South-East Asian region with an incidence of 5-66/10 000 subjects. Syncope or sudden cardiac death is the only symptom in patients with Brugada syndrome. ECG abnormalities are the hallmark of Brugada syndrome, and prompt recognition of the ECG findings is imperative in making the diagnosis of this potentially lethal condition. Priori et al. have suggested a risk-stratification scheme based on the symptoms and ECG pattern. According to this scheme, high-risk patients are those with baseline ST elevation and a history of syncope. Our patient falls into this category. These patients should be considered for immediate AICD implantation.

References

Fig. 1. ECG taken at rest shows ST segment elevation with coved pattern in leads V₁ and V₂.

Fig. 2. ECG showing nonsustained ventricular tachycardia of LBBB morphology.
Letters to the Editor

Myocardial Infarction due to Myocardial Bridging

We read with great interest the article on myocardial infarction due to myocardial bridging,\(^1\) and would like to share our experience with a similar case, a 17-year-old male who presented with acute chest pain while playing football. His electrocardiogram showed acute anterior wall myocardial infarction (AWMI) (Fig. 1) with a rise in the cardiac enzymes. He was thrombolysed. On the 7th day post-MI, a coronary angiogram showed a large myocardial bridge to the LAD, resulting in 70%–80% compression during systole (Figs 2 and 3). The left ventricular ejection fraction (LVEF) was 45% with anterior wall hypokinesia. As the myocardial perfusion scan did not show viability in the infarcted segment, revascularization procedures, such as stenting or debridging myotomy, were not considered. The patient is stable on beta-blockers, aspirin, calcium-channel blockers and ACE inhibitors. He was also investigated for the hypercoagulable state, viz. hyperhomocysteinemia, protein C and S and Lp(a), which were found to be normal.

Myocardial infarction is rarely seen at a young age. Three factors attributable to ischemia produced by myocardial bridging are: (i) length of the tunneled segment; (ii) degree of systolic compression; and (iii) increased heart rate.

In our case, the AWMI was probably due to the isolated effect of “myocardial bridging” in the LAD; an increased heart rate might have also played a role. Our patient had no other coronary risk factor, as compared to the case reported by Nayar et al., who was 53-year-old with a history of heavy smoking, which is known to produce spasm of the artery affected by the myocardial bridge. No intravascular ultrasound study (IVUS) to exclude atherosclerotic plaque was undertaken in this 53-year-old male.

Reference


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The case reported by Jain et al. is interesting, especially as the authors have emphasized that the patient had no known coronary risk factors. In the case we reported, IVUS could not be done because of the exigency of the situation. The patient had an evolving AMI and was hemodynamically unstable. A detailed study of the coronary angiogram in multiple views excluded the possibility of an atherosclerotic plaque contributing to the episode, as the plaque would have shown up in one view or the other. The coronary arteries were angiographically clear. There is a possibility that endothelial dysfunction due to chronic smoking, coupled with intimal damage in the bridged segment due to recurrent apposition of the vessel walls during systolic compression, could have led to thrombus formation, resulting in the MI. The thrombus may have undergone spontaneous lysis by the time the coronary angiography was done. This possibility is, however, remote.

Even so, this sequence of events does not detract from the statement we wished to make, that myocardial bridges (especially deep and long ones) are not as benign as thought to be. The presence of a myocardial bridge, in association with factors that increase the contractility or heart rate, can result in an acute coronary syndrome or even sudden cardiac death. The case described by Jain et al. also vindicates this statement. This raises the question as to whether we should proscribe drugs and activities that increase heart rate/contractility in patients with documented long and/or deep myocardial bridges, just as we do in patients with hypertrophic obstructive cardiomyopathy.

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Combined Subaortic and Sinus of Valsalva Aneurysm

We read with interest the case report by Sivasankaran et al.1 on the coexistence of congenital subaortic and sinus of Valsalva (SOV) aneurysms in a 19-year-old woman. However, we do not agree with authors’ contention of it being the first case reported.

In our large series of cases of subannular aneurysms (16 patients with 19 aneurysms),2 we had 5 patients who had associated SOV aneurysms. Among them, 3 had subaortic aneurysms. All were young and, interestingly, one of them had all the three types, i.e. two each of subvalvular and subaortic aneurysms with one SOV aneurysm, which makes it a unique case. We agree with the authors that such lesions arise due to congenital developmental weakness between the muscular ventricular wall and fibrous valve annulus.

References

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Reply

Our patient is the first case to be clinically recognized to have both sinus of Valsalva (SOV) and subaortic aneurysms which were identified by echocardiography and angiography.1 However, we do acknowledge that Deshpande et al.2 had already shown this association in their autopsy series. Three of their cases of subaortic aneurysm had associated SOV aneurysm. One of them had associated subvalvular aneurysm as well. While they have described in detail the subaortic and subvalvular aneurysms, there is no description of the SOV aneurysms. In our patient, the SOV aneurysm was arising from the right coronary cusp and the subaortic aneurysm was related to the left coronary sinus. Infection was the most common cause of subaortic aneurysm in the group of patients reported by Deshpande et al., while our patient did not have any evidence of infection. Hence, congenital weakness of insertions of the ventricular muscle and aortic wall with the aortic annulus is probably the explanation for this condition, as suggested by Deshpande et al. also.

References

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Selected Summaries

Amiodarone Versus Implantable Cardioverter-Defibrillator: Randomized Trial in Patients With Nonischemic Dilated Cardiomyopathy and Asymptomatic Nonsustained Ventricular Tachycardia—AMIOVIRT

Strickberger et al. J Am Coll Cardiol 2003; 41: 1707–1712

Summary

The management of patients with nonischemic dilated cardiomyopathy (NIDCM) as well as asymptomatic nonsustained ventricular tachycardia (NSVT) is not clear. The MADIT and MUSTTY trials have established strategies for the primary prevention of sudden cardiac death (SCD) in patients with ischemic cardiomyopathy, with implantable cardioverter-defibrillator (ICD) being recommended for those with inducible and nonsuppressible ventricular tachycardia (VT) with severely depressed ventricular function. However, inducibility of VT in NIDCM patients has a poor prognostic value, as shown in several studies.

Trials of amiodarone therapy in patients with dilated cardiomyopathy showed a trend only towards improved survival in a subgroup of patients with NIDCM in the CHF-STAT trial. This multicenter randomized trial was undertaken to compare the effect of amiodarone versus ICD on total mortality in this subset of patients.

Between August 1996 and September 2000, 103 patients with NIDCM, left ventricular ejection fraction (LVEF) <0.35% and asymptomatic NSVT were randomized to receive either amiodarone or an ICD. Exclusion criteria were the presence of syncope, pregnancy or concomitant therapy with class I antiarrhythmic drugs. The primary end-point was total mortality. Arrhythmia-free survival, syncope, SCD, non-SCD, noncardiac death, quality of life, and costs were the secondary end-points. The baseline characteristics, including age, ejection fraction, duration of illness, NYHA class and risk factors, were evenly matched. Patients were followed up 4-monthly and assessed for drug levels, side-effects, stored electrocardiograms, and sensing and pacing functions. The mean duration of follow-up was 2.0±1.3 years (range 0.1–4.8 years). There was no difference in the 1- and 3-year survival rates between the 52 patients on amiodarone and the 51 given ICDs (90% and 88% v. 96% and 87%, respectively). The incidence of sudden death versus non-SCD was also similar (p=0.7). Arrhythmia-free survival rates at 1- and 3-years were not significantly different, though there was a trend towards arrhythmia-free survival with amiodarone (p=0.1). The quality of life, as assessed by the Quality of Well being Schedule and State Trait Anxiety Inventory scores, did not differ significantly, while there was a trend towards 60% cost savings with amiodarone therapy.

Comments

There is only one published study on randomized trial of ICDs for the primary prevention of SCD in patients with NIDCM. The Cardiomyopathy Trial (CAT) randomized 104 patients with new-onset NIDCM, irrespective of ventricular arrhythmias to, ICD or control, and found no survival benefit of ICDs at 4 years. The AMIOVIRT trial also found no difference in survival between the groups assigned to either amiodarone or ICD. A trend towards a lower initial cost and improved arrhythmia-free survival was noted in the amiodarone group. However, certain aspects of the trial need to be noted. A major problem with amiodarone is the adverse effects of this drug. In this study, almost 50% of patients discontinued the drug, making it difficult for physicians to enforce compliance.

In this study, the mortality rate (around 10% at 1 year) was very low as compared with up to 30% in previous studies. It seems logical to assume that the low mortality rate was because of optimal medical therapy, with around 50% patients receiving β-blockers, more than 80% receiving ACE inhibitors, and 20% receiving spironolactone. It is likely that more frequent use of beta-blockers would further lower the mortality. Similarly, the advent of biventricular pacing is also likely to influence the natural history of NIDCM. Therefore, at present, it is not certain whether amiodarone or ICD would ensure better survival than optimal medical therapy in patients with NIDCM. If a high-risk subset within this group can be identified, then ICD may prove to be a useful strategy. A recent study has used T-wave alternans in the risk stratification of patients with NIDCM. Moreover, the etiology of NIDCM also has a bearing on the prognosis, with sarcoidosis or hypertrophic cardiomyopathy having a higher risk for SCD compared with the idiopathic post-viral type. The present trial favors the use of amiodarone over ICD in patients with NSVT because of cost-effectiveness and possibly better arrhythmia-free survival. For a definitive answer, results of further clinical trials including the Sudden Cardiac Death in Heart Failure (SCD-HEFT) trial are awaited.
Prevention of Coronary and Stroke Events With Atorvastatin in Hypertensive Patients who have Average or Lower-than-Average Cholesterol Concentrations in the Anglo-Scandinavian Cardiac Outcomes Trial—Lipid Lowering Arm (ASCOT—LLA)

Sever et al. Lancet 2003; 361: 1149-1158

Summary
The Anglo-Scandinavian Cardiac Outcomes Trial is a multicenter, randomized trial primarily designed to compare antihypertensive treatment strategies for the prevention of coronary heart disease (CHD) events in hypertensive patients without a prior history of CHD. By way of a 2x2 factorial design, the ASCOT study has a double-blind randomized comparison of the cardiovascular effects of atorvastatin with placebo among patients who have a total cholesterol concentration of 6.5 mmol/L or less. Inclusion criteria were either untreated hypertension (p<160/100) or treated hypertension (p<140/90) in patients 40-79 years of age, with at least three other risk factors out of the following—left ventricular hypertrophy (LVH), noninsulin-dependent diabetes mellitus (NIDDM), peripheral vascular disease (PVD), previous stroke, smoking, microalbuminuria, a family history of premature CAD, total cholesterol to HDL cholesterol ratio of ≥6. Exclusion criteria were previous myocardial infarction (MI), currently treated angina, recent cerebrovascular event, heart failure, fasting triglyceride (TG) level >4.5mmol/L, uncontrolled arrhythmias, or any important hematologic or biochemical abnormality.

A total of 19342 hypertensive patients were enrolled, out of whom 10305 with a nonfasting total cholesterol concentration of ≤6.5 mmol/L were randomly assigned to additional atorvastatin (10 mg) or placebo; these patients formed the lipid-lowering arm of the study. The primary end-points were non-fatal MI and fatal CHD. The treatment was stopped prematurely after a median follow-up of 3.3 years. Compared with placebo, the total cholesterol and LDL fraction were 1.3 mmol/L and 1.2 mmol/L lower at 1 and 3 years respectively. At 3 years, 87% of the patients were drug compliant. The primary end-point of nonfatal MI and fatal CHD was significantly lower by 36% in the atorvastatin group as compared to the placebo group.

Fatal and nonfatal stroke (p=0.024), total cardiovascular events (p=0.0005), and total coronary events (p=0.005) were also significantly lower. All-cause mortality was nonsignificantly reduced by 13% with fewer cardiovascular deaths (p=ns) and no excess deaths from cancer or from other non-cardiovascular causes.

Comments
It is a well-established fact that lowering cholesterol in high-risk cardiac patients is beneficial. In the WOSCOPS study, pravastatin lowered the total cholesterol by 20% and in the AFCAPS/TEXCAPS trial lovastatin lowered total cholesterol by 18%, and showed a significant reduction in the end-point of nonfatal MI and fatal CHD (31% and 40%, respectively).

The ASCOT study is different, as it specifically focuses on hypertensive patients. The only other study done specifically in hypertensive patients is the ALLHAT study that showed an apparently disappointing clinical benefit. There was only a 9% reduction in total cholesterol in that trial, primarily because of a substantially higher use of statins in the controls, thereby confounding the final outcome.

The 36% reduction in fatal CHD and nonfatal MI with only 10 mg atorvastatin may have been higher with longer follow-up and higher dose. There was a 27% reduction in stroke incidence. These benefits were observed without any serious side-effects of the drug, there being no case of raised liver enzymes and only 1 case of rhabdomyolysis. The findings of this study add further evidence to the concept that cardiovascular risk increases parallel to increasing serum cholesterol concentration and that a global assessment of risk rather than rigid numerical values should be the basis of the treatment strategy.

In conclusion, the ASCOT—LLA trial showed that hypertensive patients at only moderate cardiovascular risk, who conventionally would not have received statins, also had a significant reduction in cardiovascular events with the use of atorvastatin.
Antibiotic Therapy After Acute Myocardial Infarction


Summary

The antibiotic therapy after an Acute Myocardial Infarction (ANTIBIO) trial was a prospective, randomized, placebo-controlled, double-blind study undertaken to determine the influence of treatment with the anti-chlamydial antibiotic roxithromycin in patients with acute myocardial infarction (AMI). Participating patients included those with ST elevation or non-ST elevation AMI, randomized within 5 days after admission to a six-week treatment regimen with either roxithromycin 300 mg daily or placebo. Exclusion criteria were pregnancy/lactation, allergy to macrolide antibiotics, central nervous system/liver disease, concomitant use of ergotamine/dihydroergotamine-containing drugs or participation in another study. Inclusion or randomization of patients did not depend on age or seropositivity. The primary end-point was total mortality at 12 months. Secondary end-points were (i) a combined end-point of death, reinfarction, resuscitation, stroke or post-infarction angina leading to a hospital admission within 12 months; and (ii) a combined end-point of death, reinfarction, resuscitation, stroke or unstable angina leading to a hospital admission within 12 months, and (iii) the rate of PCI or CABG within 12 months. The total follow-up period was 12 months. Out of 872 patients enrolled, 433 were treated with roxithromycin and 439 with placebo. The treatment was started at a median of 4 days after the onset of symptoms. ST-elevation AMI occurred in 88% of all patients. The mean age was 61 years and 75% of patients with ST-elevation MI received reperfusion therapy, and a high percentage of patients received concomitant therapy such as aspirin, beta-blockers and ACE inhibitors. Baseline characteristics in both the groups were well matched except for a higher proportion of roxithromycin patients presenting with anterior wall AMI (48.1% vs. 40.2%) and a lower prevalence of chronic obstructive pulmonary disease (COPD) (3.5% vs. 6.9%) in this group. Discontinuation of the study drugs (before the 6-week period) was more common in the roxithromycin group (18% vs. 11%) although no specific reason could be attributed to it. Follow-up at 12 months could be achieved in 99.5% of patients (868/872). The total mortality at 12 months was 6.5% in the roxithromycin group compared with 6.0% in the placebo group (OR 1.1, 95% CI: 0.6-1.9, p=0.739). Secondary combined end-points at 12 months were also not significantly different. Even after adjusting for differences in baseline characteristics, no significant differences were found between the 2 groups. Based on these findings, the authors concluded that short-term use of roxithromycin did not reduce event rates during 1-year follow-up and, as such, their use in AMI is not indicated.

Comments

The role of infectious agents in the causation of CAD is still controversial. While mechanistic and preclinical studies have demonstrated an association of Chlamydia pneumoniae with atherosclerosis, the cause-effect relationship, especially in humans, is still not unequivocal. One of the best ways to establish their relationship (and also provide some practical solution to this disease entity) is to examine the role of anti-chlamydia antibiotics in these patients. Till date, several small (ROXIS, ACADEMIC, CLARIFY, STAMINA, AZACS, etc) and one large clinical trial (WIZARD) have addressed this issue. However, these trials have yielded conflicting results, probably due to different trial designs, type of macrolide antibiotic (clarithromycin, roxithromycin or azithromycin), type of CAD (stable/unstable angina), duration of therapy, and seropositivity of enrolled patients. One of the most important considerations for therapy for Chlamydia pneumoniae is the duration of treatment. Due to the peculiar life-cycle of Chlamydia (the infectious, extracellular, nonreplacing form of the organism is not susceptible to antibiotics, and may remain viable extracellularly for weeks-months before infecting a cell), the treatment for it is unusually long (>1 year) and treatment failure is common. The results of two ongoing trials—PROVE IT (gatifloxacin administered intermittently for more than 2 years) and ACES (azithromycin for 1 year)—are awaited. The second important issue is the methodology of the trials. Those trials have used event rates as primary end-points have shown equivocal results. On the other hand, trials of antibiotic treatment utilizing indirect noninvasive measurements, i.e. aortic aneurysmal growth, carotid artery thickness, assessment of peripheral vascular disease, symptoms, and restenosis after stent placement in the coronary arteries, have shown a benefit. The probable reason for this discrepancy is that although the number of patients in these trials are small, the end-points are available in all patients, unlike coronary events, which do not occur in all patients. Another important issue is seropositivity of the patients. Neumann et al. had found a reduction in neointimal proliferation with roxithromycin treatment after PCI and stent implantation only in patients with high serum antibody titres for Chlamydia infection. In this context, in view of relatively small sample size, and only 6-week duration of treatment, the negative results of antibiotic treatment in this trial are not entirely unexpected. Furthermore, antibody titers were also not considered.
Adherence to a Mediterranean Diet and Survival in a Greek Population


Summary

The Greek component of the European Prospective Investigation into Cancer and Nutrition (EPIC) was a population-based, prospective investigation, enrolling a total of 28,572 participants, 20-86 years old. All the participants completed an extensive validated semi-quantitative food-frequency questionnaire that aimed at ascertaining the adherence to the traditional Mediterranean diet. The traditional Mediterranean diet is typically characterized by a high intake of vegetables, legumes, fruits and nuts, unrefined cereals, fish and olive oil, but low intake of saturated fats, meat, poultry, a low-moderate intake of dairy products, and a regular but moderate intake of ethanol (primarily as wine during meals).

For each participant, intake of each food item in grams per day and total energy intake were calculated. The degree of adherence was determined by a scale devised by Trichopoulou et al. revised to include fish intake. Briefly, a value of 0 or 1 was assigned to each of the nine components with the use of the sex-specific median as the cut-off. The beneficial components were vegetables, legumes, fruits and nuts, cereals, and fish. The detrimental components were meat, poultry, and dairy products. Ethanol consumption of 10-50 g/day for men and 5-25 g/day for women was found to be beneficial. The body mass index (BMI) was 28.1 for men and 28.8 for women. The participants were followed up for a mean period of 3.7 years. During the 81,139 person-years accrued, there were 275 deaths. Broadly, a higher degree of adherence to a Mediterranean diet was associated with a reduction in total mortality. A two-point increment in diet score was associated with a 25% reduction in total mortality (p<0.001). The association was even stronger for CAD mortality (33% reduction; adjusted hazard ratio: 0.67; 95% CI: 0.47-0.94) as compared to that for cancer (24% reduction; adjusted hazard ratio: 0.76; 95% CI: 0.59-0.98). However, there was no strong association with mortality of individual components of the Mediterranean diet score, except for the intake of fruits and nuts. The ratios of monounsaturated fats to saturated fats was predictive of the total mortality. The positive association between the Mediterranean diet and low total mortality was more robust among those who were 55 years of age or more. This relation in younger participants (<55 years of age) was not significant.

Comments

The seven countries study initiated by Ancel Keys in the 1960s was the first to bring the concept of the Mediterranean diet to the forefront. This study had brought out an apparent paradox. The residents of the island of Crete had a very high intake of fat but still had very low rates of CAD, certain types of cancer, and a long life expectancy. Their diet consisted of a high consumption of plant-based foods, olive oil as the principal source of fat, moderate consumption of fish and poultry, low consumption of meat, and moderate consumption of wine with meals. It was postulated that these other features may have been responsible for the low CAD risk and prolonged life expectancy. Since then, the Mediterranean diet has been postulated as a model of healthy eating. The first clinical evidence of this concept emerged from two secondary prevention trials. The Lyon Diet Heart study enrolled 605 patients with AMI, randomly assigned to a Mediterranean-style diet or AHA step I diet. After a mean follow-up period of 27 months, the coronary event rate was reduced by 73%, and total mortality by 70% (in the Mediterranean diet group). A similar study, with Indo-Mediterranean diet in 1000 patients with CAD or at high risk for CAD, also reported a 33% reduction in fatal MI and 67% reduction in SCD. The main feature of this study was that olive oil was substituted by mustard oil (another good source of unsaturated fat) or soybean oil. In this context, the present study is the first large-scale, prospective, primary prevention study, which unequivocally shows that adherence to a Mediterranean diet remarkably reduces the risk of total mortality, particularly that of CAD. An interesting aspect highlighted by this trial is that although reduction in mortality with the Mediterranean diet as a whole is apparent, this has no strong association with individual components of the diet. The reason could be 2-fold. The effect of these components on mortality may be small, so as not to be statistically significant. Secondly, it may be that the biologic interactions between the several components are difficult to detect in small samples. The components of this diet have been individually evaluated in several other studies. The present study confirms the effects of a high ratio of monounsaturated fat to saturated fats in the reduction of mortality. Despite several advantages, such as large size, prospective nature, and better study design, this trial is not without limitations. Dietary factors such as trans-fatty acids and glycemic load were not considered. Secondly, other sources of monounsaturated fatty acids were not considered. Finally, obesity was not accounted for.
Calendar of Conferences

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

September 16–21, 2003, Transcatheter Cardiovascular Therapeutics 2003, Washington, D.C., USA
Contact: The Course Directors
55 East 59th Street, 6th Floor
New York NY 10022-1112, USA
Tel: 1 212 434 6300
Fax: 1 212 434 6386
e-mail: info@crf.org

October 26–30, 2003, 69th Annual Scientific Assembly, American College of Chest Physicians, Orlando, Florida, USA
Contact: American College of Chest Physicians
3300 Dundee Road, Northbrook IL 60062, USA
Tel: 1 847 498 1400
Fax: 1 847 498 5460

November 2–5, 2003, 76th Scientific Session, American Heart Association (AHA), Orlando, Florida, USA
Contact: American Heart Association
7320 Greenville Avenue, Dallas TX 75231, USA
Tel: 1 214 373 6300
Fax: 1 214 373 3406

November 14–15, 2003, 4th Annual Conference of Nuclear Cardiological Society of India, Vellore, India
Contact: Organizing Secretary
Department of Nuclear Medicine
Christian Medical College
Vellore, Tamil Nadu, India
Fax: 0416 2232103
e-mail: nuclear@cmcvellore.ac.in

December 4–7, 2003, 55th Annual Conference of Cardiological Society of India, Kolkata, India
Contact: Dr Asok Kumar Kar, Organizing Secretary
Indian Heart House
P-60, CIT Road, Scheme VIIM,
Kankurgachi, Kolkata 700 054, India
Fax: 033 355 6308
e-mail: csi@cal2.vsnl.net.in

January 9–11, 2004, Joint Meeting of International Society for Heart Research and International Academy of Cardiovascular Sciences, Lucknow, India
Contact: Prof VK Puri, Organizing Secretary
Department of Cardiology
CSM Medical University
Lucknow, India
Fax: 0522 225 5830
e-mail: vijaykumarpuri@hotmail.com

November 7–10, 2004, 77th Scientific Session, American Heart Association (AHA), New Orleans, Louisiana, USA
Contact: American Heart Association
7320 Greenville Avenue, Dallas TX 75231, USA
Tel: 1 214 373 6300
Fax: 1 214 373 3406

Academy of Cardiology at Mumbai—International and Indian Fellowships

Applications are invited for the Academy of Cardiology—International and Indian Fellowships (one each) beginning January, 2004 from candidates below 35 years of age and possessing DM or DNB Cardiology qualifications. Fellowships will provide funding for training in interventional/noninvasive cardiology at prestigious centers for a duration of up to one year. Interviews for the selection will be conducted by the Academy. Applications along with detailed curriculum vitae and two letters of support from seniors in the profession should be sent to the Academy of Cardiology, 102, Kirti Manor, SV Road, Santacruz West, Mumbai 400054 by September 30, 2003.