9 *Widening Indications of Pacemakers*

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Abstract: Apart from support of heart rate in patients of symptomatic bradycardia, in the last two decades, the indications of pacemakers have widened to prevent arrhythmias, optimise hemodynamic functions and suppress tachyarrhythmias. Pacemakers have been successfully used in Hypertrophic Obstructive Cardiomyopathy (HOCM) to reduce LVOT gradient and in improving cardiac output in patients of dilated cardio myopathy (DCM) with class III/class IV heart failure (Cardiac Resynchronization Therapy). Nowadays, different pacemakers are being routinely used to treat Sick Sinus Syndrome, Neurocardiogenic Syncope, Heart Transplant patients and to prevent atrial arrhythmias. They are used to prevent fatal ventricular arrhythmias and to prevent bradycardia in patients of long QT syndromes. In future genetically engineered pacemakers could be a possible alternative to implantable electronic devices for the treatment of brady arrhythmias. This article briefly discusses these expanding indications of pacemakers.

INTRODUCTION

The concept for bradycardia pacemakers originated in 1950s and over the last 5 decades, cardiac pacing has undergone phenomenal growth, both in terms of indications and sophistication of devices. The basic pacemaker system consists of a pulse generator connected to one or two leads attached to the heart. Almost all pacemakers use a lithium-iodide battery. Pacing is accomplished by transmitting electrical pulses through the lead to a distal electrode (cathode), which initiates depolarization of the myocardium. Current is returned through the anode to complete the electrical circuit.

Current pacemakers are capable of fully programmable dual-chamber pacing, rate response to activity and metabolic changes. They have telemetry of pacer functions and incorporate algorithms to respond to changes in intrinsic rhythms. They can also store a history of patients' arrhythmic events. Apart from providing bradycardia support, pacemakers are an integral part of patients' comprehensive arrhythmia and hemodynamic management strategies.

Permanent pacemakers have become standard treatment for patients with symptomatic sinus node disease and documented, or suspected, high grade atrioventricular (AV) block and in medically refractory heart failure. Permanent pacemakers were first developed for the treatment of heart block, often in young patients following surgical repair of congenital heart defects. These early pacemakers were primitive devices, allowing only for fixed rate asynchronous pacing in the ventricle (that is, VOO mode). Subsequently, sensing circuits were developed to permit inhibited modes of pacing (that is, VVI mode). Permanent pacemakers were designed primarily to prevent mortality, which was inevitable and often occurred early in patients with complete heart block.

In the last decade, there have been rapid expansions in indications in permanent pacemaker implantation. The development of dual chamber pacing and rate responsiveness allowed pacemaker therapy to progress from simply maintaining a minimal heart rate to allowing for restoration of physiologic chronotropy and normal atrioventricular activation. This led to the expansion of this technology from immediate life saving treatment to use aimed at improving hemodynamic function and quality of life, and reducing morbidity. With the development of more physiologic pacing, attempts have been made to apply pacemaker technology to the treatment of problems other than symptomatic bradycardia. These problems include pacing to prevent atrial arrhythmias, to improve hemodynamic function and symptoms in patients with hypertrophic or dilated cardiomyopathy, and to prevent neurocardiogenic syncope and these therapy results in improvement in quality of life rather than simply as a life saving measure. Thus, much of the interest in modern pacemakers is for indications other than bradycardia. It is these new indications that are the subject of this review and following text is an attempt to discuss some of these issues.

CODES FOR CARDIAC PACING

Pacemakers are coded by a specific abbreviation according to the type of pacemaker and mode of pacing. In common usage, the first three or four letters are used, but a total of five letters have been defined by the North American Society of Pacing and Electrophysiology (NAPSE) and the British Pacing and Electrophysiology Group (BPEG).

The first three letters refer to the type of pacemaker or pacing mode that is being employed. The first letter refers to the chamber(s) being paced, and the second letter refers to the chamber(s) being sensed. The letter 'A' indicates atrial pacing or sensing, and 'V' refers to ventricular pacing or sensing. If 'A' and 'V' are both being paced and/or sensed, the designation D for dual-chamber pacing or sensing is used. The third letter refers to the response to a sensed event. The pacemaker can either inhibit (I) pacing output from one or both of its leads, or it can trigger (T) pacing at a programmable interval after the sensed event.

The fourth letter designation represents either the type of programmability or whether the pacemaker is capable of providing rate-responsive pacing. Lastly, the fifth letter represents cardiac devices that are capable of treating atrial or ventricular tachyarrhythmias. In common usage, only the rate responsiveness of the pacemaker is noted in the fourth letter designation, and the fifth letter designation is only used for atrial pacemakers with antitachycardia function. Table 9.1 summarize these points.

Table 9.1: The NASPE/BPEG Pacemaker Code

Chamber paced	Chamber sensed	Response to sensed event	Programmability/ rate response
O (none)	O	O	O
A (atrium)	A	I (inhibit)	R (rate responsive)
V (ventricle)	V	T (triggered)	P (simple programmable)
D (dual)	D	D (I + T)	M (multi-programmable)
S (Single chamber, A/V)	S		C (communi-cating)

INDICATIONS OF PACING

Joint Task Force of the American College of Cardiology and American Heart Association in 1998 recommended guidelines for the indications for pacing. However, there are other clinical factors that may affect the decision to implant a pacemaker. Many indications for pacemaker implantation are influenced by the presence of symptoms. However, main symptoms such as fatigue or subtle symptoms of congestive heart failure may be recognized only in retrospect, after placement of a permanent pacemaker. Table 9.2 gives indication for pacing.

Temporary Cardiac Pacing

Temporary pacing is a modality required to provide patients with heart rate support when they experience intermittent or persistent bradyarrhythmias or to provide standby pacing for patients at increased risk for sudden complete heart block. Occasionally, temporary pacing is used to control sustained atrial or ventricular tachyarrhythmias. The final point for temporary pacing is either resolution of a temporary indication for pacing or implantation of a permanent pacemaker. The clinician must decide whether to insert a temporary transvenous pacemaker or a noninvasive external pacemaker. Temporary pacing at rates of 80 to 100 beats per minute can be used to prevent bradycardia-dependent ventricular arrhythmias or those associated with a long QT interval and *torsade de pointes*. Temporary atrial pacing is occasionally used in patients to restore atrioventricular (AV) synchrony in patients with temporary sinus arrest who have intact AV conduction. Toxic drug effects, like digitalis toxicity, or metabolic abnormalities, like hyperkalemia, may produce a temporary symptomatic bradycardia requiring temporary pacing.

Occasionally, temporary pacing is used for management of tachyarrhythmias for overdrive pacing or atrial or ventricular arrhythmias. The most common clinical setting is generally in the postoperative period after major cardiac surgery, when atrial flutter may be pace terminated into sinus rhythm.

Pacing in Sick Sinus Syndrome

Tachy-brady variant of sick sinus syndrome sinus arrest, prolonged sinus pauses, chronotropic incompetence are few most common indications for permanent pacing in sick sinus syndrome. Atrial arrhythmias, and in particular atrial fibrillation, are common in patients with sinus node dysfunction Early retrospective studies showed a major reduction in the incidence of atrial fibrillation with atrial based pacing (AAI or DDD modes) compared with ventricular pacing alone (VVI mode).[1] This led to the common practice of implanting dual chamber devices in all patients with sinus node dysfunction, despite the lack of prospective data supporting this strategy.

Recently, several large studies comparing atrial based pacing with ventricular pacing have been completed. In a single centre study from Denmark, Anderson and colleagues compared single chamber atrial pacing with ventricular pacing in 225 patients with sinus node dysfunction (DANISH).[2] They showed a significant reduction in the development of atrial fibrillation with atrial pacing. In addition to reducing the incidence of atrial fibrillation, long term follow-up of these patients revealed reductions in mortality, stroke, and congestive heart failure in the atrial pacing group. In the pacemaker selection in the elderly (PASE) study, 407 patients were implanted with dual chamber devices and were then randomized to pacing in DDDR or VVIR modes.[3] There was a reduction in the incidence of atrial fibrillation from 28 to 19% with DDDR pacing (p = 0.06) in the subgroup of patients with sick sinus syndrome, but no difference was noted in those patients with heart block. No mortality reduction was noted with DDDR pacing in this study. In the pacemaker atrial tachycardia (PAC-a-TACH) trial, 198 patients with sick sinus syndrome were randomized to ventricular or dual chamber pacing. No effect on the incidence of atrial fibrillation was noted, but there was a significant reduction in mortality with dual chamber pacing.

The Canadian trial of physiologic pacing (CTOPP) is the largest study to date to address this issue. In this study, 2568 subjects were randomized to atrial based pacing (atrial or dual chamber)

or ventricular pacing. There was an 18% reduction of atrial fibrillation with atrial based pacing in this trial, but no effects on mortality or stroke were observed.

The results of these studies, in general, support the use of atrial based pacing for the prevention of atrial fibrillation, at least in subjects with symptomatic sinus node dysfunction. The benefit of such pacing in reducing mortality is less clear. The choice of pacing mode (AAI *vs* DDDR) and the relative benefit of single chamber atrial and dual chamber pacemakers remains unknown, because there have been no controlled studies addressing this issue. Atrial pacemakers have the advantages of lower costs and increased longevity. The disadvantages of these systems include the inability to optimise AV delay, and the absence of ventricular pacing if complete heart block or a lead malfunction develops. Although the optimisation of AV delay may be important in certain patients, in general ventricular activation through the native conduction system is superior hemodynamically to right ventricular pacing.[4] If a dual chamber pacemaker is implanted in the absence of heart block, then it is reasonable to program a prolonged AV delay or use one of the new features in pacemakers that automatically prolongs the AV delay to minimize ventricular pacing. Similarly, higher base pacing rates are often employed in patients with paroxysmal atrial fibrillation to inhibit tachyarrhythmias, although the utility of this strategy is not well-documented. The potential disadvantages of atrial overdrive pacing include decreased pulse generator longevity and the development of palpitations and insomnia if constant rapid rates are used. In an effort to avoid rapid overdrive pacing, several algorithms are being tested that periodically sample the intrinsic heart rate and pace at a programmable increment above the sinus rate to maintain atrial pacing.

**Multisite Atrial Pacing—
For Prevention of Atrial Arrhythmia**

In addition to overdrive pacing, there has been increasing interest in the evaluation of atrial activation as a means to prevent tachyarrhythmias. Traditionally, atrial leads were positioned in the right atrial appendage for stability. However, with the development of active fixation mechanisms, leads can now be positioned virtually anywhere in the atrium. Saksena and his colleagues studied the role of multisite pacing in a group of patients with frequent, drug refractory paroxysmal atrial fibrillation; they showed that overdrive pacing with simultaneous stimulation of the ostium of the coronary sinus and the high right atrium significantly reduced the frequency of arrhythmia compared with single site pacing or no pacing.[5] Presumably, the mechanism of benefit of this approach is a reduction of the dispersion of activation with dual site pacing. Prospective, randomized, multicentre trials are underway to evaluate the benefit of dual site pacing in more detail in patients with sick sinus syndrome. Another approach to reducing the dispersion of atrial activation is to pace the interatrial septum either near the coronary sinus ostium or near Bachmann's bundle. This is an attractive option because it does not require additional leads. A preliminary report of this technique demonstrated a decrease of atrial fibrillation compared with pacing at traditional right atrial sites.

The 2002 guidelines provide a minor update to indications for pacing to prevent atrial fibrillation (AF).[6] As in the previous guidelines, pacing is given a Class IIb recommendation for the prevention of symptomatic drug-refractory recurrent AF; however, the new guidelines add the words "in patients with coexisting sinus node dysfunction." Moreover, the level of evidence was upgraded from "C" to "B" in the new guidelines. These changes were made to reflect several new studies suggesting that in some patients with recurrent AF and coexisting sinus node dysfunction, atrial-based pacing reduces the arrhythmia recurrence rate.

Although multiple AF pacing options are currently available, the United States Food and Drug Administration (FDA) has endorsed only one pacing option for the prevention of AF— dynamic atrial overdrive pacing, based on AF suppression in part on the Atrial Dynamic Overdrive Pacing Trial (ADOPT-A). This randomized trial demonstrated that AF suppression

with this pacing mode results in a modest decline in symptomatic AF burden, but in no statistically significant difference in quality of life.

Pacing in Acquired Atrioventricular Block

It is generally agreed that complete heart block, permanent or intermittent, at any anatomic level associated with symptoms such as dizziness, lightheadedness, syncope, congestive heart failure, or confusion is an indication for a permanent pacemaker. In the absence of symptoms, pacing is indicated for patients with third-degree AV block, especially with awake heart rates of less than 40 beats per minute or pauses of longer that 3 second.

AV nodal conduction abnormalities may or may not cause symptoms, but it is the most common indication for pacemaker implantation, more so, because even an ECG can be diagnostic, it is probably the easiest abnormality to be diagnosed and its treatment also is codified. There is geographical variation in treatment of bradyarrhythmias, with 80% of all pacemaker implantation worldwide is for sinus nodal disease, whereas in India 90% of pacemaker implantations are for AV nodal disease.

Non-randomized trials strongly suggest that permanent pacing improves survival in these patients who have complete heart block (CHB), it may be congenital or acquired.

In congenital CHB, pacing is recommended in patient with heart rate of, 50 in awake, symptomatic bradycardias, H/O syncope, and LV dysfunction.

Several changes were also made to the guidelines with regard to pacing in pediatric patients. A new Class IIa recommendation for pacing was added for children with congenital heart disease and impaired hemodynamics caused by sinus bradycardia or loss of AV synchrony. According to the guidelines, clinical experience to date indicates that children with these characteristics have an unfavorable prognosis if they are not paced. In addition, a new Class IIb recommendation was added for pacing in children and adolescents with neuromuscular diseases with any degree of AV block, with or without symptoms, because of the potential for the unpredictable progression of AV conduction disease. This recommendation is similar to the pacing recommendations for adults with neuromuscular disease and AV block.

Pacing in CCF

To improve the quality of life in these medically resistant heart failure cases, the use of pacing to improve hemodynamic function in patients with congestive heart failure and left ventricular systolic dysfunction has been the focus of intense interest. Approximately half of the deaths in this population are caused by progressive hemodynamic deterioration. So, if pacing could prevent bradyarrhythmic death and favourably affect heart failure symptoms, then it would be a very useful treatment modality.

In subjects with advanced heart failure a surprising proportion of sudden deaths are reportedly caused by bradyarrhythmias. Moreover, medications with negative chronotropic properties, such as beta blockers and amiodarone, are commonly used in this population. In addition, the incidence of bundle branch block and intraventricular conduction delays is high in the presence of dilated cardiomyopathy. Therefore, permanent pacing is frequently indicated in subjects with congestive heart failure.

The most appropriate mode of pacing has evolved over time which initially started with atrial pacing in patients with intact AV conduction was usually associated with a higher cardiac output than DDD pacing, suggesting that the pattern of ventricular activation may be important for optimising hemodynamic function. For this reason, alternative pacing sites in the right ventricle have been evaluated. VVI pacing from the right ventricular outflow tract was reported to improve cardiac output compared with pacing from the right ventricular apex in patients with sinus node dysfunction. All the sites in isolated RV pacing or atrial based pacing did not improve hemodynamics to cause major symptomatic relief. So given the interventricular delays and the intraventricular delay in activation of lateral wall of left ventricle, the left ventricular based

pacing has emerged as an exciting new approach. The first controlled study of biventricular pacing involved the use of temporary epicardial electrodes to pace simultaneously the right atrium and paraseptal locations on the right and left ventricles early after coronary artery bypass surgery.[7] Atrio-biventricular pacing was associated with a significantly higher cardiac output compared with univentricular pacing. Subsequently, this technique was applied to patients with congestive heart failure. Initially, left ventricular pacing was achieved with epicardial leads placed by thoracotomy. The morbidity of this procedure limited the systematic evaluation of the chronic effects of biventricular pacing, although promising results were noted in several uncontrolled series of patients.

Blanc and colleagues performed the left ventricular endocardial pacing.[8] Similar results were obtained in a separate group of subjects in chronic atrial fibrillation, suggesting that left ventricular activation and not optimisation of AV timing was primarily responsible for the benefits observed.[9] These studies have established that left ventricular based pacing can improve hemodynamic function. Moreover, they have helped define the patient population likely to benefit from this treatment. Hemodynamic improvement has been observed both in subjects with ischemic and non-ischemic cardiomyopathies, but is primarily observed in those with left bundle branch block and pronounced QRS prolongation. Recently, two prospective studies of the long term effects of biventricular pacing were completed. In the pacing therapies in congestive heart failure (PATH-CHF) study, an epicardial left ventricular lead was used and two pacemakers synchronized to achieve biventricular pacing. Hemodynamic and functional improvement was noted during paced periods. In the multisite stimulation in cardiomyopathy (MUSTIC) study, a coronary sinus lead was used to achieve left ventricular activation. Using a randomized, crossover design, exercise capacity and functional status were shown to improve significantly with cardiac resynchronization.

It is reassuring that recent studies have reported that left ventricular or biventricular pacing improves myocardial energetics in contrast with a dobutamine infusion. Regardless of the mechanism of sudden death in paced patients, combined biventricular pacemakers and implantable defibrillators are being developed to treat patients with life threatening arrhythmias; the trials show that this combined technology is needed to reduce mortality in this high risk population.

BVP for dilated cardiomyopathy is given class IIa recommendation in the new guidelines. In terms of pacing indications for dilated cardiomyopathy, the big change in 2002 was the addition of a new Class IIa recommendation (Level of evidence: A) for the use of BVP therapy in patients with advanced heart failure and prolonged QRS duration. Specifically, the recommendations endorse BVP in medically refractory symptomatic New York Heart Association (NYHA) class III/IV patients with idiopathic, dilated, or ischemic cardiomyopathy with a QRS >/= 130 ms, LV end-diastolic diameter >/= 55 mm, and ejection fraction </= 35%. This recommendation was supported by multiple trials, including the Multicenter InSync Randomized Clinical Evaluation (MIRACLE) trial and the Multisite Stimulation in Cardiomyopathies (MUSTIC) trial, demonstrating clinical and structural cardiac improvement with BVP therapy in this patient population.

Pacing in HOCM

Pacing in HOCM is a part of non-pharmacological therapy used in patients with obstructive hypertrophic cardiomyopathy who are often highly symptomatic despite standard medical treatment with beta blockers and calcium channel blockers. Subsequently, small studies provided objective evidence for a reduction of outflow tract gradient and increased exercise duration with pacing. The hemodynamic benefit occurs only with pacing with a short AV delay from the right ventricular apex causing full pre-excitation. This results in paradoxical septal movement reducing the outflow tract gradient. Several questions about pacing in hypertrophic obstructive cardiomyopathy still await definitive answers. What is the role of the initial hemodynamic testing

with temporary pacing before permanent pacemaker implantation? How long will the beneficial hemodynamic effects of pacing last? What is the mechanism of benefit during and after pacing? How long can the postpacing effect persist? And does pacing result in cellular changes in the myocardium?

The association between the distribution of ventricular hypertrophy in the various forms of hypertrophic obstructive cardiomyopathy and the effect of pacing also awaits further clarification. A few anecdotal reports[9] indicate that pacing may even benefit patients with nonobstructive hypertrophic cardiomyopathy.

The largest single centre series of patients paced with hypertrophic cardiomyopathy was from the National Institutes of Health. Fananapazir and colleagues reported observations on 84 patients.[10] Over a mean follow up of more than two years, symptoms were eliminated or diminished in 89% of patients. In 23% of their patients, there was regional regression of left ventricular hypertrophy, suggesting that myocardial remodelling may occur with chronic pacing.

More recently, several double blind randomized trials of pacing in hypertrophic cardiomyopathy have been completed. Unfortunately, the results of these trials have been largely disappointing. Nishimura and colleagues evaluated 19 subjects. Although quality of life improved in 63% of patients during DDD pacing, 42% improved during the control mode (AAI pacing). There were no significant differences in the functional parameters measured, although the outflow tract gradient improved with dual chamber pacing. In a multicentre European study, Kappenberger and associates showed a significant improvement in angina and dyspnoea in the majority of subjects along with a major reduction in left ventricular outflow gradient, although there was no change in left ventricular function or septal wall thickness. Finally, a report by Maron and colleagues of a multicentre North American study showed no significant effect of pacing on quality of life parameters, although again the outflow tract gradient was reduced with right ventricular apical pacing. A subset of elderly patients was identified who benefited from pacing.

Thus, despite promising early reports, the symptomatic benefit of dual chamber pacing in hypertrophic cardiomyopathy has not been documented conclusively in randomized double blind studies. No effect on mortality has been noted, so implantable defibrillators are being used with increasing frequency in high risk patients. It is clear that pacing can reduce the outflow tract gradient, but this does not result in long term functional benefit in many individuals. At present, the widespread enthusiasm for the use of pacing as primary treatment for hypertrophic cardiomyopathy is decreasing. All studies suggest that there may be some patients who benefit, but this subgroup is not well defined.

On the basis of these preliminary results, we believe that pacing has a role in refractory hypertrophic obstructive cardiomyopathy. In pacing for this indication, we use an atrioventricular interval short enough for the complete capture of the ventricles, and we use Doppler echocardiography to measure the ventricular gradient and various indicators of left ventricular filling to further optimize the atrioventricular interval. Additional controlled studies are needed to better define the long-term benefits and the effects on long-term prognosis of this novel mode of therapy.

Pacing for Neurocadiogenic Syncope

This is the most common cause of fainting and is frequently overdiagnosed but grossly under treated. Often, there are both vasodepressor (that is, hypotension caused by vasodilation) and cardioinhibitory (that is, bradycardia from sinus slowing or arrest) components to these episodes which can be reproduced with head-up tilt table testing. Despite early anecdotal reports of the benefit of pacing in patients with neurocardiogenic or vasovagal syncope, this treatment strategy did not gain widespread acceptance. That was caused in part by the observation that hypotension frequently precedes bradycardia with upright tilt.[11] Therefore, it was argued that a pacemaker will not prevent syncope which is caused by the hypotension.

Despite the doubts over the effectiveness of pacing to prevent neurocardiogenic syncope, several recent studies have demonstrated dramatic reductions in the frequency of syncope in selected groups with frequent episodes and an abnormal tilt table response. In the North American vasovagal pacemaker study, 54 patients were evaluated during the pilot phase of the study.[12] Subjects were randomized to receive a pacemaker with the rate drop response activated or to not receive a pacemaker. With the rate drop response, high rate dual chamber pacing is activated when there is a sudden rate drop. There was an 85% reduction in the risk of syncope in those implanted with a pacemaker, so this trial was terminated before the larger full study was begun. In a multicentre European study of neurocardiogenic syncope (VASIS trial), 42 patients were randomized again to pacemaker implantation with the pulse generator programmed to DDI mode with hysteresis or no pacemaker.[13] Recurrent syncope developed in 61% of paced patients and only 5% of unpaced patients. Of note, fewer than 5% of screened patients met the strict criteria of frequent syncope with a tilt table response showing pronounced bradycardia. Accordingly, this study evaluated the most severely affected patients with neurocardiogenic syncope and identified a very selected subgroup who benefit from pacing. Larger randomized studies are ongoing to evaluate pacemaker patients randomized to pacing on or off to address this issue directly. As of now the most latest NASPE/AHA guidelines recommended following changes with expanding indication.

Under the Class IIa indications, the new guidelines added a category for "significantly symptomatic and recurrent neurocardiogenic syncope associated with bradycardia documented spontaneously or at the time of tilt-table testing." This indication was given a "B" level of evidence rating. According to Gerald V. Naccarelli, this recommendation was based on several studies supporting the benefit of pacemakers for syncope reduction in patients with episodes of spontaneous or provoked bradycardia. However, the "B" rating was adopted because of concern about the lack of a control arm in most of these studies and the question of a possible placebo effect.

Pacing in Heart Transplant Recipient

Although the occasional need for pacing in heart transplant recipients has long been recognized, the indications and timing for permanent pacemaker implantation in these persons was poorly defined until recently.

Bradyarrhythmias, primarily isolated sinus node dysfunction, are the most common clinically significant arrhythmias complicating cardiac transplantation. Their overall incidence during the first few weeks after transplantation varies from 18 to 50%; as many as 36% of patients require temporary pacing, and 4 to 25% (but fewer than 10% in most series) ultimately need permanent pacing.

Several predisposing factors have been noted to contribute to sinus node dysfunction in heart transplant recipients; these include long ischemic time of the donor heart, ischemia of the donor sinus node, long aortic cross-clamping time, and bypass time.

Initially, heart transplant recipients with sinus node dysfunction frequently received permanent pacemakers shortly after surgery. This was because reports suggested that early sinus bradycardia was associated with the unreliability of lower escape mechanisms and with subsequent episodes of asystole and sudden death. However, according to most of the recent large series, early sinus node dysfunction appears to be a transient phenomenon in most cases. It typically occurs within the first 2 weeks after transplantation and has a peak incidence in the second week. Miyamoto and colleagues[14] documented the course of prolonged bradyarrhythmias (mostly sinus node dysfunction) that developed within 5 days after transplantation. Of these, 69% resolved within 7 days and 76% resolved within 20 days. Other series supported the conclusion that more than 50% recovery occurs within 3 weeks.[15] Therefore, there is little doubt that many cases of early sinus node dysfunction are transient.

It, therefore, seems reasonable to postpone the decision to implant a permanent pacemaker for sinus node dysfunction after transplantation until near the time of hospital dismissal or about 3 weeks after transplantation, whichever comes first, as long as temporary epicardial pacing leads can be used. Clinical and electrophysiologic variables are poor predictors of future pacemaker dependency, and only observation during hospitalization clarifies the need for pacemaker implantation. Even with relatively late implantation, many patients become nondependent within a few months.

The incidence of atrioventricular nodal and infranodal conduction system disease is much lower in heart transplant recipients, and its natural history is, therefore, much less clear. Atrioventricular nodal dysfunction is reported as the indication for pacing in fewer than 10% of patients with pacemakers in recent series, although other studies have found incidences as high as 25 to 28% in this population. Even in patients with sinus node dysfunction after transplantation, the incidence of concomitant atrioventricular nodal dysfunction is low.

Although there seems to be a high rate of long-term resolution of atrioventricular block in transplant recipients, the time course is not known, and no definite recommendation can be made about the appropriate timing for pacemaker implantation in these patients.

The issue of the best pacing mode for cardiac transplant recipients remains unsettled. Because atrioventricular nodal dysfunction is relatively rare and because most recipients have isolated sinus node dysfunction, the atrial-only rate-adaptive pacing mode has been suggested. On the other hand, because most patients need only backup pacing and will eventually become nondependent, one may argue that the simple ventricular-only pacing mode would suffice for most of them.

Permanent pacing is indicated in heart transplant recipients with sinus node dysfunction that persists for about 3 weeks after transplantation.

Pacing in Long QT Syndrome

The congenital long QT syndrome is an inherited anomaly of cardiac repolarization that may result in recurrent syncope and sudden death. Initial treatment with various medications and left cervical sympathectomy does not always yield satisfactory results. In the long QT syndrome, whether acquired or congenital, rapid pacing is known to prevent *torsade de pointes*. The mechanism of this effect is probably related to a reduction in bradycardia-dependent phenomena, including dispersion of refractoriness and development of after depolarizations, to which patients with the syndrome are prone. Beta-blocker therapy can be effective in the long QT syndrome because it insulates the heart from the sudden sympathetic discharge that often precipitates an arrhythmic event but, because patients with the long QT syndrome tend to have high incidences of sinus bradycardia and atrioventricular conduction disturbances. Therefore, combining β-blockers with pacing to prevent bradycardia may conceivably improve the results of β-blocker therapy.

Eldar and colleagues[16] were the first to show the efficacy of combining permanent pacing with β-blocker therapy in 21 patients. These patients (previous therapy with β-blockers, antiarrhythmic medications, or sympathectomy had failed in most of them) received pacing at rates of 75 to 125 beats per minute (sufficient to reduce the QT interval to less than 440 ms) in combination with β-blockers. Of the 18 patients who received both therapies throughout the study, only 2 had recurrent cardiac events; events in the 3 patients who did not receive both therapies throughout the study were clearly related to the interruption of drug treatment or to pacemaker malfunction. Eldar and colleagues emphasized the need for dual-chamber pacing systems; these systems are necessary because of the relatively high incidence of atrioventricular block in this population, an incidence that may be aggravated by β-blocker treatment. It is noteworthy that these results, although impressive, did not derive from a randomized controlled study.

Similar but somewhat less favorable results were reported by Moss and colleagues. In their series of 30 patients, 21 (70%) were free of recurrent arrhythmic or suspected arrhythmic events after pacemaker implantation.

We believe that a combination of β-blocker therapy and pacing has a role in patients with the symptomatic long QT syndrome who do not respond to β-blocker therapy alone or who develop serious bradycardia during β-blocker therapy. One may even argue in favor of this approach as primary therapy for patients with the long QT syndrome. Further controlled studies are needed to verify the beneficial effect of this therapy on survival.

New Frontiers—Biological Pacemakers

Genetically engineered pacemakers could be a possible alternative to implantable electronic devices for the treatment of bradyarrhythmias. The strategies include upregulation of beta adrenergic receptors, conversion of myocytes into pacemaker cells and stem cell therapy. Pacemaker activity in adult ventricular myocytes is normally repressed by the inward rectifier potassium current (I_{K1}). The I_{K1} current is encoded by the Kir 2 gene family. Use of a negative construct that suppresses current when expressed with wild-type Kir 2.1 is an experimental approach for genesis of genetic pacemaker. Hyperpolarization activated cyclic nucleotide gated (HCN) channels which generate If current, the pacemaker current of heart can be delivered to heart by using stem cell therapy approach and viral vectors. The unresolved issues include longevity and stability of pacemaker genes, limitations involved in adenoviral and stem cell therapy and creation of genetic pacemakers which can compete with the electronic units.

Effects of transferring the human β_2 adrenergic receptor were studied by Edelberg JM et al[17] in chronotropy studies with isolated myocytes, and transplanted as well as endogenous murine heart. Murine embryonic cardiac myocytes were transiently transfected with plasmid constructs. The total percentage of spontaneously contracting myocytes was greater in β_2AR transfected cells compared with controls. Also the percentage of myocytes with chronotropic rates more than 60 beats per minute was greater in β_2AR population than controls. To study the *ex vivo* effects of targeted expression of β_2AR, a murine neonatal cardiac transplantation model was used. Injection of β_2AR construct increased the heart rate by 40%. These studies demonstrate that local targeting of gene expression may be a feasible modality to regulate the cardiac activity.

LIMITATIONS OF APPROACHES TO DEVELOPMENT OF BIOLOGICAL PACEMAKER

Use of viruses to deliver the necessary genes has inherent problems. Replication deficient adenoviruses that have little infectious potential lead to only transient improvement in pacemaker function as well as potential inflammatory responses. Retroviruses carry a risk of carcinogenicity and infectivity. Limitations of stem cell therapy include immunogenicity of cell, the potential for neoplasia, proper engineering of pure cardiac lineages and spatial non uniformity of implants. Regulating the level of expression to achieve optimal pacemaker rate is critical. Biological pacemaker needs an optimal cell mass and optimal cell-cell coupling for long-term normal function.

A major issue is duration of efficacy of biological pacemakers. The duration of pacemaker function in approaches using viruses depend on how long the viruses and resulting protein constructs survive in the host. To ensure long term function the appropriate delivery system in which the construct is effective for long periods must be identified. What will be the longevity and stability of next generation of pacemaker genes?

The onset of pacemaker function after a pause following the last intrinsic beat is a critical factor. Can a pacemaker gene inserted into proximal conduction system create a functioning biological pacemaker which can drive the ventricle in demand mode when the sinus node signal

fails? This requires proper engineering of genes. Considering the cell-cell coupling differences in gene therapy and stem cell therapy, the engineering of mutant genes will differ importantly between approaches.

The autonomic responsiveness of biological pacemakers, the ideal site for implantation, the extent of recovery of diseased sinus node and the ideal construct to be preferred remain unanswered questions. None of the studies tested whether a biological pacemaker could be engineered into the ventricular conducting system. Will the functional characteristics of biological pacemakers compete with that of electronic units available?

CONCLUSION

In recent years, new frontiers have opened in cardiac pacing. Indications for pacing now include conditions not previously known to benefit from pacing therapy, conditions in which indications for pacing have not been clear, and conditions in which selection criteria for pacing have been poorly defined. In summary, pacemaker indications are expanding as this technology is being applied to the prevention of arrhythmias and to the optimisation of hemodynamic function.

Encouraging results have been reported on the use of pacing for hemodynamic and symptomatic benefit in patients with drug-resistant hypertrophic obstructive cardiomyopathy. We believe that the available information probably justifies the use of pacing as an alternative to cardiac surgery in drug-refractory cases. Preliminary observations in patients with dilated cardiomyopathy await further confirmation. Studies are needed to clarify the mechanisms of hemodynamic benefit in these two groups of patients and to establish better selection criteria for pacing therapy and appropriate programming of atrioventricular delay.

Preliminary results and theoretical reasoning suggest that various atrial pacing techniques may help to minimize the recurrence of paroxysmal atrial fibrillation in some patients who do not have traditional indications or who have borderline indications for pacing. Further studies are needed to improve selection criteria, to define the best pacing mode, and to clarify the importance of atrial synchronization in the prevention of atrial fibrillation.

Cardiac transplant recipients are a growing group of patients, and the question of their need for pacing is often raised. We believe that with our current, improved understanding of the natural history of bradycardia in patients after transplantation, better selection criteria can be established to minimize the unnecessary early implantation of pacemakers. The decision to pace for sinus node dysfunction should probably be postponed for about 3 weeks after transplantation, if possible.

Recent studies of the treatment of patients with the long QT syndrome have suggested that pacing may be a mainstay of therapy that helps to prevent syncope and sudden death. According to some authors, it has become a first-line therapy. It should be emphasized that this conclusion has been reached on the basis of small, non-randomized studies.

Better criteria for selecting patients for pacing are also being developed for patients with neurally mediated syncope. An improved understanding of the mechanisms of hemodynamic response and appropriate classification of patients according to the patterns of hemodynamic response will certainly improve the selection of patients with neurally mediated syncope of predominantly cardioinhibitory mechanism for permanent pacing.

The incidence of atrial fibrillation is decreased with atrial based pacing compared to ventricular pacing. However, it remains unclear if standard dual chamber or atrial pacing prevents atrial fibrillation in the absence of bradycardia, although dual site pacing is a promising approach for this problem. Multiple studies have now shown a hemodynamic benefit from biventricular pacing in patients with dilated cardiomyopathy and pronounced conduction system disease. Ongoing studies will help identify better the patient population that benefits most from this treatment, the optimal lead positions for pacing and the effect of long term pacing on ventricular arrhythmias and mortality.

The role of pacing in obstructive hypertrophic cardiomyopathy is less clear, as much of the benefit previously observed was likely caused by factors other than pacing. Although some

patients with obstructive physiology likely benefit from pacing, this population is not well defined. Finally, randomized studies have established the role of dual chamber pacing to prevent neurocardiogenic syncope, at least in the subset of patients with frequent episodes and a prominent cardioinhibitory component to their hemodynamic response. As pacemaker technology is combined with other devices such as defibrillators, drug pumps, hemodynamic monitors, and non-invasive measures of arrhythmia vulnerability (for example, heart rate variability and T-wave alternans), this therapy will likely expand to help in the prevention and treatment of other hemodynamic and arrhythmic problems.

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