ELECTROPHYSIOLOGY

Permanent pacing: new indications

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Over the past 40 years, permanent pacemakers have become standard treatment for patients with symptomatic sinus node disease and documented, or suspected, high grade atrioventricular (AV) block. 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.

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 haemodynamic function and quality of life, and reducing morbidity. While it is clear that modern dual chamber pacemakers can increase exercise capacity in subjects with chronotropic incompetence and prevent pacemaker syndrome caused by ventricular pacing, the effects on other end points including mortality and arrhythmia prevention remain controversial. 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 haemodynamic function and symptoms in patients with hypertrophic or dilated cardiomyopathy, and to prevent neurocardiogenic syncope. Thus, much of the interest in modern pacemakers is for indications other than primary bradycardia. It is these new indications that are the subject of this review.

Sick sinus syndrome

Atrial arrhythmias, and in particular atrial fibrillation, are common in patients with sinus node dysfunction. This tachy-brady variant of sick sinus syndrome is one of the most common indications for permanent pacing. 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] These reports also suggested that the rates of congestive heart failure, strokes, and mortality were all reduced with atrial based pacing. 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.[2] They showed a significant reduction in the development of atrial fibrillation with atrial pacing. This study also established the relative safety of atrial pacing with no ventricular back up, as the rate of heart block requiring pacemaker revision to a dual chamber system was low (0.6%/year). 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 randomised 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. One possible explanation for the failure to observe benefit with dual chamber pacing in this study was the relatively high crossover rate (26%) from VVIR to DDDR mode. The much higher crossover rate was likely due to the study design, where randomisation was by "software" (by programming the device mode), in contrast to randomisation by "hardware" (the positioning of the leads) in the Danish study. Since it is much easier to reprogram a device than to revise a pacing system to implant an atrial lead, the crossover rate was higher. In the pacemaker atrial tachycardia (PAC-a-TACH) trial, 198 patients with sick sinus syndrome were randomised 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 largest study to date evaluating the role of pacing mode on atrial fibrillation was the Canadian trial of physiologic pacing (CTOPP).[4] In this study, 2568 subjects were randomised 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. It is noteworthy that the mean duration of follow up in this trial was three years, while a mortality benefit of atrial pacing was only observed in the study of Andersen and colleagues[2] when the mean follow up was extended to 5.5 years.

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 in

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less clear. The choice of pacing mode (AAI *v* 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 develop. Although the optimisation of AV delay may be important in certain patients, in general ventricular activation through the native conduction system is superior haemodynamically to right ventricular pacing.[5] The risks of developing heart block can be minimised by avoiding atrial pacemakers in subjects with bundle branch block or other severe intraventricular conduction delays, in patients who show atrioventricular block (Mobitz I or II) at pace rates of 130 beats per minute or less, or in patients where it is anticipated that potent AV nodal blocking drugs such a amiodarone will be needed in the future. 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 minimise ventricular pacing.

In addition to the effect of pacing mode on the incidence of atrial fibrillation, atrial rate and pacing site can also have an important impact on atrial arrhythmias. Overdrive pacing is routinely used following cardiac surgery to prevent postoperative atrial fibrillation. 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. In fact a recent study comparing maintaining atrioventricular synchrony with no atrial pacing (VDD mode) and frequent dual chamber pacing (DDDR mode) showed no difference in the frequency of atrial fibrillation.[6] 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. This strategy preserves the normal fluctuations in heart rate, although the ability to suppress atrial fibrillation with this degree of overdrive pacing is not yet established. It is likely that sufficient overdrive to achieve almost continual atrial pacing will be necessary to reduce the incidence of atrial fibrillation.

Pacing issues in sick sinus syndrome patients

- What is the optimal pacing mode (AAIR or DDDR)?
- Do antiarrhythmic drugs enhance the effect of pacing?
- What is the role of atrial or ventricular lead position?
- What is the optimal pacing rate?

Issues in multisite pacing

- Is pacing in the distal coronary sinus superior to pacing at the ostium?
- Where is the optimal right atrial pacing site?
- How much overdrive is needed to optimise the pacing benefit?
- Can intra-atrial septal pacing (Bachmann's bundle) achieve the same benefit as dual site pacing?

Multisite atrial pacing

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.[7] Presumably, the mechanism of benefit of this approach is a reduction of the dispersion of activation with dual site pacing. Prospective, randomised, multicentre trials are underway to evaluate the benefit of dual site pacing in more detail in patients with sick sinus syndrome. In support of this concept, following open heart surgery, biatrial pacing with temporary epicardial leads positioned on the right and left atria reduces postoperative atrial fibrillation.[8] 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.

Congestive heart failure

Over the past decade the use of pacing to improve haemodynamic function in patients with congestive heart failure and left ventricular systolic dysfunction has been the focus of intense interest. In subjects with advanced

heart failure a surprising proportion of sudden deaths are reportedly caused by bradyarrhythmias.[9] Moreover, medications with negative chronotropic properties, such as β 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. However, approximately half of the deaths in this population are caused by progressive haemodynamic deterioration, so if pacing could prevent bradyarrhythmic death and favourably affect heart failure symptoms, then it would be a very useful treatment modality.

Initially, standard dual chamber pacemaker implantation with pacing from the right ventricular apex was investigated. The initial studies evaluated pacing with an AV delay of 100 ms; striking improvements in left ventricular ejection fraction and pulmonary congestive symptoms were observed. Unfortunately, controlled studies have failed to confirm the benefit of short AV delay pacing in this patient population. We were unable to demonstrate any benefit, either acutely or chronically, in a double blind, randomised, crossover trial in patients with advanced heart failure.[10] Similarly, Innes and colleagues found that dual chamber pacing with a short AV delay did not acutely improve haemodynamic function in 12 patients with heart failure despite a significant increase in left ventricular filling time.[11] Finally, Linde and associates were unable to demonstrate significant clinical improvement over a three month follow up period in a group of 10 patients with New York Heart Association (NYHA) functional class III or IV heart failure paced with an optimised AV delay.[12]

Atrial pacing with intact AV conduction is usually associated with a higher cardiac output than DDD pacing,[5] suggesting that the pattern of ventricular activation may be important for optimising haemodynamic 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. However, more recently we and others have shown no difference in acute haemodynamic function with DDD pacing from either the right ventricular apex or outflow tract. Compared with AAI pacing at the same rate, there is haemodynamic deterioration with VVI pacing from either right ventricular site.[13] In a well designed chronic study, Victor and colleagues compared apical and outflow tract pacing in patients with complete heart block and chronic atrial fibrillation.[14] Each patient received a dual chamber pacemaker with one lead in the right ventricular apex and the other in the outflow tract. No effect on exercise tolerance, ejection fraction or haemodynamic parameters was observed in this prospective randomised evaluation.

In summary, pacing mode, but not right ventricular pacing site, affects haemodynamic parameters in the setting of congestive heart failure. However, all of the studies have been small, so it remains possible that there are subsets of patients or unique approaches to selecting pacing sites, such as activation mapping, that would benefit from right ventricular pacing in the absence of bradycardic indications.

In contrast to the generally disappointing results with right ventricular pacing, 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.[15] Atriobiventricular 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.[16 17] More recent acute studies have shed important insights into the benefit of biventricular pacing.

Blanc and colleagues performed acute haemodynamic studies in 23 patients with severe heart failure and raised pulmonary capillary wedge pressures. Haemodynamic parameters were unchanged with pacing performed from either the right ventricular apex or outflow tract, but were greatly improved by biventricular or left ventricular endocardial pacing.[18] 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.[19] Kass and colleagues found a significant improvement in systolic function with left ventricular pacing (via the coronary sinus) in 14 patients with severe dilated cardiomyopathy.[20] Results with biventricular pacing were worse than with single site left ventricular pacing.

These acute studies have established that left ventricular based pacing can improve haemodynamic function. Moreover, they have helped define the patient population likely to benefit from this treatment. Haemodynamic improvement has been observed both in subjects with ischaemic and non-ischaemic 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 synchronised to achieve biventricular pacing. Haemodynamic 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 randomised, crossover design, exercise capacity and functional status were shown to improve significantly with cardiac resynchronisation.

Despite these encouraging results, many questions remain unanswered with regard to the benefit of left ventricular based pacing to achieve cardiac resynchronisation. For instance, is biventricular pacing necessary or can left ventricular pacing alone achieve the same long term benefit? The patient population that benefits most is not well defined. Most attention has been directed towards evaluating subjects with severe congestive heart failure (NYHA class III or IV) and left bundle branch block. Typically a QRS duration of at least 150 ms is necessary to show an acute haemodynamic improvement with biventricular pacing. This obviously will limit the number of patients who could benefit from this technology if such conduction system disease is necessary for long term functional benefit. The optimal position of left ventricular leads is not well studied in part because of the limitations of positioning leads in the tortuous coronary venous system, although many investigators feel that posterior and lateral sites are best. New leads and delivery systems have been designed to allow for better access to the coronary venous system. Finally, the effect of biventricular pacing on mortality is unknown. All studies to date have continued to observe sudden cardiac death in paced patients with congestive heart failure. Hopefully, this is not caused by an increased mortality or proarrhythmic effect of this treatment, as was noted for many positive inotropic agents. It is reassuring that recent studies have reported that left ventricular or biventricular pacing improves myocardial energetics in contrast with a dobutamine infusion.[21] 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, in case prospective trials show that this combined technology is needed to reduce mortality in this high risk population.

Pacing issues in congestive heart failure

- What is the optimal stimulation site for right and left ventricular leads?
- Is biatrial (that is, four chamber) pacing necessary with biventricular pacing?
- What are the optimal atrioventricular and intraventricular pacing delays?
- Does a single left ventricular lead provide sufficient haemodynamic benefit or is it necessary to employ simultaneous right ventricular (that is, biventricular) stimulation?
- Does the aetiology (that is, ischemic *v* dilated) or severity of heart failure predict clinical benefit?
- What is the role of pacing in systolic versus diastolic dysfunction?
- Does biventricular pacing favourably affect mortality?

Hypertrophic cardiomyopathy

Patients with obstructive hypertrophic cardiomyopathy often are highly symptomatic with dyspnoea, chest pain, and fatigue. In those patients who remain symptomatic despite standard medical treatment with β blockers and calcium channel blockers, nonpharmacologic approaches are often employed. Such approaches include surgical myotomy and myomectomy, often with mitral valve replacement, chemical septal ablation with ethanol, and dual chamber pacing. Interest in permanent pacing for the treatment of hypertrophic cardiomyopathy began in the 1970s following several case reports and small series demonstrating symptomatic improvement in those subjects with outflow tract obstruction. Subsequent small studies provided objective evidence for a reduction of outflow tract gradient and increased exercise duration with pacing. The haemodynamic benefit occurs only with pacing with a short AV delay from the right ventricular apex causing full preexcitation. This results in paradoxical septal movement reducing the outflow tract gradient.

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.[22] 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 randomised 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.[23] 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.[24] 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.[25] 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

Pacing issues in hypertrophic cardiomyopathy

- Is there a subgroup of patients that can be identified clinically who benefit consistently from pacing?
- Does an "optimum" AV delay need to be identified for each individual?
- Does the magnitude of the reduction of the outflow tract gradient predict symptomatic improvement?
- Does pacing lead to permanent structural or biochemical changes in the ventricular septum?
- What is the role of pacing in symptomatic patients with non-obstructive cardiomyopathy?

documented conclusively in randomised 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. One explanation for the discrepancy between the results of randomised and observational studies is elucidated by the analysis of Linde and colleagues, who evaluated the effect of pacemaker implantation in this population.[26] They studied patients who underwent dual chamber pacemaker placement but were programmed to a non-pacing mode. Despite the lack of pacing, most quality of life parameters improved. Such effects of the administration of inactive drugs are well described and is why placebo control groups are typically included in studies. Similarly, a potent placebo effect occurs with device implantation in this population. 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.

Neurocardiogenic syncope

Syncope is a common cause of emergency room visits and hospital admissions. Bradycardia is one of the well described mechanisms of syncope, and pacemaker implantation for the treatment of syncope in the setting of sick sinus syndrome or high grade heart block is well established. Probably the most common cause of the transient loss of consciousness is neurocardiogenic syncope. 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.[27] Therefore, it was argued that a pacemaker will not prevent syncope which is caused by the hypotension.

Despite the pessimism about the potential role 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.[28] Subjects were randomised 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 randomised again to pacemaker implantation with the pulse generator programmed to DDI mode with hysteresis or no pacemaker.[29] 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. In addition, the control groups in these studies did not have a device implanted, so a placebo effect of pacemaker implantation cannot be excluded as a cause of the benefit observed. Other studies are ongoing to evaluate pacemaker patients randomised to pacing on or off to address this issue directly.

Conclusions

In summary, pacemaker indications are expanding as this technology is being applied to the prevention of arrhythmias and to the optimisation of haemodynamic function. The incidence of atrial fibrillation is decreased with atrial based pacing compared to ventricular pacing. However, it remains unclear if standard

Pacing issues for neurocardiogenic syncope

- Does the haemodynamic response to head-up tilt predict pacemaker responders?
- What pharmacologic agents are most effective when used with pacemakers?
- What is the optimal dual chamber pacing rate to prevent syncope?
- What is the role of advanced pacing features such as sudden rate drop in preventing syncope?
- Can clinical criteria be used to identify subgroups that benefit from pacing?

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 haemodynamic 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, randomised 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 haemodynamic response. As pacemaker technology is combined with other devices such as defibrillators, drug pumps, haemodynamic 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 haemodynamic and arrhythmic problems.

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