

Evolving Indications for Permanent Pacemakers

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New indications for permanent cardiac pacing have been developed in recent years, with numerous studies demonstrating improved clinical outcomes in a variety of disorders. Because hypertrophic obstructive cardiomyopathy, dilated cardiomyopathy, heart failure, neurocardiogenic syncope, and atrial fibrillation are common conditions, every clinician should be aware of evolving alternative therapies for them.

Observational studies in patients with refractory, symptomatic hypertrophic obstructive cardiomyopathy and significant left ventricular outflow gradient at rest suggest that cardiac pacing may result in symptomatic and hemodynamic improvement. Clinical trials have not shown conclusive evidence regarding the long-term benefit from pacing in these patients, and it is unclear whether pacing will be a preferred treatment option. Preliminary data suggest that pacing is a viable adjunctive therapeutic approach for improving symptoms in patients with dilated cardiomyopathy and heart failure. Mortality benefit has yet to be estab-

lished, but it is to be hoped that ongoing randomized clinical trials will provide definitive information on that issue. Patients with refractory neurocardiogenic syncope or those who are intolerant of medical treatment may benefit from pacing therapies, especially those that use rate-drop sensor algorithms. Batrial pacing has emerged as a technique that resynchronizes atrial electrical activity and has been shown to prevent atrial fibrillation. Multisite atrial pacing for the prevention of atrial fibrillation is considered investigational but seems promising. Newer indications for pacing are expected to result in improved clinical outcomes for hypertrophic obstructive cardiomyopathy, dilated cardiomyopathy and heart failure, neurocardiogenic syncope, and the prevention of atrial fibrillation.

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For a glossary of terms, see end of text.

In 1952, Zoll described the feasibility of externally pacing the heart by applying voltage across the chest wall with two paddles, thereby passing current through the heart (1). After this breakthrough, the first units for transvenous pacing were implanted in 1960 (2). At present, major advances in all aspects of cardiac pacing have occurred. The indications for implantation of permanent pacemakers have been revised and updated during the past 15 years. Beyond sinus node dysfunction, carotid sinus hypersensitivity, and atrioventricular block, the indications have been vastly expanded. In recent years, pacing for the purpose of improving hemodynamics has generated a great deal of interest, leading to new and evolving indications for the implantation of permanent pacemakers.

The purpose of this paper is to review the current clinical experience and future trends in cardiac pacing in four specific areas: 1) hypertrophic cardiomyopathy, 2) dilated cardiomyopathy and heart failure, 3) neurocardiogenic syncope, and 4) the prevention of atrial fibrillation.

METHODS

We searched MEDLINE for literature on evolving indications of cardiac pacing, focusing on advances in these four specific areas. Because published reports on these topics are limited, all of the peer-reviewed articles,

abstracts, and original articles found were reviewed. The data were manually extracted, classified, and summarized according to the specific indications.

PERMANENT PACING IN HYPERTROPHIC OBSTRUCTIVE CARDIOMYOPATHY

The treatment of hypertrophic obstructive cardiomyopathy has traditionally been pharmacologic or surgical. The observation that electrical stimulation of the heart has a beneficial effect on outflow obstruction was first reported in acute pacing studies in 1967 (3). Inversion of the ventricular activation sequence by right ventricular apical stimulation can improve the hemodynamics and symptoms of hypertrophic obstructive cardiomyopathy (4, 5). Hassenstein and associates (5) were the first to describe this approach. They reported a 56% reduction in left ventricular outflow tract gradient during paced rhythm in four patients, all of whom reported symptomatic improvement. These findings were confirmed by Duck and colleagues (6), who observed similar hemodynamic results in a series of 21 patients. The reduction in gradient was associated with a decrease in left ventricular filling pressure. Jeanrenaud and coworkers (7) demonstrated that in patients with hypertrophic obstructive cardiomyopathy, synchronized atrial and right ventricular apical stimulation reduces the sub-aortic pressure gradient by 43% without altering aortic

pressure or cardiac output. Right ventricular apical stimulation was superior to right ventricular outflow tract stimulation in terms of reducing left ventricular outflow tract obstruction gradient (8), although this difference was not evident in other studies. Possible additional mechanisms for improvement by pacing in patients with hypertrophic obstructive cardiomyopathy include rightward shift of the end-systolic pressure–volume relationship; decreased mitral regurgitation; regression of left ventricular hypertrophy; and improvement of neurohormonal profiles, such as decreased atrial natriuretic peptide levels.

In addition, the key factor in pacing for hypertrophic obstructive cardiomyopathy is the atrioventricular interval. The optimum atrioventricular interval during dual-chamber pacing is determined by two main factors: maintenance of early right ventricular apical activation and optimal left ventricular filling pressures (7). First, the effective atrioventricular interval during pacing must be shorter than the atrioventricular interval in sinus rhythm so that the ventricular activation sequence is altered and early apical activation is obtained. Second, optimum left ventricular filling is necessary (9) and can be obtained only by maintaining appropriate atrioventricular synchronization. It is important to recognize that all of the adjustments of the atrioventricular delay that use echocardiographic and invasive hemodynamic assessments to obtain an optimal atrioventricular interval are performed in the supine position. They do not necessarily reflect the loading conditions of the hypertrophied ventricle when the patient is standing, ambulating, or exercising.

Fananapazir and associates (10) reported on the short-term beneficial results of long-term dual-chamber pacing (DDD) in 44 patients with hypertrophic obstructive cardiomyopathy and severe drug-refractory symptoms. At 6 to 12 weeks, dual-chamber pacing (DDD) was associated with substantial improvement of symptoms and reduced obstruction of the left ventricular outflow tract (10). In a long-term study (11), dual-chamber devices (DDD) were implanted in 84 patients with hypertrophic obstructive cardiomyopathy who had severe drug-refractory symptoms. At a mean follow-up of 2.3 years, symptoms were eliminated in 28 patients (33%), improved in 47 patients (56%), and remained unchanged in 7 patients (8%). Two patients died suddenly. Left ventricular outflow tract gradients were sig-

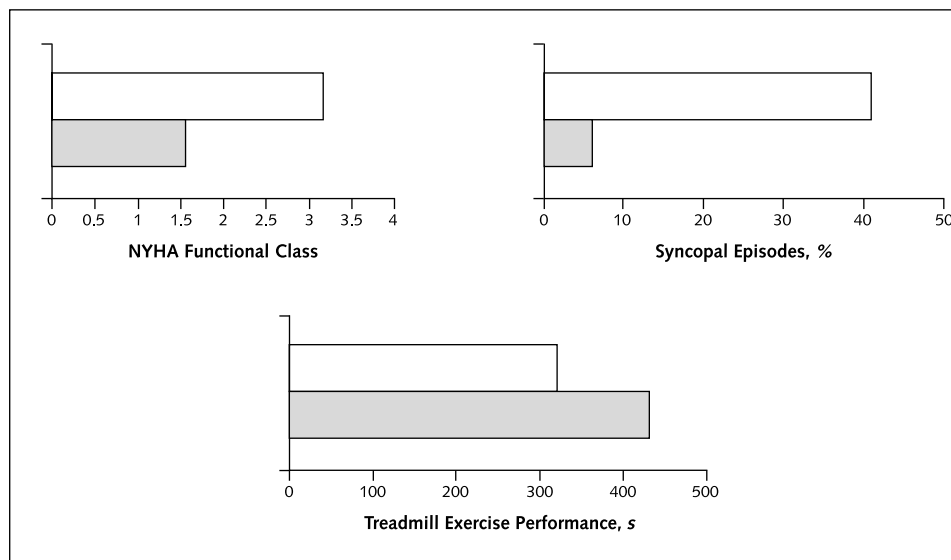
nificantly reduced at follow-up (mean [\pm SD], 29 ± 34 mm Hg) in 74 patients with substantial left ventricular outflow tract obstruction at rest (96 ± 41 mm Hg). In most patients, New York Heart Association (NYHA) functional class improved, the recurrence of syncopal episodes decreased, and treadmill exercise performance improved (Figure 1). Twenty-nine of the 75 patients in whom symptoms were improved or eliminated (39%) were not receiving any drugs at their last follow-up visit. Fifteen patients who had left bundle-branch block before pacing with severe left ventricular outflow tract obstruction despite the abnormal septal electrical activation showed substantial improvement with dual-chamber pacing (DDD) and optimal atrioventricular delay (11).

The effects of pacing in patients without significant left ventricular outflow tract obstruction at rest have not been adequately studied. Gadler and colleagues (12) studied 19 patients with a left ventricular tract obstruction gradient that was less than 40 mm Hg at rest but exceeded 50 mm Hg during provocation with isoproterenol. In that study, benefit from pacing treatment was similar to that seen in patients with substantial obstruction at rest.

These observational studies have led to randomized clinical trials. In a double-blind crossover trial, Nishimura and coworkers (13) randomly assigned 19 patients to dual-chamber pacing (DDD) for 3 months or backup (placebo) pacing (AAI [atrial]) for 3 months. The pacing modes were then reversed for an additional 3 months. The left ventricular tract obstruction gradient decreased significantly after dual-chamber pacing (DDD) compared with the baseline gradient ($P < 0.05$) and the gradient after placebo (backup pacing [AAI]) ($P < 0.05$). Quality-of-life scores and exercise duration improved significantly from baseline after dual-chamber pacing (DDD) but did not significantly differ between the dual-chamber pacing group (DDD) and the placebo group. Overall, symptoms improved in 63% of patients in the dual-chamber pacing group (DDD) and 42% of patients in the placebo group, suggesting a possible placebo effect. In addition, 31% of patients with dual-chamber pacing (DDD) had no change and 5% had worsening symptoms.

The Pacemaker in Cardiomyopathy (PIC) Study Group (14) performed a multicenter, randomized, double-blind, crossover study in 83 patients (mean age, 53

Figure 1. Long-term results of dual-chamber pacing (DDD) in 84 patients with obstructive hypertrophic cardiomyopathy.



New York Heart Association (NYHA) functional class improved from an average of 3.16 to 1.55, the number of syncopal episodes decreased from 35 to 5 (42% of patients to 6% of patients), and treadmill exercise performance improved by 35% (11). For all comparisons, $P < 0.001$. The white bars represent findings before pacing, and the gray bars represent findings after pacing.

years) who had refractory symptoms or could not tolerate classic drug treatment. After 12 weeks of active (dual-chamber pacing [DDD] with optimal atrioventricular delay) or inactive pacing (AAI at 30 pulses/min), regardless of which phase was first, the left ventricular outflow tract pressure gradient was significantly reduced with active pacing. Exercise tolerance improved by 21% in patients who at baseline tolerated less than 10 minutes of Bruce protocol; quality-of-life score and symptoms of dyspnea and angina also improved significantly in 84% of all patients. This study documented that pacing is beneficial in patients with hypertrophic obstructive cardiomyopathy, a resting gradient of more than 30 mm Hg, and symptoms refractory to conventional medical treatment. Since the investigators evaluated patients with and those without an acute gradient reduction and found no difference between them (14), the relationship between maximal gradient and severity of symptoms is controversial and supports the observations of Nishimura and coworkers (13).

It seems, therefore, that pressure gradient reduction by pacing is not the only factor that explains the efficacy of pacing in hypertrophic obstructive cardiomyopathy. In addition, patients with hypertrophic obstructive cardiomyopathy may have diastolic dysfunction (15), and

pacing may influence this condition. Reduction in functional mitral regurgitation may also play a role. The PIC Study Group reported 1-year follow-up data in 75 patients (16). Their findings demonstrate that atrioventricular pacing with a short atrioventricular delay has a favorable effect in hypertrophic obstructive cardiomyopathy, not only on hemodynamic factors (such as left ventricular outflow tract obstruction) but also on quality-of-life factors. The M-PATHY Study Group (17) assessed pacing in 48 patients with symptomatic hypertrophic obstructive cardiomyopathy who had a basal gradient of at least 50 mm Hg, refractory to drug therapy. Patients were randomly assigned to receive 3 months each of dual-chamber pacing (DDD) and pacing backup (AAI at 30 pulses/min) in a double-blind crossover study, followed by an uncontrolled and unblinded 6-month pacing trial. With randomization, patients who received pacing and those who received backup pacing did not differ significantly with regard to symptoms or exercise capacity. After 6 additional months of unblinded pacing, functional class and quality-of-life score were improved compared with baseline, but peak oxygen consumption was unchanged. The outflow gradient was significantly decreased by 40% in 57% of patients but showed no change or increased in 43% of

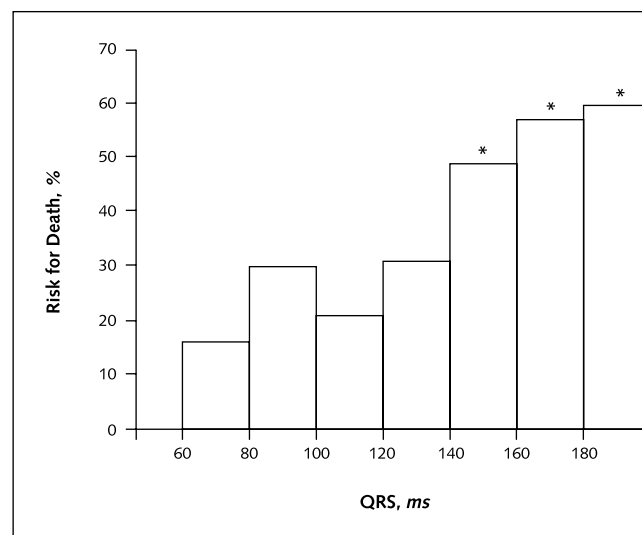
patients. In the overall study group, left ventricular wall thickness showed no remodeling over the 12 months of follow-up. A small subset (12%) of patients at least 65 years of age showed a clinical response, suggesting that dual-chamber pacing could be a therapeutic option for some elderly patients.

The issue of long-term benefits of dual-chamber pacing (DDD) for hypertrophic obstructive cardiomyopathy remains controversial at this point. Pacing has not been shown to affect total mortality in patients who are at variable risk for sudden arrhythmic death. The poor correlation between reduction in left ventricular outflow tract gradient and symptom relief implies a substantial placebo effect or other mechanisms that are not well understood. On the basis of current clinical data, the patients with hypertrophic obstructive cardiomyopathy who will probably benefit the most from pacing therapy are those who are refractory to or intolerant of medical therapy, those who are at high risk or unwilling to have surgical myomectomy, or those who have another indication for pacing. It is still not clear whether pacing will be a preferred option in the treatment of hypertrophic obstructive cardiomyopathy in light of the promising results of transcatheter septal ablation.

ROLE OF PACING IN DILATED CARDIOMYOPATHY AND HEART FAILURE

Heart failure is characterized not only by diminished contractility but also by dysrhythmia and conduction system abnormalities. Up to 53% of patients with heart failure have intraventricular conduction delays that result in abnormal depolarization of the heart and mechanical asynchrony of the ventricles (18). Clinical consequences of ventricular asynchrony, which is usually manifested by left bundle-branch block, include abnormal interventricular septal wall motion (19); a reduction in the peak rate at which left ventricular pressure increases (20); reduced diastolic filling times (19, 20); and prolonged duration of mitral regurgitation, tricuspid regurgitation, or both (19, 21). Evidence now indicates that heart failure is not solely a disease of diminished contractility and detrimental neurohormonal activation but also one of conduction defects, which results in ventricular dysynchrony that worsens ventricular performance. The latter problem is not being addressed by standard medical therapy. Shamim and associates (22) showed that as many as 40% of patients with advanced

Figure 2. Impact of QRS duration on risk for death in patients with heart failure (22).



* $P < 0.001$.

heart failure may have a wide QRS complex. Those with a QRS duration of at least 140 milliseconds are at significantly increased risk for death (Figure 2).

Cardiac pacing may be able to correct ventricular dysynchrony by resynchronizing electrical depolarization and thereby restoring synchronous mechanical activity of the heart. Experience with standard dual-chamber pacing has shown that restoration of optimal atrioventricular timing can result in clinical improvement in some patients. Hochleitner and colleagues (23) were the first to report improvement of both symptoms and ejection fraction in 16 patients with dilated cardiomyopathy who received dual-chamber pacing (DDD) with an atrioventricular delay of 100 milliseconds. Their patients were followed for up to 5 years (24). The considerable clinical improvement achieved after implantation was maintained throughout the follow-up period or until death and was associated with a consistent decrease in NYHA functional class and an increase in left ventricular ejection fraction. Subsequent studies involving small series of patients failed to show any consistent improvement with dual-chamber pacing in patients with dilated cardiomyopathy, regardless of whether the cause was idiopathic or ischemic (25, 26). Nishimura and coworkers (27) demonstrated that dual-chamber pacing in 15 patients with dilated cardiomyopathy improved hemodynamic variables. Optimization of the timing of

mechanical atrial and ventricular synchrony were key to the clinical improvement. Reestablishment of the optimal diastolic period and abolition of diastolic mitral regurgitation may also have contributed to the hemodynamic improvement. The greatest benefit of dual-chamber pacing was seen in patients with a relatively large increase in left ventricular pressure during atrial contraction.

Biventricular pacing offers an alternative to dual-chamber (DDD) pacing for the management of heart failure. Early studies with small numbers of patients suggested that biventricular pacing is hemodynamically superior to left ventricular and right ventricular pacing and is also associated with improvement in NYHA functional class (28–31). Most patients studied with biventricular pacing had severe symptomatic heart failure, NYHA class III and IV, poor ejection fraction, left ventricular dilatation, and interventricular conduction delay. Biventricular pacing may allow ejection to occur in both ventricles before repolarization of the septum. Simultaneous activation of the right and left ventricles through biventricular pacing with an optimal atrioventricular delay may also result in a longer filling time by allowing the left ventricle to complete contraction and begin relaxation earlier. The Pacing Therapies for Congestive Heart Failure (PATH-CHF) study (32) was a single-blind, crossover, randomized, controlled trial. Twenty-seven patients with chronic heart failure, severe left ventricular systolic dysfunction, and left ventricular conduction disorders had endocardial pacing leads implanted in the right atria and right ventricle and an epicardial lead implanted on the left ventricle. Overall, biventricular and left ventricle pacing accelerated the rate of increase in left ventricular pressure and increased pulse pressure more than right ventricle pacing ($P < 0.01$), whereas left ventricle pacing accelerated the rate of increase in left ventricular pressure more than biventricular pacing ($P < 0.01$) (33). Auricchio and associates (33) concluded that left ventricle stimulation is required for maximum acute hemodynamic benefit, and the maximum benefit at any site occurs with a patient-specific atrioventricular delay.

Gras and coworkers (34) reported the initial results of the InSync Study, a European and Canadian multicenter trial that examines the safety and efficacy of a multisite pacemaker and of left ventricular pacing leads implanted through a cardiac vein as a supplemental

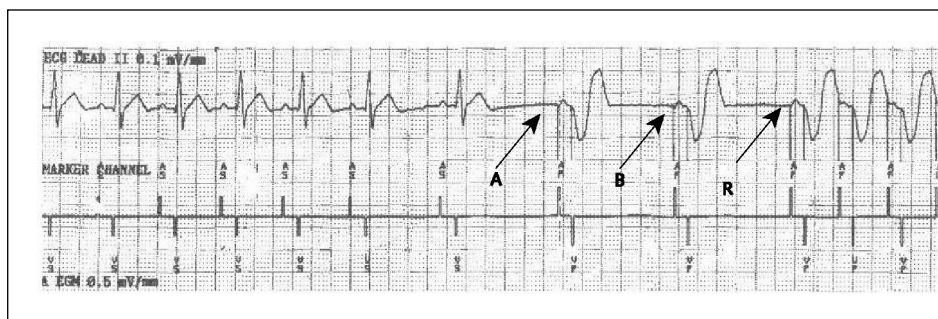
treatment for refractory congestive heart failure. The mean age of patients was 68 years, and 78% were male. Heart failure was classified as NYHA functional class III in 68% of patients and class IV in 32% of patients. The cause of heart failure was ischemic in 43% of patients. The mean QRS duration at baseline was 182 ± 29 milliseconds, and the mean left ventricular ejection fraction was 0.22. The lead system was implanted successfully in 68 of the 81 patients enrolled in the study (84%), and the patients were followed for 10 months. No implant-related complications occurred. During follow-up, 7 of 10 patients who exited the study died. Surviving patients showed a clinical benefits, which was corroborated by a significant improvement in NYHA functional class, significant improvement in the Minnesota Living with Heart Failure Quality-of-Life Questionnaire score, and a longer distance covered during a 6-minute walk test. This clinical improvement was associated with a significant narrowing of the paced QRS complex during biventricular pacing, a significant decrease in the interventricular mechanical delay, and a trend toward an increase in the duration of ventricular filling.

Atrial-based biventricular pacing may be valuable as an adjunct to defibrillation therapy when implantable devices are used in patients with prolonged QRS, severely symptomatic heart failure, significant left ventricular systolic dysfunction, and malignant ventricular arrhythmias. To further evaluate these promising results of biventricular pacing in severe heart failure, several randomized, controlled clinical trials are ongoing, such as the Multicenter InSync Randomized Clinical Evaluation (MIRACLE) and its subgroup, the MIRACLE-Implantable Cardiac Defibrillator (MIRACLE-ICD) study (35); the VIGOR Congestive Heart Failure trial (36); and the VENTAK Congestive Heart Failure trial (36). These studies should provide more definitive data on the safety, long-term efficacy, and survival effects of this new therapeutic strategy in high-risk patients who have received optimal medical treatment for heart failure.

PERMANENT PACING FOR THE TREATMENT OF NEUROCARDIOGENIC SYNCOPE

Patients with frequent vasovagal syncope have poor quality of life and are often resistant to standard pharmacologic treatment (37). Although an expert consensus panel has recommended permanent pacing for neurocar-

Figure 3. Dual-chamber pacemaker (DDD) electrocardiogram showing rate-drop responsiveness sensor mode.



A and B = the first two atrioventricular sequential paced beats after the pause at an escape rate of 50 pulses per minute. R = the point at which the rate-drop response sensor is activated and the pacemaker begins atrioventricular sequential pacing at a faster rate.

diogenic syncope (38, 39), concerns have been raised about its appropriateness and usefulness. Most patients may have had only one or two syncopal episodes, but for some patients with neurocardiogenic syncope, syncopal episodes are chronic, recurring, and troublesome. The likelihood of recurrence can be predicted clinically by the frequency of episodes in a patient's history (37). The risk for recurrent syncope after positive results on a tilt-table test at 1 year of follow-up ranges from 24% (40) to 73% (41) in high-risk patients who have had at least six previous syncopal spells. Menozzi and colleagues (42) studied 25 patients with neurocardiogenic syncope and an asystolic response of more than 3 seconds during carotid sinus massage and eyeball compression. All patients received a pacemaker able to detect and store in its memory all asystolic episodes. The actuarial estimates of occurrence of asystolic episodes more than 3 and more than 6 seconds in duration were 82% and 53%, respectively, after 2 years of follow-up. In this study, only patients with an asystolic response of more than 6 seconds were at high risk for presyncopal or syncopal symptoms. Several studies have evaluated the benefit of temporary pacing during a second tilt-table test by studying patients who had positive results on tilt-table tests with marked bradycardia. The results of these studies were mixed (43–46); almost all conscious patients developed a vasovagal reaction but did not progress to frank syncope. Temporary dual-chamber pacing prevented the development of neurocardiogenic syncope in 23 of 42 patients (55%).

The goal of cardiac pacing is to overcome transient bradycardia during neurocardiogenic syncope and, if possible, to provide enough heart rate support to com-

pensate for transient vasodilatation, which is common in such cases (37). This goal can be achieved by using several sensor algorithms. The three sensors now available include rate smoothing, rate hysteresis, and rate-drop response, each of which has been assessed clinically (47–49). Rate smoothing is a pacing algorithm designed to eliminate pronounced variations in heart rate due to sudden changes in sinus rate by progressively shortening successive paced RR intervals until the optimal paced rate is reached. Rate hysteresis is a pacing feature in which the escape interval that activates pacing is longer than the subsequent paced RR intervals, giving the heart a greater opportunity to beat on its own. Rate-drop response is a programmable algorithm that provides dual-chamber high-rate pacing for a programmed period immediately following a sudden reduction in heart rate (Figure 3).

Permanent cardiac pacing has been evaluated in a number of studies lasting several years. Petersen and associates (47) reported the results of dual-chamber pacing (DDD) with rate hysteresis in 37 patients with syncope over an average follow-up of 50 months; 62% remained free of syncope and 89% improved. Benditt and colleagues (48) reported encouraging results in a study of 28 high-risk patients who fainted once monthly on average. All received dual-chamber pacing (DDD) with rate-drop response. Over a follow-up of 6 months, 78% of patients did not faint and syncope frequency decreased by 67%. In another study, Sheldon and coworkers (49) evaluated dual-chamber pacing (DDD) and rate smoothing in 12 patients who had an average of three fainting episodes per month. They found that the frequency of syncope decreased by 93% and that quality of

life improved. These three studies consistently showed that most patients stopped fainting or had fewer fainting episodes after insertion of a permanent cardiac pacemaker.

Ammirati and associates (50) performed a small randomized clinical trial comparing rate hysteresis and rate-drop response. Twenty patients with frequent syncope received a dual-chamber pacemaker (DDD) with either sensor mode. Three patients in the group who received rate hysteresis fainted, whereas no patients fainted in the group that received the pacemaker with rate-drop response. This study, although small, suggests that rate-drop response is superior to rate hysteresis in preventing syncope. Novel syncope sensors that sense QT intervals, right ventricular pressure (including peak increase in ventricular pressure), core temperature, and indices of contractility are under investigation (37).

Randomized, controlled studies have been done to further evaluate these promising results. The North American Vasovagal Pacemaker Study (VPS) (41) tested whether permanent pacing with rate-drop response would reduce the likelihood of syncope in patients with frequent vasovagal syncope. Patients were eligible if they had fainted at least six times before tilt-table testing or if they had fainted within the first year after a positive tilt-table test result and had a predefined degree of bradycardia. Patients were randomly assigned to receive a pacemaker with automatic rate-drop response or the best medical therapy as determined by their treating physicians. The primary outcome measure was time to first recurrence of syncope. The study enrolled 54 patients who were randomly assigned equally to pacemaker or medical treatment. Six of 27 patients receiving pacemakers had a recurrence of syncope, whereas 19 of 27 patients treated medically experienced recurrence. The hazard ratio for recurrence in pacemaker recipients compared with medically treated patients was 0.087, which corresponds to a 91% reduction in the risk for recurrent syncope. The rate of presyncope occurrence did not differ between groups.

The VPS was the first randomized trial to show benefit from pacing. However, it had several limitations: 1) It was an open-label study, 2) the patients were highly selected, and 3) medical therapy was not standardized. The second VPS (VPS-II), which is ongoing, was designed to overcome some of these limitations. It is an ongoing, multinational, randomized clinical trial assess-

ing whether dual-chamber pacing (DDD) mode with rate-drop response is superior to placebo and to dual-chamber pacing (DDD) at an escape rate of 45 beats/min. Patients are eligible if they have had at least six syncopal episodes and a positive result on a tilt-table test; bradycardia need not be induced during the test. The primary outcome measure is first recurrence of syncope, and the study should be completed by 2002 (37).

The economics of treating vasovagal syncope depend on the severity of attacks. For patients who have syncope without warning, injury is a consideration, and a correctly chosen cardiac pacemaker may be warranted. Findings indicate that an economic argument favors using pacemakers in patients with severe vasovagal syncope (51). However, prospective studies examining this issue are not currently available. For high-risk patients (those with recurrent syncope and positive results on tilt-table tests) or patients who are intolerant of or refractory to medical treatment for neurocardiogenic syncope, permanent dual-chambered pacemaker implantation with rate-drop response should be considered.

PERMANENT PACING FOR THE PREVENTION OF ATRIAL FIBRILLATION

The role of permanent pacing for prevention of atrial fibrillation in at-risk patients is a relatively new concept. Existing retrospective studies support the superiority of atrial-based pacing over ventricular stimulation with respect to decreasing the incidence of atrial fibrillation (52). The antiarrhythmic mechanism is not well understood, but atrial resynchronization and reduction of site-dependent conduction delay of atrial premature depolarizations, reduction of bradycardia-induced dispersion of atrial refractoriness, and the change in atrial activation pattern during pacing that may make intra-atrial reentry less likely may be relevant. Andersen and coworkers (53), in a randomized study comparing atrial pacing (AAI) and single-chamber ventricular pacing (VVI), showed a lower incidence of atrial fibrillation in the group that received atrial pacing (14% vs. 23%; $P = 0.12$). An important subsidiary finding in this study is that the incidence of thromboembolic events was also significantly lower in patients treated with atrial pacing (5.5% vs. 17%; $P = 0.0083$). Randomized trials currently under way, such as the Mode Selection Trial (MOST), the Systematic Trial of Pacing to Prevent

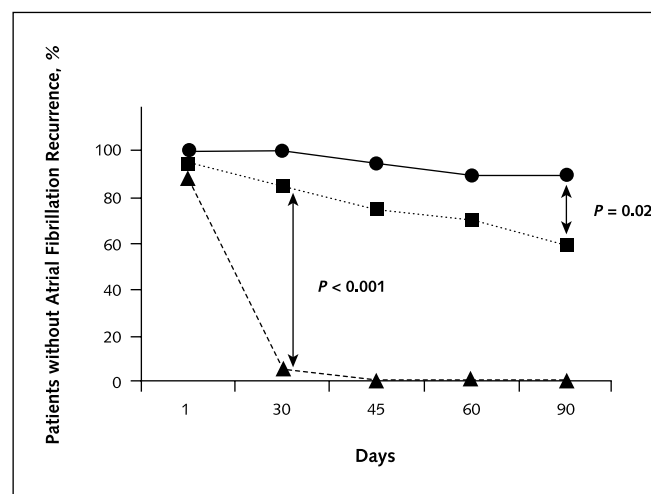
Atrial Fibrillation (STOP-AF) (54), and the Canadian Trial of Physiologic Pacing (CTOPP), may finally answer questions regarding pacing mode in relation to the risk for atrial fibrillation and the effect of pacing on congestive heart failure, thromboembolic events, and overall survival (51).

Biatrial pacing has emerged as a technique that re-synchronizes the electrical activity of the two atria, expressed as normalization of P-wave structure and duration in contrast to single right atrial or coronary sinus pacing (55). Saksena and colleagues (56) and Prakash and coworkers (57) developed and applied a novel technique of dual-site right atrial pacing that involves pacing at the high right atrium and coronary sinus ostium. They demonstrated that dual-site right atrial pacing is feasible, effective, and safe for long-term application. Mean drug use (\pm SD) for all antiarrhythmic classes decreased from 4 ± 1.9 drugs before implantation to 1.5 ± 0.5 drugs after implantation ($P < 0.01$) (56). Although atrial pacing substantially prolongs arrhythmia-free intervals in patients with drug-refractory paroxysmal atrial fibrillation, dual-site right atrial pacing may offer additional benefits and should be considered as the primary mode or should be used in patients who are not responsive to single-site pacing (56).

The antiarrhythmic mechanisms of multisite pacing are unknown but could be related to atrial resynchronization or improved hemodynamics because the left atrioventricular interval is decreased (58). Yu and associates (59) demonstrated that biatrial stimulation significantly decreased both the atrial conduction delay and prolonged electrogram width occurring at the right posterior interatrial septum that is caused by an early premature depolarization of the high right atrium. Conduction delay of the early high right atrial premature complex was less pronounced during dual-site atrial pacing (60). Furthermore, under the influence of dual-site pacing, both the refractory period and the conduction velocity of atrial premature depolarization originating distant from the pacing site were increased compared with single-site stimulation (61).

Recently, Delfaut and coworkers (62) studied 30 consecutive patients who had implanted dual-chamber rate-responsive pacemakers and two atrial leads. In addition, they had drug-refractory symptomatic atrial fibrillation and documented primary or drug-induced bradycardia. The mean arrhythmia-free intervals in-

Figure 4. Dual-site right atrial pacing compared with single-site right atrial pacing.



Dual-site right atrial pacing significantly increased the proportion of patients free of atrial fibrillation recurrence at 90 days (89% vs. 62%). All patients in the control group had recurrence of atrial fibrillation by 45 days (62). The solid line indicates patients who received dual-site right atrial pacing, the dashed line indicates patients who received single-site right atrial pacing, and the dotted line indicates controls.

creased from 9 ± 10 days in the control period preceding implantation to 143 ± 110 days ($P < 0.0001$) in single-site right atrial pacing and 195 ± 96 days in dual-site right atrial pacing ($P < 0.005$ vs. single-site pacing and $P < 0.001$ vs. control). Dual-site right atrial pacing significantly increased the proportion of patients free of atrial fibrillation recurrence compared with single-site right atrial pacing (89% vs. 62%; $P = 0.02$) (Figure 4). Effective rhythm control was achieved in 86% of patients during dual right atrial pacing. Seventy-eight percent of patients at 1 year and 56% at 3 years remained free of symptomatic atrial fibrillation. The number of patients without any antiarrhythmic drug treatment increased slightly. The need for cardioversion was reduced after pacemaker implantation ($P < 0.05$), and anti-thrombotic therapy was reduced ($P < 0.06$) without any thromboembolic event (62).

Levy and colleagues (63) performed a randomized, single-blind study in 19 patients with drug-refractory atrial fibrillation and compared biatrial pacing with conventional right atrial pacing. The duration of each pacing mode was 3 months. They found a significant reduction in the total duration of atrial fibrillation with either right or biatrial pacing when compared with the

control period. Most of this benefit was in the subgroup of 12 patients with paroxysmal atrial fibrillation. The number of episodes of atrial fibrillation did not change significantly. When they compared right atrial pacing with biatrial pacing, no difference could be demonstrated with regard to the duration or frequency of atrial fibrillation episodes, suggesting that biatrial pacing may have no incremental antiarrhythmic effect compared with conventional right atrial pacing (63). These results differ from those of previous studies (59, 62).

Interatrial septum pacing is an alternative method to achieve synchronous depolarization of both atria without concern for interatrial conduction time. Interatrial septum pacing was performed by Padeletti and coworkers (64) in 25 patients with sinus bradycardia and paroxysmal atrial fibrillation. During a mean follow-up of 9 months, only 2 patients had recurrent atrial fibrillation ($P < 0.01$). Further randomized, controlled studies are necessary to establish the exact role of this technique with respect to conventional or multisite pacing in patients with paroxysmal atrial fibrillation.

In theory, multisite atrial pacing reduces atrial arrhythmias by reducing total atrial activation time, resulting in more uniform repolarization. This leads to reduced dispersion of refractoriness, which tends to be less arrhythmogenic. The clinical relevance of this concept has not yet been proved by large randomized trials, but two such trials are ongoing: the European Multicenter Synchronous Biatrial Pacing trial (SYNBIAPACE) and the Dutch Dual Right Atrial Pacing for Prevention of Atrial Fibrillation (DRAPPAF) study.

Multisite atrial pacing may be valuable as stand-alone therapy or as an adjunct to defibrillation therapy with implantable devices for paroxysmal atrial fibrillation in patients who are intolerant of or refractory to antiarrhythmic drug therapy. At this time, permanent dual-site atrial pacing as the sole method for prevention of atrial fibrillation or as an adjunctive method without another indication for pacing is considered investigational.

CONCLUSION

Dual-chamber pacing with an optimal atrioventricular delay has been shown to improve symptoms and hemodynamic variables in patients with severely symptomatic hypertrophic obstructive cardiomyopathy who

have significant left ventricular outflow tract obstruction at rest and who are refractory to medical treatment. However, randomized clinical trials have not shown conclusive evidence regarding the long-term benefit from pacing in these patients. Moreover, the relationship between reduction in left ventricular outflow obstruction gradient and improvement of symptoms is controversial; there may be a partial but significant placebo effect. It is unclear whether pacing will be a preferred option in the treatment of hypertrophic obstructive cardiomyopathy, especially in light of new transcatheter therapies, such as septal ablation.

In dilated cardiomyopathy and heart failure, abnormal electrical depolarization of the heart associated with prolonged QRS duration (>140 milliseconds) results in mechanical asynchrony of the ventricles. Conventional medical therapy for heart failure does not address this issue. Cardiac pacing represents a viable adjunctive therapeutic approach for improving ventricular dyssynchrony. Preliminary data with atrial-based biventricular pacing have shown promising results as a supplemental treatment for refractory heart failure. Clinical improvement, a decrease in the interventricular mechanical delay with resultant increase in diastolic ventricular filling period, occurred in association with narrowing of the QRS complex during biventricular pacing. Several ongoing randomized, controlled clinical trials should provide more definitive data on the safety, efficacy, and mortality benefit of this new therapeutic strategy in high-risk patients who have received optimal medical management.

Patients with frequent syncopal episodes and a positive tilt table test result for neurocardiogenic syncope who are intolerant of or refractory to medical treatment have shown benefit from pacing therapies with specific rate-drop sensor algorithms. To further evaluate the role of permanent pacing with automatic rate-drop response for neurocardiogenic syncope, a second large multinational randomized clinical study is ongoing.

The role of pacing as the sole therapy for prevention of atrial fibrillation is a relatively new concept. Biatrial pacing has emerged as a new pacing technique for preventing paroxysmal atrial fibrillation. In patients with paroxysmal atrial fibrillation, biatrial pacing has resulted in an increase in the mean arrhythmia-free interval, decreased need for cardioversion, and decreased need for antithrombotic therapy. The clinical relevance of this

concept remains to be proven by randomized trials, several of which are ongoing. Currently, multisite pacing for the prevention of atrial fibrillation should be considered investigational.

The current guidelines from the American College of Cardiology–American Heart Association for implantation of cardiac pacemakers and arrhythmia devices (39) were published in 1998, before many of the clinical studies discussed in this paper were published. These guidelines state that hypertrophic obstructive cardiomyopathy, dilated cardiomyopathy, and neurocardiogenic syncope are class IIb indications for permanent pacing. Pacing as the sole therapy for preventing atrial fibrillation was not discussed in that report.

GLOSSARY

AAI, DDD, VVI: The letter code (NBG code) for identifying the pacing modes developed by the North American Society of Pacing and Electrophysiology and the British Pacing and Electrophysiology Group. The first letter represents the heart chamber(s) being paced, the second letter represents the heart chamber(s) being sensed, and the third letter represents the type of response from the pulse generator upon sensing. For the first two letters, A = atrium, V = ventricle, and D = double; for the third letter, I = inhibits pacing and D = triggers and inhibits pacing.

Atrioventricular interval or delay: In a dual-chamber pacemaker mode, the atrioventricular interval or delay is the period of time between an atrial event (sensed or paced) and a scheduled paced ventricular event.

Atrioventricular synchrony: The normal activation sequence of the heart in which the atria contract and then, after an appropriate delay, the ventricles contract.

Class IIb indication: According to the guidelines established by the American College of Cardiology and the American Heart Association, class II indications are conditions for which there is conflicting evidence, a divergence of opinion, or both about the usefulness or efficacy of a procedure or treatment. A class IIb designation indicates that usefulness or efficacy is less well established by evidence opinion.

Pacing backup: Stands for an inactive pacing mode, the “placebo” used in patients randomly assigned to placebo in clinical trials. The mode used as a placebo was AAI with an escape rate of 30 pulses per minute.

Rate-drop response: A programmable algorithm that provides dual-chamber high-rate pacing for a programmed period immediately following a sudden reduction in heart rate.

Rate hysteresis: A pacing feature in which the escape interval that activates pacing is longer than the subsequent paced RR

intervals, giving the heart a greater opportunity to beat on its own.

Rate smoothing: A pacing algorithm designed to eliminate pronounced variations in heart rate due to sudden changes in sinus rate by progressively shortening successive paced RR intervals until the optimal paced rate is reached.

Transcatheter septal ablation: A technique used in patients with hypertrophic obstructive cardiomyopathy who would be considered candidates for surgical myectomy. It involves injection of alcohol into the first septal perforator vessel by using transluminal percutaneous balloon catheter with balloon inflation of the distal left anterior descending coronary artery.

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