The Role of Pacemakers in the Management of Patients with Atrial Fibrillation

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KEYWORDS

- Pacemaker • Implantable cardioverter defibrillator
- Atrial fibrillation • Sinus node dysfunction
- Atrioventricular junction ablation

This article reviews the wide range of implantable device–based therapies (mainly pacemakers) that are being used in the management of atrial fibrillation (AF), atrial flutter, and atrial tachycardia (AT). Pacemakers have an important and evolving role in the management of some patients with AF. The frequency of their use relative to other nonpharmacologic strategies has increased over time as the incidence and prevalence of AF increase, especially in the elderly. In fact, almost all the increase in pacemaker implantation rates has been for the indication of sinus node dysfunction (SND). The clinical burden of AF in the elderly population is staggering. In the groups aged 70 to 79 years and 80 to 89 years, the prevalence of AF is at least 4.8% and 8.8%, respectively. By 2050, it is estimated that 50% of the patients with AF are going to be more that 80 years old.[1] **Box 1** summarizes the most common strategies that have been used for device-based management of patients with AF. The goals of this article are first to review the evolution of the important current paradigms of pacing as they relate to AF and then to discuss how pacemakers are used in the specific subpopulations of patients with AF.

The most common indication for pacemaker implantation in the United States is for SND. AF is a primary feature of SND in many patients. In effect, understanding the role of pacemakers in the management of AF requires an understanding of the role of pacemakers in SND. Pacemaker implantation practice patterns in the United States vary from those in Europe. Dual-chamber (rather than single-chamber) pacemakers are usually implanted in the United States for patients who have sick sinus syndrome and paroxysmal AF even if there is no AV conduction abnormality at the time of implantation. In one study, the incidence of developing AV block was 8.4% over a period of 34 months.[2] In a European study of patients who received a single-chamber (AAI) pacemaker for sick sinus syndrome, there was a 1.7% annual incidence of AV block.[3] Because the incidence of AV block is not insignificant, in the United States, patients who have paroxysmal AF and sick sinus syndrome almost universally receive dual-chamber pacemakers. With careful patient selection, however, the incidence of development of AV block can be as low as 0.6%.[4] Thoughtful pacemaker programming and careful pacemaker mode selection with the goal of maintaining "physiologic pacing" are critical.

In the current American College of Cardiology (ACC)/American Heart Association (AHA)/Heart Rhythm Society (HRS) guidelines, AF is described as permanent or chronic if it is long standing (eg,

A version of this article originally appeared in *Medical Clinics of North America*, volume 92, issue 1.
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Cardiol Clin 27 (2009) 137–150
doi:10.1016/j.ccl.2008.09.009
0733-8651/08/$ – see front matter

Box 1
Device-related applications for the management of atrial fibrillation

Rate control

Pacing to facilitate the use of rate-lowering agents

Pacing in chronic AF

Pacing for rate regularization

Pacing in conjunction with AV node ablation or modification

Rhythm control or maintenance of sinus rhythm

Pacing to facilitate the use of antiarrhythmic medication

Pacing to maintain or promote sinus rhythm

Algorithms to promote sinus rhythm

Multisite pacing (dual site, biatrial)

Novel site pacing

Pacing or defibrillation to terminate AF

longer than 1 year) and if cardioversion has failed or has been foregone. AF is called persistent if it lasts more than 7 days regardless of whether cardioversion is needed to restore sinus rhythm; it is considered paroxysmal if episodes of AF terminate spontaneously.[5] Pacemakers have applications in each of these clinical types of AF.

PHYSIOLOGIC PACING

An appreciation of the role of pacemakers in the management of AF (especially in the context of SND) requires an understanding of the evolution of the meaning of "physiologic pacing" and optimal pacing modalities. The function of a pacemaker is to approximate normal cardiac function as much as possible. Therefore, careful mode selection (eg, AAI, VVI, DDI, DDD) and proper programming (eg, AV delay, hysteresis, mode switch rates) are needed to optimize the beneficial effects and minimize the potentially detrimental effects of pacing. Although "demand" ventricular pacemakers have been in clinical use since the 1960s, and although it seems intuitive that dual-chamber pacing would be superior to ventricular demand pacing, the body of clinical data needed to support this conclusion took almost 20 years to accumulate. The benefits of dual-chamber AV synchronous pacing in patients with SND and paroxysmal AF are now widely accepted. More recently, the potentially adverse effects of ventricular pacing (synchronous or asynchronous) have been recognized and are summarized in **Box 2**. Some of

Box 2
Potential adverse effects of ventricular pacing right ventricle in sinus node dysfunction

Ventricular dyssynchrony

Altered cardiac hemodynamics attributable to loss of "atrial kick"

Atrial proarrhythmia

Ventricular proarrhythmia

Increased valvular regurgitation

Adverse electrical remodeling of the atria promoting AF

Pacemaker syndrome

these effects are not unique to dyssynchronous pacing but may occur with dual-chamber pacing and are discussed elsewhere in this article. Even ventricular proarrhythmia (ventricular tachycardia and ventricular fibrillation) has been described with single-chamber ventricular and dual-chamber pacing.[6] Ventricular remodeling, hemodynamic parameters, quality-of-life (QOL) measures, and clinical end points (eg, incidence of AF, stroke risk, congestive heart failure [CHF], mortality) have all been investigated. In terms of the incidence of AF, the data from the large clinical trials supporting physiologic pacing are fairly compelling. In terms of the other clinical end points, such as QOL, stroke risk, and mortality, however, the data are not entirely consistent and continue to evolve. Hemodynamic studies have demonstrated that AV synchrony improves stroke volume and cardiac output and reduces right atrial pressure and pulmonary-capillary wedge pressures. A significant number of patients who receive a single-chamber ventricular (VVI) pacemaker for sick sinus syndrome develop pacemaker syndrome, consisting of such symptoms as fatigue, palpitations, and chest pain. These symptoms resolve after patients receive atrioventricular (AV) synchronous pacing.[7,8] When comparisons are made within an individual patient testing different pacing modes rather than between patients, dual-chamber synchronous pacing is strongly preferred to single-chamber ventricular pacing.[9]

Table 1 summarizes the key clinical findings in the eight major randomized studies that have demonstrated the benefits of AV synchronous pacing or atrial-based pacing. These trials have collectively enrolled nearly 9000 patients. Although it was a small study with limited power, the Danish study was the first randomized prospective study to support the concept that selection-specific pacing modalities could improve outcomes in patients

Table 1
Clinical Trials in Pacing

Trial	Year	Average Follow-Up (years)	Design	Key Findings
Danish (Andersen and colleagues)[4]	1994	5.5	AAI versus VVI in 225 patients with SSS	At long-term follow-up (mean of 5.5 years), the incidence of paroxysmal AF and chronic AF was reduced in the AAI group. Overall survival, heart failure, and thromboembolic events were reduced with atrial-based pacing.
PASE[7]	1998	2.5	Single-blind assignment of VVIR or DDDR mode in 407 patients with SSS, AV block, and other indications	Patients with SSS showed a trend toward a lower incidence of AF and all-cause mortality (AF: 19% versus 28%, $P = .06$; mortality: 12% versus 20%, $P = .09$). QOL was not different between the two pacing modes. Twenty-six percent of patients developed pacemaker syndrome when paced in the VVIR mode
Mattioli and colleagues[54]	1998	2.0	VVI/VVIR versus AAI/DDD/DDDR/VDD pacing in patients with AV block (n = 100) and SSS (n = 110)	Incidence of AF was 10% at 1 year, 23% at 2 years, and 31% at 5 years. An increase in the incidence of chronic AF was observed in patients with SSS in the VVI/VVIR arm.
Canadian Trial of Physiologic Pacing (CTOPP)[10]	2000	6.0	2568 patients randomized to ventricular pacing (VVIR) versus physiologic pacing (DDDR or AAIR) for any appropriate indication	The annual rate of AF was less with physiologic pacing. No difference was observed in stroke or cardiovascular death between the two groups. There was a 27% reduction in the annual rate of progression to chronic AF.
Mode Selection in Sinus-Node Dysfunction Trial (MOST)[11]	2002	4.5	2010 patients with sinus node dysfunction (only) randomized to VVIR versus DDDR programming; more than 50% had prior AF	AF was reduced in patients randomized to physiologic pacing. No difference in mortality and stroke rates was observed between pacing modes. Thirty-one percent of patients crossed over from the VVIR to the DDDR mode, 49% of which was attributable to pacemaker syndrome.
Pacemaker Atrial Tachycardia (PAC-ATACH)[13]	2001	2.0	198 patients with sinus node dysfunction and a history of atrial arrhythmias randomized to DDDR pacing or VVIR pacing	Abstract only; full report remains to be published. Mortality was lower in the dual-chamber group. (3.2% versus 6.8%; $P = .007$) There was no difference in the AF recurrence rate.
United Kingdom Pacing and Cardiovascular Events (UKPACE)[12]	2002	4.6	2021 patients, aged >70 years randomly assigned to three arms: DDD (50%), VVIR (25%), and VVI 25%)	There was no difference in all-cause mortality, rate of stroke, or incidence of AF between the dual-chamber group and ventricular pacing group.
Search Atrioventricular Extension and Managed Ventricular Pacing for Promoting Atrioventricular Conduction (SAVEPACe)[17]	2007	1.7	530 patients in DDD mode and 535 patients in AAI←→DDD mode for symptomatic sinus node dysfunction; nearly an equal number of patients in both groups (38%) had paroxysmal AF	Persistent AF occurred in 12.7% of patients in the conventional pacing group and 7.9% of patients in the minimal ventricular pacing group.

with sick sinus syndrome (SSS).[4] Another study, the Pacemaker Selection in the Elderly (PASE) trial, did not show a difference in the QOL scores between those patients programmed to the VVIR versus DDDR mode; however, up to 45% of patients with SSS who were in VVIR mode developed pacemaker syndrome.[7] The Canadian Trial of Physiologic Pacing (CTOPP) showed a clear benefit for physiologic pacing in terms of reducing the incidence of AF, but it did not demonstrate a preferential advantage in patients with SSS. In addition, the CTOPP study demonstrated a higher rate of perioperative complications in those patients who received a dual-chamber pacemaker compared with those who received a single-chamber device (9.0% versus 3.5%, respectively). The risk for AF was lower for physiologic pacing (21.5%) than for ventricular pacing (27.1%).[10] The power of the Mode Selection in Sinus-Node Dysfunction Trial (MOST) may have been compromised because of the high rate of crossover from VVI mode to DDD mode. Nevertheless, this trial, contrary to the CTOPP study, showed improvements in QOL scores after reprogramming to a dual-chamber mode.[11] The United Kingdom Pacing and Cardiovascular Events (UKPACE) trial is remarkable for its negative results. Patients received single-chamber (VVI or VVIR) pacemakers or dual-chamber pacemakers for AV block. Patients with permanent AF or paroxysmal AF that was present for more than 3 months were excluded from the trial. There was no benefit from dual-chamber pacing modes over single-chamber modes in terms of stroke rate or AF.[12] The Pacemaker Atrial Tachycardia (PAC-ATACH) trial is the only trial to demonstrate a mortality benefit for dual-chamber pacing compared with ventricular pacing; however, the results of that trial have been presented only in abstract form.[13] A recent meta-analysis by Healey and colleagues[14] pooled data from five of these trials (Danish, PASE, CTOPP, MOST, and UKPACE) to detect clinically significant outcomes that the individual trials were not powered to detect. The combined data from these trials represent 35,000 patient-years of follow-up and demonstrated that although the incidence of AF was less with atrial-based pacing compared with ventricular-only pacing, there was no significant benefit in terms of all-cause mortality. Despite the reduced incidence of AF, there was no significant reduction in the risk for stroke.

In a secondary analysis of the MOST data, two additional important findings were reported. Increasing proportions of ventricular pacing were found to be associated with an increasing incidence of AF during VVIR and DDDR pacing. Also, greater percentages of ventricular pacing were associated with a greater risk for hospitalization for heart failure.[11] If ventricular pacing occurred more than 40% of the time, there was a twofold increase in the risk for developing CHF. This study suggests that the relative benefits of AV synchronous pacing compared with ventricular only pacing are attributable to the deleterious effects of right ventricular (RV) pacing rather than to the presumed advantages of AV synchronous pacing. The CTOPP and MOST studies had relatively few patients with true atrial only–based pacing (AAI) without the confounding effect of ventricular pacing. In the MADIT II study, patients who received an implantable cardioverter defibrillator (ICD) had higher survival rates but also demonstrated a trend toward increased rates of CHF; 73 patients (14.9%) in the conventional therapy group and 148 in the defibrillator group (19.9%) were hospitalized with heart failure ($P = .09$).[15] In the Dual Chamber and VVI Implantable Defibrillator (DAVID) trial, a composite end point of time to death and first hospitalization for CHF was compared in patients who had ICDs programmed to receive dual-chamber pacing (DDDR-70) or ventricular backup pacing (VVI-40).[16] At 1 year, 83.9% of the patients in the VVI-40 group were free from the composite end point compared with 73.3% of patients in the DDDR-70 group. Hospitalization for CHF occurred in 13.3% of VVI-40 patients compared with 22.6% of DDD-70 patients, trending in favor of the VVI-40 group. Although the DAVID study looked only at an ICD population, it has had a major impact on the programming of dual-chamber pacemakers. By highlighting the deleterious effects of RV pacing, it underscores the importance of mode selection in patients with SND and paroxysmal AF. The programmed parameters of a pacemaker or ICD should promote minimal ventricular pacing.

All major pacemakers have features that allow for maximization of the AV delay to promote intrinsic ventricular depolarization. Algorithms even exist that allow the dual-chamber pacemaker to change from single-chamber atrial-based pacing (AAIR) to dual-chamber AV sequential pacing (DDDR) automatically. When selected, the device operates in an AAIR mode until AV block occurs and then instantly changes to a DDDR mode (**Fig. 1**). In a study by Sweeney and colleagues (Search Atrioventricular Extension and Managed Ventricular Pacing for Promoting Atrioventricular Conduction [SAVE PACe]),[17] there was a 40% relative risk reduction in the development of persistent AF as compared with conventional dual-chamber pacing for patients with SND and normal left ventricular (LV) function. There was no difference in mortality between the two groups.

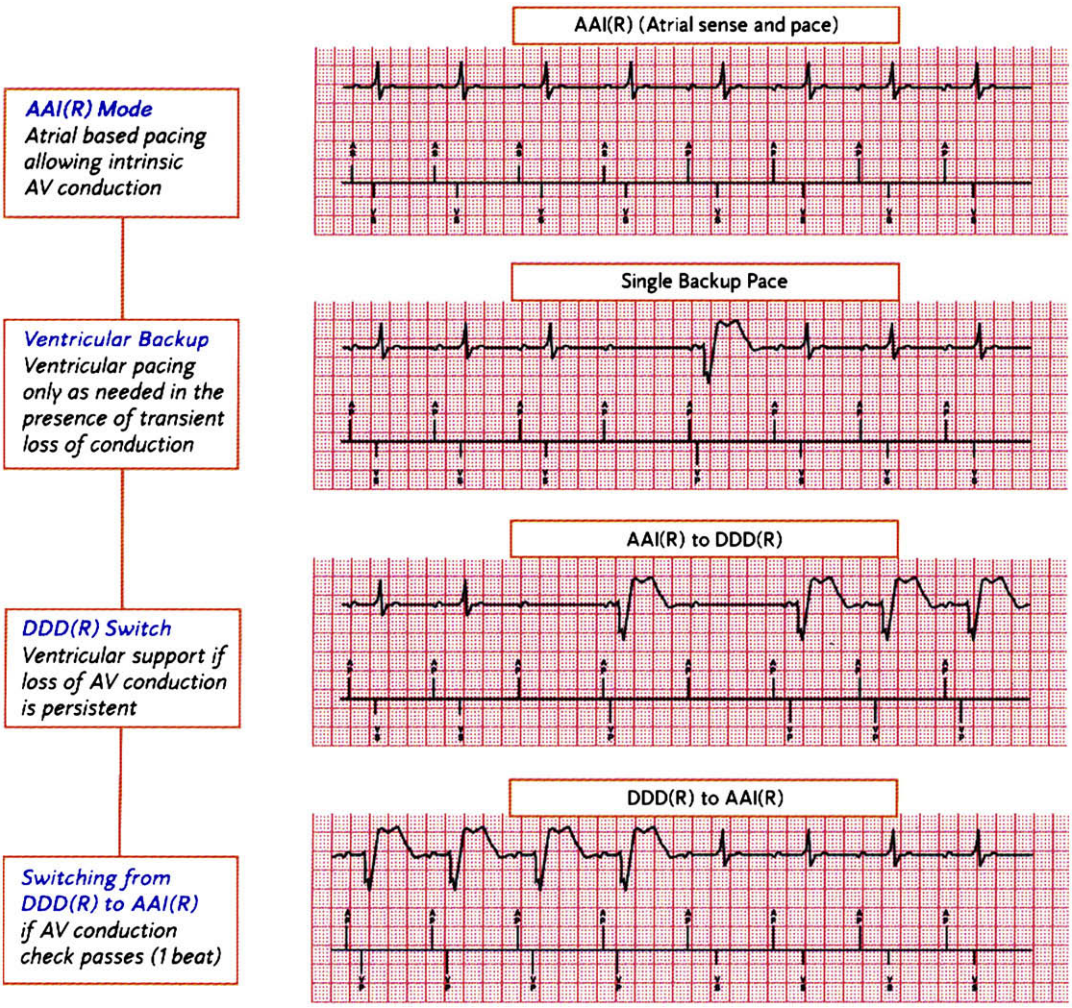

Fig. 1. Managed ventricular pacing (MVP; Medtronic, Inc., Minneapolis, Minnesota) is an atrial-based pacing mode that significantly reduces unnecessary right ventricular pacing by primarily operating in an AAIR pacing mode while providing the safety of a dual-chamber backup mode if necessary. As shown in the figure, the algorithm allows for a single blocked beat before a back-up ventricular paced beat is delivered. Mode switch occurs only if two blocked beats occur. Two sequential blocked beats cannot occur because of back-up ventricular pacing.

Data from the MADIT II and DAVID studies only involved patients with severe LV dysfunction. This raises the question as to whether or not the detrimental effects of RV pacing (in terms of heart failure and mortality) are seen in patients with lesser degrees of LV dysfunction or normal LV function. There are limited data with which to answer this question. If physiologic pacing can be thought of as the pacing mode that most closely mimics normal cardiac physiology while yielding the best outcomes with the least detrimental effects, it seems that atrial-based pacing that promotes intrinsic conduction and minimizes RV apical pacing (in patients with no cardiac resynchronization therapy [CRT] indications) is the mode of choice. AV synchrony alone is not adequate.

PACEMAKER DIAGNOSTICS

Pacemaker diagnostics not only can provide insight into the burden of AF but can reveal the presence of asymptomatic AF that was not previously suspected.[18] Routine interrogation of a pacemaker implanted for SND may reveal episodes of AF that have been stored in the memory as mode switch episodes or atrial high-rate episodes. ''Mode switch'' refers to a programmable function allowing the pacemaker to change from a dual-chamber pacing mode (DDD) to a nontracking mode (DDI or

VVI). This feature is available in all current pacemakers and ICDs. Once selected, it is an automatic function and does not require office-based reprogramming. An atrial arrhythmia that meets a programmed duration (a few seconds) and rate (usually 160 beats per minute [bpm]) results in a mode switch event and an entry into the log. When the atrial arrhythmia terminates, dual-chamber pacing is resumed. Mode switching prevents rapid ventricular pacing in response to the tracking of rapid atrial rhythms. The frequency and duration of atrial arrhythmias, including AF and atrial flutter, can be recorded and stored. Most current pacemakers are capable of storing intracardiac electrograms, sometimes allowing the clinician to distinguish between AF, AT, and atrial flutter. Some older devices are only capable of reporting the number and duration of mode switch episodes without storing any associated electrograms. In these cases, an event monitor may be needed to document the atrial arrhythmias. Overall, the false-positive detection of AF is reported at approximately 2.9%.[19] In contrast, the results of the Balanced Evaluations of Atrial Tachyarrhythmia in Stimulated Patients (BEATS) study showed that ATs could occur in 54% of patients with stored electrograms compared with only 15% of patients screened by surface electrocardiograms and 24-hour Holter monitors.[20] Artifact and oversensing of atrial or far field ventricular events can result in inappropriate mode switch episodes. Stored data should be reviewed and interpreted by someone who is knowledgeable in the interpretation of intracardiac electrograms. Capucci and colleagues[21] demonstrated that patients with device-monitored AF for longer than 24 hours had an increased risk for embolic events. Identification of appropriate mode switches can have a significant impact on the management of patients in terms of initiation of anticoagulation, perhaps reducing the risk for future thromboembolic events. All major manufacturers of pacemakers and ICDs have the capability of some form remote monitoring. Remote monitoring frequency and alerts can be individualized to meet the needs of the each patient and each physician.

Fig. 2 shows the interrogation report from a dual-chamber pacemaker. It was implanted for symptomatic sinus bradycardia in a 73-year-old patient not previously known to have AF. During the 1 month after implantation, the patient had 186 episodes of atrial high rates, 4 of which were longer than 1 minute in duration. The longest mode switch episode lasted almost 6 hours. These episodes were asymptomatic. Based on these findings, the initiation of warfarin sodium was discussed with the patient and the dose of the beta-blocker was increased. **Fig. 3** shows an example of a stored

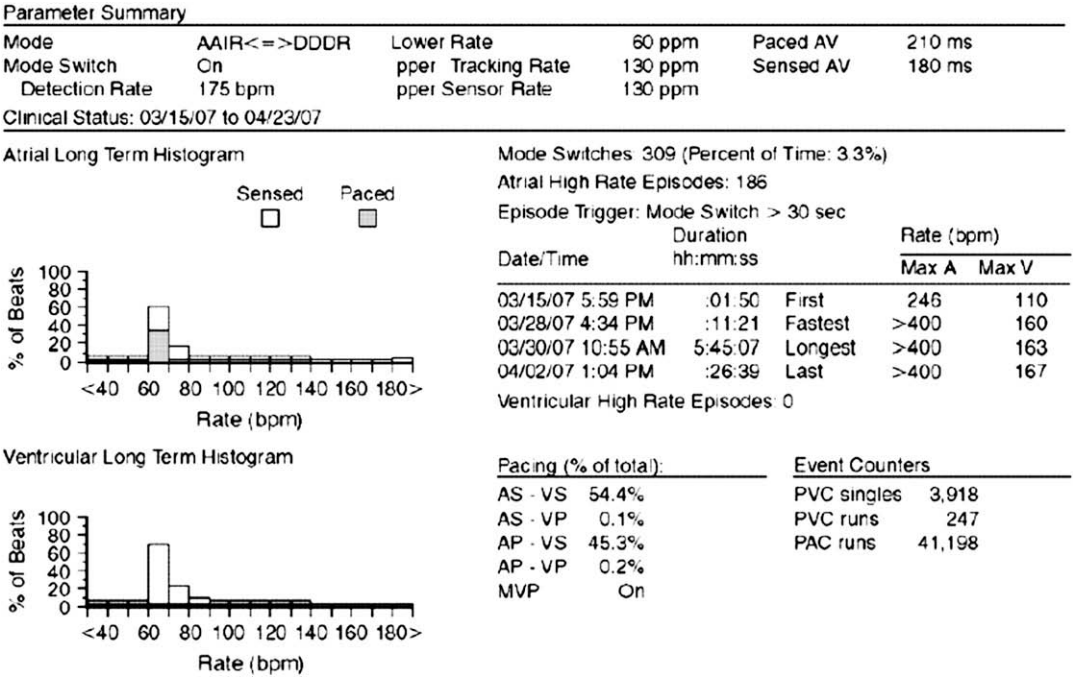

Fig. 2. Arrhythmia summary report from a dual-chamber pacemaker (Adapta Dual Chamber Pacemaker; Medtronic, Inc., Minneapolis, Minnesota).

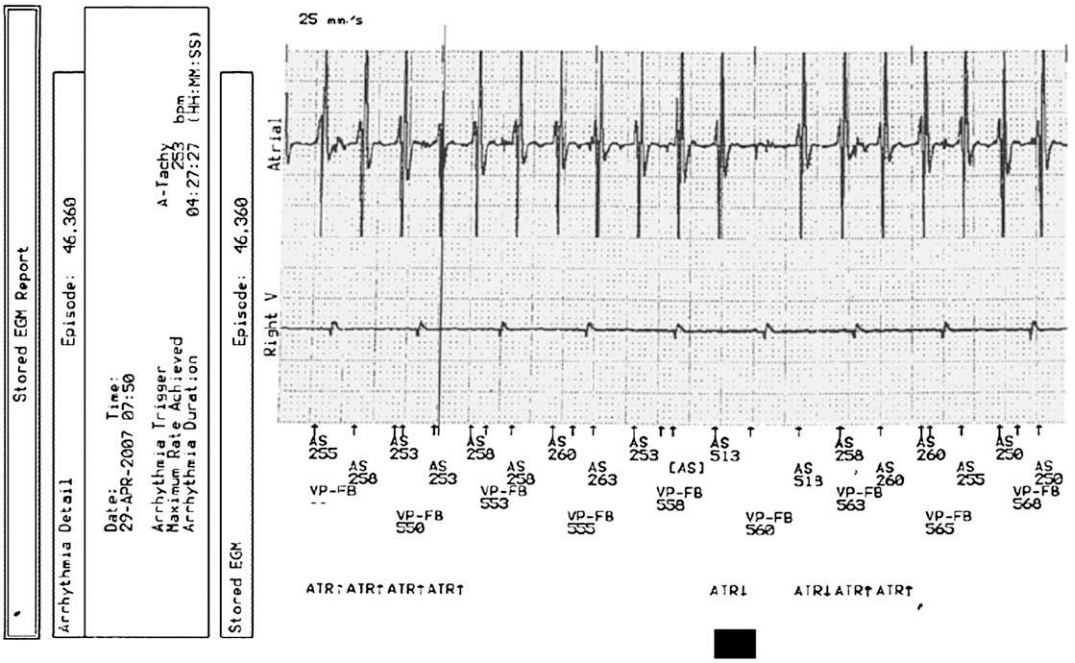

Fig. 3. Example of stored electrograms (EMGs) from an appropriate mode switch episode. The atrial channel shows a rapid irregular atrial rate with a maximum atrial rate of 253 bpm.

electrogram of an atrial tachyarrhythmia resulting in an appropriate mode switch.

In addition to mode switch events, pacemaker diagnostics can provide other important information. Rate histograms can provide insight into the adequacy of the rate response and suggest the need for more a sensitive sensor setting to provide appropriate chronotropic support in a patient with AF and a slow ventricular rate. Rate histograms can help to assess the adequacy of rate control in patients with AF. It is also important to know the percentage of ventricular pacing in patients with intact AV conduction. The practice of maximizing the AV delay to promote intrinsic AV conduction is supported by data from the DAVID, MADIT II, and MOST studies.

Chronic or Permanent Atrial Fibrillation

It is not uncommon for patients with chronic AF to require a permanent pacemaker. Over time, these patients may develop a slow ventricular response resulting in symptomatic bradycardia. Progressively slower conduction is often the result of age-related degeneration of the conduction system. Because this process is gradual, some elderly patients do not readily recognize or complain of the symptoms of exercise intolerance, dyspnea on exertion, and easy fatigability that can accompany bradycardia and chronotropic incompetence. Physicians and patients frequently dismiss these nonspecific symptoms as a natural consequence of aging. In addition, comorbid conditions may be present, which can result in similar symptoms confounding the diagnosis of SSS. Therefore, a Holter monitor or event monitor may be needed to obtain true symptom-rhythm correlation. A single-chamber rate-responsive pacemaker (VVIR) can provide symptom relief and improve functional capacity.

Bradycardia may also be an unavoidable consequence of the medications used to prevent a rapid ventricular response associated with AF. Beta-blockers, calcium channel blockers, and digoxin are used to control rapid ventricular rates during AF but can result in intermittent symptomatic bradycardia or long pauses that can lead to syncope or presyncope. Of note, pauses up to 2 to 3 seconds during sleep are not unusual and are not solely an indication for pacing. Instead, this bradycardia is just a function of the relatively high vagal tone that is present during sleep. Dosage adjustment of medications or the use of beta-blockers with intrinsic sympathomimetic activity (ISA) can sometimes mitigate the bradycardia or pauses but can also result in suboptimal rate control when a patient is active and awake. A pacemaker is indicated to facilitate the use of medications that are considered essential and for which there are no other suitable alternatives. Typically,

pacemakers in these patients are programmed to VVI or VVIR mode with a lower rate of 60 bpm. Pharmacologic therapy prevents extreme tachycardia.

Whatever the indication, a rate-responsive pacemaker can also provide an appropriate chronotropic response to the patient's physiologic needs. Current pacemakers use a variety of sensor-driven algorithms to increase the heart rate according to the patient's needs. The two most common sensors are accelerometers (based on movement) and minute ventilation monitors (based on thoracic impedance). Some devices can use both in combination. Optimal use of these devices requires routine office-based follow-up and reprogramming.

Regulation of Atrioventricular Nodal Conduction by Pacing

During AF, the rapid ventricular rate and irregular ventricular response contribute to deleterious hemodynamic effects. Irregular ventricular response can result in decreased cardiac output and increased wedge pressure independent of mean rate.[22] It has also been shown that cycle length variability has more influence on ventricular performance at faster heart rates. Ventricular pacing can result in concealed conduction into the AV node and His-Purkinje system, resulting in slowing of AV conduction. Algorithms have been developed that result in pacing slightly faster than the mean ventricular rate but with more regular ventricular response. Despite the expected benefits, the clinical trials that studied regularization algorithms yielded mixed and somewhat disappointing results. In the AF Symptoms Study, the effect of ventricular rate regularization on the end points of QOL, AF symptoms, and exercise capacity was evaluated. The investigators reported that ventricular rate regulation had a positive impact on reported symptoms, particularly palpitations, but did not have a significant impact on overall QOL or functional capacity.[23] Based on these studies, ventricular pacing during chronic rapid AF using regularization algorithms cannot be considered an alternative to atrioventricular junction (AVJ) ablation.

Atrioventricular Junction Ablation

It is not possible to achieve typical heart rate targets in many patients with chronic or paroxysmal AF with medical therapy alone. A resting heart rate of 80 bpm or less, 24-hour Holter average of 100 bpm or less, and heart rate of 120 bpm or less with modest activity are reasonable empiric goals for rate control but should be individualized based on symptoms. For patients in whom pharmacologic therapy cannot reach the desired rate targets and for whom there are no other alternatives, ablation of the AVJ and pacemaker implantation is the preferred strategy. Although more commonly used in patients with chronic AF, it is also performed in select patients with paroxysmal AF and in whom antiarrhythmic drugs (AADs) do not provide adequate rhythm control or in whom AF ablation is not the preferred option. These patients should receive a dual-chamber pacemaker with mode switch capability to maintain AV synchrony when the patient is in sinus rhythm. Otherwise, a standard single-chamber ventricular rate-responsive pacemaker is all that is need in patients with preserved LV function and chronic AF.

The benefits of AVJ ablation and pacemaker implantation are significant and were summarized in a meta-analysis covering 21 studies that included 1181 patients.[24] Echocardiographic parameters, such as ejection fraction (EF), have been shown to improve, as have the number of office visits, hospital admissions, and the New York Heart Association (NYHA) functional capacity. QOL measures, such as QOL scores, activity level, exercise intolerance, symptom frequency and severity, were also improved.[24]

Despite the expected advantages, there are some serious disadvantages that should be considered and explained to patients. The most obvious is that the procedure, unlike medications, is generally irreversible and renders the patient pacemaker dependent for life. The procedure itself is generally of low risk, nearly 100% successful, and usually not technically difficult. Patients are exposed to a small risk for thromboembolic events if their anticoagulation is stopped for the ablation procedure. There is a small risk for vascular complications, such as hematoma and pseudoaneurysm formation. A recurrence rate of 5% necessitating repeat ablation has been reported. Although practice patterns vary widely, there is growing evidence that pacemaker implantation and pacemaker generator replacements can be performed safely while patients are on therapeutic doses of coumadin.[25,26] Most importantly, AVJ ablation does not obviate the need for long-term anticoagulation. AV synchrony is not preserved, and in those patients with significant diastolic dysfunction, the expected symptomatic improvement may be lessened by the loss of the ''atrial kick.''

There was a concern that patients are at risk for sudden death after AVJ ablation and pacemaker implantation. Based on reported survival data, the risks for sudden death and total mortality are 2% to 6% at 1 year, respectively. Long-term (6 years) mortality is similar in patients undergoing pacing and ablation compared with continued medical

therapy, however.[27] The increased risk is thought to be attributable to bradycardia-dependent arrhythmias (torsades de pointes). Programming the lower rate of the pacemaker at 80 to 90 bpm for the first month has been shown to minimize this risk.[28] Another concern is the risks associated with lead dislodgement in these patients, who are usually pacemaker dependent. Because of these concerns, many physicians implant the pacemaker several weeks in advance of the ablation procedure. The use of a CRT device or standard RV pacing device in patients with significant LV dysfunction is discussed elsewhere in this review.

Paroxysmal or Persistent Atrial Fibrillation

The results of the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) trial do not apply to every subset of patients with AF; therefore, rhythm control remains an appropriate strategy in many patients with paroxysmal AF.[29] Such factors as symptoms, QOL, and the interplay between AF and comorbidities are important considerations when selecting a rhythm control strategy over a rate control strategy. For example, patients with diastolic dysfunction or valvular heart disease, such as aortic or mitral stenosis, do not tolerate AF and require aggressive rhythm control. Some patients are also at risk for developing CHF or tachycardia-induced cardiomyopathy. Despite their limited efficacy and potential for side effects, including proarrhythmia, AADs play an important role in the treatment of AF. Symptomatic bradycardia and bradycardia-dependent polymorphic ventricular tachycardia (VT) have been reported with sotalol, propafenone, and, rarely, with amiodarone. These medications can also exacerbate AV conduction disease, which is sometimes seen in patients with SND. Pauses seen immediately after termination of AF may also be prolonged by these drugs. Pacemakers can be used to facilitate the use of these medications.

There has been a great deal of interest in preventing AF in patients with paroxysmal AF by the use of device-based algorithms designed to address two aspects of the pathophysiology of AF: triggers and substrate. Clinical and experimental data suggest that AF may be triggered by atrial premature complexes (APCs). The atria of some patients may be more susceptible to AF because of inhomogeneous atrial refractoriness. These patients sometimes have atrial myopathy and often have atrial remodeling and enlargement. Overdrive pacing, multisite pacing (dual and biatrial), and alternate site pacing are device-based strategies designed to reduce AF burden by addressing these pathophysiologic mechanisms.

The Atrial Pacing Periablation for the Prevention of AF (PA[3]) trial was the first to examine the effect of pacing on the frequency and duration of AF in patients with medically refractory AF who were also being considered for AVJ ablation and pacemaker implantation.[30] These patients did not otherwise have a bradycardia indication for pacemaker implantation. This study showed that atrial rate-adaptive pacing does not prevent paroxysmal AF recurrence or reduce the frequency or duration of AF. The duration of this study was short term (3 months), and no specific overdrive pacing algorithms were used.

Overdrive pacing algorithms seek to reduce APCs and prevent pauses and bradycardia. Fixed-rate atrial pacing alone (lower rate of 70 bpm) has been shown to have no effect on AF burden. The major device manufacturers have algorithms that attempt to reduce AF recurrence and overall AF burden. The dynamic atrial overdrive algorithm (DAO; St. Jude Medical, Sylmar, California) is one example that has been shown to achieve a modest reduction in symptomatic AF burden[31] and has been given US Food and Drug Administration (FDA) labeling for this indication. The effect of this algorithm on total AF burden is unknown. Overall, several other pacing algorithms have been studied in a relatively small number of patients yielding, at best, inconsistent results on the effect on AF burden. Therefore, the clinical utility of these algorithms is limited.

Multisite atrial pacing involves placement of one lead in the high right atrium and another lead near the coronary sinus ostium (dual site) or into the coronary sinus to pace the left atrium (biatrial). Small nonrandomized studies show conflicting results in terms of reducing AF burden.[32,33] A prolonged P wave duration (>120 milliseconds) may be a necessary condition for multisite pacing to be beneficial compared with single-site pacing.[34] Larger clinical trials have not demonstrated a significant AF burden reduction. In one study, dual-site right atrial pacing reduced the recurrence risk for AF compared with standard pacing only in those patients treated with AADs.[35] Biatrial pacing seems to have a limited routine clinical application when used acutely in postoperative patients. A meta-analysis involving eight studies enrolling 776 patients reported a significant reduction in the risk for developing AF in patients after heart surgery who received temporary biatrial pacing using two epicardial wires.[36]

The premise of alternate-site atrial pacing is that more uniform interatrial conduction can be achieved by pacing at the interatrial septum. The resultant decrease in heterogeneity of atrial refractoriness is expected to reduce AF burden. Pacing can

be done from the high atrial septum (Bachmann's bundle) or the low atrial septum (near the coronary sinus os). The Atrial Septal Pacing Efficacy Clinical Trial (ASPECT) is a small study that demonstrated no reduction in AF burden with septal or Bachmann's bundle pacing sites compared with traditional right atrial appendage pacing sites, even when combined with atrial pacing algorithms.[37] Other studies have yielded conflicting results in a relatively small number of patients. The variability in results may be attributable to the difficulty in confirming the location or positioning the lead near Bachmann's bundle.

In summary, there are not enough long-term clinical data to support the recommendation of overdrive pacing algorithms, multisite pacing, or alternate-site pacing as a primary indication for pacemaker implantation in the management of AF. The results of some of the available studies have likely been confounded by the presence of ventricular pacing. In fact, data from the MOST suggest that for every 1% increase in ventricular pacing, there is a 1% decline in the benefit of dual-chamber atrial-based pacing in terms of AF.

Cardiac Resynchronization Therapy and Atrial Fibrillation

CRT, also known as biventricular pacing, is an important treatment modality in patients who have moderate and advanced CHF. The current ACC/AHA/HRS guidelines indicate that patients with a left ventricular ejection fraction (LVEF) less than or equal to 35%, sinus rhythm, and NYHA class III or ambulatory class IV symptoms despite recommended optimal medical therapy and who have cardiac dyssynchrony (currently defined as a QRS duration greater than 120 milliseconds) should receive CRT. Many patients who are candidates for CRT also have a history of paroxysmal or chronic AF. In patients who were candidates for CRT defibrillators (CRT-Ds), a history of paroxysmal AF is associated with as much as a 25% incidence of AF within the first 6 months from the time of implantation. Patients with a CRT indication are also at high risk for developing AF. The prevalence and incidence of AF increases with increasing severity of heart failure.[38] The risk for AF may be as high as 50% in patients who have class IV CHF.[39] In fact, either condition is known to predispose to the other condition. There are several issues to examine when considering the benefits of CRT in patients who have chronic and paroxysmal AF.

First, in those patients with existing CRT devices, what are the hemodynamic and clinical impacts of the development of AF? The effects parallel those that are seen in patients who have heart failure but do not have a CRT device. The most immediate effect on AF of biventricular pacing is the loss of AV synchrony, possibly leading to decompensated heart failure. In one small study of acute hemodynamics, systolic function as measured by dP/dT was worse in patients who had heart failure with RR-irregularity and rapid ventricular rates (120 bpm) but was better when ventricular rates were regular at approximately 120 bpm or when ventricular rates were in the normal range (80 bpm).[40] The timing of ventricular pacing is based on sensed or paced atrial events. AV synchrony can be maintained only during sinus rhythm. Most CRT devices have algorithms that promote biventricular pacing even during AF, despite the loss of AV synchrony. These algorithms are imperfect, and despite device-reported biventricular pacing of greater than 90%, clinical benefits are less certain. This is attributable to variable degrees of fusion between the intrinsic conduction and the paced ventricular complex. Furthermore, these algorithms tend to result in pacing rates that are, on average, faster than during intrinsic conduction (up to the programmed upper pacing rate), raising the concern of tachycardia-induced cardiomyopathies.

Does CRT reduce the likelihood of developing AF? As in patients with normal LV function, the benefits of biventricular pacing in patients with a CRT device in terms of the reduction of AF burden are mixed and uncertain. In a small cohort study, the annual incidence of AF was 2.8% in the CRT group and 10.2% in the control group ($P = .025$).[41] Analysis of data from the Cardiac Resynchronization in Heart Failure Trial did not show that the incidence of AF was affected by CRT, however.[42] Most studies do not show any benefit of CRT pacing on the incidence of AF.

What is the effect of chronic AF on CRT benefit? Large-scale clinical trial data elucidating the benefits of CRT in patients with AF are limited. The Multisite Stimulation in Cardiomyopathies (MUSTIC) study reported on a small number of patients with chronic AF who received a CRT device. Patients in the sinus rhythm group and the AF group showed improvements in heart failure class, in the 6-minute walk test results, and in the need for hospitalization.[43] The improvement was greater in the sinus rhythm group. In a recent prospective observational study, the benefit of CRT in patients who had heart failure with AF was similar to that seen in patients who had heart failure without AF, even at 3 years of follow-up.[44] In a study by Molkoek and colleagues,[45] patients with normal sinus rhythm and with chronic AF derived benefit from CRT. Heart failure class, QOL score, and exercise

capacity were improved in both groups. In the group with AF, those who had a previous AVJ ablation derived the most benefit. Those patients who had not previously had an AVJ ablation did not show an improvement in QOL scores at 6 months. There were more nonresponders in the AF group than in the sinus group (36% versus 20%; $P<.05$). The Atrioventricular Junction Ablation Followed by Resynchronization Therapy in Patients with CHF and AF (AVERT-AF) study is a prospective, randomized, double-blind, multicenter trial that is going to test the hypothesis that AVJ ablation followed by biventricular pacing significantly improves exercise capacity and functional status as compared with pharmacologic rate control in patients with chronic AF and depressed EF, regardless of rate or QRS duration. Enrollment is scheduled to be completed in 2008.[46]

Another unresolved issue is the timing of implantation of a CRT-D device versus a standard pacemaker relative to AVJ ablation. Given that there can be an improvement of the LVEF in some patients after AVJ ablation, some practitioners implant a standard dual-chamber pacemaker in patients with borderline LVEF (30%–35%). The EF is then re-evaluated after a specific period of time (ie, 6 months), and the need for a CRT device is determined.[47] Others elect to implant a CRT-D or CRT pacemaker without defibrillation capability (CRT-P) at initial implantation to avoid the need for another procedure within a relatively short period.

A CRT-P is a consideration in patients with a more preserved EF. The Post Atrioventricular Nodal Ablation Evaluation (PAVE) trial has provided some important insights into the type of pacing that is best in this group of patients. This trial compared chronic biventricular pacing with RV-only pacing in patients undergoing AVJ ablation for the management of AF with rapid ventricular rates. The mean LVEF was 46% $\pm$ 16% in the two groups. The mean LVEF in the RV pacing group was 45% at the onset of the study and 41% at 6 months ($P<.05$).[48] There are no guidelines for the use of a CRT-P in patients with moderate LV dysfunction who are undergoing AVJ ablation.

Atrial Therapies

Some implantable devices are capable of delivering electrical therapy to manage AF and atrial flutter. These therapies include antitachycardia pacing with burst and ramp pacing in the atrium, high-frequency (50 Hz) burst pacing, and atrial defibrillation. All three have been successfully used in terminating ATs and atrial flutter.

Pacing therapies are more suitable for relatively slow AT with a regular cycle length. They are not well suited for AF. AF has been known to organize into atrial flutter or AT that may be more susceptible to pace termination, however. There is no evidence that 50-Hz burst pacing has any significant efficacy in terminating AF or in reducing the overall burden of AF in humans. There are conflicting data with respect to the effect that these therapies have on the overall burden of AF. In the ATTEST trial, prevention and termination algorithms were tested prospectively and failed to show a reduction in AF burden.[49] In another prospective trial, atrial therapies resulted in a reduction of AT burden from a mean of 58.5 to 7.8 hours per month. This study enrolled patients with a standard ICD indication and atrial tachyarrhythmias.[50]

Stand-alone implantable atrial defibrillators are not used clinically and are not currently marketed in the United States. ICDs with atrial defibrillation capability have been developed, but their use is limited by the painful nature of the shock. The pain threshold for an atrial defibrillation shock is far less than the threshold for successful AF. The ADSAS 2 study demonstrated that premedication with oral midazolam has been effective in mitigating some of the perceptions of pain.[51] This option can only be used in select highly motivated patients.

Currently, there are no guidelines that advocate using devices with these features as a primary means to manage ATs. Most physicians use these features as adjunctive therapy in patients with other standard indications for pacemakers or ICDs. Overall, they have limited utility.

SUMMARY

The role of pacemakers in the management of patients with AF and in the prevention of AF has been extensively studied. Based on well-designed prospective clinical trials, only a few of these strategies can be recommended for routine clinical use in related subpopulations. From the available studies, several key considerations are apparent:

1. The definition of physiologic pacing has evolved. It is no longer enough to maintain AV synchrony with a dual-chamber atrial-based pacemaker. A single-chamber ventricular-based pacemaker should be avoided in patients with paroxysmal AF and SND. When possible, intrinsic AV conduction should be promoted to minimize the deleterious effects of RV pacing. Therefore, mode selection is important (AAI$\leftarrow\rightarrow$DDD, DDI, or DDD with long AV delays). Unresolved questions include the

maximum hemodynamically acceptable AV delay and the optimal site for RV pacing.[52]

2. In appropriate patients, pacemaker implantation and AVJ ablation provide clinical and mortality benefits. The procedure should be considered in any patient with suboptimal rate control and in any patient who is at risk for developing or has developed tachycardia-mediated cardiomyopathy. Although this procedure is most often done in patients with chronic AF, it is also appropriate for some patients with paroxysmal AF.
3. The benefits of pacing in patients with a CRT device may be maximized in those patients with AF who have undergone AVJ ablation. In patients with chronic AF who are receiving a CRT device, AVJ ablation can be recommended if adequate rate control to allow LV pacing cannot be achieved by medical therapy. This issue is unresolved in patients with paroxysmal AF who receive a CRT device.
4. Pacing in chronic AF to promote ventricular rate regularization has limited clinical value, and careful attention should be paid to overall adequacy of rate control. An average ventricular rate greater than the upper pacing limit may lead to tachycardia-mediated cardiomyopathy and signals the need for more aggressive rate control or AVJ ablation.
5. Pacing algorithms that attempt to prevent AF have limited value. As a sole indication, they are not widely accepted or recommended as a primary indication for pacemaker implantation in patients with paroxysmal or persistent AF.[53]
6. Multisite and novel site pacing strategies do not have broad clinical applications at this time. An exception is the use of short-term multisite pacing at the time of cardiac surgery.

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