Pacing therapy for prevention of atrial fibrillation

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The role of permanent pacing for the prevention of atrial fibrillation is reviewed. A moderate decrease in the incidence of acute and chronic atrial fibrillation has been seen with atrial pacing compared with ventricular pacing, especially in patients with sinus node dysfunction based on a meta-analysis of clinical trials. A variety of different pacing algorithms have been studied in small numbers of patients for only short durations of time and have shown an inconsistent effect on different measures of atrial fibrillation burden. The interatrial septum or Bachmann's bundle has been shown in some, but not all, studies to have a beneficial effect on reducing the incidence of atrial fibrillation. Less well studied is the combined benefit of alternate site atrial pacing combined with atrial fibrillation prevention pacing algorithms. Device measurement of the duration of atrial fibrillation appears to be an accurate measure of disease burden, and preliminary evidence suggests that atrial fibrillation burden is associated with an increased risk of stroke and death. Future studies are needed to demonstrate the long-term efficacy of device algorithms for the prevention or termination of atrial fibrillation.

KEYWORDS Pacing; Pacemaker; Atrial fibrillation; Antitachycardia pacing

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Atrial fibrillation (AF) is the most common sustained arrhythmia seen in clinical practice. Recent large multicenter studies have shown the limitations of strategies focused on maintenance of sinus rhythm with antiarrhythmic drugs. It is unlikely that ablation will become an option for many patients in the near future, particularly for elderly patients. Alternative strategies for the treatment of this problem, particularly for the elderly, should be evaluated. The purpose of this paper is to review the design and summarize the data on the role of pacing to prevent AF.

Pacing mode and AF

The earliest studies of pacing and AF consist of a large number of nonrandomized, noncontrolled observational studies that suggested that ventricular pacing was associated with an increased risk of AF compared with atrial pacing. These studies led to the design and implementation of large, multicenter prospective clinical trials comparing the role of atrial pacing (either in the AAI(R) or DDDR mode) to the VVI(R) mode. A meta-analysis of these trials, which included 35,000 patient-years of follow-up, showed that atrial pacing is superior to ventricular pacing and resulted in a significant reduction in AF (HR 0.80, 95% confidence interval [CI] 0.72–0.89, $P = .00003$). There was a suggestion of a greater benefit of atrial pacing in patients with sinus node dysfunction, but these results must be interpreted cautiously. An important consideration that may have limited the benefit of atrial pacing in the prevention of AF is the observation that most patients in these trials received DDD pacemakers, and the resultant increase in right ventricular pacing may have counterbalanced the reduction in the incidence of AF.[1]

Retrospective analysis of data from the MOST (Mode Selection Trial) trial showed that the risk of AF increased linearly with the cumulative percentage of ventricular pacing from 0% to 85% in both the DDDR (HR 1.36, 95% CI 1.09–1.69) and VVIR (HR 1.21, 95% CI 1.02–1.43) groups. The model results were unaffected by adjustment for known baseline predictors of AF.[2] Another analysis from the MOST trial emphasized the clinical impact of device measurement of atrial arrhythmia episodes. In this study, the presence of any atrial high-rate episodes was an independent predictor of total mortality (HR for atrial episodes compared with no episodes over a median follow-up of 27 months was 2.48, 95% CI 1.25–4.91, $P = .0092$) and for death or nonfatal stroke (HR 2.79, 95% CI 1.51–5.15, $P = .0011$).[3] These observations have been extended to the increased risk of arterial embolism for AF episodes lasting longer than 1 day.[4] Analysis of the data from the Cardiac Resynchronization in Heart Failure Trial did not show any benefit of biventricular pacing on the development of AF.[5] The accuracy of device measurement of AF episode frequency and duration has been validated by a number of studies comparing the accuracy of device atrial arrhythmia detection to Holter monitoring. It is essential that the devices be programmed appropriately to avoid far-field R-wave oversensing and atrial undersensing to ensure a high sensitivity and specificity for AF detection. A large ongoing clinical trial of elderly hypertensive patients undergoing pacemaker implantation for standard bradycardia indications is assessing the value of asymptomatic atrial high-rate events for the prediction of stroke and other vascular events.[6]

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Atrial pacing for prevention of AF

There are few studies evaluating the mechanism(s) by which atrial pacing might prevent the development of AF. Experimental and clinical studies suggest that AF may be controlled through either elimination or suppression of triggers (premature atrial complexes, or PACs) or by alteration of atrial substrate (inhomogenous atrial refractoriness promoting reentrant or mother wavelets). Atrial pacing may potentially prevent AF by pacing suppression of triggers, reducing dispersion of atrial refractoriness (e.g., multisite pacing), and continuous atrial pacing at selected sites to decrease total atrial activation time.

Preventive pacing algorithms are primarily designed to decrease premature atrial contractions and to prevent pauses. The results of trials of fixed-rate atrial pacing have not been positive. The Atrial Pacing Peri-Ablation for Paroxysmal Atrial Fibrillation Trial studied the effect of DDD pacing at a lower rate of 70 bpm compared with DDI pacing at 30 bpm before planned atrioventricular junction ablation in 97 patients. The patients in this study had at least three episodes of AF a year and were refractory or intolerant to medical therapy. Diagnostic data were collected for 3 months after a 2-week period of antiarrhythmic drug stabilization and lead maturation. Atrial pacing significantly reduced the number of PACs from baseline but had no effect on AF prevention when measured as the time from first episode of AF recurrence.[7] In a second part to this study, 76 patients were studied after AV Junction (AVJ) ablation and were randomized to DDDR or VDD pacing in a crossover study design for 3 months. There was no difference in the time to first AF recurrence, AF burden, or progression to chronic AF.[8] Criticisms of this study include the failure of the pacing algorithms to result in atrial pacing more than 90% of the time, the lack of stored electrograms, a high crossover rate, and the failure to use an endpoint that measured the burden of AF.

A variety of algorithms exist to ensure constant atrial pacing capture. These include the dynamic atrial overdrive algorithm (DAO; St. Jude Medical, Sylmar, CA), which increases the atrial pacing rate when two P waves (consecutive or nonconsecutive) are sensed in a window. The atrial preference pacing (Guidant, St. Paul, MN) algorithm increases the atrial pacing rate when sensed atrial events occur. Other pacing algorithms include atrial rate stabilization (Medtronic, Minneapolis, MN), which paces after a PAC to avoid short-long cycles, and post–mode switch overdrive pacing, which paces at an elevated rate for a defined period of time after a mode-switch event, and atrial pacing preference, which increases the pacing rate when an atrial event is sensed. More specific details about each of the individual algorithms can be found in the manufacturers' technical manuals.

Importantly, these algorithms have not been studied over long periods of time. Potential concerns include patient discomfort from high-rate atrial pacing, risk of tachycardia-induced cardiomyopathy, and time-related failure of the algorithm due to disease progression. Finally, another potential concern is the deleterious effects on ventricular function of high-rate ventricular pacing, which may detract from the benefit of high-rate atrial pacing. The device companies have paid attention to these observations and developed algorithms to minimize the amount of ventricular pacing. It is possible that if these pacing trials are repeated with newer devices incorporating these algorithms, a greater benefit of preventive pacing will be observed.

Results of clinical trials with these algorithms have been mixed. Several short-term studies have shown no beneficial effect of overdrive pacing on the overall incidence of AF. A large study measured the effect of the DAO algorithm on symptomatic AF randomized 399 patients to either DDDR pacing with the DAO algorithm on compared with DDDR pacing with the algorithm off.[9] Symptomatic AF was measured as the days of electrocardiogram-documented episodes of AF. This definition biased the results against the algorithm because any day with more than 20 seconds of AF was counted as "1 day of AF." The DAO group demonstrated a 25% reduction in AF burden. The absolute risk reduction diminished over time, from 1.25% at 1 month to 0.36% at 6 months. Additional benefit was noted by a progressive reduction in the number of episodes of AF after 6 months of follow-up.[9] Other studies have not been able to demonstrate any significant benefit from atrial pacing for prevention of AF, including the Atrial Septal Pacing Clinical Efficacy Trial and the PIPAF (Pacing in Prevention of AF) trials.[10,11] In an analysis of the PIPAF trial, the greatest benefit to atrial overdrive pacing was noted in the group of patients who had the least amount of concomitant ventricular pacing.

Multisite pacing to prevent AF

To decrease total atrial activation time, dual-site right atrial pacing was pioneered in patients with prolonged intra-atrial conduction time. Dual-site pacing may be accomplished by pacing from the high right atrium and the coronary sinus os or from two sites in the right atrium, one site typically near the coronary sinus ostium. In several studies, no benefit to dual-site pacing compared with single-site right atrial pacing has been demonstrated.[12,13] The only subgroup that may benefit from dual-site pacing is the group of patients treated with antiarrhythmic drug therapy. The utility of this approach is limited by the need to connect the two atrial leads together and the concern about far-field R-wave oversensing resulting in inhibition of atrial pacing or inappropriate atrial pacing. It is not known how dual-site pacing compares with pacing from alternative right atrial pacing sites alone.

Alternative pacing sites

Pacing from the right atrial septum, Bachmann's bundle, or the low interatrial septum near the triangle of Koch or coronary sinus has been studied. Studies of septal pacing show decreased P-wave duration compared with single-site right atrial pacing.[14] Several studies of atrial septal pacing have shown a decrease in AF frequency and burden com-