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Prevention of Recurrent Atrial Fibrillation With Chronic Dual-Site Right Atrial Pacing

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Objectives. **We investigated 1) the feasibility, safety and efficacy of multisite right atrial pacing for prevention of atrial fibrillation (AF); and 2) the ability of atrial pacing in single- and dual-site modes to increase arrhythmia-free intervals in patients with drug-refractory AF.**

Background. **We recently developed and applied a novel technique of dual-site right atrial pacing in an unselected group of consecutive patients with AF requiring demand pacing. A prospective crossover study design was used to evaluate single- and dual-site right atrial pacing modes.**

Methods. **The frequency of AF during the 3 months before pacemaker implantation was analyzed. Consecutive consenting patients underwent insertion of two atrial leads and one ventricular lead with a DDDR pulse generator. Patients were placed in a dual-site pacing mode for the first 3 months and subsequently mode switched to single site pacing for 3 months. Mode switching was repeated at 6-month intervals thereafter.**

Results. **Atrial pacing resulted in a marked decline in AF recurrences ($p < 0.001$). During dual-site pacing with an optimal drug regimen, there was no AF recurrence in any patient compared with five recurrences in 12 patients during single-site pacing ($p = 0.03$). The mean (±SD) arrhythmia-free interval before pacing (14 ± 14 days) was prolonged with dual- (89 ± 7 days, $p < 0.0001$) and single-site pacing (76 ± 27 days, $p < 0.0091$). Symptomatic AF episodes showed a declining trend during dual- and single-site pacing compared with those during the preimplantation period ($p = 0.10$). Mean antiarrhythmic drug use for all classes declined from 4 ± 1.9 drugs before implantation to 1.5 ± 0.5 ($p < 0.01$) drugs after implantation. Twelve (80%) of 15 patients remained in atrial paced rhythm at 13 ± 3 months.**

Conclusions. **We conclude that multisite right atrial pacing is feasible, effective and safe for long-term application. Atrial pacing significantly prolongs arrhythmia-free intervals in patients with drug-refractory paroxysmal AF. Dual-site right atrial pacing may offer additional benefits and should be considered either as the primary mode or in patients unresponsive to single-site pacing.**

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Atrial fibrillation (AF) and flutter have the highest prevalence rates of all cardiac arrhythmias. Therapeutic control has been generally difficult. Despite widespread application of antiarrhythmic drug therapy, arrhythmia recurrence is common, accounting for repetitive hospital admissions for modification of antiarrhythmic regimens, anticoagulation and electrical cardioversion. In many reports, up to 50% of patients may experience a relapse during a given drug regimen within 1 year (1). Transthoracic and, more recently, internal atrial defibrillation shocks have been used for arrhythmia termination (2,3). Defibrillation shock therapy is usually painful and requires anesthesia as well as cardiac monitoring for patient comfort and safety. Thus, it cannot be applied with great frequency and requires that patients have the ability to maintain sinus rhythm for prolonged periods. Interventions such as defibrillation therapy are usually withheld after a few attempts in most patients with recurrent AF. As a result, chronic AF ensues. The efficacy of demand atrial pacing in reducing the frequency of recurrent AF has been suggested (4) in some patient groups with bradycardia-dependent AF. Biatrial pacing has been reported (5) to be associated with low recurrence rates of atrial flutter and fibrillation in patients with severe interatrial conduction disturbances. However, no prospective study has verified the benefits of single- or dual-site atrial pacing in unselected patients with AF. Even more uncommon is a quantitative assessment of this benefit. Although atrial defibrillators are being considered to revert recurrences of AF, shock therapy remains painful. Reducing AF recurrence rates is essential to successful use of such devices. Quantitative assessment of arrhythmia-free intervals bears directly on their feasibility.

We recently developed and applied a novel technique of dual-site atrial pacing, wholly from the right atrium, and applied it to an unselected consecutive series of patients with drug-refractory AF. A prospective crossover study was performed that compared recurrence of arrhythmia in a dual-site right atrial pacing mode with single-site high right atrial pacing

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as well as in each pacing mode with a lead-in control period. The study design was used to evaluate the comparative and absolute value of either pacing method. The clinical results of this study are reported herein.

Methods

Patient selection. Patients included in this report fulfilled the following criteria: 1) They had symptomatic drug-refractory AF; 2) all patients had to have experienced two or more episodes of sustained AF in the 3-month period before device insertion; 3) coexisting bradyarrhythmias in the absence or presence of drug therapy requiring rate support were present; 4) written informed consent for insertion of two atrial leads was obtained.

Study design. Patients with symptomatic refractory AF despite antiarrhythmic drug therapy were fully evaluated for individual recurrences of arrhythmia over the 90-day period before pacemaker insertion. This period was the lead-in drug treatment phase performed on a retrospective basis (Fig. 1). A complete record of each documented episode of onset, duration, treatment and termination was obtained. Consecutive consenting patients meeting enrollment criteria underwent implantation of two atrial leads and one ventricular lead connected to a dual-chamber rate-responsive pacemaker. Atrial pacing was performed at implantation from the high right atrium and coronary sinus ostium locations individually and in the dual-site right atrial pacing mode.

Study definitions. The following definitions were used: 1) *paroxysmal arrhythmia* = sustained arrhythmic episode >30 s in duration, spontaneously terminating before ≤7 days; 2) *chronic arrhythmia* = sustained arrhythmic episode >1 month in duration with a history of episodes ≥7 days in duration; 3) *sustained arrhythmia* = arrhythmic episode ≥30 s in duration; 4) *recurrence* = electrocardiographically documented episode of sustained AF or recurrence of symptoms associated with previously electrocardiographically documented AF.

Study protocol. Implantation variables for pacing threshold, sensing and lead impedance were obtained for each atrial site, in the dual-site mode and at the right ventricular apex. After device implantation, concomitant antiarrhythmic therapy was established for prevention of AF. Early recurrences of AF were evaluated for compliance with the prescribed pacing and drug regimen as well as the ability to maintain continuous atrial pacing. Failure to comply or inability to maintain continuous atrial pacing resulted in adjustment of the drug regimen. Patients were programmed to the dual-site pacing output using polarity programming with the pacemaker. DDDR pacing was used with a lower rate limit of 80 or 90 beats/min to ensure consistent atrial pacing at rest. Rate response was clinically selected to ensure atrial pacing during activity.

After hospital discharge, patients entered the crossover trial. Dual-site right atrial pacing was programmed for the initial 90 days and drug therapy continued (combination therapy phase 1). At the completion of this period, consenting patients underwent device reprogramming to single-site high right atrial pacing alone for the next 90 days (combination therapy phase 2). Patients with sustained recurrences despite compliance with the drug and pacing regimen were deemed to have completed the individual phase. They underwent cardioversion and reprogramming to the other pacing mode and entered the next phase of therapy.

The primary end points were the number of patients with recurrence of AF and the time interval to the first sustained recurrence of AF despite compliance with the treatment regimen in the lead-in drug phase as well as each combination treatment phase. Secondary end points analyzed symptom-free intervals, antiarrhythmic drug therapy requirement and need for cardioversion. An additional analysis of these intervals was performed that included the drug optimization period with implantation as the onset of phase 1. The safety of the technique was assessed using standard categories of morbidity and mortality for the perioperative 30-day period as well as for the longer term follow-up for each combination treatment phase.

Device implantation. Standard techniques for insertion of a dual-chamber pacemaker system were used. Percutaneous subclavian vein cannulation as well as cephalic vein isolation was attempted in all patients. Subclavian vein entry was necessary in all patients for one or more leads. The right ventricular apical lead (Medtronic model 5024 or 4058, Medtronic Inc.) was positioned first under fluoroscopic guidance. The first atrial pacing electrode (Medtronic model 4058) was then positioned using a curved stilette with primary and secondary curvatures. Initially, the lead was passed into the coronary sinus under fluoroscopy and the lead position verified by sensed electrograms and paced electrocardiographic (ECG) configuration. The lead was then withdrawn to the coronary sinus ostium, and a secondary tip curvature of the stilette used to lodge it at the rim of the ostium, generally posteriorly. The lead was fixed at this site, and pacing and sensing thresholds were obtained. Paced P wave configuration was consistent with ostial pacing in this location (inverted P waves in leads II, III and aVF with a shorter PR interval than sinus rhythm). The second atrial lead (Medtronic model 4058) was then passed and fixed in the high right atrium, usually in the right atrial appendage under fluoroscopic control. In postoperative surgical patients with an amputated appendage, it was fixed in the high lateral right atrium. Bipolar pacing thresholds were obtained for all three leads. The two atrial lead tip electrodes were then cross connected to form a bipole using a Medtronic model 5866-38M Y connector with the high right atrial lead as the cathodal electrode and the coronary sinus lead as the anodal electrode. Bipolar pacing variables in the dual-site atrial pacing mode were then obtained. The right ventricular lead was inserted in the ventricular port of a Medtronic model 7086 Elite II DDDR pacemaker (Fig. 1). The in-line bipolar lead from the Y connector was inserted into the atrial port of the pacemaker. The pulse generator was then placed in a prepectoral pocket and the pocket closed using standard techniques.

Figure 1. A, Chest radiograph (posteroanterior view) of the pacemaker generator and the three pacing/sensing leads. The ventricular lead is seen with its tip at the apex of the right ventricle. The two atrial leads are seen at the right atrial appendage (superior lead) and at the coronary sinus ostium (inferior lead). **B,** Lateral view of the pacing system. The coronary sinus ostium lead is located posteriorly and inferiorly; the high right atrial lead is seen located superiorly and anteriorly; and the ventricular lead is at the right ventricular apex.

Using the bipolar pacing mode from the pulse generator, simultaneous dual-site atrial pacing using the tip electrodes of both atrial leads could be established and was electrocardiographically verified. The paced P wave was biphasic in configuration and had a terminal negative component in the inferior leads. In the programmable unipolar mode, single-site atrial pacing from the high right atrium could be established. On completion of the procedure, the pacemaker was programmed to bipolar atrial and ventricular pacing in the DDDR mode. The lowest atrial and ventricular rate was programmed to 80 or 90 beats/min to establish continuous pacing at rest. Rate response was selected at levels likely to establish continuous pacing during exercise. Drug regimen selection was then performed in the postimplantation period to maintain continuous atrial pacing. Drugs used were based on previous patient experience and utilized previously tolerated but ineffective agents for AF suppression.

Patient follow-up. Patient follow-up after hospital discharge was designed to assess arrhythmia control and device system performance. Postoperative clinic visits with a standard 12-lead ECG were scheduled after hospital discharge at 1 week, 1 month, 3 months and every 3 months thereafter. Patients were instructed to report symptoms of palpitations, chest pain, dyspnea or other symptoms consistent with arrhythmia recurrence in interval periods. Patients with symptoms were provided transtelephonic event monitors. Twenty-four hour ambulatory ECG monitoring was performed after 1 month of each combination therapy in all patients. Device system performance was assessed using monthly transtelephonic monitoring and device interrogation and assessment of all pacing variables at each clinic visit. Effective single- and dual-site atrial pacing was confirmed using the ECG configuration of the P wave as well as sensed electrogram variables.

Statistical analysis. A minimal follow-up period of 1 year was required of all study patients. Patients were censored from follow-up at death or device system explantation. Comparison of primary and secondary end points was performed using appropriate statistical tests (e.g., paired *t* test, McNemar's test and, for repeated measures analysis of variance (ANOVA), the Wilks lambda statistic).

Results

Patients. Fifteen patients (nine men, six women; mean [±SD] age 68 ± 12 years, range 41 to 81) with AF and bradyarrhythmias warranting permanent pacing were enrolled in the study. Coronary artery disease was present in six patients, hypertension in one, congenital heart disease in one and cardiomyopathy in two. The primary indication for pacing was sick sinus syndrome in six patients, drug-induced bradyarrhythmias in three, conduction system disease in three and neurocardiogenic syncope due to bradycardic mechanisms in three. The mean left atrial diameter on echocardiographic measurement was 3.7 ± 0.6 cm, and the mean left ventricular ejection fraction was 49 ± 12% (Table 1).

Previously unsuccessful drug trials of class I and III antiar-

Table 1. Demographic and Clinical Data, Antiarrhythmic Drug Use Before and After Pacemaker Implantation and Clinical Outcome With Respect to Arrhythmia Recurrence in 15 Study Patients

Pt No./ Gender	Age (Yr)	Clinical Arrhythmia	Arrhythmia Frequency (episodes/mo)	Previous Drugs Used	Cardiac Disease	LA Diameter (mm)	LVEF (%)	Pacemaker Indication	Postop Drug Therapy	Outcome	
										Phase 1	Phase 2
1/M	41	PAF	1	S,D,PCA,PR	None	28	60	SSS	PR	SR	SR
2/M	73	PAFL/AF	4	S,A,PCA,DIG,PP	CAD	30	36	AVB	S,DIG,PP	SR	SR
3/M	79	CAF	30	PCA,D,DIG	DCM	38	15	AVB	PCA,DIG	SR	AF
4/F	55	PAF	8	Q,PCA,D,DIG	None	30	60	SSS	DIL	SR	SR
5/F	78	PAFL	30	Q,PCA,DIG,V	CAD	35	50	SSS	NONE	SR	Refused mode change
6/F	77	CAF	30	S,PCA,PR,DIG	HT	50	60	DB	S	SR	SR
7/M	77	PAFL/AF	1	None	None	32	32	CSH	None	SR	Refused mode change
8/F	76	PAFL/AF	30	PCA,Q,S,D,PR,DIG	None	35	50	SSS	D,DIL,DG	SR	AF
9/M	72	PAF/AFL	2	D,Q,PP	CAD	38	50	SSS	D,DIG	SR	AF
10/M	57	PAFL	1	Q,PCA,V,D	HCM	35	50	HCM	ME,V	SR	SR
11/M	63	PAFL/AF	30	D,PCA,PR,S	CAD	40	40	SSS	D	SR	AF
12/F	66	PAFL/AT	30	PCA,D,V,DIL,ME	CHD	40	50	DB	ME	SR	AT
13/M	81	PAFL	2	ME	CAD	40	39	NCS	None	SR	SR
14/M	57	PAF	1	PP	None	36	60	AVB	I	SR	SR
15/F	72	PAF	30	A,PCA,V,DIG,D,PR	CAD	50	50	DB	A,V,DG	SR	Refused mode change

A = amiodarone; AF = atrial bifibrillation; Arrhythmia Frequency = number of sustained symptomatic episodes/month before pacemaker implantation AT = atrial tachycardia; AVB = atrioventricular block; CAD = coronary artery disease; CAF = chronic atrial fibrillation; CHD = congenital heart disease; CSH = carotid sinus syncope; D = disopyramide; DB = drug-induced bradycardia; DCM = dilated cardiomyopathy; DIG = digoxin; DIL = diltiazem; F = female; HCM = hypertrophic cardiomyopathy; HT = hypertension; LA = left atrial; LVEF = left ventricular ejection fraction; M = male; ME = metoprolol; NCS = neurocardiogenic syncope; PAF = paroxysmal atrial fibrillation; PAFL = paroxysmal atrial flutter; PCA = procainamide; Postop = postoperative; PP= propanolol; PR = propafenone; Pt = patient; Q = quinidine; S = sotalol; SR = sinus rhythm; SSS = sick sinus syndrome; V = verapamil.

rhythmic agents for AF averaged 2.7 ± 1.6 agents. All patients had frequent recurrent AF, and 14 had one or more documented episodes of AF within 1 month before pacemaker implantation. The average interval from the last documented episode of AF to implantation was 10.6 ± 21.7 days. Before implantation, the mean frequency of AF episodes, according to documented ECG strips, was 1.5 ± 1.7 episodes/week; the mean arrhythmia-free interval was 14 ± 14 days, and the mean frequency of symptoms (presyncope, dyspnea or palpitations) was 3.1 ± 4.1 episodes/week. Antiarrhythmic agents used in these patients before pacemaker insertion included quinidine, propafenone, disopyramide, sotalol, amiodarone and procainamide. Digoxin and class II or IV agents had also been used in combination with class I or III drugs in selected patients. Combinations used verapamil (two patients), diltiazem (two patients) and beta-adrenergic blocking agents (four patients) with class I or III drugs. All patients received a Medtronic model 7086 Elite II pacemaker and model 4058 or 5024 leads. Subclavian vein access was used alone in 4 patients, whereas combined subclavian and cephalic vein insertion was used in 11. Figure 1 is an illustration of the device system in situ. Note the three electrode systems with the location of the atrial leads in the anterior high right atrial and the posterior coronary ostial sites. A Y connector is seen in the pectoral pocket with the generator.

Three patients were discharged, without antiarrhythmic drug therapy, in the DDDR pacing mode using dual-site atrial pacing alone for AF prevention. Twelve patients were discharged with concomitant antiarrhythmic therapy that included class IIIA agents in four patients, class IC agents in one, class II agents in five, class III agents in three, class IV in five and digoxin in four. Drug combinations were used in six patients. Three patients initially refused mode switching from the dual-site to the single-site atrial pacing mode at 3 months of follow-up because of a perceived improvement in clinical status. All patients are receiving warfarin or aspirin therapy.

Pacing system performance. The mean pacing threshold at the high right atrium at implantation was 1.18 ± 0.32 V, and that at the coronary sinus ostium was 1.37 ± 0.25 V ($p = 0.06$) at a pacing pulse width of 0.5 s. The sensed P wave amplitude at the high right atrium was 2.78 ± 1.71 mV, and that at the coronary sinus ostium was 2.26 ± 0.82 mV ($p = 0.35$). The mean pacing threshold in the dual atrial pacing mode was 1.56 ± 0.52 V, significantly higher than that at the high right atrium ($p = 0.02$) but not at the coronary sinus ostium ($p = 0.22$) (Fig. 2A). The sensed P wave amplitude in dual-site mode was 2.58 ± 0.95 mV. The mean pacing threshold in the right ventricle was 0.61 ± 0.24 V, and the sensed R wave amplitude was 14.6 ± 6.5 mV.

Figure 2B shows the atrial pacing thresholds of the lead system at the last (mean 8 months) follow-up visit. Note that long-term pacing thresholds are higher in the dual-site mode ($p < 0.01$). The pacemaker pulse generator was programmed to a low rate of 80 beats/min (14 patients) or 90 beats/min (1 patient). In one additional patient, the device initially programmed at 80 beats/min was reprogrammed to the higher rate during follow-up. The DDDR mode was used in all patients with an activity threshold of medium in 14 patients and low in 1. The rate response used was seven in all patients. The upper rate limit was 130 or 140 beats/min in all patients.

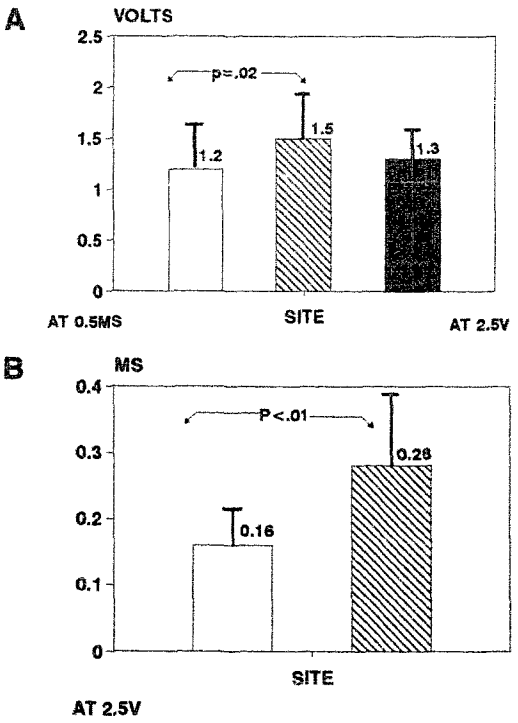

Figure 2. A, Atrial pacing thresholds in volts at implantation in the right atrial appendage **(dotted column)**, coronary sinus ostium **(solid column)** and the dual-site pacing mode **(hatched column).** The pacing threshold with the dual-site mode is significantly higher than that for the right atrial appendage. **B,** At a mean follow-up period of 8 months, the pacing threshold with dual-site pacing is significantly higher than that at the right atrial appendage.

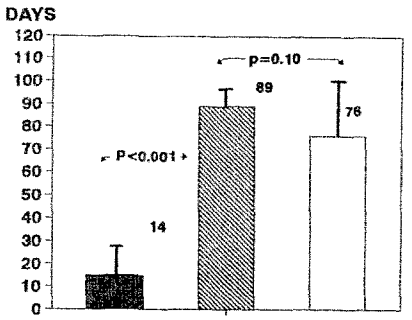

Figure 3. Mean arrhythmia-free intervals (±SD) in days with dual-site **(hatched column)** and high right atrial pacing **(dotted column)** and the preimplantation lead-in period **(solid column).** There is a significant increase in the arrhythmia-free interval after implementation of atrial pacing with both the dual-site and high right atrial pacing modes, and the arrhythmia-free interval is greater with the dual-site than the high right atrial mode.

Complications. Marked elevation of the right ventricular threshold was observed in two patients at 9 and 43 days after implantation, respectively. The lead was observed to be in the right ventricular apex in both patients and required repositioning for better thresholds in both instances. There was one atrial lead dislodgment from the high right atrium in a postoperative cardiac surgical patient. This lead was repositioned in the lateral high right atrium. There was no coronary sinus ostial lead dislodgment. One patient had pneumothorax with subclavian puncture requiring evacuation. One patient required pacemaker pocket revision due to her asthenic habitus. Subsequently, she experienced pocket infection after a surgical procedure at a contiguous axillary location, resulting in device explantation 7 months after implantation. One atrial lead was noted to oversense and was determined to have a loss of adhesive coating over the set screw in the Y connector, resulting in oversensing of muscular signals and requiring reinsulation with medical adhesive.

Arrhythmia recurrence. Four patients had documented recurrences, usually transient, of sustained AF in the dual-site pacing mode during the drug optimization period. Spontaneous termination of recurrent AF occurred in three patients, and direct current (DC) cardioversion was required in one. These patients either had no antiarrhythmic therapy (one patient) or were taking disopyramide (three patients). In one patient, failure to maintain continuous atrial pacing was noted. In these four patients a different but previously ineffective antiarrhythmic drug was then started (two patients), or the dose of the existing drug was increased (one patient), or the dosing schedule was altered (one patient) to achieve continuous atrial pacing. With these modifications, all 15 patients were followed up for a full 3 months on the optimized drug regimen to complete phase 1. There was no recurrence of AF in any patient during this period. The patients were then maintained on the same regimen in the single-site high right atrial pacing mode in phase 2. Five patients experienced recurrent AF in this pacing mode, occurring 30 to 85 days after entering this phase. Using McNemar's test, there is a statistically significant difference in the arrhythmia suppression between the two modes ($p = 0.03$) once the final drug plus device regimen was established. All 4 patients showing an early recurrence with device therapy alone or with low drug dosage experienced recurrent AF with the final drug plus device regimen selected in the high right atrial pacing mode.

The mean arrhythmia-free interval in the initial drug and dual-site pacing mode was 77 ± 26 days and was higher than the preimplantation arrhythmia-free interval (14 ± 14 days) or the time interval between the last documented AF episode and device implantation (11 ± 22 days). Repeated measures ANOVA for patients completing dual- and single-site pacing showed a statistically significant difference in mean arrhythmia-free interval between preimplantation, dual- and single-site values (Wilks lambda 0.03, $p < 0.0001$). Analysis of paired differences showed that the arrhythmia-free interval (Fig. 3) for the optimized final drug and dual-site pacing mode (89 ± 7 days) was also higher than the preimplantation arrhythmia-free interval ($p < 0.0001$) as well as the initial dual-site pacing mode ($p < 0.03$). Single-site pacing similarly had longer arrhythmia-free intervals (76 ± 27 days) than the preimplantation period ($p < 0.0001$). The arrhythmia free-intervals in the optimized drug plus device treatment mode

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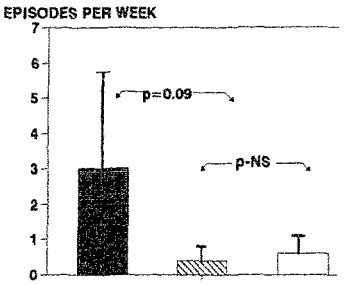

Figure 4. Patient symptoms with respect to arrhythmia before and after the implementation of atrial pacing. There is a significant decrease in patient symptoms (number of symptomatic atrial fibrillation [AF] episodes/per week) with both atrial pacing modes. However, there is no difference in symptomatic AF episodes between the two pacing modes. Symbols as in Figure 3.

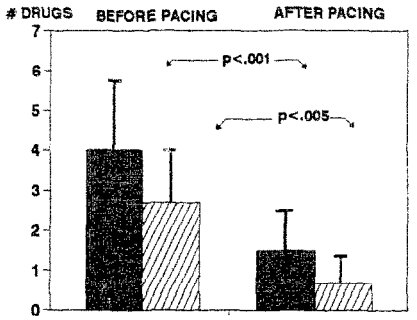

Figure 5. Comparison of antiarrhythmic drug use before and after atrial pacing. **Solid columns** indicate drugs of all classes, whereas **hatched columns** represent class I and III antiarrhythmic drugs. There is a significant decrease in the mean number of drugs used after implementation of atrial pacing in all classes and classes I and III.

showed a trend to higher values for the dual-site mode than the single-site mode ($p = 0.10$), recognizing that either interval is limited by a maximum of 90 days by study design (Fig. 3). Thus, patients remaining arrhythmia free at the end of a given phase may actually achieve longer arrhythmia-free intervals in clinical practice with either mode. The postimplantation symptomatic frequency for the unoptimized and optimized dual-site mode (0.5 ± 0.6 and 0.29 ± 0.45 symptomatic episodes/week, respectively) showed a trend to lower values than the preimplantation frequency (3.1 ± 4.1 symptomatic episodes/week, $p = 0.09$) for paired data (Fig. 4). There was no difference in symptoms between the dual- and single-site modes (0.29 ± 0.45 vs. 0.47 ± 0.48 symptomatic episodes/week, $p = 0.56$). At the completion of phase 1, 15 patients were in an atrial-based rhythm, whereas 7 of 12 patients with mode-switched devices were in this rhythm at the end of phase 2 ($p < 0.05$). Cardioversion for termination of recurrent AF was necessary in one patient in phase 1 and four patients in phase 2 ($p < 0.05$). Atrial-based pacing was successfully reestablished with the dual-site mode in phase 3 in two of the five patients with recurrences in phase 2.

Drug therapy. Figure 5 shows the mean number of antiarrhythmic drugs used in the study patients before and after initiation of atrial pacing. There is a significant decline in the total mean drug usage. This decline is largely due to a decline in the use of class I and III drugs. Three patients received no drug therapy; six patients had single-drug therapy; and the remaining six patients were receiving one class I or III drug in combination with digoxin, a calcium channel blocking agent or a beta-blocker. Of these six patients, three were taking a total of two agents, and three were taking three agents.

Discussion

Atrial fibrillation recurrences in paced patients. Prevention of AF by nonpharmacologic methods is now being widely investigated. Surgical ablation has been effective in the prevention of recurrent AF in selected patients but carries the risk of morbidity, atrial hemodynamic dysfunction and even mortality (6). Catheter ablative methods remain largely investigational in AF (7,8). Pacing techniques have been applied for suppression of atrial and ventricular premature beats as well as sustained tachycardias (9–12). Fisher et al. (9) noted the suppression of ventricular premature beats with ventricular pacing in a prospective clinical trial. However, long-term use of antitachycardia pacing methods has been largely restricted to reversion of sustained atrial and ventricular tachycardias (13–15). Demand atrial pacing can reduce the frequency of recurrent AF in patients with sick sinus syndrome (4,16,17). During long-term follow-up, patients with sinus node dysfunction treated with single-site atrial or ventricular pacing had an incidence of AF that varied from 5% to 7% for atrial pacing versus 32% to 47% for ventricular pacing at 3 to 5 years (16–18). Patients with concomitant supraventricular arrhythmias and sick sinus syndrome in the same series had significantly higher rates of recurrence of AF, ranging from 9% to 41% with atrial pacing during the same follow-up. These findings were extended in a prospective study where the incidence of AF in patients with sinus node dysfunction alone was 18% with atrial pacing and 40% with ventricular pacing at 5 years (19).

The benefit of cardiac pacing in an unselected cohort with drug-refractory AF and bradycardias, as in our study, is unknown. In drug trials (20) using a cohort with frequent drug-refractory AF, a mean arrhythmia-free interval of 3 days was seen with placebo treatment and increased to 15 days with flecainide therapy. In another drug trial in this cohort, Pritchett et al. (21) reported that only 10% of their patients taking placebo and 25% taking propafenone were free of recurrence of AF at the 90-day follow-up visit.

Multisite atrial pacing: technical and electrophysiologic considerations. Multisite pacing methods for arrhythmia suppression have been applied in ventricular arrhythmias with limited success (22). More recently, simultaneous biatrial pacing has been reported (5) to be associated with low recurrence rates of atrial flutter and fibrillation in patients with severe interatrial conduction disturbances, often seen with hypertrophic cardiomyopathy. However, technical difficulties

with coronary sinus lead placement and maintenance required in this pacing mode and the select patient cohort could limit its general applicability. The conceptual advantages of the right atrial approach to multisite pacing are in part largely technical, with the potential for reduced lead dislodgment. This was indeed validated with the absence of coronary ostial lead dislodgment in the present initial series over a follow-up period >1 year. Electrophysiologic advantages could also exist. The isthmus between the tricuspid valve and inferior vena cava is a key slow conduction zone in type 1 atrial flutter, which may in some patients precede development of AF. The triangle of Koch has been suggested by anatomic studies to have anatomic and electrical continuity with atrial fibers from the right and left atrium contributing to the interatrial septum (Rossi L, personal communication, 1994). These regions are considered by many to be a key zone for arrhythmogenesis in patients with AF. Simultaneous electrical stimulation at the high right atrium and coronary sinus ostium can eliminate dispersion of atrial refractoriness; abbreviate right and left atrial activation; and eliminate, reduce or modify areas of delayed activation (23,24). The initiation of AF may require both electrical conditions of dispersed refractoriness as well as anatomic sites of conduction block in one or both atria to generate multiple wavelets (25). We analyzed the immediate electrophysiologic effects of dual-site right atrial pacing and observed abbreviation of P wave duration and regional atrial activation times in both the right and left atria (23,24). Suppression of inducible AF in patients with marked dispersion of refractoriness has also been observed in these short-term studies (23). These electrophysiologic findings may provide the theoretic basis for reduced AF recurrence rates during dual-site atrial pacing and perhaps even during single-site pacing modes.

Arrhythmia-free intervals in atrial pacing. The ability of atrial pacing to increase arrhythmia-free intervals in patients with drug-refractory paroxysmal AF has been established by our data. The relatively few patients with chronic AF in this initial experience does not permit the same conclusion in this patient cohort. Our results also clarify the often reported observation of reduced recurrence of AF in atrially paced patients with sick sinus syndrome with coexisting atrial arrhythmias. Interestingly, there was no difference in recurrence of AF in patients with primary sinus node disease and other indications for cardiac pacing in this series. In fact, most AF episodes do not commence with sinus or ventricular pauses in Holter monitor analyses. This would imply that overdrive atrial pacing had a primary effect on the atrial substrate rather than simply prevention of atrial or ventricular bradycardic pauses that may precede bradycardia-dependent AF (26). The maximal possible arrhythmia-free interval in phase 1 and 2 was 90 days. The time dependence of AF recurrence was recognized in the study design. The majority of AF recurrences occur within the first 3 months in most drug studies (20,21). Our measurements of arrhythmia-free intervals are clearly underestimates because many patients would have and have had longer arrhythmia-free periods. We chose the 3-month period as a watershed with the view that more than four cardioversions/year would be unacceptable in terms of patient tolerance with an implantable atrial defibrillator or certainly with external DC cardioversion. In addition, electrophysiologic and mechanical remodeling of the atrium to the extent feasible in these patients may be largely completed by this time (27). This could reduce propensity to AF in the long term. The dual-site mode was utilized first in an attempt to test the efficacy of this pacing mode in the highest density period of arrhythmia recurrence. Although such a design actually favors a better result for the single-site mode, the data in this study suggest a distinct benefit for the dual-site mode. This would further strengthen the conclusions regarding incremental benefit of multisite pacing over single-site pacing. A marked decrease in antiarrhythmic drug use is also important. Reduced use of class I agents could have a favorable effect on survival. Digoxin and class II drugs were often needed to establish continuous atrial pacing. The virtual elimination of cardioversion during follow-up and the absence of readmittance to the hospital in all but two patients for recurrence of AF also supports the benefit of this nonpharmacologic approach to the prevention of AF. Atrial pacing modes may significantly contribute to the feasibility of wide application of an implantable atrial defibrillator or the use of dual-chamber pacemakers for the management of AF.

Study limitations. The lead-in period may underestimate recurrence of arrhythmias because of the requirement of ECG documentation. The subsequent phases used either ECG end points or symptoms with previous ECG validation. However, some drugs, most prominently sotalol, have been reported (28) to reduce symptoms associated with recurrence. Thus, in the absence of continuous ECG monitoring, we cannot exclude brief asymptomatic recurrences while a control arm of drug therapy was considered. The increased study complexity and previous demonstration of drug refractoriness raised concerns about submitting patients to the risk of recurrence of AF and repeated cardioversion. The methodology used in the present study parallels the standard design of many drug trials. Brief asymptomatic episodes are also unlikely to prompt hospital admission. Finally, treatment algorithms in implantable devices seek to avoid intervention in transient and minimally symptomatic atrial arrhythmias. Thus, our study data should reflect events needing clinical intervention. The lack of random assignment to each pacing mode may favor one mode over another.

Conclusions. Multisite right atrial pacing is feasible and safe and effective for long-term application. Single- and dual-site right atrial pacing significantly prolongs arrhythmia-free intervals in patients with drug-refractory paroxysmal AF. Dual-site right atrial pacing may offer additional benefits and should be considered either as the primary mode or in patients unresponsive to single site pacing. Technical and technologic development to improve its ease and application is needed. Further study of the electrophysiologic changes associated with this pacing mode are warranted. Such pacing modes may be valuable as stand-alone therapy or as an adjunct to defibrillation therapy in implantable device therapy for AF.

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