Biattrial Pacing for Paroxysmal Atrial Fibrillation
A Randomized Prospective Study Into the Suppression of Paroxysmal Atrial Fibrillation Using Biattrial Pacing
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OBJECTIVES
The purpose of this study was twofold: to assess whether biattrial pacing is superior to single-site pacing and capable of reducing the frequency of episodes of paroxysmal atrial fibrillation (PAF); and to compare pacing of the proximal coronary sinus (PCS) with the distal coronary sinus (DCS) and the effects of sequential or simultaneous biattrial pacing.

BACKGROUND
Interradial conduction abnormalities have a role in the initiation of PAF. Biattrial pacing alters the site and timing of atrial depolarization and may benefit those with drug-resistant PAF.

METHODS
Nineteen patients with PAF who were intolerant of or refractory to medication were studied. All received right atrial (RA) and coronary sinus (CS) leads (either PCS or DCS). For three months the pacemaker was set in sensing mode only. Subsequently each patient completed three-month periods in random order in the following modes: RA pacing, CS pacing, biattrial pacing using inter-atrial delays of 15 and 70 ms.

RESULTS
Sixteen patients received a benefit from one or more pacing modes. The greatest reduction in PAF episodes was seen during biattrial pacing, especially with leads sited at the high right atrium (HRA) and distal CS (p = 0.0048). There was no difference for sequential or simultaneous pacing. Three patients derived no benefit.

CONCLUSIONS
In selected patients, biattrial pacing causes a significant decrease in atrial fibrillation episodes. Optimal lead sites were at the HRA and DCS. Simultaneous pacing conferred no benefit over sequential pacing. (J Am Coll Cardiol 2002;40:457–63) © 2002 by the American College of Cardiology Foundation

Atrial fibrillation (AF) is the most common clinically encountered arrhythmia in the adult population (1–4). Up to 60% of the cases presenting with AF may do so in the paroxysmal form of this arrhythmia (2). Pharmacological control is the first line of therapy, but AF may be associated with low success rates, high recurrence rates, or patient intolerance. There is therefore considerable interest in non-pharmacological therapy in the maintenance of sinus rhythm (5).

A variety of abnormalities of atrial electrophysiology are found in patients susceptible to AF (6–12). Interradial conduction block in particular results in delayed activation of the atria, and such patients have a high incidence of atrial tachyarrhythmias (13). Other triggers for paroxysmal atrial fibrillation (PAF) include atrial premature complexes and sinus bradycardia (14). In patients with sinus bradycardia, atrial pacing has been observed to prevent PAF (15), presumably in part because of correction of rate. Special algorithms have also been proposed for suppression of pauses or atrial premature beats, which may be triggers for AF (16).

Biattrial pacing has been used in patients with and without bradycardia or organic heart disease (17). It is aimed at restoring inter-atrial synchrony, based on the hypothesis that patients with refractory PAF have increased inter-atrial conduction times, predisposing them to their arrhythmia (18). Although there is some information on proximal coronary sinus (PCS) pacing (19), there is little information on distal coronary sinus (DCS) pacing or the effect of varying right to left inter-atrial pacing intervals on the incidence of AF.

The aim of the present study has been to assess whether biattrial pacing is superior to single-site pacing, capable of reducing the frequency of clinical episodes of PAF in patients without underlying sinus bradycardia or sinus pauses. It compares pacing of the PCS with pacing of the DCS and compares the effects of sequential with simultaneous biattrial pacing on the suppression of clinically symptomatic episodes of PAF.

METHODS
Patients. We recruited 19 patients with recurrent PAF who were refractory to, or unable to, tolerate two or more antiarrhythmic drugs. Patients with evidence of sinus node disease were specifically excluded. The study was approved by the Maidstone NHS Trust Ethics Committee, and all patients gave written, informed consent. All patients were reliable witnesses to their symptoms of palpitations, which

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correlated entirely with episodes of AF in more than 192 h of Holter monitoring (i.e., 4 × 48 h of continuous electrocardiograph recordings) per patient.

The study population involved 19 patients consisting of nine male and 10 female patients with a mean age of 62 years. Analysis of their concurrent medical history showed that seven had coexistent hypertension, one with ischemic heart disease and four with thyroid disease secondary to previous amiodarone use. All except one patient had normal left ventricular function. Table 1 summarizes the patients and their details, including current and previous drug therapy. Patient number does not refer to the order of implantation.

**Study methodology.** All patients underwent echocardiography and assessment of sinus node function by Holter monitoring and exercise testing. Patients with sinus node dysfunction were excluded. The monthly count of PAF episodes was taken from a three-month period, and the mean value was calculated. Duration of the PAF episodes had to be >1 min, although usually episodes lasted up to several hours prior to pacing.

**Pacing methodology.** Each patient underwent implantation of two permanent pacing leads, a right atrial (RA) active fixation lead (CPI sweet tip model 4269) and a coronary sinus (CS) Medtronic 2188 lead. The RA lead was sited in either the high right atrium (HRA) close to the sinus node or RA appendage (RAA). The CS lead was sited in either the PCS (i.e., 0 to 35 mm from coronary os) as observed on fluoroscopy or the DCS (35 to 60 mm from coronary os) as observed on fluoroscopy. Optimal threshold and lead stability was obtained by standard manipulation of the pre-formed CS lead tip. The permanent lead positions are illustrated in Figures 1 and 2.

The position of the leads was assigned randomly to each

<table>
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<tr>
<th>Patient</th>
<th>Gender</th>
<th>Age</th>
<th>LA Size (cms)</th>
<th>LV Function</th>
<th>Comorbidity</th>
<th>RA Pacing Site</th>
<th>Mean AF Episodes Per Month</th>
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<td>HRA</td>
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<td>f,b</td>
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<td>HRA</td>
<td>15</td>
<td>nil</td>
<td>a,f,s,b</td>
</tr>
</tbody>
</table>

a = amiodarone; AAD = antiarrhythmic drug therapy; b = beta blocker; d = disopyramide; dx = digoxin; f = flecainide; HRA = high right atrium; HT = hypertension; IHD = ischemic heart disease; LA = left atrium; LV = left ventricle; n = normal LV function; p = propafenone; r = reduced LV function; RA = right atrial; RAA = right atrial appendage; s = sotalol; Thyr = hypothyroidism due to previous amiodarone; v = verapamil.
The recurrence of PAF was evaluated before pacemaker implantation there were 15 monthly monitoring for each patient, during which the heart assuming a conduction velocity in the atrium of approximately 0.6 mm/ms (20).

The recurrence of PAF was evaluated using patient documentations and after pacing by means of patient symptom diaries. Statistical analysis. The paired Student t test with two-tailed distribution was used to evaluate statistical significance of the results.

RESULTS

There was no correlation with any of the baseline clinical variables and efficacy of AF prevention. Drug therapy was unaltered during the study and was unrelated to patient outcome. There was one case of lead displacement that occurred from the PCS position within 24 h of placement (Patient 3). The Medtronic 2188 lead was repositioned in the CS os with no further displacement or complication. There were no other acute or chronic adverse events. None of the patients developed sustained AF. There was no increase in episodes per month for any patient in any pacing mode. Results are summarized in Tables 3 and 4 and illustrated in Figures 3 and 4.

Effect of lead position on PAF. The effects of single-site atrial pacing are summarized in Table 3. The effects of dual-site atrial pacing, both sequential and simultaneous, are summarized in Table 4. Only three patients (Patients 2, 8, 10) derived no benefit from any of the pacing modalities. Those patients with no benefit from a pacing modality had no significant difference in the number or duration of their episodes of PAF, and none developed sustained AF. The alteration in duration of episodes was relevant only for those patients deriving benefit, but not total suppression of AF, from their pacing modalities.

EFFECT OF RA ATRIAL PACING. Right atrial pacing alone at 70 beats/min, whether from the HRA or the RAA, led to a reduction in the mean number of symptomatic episodes per month of PAF in 12 patients. In seven patients there was no change in the number or duration of episodes. The overall mean reduction was 6.37 episodes per month (p = 0.0031) with a standard deviation of 8.13. Pacing from the RAA at 70 beats/min versus pacing from the HRA at 70 beats/min showed benefit from both sites. Statistical significance (Student t test) is shown in Table 3, which shows that the reduction is highly significant overall, with the greatest reduction in AF episodes obtained from pacing the RAA.

Table 2. Anatomic Combinations of Site of Endocardial Pacing Leads

<table>
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<th>RAA</th>
<th>Total</th>
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<td>3</td>
<td>8</td>
</tr>
<tr>
<td>DCS</td>
<td>6</td>
<td>5</td>
<td>11</td>
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</table>

DCS = distal coronary sinus; HRA = high right atrium; PCS = proximal coronary sinus; RAA = right atrial appendage.
Table 3. Single Site Pacing

<table>
<thead>
<tr>
<th>Site</th>
<th>Number of Patients</th>
<th>Patients Free of Symptoms</th>
<th>Patients Deriving Benefit</th>
<th>Patients Deriving No Benefit</th>
<th>Mean Reduction in AF Episodes per Month</th>
<th>Standard Deviation</th>
<th>p Value</th>
<th>Reduction in Duration of PAF Episodes (h)</th>
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</thead>
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<td>62.50</td>
<td>4</td>
<td>50.00</td>
<td>12.50</td>
<td></td>
<td>9.13</td>
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<tr>
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<td>18.18</td>
<td>5</td>
<td>45.45</td>
<td>37.50</td>
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<td>4.36</td>
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<tr>
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<td>3</td>
<td>37.50</td>
<td>2</td>
<td>25.00</td>
<td>37.50</td>
<td></td>
<td>6.40</td>
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<tr>
<td>DCS 16 ms</td>
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<td>3</td>
<td>37.50</td>
<td>2</td>
<td>25.00</td>
<td>45.45</td>
<td></td>
<td>6.40</td>
</tr>
<tr>
<td>All RA 16 ms</td>
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<td>3</td>
<td>15.79</td>
<td>9</td>
<td>47.37</td>
<td>18.18</td>
<td></td>
<td>6.00</td>
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<tr>
<td>All CS 16 ms</td>
<td>19</td>
<td>6</td>
<td>31.58</td>
<td>7</td>
<td>36.84</td>
<td>6.37</td>
<td></td>
<td>8.13</td>
</tr>
</tbody>
</table>

AF = atrial fibrillation; All BiA 16 ms = biatrial paced with interatrial delay of 16 milliseconds; All BiA 70 ms = biatrial paced with interatrial delay of 70 milliseconds; DCS 16 ms = biatrial pacing with distal coronary sinus lead and delay of 16 milliseconds; DCS 70 ms = biatrial pacing with distal coronary sinus lead and delay of 70 milliseconds; PAF = paroxysmal atrial fibrillation; PCS 16 ms = biatrial pacing with proximal coronary sinus lead and delay of 16 milliseconds; PCS 70 ms = biatrial pacing with proximal coronary sinus lead and delay of 70 milliseconds.

EFFECT OF CS SINGLE-SITE PACING. Pacing from the CS alone at 70 beats/min benefited 13 of 19 patients. In six patients there was no change in their symptoms. The statistical analysis (Student t test) shows that the reduction in symptoms from pacing CS sites is highly significant when compared with the pre-pacing control state. A greater percentage derived benefit from distal than from PCS pacing (p < 0.05).

Effect of biatrial sequential (70-ms interval) pacing. Fifteen of nineteen patients obtained symptomatic benefit (Table 4). The mean reduction was 8.58 episodes per month with a standard deviation of 9.22. Statistical analysis (Table 4) shows this effect to be highly significant (p = 0.000738).

Effect of Pacing RA and PCS. Biatrial pacing including the PCS site benefited six of eight patients (see Table 4). The mean reduction in symptoms was 7.38 episodes per month (p = 0.084).

Effect of Pacing RA and DCS. Biatrial pacing including the DCS benefited nine of 11 patients (Table 4). The average reduction in symptoms was 8.71 episodes per month with a standard deviation of 8.71 (p = 0.0048).

Biatrial simultaneous (16-ms interval) pacing. Fifteen of 19 patients benefited from biatrial pacing with 16-ms inter-atrial pacing delay, including PCS and DCS positions (Table 4). The mean reduction of symptoms was 8.74 episodes per month (p = 0.0007) with a standard deviation of 9.43. Six of the eight patients paced from the PCS had a reduction in the frequency of symptoms. The mean reduction in symptoms was 7.38 episodes per month (p = 0.0834) with a standard deviation of 10.34.

Nine of the 11 patients derived benefit from DCS pacing. The mean reduction in symptoms was 9.73 episodes per month. Statistical analysis (Table 4) shows the reduction in symptoms with biatrial pacing with a 16-ms inter-atrial delay to be statistically significant when proximal and distal coronary sinus positions are compared together (p = 0.0007). Pacing from the DCS is also statistically significant (p = 0.0053). Although six of the eight patients who underwent biatrial pacing via the PCS with a short inter-atrial delay benefited from this program, the magnitude of the changes did not reach statistical significance (p = 0.08).

Examination of the change in episodes of AF showed the reduction in symptoms by pacing the DCS to be statistically significant (i.e., p < 0.05) whether pacing was carried out from the DCS alone or as part of biatrial pacing at 70 and 16 ms inter-atrial delay.

Although PCS pacing led to an improvement in symptoms of five of eight patients for single-site pacing, and in six of eight patients with biatrial pacing, the reduction in symptoms by PCS pacing either alone or biatrially at 70 ms or 16 ms did not reach statistical significance as p > 0.05. All these changes are illustrated in Figures 3 and 4.

Role of inter-atrial conduction delay. Although inter-atrial conduction time was not a criterion for entry into the

Table 4. Biatrial Pacing

<table>
<thead>
<tr>
<th>Site</th>
<th>Number of Patients</th>
<th>Patients Free of Symptoms</th>
<th>Patients Deriving Benefit</th>
<th>Patients Deriving No Benefit</th>
<th>Mean Reduction in AF Episodes per Month</th>
<th>Standard Deviation</th>
<th>p Value</th>
<th>Reduction in Duration of PAF Episodes (h)</th>
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AF = atrial fibrillation; All BiA 16 ms = biatrial paced with interatrial delay of 16 milliseconds; All BiA 70 ms = biatrial paced with interatrial delay of 70 milliseconds; DCS 16 ms = biatrial pacing with distal coronary sinus lead and delay of 16 milliseconds; DCS 70 ms = biatrial pacing with distal coronary sinus lead and delay of 70 milliseconds; PAF = paroxysmal atrial fibrillation; PCS 16 ms = biatrial pacing with proximal coronary sinus lead and delay of 16 milliseconds; PCS 70 ms = biatrial pacing with proximal coronary sinus lead and delay of 70 milliseconds.
study, 16 of 19 patients had a prolonged inter-atrial conduction time (>100 ms in sinus rhythm). Three patients (Patients 2, 8, 10) had normal inter-atrial conduction times in sinus rhythm. It is these patients who had no benefit form any of the above pacing modalities.

**DISCUSSION**

The mechanism of AF involves multiple random waves of reentrant electrical circuits moving from one area of atrial muscle to another (21). This is thought to occur on the basis of an abnormal atrial substrate in which inter-atrial conduction delays, short atrial refractory periods with increase in dispersion, and various triggering foci assist in the setting up and sustaining of such circuits. A combination of delayed intra- and inter-atrial conduction and heterogeneous refractoriness and recovery of excitability may contribute to the abnormal atrial substrate necessary to sustain the multiple reentrant wavelets leading to AF. Atrial ectopic beats with irregular coupling intervals may further alter the electro-
physiological properties and trigger AF. The development of AF leads to electrophysiological, mechanical, and cellular changes that perpetuate AF (6–12).

It has also been shown that a focal trigger can be responsible for the initiation of AF. Electrophysiological studies have shown the foci to be in the pulmonary veins in up to 90% of patients with AF. Pulmonary venous sites have also been shown to be the commonest site of origin of “focal AF,” characterized by extrasystoles, irregular atrial tachycardia, and AF due to the same focus firing irregularly at different rates (22–24).

Effect of pacing on AF triggers. Atrial pacing may suppress PAF by different mechanisms. First, atrial pacing can suppress atrial ectopics or remove pauses, which can be the trigger for paroxysms. The importance of atrial-based pacing in preventing AF has been observed in patients with sick sinus syndrome. A variety of mechanisms have been proposed by which atrial pacing may modulate the initiating mechanisms and reduce the frequency of PAF in these patients. These include the elimination of significant pauses by either atrial pacing at the conventional fixed rate, constant higher rate pacing for overdrive suppression, or physiological AAIR pacing to achieve constant overdriving (16).

In a large number of retrospective studies on patients with sick sinus syndrome, significant reduction of AF recurrences with atrial pacing compared with ventricular pacing has been documented. Whether this was because of the proarhythmic effect of ventricular pacing or the beneficial effect of atrial pacing is unclear (25–27). The dual site atrial pacing to prevent atrial fibrillation (DAPPAF) study (28) compared dual-site atrial pacing, single-site atrial pacing, and support pacing modalities for the prevention of AF. Patients included had episodes of PAF and a bradyarrhythmic condition (25–27). The dual site atrial pacing to prevent atrial fibrillation (DAPPAF) study (28) compared dual-site atrial pacing, single-site atrial pacing, and support pacing modalities for the prevention of AF. Patients included had episodes of PAF and a bradyarrhythmia in need of pacing. Echo analysis suggests that DDDR pacing may be detrimental to ventricular function and that AAIR pacing may be more effective.

However, our patient group specifically excluded patients with sinus node dysfunction, 16 of whom derived benefit from one or more pacing modalities. Other workers have shown the benefit of atrial pacing in patients with non-bradyarrhythmia-dependent PAF in the absence of sinus node disease (11,18,19). Thus, our single-site pacing at 70 beats/min may be beneficial because of the above-mentioned “rate smoothing” mechanisms. Levy et al. (29) also observed this phenomenon.

Effect of biatrial pacing on atrial substrate. Early studies by Daubert et al. (17) in patients with advanced inter-atrial conduction block showed that pacing simultaneously from the HRA and CS is associated with reduced AF recurrences. This is attributed to atrial resynchronization and alleviation of inter-atrial block. Dislodgment of the CS lead in 20% of the patients was the biggest limitation in this mode of pacing and appears to have been overcome, as we have shown, by the use of specifically designed leads such as the Medtronic 2188 lead used in the present study.

Saksena et al. (30) and Prakash et al. (31) evaluated the role of dual-site RA pacing in patients with drug-refractory AF. They demonstrated that dual-site RA pacing (HRA/CS os) resulted in an increase in AF-free interval and a reduction in the need for antiarrhythmic therapy. At one year approximately 80% of patients were free of frequent or chronic AF. Other studies have shown biatrial pacing to reduce the frequency of PAF episodes in patients either with or without surface P-wave prolongation (17,32,33).

Our study examines the role of single-site and biatrial pacing in the suppression of PAF in patients with frequent episodes of AF (mean 15.9 episodes per month) who had no underlying bradycardia. Although the study group was comparatively small (19 patients), all acted as their own controls to extensively evaluate the role of single-site RA pacing, single-site CS pacing, biatrial pacing (RA + CS), and finally, the effect of inter-atrial pacing intervals.

Sixteen of nineteen patients in our study derived benefit from single-site pacing alone. Overall there was no difference in the effect of single-site atrial pacing from the RA compared with pacing from the CS. However, subgroup analysis showed that the greatest benefit from single-site pacing occurred from the RAA.

The possible reasons for this are unclear, but the RAA may represent the optimal single site for atrial resynchronization in this study. Previous work by Bennett (34) and Katsivas et al. (35) has shown that RA septal pacing shows benefit in patients with PAF, presumably for the same reason.

The greatest benefits in terms of reduction of episodes per month of PAF in our study group were undoubtedly seen during biatrial pacing, particularly utilizing the DCS. Although RA plus PCS pacing showed an improvement in episodes, the benefit did not reach statistical significance, possibly because of the small numbers.

Atrial resynchronization is likely to have played an important role. The benefit of coupling the RA with a pacing site in the mid to distal coronary sinus supports Daubert’s data (17–19). The explanation may be analogous to optimizing depolarization in atrial defibrillation (36,37), i.e., the capture and depolarization of the largest volume of atrial myocardium within the smallest possible time. Varying the inter-atrial (RA–left atrial) pacing interval from 70 ms (“sequential”) to 16 ms (“simultaneous”) did not appear to confer any further benefit.

Our results suggest that pacing rate as well as site (anatomy) has a role in optimizing the clinical benefits of biatrial pacing even in those without sinus bradycardia. This adds weight to the theories that no single mechanism is present in any one patient in at any time.

Study limitations. The study included a comparatively small number of patients. However, all patients acted as their own controls to allow comparison of multiple pacing sites and intervals. An important limitation is the lack of pacemaker event logs. Unfortunately, at the time of the study, these had to be sacrificed for the customized generator software. Future pacing studies in patients with PAF should include pacemaker Holter functions.
The patients were not selected on the basis of their inter-atrial conduction delay, although this may influence outcome. Future studies are planned to include formal measurements of this parameter.

Conclusions. We investigated the ability of single-site RA, single-site CS, and biaxial pacing to prevent the recurrence of AF in 19 patients with symptomatic drug-resistant PAF.

We have confirmed that the technique is safe in both the long and short term and straightforward to perform. We suggest that optimal benefits in selected patients are achieved by combining an increase in the heart rate (in this study 70 beats/min, although the effects of higher rates of “overdrive” have yet to be established) with biaxial pacing. The optimal site for the RA lead may be the RAA, whereas the optimal CS site appears to be distal. Simultaneous inter-atrial conduction delay, although this may in

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pacing. It is possible that optimal benefit in this group of patients without underlying bradycardia may be obtained in those with inter-atrial conduction delay.

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