Electrical Remodeling of the Atria Following Loss of Atrioventricular Synchrony
A Long-Term Study in Humans

Paul B. Sparks, MBBS, PhD; Harry G. Mond, MD; Jitendra K. Vohra, MD; Shenthar Jayaprakash, MD; Jonathan M. Kalman, MBBS, PhD

Background—Evidence suggests that an increased incidence of atrial fibrillation occurs in patients undergoing single-chamber ventricular pacing (VVI) when compared with those undergoing single-chamber atrial pacing (AAI) or those having dual-chamber atrioventricular pacing (DDD). The mechanism for this is unknown. We hypothesized that long-term loss of atrioventricular (AV) synchrony leads to atrial electrical remodeling: a potential explanation for this difference.

Methods and Results—The study was a prospective, randomized comparison between 18 patients paced in VVI mode and 12 patients paced in DDD mode for 3 months. Under autonomic blockade, effective refractory periods (ERPs) from the lateral right atrium (RA), RA appendage, RA septum, and coronary sinus–corrected sinus node recovery times (cSNRTs), as well as P-wave duration (PWD), and biatrial diameters were measured at baseline and 3 months. The VVI group was then programmed to DDD pacing and reevaluated after a further 3 months. After long-term VVI pacing, ERPs at all 4 atrial sites increased significantly in a nonuniform fashion in association with biatrial dilatation. PWD and cSNRTs also prolonged significantly. With the reestablishment of AV synchrony, ERPs, PWD, cSNRTs, and biatrial dimensions returned to baseline levels. In the 12 patients who underwent long-term DDD pacing from baseline, no significant changes in atrial electrophysiology or biatrial dimensions were demonstrated.

Conclusions—Long-term loss of AV synchrony induced by VVI pacing is associated with atrial electrical remodeling, which is reversible after the reestablishment of AV synchrony with DDD pacing. This process may be partly responsible for the higher incidence of atrial fibrillation in patients undergoing VVI pacing compared with AV sequential pacing. (Circulation. 1999;100:1894-1900.)

Key Words: atrium ▪ electrophysiology ▪ fibrillation ▪ pacemakers ▪ remodeling

Electrical remodeling of the atrium has been clearly demonstrated in animal models and in humans. In studies of electrical remodeling, it has been shown that atrial fibrillation (AF) begets AF due to a fall in atrial effective refractory periods (ERPs), suggesting that this is a major mechanism for the development of the chronic form of the arrhythmia. However, not all investigators have observed a decrease in atrial ERPs in other situations associated with AF. Some authors have observed that the remodeling process is considerably more complex than a simple relationship to a fall in refractoriness. Experimental observations in a canine model suggest that increases in atrial size and pressure cause an increase in atrial refractoriness and dispersion of ERPs, which slow conduction velocity and increase AF inducibility. Conversely, in isolated rabbit atria, Ravelli and Allessie observed a fall in atrial ERPs with short-term atrial stretch. Human data have, thus far, been limited to short-term pacing studies; here, too, conflicting data exist. An emerging body of evidence suggests that long-term asynchronous ventricular pacing (VVI) is associated with an increased incidence of AF; ongoing multicenter trials are addressing this issue. The mechanism underlying this observation is unknown. We hypothesized that the long-term loss of atrioventricular (AV) synchrony associated with VVI pacing leads to atrial electrical remodeling as a potential explanation for this difference. Serial electrophysiological studies were used to prospectively evaluate the effects of a long-term loss in AV synchrony on atrial refractoriness, atrial conduction, and sinus node function in patients with dual-
variables of the underlying atrial rhythm were sinus before study entry. No patient had paroxysmal or long-term AF. All patients gave informed consent to the study, which was approved by the Board of Medical Research of The Royal Melbourne Hospital. The study methodology is summarized in Figure 1.

All patients underwent implantation of bipolar atrial and ventricular leads connected to a dual-chamber pacemaker. The atrial lead was positioned in the right atrial (RA) appendage, and the ventricular lead was placed at the right ventricular apex. Multiprogrammable pacemakers with extended memory and the capability for noninvasive, programmed stimulation were implanted, which permitted the retrieval of sensing and pacing frequencies during interval periods. The noninvasive, programmed stimulation function of the pacemaker was invoked to evaluate ERPs from the electrode implanted in the RA appendage, as described above.

To estimate intrastudy variability, the atrial RA ERPs at 600 and 450 ms were determined twice in 10 patients at baseline. After initial ERP determinations, the catheter was withdrawn into the inferior vena cava and then repositioned where the initial ERP was assessed. Intrastudy variability was 3.04% at 600 ms and 4.22% at 450 ms.

Attrial dispersion of refractoriness was calculated by subtracting the minimum ERP from the maximum ERP determined at the lateral RA, RA appendage, midinteratrial septum, and DCS sites. To determine whether changes in ERPs were uniform, the percentage change at each site was compared.

The corrected sinus node recovery time (cSNRT) was assessed at cycle lengths of 600 and 450 ms after a 30-s pacing train.6 Pacing was performed from the high lateral RA, repeated 3 times, and averaged. Patients with abnormally prolonged cSNRTs at baseline (>1500 ms) were excluded from analysis.

The unpaced PWD in sinus rhythm was analyzed as a marker of interatrial conduction time; it was measured from lead II of the surface ECG and averaged from a series of 20 consecutive, unpaced P-waves separate from the QRS complex.6 Measurements were performed using electronic calipers.

The presence of ventriculoatrial conduction was defined as a 1:1 ventriculoatrial relationship during pacing from the permanent ventricular lead at a rate of 75 beats/min followed by an atrial electrogram on the temporary lateral RA electrode for a 15-s period.

Long-Term Pacing
Randomization to long-term pacing was then done using a 3:2 VVI:DDD design (Figure 1). This ratio was determined a priori, because considerable drop-out in the VVI group was anticipated due to intolerance to the loss of AV synchrony. At baseline, 18 patients were programmed to VVI at 75/min, and 12 patients were programmed to DDD at 75/min, with an AV delay of 180 ms.

Three-Month Follow-Up
Patients returned after 3 months for transthoracic echocardiography and EPS, as described in detail above. Patients originally randomized to VVI pacing were then reprogrammed to DDD. These patients were followed for a subsequent 3-month period and reevaluated at 6 months. The patients originally randomized to DDD pacing remained in the DDD mode and were not studied further.

Six-Month Follow-Up
Patients who had been reprogrammed to DDD pacing (from VVI) at 3 months returned for a third echocardiographic and electrophysiological evaluation.

Electrophysiological Function
Three intracardiac quadripolar electrodes with an interelectrode spacing of 2, 5, and 2 mm were inserted via the right femoral vein and positioned in the distal coronary sinus (DCS), lateral RA free wall, and midtrial septum under fluoroscopic guidance. Then, autonomic blockade with atropine (0.04 mg/kg) and propranolol (0.2 mg/kg) was administered intravenously over 10 minutes. The mean dose of atropine was 2.4±0.5 mg, and the mean dose of propranolol was 10.0±3.2 mg. The pacemaker was then temporarily reprogrammed to VVI pacing at 30 beats/min to allow the underlying atrial rhythm to become manifest and to facilitate the evaluation of ERPs, sinus node function, and P-wave duration (PWD).

Fifteen minutes after autonomic blockade, ERPs were evaluated at twice diastolic threshold (for a pacing threshold of <2 mA) at cycle lengths of 600 and 450 ms. An incremental technique was used, starting with an S2 coupling interval of 170 ms, which was increased in increments of 5 ms. The ERP was defined as the longest coupling interval failing to propagate to the atrium. ERPs were measured from the lateral RA, midinterrtrial septum, and DCS 3 times during each cycle length. If the maximum and minimum measurements differed by >10 ms, 2 more measurements were taken, and the total was averaged. Right and left anterior oblique digital images were archived to help standardize catheter locations for subsequent studies. The noninvasive, programmed stimulation function of the pacemaker was invoked to evaluate ERPs from the electrode implanted in the RA appendage, as described above.

To estimate intrastudy variability, the lateral RA ERPs at 600 and 450 ms were determined twice in 10 patients at baseline. After initial ERP determinations, the catheter was withdrawn into the inferior vena cava and then repositioned where the initial ERP was assessed. Intrastudy variability was 3.04% at 600 ms and 4.22% at 450 ms.

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The presence of ventriculoatrial conduction was defined as a 1:1 ventriculoatrial relationship during pacing from the permanent ventricular lead at a rate of 75 beats/min followed by an atrial electrogram on the temporary lateral RA electrode for a 15-s period.
LVESD, left ventricular end-systolic diameter. Statistical significance was established at \( P < 0.05 \).

Ten of the 12 patients (83%) randomized to DDD reprogramming to the DDD mode, atrial sensing/atrial pacing demonstrated 100% ventricular pacing. At 6 months, after reprogramming to DDD pacing, atrial dimensions returned to values comparable to baseline.

### Atrial Dimensions

After DDD pacing for 3 months, left atrial and RA dimensions did not change significantly from baseline (Table 2). After VVI pacing for 3 months, left atrial superior-inferior dimensions increased from 4.7 \( \pm \) 0.4 to 5.1 \( \pm \) 0.2 cm (\( P < 0.01 \)), and medial-lateral dimensions increased from 4.1 \( \pm \) 0.5 to 4.6 \( \pm \) 0.5 cm (\( P < 0.05 \)). RA dilatation also developed, with superior-inferior dimensions increasing from 4.3 \( \pm \) 0.3 to 5.3 \( \pm \) 0.7 cm (\( P < 0.01 \)) and medial-lateral dimensions increasing from 3.9 \( \pm \) 0.3 to 4.5 \( \pm \) 0.3 cm (\( P < 0.01 \)). At 6 months, after reprogramming to DDD pacing, atrial dimensions returned to values comparable to baseline.

### Atrial ERPs and Rate Adaptation

After long-term VVI pacing, lateral RA, RA appendage, septal, and DCS ERPs increased significantly at both 600 and 450 ms drive cycle lengths (Table 3 and Figures 2 and 3). The proportional increase in ERPs at all sites was more marked at a cycle length of 600 ms than one of 450 ms (Figure 4). After programming to DDD and reassessment after 3 months, ERPs at all 4 sites and at both cycle lengths returned to values comparable to baseline. At baseline, 3 months, and 6 months, a consistent increase in atrial refractoriness was demonstrated, with increasing cycle lengths, suggesting the presence of ERP adaptation to rate.

The group randomized to DDD pacing displayed no significant differences in atrial ERPs from baseline at cycle lengths of 600 and 450 ms at any site. ERPs increased with increasing rate at the 4 atrial sites, also suggesting the presence of ERP adaptation to rate.

### ERP Dispersion

Increases in refractoriness occurred in a nonuniform fashion. Absolute and relative increases in ERP were more marked at the lateral RA and septum compared with the RA appendage and DCS (\( P < 0.05 \)). Relative increases were 18.5%, 19.6%, 10.7%, and 8.6%, respectively, at 600 ms and 13.9%, 15.7%, 8.2%, and 5.5%, respectively, at 450 ms (Figure 4). After reprogramming to DDD, relative decreases after a further 3 months of pacing were 15.8%, 19.4%, 9.8%, and 8.1%, respectively, at 600 ms and 15.6%, 13.1%, 9.5%, and 6.5%, respectively, at 450 ms. Relative decreases in refractoriness were more pronounced in the lateral RA and septum compared with the DCS and RA appendage.

### Statistical Analysis

Variables are reported as mean \( \pm \) SD. A repeated measures ANOVA was used to compare continuous variables. Scheffe’s F test was used for multiple comparisons. Intrastudy ERP variability was calculated using the following formula \( \frac{\sum \text{observation 1}}{\text{total observations}} - \frac{\text{observation 2}}{\text{total observations}} \) to calculate differences between categoric variables were evaluated with 2 \( \times \) 2 contingency tables using the \( \chi^2 \) test. Statistical significance was established at \( P < 0.05 \).

### Results

#### Patient Characteristics

No significant differences in clinical variables were present after randomization to VVI and DDD pacing (Table 1). Two patients from the VVI group were excluded before the second EPS due to antiarrhythmic treatment initiated after the development of AF. One 85-year-old man in the group randomized to VVI pacing died suddenly 2 months after the second EPS during the DDD phase of the study.

#### Pacemaker Telemetry

All patients randomized to VVI for the initial 3-month period demonstrated 100% ventricular pacing. At 6 months, after reprogramming to the DDD mode, atrial sensing/atrial pacing with 100% ventricular pacing was demonstrated in all patients. Ten of the 12 patients (83%) randomized to DDD pacing for the initial 3 months demonstrated atrial sensing/atrial pacing with 100% ventricular pacing; the remaining 2 patients in this group demonstrated atrial sensing/atrial pacing with 75% to 90% ventricular pacing.

### Atrial Dimensions

TABLE 2. Atrial Dimensions in the VVI/DDD Crossover Group and the DDD Group

<table>
<thead>
<tr>
<th>Dimensions, cm</th>
<th>VVI/DDD Cross-Over Group</th>
<th>DDD Control Group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>3 mo</td>
</tr>
<tr>
<td>LA sup-inf</td>
<td>4.7 ( \pm ) 0.4</td>
<td>5.1 ( \pm ) 0.2*</td>
</tr>
<tr>
<td>LA med-lat</td>
<td>4.1 ( \pm ) 0.5</td>
<td>4.6 ( \pm ) 0.5†</td>
</tr>
<tr>
<td>RA sup-inf</td>
<td>4.3 ( \pm ) 0.3</td>
<td>5.3 ( \pm ) 0.7*</td>
</tr>
<tr>
<td>RA med-lat</td>
<td>3.9 ( \pm ) 0.3</td>
<td>4.5 ( \pm ) 0.3*</td>
</tr>
</tbody>
</table>

LA indicates left atrium; med-lat, medial-lateral; and sup-inf, superior-inferior.
*\( P < 0.01 \) vs baseline; †\( P < 0.05 \) vs baseline; ‡\( P < 0.01 \) vs 3 months; §\( P < 0.05 \) vs 3 months.
Baseline ERP dispersion was similar between the DDD and VVI groups at 600 ms (59±21 versus 42±25 ms; P=0.13) and 450 ms (60±30 versus 49±22 ms; P=0.37).

Although the increases in refractoriness after 3 months of VVI pacing were nonuniform, the dispersion of refractoriness as prospectively defined did not change significantly. ERP dispersion after DDD pacing for a further 3 months demonstrated a nonsignificant decrease at 600 and 450 ms (Table 3).

In the group assigned to DDD pacing from baseline, ERP dispersion after DDD pacing for 3 months decreased significantly at both 600 and 450 ms.

**Sinus Node Function**

Two patients were excluded from analysis because of cSNRTs >1500 ms at baseline. After long-term VVI pacing, cSNRTs increased significantly at drive cycle lengths of 450 ms (271±257 versus 573±311 ms; P<0.01) and 600 ms (321±258 versus 442±244 ms; P=0.02). At 6 months, after reestablishment of AV synchrony with DDD pacing, cSNRTs

### Table 3. ERPs at Baseline and After VVI or DDD Pacing

<table>
<thead>
<tr>
<th></th>
<th>VVI/DDD Crossover Group</th>
<th>DDD Control Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>ERP dispersion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LRA-ERP</td>
<td>239±30</td>
<td>240±27</td>
</tr>
<tr>
<td>RAA-ERP</td>
<td>257±23</td>
<td>258±13</td>
</tr>
<tr>
<td>RAS-ERP</td>
<td>249±29</td>
<td>254±25</td>
</tr>
<tr>
<td>DCS-ERP</td>
<td>268±25</td>
<td>268±31</td>
</tr>
<tr>
<td>ERP dispersion</td>
<td>42±25</td>
<td>42±20</td>
</tr>
<tr>
<td>ERP dispersion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LRA-ERP</td>
<td>232±30</td>
<td>229±22</td>
</tr>
<tr>
<td>RAA-ERP</td>
<td>241±20</td>
<td>242±14</td>
</tr>
<tr>
<td>RAS-ERP</td>
<td>226±25</td>
<td>241±20</td>
</tr>
<tr>
<td>DCS-ERP</td>
<td>256±24</td>
<td>247±23</td>
</tr>
<tr>
<td>ERP dispersion</td>
<td>49±22</td>
<td>45±25</td>
</tr>
</tbody>
</table>

LRA indicates lateral right atrium; RAA, right atrial appendage; RAS, right atrial septum; and DCS, coronary sinus.

*P<0.01 vs baseline; †P<0.05 vs baseline; ‡P<0.01 vs 3 months; §P<0.05 vs 3 months.
reestablishment of AV synchrony with DDD pacing for 3 months, all parameters returned to values comparable to baseline.

Asynchronous Pacing and the Development of AF

Long-term asynchronous ventricular pacing is associated with an increased incidence of AF compared with atrial pacing. Observational studies demonstrate a 2- to 3-fold increase in the incidence of AF for ventricular pacing compared with atrial pacing, and evidence from several prospective, randomized trials have supported these findings. However, the mechanism by which asynchronous ventricular pacing leads to this increased incidence of AF is unknown.

Electrical Remodeling With Rapid Atrial Rates

The concept of atrial electrical remodeling was initially described in animal models in which rapid atrial pacing or induced AF produced changes in atrial electrophysiological properties that supported the initiation and perpetuation of AF. These changes included a shortening of atrial refractoriness, loss of rate-dependent shortening of ERP with increasing rate, increased dispersion of refractoriness, prolongation of intra-atrial conduction, and sinus node dysfunction. Electrical remodeling has also been demonstrated in humans, in whom several minutes of AF is sufficient to induce atrial ERP abbreviation for ≤8 minutes, with heightened susceptibility to AF. However, not all investigators have observed a decrease in atrial ERPs in other situations known to be associated with AF, suggesting that the development of AF is a complex and heterogeneous process.

Discussion

This serial electrophysiological study of pacemaker recipients presents new information regarding electrophysiological remodeling of the atrium in humans after the long-term loss of normal AV synchrony. To our knowledge, this is the first prospective evaluation of long-term changes in atrial electrophysiology in humans.

Long-term VVI pacing was associated with biatrial dilatation and significant changes in atrial electrophysiology. After VVI pacing for 3 months, a significant and nonuniform increase in ERPs occurred in the RA free wall, midinteratrial septum, RA appendage, and DCS at drive cycle lengths of 600 and 450 ms. Accompanying these changes was an increase in PWD, suggesting the development of slowed conduction. Long-term VVI pacing was also associated with a significant increase in cSNRT. These changes were not observed in patients paced in the DDD mode in whom AV synchrony was preserved.

The electrophysiological phenomena occurring as a consequence of long-term VVI pacing were reversible. After the reestablishment of AV synchrony with DDD pacing for 3 months, all parameters returned to values comparable to baseline.

A paucity of human studies exist that evaluate the effects of short-term atrial stretch on electrophysiological parameters; here, too, conflicting data exist. Increasing RA pressure with volume loading is associated with both an increase in atrial refractoriness and AF inducibility. However, atrial pressure elevation caused by AV interval manipulation has
been associated with either an increase or no change in atrial ERPs.\textsuperscript{9,10} Our findings of nonuniform prolongation of atrial ERPs, increased PWD, and impairment of sinus node function after long-term loss of AV synchrony are consistent with those from prior human studies of short-term atrial dilatation and animal studies of long-term atrial dilatation.\textsuperscript{5,9,18,20,22} Persistence of ERP adaptation to rate contrasts with animal studies of electrical remodeling that show loss of rate adaptation.\textsuperscript{1,2} However, our findings are consistent with those of Pandozi et al.,\textsuperscript{28} who demonstrated ERP adaptation to rate after cardioversion of long-term AF in humans, despite the presence of electrical remodeling. Long-term DDD pacing produced a decrease in ERP dispersion, raising the possibility that this effect may play a part in the described prevention of AF paroxysms after dual-chamber pacemaker implantation.\textsuperscript{29}

### Potential Mechanisms for Electrical Remodeling and AF After Loss of AV Synchrony

Stretch-activated channels have recently been identified in the atrium, and they may play a role in the observed ERP lengthening.\textsuperscript{30} Long-term atrial stretch may lead to fibrosis and glycogen accumulation in atrial tissue; the electrical changes observed may be a manifestation of these structural derangements.\textsuperscript{24,25,31} A change in the expression and conformation of atrial connexins might also underlie the observed changes in electrophysiology.\textsuperscript{32}

It is important to consider why the changes observed after long-term VVI pacing might be associated with AF. Indeed, an increase in atrial ERPs alone would be expected to prevent AF due to an overall lengthening of wavelength. Potential mechanisms could be considered under the categories of substrate and triggers.

#### Substrate

First, the increase in atrial size and conduction slowing may facilitate multiple wavelet reentry and increase the ability to sustain AF.\textsuperscript{1,3,5–7,26} Second, the nonuniform increase in refractoriness might increase the propensity for reentry by favoring the development of functional block.\textsuperscript{5,5} Finally, sinus node dysfunction may induce heterogeneity of atrial recovery of excitability, promoting fractionation of impulse propagation and the development of multiple reentrant circuits.\textsuperscript{6,33}

#### Triggers

Atrial early after depolarizations occurring in association with atrial stretch and atrial ERP prolongation may result in a polymorphic atrial tachyrhythmia, degenerating into AF.\textsuperscript{34} AF in humans could potentially develop through this mechanism in the setting of atrial dilatation and ERP prolongation. Loss of AV synchrony might also lead to AF through the genesis of atrial ectopy. Preliminary studies in animals have demonstrated atrial ectopy and tachyrhythmias in association with increased atrial ERPs after atrial dilatation. These foci display a similar distribution to those observed in human focal AF (pulmonary vein ostia and crista terminalis).\textsuperscript{35}

### Limitations

Right heart catheterization to assess atrial pressures was not performed because of the risks of displacing recently implanted pacing leads. AF inducibility was not assessed due to the possibility of inducing sustained AF, which would require cardioversion in patients who were not anticoagulated. We attempted to control for potential ERP variations between and within patients by using archived images to standardize catheter positions. Patients also had permanently implanted atrial leads, which allowed noninvasive, programmed stimulation from a fiducial RA site. ERP changes occurring with this lead paralleled those observed with the temporary electrodes. Finally, an intrastudy variation in ERPs of <5% was observed at baseline.

### Conclusions

Long-term loss of AV synchrony induced by VVI pacing is associated with reversible electrical remodeling of the atrium. This electrical remodeling is characterized by a nonuniform prolongation of atrial ERPs and an increase in PWD, suggesting slowing of atrial conduction and impairment of sinus pacemaker function. These phenomena are accompanied by biaxial enlargement and do not occur in patients paced synchronously in the DDD mode. This atrial electrical remodeling process suggests a possible mechanism for the increased incidence of AF occurring in patients undergoing long-term asynchronous VVI pacing.

### Acknowledgment

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### References

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