Atrial Therapies Reduce Atrial Arrhythmia Burden in Defibrillator Patients

Paul A. Friedman, MD; Barbara Dijkman, MD; Eduardo N. Warman, PhD; H. Amy Xia, PhD; Rahul Mehra, PhD; Marshall S. Stanton, MD; Stephen C. Hammill, MD; for the Worldwide Jewel AF Investigators

Background—Approximately 25% of patients who receive an implantable cardioverter-defibrillator (ICD) to treat ventricular tachyarrhythmias have documented atrial tachyarrhythmias before implantation. This study assessed the ability of device-based prevention and termination therapies to reduce the burden of spontaneous atrial tachyarrhythmias.

Methods and Results—Patients with a standard indication for the implantation of an ICD and 2 episodes of atrial tachyarrhythmias in the preceding year received a dual-chamber ICD (Medtronic 7250 Jewel AF) that uses pacing and shock therapies for prevention and/or termination of atrial tachyarrhythmias. In a multicenter trial, patients were randomized to 3-month periods with atrial therapies “on” or “off” and subsequently crossed over. Analysis was performed on the 52 of 269 patients who had episodes of atrial tachyarrhythmia and had ≥30 days of follow-up with atrial therapies on and off. The atrial therapies resulted in a reduction of atrial tachyarrhythmia burden from a mean of 58.5 to 7.8 h/mo. A paired analysis (Wilcoxon signed-rank test) showed that the median difference in burden (1.1 h/mo) was highly significant (\(P=0.007\)). When the subgroup of 41 patients treated only with atrial pacing therapies was analyzed, the reduction in burden persisted (\(P=0.01\)).

Conclusions—In this study, patients with a standard ICD indication and atrial tachyarrhythmias had a significant reduction in atrial tachyarrhythmia burden with use of atrial pacing and shock therapies. (Circulation. 2001;104:1023-1028.)

Key Words: tachyarrhythmias ▪ atrium ▪ atrial flutter ▪ fibrillation ▪ defibrillation ▪ pacing

The incidence of paroxysmal atrial fibrillation (AF) in patients who receive an implantable cardioverter-defibrillator (ICD) to treat ventricular tachyarrhythmias is ≈25% at the time of the implantation. Furthermore, ICD patients will develop a first episode of paroxysmal AF after the implantation at an annual rate of ≈2.6%. Management of atrial tachyarrhythmias in patients with ICDs is important because of the potential for increased morbidity and mortality and the cost of care. The Antiarrhythmics Versus Implantable Defibrillators trial showed that AF was an independent predictor of mortality in ICD patients, and other studies have shown that AF is associated with increased mortality in patients with depressed ventricular function. In addition, atrial tachyarrhythmias may be symptomatic and may precipitate symptoms in patients with congestive heart failure. Sustained atrial tachyarrhythmias may also increase the need for anticoagulation.

Antiarrhythmic drugs have been the mainstay of therapy for the management of patients with AF. Drug therapy is often unsatisfactory, however, because of limited efficacy, risk of proarrhythmia, and undesirable side effects, particularly in patients with depressed ventricular function. In patients who must already be exposed to the procedural risk of ICD placement for ventricular arrhythmias, a dual-chamber ICD that offers therapies for both atrial and ventricular tachyarrhythmias may represent a significant advance in arrhythmia management.

A new dual-chamber ICD has been introduced (Medtronic 7250 Jewel AF) that automatically detects and treats episodes of AF, atrial tachycardia (AT), ventricular fibrillation, and ventricular tachycardia and provides anti-bradycardia pacing. This device also uses separate algorithms for the prevention of atrial tachyarrhythmias. The primary objective of this study was to evaluate the effect of the combination of prevention and termination therapies on the percentage of time an ICD patient spends in atrial tachyarrhythmia (AT/AF burden). A second objective was to determine the effect of these atrial therapies on the frequency of AT/AF episodes.
Figure 1. AT/AF detection zones in Jewel AF 7250. AFDI indicates AF detection interval; ATDI_{min}, minimum AT detection interval; ATDI, AT detection interval. Minimum AFDI is 100 ms and corresponds to atrial blanking period. Nominal values are shown for AFDI, ATDI_{min}, and ATDI.

Methods

Study Population and Implantation Procedure

The study was conducted with 269 patients enrolled in 60 centers and followed up for 6 months. All patients had a clinical indication for the implantation of a ventricular ICD and 2 episodes of AF and/or AT in the preceding year with ECG documentation of $\geq 1$ episode. Patients with chronic fibrillation (unable to sustain sinus rhythm) were excluded. All patients gave written informed consent according to a protocol approved by the Human Subjects Committee of the institution at which the devices were implanted. The ICD pulse generator and electrodes were inserted through a single left pectoral incision by standard methods. A 2-lead system was implanted in 84.6% of patients, a 3-lead system in 14.6%, and a 4-lead system in 0.8%. A step-up atrial defibrillation threshold protocol was recommended but not required.

Device Characteristics

A detailed description of the detection and termination algorithms was reported previously. The device discriminates AT from AF on the basis of 2 programmable detection zones, which may overlap (Figure 1). If the median atrial cycle length is in the overlap zone, the rhythm is classified as AT if it is regular and AF if it is irregular. Outside of the overlap zone, the rhythm is classified as AF if the median cycle length is in the AF zone and AT if it is in the AT zone. Programming of the AT/AF detection intervals was left to the discretion of the physician.

The 2 prevention algorithms and 4 types of termination therapies that are available in the device are listed in Table 1. For AT episodes, the first 3 programmable therapies are pacing and the last 3 are shocks. The first 2 therapies may be programmed to either a burst+ or ramp, but the third therapy can only be programmed to a 50-Hz burst. For AF episodes, the first programmable therapy is pacing (50-Hz burst) followed by a maximum of 5 shock therapies. For both AT and AF, any of the 6 possible therapies can be programmed to be

<table>
<thead>
<tr>
<th>Therapy Type</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>AT/AF prevention</td>
<td></td>
</tr>
<tr>
<td>Atrial rate stabilization</td>
<td>Prevent long pauses after premature atrial complexes by delivering an atrial pace with an interval equal to the previous one plus a programmable increment (nominal 100 ms).</td>
</tr>
<tr>
<td>Overdrive switchback delay</td>
<td>High-rate DDI pacing is continued for a programmable duration immediately after an atrial tachyarrhythmia to overdrive suppress ectopy</td>
</tr>
<tr>
<td>AT/AF termination</td>
<td></td>
</tr>
<tr>
<td>Atrial burst+</td>
<td>Atrial burst delivered at programmable percentage of AT cycle length followed by 2 extrastimuli</td>
</tr>
<tr>
<td>Atrial ramp</td>
<td>Atrial autodecremental ramp initiated at programmable percentage of AT cycle length</td>
</tr>
<tr>
<td>Atrial 50 Hz burst pacing</td>
<td>A train of atrial pacing pulses at 20-ms intervals delivered for programmable duration (0.5 to 3 s)</td>
</tr>
<tr>
<td>Atrial defibrillation</td>
<td>Atrial shocks delivered over a programmable pathway at programmable energies of 0.4 to 27 J (independent of ventricular shock programming)</td>
</tr>
</tbody>
</table>
the device before arrhythmia redetection. If a shock was delivered at any time during an episode, pacing was considered unsuccessful.

Atrial tachyarrhythmia burden was defined as the total duration of all spontaneous AT/AF episodes divided by the corresponding follow-up time. Atrial tachyarrhythmia frequency was defined as the number of spontaneous AT/AF episodes divided by the time the patient was in sinus rhythm (ie, follow-up time minus time in AT/AF). The time in sinus rhythm was used to calculate AT/AF frequency because the prevention algorithms are operative and can reduce the frequency of AT/AF only during sinus rhythm. The follow-up time between 2 consecutive device interrogations was adjusted (reduced) to account for lost episodes. Episodes were lost when the number of episodes exceeded the device memory capabilities (30 treated and 128 untreated). The follow-up time was reduced because of lost episodes in the on period in 1 patient and in the off period in 6 patients. Paired comparisons of burden and frequency between the off and on periods were performed with a Wilcoxon signed-rank test because the data did not follow a normal distribution. An analysis was performed to determine whether there was a significant order effect, ie, treating patients in an on-then-off sequence versus an off-then-on sequence. Because no such effect was seen, data from the 2 randomized groups were combined.

### Results

Characteristics at the time of enrollment for all 269 patients who were randomized in the device clinical trial and for the 52 patients who were the subject of this analysis (discussed below) are summarized in Table 2. The 269 randomized patients had a mean ejection fraction of 34.5\%, and 80% had class II or worse heart failure. A history of AF was present in 81% of the patients, atrial flutter in 33%, and both in 22%. Despite the requirements of 2 AT/AF episodes in the year before enrollment, an atrial episode within the first 6 months of follow-up was observed in only 158 of the 269 subjects (59%). The devices were programmed with a median AT detection interval of 320 ms (range, 250 to 450 ms), AF detection interval of 270 ms (range, 150 to 300 ms), minimum AT detection interval of 170 ms (range, 100 to 300 ms) (Figure 1), and a median time to pacing therapy delivery of 1 minute (range, 0 to 30 minutes).

Of the 158 patients with AF/AT episodes during the course of the randomized study, 52 were included in this analysis. Reasons for exclusion included lack of crossover (n = 47) or <30 days of follow-up in each arm (n = 7) and nonprotocol programming of atrial therapies (eg, atrial prevention on with therapies off or other deviation, n = 52).

For the 52 patients with episodes who were properly followed up and programmed, the mean durations of the on and off arms were 98 ± 22 and 89 ± 30 days, respectively. In these 52 patients, the programming for the on period included ≥1 atrial pacing therapy, with a mean time to initiation of 4 minutes in 44 patients (median, 1 minute; range, 0 to 60 minutes), and ≥1 atrial shock therapy, with a mean time to shock of 104 minutes in 32 patients (median, 30 minutes; range, 1 to 1440 minutes). Atrial tachyarrhythmia burden was significantly reduced with the use of prevention and termination therapies. Individual patient results are shown in Figure 2A. During the off period, the mean burden was 58.5 h/mo (median, 2.82 h/mo; range, 0 to 470 h/mo), versus 7.8 h/mo (median, 0.63 h/mo; range, 0 to 66 h/mo) with therapies on. This reflects an 87% reduction in mean burden. The median off—on difference was 1.1 h/mo (P = 0.007).

<table>
<thead>
<tr>
<th>TABLE 2. Patient Demographics</th>
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<tbody>
<tr>
<td>Total</td>
</tr>
<tr>
<td>Sex, M/F, %</td>
</tr>
<tr>
<td>Age, y, mean ± SD</td>
</tr>
<tr>
<td>Primary indication for ICD, %</td>
</tr>
<tr>
<td>SCD</td>
</tr>
<tr>
<td>VT</td>
</tr>
<tr>
<td>SCD/VT</td>
</tr>
<tr>
<td>Other</td>
</tr>
<tr>
<td>Primary cardiovascular history, %</td>
</tr>
<tr>
<td>Coronary artery disease</td>
</tr>
<tr>
<td>Myocardial infarction</td>
</tr>
<tr>
<td>Valvular heart disease</td>
</tr>
<tr>
<td>Bradycardia</td>
</tr>
<tr>
<td>Congestive heart failure</td>
</tr>
<tr>
<td>Ejection fraction, %, mean ± SD</td>
</tr>
</tbody>
</table>

SCD indicates sudden cardiac death; VT, ventricular tachycardia; and SVT, supraventricular tachycardia.

Review of the individual patient responses in Figure 2 shows that there were 10 major responders (burden reduction >100 h/mo), who accounted for the majority of the mean burden reduction. All 10 major responders had ≥1 episode longer than 48 hours during the off period versus only 2 of the remaining 42 patients (P = 0.001). Responders were also found to have higher ejection fractions (46 ± 18% versus 31 ± 14%, P = 0.02). No differences were found in the other patient baseline characteristics, use of antiarrhythmia medications, pacing success rate, AT/AF ratio, and average atrial arrhythmia cycle length.

There was a trend toward a reduction in the number of AT/AF episodes per month of sinus rhythm. The mean frequency was 21.6/mo (median, 1.35/mo; range, 0 to 176/mo) with therapies off, versus 6.9/mo (median, 1.27/mo; range, 0 to 52/mo) with therapies on (P = 0.07). Individual patient results are shown in Figure 2B. There was no
correlation between changes in burden and changes in frequency (Figure 3). Patients with few long episodes had the largest burden reduction, whereas patients with many short episodes had the largest frequency reduction. Consequently, most of the patients with large burden reduction had small changes in frequency, and most of the patients with large frequency reduction had small changes in burden. There were 332 AT/AF episodes that were treated in 34 patients. In the 211 episodes treated as AT (64%), pacing therapies successfully terminated 62%. In the 121 episodes treated as AF (36%), pacing therapies successfully terminated 24%. The combined pacing success rate for all AT/AF episodes was 49%. The average number of pacing sequences delivered for successful termination was 4.2 with ramp and/or burst+ combined and 6.6 with ramp, burst+, and/or 50 Hz combined. Shock therapies successfully terminated 18 of 23 AT/AF episodes (78%). None of the atrial shock therapies resulted in ventricular proarrhythmia. In addition, 21 shock therapies were delivered in 4 patients because of inappropriate ventricular tachycardia/ventricular fibrillation detection.

A subanalysis of burden and frequency was performed in 41 patients in whom no shocks were delivered (ie, only pacing therapies used). The AT/AF burden reduction persisted in this subgroup treated only with pacing therapies (Figure 4A). During the period with therapies off, the mean AT/AF burden was 53.6 h/mo (median, 2.7 h/mo; range, 0 to 470 h/mo) versus 6.2 h/mo (median, 0.1 h/mo; range, 0 to 66 h/mo) with therapies on. This reflects an 89% reduction in mean burden. The median off–on difference in burden was 0.54 h/mo ($P=0.01$). The corresponding number of AT/AF episodes per month of sinus rhythm is shown in Figure 4B. The mean number of episodes was 22.3/mo (median, 1.1/mo; range, 0 to 176/mo) with therapies off versus 6.5/mo (median, 1.0/mo; range, 0 to 52/mo) with therapies on ($P=0.16$).

**Discussion**

This study found that in patients with a clinical history of AF (81% of patients) and/or atrial flutter and depressed ventricular function, therapies for termination and prevention of atrial tachyarrhythmias significantly reduced the atrial tachyarrhythmia burden ($P=0.007$). Moreover, this burden reduction persisted even when patients treated only with painless pacing therapies were considered. The absolute burden reduction was highly variable among patients and tended to be greatest in those patients who had more persistent episodes (>48 hours) during the off period. In addition, device-based atrial therapies resulted in a trend toward reduction in the frequency of atrial arrhythmias ($P=0.07$). Thus, the reduction in burden stemmed from both shorter and fewer episodes. Importantly, the presence of an implanted device permitted accurate determination of arrhythmia burden, independent of symptoms, which has been a limiting factor in other studies that used antiarrhythmic drugs to treat atrial tachyarrhythmias.7 We could not determine from the present analysis whether the frequency reduction stemmed solely from effective preventive atrial pacing or whether reverse remodeling8 of an adverse atrial electrophysiological milieu due to prompt arrhythmia termination played a role. Nonetheless, the observed episode reduction may be particularly important because it may enhance tolerability of device therapy for atrial arrhythmias.

**Pacing Therapies for the Termination of Atrial Tachyarrhythmias**

The patient discomfort associated with defibrillation has spurred interest in the development of less painful methods to terminate AF. Antitachycardia pacing has been highly effective in isthmus-dependent (typical) atrial flutter, which is a highly organized rhythm with a large excitable gap.9,10 Rate-adaptive antitachycardia pacing has not been effective in disorganized rhythms, such as atypical flutter or AF.11 The demonstration that AF has an excitable gap and that high-rate

![Figure 2. Effect of atrial therapies on AT/AF burden and frequency in 52 patients. A. Comparison of AT/AF burden in each patient between periods with atrial therapies on and off. Burden was significantly decreased during on period ($P=0.007$). B. Comparison of frequency of AT/AF episodes in each patient between periods with atrial therapies on and off. Nonsignificant reduction in frequency was observed during on period ($P=0.07$).](http://circ.ahajournals.org)
overdrive pacing can capture up to a 4-cm region of the atrium in a fibrillating animal model, however, has suggested a rationale for the use of this form of pacing for AF termination.\textsuperscript{12}

Clinical trials of high-frequency (50-Hz) burst pacing in short cycle length or long-standing AF have been disappointing.\textsuperscript{13} In atypical flutter, however, which may be a precursor to AF, the results have been more promising, with short-term success rates of up to 65%.\textsuperscript{11} In the present study, although the documented clinical arrhythmia was AF in 81\% of the patients, 64\% of spontaneous episodes were initially treated as an AT, suggesting that many episodes of clinical fibrillation begin with a more organized rhythm that subsequently degenerates. The presence of an indwelling device capable of prompt arrhythmia detection may permit termination with pacing techniques during the early, more vulnerable phase of arrhythmogenesis.

Presumably, the use of pacing therapies reduced the need for shocks, because pacing therapies were effective in terminating 49\% of all AT/AF episodes. Because the programming of shocks was left to the discretion of the physicians, only 11 of the 52 patients included in the analysis received shocks. Of the 41 patients who received only pacing therapies, the median reduction in burden with therapies was 0.54 h/mo ($P=0.01$). This is an important finding and suggests that a device with pacing and shock therapies may have much more clinical utility than a shock-only device.

**Role of an Atrial Defibrillator in Patients With Structural Heart Disease**

Previous experience with implantable atrial defibrillators has been limited to patients with structurally normal hearts.\textsuperscript{14} The role for this therapy may be particularly compelling, however, in patients with structural heart disease. Patients with depressed ventricular function and AF have an increased mortality compared with those with normal sinus rhythm independent of the ventricular heart rate, raising the possibility that atrial rhythm control may introduce a mortality benefit.\textsuperscript{3} In addition, patients with an indication for a ventricular defibrillator must be exposed to the risk of device implantation, so that a device capable of treating both atrial and ventricular arrhythmias may add therapeutic benefit with little or no additional risk. Although maintenance of sinus rhythm is more difficult in the setting of cardiac structural abnormalities,\textsuperscript{15} we found that atrial tachyarrhythmia burden was significantly reduced in this population. Reduction in AT/AF burden may improve quality of life, reduce tachycardia-induced cardiomyopathy, and/or reduce the number of hospitalizations. The clinical benefits of lowering the AT/AF burden in these patients were not evaluated in this study, however, and will need to be investigated in a prospective trial.

**Limitations**

Patients with no AT/AF episodes during the 6 months of follow-up (n=111) or with episodes whose device programming was not in compliance with the study protocol (n=106) were excluded from this analysis. We felt justified in excluding patients without episodes, because any antiarrhythmic therapy would be ineffective if it were delivered to patients without arrhythmias. The lack of adherence to the study protocol may have biassed the patient’s inclusion and thus affected study outcome. The study duration covered only a period early after device implantation.

Use of antiarrhythmic drugs (amiodarone, sotalol, or class I drugs) was stable in 69\% of the 52 patients during the 6 months of follow-up. Antiarrhythmic drug changes may have modified AT/AF burden and/or frequency in some patients. Because both prevention and termination therapies were used and because the type of atrial pacing was selected by the physician, we were unable to determine the relative impact of each of these elements independently on burden reduction.

**Conclusions**

The use of pacing and shock therapies for atrial tachyarrhythmia prevention and termination reduced arrhythmia burden in this study. Atrial arrhythmia burden is reduced because of the presence of shorter and possibly fewer episodes. These therapies may be useful in managing patients with a ventricular ICD indication and atrial tachyarrhythmias if the clinical value of AT/AF burden reduction can be demonstrated.

**References**

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