Safety and Efficacy of Advanced Atrial Pacing Therapies for Atrial Tachyarrhythmias in Patients With a New Implantable Dual Chamber Cardioverter-Defibrillator

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OBJECTIVES
This study evaluated the safety and efficacy of atrial pacing therapies for the treatment and prevention of atrial tachycardia (AT) or atrial fibrillation (AF) in a new dual chamber implantable cardioverter defibrillator (ICD).

BACKGROUND
Patients with an ICD may also experience AT or AF that is amenable to pace termination. The efficacy of atrial antitachycardia pacing (ATP) therapies for atrial tachycardia or atrial fibrillation (AT/AF) was determined in 151 patients after implantation of a GEM III AT ICD (Medtronic Inc., Minneapolis, Minnesota). The percentage of episodes successfully terminated was adjusted for multiple episodes per patient.

METHODS
A total of 717 of 728 (96%) episodes classified as AT or AF were judged to be appropriate detections. By device classification, atrial ATP terminated 187 of 383 (40% adjusted) episodes classified as AT compared with 65 of 240 episodes classified as AF (26% adjusted, p = 0.013). Atrial Ramp or Burst+ ATP terminated 184 of 378 episodes of AT (39% adjusted), whereas 50-Hz Burst pacing therapy terminated only 12 of 109 episodes of AT (12% adjusted) and 65 of 240 episodes of AF (26% adjusted). If efficacy was defined as termination of AT/AF within 20 s of delivery of the pacing therapy, ATP therapies terminated 139 of 383 (32% adjusted) episodes of AT compared with 34 of 240 episodes of AF (15% adjusted, p = 0.003). Efficacy was dependent on AT cycle length. Frequent transitions between AT and AF predicted inefficacy of atrial ATP (p < 0.001). Ventricular proarrhythmia secondary to atrial ATP was not observed. Atrial ATP therapies terminate many episodes of AT without ventricular proarrhythmia. The addition of 50-Hz Burst pacing has minimal efficacy for AT/AF. (J Am Coll Cardiol 2002; 40:1653–9) © 2002 by the American College of Cardiology Foundation

RESULTS
Atrial fibrillation is a frequent comorbidity in patients who receive an ICD (7–9). Moreover, AT occurs frequently in patients with AF and may precede the initiation of AF (6–9). Atrial tachycardia pacing therapies have been reported to terminate as many as 50% of episodes of AT in patients with symptomatic bradycardia receiving pacemakers or ICDs with atrial ATP therapies (5,8). The present study evaluated the safety and efficacy of a new generation ICD incorporating ATP therapies for the termination of AT, novel pacing therapies for the prevention of AF, and expanded diagnostic features to validate AF and AT detection and to quantify the frequency and duration of AF or AT over time in the ICD population. The predictors of atrial ATP efficacy were also evaluated.

CONCLUSIONS
Data suggest that atrial pacing may prevent atrial fibrillation (AF) in some patients (1–4). Novel pacing therapies designed to suppress the triggers for AF or to modify the electrophysiologic substrate predisposing to AF are presently undergoing clinical investigation (3). In addition, antitachycardia pacing (ATP) therapies are now available in some pacemakers and implantable cardioverter defibrillators (ICD) for termination of atrial flutter or atrial tachycardia (AT) that might degenerate into AF (5–9).

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METHODS

Study population. Patients with a history of sustained ventricular tachycardia (VT) or ventricular fibrillation (VF) were invited to participate in the Medtronic GEM III AT (Model 7276, Medtronic Inc., Minneapolis, Minnesota) clinical evaluation at 37 centers worldwide (Canada = 7, Europe = 30). All patients gave written informed consent to a protocol approved by the medical ethics committee of the institution at which the devices were implanted.

GEM III AT characteristics. The GEM III AT ICD is a multiprogrammable dual-chamber ICD with the ability to detect and treat episodes of atrial and ventricular tachyarhythmias. A previously described algorithm (PR logic,
Medtronic Inc.) is used to discriminate ventricular from supraventricular tachyarrhythmias based on the ratio and timing of P waves with respect to R waves (7–9). Atrial tachyarrhythmias are detected when the median atrial cycle length is less than the programmed AT or AF detection interval and the A:V ratio is greater than 1:1 for at least 32 ventricular beats. If the P:R pattern shows evidence of a short-long atrial interval and a short A-V or V-A interval, consistent with far field R-wave oversensing, that ventricular interval is not considered as evidence for AT or AF detection. The device discriminates AT from AF based on two programmable detection zones, which can overlap (Fig. 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. An atrial tachyarrhythmia ends with the detection of five consecutive sinus or paced beats with a normal A:V pattern or if the median atrial cycle length falls outside of the programmed AF and AT detection limits for 3 min.

The ICD was programmed to store information on 128 untreated and 25 treated episodes between interrogations. Stored information consisted of: date, time, and duration of the event, median atrial cycle length, therapy sequences and therapy efficacy; 10 s of electrogram before therapy; marker events and Marker Channel interval information for 120 intervals before therapy, 120 intervals before termination, and the number of transitions between atrial tachycardia or atrial fibrillation (AT/AF) during an episode. If the number of treated episodes between interrogations exceeded the device memory storage, only a count was kept of additional episodes.

**Atrial AT/AF therapies.** Atrial therapies to treat AT/AF episodes include three pacing algorithms for prevention (6,7), three pacing therapies for termination, and high-voltage shocks. The pacing prevention algorithms have been described in detail elsewhere (5). Atrial ATP pacing therapies included Ramp and Burst+ (a burst drive train followed by two extra-stimuli delivered at programmed decremental intervals) pacing and 50-Hz Burst pacing. The 50-Hz Burst pacing could only be programmed as a third or subsequent therapy for AT. For AF, pacing therapies consisted of 50-Hz Burst pacing only. The atrial ATP therapies were programmed as outlined in Table 1. Atrial cardioversion therapies were programmed at the discretion of the individual physician. Ventricular therapies were enabled in all patients.

By protocol, AF was classified by the ICD as an irregular atrial tachyarrhythmia >1 min duration with cycle length between 100 to 230 ms. Atrial tachycardia was classified as a regular tachyarrhythmia >1 min duration with a cycle length between 180 to 330 ms (Fig. 1).

The ICD system was evaluated before hospital discharge, then one and three months after implant. All detected tachyarrhythmias were retrieved by the programmer and reviewed by the local investigator for appropriate classification of detected event and outcome of therapy. All detected AF and AT events with stored electrograms were reviewed by one investigator (A.M.G.).

**Data analysis.** The rhythm (AT or AF) detected at the time of the first atrial ATP therapy was used to classify the episode. The number of transitions between AT/AF was retrieved from the data logs for each episode. A therapy was classified by the device as successful if five consecutive sinus or atrial paced events occurred before redetection of AT/AF. Examples of pace termination of AT and AF by Ramp

![AF Detection Zone](image1)

![AT Detection Zone](image2)

**Figure 1.** Atrial tachycardia (AT) and atrial fibrillation (AF) detection zones programmed in the study population. The minimum and maximum AF detection intervals were 100 and 230 ms, respectively. The minimum and maximum AT detection intervals were 180 and 330 ms, respectively. The overlap zone was 180 to 230 ms.

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### Table 1. Programming Parameters

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Programming</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atrial pacing preference</td>
<td>On, Upper pacing rate 120 beats/min</td>
</tr>
<tr>
<td>Atrial rate stabilization</td>
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</tr>
<tr>
<td>Post mode switch</td>
<td>overdrive pacing</td>
</tr>
<tr>
<td>Rate responsive pacing</td>
<td>On</td>
</tr>
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<td>VT/VF detection</td>
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<td>AT/AF detection</td>
<td>Both On</td>
</tr>
<tr>
<td>AF detection</td>
<td>1-min delay</td>
</tr>
<tr>
<td>AF zone</td>
<td>100–230 ms</td>
</tr>
<tr>
<td>AT zone</td>
<td>180–330 ms</td>
</tr>
<tr>
<td>At least 1 AT or AF therapy</td>
<td>On:</td>
</tr>
<tr>
<td>† First atrial ATP: Ramp—minimum of 5 pulses, A-S1 97%, minimum 4 sequences</td>
<td></td>
</tr>
<tr>
<td>† Second atrial ATP: Burst+-—minimum of 15 pulses, A-S1 94%; S1-S2 91%, S2-S3 10 ms, minimum 3 sequences</td>
<td></td>
</tr>
<tr>
<td>† Third atrial ATP 50-Hz Burst (physician discretion)</td>
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</table>

A-S1 = pacing interval of first ramp pulse-% of pre-therapy AT/AF interval; AF = atrial fibrillation; AT = atrial tachycardia; ATP = atrial tachycardia pacing; S1-S2 = pacing interval of the first extra-stimulus as a % of pretherapy AT/AF interval; S2-S3 = interval decrement between S1-S2 interval and second extra-stimulus; VF = ventricular fibrillation; VT = ventricular tachycardia.
and 50-Hz Burst therapies are shown in Figure 2. A primary termination was defined as immediate restoration of sinus- or atrial-paced rhythm after ATP therapy (Fig. 1, upper panel). A secondary termination was defined as a transient atrial tachyarrhythmia persisting after atrial ATP therapy (Fig. 1, lower panels). Given that many episodes of AT/AF may terminate spontaneously, a more conservative definition of atrial ATP therapy efficacy was also evaluated—termination of AT or AF within 20 s of delivery of the last atrial ATP therapy. This definition of ATP efficacy was selected based on two observations: 1) our previous study demonstrating that when atrial ATP successfully terminated atrial flutter or AT via a secondary termination (acceleration to AF), the AF spontaneously terminated within 9 s of delivery of atrial ATP (10); and 2) five consecutive sinus- or atrial-paced beats required by the device for classification of termination requires 6 to 11 s (based on review of episodes in the study population).

The SAS System statistical software was used for data analysis. Continuous data were reported as mean ± 1 SD. Atrial ATP efficacy was expressed as the incidence of successful terminations with 95% confidence intervals. The Generalized Estimating Equations method was used to account for the correlated data that arises from utilizing multiple episodes in some patients (11). All efficacy estimates reported are the adjusted estimates. Univariate predictors of AT/AF development and atrial ATP efficacy were determined. Regression analysis was applied to determine independent predictors of AT/AF development and the efficacy of atrial pacing therapies. Differences were significant if p < 0.05.

RESULTS

The patient demographics are shown in Table 2. Patients were followed for 79 ± 41 days. Patients were predominantly male with left ventricular dysfunction in the setting of coronary artery disease. Most patients had a prior history of AT/AF.

Ventricular tachyarrhythmia detection and therapy. The device classified 546 episodes in 47 patients as VT (n = 450) or VF (n = 96). The investigators confirmed that 493
episodes (90%) were VT or VF. The adjusted positive predictive value of VT and VF detection was 0.80 (95% confidence interval [CI], 0.67 to 0.89). The VT and VF therapies were successful in >99% of episodes.

**Detection of AT/AF.** Intermittent undersensing of persistent AF occurred in two patients. Episodes were censored from data analysis when undersensing occurred during the episode. Episodes of paroxysmal AT/AF with stored atrial electrograms (n = 728) occurred in 43 patients. Eleven episodes (1.5%) in two patients were inappropriately classified as AT or AF by the device due to far field R-wave oversensing. Thus, the positive predictive value of AT/AF detection was 0.96 (95% CI, 0.84 to 0.99). This low occurrence of inappropriate detection due to far field R-wave oversensing was observed despite the presence of far field R-wave oversensing before onset in 6.5% (48/728) of device-classified AT/AF episodes.

**Atrial ATP therapies.** A total of 4,315 spontaneous episodes of AT or AF were detected by the device, and atrial ATP therapies were delivered for 623 of these episodes. Most episodes did not include an intracardiac electrogram. A total of 36% of episodes were <1 min in duration, 40% were 1 to 10 min in duration, and 2% were greater than 24 h in duration. Internal atrial cardioversion was only utilized twice by the investigators after implantation, for induced episodes. Primary terminations occurred in 27 of 623 (4%) treated episodes. A primary termination of device-classified AT or AF was observed for only one treatment with 50-Hz Burst. The efficacy of the atrial ATP therapies based on device classification of termination are shown in Figure 3, solid squares. Atrial ATP successfully terminated 187 of 383 (40%) adjusted episodes classified as AT compared with 65 of 240 (26% adjusted) episodes classified as AF (p = 0.013). The overall efficacy for termination of device-classified AT or AF was 35% adjusted. The efficacy of atrial ATP therapies defined as termination of AT/AF within 20 s of delivery of the last therapy is shown in Figure 3, solid circles. Atrial ATP terminated 32% of AT episodes compared with 15% of device-classified AF episodes (p = 0.003), and the overall efficacy was 26% (adjusted efficacy rates).

Atrial tachycardia pacing efficacy was dependent on the cycle length of the atrial tachyarrhythmia as shown in Figure 4 (odds ratio, 1.009; 95% CI, 1.003 to 1.016). For every 50 ms increase in cycle length of AT episodes treated by Ramp or Burst+, the odds of effective termination increased by 59%.

**Ramp and Burst+ versus 50-Hz Burst pacing.** The efficacy of Ramp or Burst+ ATP and 50-Hz Burst pacing are shown in Figure 5. By device classification of efficacy,
Ramp or Burst+ ATP therapies successfully terminated 184 of 378 episodes of AT (39% adjusted), whereas 50-Hz Burst pacing successfully terminated only 12 of 109 episodes of AT (12% adjusted, p < 0.001). Indeed, 50-Hz Burst pacing had minimal efficacy (12% of all episodes starting as device-classified AF or AT) if a successful termination was defined as restoration of sinus or atrial paced rhythm within 20 s of delivery of the last pacing therapy.

Predictors of AF and AT development and response to therapy. Logistic regression analysis identified a prior history of AT/AF as the only predictor of AT/AF occurrence after ICD implantation (odds ratio, 11.7; 95% CI 4.2 to 32.1; p < 0.001). Regression analysis identified a prior history of VT (odds ratio, 5.18; 95% CI, 1.36 to 19.67; p = 0.016) and the use of angiotensin-converting enzyme (ACE) inhibitors (odds ratio, 4.07; 95% CI, 1.47 to 11.25; p < 0.01) as predictors of atrial ATP efficacy. Frequent transitions between AT and device-classified AF during a tachyarrhythmia episode predicted failure of ATP therapy (odds ratio, 0.26; 95% CI, 0.19 to 0.37; p < 0.001). This analysis was based on termination of AT/AF within 20 s of delivery of the last therapy.

DISCUSSION

The present study confirms the observations of previous studies that AT occurs frequently in patients with a history of AF in association with VT and VF (8–10). Furthermore, AT is frequently terminated by atrial ATP therapies (6,9). The present study provides new insights into the definition of atrial ATP efficacy as well as the predictors of ATP efficacy. In addition, the data analysis suggests that 50-Hz Burst pacing therapy has minimal efficacy for termination of AT or device-classified AF.

Atrial ATP efficacy. It has been hypothesized that pace termination of AT may prevent the development of AF or reduce overall AF burden (3,7,12). At present, long-term studies confirming the benefit of atrial ATP therapies for the prevention of AF are unavailable. In the present study, using a device-based classification of arrhythmia termination, atrial ATP therapies terminated 40% of AT and 26% of device-classified AF. In the present study, the atrial ATP efficacy rate for AT was lower than that reported by other investigators (5,8). By protocol, the definition of AF was more conservative, and, hence, more episodes were classified and treated as AT. Faster episodes of AT, some of which may have been AF, were less likely to be terminated by ATP therapies.

The utility of device-based arrhythmia diagnostics depends directly on the accuracy of arrhythmia detection. Analysis of stored AT/AF episodes from the present study indicated a positive predictive value for device-classified AT/AF detection of 0.96. Application of sophisticated detection algorithms in the present study led to a very low incidence of inappropriate AT/AF detection due to far field R-wave oversensing, thus making device-based diagnostic information more reliable.

Atrial ATP therapies have been reported to terminate many episodes of paroxysmal AT or atrial flutter in the pacemaker and ICD patient populations (5–9). However, atrial ATP may accelerate atrial flutter or AT to AF before termination (10,13). It has been thought that the creation of a more “disorganized” atrial arrhythmia might predispose to spontaneous termination of this secondary arrhythmia. The time frame for resumption of sinus rhythm after the induction of AF has been reported to be variable. We have previously reported that atrial ATP therapies delivered by intracardiac stimulation terminated 73% of episodes of atrial flutter (10). Transient AF was induced in 68% of patients during the application of ATP therapies, but the longest episode lasted only 9 s. Other investigators have also observed a high incidence of transient AF during pace termination of atrial flutter that lasted as long as 24 h (13). Because the present study population experienced frequent paroxysmal AT/AF with many episodes spontaneously terminating within 1 min of onset, a more conservative definition of atrial ATP efficacy seems appropriate. By design, the GEM III AT defines termination of AT/AF by ATP as efficacious if sinus- or atrial-paced rhythm occurs before redetection of AT/AF. Although this redetection time is variable, the device allows up to 3 min from the last therapy for redetection to occur. Efficacy defined as termination of AT or device-based AF within 20 s of delivery of atrial pacing therapy seems more appropriate because we
have previously demonstrated that the longest episode of transient AF during pace termination of atrial flutter was 9 s (10), and between 6 to 11 s are required for the device to recognize restoration of sinus- or atrial-paced rhythm. This more conservative definition indicates that atrial ATP efficacy is lower than previously reported. In the present study, applying this conservative definition, atrial ATP terminated 26% of all atrial tachyarrhythmias and 32% of AT episodes. Transitions between device-classified AT and AF have been observed in some patients. Although a local atrial electrogram may appear very organized, less organized arrhythmias may be observed in other parts of the atria (14). This might explain why not all episodes classified by the device as AT are effectively pace-terminated.

**50-Hz Burst pacing.** Previous investigators have demonstrated that an excitatory gap exists in patients with AF and that atrial overdrive pacing may capture local areas of the myocardium (15,16). However, local stimulation of atrial muscle did not terminate AF. Some investigators have suggested that rapid atrial pacing with 50-Hz Bursts might terminate AF. More recent clinical data has not supported this concept (17,18) although 50 Hz Burst pacing has been found to be marginally effective for termination of rapid atrial flutter (18). When ATP efficacy is defined as termination of device-classified AT or AF within 20 s of delivery of ATP therapy, 50-Hz Burst pacing terminated 4% of the episodes classified by the device as AT and 15% of episodes classified as AF. Some episodes classified as AF could have been rapid atrial flutter. The higher efficacy rates for 50-Hz Burst pacing reported using the device classification of efficacy in the present study, and other studies likely reflect spontaneous terminations of AT/AF. Primary terminations of device-classified AT or AF with 50-Hz Burst pacing were rare, further supporting the concept that many episodes terminating after delivery of this therapy reflect spontaneous terminations.

It cannot be concluded that 50-Hz Burst pacing was less efficacious for AT compared with other ATP therapies because this therapy was only delivered after unsuccessful Ramp or Burst+ therapies for AT. However, the incremental benefit of 50-Hz Burst pacing for AT after the delivery of Ramp or Burst+ ATP therapies is small.

**Predictors of atrial ATP efficacy.** Consistent with previous reports, atrial ATP therapies were more effective for episodes classified as AT on the onset of therapy (8). Ramp and Burst+ therapies were also more effective for tachycardias with longer cycle lengths. Atrial tachycardia pacing efficacy rates increased substantially for every 50-ms increase in the AT cycle length. Frequent transitions between device-classified AT and AF were associated with therapy failure. Whether this reflects that unsuccessful episodes were longer and, therefore, more transitions in rate and regularity occurred, or whether this identifies an arrhythmia characteristic that is unresponsive to ATP, is uncertain. Israel et al. (6) have also reported that more organized ATs are likely to be pace-terminated compared with less organized arrhythmias (6). In addition, the use of ACE inhibitors was predictive of atrial ATP efficacy. Angiotensin-converting enzyme inhibitors have been reported to reduce the magnitude of atrial fibrosis in experimental models of AF (19). Whether this effect modulates the electrophysiologic substrate to increase ATP efficacy requires further study.

**Implications for programming atrial ATP.** Many episodes of AF last <1 min in duration. Other investigators have reported that most episodes of AT remain stable over this time frame (6). Hence, a 1-min delay before delivery of ATP therapy would avoid unnecessary therapy for short episodes and reduce the probability of inducing sustained AF. Arrhythmias that frequently transition between device-classified AT and AF are less responsive to ATP therapy, and programming ATP therapies over the long term may not be beneficial in such patients. Atrial 50-Hz Burst pacing has minimal efficacy in addition to Ramp and Burst+ ATP therapies. The programming parameters summarized in Table 1 could be considered as initial programming parameters for patients receiving this ICD.

**Ventricular therapies.** The VT and VF detection and therapy efficacies are similar to those reported for other ICDs. Importantly, there was no evidence of ventricular proarrhythmia secondary to atrial ATP therapies.

**Study limitations.** The present study was not designed to evaluate the efficacy of the pacing prevention therapies. Follow-up was relatively short, and it is possible that ATP efficacies may change over time. In addition, review of the AT episodes not treated in most cases was not possible due to the lack of intracardiac electrograms. It is possible that some atrial ATP therapies converted AT to AF. It was not possible to assess this outcome in the present study. It is possible that some episodes of AT/AF were not detected due to intermittent undersensing.

**Conclusions.** Atrial tachycardia occurs frequently in patients with AF and VT. Atrial ATP therapies safely terminate many episodes of AT although efficacy rates are lower than previously reported. Atrial 50 Hz Burst pacing has minimal incremental benefit compared with Ramp or Burst+ therapies for AT and minimal efficacy for the termination of device-classified AF.

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