Do Atrial Tachyarrhythmias Beget Ventricular Tachyarrhythmias in Defibrillator Recipients?

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OBJECTIVES
This study was designed to analyze the incidence of “dual tachycardia”—ventricular tachycardia (VT) or ventricular fibrillation (VF) preceded by paroxysmal atrial tachycardia (AT) or atrial fibrillation (AF)—in patients receiving dual-chamber implantable cardioverter defibrillators (ICDs).

BACKGROUND
Paroxysmal AT/AF occurs commonly in patients who receive ICDs for the treatment of life-threatening VT/VF. Although AF is associated with an adverse prognosis in the setting of structural heart disease, the relationship between AT/AF and VT/VF is unclear.

METHODS
We followed 537 patients undergoing implantation of the Jewel AF ICD (Model 7250, Medtronic, Minneapolis, Minnesota) for 11.4 ± 8.2 months. These included 398 patients with a history of at least two episodes of AT or AF during the preceding year as well as 139 patients enrolled because of VT/VF alone.

RESULTS
There were 233 dual tachycardia episodes in 45 patients during follow-up. Overall, 8.9% of episodes detected as VT/VF were dual tachycardias, and 20.3% of patients with VT/VF had at least one dual tachycardia episode. The median duration of AT/AF preceding the first VT/VF detection was 1.09 h (25% to 75% quartile 0.24 to 33.4 h). When AT/AF continued between two consecutive VT/VF detections, the median interdetection interval was 11 min. When AT/AF terminated either because of a ventricular therapy or spontaneously, the median interdetection interval was prolonged to 71 h (p < 0.001).

CONCLUSIONS
Dual tachycardia is common in ICD recipients with a history of AT/AF. The duration of AT/AF preceding the first VT/VF detection is ≤1 h about 50% of the time. Termination of the AT/AF significantly delays the time to the next VT/VF detection. (J Am Coll Cardiol 2002;40:335–40) © 2002 by the American College of Cardiology Foundation

Given the epidemiology of atrial fibrillation (AF), it is not surprising that atrial tachyarrhythmias, including AF and atrial flutter, are common in patients who have received implantable cardioverter defibrillators (ICDs) (1,2) for the management of life-threatening ventricular arrhythmias. The incidence of AF is markedly increased with advancing age and in patients with structural heart disease, and AF is associated with an independent adverse prognosis in this setting (3,4). It is likely that this increased mortality is multifactorial and that increases in heart failure and stroke as well as drug toxicity may play a role (5). Also, atrial tachyarrhythmias, either directly as a result of tachycardia-induced changes in ventricular refractoriness or indirectly as a result of hemodynamic alterations, ischemia or neurohumoral activation, may facilitate the induction or perpetuation of ventricular tachyarrhythmias in these patients.

Data from single-chamber ICDs suggest that about 10% of ventricular episodes in ICD recipients are preceded by some form of supraventricular tachycardia (SVT), most commonly AF (6). However, in the absence of a direct atrial electrogram recording, interpretation of these data is limited by the inability to confirm the diagnosis of an atrial tachyarrhythmia. A recent prospective study has shown that patients with persistent AF receiving single-chamber ICDs have a higher incidence of ventricular therapies than patients in sinus rhythm at the time of implant (7). The advent of newer dual-chamber ICDs permits the simultaneous recording of atrial and ventricular electrograms and should allow more precise documentation of the presence of atrial tachyarrhythmias preceding ventricular episodes. The purpose of the present study, therefore, was to analyze the incidence of “dual tachycardia”—ventricular fibrillation (VF) or ventricular tachycardia (VT) preceded by paroxysmal AF or atrial tachycardia (AT)—in patients receiving a novel dual-chamber ICD, which incorporates a sophisticated dual-chamber algorithm for detecting and discriminating between atrial and ventricular tachyarrhythmias (8,9), as well as the capacity to deliver therapies aimed at preventing and terminating atrial arrhythmias (9,10). We also analyzed the predictors of dual tachycardia and the association between atrial and ventricular tachyarrhythmias.

METHODS

Device characteristics. The Jewel AF ICD (Model 7250, Medtronic Inc, Minneapolis, Minnesota) is a 55-cc multi-
programmable dual-chamber device capable of DDD pacing as well as detecting and treating episodes of atrial and ventricular tachyarrhythmias. The ventricular termination therapies include ramp and burst antitachycardia pacing as well as shocks (0.4 to 27 J). Atrial therapies include two pacing algorithms for prevention, three pacing therapies for termination, and shocks (0.4 to 27 J). The two prevention algorithms are “atrial rate stabilization” and “switch back delay” (10). Atrial pacing therapies for termination include two forms of antitachycardia pacing (ramp and burst+, that is, burst with two extrastimuli) and 50-Hz burst pacing (9,10).

The lead system includes a bipolar atrial and ventricular electrode for dual-chamber pacing and sensing. In addition, ventricular and supraventricular shocking electrodes are required. An optional third high-voltage electrode may be placed in the coronary sinus.

A dual-chamber algorithm (“PR logic”) is used to discriminate ventricular from supraventricular tachyarrhythmias on the basis of the ratio and timing of P-waves with respect to R-waves (8–10). The device always delivers ventricular therapy when the median RR interval is less than the programmed SVT minimum interval (nominally 320 ms) (11). Atrial tachyarrhythmias are detected when the median atrial cycle length (12 beats) is less than the programmed AT or AF detection interval and the A:V ratio is >1:1 for at least 32 ventricular beats (8–10). The device discriminates AT from AF based on two programmable detection zones, which can overlap. 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 (8–10).

**Patients and implant procedure.** Two groups of patients were enrolled in the study. Patients with VT/AT (n = 398) had a documented history of at least two episodes of AT or AF in the preceding year, with electrocardiogram documentation of at least one of the episodes. In addition, these patients were required to have had a qualifying ventricular arrhythmia: either a history of cardiac arrest because of VT or VF (not associated with acute myocardial infarction and not associated with any reversible cause) or spontaneous or inducible hemodynamically unstable sustained monomorphic VT. Ventricular tachycardia–only patients (n = 139) had a qualifying ventricular arrhythmia, but a history of AT was not required. Patients with chronic AF were not eligible for device implantation. 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.

Selection of detection and therapy settings was left to the implanting physician’s discretion. However, patients in the VT/AT group were randomized to having atrial prevention and treatment therapies activated or deactivated for the first three-month follow-up period, with crossover for the second three-month period (10). Patients were followed up with routine device interrogations at one month, three months and six months postimplant and then every six months thereafter with additional device checks as clinically indicated.

**Data analysis.** We prospectively defined “dual tachycardia” as VT or VF that initiated in the setting of an ongoing AT or AF episode. This definition specifically does not include atrial tachyarrhythmias initiated during ongoing ventricular tachyarrhythmias. Appropriate classification of each detected arrhythmia episode (atrial and ventricular) was prospectively made by an investigator participating in the multicenter clinical trial of the device (9), based on review of the electrograms and event markers stored in the device memory buffer. In addition, each dual tachycardia episode was independently re-reviewed by two of the present authors (DEE and KMS). For an episode to be classified as a dual tachycardia, the electrogram or marker channel in the printed episode report had to show the sudden onset of VT/VF during an ongoing episode of AT/AF (Figs. 1 and 2). In 44/45 patients with confirmed dual tachycardia episodes, a Vtip-Aring or Atip-Vring electrogram during the episode was available for review. In the remaining patient, an Atip-Aring electrogram was available. In this patient, a dual tachycardia was diagnosed on the basis of: 1) the marker channel showing the abrupt onset of rapid regular ventricular activity during ongoing AF; and 2) the termination of the rapid ventricular rate but not the AF following a ventricular shock.

Statistical analyses were performed using SAS statistical software (SAS Institute, Cary, North Carolina). Continuous data were reported as the mean ± SD or as the median along with the 25% to 75% quartiles. Comparisons between groups were performed using either a Student t test or a Wilcoxon rank-sum test. The null hypothesis was rejected when p < 0.05. The total number of dual tachycardia episodes divided by the total number of VT/VF episodes gave an estimate of the relative occurrence of dual tachycardia in the study population. Because this estimate was biased towards those patients having the greatest number of episodes, the estimate was adjusted using the generalized estimating equation (GEE) model with an exchangeable correlation structure to remove the bias (12,13). In addition to removing bias from the estimate, the GEE model also generated 95% confidence intervals (CIs) for the estimate.
RESULTS

Patient demographics are shown in Table 1. The 537 patients with an implanted device were followed for 11.4 months (range 0 to 33 months). The patients were predominantly men (83%). The mean ejection fraction was 35 ± 16% and 81% had a New York Heart Association functional class ≥II. The most frequently used antiarrhythmic medications at enrollment were amiodarone (31%) and digoxin (36%).

Figure 1. Electrogram (Atip-Vring EGM) recording (0.5 mv/mm) at a chart speed 25 mm/s, showing a typical episode of dual tachycardia in one patient. Upward markers indicate atrial events; downward markers indicate ventricular events. The short triple atrial markers indicate ongoing atrial fibrillation (AF) detection (FD). Intermediate-height ventricular markers (VS) indicate sensed R-waves (VS); short double ventricular markers indicate ventricular fibrillation (VF) sense (FS); short triple markers indicate VF detection (FD). The vertical arrows show atrial activation complexes during device-defined AF. The short horizontal arrows show R-waves with intrinsic conduction. The ventricular rate accelerates abruptly; at the same time there is a change in the morphology of the ventricular electrogram (long horizontal arrow). The median RR interval of this device-defined VF episode was 260 ms.

Figure 2. Electrogram (Atip-Vring EGM) recording (1 mv/mm) at a chart speed 25 mm/s, showing a typical episode of dual tachycardia from another patient. The markers are the same as in Figure 1. The vertical arrows show atrial activation complexes during device-defined atrial fibrillation. The short horizontal arrow shows an R-wave with intrinsic conduction. The ventricular rate accelerates abruptly; at the same time there is a change in the morphology of the ventricular electrogram (long horizontal arrow). The median RR interval of this device-defined ventricular fibrillation episode was 250 ms.
Table 1. Patient Demographics at Time of Enrollment (n = 537)

<table>
<thead>
<tr>
<th>Age, yrs (mean ± SD)</th>
<th>64.4 ± 12.1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male (n, %)</td>
<td>443 (82.5%)</td>
</tr>
<tr>
<td>Ejection fraction (mean ± SD)</td>
<td>34.7 ± 16.0</td>
</tr>
<tr>
<td>NYHA functional class</td>
<td>n (%)</td>
</tr>
<tr>
<td>I</td>
<td>89 (16.6%)</td>
</tr>
<tr>
<td>II</td>
<td>281 (52.3%)</td>
</tr>
<tr>
<td>III</td>
<td>143 (26.6%)</td>
</tr>
<tr>
<td>IV</td>
<td>12 (2.2%)</td>
</tr>
<tr>
<td>Unknown</td>
<td>12 (2.2%)</td>
</tr>
<tr>
<td>Primary indication</td>
<td></td>
</tr>
<tr>
<td>SC only</td>
<td>116 (21.6%)</td>
</tr>
<tr>
<td>VT only</td>
<td>339 (63.1%)</td>
</tr>
<tr>
<td>SC and VT</td>
<td>67 (12.5%)</td>
</tr>
<tr>
<td>Other</td>
<td>15 (2.8%)</td>
</tr>
<tr>
<td>History of coronary artery disease</td>
<td>364 (67.8%)</td>
</tr>
<tr>
<td>History of myocardial infarction</td>
<td>296 (55.1%)</td>
</tr>
<tr>
<td>History of congestive heart failure</td>
<td>211 (39.3%)</td>
</tr>
<tr>
<td>History of cardiomyopathy</td>
<td>265 (49.3%)</td>
</tr>
<tr>
<td>History of valvular heart disease</td>
<td>69 (12.8%)</td>
</tr>
<tr>
<td>History of AF</td>
<td>348 (64.8%)</td>
</tr>
<tr>
<td>History of atrial flutter</td>
<td>136 (25.3%)</td>
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<tr>
<td>Antiarrhythmic drug use at enrollment</td>
<td></td>
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<tr>
<td>Amiodarone</td>
<td>165 (30.7%)</td>
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<tr>
<td>Sotalol</td>
<td>36 (6.7%)</td>
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<tr>
<td>Class I</td>
<td>42 (7.8%)</td>
</tr>
<tr>
<td>Beta-blocker</td>
<td>88 (16.4%)</td>
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<tr>
<td>Digoxin</td>
<td>193 (35.9%)</td>
</tr>
<tr>
<td>Ca-channel blocker</td>
<td>17 (3.2%)</td>
</tr>
</tbody>
</table>

AF = atrial fibrillation; NYHA = New York Heart Association; SCD = sudden cardiac death; VT = ventricular tachycardia.

There were a total of 2,602 spontaneous VT/VF detections classified by the investigator as appropriate in 222 patients. There were 233 VT/VF episodes classified as dual tachycardia in 45 patients. Overall, 8.9% of the VT/VF episodes (233/2,602) were dual tachycardias and 20.3% of patients with VT/VF had at least one dual tachycardia episode. Using the GEE model to adjust for multiple episodes per patient, 11.9% (95% CI 8.6% to 16.2%) of VT/VF episodes were dual tachycardias. When VT and VF episodes were analyzed separately, 142/1,927 (7.4%) VT episodes were dual tachycardias. When the GEE model was used to adjust the estimate, 10.1% (95% CI 6.3% to 15.8%) of all VT episodes were dual tachycardias. When only VF episodes were considered, 91/714 (13.4%) of these episodes were dual tachycardias. When the GEE model was used to adjust the estimate, 15.0% (95% CI 10.6% to 20.9%) of VF episodes were dual tachycardias. The dual tachycardia episodes that the device detected as VT had an average cycle length of 352 ± 42 ms, significantly longer than the average cycle length of the VF episodes (260 ± 45 ms, p < 0.001).

The occurrence of dual tachycardia did not appear to be influenced by a period of altered ventricular or atrial irritability in the immediate postimplant period. The median time to onset of the 231 dual tachycardias was 186 days (25% to 75% quartile, 86 to 445 days). Only eight episodes of dual tachycardia in seven patients were observed in the first week postimplant.

Of the 233 dual tachycardia episodes, 115 (49.3%) were classified as AT at the time of VT/VF detection; 118 (50.6%) were classified as AF. The average of the median cycle length of the AT episodes was 233 ± 38 ms, significantly longer than the average of the median cycle length of the AF episodes (171 ± 38 ms, p < 0.001). The duration of AT/AF preceding the onset of VT/VF was also analyzed. Because multiple VT/VF events frequently occurred during a single AT/AF episode, only the interval from AT/AF detection to the first VT/VF detection was included. For 41 VT episodes, the median duration of AT/AF preceding VT detection was 1.2 h (25% to 75% quartile, 0.15 to 29.4 h). For 45 VF episodes, the median duration of AT/AF preceding VF detection was 1.03 h (25% to 75% quartile, 0.34 to 112 h).

Ventricular therapies were delivered to treat 205 (88%) of the 233 dual tachycardia episodes. The VT/VF in the remaining 28 episodes terminated spontaneously before a therapy could be delivered. Although a ventricular therapy (ATP or shock) successfully terminated 100% of the 205 VT/VF episodes that were treated, the ventricular therapy terminated AT/AF in only 82 (40%) of these 205 dual tachycardias. An analysis was performed to test the hypothesis that if AT/AF continued after VT/VF terminated, the time to the next VT/VF detection would be shorter (that is, AT/AF would cause clustering of VT/VF events). When AT/AF continued between two consecutive VT/VF detections (91 episodes), the median interdetection interval was 15 min (25% to 75% quartile, 2.5 to 285 min). When AT/AF terminated (through a ventricular therapy or spontaneously) and sinus rhythm persisted for at least 1 min (74 episodes), the median interdetection interval was 108 h (25% to 75% quartile, 0.5 to 678 h).

There were 15 patients identified that had at least one dual tachycardia where AT/AF terminated before the next VT/VF detection and at least one dual tachycardia where AT/AF continued to the next VT/VF detection. A paired comparison (Wilcoxon signed-rank test) was performed in these 15 patients. The median VT/VF interdetection interval was determined in each patient and then across the 15 patients. When AT/AF continued, the median interdetection interval was 11 min (25% to 75% quartile, 3 to 96 min) compared to 71 h (25% to 75% quartile, 14 to 508 h) when AT/AF terminated (p < 0.001).

DISCUSSION

The principal finding of the present study is that 8.6% of all VT/VF episodes were dual tachycardia—VT or VF occurring during and preceding by a paroxysm of AT or AF—in ICD recipients. Furthermore, 20.3% of the patients that had VT/VF events during follow-up had at least one dual tachycardia episode. Even more notable, when the atrial tachyarrhythmia persisted despite a successful ventricular therapy. It should be emphasized that
the definition of dual tachycardia that we employed specifically excluded atrial arrhythmias initiating during ongoing ventricular tachyarrhythmias.

**Atrial tachyarrhythmias in ICD recipients.** Atrial fibrillation is the most frequently encountered sustained arrhythmia in clinical practice (14) and, with changing demographics, has been growing in prevalence (15). Atrial fibrillation is particularly common in patients with left ventricular dysfunction, occurring in 10% to 35% of patients with congestive heart failure (16). Therefore, it is not surprising that atrial tachyarrhythmias are frequent in ICD recipients, the vast majority of whom have structural heart disease (1,2).

Drug therapy of atrial tachyarrhythmias in defibrillator recipients is often unsatisfactory because of limited efficacy (17), ventricular proarrhythmia (18), drug-device interactions (19) and the frequent inability to tolerate antiarrhythmic drugs because of negative inotropic effects or organ toxicity.

In the presence of heart disease, AF is a powerful predictor of overall mortality (3,4). This may be related to the occurrence of thromboembolism, to the adverse hemodynamic effects of AF and to the toxic effects of drug therapy of AF (5). Epidemiologic data conflict as to whether the presence of AF is independently associated with an increase in the risk of sudden death. A retrospective analysis of the Studies Of Left Ventricular Dysfunction trials showed that the presence of AF at baseline was associated with an increase in total mortality, but did not predict the occurrence of sudden death among patients with mild-to-moderate congestive heart failure (20). On the other hand, in an analysis of almost 400 patients with severe congestive heart failure, Middlekauf et al. (21) found that baseline AF was associated with a dramatic increase in the risk of sudden cardiac death. More recently, Gronefeld et al. (7) reported that persistent AF was a strong independent predictor (relative risk 1.8) of the occurrence of ventricular tachyarrhythmias among ICD recipients when compared to patients with persistent sinus rhythm.

These epidemiologic data apply to patients with persistent AF; there are relatively sparse data regarding the prognostic implications of paroxysmal AF in patients with structural heart disease. A retrospective analysis of patients from the Vasodilator-Heart Failure Trial studies found that patients with AF had no increase in sudden death compared with those in sinus rhythm (22). Although approximately 10% of patients in this trial had AF or atrial flutter on one but not all of their Holter monitors, these patients were excluded from the pooled survival analysis.

**Does AT/AF beget VT/VF?** The present data suggest that there may be an association between ventricular tachyarrhythmias and paroxysmal atrial tachyarrhythmias among ICD recipients. This observation is consistent with the previous observation that 10% of ventricular therapies in single-chamber ICD recipients were preceded by AF with a rapid ventricular response (6). Although the present investigation does not permit analysis of the mechanism by which AT/AF led to VT/VF, three possible mechanisms may be involved: 1) direct causation, 2) indirect causation and 3) an epiphenomenon. First, it is possible that there may be a direct link. A rapid ventricular rate during an atrial tachyarrhythmia will directly reduce ventricular refractoriness. In addition, the irregular rhythm of AF leads to short-long-short sequences that may be intrinsically proarrhythmic (23). When ICD patients with persistent AF were compared to patients with persistent sinus rhythm, the baseline heart rate preceding VT/VF did not differ between the two groups (7). However, there was high incidence of short-long-short sequences preceding VT/VF in the patients with persistent AF (7).

Atrial tachyarrhythmias also may indirectly affect ventricular electrophysiology through their associated hemodynamic changes. Cardiac output falls in AF through the loss of atrial mechanical function and decreased diastolic filling time. In addition, the presence of an irregular rhythm may in and of itself reduce cardiac output (24). A decrease in cardiac output during a paroxysm of AF or atrial flutter may increase preload and, via mechanoelectrical coupling, may increase susceptibility to ventricular arrhythmias (25). The hemodynamic effects of atrial tachyarrhythmias may also cause a reflex increase in sympathetic tone and decrease in parasympathetic tone, which favors the development of ventricular arrhythmias (26,27). Finally, atrial tachyarrhythmias may induce ischemia, either through tachycardia or a reduction in cardiac output.

However, the occurrence of dual tachycardia may also represent an epiphenomenon. Thus, it is possible that onset of a ventricular tachyarrhythmia during an atrial tachyarhythmia might represent a common antecedent for both (such as ischemia or excess sympathetic tone). It should be emphasized that these three mechanisms are not mutually exclusive.

If there is a causal relationship—if AT/AF does beget VT/VF—then the present data have important implications. If prospectively validated, they would suggest that atrial tachyarrhythmias should be aggressively treated in ICD recipients and other patients with structural heart disease. Consideration to the implantation of devices with the capacity to prevent and treat atrial as well as ventricular tachyarrhythmias, particularly in those patients with a history of AF, would also be appropriate. The short interval to recurrence of VT/VF when ventricular therapies fail to terminate AT/AF suggests that ventricular shock programming should use energies and shock vectors that optimize conversion of atrial tachyarrhythmias.

**Study limitations.** It should be emphasized that these data were analyzed retrospectively and that they require independent and prospective validation. Furthermore, we did not prospectively acquire the data that would have been required to better define the mechanism underlying the association. In particular, insufficient RR intervals were collected before the onset of ventricular events to accurately determine the RR interval pattern before VT/VF onset. Although all dual
tachycardia episodes were carefully reviewed, it was not possible to exclude the possibility that some VT/VF episodes were supraventricular tachycardias with rapid conduction to the ventricles. It also should be strongly emphasized that it has not been shown whether device-based treatment of antecedent atrial tachyarrhythmias would reduce the incidence of VT/VF tachycardia. Finally, it should be noted that the classification of ventricular episodes as VT or VF and atrial episodes as AT or AF was a device-based classification that relied on cycle length and the cycle length regularity obtained from bipolar recordings in the atrium and ventricle.

Summary. Dual tachycardia—VT or VF occurring during a paroxysm of AT or AF—occurs commonly in ICD recipients with a history of atrial arrhythmias. The duration of AT/AF preceding the first VT/VF detection is <1 h about 50% of the time. Furthermore, the time to the next recurrence of a ventricular tachyarrhythmia episode is substantially prolonged in patients with dual tachycardia in whom the atrial tachyarrhythmia is terminated at the time of a ventricular therapy, as compared with those in whom the atrial tachyarrhythmia persists. These observations suggest the possibility that atrial tachyarrhythmias may increase the risk of ventricular tachyarrhythmias, in which case strategies aimed at the prevention and aggressive treatment of atrial arrhythmias would be warranted in ICD recipients.

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REFERENCES