Pause-Dependent Polymorphic Ventricular Tachycardia During Long-Term Treatment With Dofetilide

A Placebo-Controlled, Implantable Cardioverter-Defibrillator-Based Evaluation

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OBJECTIVES
To compare the incidence of pause-dependent polymorphic ventricular tachycardia (PVT) in patients with implantable cardioverter-defibrillators (ICDs) randomly assigned to the QT-prolonging antiarrhythmic dofetilide or placebo.

BACKGROUND
Drug-related torsade de pointes (TdP) is usually recognized within days of initiating therapy, but its incidence during long-term therapy is unknown.

METHODS
We assessed the frequency of TdP and ICD electrograms compatible with TdP in a multicenter study that randomized ICD patients to placebo (n = 87) or dofetilide (n = 87). As reported elsewhere, the number of patients with a primary trial end point (ICD intervention for VT or ventricular fibrillation) was similar in the two groups. For this analysis, a qualifying event was TdP (on electrocardiogram) or an intracardiac electrogram showing pause-dependent PVT.

RESULTS
A total of 620 electrograms obtained in 131 patients were analyzed blindly by prospectively defined criteria for episodes of pause-dependent polymorphic VT. These were identified in 15/87 (17%) patients receiving dofetilide and 5/87 (6%) patients on placebo (p = 0.05). Five of these episodes were early (<3 days), all of which were TdP on dofetilide. There were 15 late events, 10 on dofetilide and five on placebo (p = 0.29). The median time to a late event was 22 days (range 6 to 107 days) for dofetilide and 99 days (range 34 to 207 days) for placebo.

CONCLUSIONS
Pause-dependent PVT was more common among patients receiving dofetilide, although total VT incidence was similar in the two groups. These data suggest that in ICD patients either long-term dofetilide therapy is associated with an increased risk of TdP or the drug alters VT morphology.

Drugs that prolong the QT interval can suppress arrhythmias by lengthening myocardial refractoriness but also may produce the pause-dependent polymorphic ventricular tachycardia (PVT) torsade de pointes (TdP). Most agents causing TdP block the rapid component of the outward delayed rectifier repolarizing potassium current, I_{Kr}, and advocated to reduce potential risk for TdP (2–4). Reports of the incidence of TdP with various QT interval-prolonging agents (0.5% to 8%) usually refer to the first several hours or days of therapy (2,4–7). Although it is well recognized that drug-related TdP can occur during long-term therapy (2,3), the incidence during chronic therapy is unknown.

Drug-related TdP is associated with a pause-dependent (“short-long-short”) pattern of initiation and with QT interval dispersion in the surface electrocardiogram (ECG) (1,8). These patterns are consistent with experimental data implicating pause-dependent afterdepolarizations as the trigger and dispersion of refractoriness as a marker for favoring functional reentry to sustain TdP (8,9). Studies utilizing analysis of stored implantable cardioverter-defibrillator (ICD) recordings found that 14% to 26% of episodes of monomorphic VT (MVT) had a pause-dependent onset similar to that preceding TdP (10,11). It has also been reported that this mode of onset is associated with increased QT dispersion in the surface ECG (10). These observations suggest a role for enhanced dispersion of refractoriness not only in TdP but also in MVT. It is conceivable, therefore, that action potential prolonging
agents might facilitate the initiation of MVT in patients with an underlying anatomical substrate for reentry.

Dofetilide is a new, highly selective and potent I_{Kr} blocking antiarrhythmic agent (12,13). The drug has been shown to prolong action potential and QT interval duration in a concentration-dependent manner (12,14). Data from two large randomized, placebo-controlled clinical trials indicate that dofetilide is effective in the conversion to and maintenance of sinus rhythm in patients with persistent atrial fibrillation (15,16). In another large placebo-controlled study, dofetilide did not affect mortality in high-risk patients with congestive heart failure and severe left ventricular dysfunction (17). In small dose-ranging studies, dofetilide was also found to be effective in acute suppressing inducible inducible sustained VT during serial electrophysiologic testing in 43% to 46% of patients (18,19).

Torsade de points has been well recognized early in treatment with dofetilide (15–18,20). However, as with other drugs, the incidence of this problem during long-term treatment is unknown. In a double-blind, placebo-controlled study in patients with ICDs, dofetilide did not affect the time to first ICD intervention (antitachycardia pacing or shock) for VT or ventricular fibrillation (VF) (20). The availability of this large cohort of patients at risk for TdP (due to advanced structural heart disease) prompted the analysis of ICD electrograms that we now report from that study. Our goal was to determine the pattern of arrhythmia onset (on surface ECG or from intracardiac electrograms) in order to assess whether dofetilide enhances the risk of TdP or polymorphic VT during long-term therapy.

**METHODS**

**Study design.** Stored intracardiac electrograms and surface ECGs were obtained from 174 ICD patients randomized to receive dofetilide (n = 87) or placebo (n = 87) during therapy planned for up to one year (20). All ICDs were capable of storing intracardiac electrograms; the vast majority (165/174) were Ventritex Cadence (St. Jude Medical, St. Paul, Minnesota) devices. Drug therapy was initiated in hospital for >2 days in all subjects. Prior to initiation of drug therapy, serum K+ level was ±4 mEq/L. The starting dofetilide dose, 500 µg twice daily, was adjusted downward on the basis of estimated creatinine clearance or if the corrected QT interval increased by 15% over baseline after the start of dosing. Patients with a history of congenital or drug-associated QT prolongation, and those with baseline QT prolongation or receiving QT prolonging drugs, were not eligible for the study.

ICD therapies occurred in 131 patients. A total of 620 stored ICD electrograms obtained in these patients were reviewed by two investigators blinded to the study group, and only those recordings demonstrating arrhythmia onset (at least three RR intervals preceding the arrhythmia event) were accepted for further analysis. The following interval measurements were made for each tachycardia: 1) two cycle lengths preceding the last baseline electrogram; 2) mean cycle length of the first 10 beats of tachycardia; and 3) the coupling interval of the last baseline beat to the first beat of tachycardia. All measurements were performed using calipers. Treatment groups were analyzed on an intention-to-treat basis.

**Definitions.** The following prospectively formulated ICD electrogram definitions were used: VT was defined as a sudden change in rate and electrogram morphology compared with baseline rhythm. The tachycardia was considered monomorphic when it displayed uniform electrogram morphology. The tachycardia was considered polymorphic when: 1) each electrogram morphology was different from the previous (a minimum 10 consecutive beats), and 2) the mean cycle length of tachycardia in the first 10 beats was ≥240 ms. Ventricular fibrillation was diagnosed if the arrhythmia displayed a polymorphic electrogram morphology at a mean cycle length of <240 ms or no distinct isoelectric segment was present. Pause-dependent onset was present when the cycle preceding the last baseline beat was longer than both the preceding cycle and coupling interval by more than 10% (“short-long-short” sequence). Pause-dependent PVT was diagnosed if the duration of a PVT episode was ≥10 beats (Fig. 1). This duration limit was set because of the common phenomenon of the first beats of MVT being different from the rest (11). Torsade de points was defined by surface ECG as pause-dependent PVT associated with QT interval prolongation and lasting ≥10 beats.

**Statistical analysis.** Mean ± SD was calculated for continuous variables, and absolute and relative frequencies were measured for discrete variables. Continuous variables were compared between groups using Student t test, and categorical variables using Fisher exact test. The number of
patients displaying pause-dependent polymorphic arrhythmia (PVT or TdP) on each therapy was compared by Fisher exact test. A p value ≥0.05 was considered statistically significant.

**RESULTS**

The clinical characteristics and preliminary analysis of the study’s primary end point have been presented in abstract (20). In brief, the placebo and dofetilide groups were well-matched for gender (88% male), age (mean 64 years), New York Heart Association functional class (57% class II), percentage with ejection fraction <35% (77%), concurrent medications and primary arrhythmia diagnosis (21% VF; 79% VT). The 620 stored ICD electrograms were recorded in 59 patients on dofetilide (266 recordings) and in 72 patients on placebo (354 recordings). A total of 405 recordings, 174/266 (64%) in the dofetilide group and 231/354 (65%) in the placebo group, included the onset of the tachycardia and so were accepted for further analysis. Of these, 166 (95%) electrograms from 49 patients receiving dofetilide and 228 (99%) electrograms from 56 patients on placebo met the criteria for VT/VF. A summary of stored ICD electrograms analyzed according to the mode of therapy and type of arrhythmia is presented in Table 1. The total incidence of ventricular arrhythmia identified from intracardiac electrograms or surface ECG did not differ between the two groups: 56/87 (64%) on placebo and 55/87 (65%) in the placebo group, included the onset of the tachycardia and so were accepted for further analysis. Of these, 166 (95%) electrograms from 49 patients receiving dofetilide and 228 (99%) electrograms from 56 patients on placebo met the criteria for VT/VF. A summary of stored ICD electrograms analyzed according to the mode of therapy and type of arrhythmia is presented in Table 1. The total incidence of ventricular arrhythmia identified from intracardiac electrograms or surface ECG did not differ between the two groups: 56/87 (64%) on placebo and 55/87 (65%) on dofetilide.

**Pause-dependent polymorphic ventricular arrhythmia (PVT and TdP).** Qualifying events were identified in 15/87 patients (17%) receiving dofetilide versus 5/87 patients (6%) on placebo (p < 0.05; Table 2). Five of these events were early (<3 days on therapy), all of which were typical ECG-defined TdP on dofetilide. There were 15 late events (≥3 days), 10 on dofetilide and five on placebo (p = 0.29). Of the 15 patients with late events, the median time on therapy was 22 days (range 6 to 107 days) for dofetilide-treated patients and 99 days (range 34 to 207 days) for patients on placebo. The 15 late events included 12 cases of pause-dependent PVT and three late cases of documented TdP, two during treatment with dofetilide (days 8 and 289) and one on placebo (day 64). The case of TdP in the placebo group occurred shortly after treatment with amiodarone was started following discontinuation of double-blind therapy for lack of efficacy. Nine of 15 patients (60%) on dofetilide and three of five patients (60%) on placebo had more than one episode of the arrhythmia (range 2 to 6 for dofetilide and 2 to 3 for placebo). All episodes of documented TdP were terminated by a single ICD shock. Eight of 24 (33%) late pause-dependent PVT episodes in the dofetilide group and six of nine episodes (66%) in the placebo group terminated spontaneously; the remaining episodes were terminated by the ICD. The first QTc interval recorded in 13 patients after the occurrence of the first pause-dependent episode of PVT did not differ significantly between those receiving dofetilide (n = 9) versus placebo (n = 4); 495 ± 26 ms (range 447 to 530 ms) for dofetilide, and 468 ± 70 ms (range 380 to 576 ms) for placebo.

**VT morphologies.** Twenty-three percent of patients receiving dofetilide had either PVT or TdP, compared with 10% in the placebo group (p < 0.05; Table 2).

Monomorphic ventricular tachycardia was common and its incidence was similar in the two groups: 47/87 (54%) on placebo and 39/87 (45%) on dofetilide. Among patients with MVT, multiple episodes occurred in 38/47 (80%) patients on placebo and in 24/39 (61%) on dofetilide (p < 0.05). Electrogram morphologies were similar among episodes in 25/38 (66%) patients on placebo and 18/24 (75%) patients on dofetilide. The incidence of pause-dependent MVT (Fig. 2) was similar in the two groups: 18% for dofetilide and 20% for placebo. The pattern of initiation of MVT in patients with multiple episodes was reproducible in

### Table 1. Analyzed Stored ICD Electrograms

<table>
<thead>
<tr>
<th></th>
<th>Total VT/VF</th>
<th>PVT</th>
<th>MVT</th>
<th>VF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo (n = 231)</td>
<td>228 (99%)</td>
<td>32 (14%)</td>
<td>192 (84%)</td>
<td>4 (2%)</td>
</tr>
<tr>
<td>Dofetilide (n = 174)</td>
<td>166 (95%)</td>
<td>38 (22%)</td>
<td>127 (73%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Total (n = 405)</td>
<td>394 (97%)</td>
<td>70 (17%)</td>
<td>319 (79%)</td>
<td>5 (1%)</td>
</tr>
</tbody>
</table>

The data are presented as number of recordings (% of Total number of recordings for which there was an onset in the corresponding group). n = total number of recordings for which there was an onset in the corresponding group.

ICD = implantable cardioverter-defibrillator; MVT = monomorphic ventricular tachycardia; PVT = polymorphic ventricular tachycardia; VT = ventricular tachycardia; VF = ventricular fibrillation.

### Table 2. Incidence of Polymorphic Ventricular Tachycardia by Patient

<table>
<thead>
<tr>
<th></th>
<th>Pause-Dependent PVT*</th>
<th>TdP</th>
<th>Pause-Dependent PVT + TdP†</th>
<th>Nonpause-Dependent PVT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo (n = 87)</td>
<td>5 (6%)</td>
<td>1 (1%)</td>
<td>5 (6%)</td>
<td>4 (5%)</td>
</tr>
<tr>
<td>Dofetilide (n = 87)</td>
<td>9 (10%)</td>
<td>7 (8%)</td>
<td>15 (17%)</td>
<td>5 (6%)</td>
</tr>
<tr>
<td>p</td>
<td>NS</td>
<td>NS</td>
<td>&lt; 0.05</td>
<td>NS</td>
</tr>
<tr>
<td>Total (n = 174)</td>
<td>14 (8%)</td>
<td>8 (5%)</td>
<td>20 (13%)</td>
<td>9 (5%)</td>
</tr>
</tbody>
</table>

The data are presented as actual number of patients (% of total number of patients in the corresponding group). *Not including TdP; †one patient in each group had both TdP and PVT on separate occasions. 

n = number; PVT = polymorphic ventricular tachycardia; TdP = torsades de pointes.
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**DISCUSSION**

**Pause-dependent polymorphic arrhythmia.** The major finding of the present study is that therapy with dofetilide was associated with a significantly higher incidence of pause-dependent polymorphic ventricular arrhythmia, defined by intracardiac electrograms or TdP on the surface ECG (15/87, 17%), compared with placebo (5/87, 6%, p < 0.05). In 10 (11%) patients treated with dofetilide and five (6%) patients receiving placebo, pause-dependent polymorphic ventricular arrhythmia occurred with a delay >3 days after initiation of therapy (p = 0.29).

Whether the cases of pause-dependent PVT identified in the stored ICD recordings represent TdP cannot be determined from our study. All of them occurred late in an out-of-hospital setting in which electrocardiographic documentation was not available. It is well-recognized that pause-dependent PVT can occur in the absence of an abnormally prolonged QT interval or antiarrhythmic treatment, particularly in patients with advanced ischemic heart disease (21–23), and pause-dependent PVT did occur in the placebo group in this study. The pause dependence suggests that dispersion of repolarization may play a role, although the issue of the effect of dofetilide on dispersion of repolarization is controversial (14,24–26). The total incidence of ventricular arrhythmia was similar in the two groups. Therefore, an alternative explanation for the higher incidence of PVT with dofetilide would be that dofetilide changes VT morphology and/or initiation pattern. Self-sustaining reentrant activation due to spiral wave activity (or scroll waves in three dimensions) has been proposed as a common mechanism underlying both MVT and PVT (27,28). According to this hypothesis, the electrocardiographic manifestation of the arrhythmia is determined by the stability of the spiral core. Both action potential prolongation and dispersion of refractoriness may cause destabilization of the spiral core, thereby leading to irregular patterns of activation with a polymorphic appearance of the arrhythmia on the ECG (27,29).

**MVT.** The incidence of MVT was similar in both groups of patients, although multiple episodes occurred more frequently in patients on placebo. The latter finding suggests that dofetilide may reduce the number of recurrences of this type of VT. This is consistent with previous experimental (30,31) and clinical (18,19) studies, which showed that dofetilide reduced the inducibility rate of sustained MVT. Such an effect on MVT is consistent with an increase in wavelength of the reentry circuit due to lengthening of tissue refractoriness (32). In contrast to previous experimental and clinical data showing an increase in the cycle length of MVT by dofetilide (19,31), we found that the mean cycle length of MVT did not differ significantly between dofetilide and placebo. An interesting finding relates to the effect of dofetilide on antitachycardia pacing. In dofetilide-treated patients, the efficacy of antitachycardia pacing (which was programmed by individual investigators) was significantly greater and yet the cycle length of pace-terminated arrhythmia was significantly shorter. The mechanism underlying these findings is unclear. Both a faster VT rate and an excitable gap narrowed by an action-potential-prolonging drug would be predicted to unfavorably affect the ability to penetrate the reentry circuit during pacing maneuvers (33). It is possible, although highly speculative, that in patients treated with dofetilide, a relatively narrow excitable gap may permit a smaller increment in wavelength during pacing to extinguish reentry (34). The magnitude of lengthening of ventricular refractoriness during pacing may also be higher in patients treated with dofetilide, although reverse use-dependence of the effect of dofetilide on action potential prolongation would argue against this mechanism (12).

**Study limitations.** Prestudy electrograms were not available to assess the possibility that one effect of dofetilide is to alter VT morphology. Furthermore, only stored ICD electrograms for which an onset of tachyarrhythmia was present were analyzed. This could affect the incidence of different types of the tachyarrhythmia in the studied groups, although the relative number of electrograms with and without an onset was similar in the both groups. Lack of availability of QT interval data at the instant of pause-dependent PVT identified in the stored ICD electrogram hampers interpretation of the underlying mechanisms.
Several potential limitations relate to the stored ICD electrogram analysis. Local bipolar recordings from a closely spaced ICD electrogram configuration may not reliably reflect surface ECG morphology of VT (35). It is also possible that a polymorphic pattern of VT could fail to be detected by a single-lead recording. In addition, analysis of stored ICD electrogram morphology in this study did not allow definite discrimination between VT and supraventricular tachycardia with aberrant conduction. Short-lived (self-limited) episodes of TdP may not have been detected.

**Clinical implications.** Our findings pertain to a highly selected population of patients with VT, those receiving ICDs for clinical VT/VF. Generalization of this findings to other populations of patients may be inappropriate. Indeed, dofetilide has been approved for use in patients with atrial fibrillation and flutter, and not VT/VF. The safety of the drug was examined in the Danish Investigation of Arrhythmias and Mortality on Dofetilide (DIAMOND) study, which randomized patients with advanced left ventricular dysfunction to dofetilide or placebo (17,36). The DIAMOND study showed that with in-hospital initiation of dofetilide in patients with advanced left ventricular dysfunction to dofetilide or placebo (17,36). The DIAMOND study showed that with in-hospital initiation of drug (allowing detection and treatment of TdP), there was no change in mortality compared to placebo, even in this high-risk group; subset analysis shows the same result, and a decreased rehospitalization rate in patients with AF. The programmed antibradycardia pacing rate in the 20 patients with pause-dependent PVT was <70/min in all but one (in whom it was 70/min). Hence, consideration should be given to raising the antibradycardia pacing rate in patients with ICDs receiving dofetilide or other QT prolonging agents.

**Conclusions.** Pause-dependent PVT occurred in placebo-treated patients but was more common among those receiving dofetilide. Because the total incidence of VT or VF was similar in dofetilide- and placebo-treated patients, this study suggests either that long-term dofetilide therapy is associated with an increased risk of TdP or that the drug changes VT morphology and/or initiation pattern.

Treatment with dofetilide did not affect the incidence, initiation pattern or cycle length of MVT but was associated with better response of the tachycardia to overdrive pacing. The trend toward a lower incidence of multiple episodes of MVT in patients receiving dofetilide suggests that the drug may reduce the number of recurrences of this type of VT.

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