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Time- and Rate-Dependent Alterations of the QT Interval Precede the Onset of Torsade de Pointes in Patients With Acquired QT Prolongation

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Objectives. **The purpose of this study was to determine whether the QT interval dynamics that precede torsade de pointes are consistent with the initiation of this arrhythmia by early afterdepolarization-induced triggered activity.**

Background. **Early afterdepolarization-induced triggered activity has been suggested as an electrophysiologic mechanism for torsade de pointes. Consequently, the initiation of torsade de pointes should involve time- and rate-dependent alterations of ventricular repolarization similar to those known to modulate the development of early afterdepolarizations.**

Methods. **RR and QT intervals were measured in digitized 24-h ambulatory electrocardiographic recordings obtained from seven patients with acquired prolongation of ventricular repolarization. Each patient had one or more episodes of torsade de pointes. The relation between RR and QT intervals was determined before, during and after multiple episodes of torsade de pointes.**

Results. **In patients with multiple episodes of ventricular arrhythmias, the onset of the arrhythmias was associated with a critical prolongation of the QT interval. In some episodes, prolongation of the QT interval was associated with sudden prolongation of the sinus cycle length, whereas in other episodes, the QT interval prolonged progressively at a constant cycle length.**

Conclusions. **The association between a critically prolonged QT interval and the onset of ventricular arrhythmias suggests that the initial complex of torsade de pointes is an early afterdepolarization-induced triggered response. However, prolongation of the QT interval itself was not sufficient to account for the initiation of torsade de pointes, suggesting that other, as yet unidentified factors are required.**

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The electrophysiologic mechanism for torsade de pointes, a polymorphic ventricular tachycardia characterized by a twisting of R wave polarity (1), has not been established. Current hypotheses with respect to the mechanism for this arrhythmia include a dispersion of repolarization that predisposes to the development of reentry and triggered activity initiated by early afterdepolarizations (2–6). Distinguishing between these two mechanisms may have clinical implications with respect to the selection of appropriate therapeutic interventions (2–7). In addition, criteria used to invoke or eliminate early afterdepolarization-induced triggered activity as a mechanism for torsade de pointes might also be used to determine whether such a mechanism can account for the development of ventricular arrhythmias in other forms of heart disease (8–10).

As reported by Locati et al. (11), oscillations of the RR interval, typically of the "short-long" type, precede the initiation of ventricular arrhythmias in patients with acquired prolongation of repolarization. The presence of a "short-long" sequence would be expected to prolong action potential duration (reflected by a prolongation of the QT interval), which might facilitate the initiation of early afterdepolarization-induced triggered activity (9,10). The purpose of the present study was to determine whether, in fact, prolongation of the QT interval preceded the development of episodes of ventricular arrhythmias in patients with acquired prolongation of repolarization.

Methods

Patient group. The criteria for patient selection have been described previously by Locati et al. (11). Briefly, seven patients with acquired prolongation of ventricular repolarization, in whom one or more episodes of torsade de pointes had been recorded on a 24-h ambulatory electrocardiographic (ECG) monitor, were selected from the data base of the

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Table 1. Clinical Characteristics of Patients

Pt No.	Age/Gender	Cardiac Disease	Reason for Holter Monitoring	Underlying Arrhythmia	Ongoing Therapy	Provoking Factor
1	75/F	ANH	Syncope	PAF	Quin, Amio	$HypoK^+$, Quin
2	85/F	IHD	Control	PAC	Quin	$HypoK^+$, Quin
3	59/F	IHD, RVD (MR)	Control	PAF	Quin	Quin
4	80/M	DCM, HTN	Control	PAF, PVC	Quin, Amio, Diur	$HypoK^+$, Quin
5	75/F	IHD, CHF, HTN	Malaise	SR, LBBB	Bepr, Amio, Diur	Bepr
6	72/F	ANH, HTN	Syncope	VB	Diur	$HypoK^+$
7	62/F	RVD (MS)	Control	PAF	Amio, Diur	$HypoK^+$

Amio = amiodarone; ANH = apparently normal heart; Bepr = Bepridil; CHF = chronic heart failure; Control = assessment of cardiac treatment; DCM = dilated cardiomyopathy; Diur = diuretic drugs; F = female; HTN = hypertension; $HypoK^+$ = hypokalemia; IHD = ischemic heart disease; LBBB = left bundle branch block; M = male; Malaise = presyncope or palpitations; MR = mitral regurgitation; MS = mitral stenosis; PAC = premature atrial complexes; PAF = paroxysmal atrial fibrillation; Pt = patient; PVC = premature ventricular complexes; Quin = hydroquinidine; RVD = rheumatic valve disease; SR = sinus rhythm; Syncope = complete loss of consciousness; VB = ventricular bigeminy.

Cardiology Unit of the Hôpital Lariboisiere, Paris, France. The clinical characteristics of the patients are given in Table 1. All patients had a known rhythm disorder, but none had a history of nonsustained or sustained ventricular tachycardia and none was taking antiarrhythmic medication for treatment of ventricular arrhythmias. The mean (±SEM) QT interval of the patients was 640 ± 31 ms, and the rate-corrected QT interval ($QT/[RR]^{1/2}$) was 600 ± 19 ms. Prolongation of the QT interval was associated with quinidine administration, with or without hypokalemia (serum $[K^+]$ <3.5 mEq/liter), in four patients, with hypokalemia alone in two patients and with bepridil administration in one patient. Four of the patients also were taking amiodarone, which may have contributed to QT prolongation.

Data analysis. Electrocardiographic recordings were obtained using portable battery-operated, two-channel cassette recorders (ICR model 7200, ELA model 2448 or Marquette model 8500) and were read using a Del Mar 563 (Del Mar Avionics) analysis system to create a digitized record of the entire 24 h. These files subsequently were transferred to a Power Macintosh 7100/66 or 8100/80 (Apple Computer, Inc.) and analyzed using script files written in MATLAB 4.2c (The Mathworks Inc.). The RR intervals were identified using algorithms based on those described by Pan and Tompkins (12). QT intervals were calculated after labeling the peak of the T wave (i.e., maximal positive or negative deflection) within a window of 600 ms from the associated R wave. After automated analysis of the entire tape, text files of 2- to 25-min segments of the tape containing regions of particular interest were transferred to AcqKnowledge 3.0, where they were upsampled to 1,000 Hz using linear interpolation. The RR and QT intervals were then measured manually using the AcqKnowledge analysis program. The resulting data files were transferred to StatView (Abacus Concepts) for further analysis and display.

Measurements. The RR intervals were measured as the interval between peak R wave deflections. For analysis of the relation between RR and QT intervals preceding an episode of ventricular arrhythmias, QT intervals were measured as the interval between the peak R wave deflection and the peak of the T wave. If more than one peak was present in the T wave, measurements were made to the last peak. Measurements also were made from the peak of the R wave to the end of the T wave, defined as the return to the isoelectric line, in two patients (Patients 2 and 5). In these patients, the QT interval dynamics were essentially the same, regardless of whether the R to peak of T or the R to end of T measurements were used for the analysis. Because the initial deflection of the first premature ventricular complex of an episode of ventricular arrhythmias always occurred at or after the peak of the T wave, the R to peak of T interval could be measured for all complexes up to and including the final sinus complex preceding the onset of ventricular arrhythmias. For this reason, measurements of R to peak of T were used for the analyses presented subsequently.

For analysis of QT intervals during episodes of ventricular arrhythmias, the QT interval was measured as the interval between the peak R wave deflection and the end of the T wave (as described in more detail in the Results). Measurements were made to the end of the T wave because the end of the T wave could be identified more reliably than the peak of the T wave during episodes of ventricular arrhythmias. All QT intervals are presented as absolute values and were not corrected for heart rate.

The RR and QT intervals initially were determined using the automated analysis system. Thereafter, the RR and QT intervals during the 2 min that preceded each episode of ventricular arrhythmias and during selected periods of sinus rhythm in the absence of arrhythmias were measured manually. The resolution of the automated measurements was 4 ms and the resolution of the manual measurements was 1 ms. For the manual measurements, repeated measurements of the same record by the same investigator varied by 2 to 4 ms.

Statistical analysis. Data are expressed as mean value ± SEM. Linear regression analysis was performed using a commercially available program (StatView). The slopes of the regression lines were compared using *t* tests. The p value $<$ 0.05 was considered statistically significant.

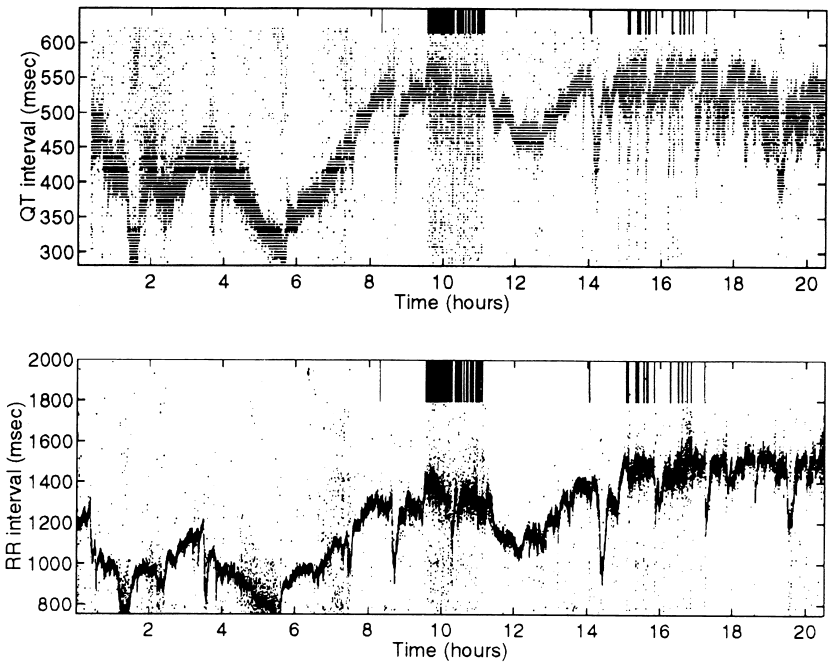

Figure 1. QT **(upper panel)** and RR **(lower panel)** intervals during ambulatory ECG monitoring in a patient with acquired prolongation of repolarization (Patient 2). Episodes of ventricular arrhythmias that included torsade de pointes are indicated by the **vertical lines**. (See text for discussion.)

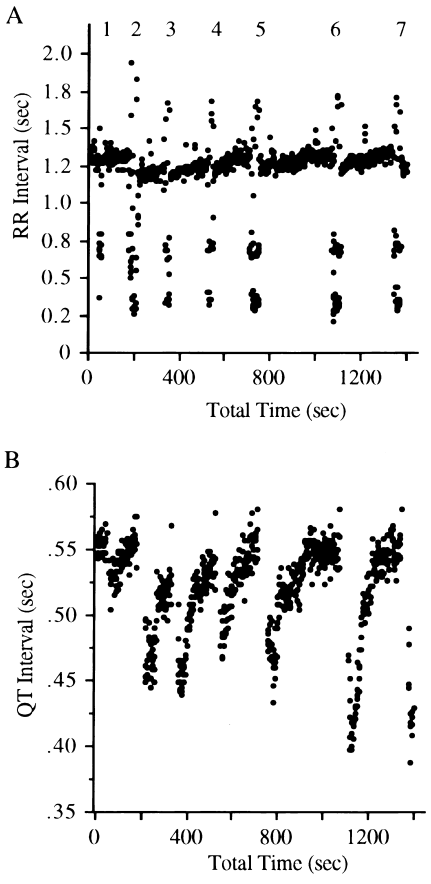

Figure 2. RR and QT intervals during periods of normal sinus rhythm and ventricular arrhythmias in a patient with acquired prolongation of repolarization (Patient 2). **A,** RR intervals during seven episodes of ventricular arrhythmias (numbered 1 to 7) interspersed with periods of sinus rhythm. **B,** QT intervals corresponding to the RR intervals in **A**. QT intervals during the episodes of ventricular arrhythmias are excluded. (See text for discussion.)

Results

Characteristics of the ventricular arrhythmias. Of the seven patients, one patient developed a single episode of torsade de pointes during the recording period, three patients developed two episodes and the remaining three patients developed multiple episodes (7, 16 and 34 episodes, respectively). In addition to episodes of torsade de pointes, all patients developed episodes of ventricular arrhythmias that included single premature ventricular complexes and salvos of premature ventricular complexes interspersed with sinus complexes. In two patients, virtually incessant ventricular arrhythmias were present over the entire recording period. One of these patients had a single episode of torsade de pointes and the other patient had two episodes. In the remaining five patients, ventricular arrhythmias were episodic. Consequently, it was possible to compare the RR and QT intervals that preceded episodes of ventricular arrhythmias with those that did not.

Initiation of premature ventricular complexes. During the 24-h period of ambulatory ECG monitoring, episodes of ventricular arrhythmias were associated in all patients with periods of prolonged QT intervals. As expected, the prolonged QT intervals typically were associated with long RR intervals. An example of the correspondence of episodes of ventricular arrhythmias with the QT and RR intervals is shown in Figure 1. Both episodes that contained torsade de pointes and those that contained only single premature ventricular complexes or salvos of premature ventricular complexes were associated with periods of the record that showed the longest QT intervals.

To examine the relation between RR and QT intervals and the initiation of episodes of ventricular arrhythmia in more detail, the RR and QT intervals were measured manually with high resolution before, during and after multiple episodes of ventricular arrhythmias. Figure 2 shows the sequences of the

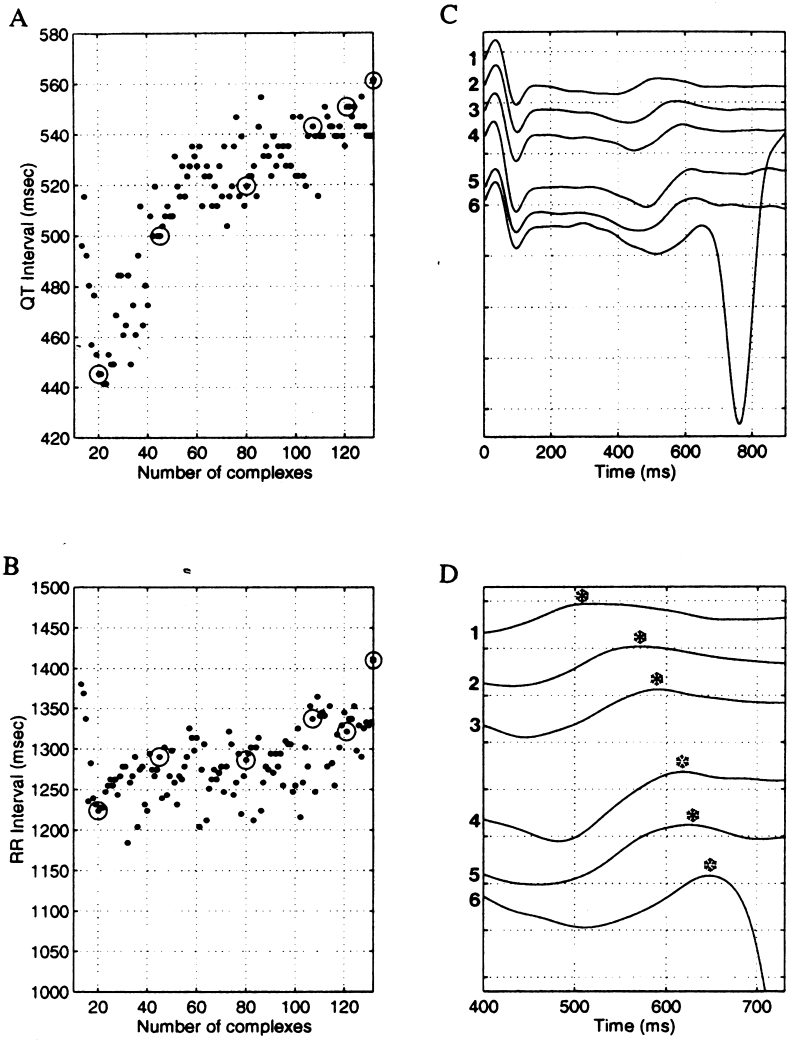

Figure 3. QT (**A**) and RR (**B**) intervals preceding the onset of ventricular arrhythmias in a patient with acquired prolongation of ventricular repolarization (Patient 2). The ECG recordings for the six circled complexes in **A** and **B** are shown in **C**, aligned by the R wave. The terminal portions of the T waves for these complexes are shown in **D** at an expanded time scale. The **asterisks** indicate the fiducial point on the T wave for the QT measurements. The QT interval increased progressively throughout the record, culminating in a premature ventricular complex (recording 6) that initiated an episode of ventricular arrhythmias. Note that RR intervals 2 and 3 were similar, as were RR intervals 4 and 5, yet the corresponding QT intervals differed.

RR and QT intervals for seven episodes of ventricular arrhythmias and the intervening periods of sinus rhythm for Patient 2. Immediately after each episode of ventricular arrhythmias, the RR interval tended to shorten. Subsequently, the RR interval either prolonged throughout the time between episodes of ventricular arrhythmias or prolonged initially and was relatively constant thereafter. The QT interval shortened initially after each episode of ventricular arrhythmias. The QT interval then prolonged, at first rapidly and then more slowly, before the onset of the next episode.

The first premature ventricular complex of an episode of ventricular arrhythmias was preceded by a QT interval that was longer than any of the QT intervals since the end of the previous episode of arrhythmias. Examples of this phenomenon are shown in Figures 3 and 4. Prolongation of the QT interval before initiation of an episode of ventricular arrhythmias typically was associated with prolongation of the RR interval (Fig. 3 and 4). However, the QT interval was not solely a function of the immediately preceding RR interval. For example, the final stage of QT prolongation shown in Figure 4A occurred during a gradual lengthening of the RR interval. Longer RR intervals and "short-long" RR interval sequences that occurred at earlier times produced less prolongation of the QT interval. Similarly, in Figure 4B, long RR intervals occurred both at 270 s and just before the initiation of the first premature ventricular complex (RR = 1,413 and 1,432 ms, respectively), yet the second RR interval produced the greater prolongation of the QT interval. In Figure 4C, two marked prolongations of the RR interval at 805 s (RR = 1,441 ms) and 1,004 s (RR = 1,488 ms) failed to increase the QT interval sufficiently to initiate a premature ventricular complex, whereas greater QT prolongation and initiation of a premature ventricular complex occurred after a shorter RR interval (RR = 1,365 ms) at a later time (1,071 s).

Given that the QT interval was not solely a function of the preceding RR interval, we determined whether the relation between the RR and QT intervals differed according to the time at which the intervals were recorded (i.e., immediately before or after an episode of ventricular arrhythmias or during a period of no arrhythmias). As shown in Figure 5A, the slope of the linear relation between the RR and QT intervals was less steep for the 10 intervals that preceded an episode of

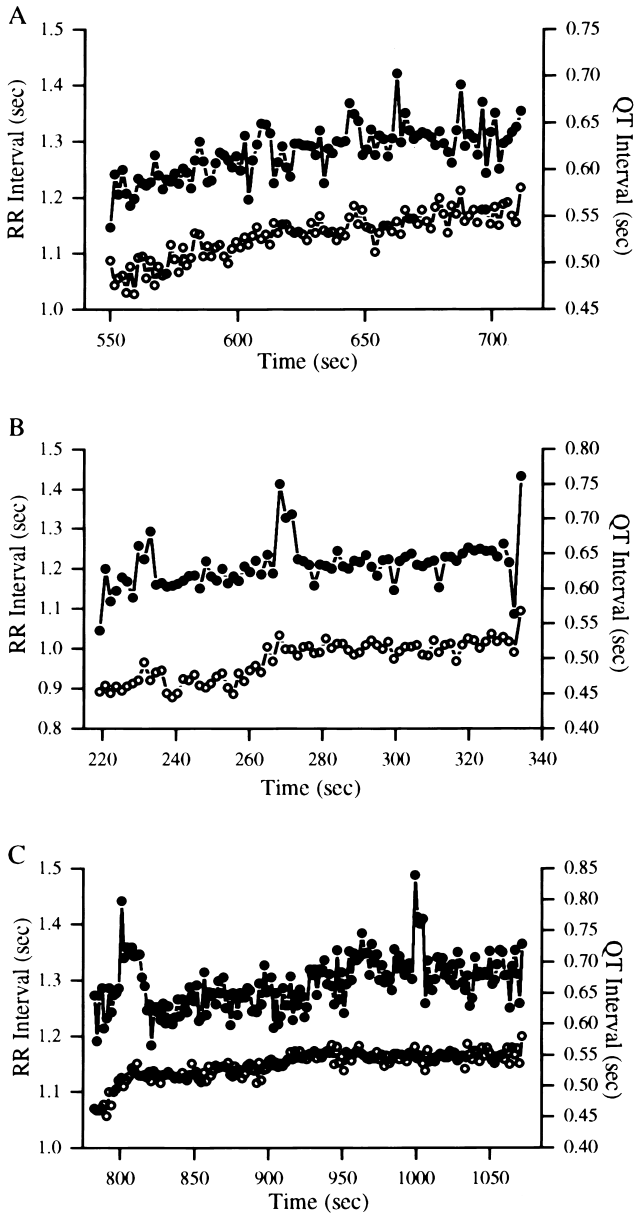

Figure 4. RR and QT intervals preceding the onset of ventricular arrhythmias in a patient with acquired prolongation of ventricular repolarization (Patient 2). **A–C,** Time series of RR (**solid circles**) and QT intervals (**open circles**) beginning with the first sinus complex after an episode of ventricular arrhythmias and ending with the last sinus complex preceding the initial premature ventricular complex of the 5th, 2nd and 7th episodes, respectively, of ventricular arrhythmias shown in Figure 2. (See text for discussion.)

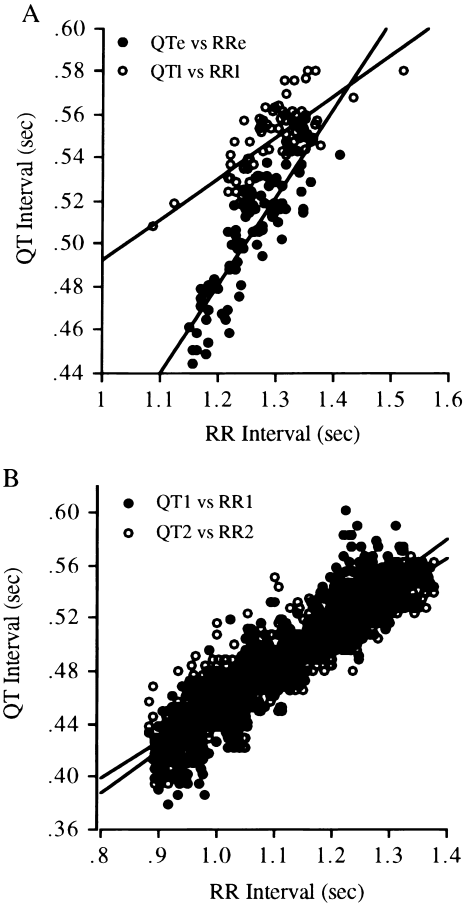

Figure 5. Relation between the QT and RR intervals in a patient with acquired prolongation of ventricular repolarization (Patient 2). **A,** Relation between the QT and RR intervals for the periods of sinus rhythm separating the seven episodes of ventricular arrhythmias shown in Figure 2. The QT/RR relations are shown for the last 10 intervals preceding episodes of ventricular arrhythmias (late [QTl and RRl], **upper left**) and for the remaining intervals (early [QTe and RRe]). There was an upward shift of the QT interval for a given RR interval preceding the onset of ventricular arrhythmias. The upward shift of the QT interval was greater for short RR intervals than for long RR intervals, resulting in a more shallow slope for the relation between the RR and QT intervals (0.190 vs. 0.411). **B,** Relation between the QT and RR intervals for two periods of sinus rhythm (QT, RR and QT_2, RR_2 complexes near 31,000 and 48,000 in Fig. 1; 1,200 intervals). The slopes of the relation between the RR and QT intervals did not differ between the two periods of sinus rhythm (0.319 vs. 0.277) and were intermediate to the slopes obtained for early and late intervals in **A**. (See text for further discussion.)

ventricular arrhythmias than for earlier intervals. Consequently, just before the onset of an episode of ventricular arrhythmias, the QT interval was longer for any given RR interval than immediately after an episode of arrhythmias (Fig. 5A) or during a period of sinus rhythm in the absence of arrhythmias (Fig. 5B).

A reduction in the slope of the QT/RR interval relation before initiation of an episode of ventricular arrhythmias occurred in four of the five patients having multiple episodes of arrhythmias (all slopes <0.190). In Patient 5, the relations between the QT and RR intervals were not significantly different just before or after an episode of ventricular arrhythmias (Fig. 6). In this patient, prolongation of the QT interval preceding the onset of an episode of ventricular arrhythmias always was associated with prolongation of the RR interval.

Determinants of the number of consecutive premature ventricular complexes. Our next objective was to determine whether changes in the QT interval could account for the patterns of premature ventricular complexes that occurred

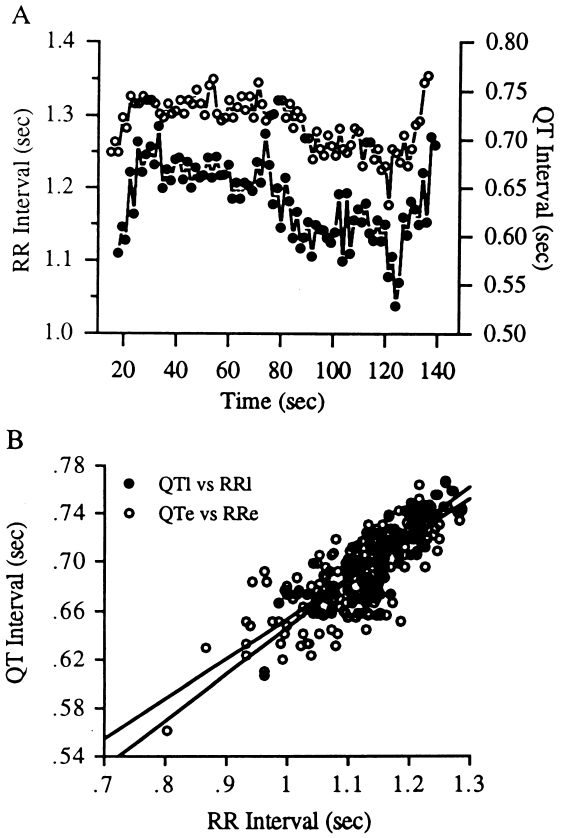

Figure 6. Relation between the QT and RR intervals in a patient with acquired prolongation of ventricular repolarization (Patient 5). **A,** Time series of RR (**solid circles**) and QT (**open circles**) intervals beginning with the first sinus complex after the end of an episode of ventricular arrhythmias and ending with the last sinus complex preceding the next episode of ventricular arrhythmias. **B,** QT/RR interval relation for the periods of sinus rhythm separating five episodes of ventricular arrhythmias. The intervals were divided into early and late, as described in Figure 5 (see legend, **upper left**). There was no significant difference between the slopes of the QT/RR interval relation for early or late intervals (0.328 vs. 0.384, **lower right**).

during episodes of ventricular arrhythmias and for the termination of such episodes. For this part of the study, it was assumed that the premature ventricular complexes during episodes of ventricular arrhythmias were caused by early afterdepolarization-induced triggered responses. Therefore, the sequence of a sinus complex followed by a premature ventricular complex, for example, would correspond to a single cellular action potential followed by an early afterdepolarization-induced triggered response (Fig. 7). The total duration of the action potential would then correspond to the QT interval encompassed by the sinus-initiated complex and the triggered complex. The duration of any given action potential would be expected to be proportional to the diastolic interval between action potentials (i.e., the longer the diastolic interval, the longer the action potential duration) (13–15). Moreover, the longer the action potential duration, the higher the probability that a triggered response would occur (9,10). From the standpoint of the ECG, it follows that the longer the TQ interval, the longer the subsequent QT interval.

Figure 8A illustrates the relation between the QT interval, measured as described earlier, and the TQ interval for all complexes associated with seven episodes of ventricular arrhythmias in Patient 2. Displayed in this way, there appears to be no particular relation between the preceding TQ interval and the subsequent QT interval. However, if the intervals are sorted in rough order of their occurrence, a more useful picture emerges, as shown in Figure 8B.

The QT intervals corresponding to sinus complexes that occurred before or after the episode of arrhythmias (QT1 and QT5 in Fig. 8B) remained <1,000 ms and were preceded by TQ intervals <1,000 ms. The QT intervals associated with the first two premature ventricular complexes of an episode (i.e., sinus-premature ventricular complex, sinus-premature ventricular complex [QT2]) were approximately twice those of the sinus complexes, as expected (Fig. 7). They occurred primarily after TQ intervals of 800 to 1,000 ms, indicating a further progression of the time-dependent prolongation of the QT interval shown in Figure 5.

The QT intervals during torsade de pointes (QT3 in Fig. 8B) occurred at somewhat longer TQ intervals than the single premature ventricular complexes, although the overlap in cycle lengths suggests that further time-dependent prolongation of the QT interval occurred. After torsade de pointes, the QT intervals (QT4) returned to the range expected for single premature ventricular complexes and couplets. However, these QT intervals were preceded by TQ intervals that were longer than those that preceded the initial single premature ventricular complexes and couplets (1,500 to 1,950 ms vs. 640 to 1,260 ms, respectively).

The mean trends for the QT and TQ intervals for Patient 2 are shown in Figure 9. During episodes of arrhythmias, the TQ interval increased progressively, from TQ1 through TQ4, whereas the QT interval increased initially, from QT1 through QT3 (torsade de pointes), and then decreased after the episode of torsade de pointes (QT4). Both the TQ (TQ5) and QT (QT5) intervals became shortened immediately after the episodes of arrhythmias ended. Similar results were observed in the other four patients who had multiple episodes of ventricular arrhythmias.

Discussion

New findings. The results of this study indicate that a critical prolongation of the QT interval was associated with the initiation of ventricular arrhythmias in patients with acquired prolongation of ventricular repolarization. Moreover, the QT interval was a function not only of the immediately preceding RR interval, but also of previous RR intervals. For any given RR interval, the QT interval was shortest immediately after an episode of ventricular arrhythmias, prolonged rapidly over the next 10 to 20 beats and then more slowly before the onset of the next episode of ventricular arrhythmias. Consequently, the QT dynamics associated with the initiation and termination of torsade de pointes were complex and not adequately explained by short-term RR interval patterning.

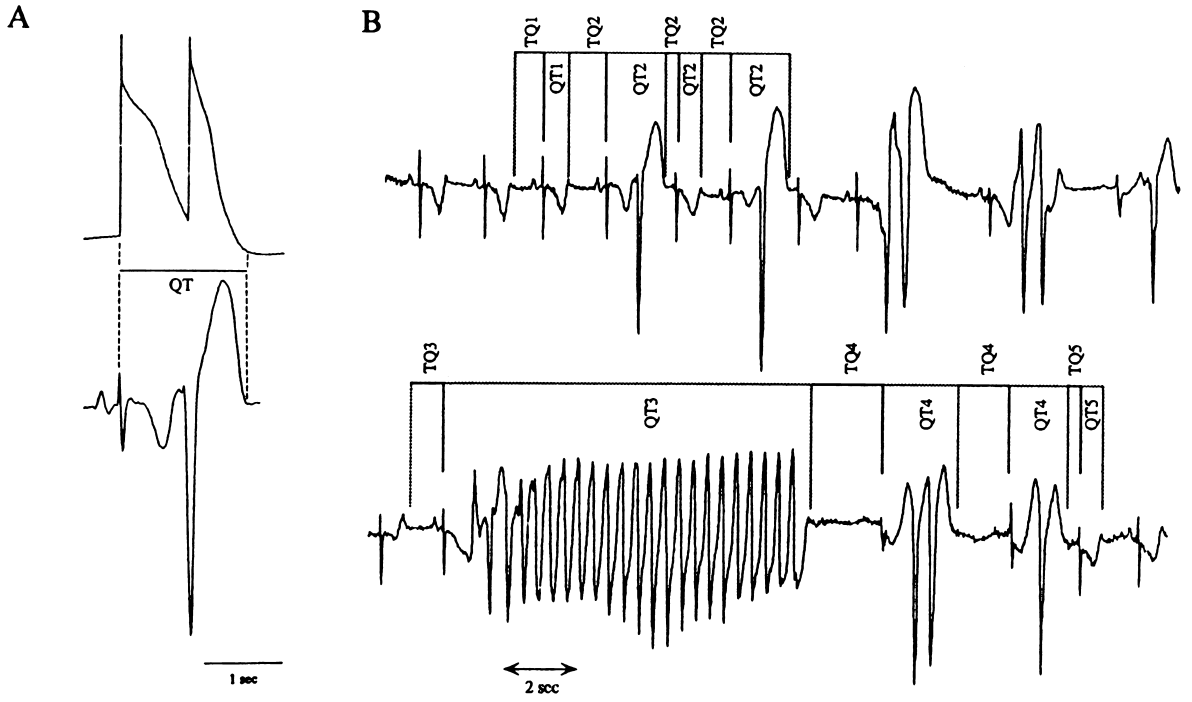

Figure 7. Relation between QT and TQ intervals during episodes of ventricular arrhythmias in patients with acquired prolongation of ventricular repolarization. **A,** Hypothetic correspondence between a cellular action potential and early afterdepolarization-induced triggered response (**upper record**) and the QT interval of the scalar ECG (**lower record**). **B,** Example of QT and TQ intervals measured during an episode of ventricular arrhythmias: 1 = intervals during sinus rhythm preceding initiation of arrhythmias; 2 = intervals associated with first three complexes during episodes of ventricular arrhythmias; 3 = intervals associated with torsade de pointes; 4 = intervals associated with complexes that followed torsade de pointes before the end of the episode; and 5 = intervals associated with sinus complexes immediately after termination of the episode.

Rate- and time-dependent alterations of ventricular repolarization. Although the electrophysiologic mechanism responsible for the maintenance of torsade de pointes remains to be determined, there appears to be general agreement that this arrhythmia is initiated by a premature ventricular complex, usually in the setting of bradycardia and usually after a pause (2–6,16,17). The mechanism for the premature ventricular complex has not been established. The results of the present study suggest that the premature ventricular complex is not a random event, but one predicated on a critical prolongation of the QT interval. The QT interval, in turn, is dependent not only on the immediately preceding RR interval, but also on the cumulative effects of the bradycardia that precedes an episode of ventricular arrhythmias and on the tachycardia that occurs during the episode.

As a first approximation, the rate and time dependence of the QT interval can be attributed to the relation between the QT and TQ interval and the upward and downward shifts of that relation produced by bradycardia and tachycardia, respectively. This behavior derives from the dependence of action potential duration on the preceding diastolic interval, and the dependence of that relation on the preceding pacing cycle length ("memory") (13–15). Because of memory, adaptation of action potential duration or the QT interval to an abrupt change in heart rate is not immediate but occurs in at least two phases: the majority of the adaptation occurs rapidly, within 1 to 10 beats, whereas the remainder of the adaptation may occur over several hundred subsequent beats (13–15,18–21). The slow adaptation phase may be prolonged further by surgical interruption or pharmacologic blockade of cardiac sympathetic nerves (20,21).

In the present study, the effects of bradycardia on the QT interval included both a rapid and a slow phase of adaptation. After an episode of ventricular arrhythmias, abrupt slowing of the heart rate initially was accompanied by a marked prolongation of the QT interval, which in most cases was insufficient to initiate further arrhythmias. Subsequently, the more slowly developing adaptation of the QT interval to the bradycardia, as reflected in the upward shift of the QT/TQ relation over a time course of minutes, eventually precipitated another episode of arrhythmias. In contrast, the rapid downward shift of the QT/TQ relation that occurred within the 5- to 16-s duration episodes of torsade de pointes apparently was sufficient to terminate the arrhythmia, despite the fact that the QT interval probably did not reach steady state.

Potential contribution of triggered activity to torsade de pointes. Experimental studies of early afterdepolarization-induced triggered activity have shown that the emergence of triggered activity requires a prolonged period of bradycardia

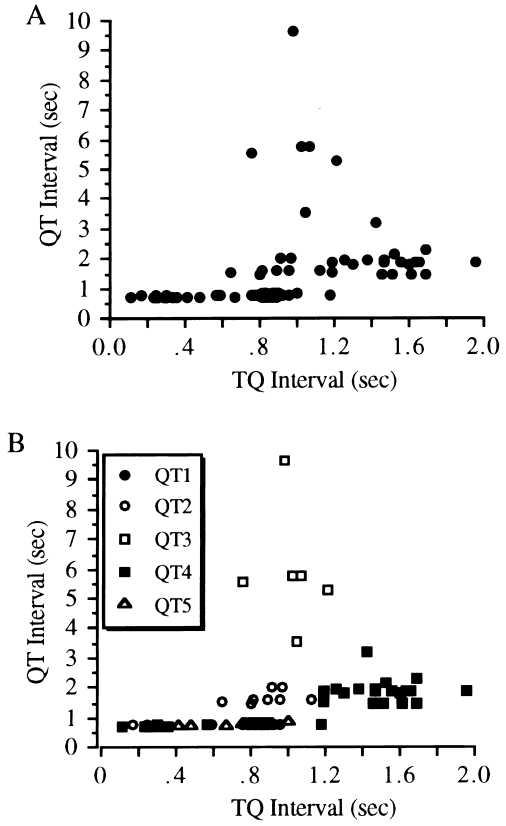

Figure 8. Relation between QT and TQ intervals during episodes of ventricular arrhythmias in a patient with acquired prolongation of ventricular repolarization. **A,** QT interval as a function of TQ interval for episodes of ventricular arrhythmias 2, 3, 5, 6 and 7 in Figure 2. **B,** The same QT intervals as in **A** according to their time of occurrence (see legend, **upper left**). As shown in Figure 7, QT1 and QT5 are the QT intervals during sinus rhythm before and after the episodes of ventricular arrhythmias, respectively; QT2 represents the QT intervals of the first three ventricular complexes (including intervening sinus complexes); and QT3 and QT4 are the QT intervals during and after a run of torsade de pointes, respectively. (See text for discussion.)

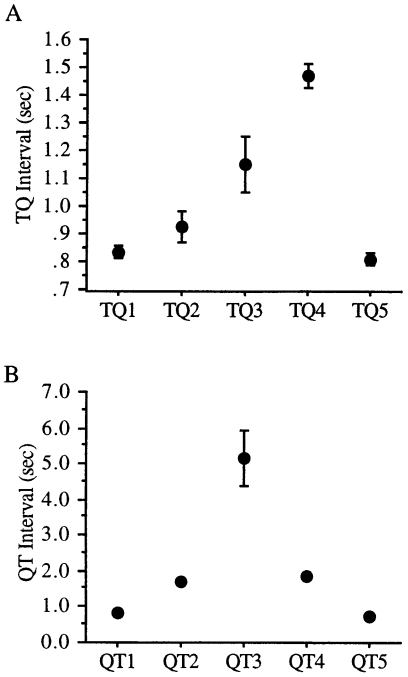

Figure 9. QT and TQ intervals associated with episodes of ventricular arrhythmias in a patient with acquired prolongation of ventricular repolarization (Patient 2). **A,** Mean TQ intervals, where TQ1 and TQ5 are the TQ intervals during sinus rhythm before and after the episodes of ventricular arrhythmias, respectively; TQ2 represents the TQ intervals of the first two ventricular complexes (including intervening sinus complexes); and TQ3 and TQ4 are the TQ intervals during and after a run of torsade de pointes. **B,** Mean QT intervals for the same time periods as in **A.** (See text for discussion.)

and that triggered activity is suppressed during rapid pacing (9,10,22,23). In addition, studies in spontaneously discharging Purkinje fibers have shown that early afterdepolarization-induced triggered activity is suppressed for some time after the cessation of rapid pacing (24). The postoverdrive suppression of early afterdepolarization-induced triggered activity may occur concurrently with overdrive suppression of automaticity. Consequently, after a period of rapid pacing, the spontaneous discharge rate is slowed, yet no early afterdepolarization-induced triggered activity occurs. With time, the spontaneous discharge rate increases, as does the incidence of triggered activity. If the spontaneous discharge rate becomes sufficiently rapid, triggered activity is suppressed.

Based on experimental studies it is expected that ventricular arrhythmias initiated by early afterdepolarization-induced triggered activity would be most likely to occur during periods of bradycardia, would be suppressed by the rapid rates that occur during a tachyarrhythmia and would not recur immediately after restoration of bradycardia. These characteristics applied to the arrhythmias in the present study, as well to the ventricular arrhythmias in patients with acquired prolongation of repolarization studied previously (2–6).

Triggers versus substrate. Although the initiation of ventricular arrhythmias was associated with prolongation of the QT interval, not every long QT interval precipitated a premature ventricular complex. This observation indicates that factors in addition to a prolonged QT interval were required for the initiation of ventricular arrhythmias. Candidates for such factors include changes in serum drug and potassium levels (9,10,25). In addition, changes in heart rate may have altered drug binding to various ion channels (26–28). It also seems likely that alteration of autonomic nervous system tone contributed to modulation of the QT interval in these patients, both indirectly, through its influence on heart rate, and directly, through its influence on the ionic mechanisms responsible for repolarization and for the development of early afterdepolarizations (2–6,11,29–31).

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