Heart Rhythm Disorders

The Morphology of the QT Interval Predicts Torsade de Pointes During Acquired Bradyarrhythmias

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Objectives
The purpose of this study was to define the electrocardiographic (ECG) predictors of torsade de pointes (TdP) during acquired bradyarrhythmias.

Background
Complete atrioventricular block (CAVB) might lead to downregulation of potassium channels, QT interval prolongation, and TdP. Because potassium-channel malfunction causes characteristic T-wave abnormalities in the congenital long QT syndrome (LQTS), we reasoned that T-wave abnormalities like those described in the congenital LQTS would identify patients at risk for TdP during acquired bradyarrhythmias.

Methods
In a case-control study, we compared 30 cases of bradyarrhythmias complicated by TdP with 113 cases of uncomplicated bradyarrhythmias. On the basis of the criteria used for the congenital LQTS, T waves were defined as LQT1-like (long QT interval with broad T waves), LQT2-like (notched T waves), and LQT3-like (small and late) T waves.

Results
Neither the ventricular rate nor the QRS width at the time of worst bradyarrhythmia predicted the risk of TdP. However, the QT, corrected QT (QTc), and T_{peak}–T_{end} intervals correlated with the risk of TdP. The best single discriminator was a T_{peak}–T_{end} of 117 ms. LQT1-like and LQT3-like morphologies were rare during bradyarrhythmias. In contrast, LQT2-like "notched T waves" were observed in 55% of patients with TdP but in only 3% of patients with uncomplicated bradyarrhythmias ($p < 0.001$). A 2-step model based on QT duration and the presence of LQT2-like T waves identified patients at risk for TdP with a positive predictive value of 84%.

Conclusions
Prolonged QT interval, QTc interval, and T_{peak}–T_{end} correlate with increased risk for TdP during acquired bradyarrhythmias, particularly when accompanied by LQT2-like notched T waves. (J Am Coll Cardiol 2007;49:320–8) © 2007 by the American College of Cardiology Foundation

Torsade de pointes (TdP) is a polymorphic ventricular tachycardia caused by a long QT syndrome (LQTS) (1). Bradyarrhythmias, particularly complete atrioventricular block (CAVB), are among the numerous causes of QT prolongation and TdP. In fact, the very first description of TdP by Dessertenne (2) showed CAVB leading to this tachyarrhythmia. Although this description was published 40 years ago, remarkably little is known about the electrocardiographic (ECG) predictors of this potentially lethal complication of bradyarrhythmias (3,4). Moreover, although detailed experiments show that prolongation of ventricular repolarization is a prerequisite for TdP in animal models of CAVB (5), QT prolongation per se is *not* mentioned as indication for pacemaker implantation in acquired atrioventricular block (AVB) or sinus node dys-

function in current American Heart Association/American College of Cardiology (AHA/ACC) guidelines (6). We therefore conducted the present study to define the predictors of TdP during bradyarrhythmias with emphasis on T-wave morphology. We focused on T-wave morphology because: 1) in animal studies, QT prolongation during AVB is due to downregulation of potassium channels (5); and 2) malfunction of the very same potassium channels causes specific T-wave changes in the congenital form of LQTS (7). Therefore, we reasoned that the occurrence of T-wave changes like those observed in the *congenital* LQTS would correlate with increased risk for TdP during *acquired* bradyarrhythmias.

Methods

In a retrospective case-control study, we first identified 30 cases of TdP complicating bradyarrhythmias. Torsade de pointes was defined as a ventricular tachycardia (faster than 150 beats/min and lasting ≥5 beats) that originated from

the terminal part of the QT interval and had a polymorphic configuration. In fact, TdP lasted more than 10 beats in all but 2 patients, degenerated to ventricular fibrillation in 12 (41.4%), and culminated in death (from complications incurred during resuscitation) in 2 patients. In all cases, bradyarrhythmia was the sole cause of TdP.

We then evaluated the records of 113 consecutive patients hospitalized with bradyarrhythmias that were severe enough to warrant consultation regarding the need for cardiac pacing but were *not* complicated by TdP. Patients with congenital AVB or with bradyarrhythmias occurring during acute myocardial infarction or vasovagal syncope were excluded.

Measurements. We reviewed all the ECGs recorded during hospitalization and analyzed the traces showing the worst bradyarrhythmia. The ECGs were recorded at standard gain (10 mV/mm) and speed (25 mm/s). The QT interval was measured from the onset of the QRS interval to the end of the T-wave in all the leads where the end of the T-wave could be clearly defined. The longest QT interval in any of these leads was used as "QT." This QT interval was then corrected for the heart rate with the preceding time duration between 2 consecutive R waves of the ECG (RR interval) and the Bazett formula (corrected QT [QTc] interval = QT/square root of RR interval in s). The T_{peak}–T_{end} was the interval from the summit of the T-wave to the end of the QT interval. Whenever double T waves (also known as "notched T waves" [8], T-wave "humps" [9], or "pathologic U waves" [10]) existed, the first

and second component of the T-wave were labeled T1 and T2. The QT interval was then measured from the onset of the QRS interval to the end of T2 (10), whereas T_{peak}–T_{end} was measured from the summit of T1 to the end of T2. T1>>T2 denoted that T1 was taller than T2 by >10 mV. "Physiologic U-waves," defined as U waves that are smaller than the T-wave and are completely separated from it by an isoelectric line (10), were not counted as part of any of the QT interval.

T-wave morphology was defined as in the congenital LQTS (7,11,12): 1) *"LQT1-like morphology"* denoted a long QT interval (QTc interval ≥450 ms) with broad T waves (Fig. 1); 2) *"LQT2-like morphology"* denoted a long QT interval with double (notched) T waves (Fig. 2); and 3) *"LQT3-like morphology"* denoted a long QT interval with small T waves separated from the QRS interval by a long isoelectric ST-segment (Fig. 3). We also noted the presence of "inverted" and "deep inverted" T waves. Finally, we identi-

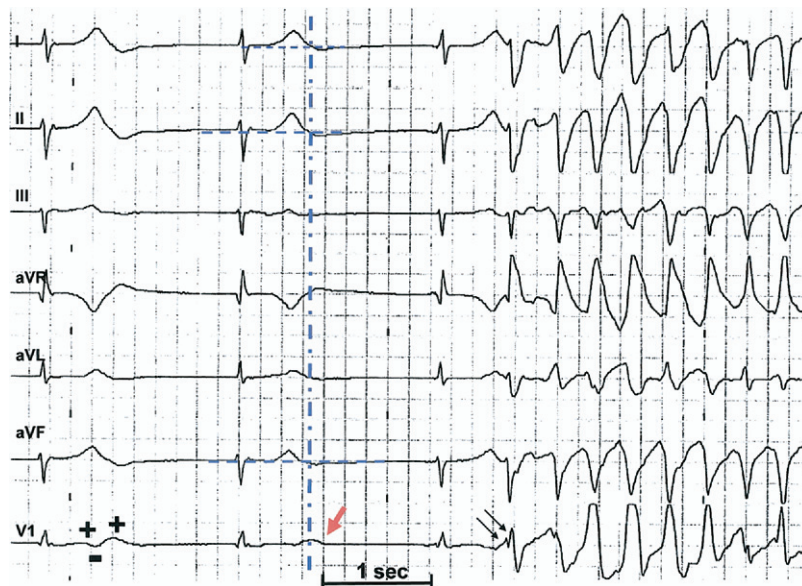**Figure 1**   **Sinus Node Dysfunction in the Absence of Drugs Complicated by Torsade de Pointes in a 70-Year-Old Woman**

There is extreme sinus bradycardia with a wide-QRS escape rhythm of 32 beats/min. The broad T waves in leads I, II, and aVF were defined as LQT1-like. The triphasic repolarization waves (marked +/−/+ in the first complex) in lead V_1 were defined as "bump-sign." The **dotted blue lines** define the baseline and the return of the T-wave to the baseline, which is the "end of the T-wave" with conventional definitions. Note the late repolarization wave in V_1 (the last component of the "bump-sign" marked with a **red arrow**). Also, note that in lead V_1 the first complex of torsade de pointes **(double arrow)** originates from the very late repolarization wave of the "bump-sign" **(arrow)** (see text for discussion).
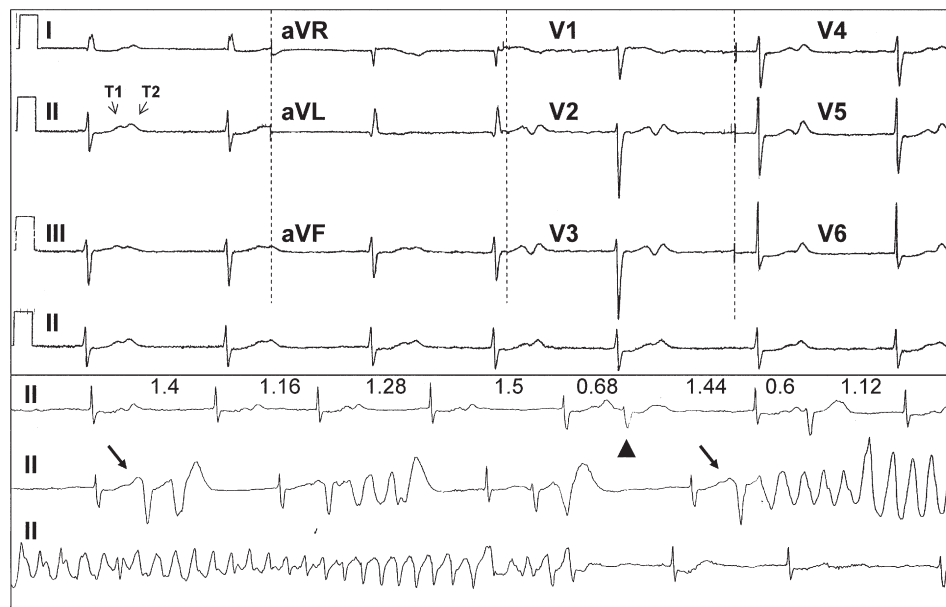
Figure 2 **Atrial Fibrillation With Slow Ventricular Rate
(36 to 40 beats/min) in an 83-Year-Old Woman Presenting With Effort Intolerance**

The patient's only medication, verapamil, was stopped 48 h before this electrocardiogram. The potassium level was 4 meq/l. Note the LQT2-like morphology (T1-T2) in the inferior and anterior leads (with T2>>T1 in V_4 to V_6). **(Lower panel)** Shortly thereafter, this patient had torsade de pointes. Note that the irregularity of ventricular rate during atrial fibrillation creates short and long cycles (time duration between 2 consecutive R waves of the ECG [RR intervals] shown in seconds). The longest cycle (RR interval of 1.5 s) antecedes the complex that is followed by the first extrasystole **(arrowhead)**, which probably represents triggered activity. A series of short-long sequences ensues and culminates in torsade de pointes. As expected, the torsade de pointes complexes originate from T2 **(arrows)**.

fied a specific QT morphology that has not been observed among patients with congenital LQTS. We used the term "bumps-ahead" sign for this complex T-wave, because it consisted of a triphasic wave (positive, then negative, and then positive again) that resembles the road-sign that warns drivers of incoming road-bumps (Fig. 4). As mentioned previously, the QT interval was measured in leads where the end of positive T waves could be clearly defined. Accordingly, leads with "bumps-ahead" sign were not used to define the QT interval length.

Statistical analysis. Values are expressed as mean ± SD. The differences between the groups were analyzed by independent samples, Student *t* test for parametric data, and the Phi and Cramer's V, chi-square for non-parametric data. Receiver-operating characteristic (ROC) analysis was used to determine optimal cutoff values of continuous variables for prediction of TdP (optimal cutoff value was the point with the highest sum of sensitivity and specificity). The area under the curve was used to quantify the ability of the different variables to predict TdP. Univariate and multivariate logistic regression models were used to assess the additive value of variables for prediction of TdP episodes. All tests were 2-sided, and a p value < 0.05 was considered statistically significant. Analyses were performed by an SPSS version 13.0 software package (SPSS Inc., Chicago, Illinois).

Results

Clinical characteristics. The 30 patients with TdP had similar age, clinical background, drug-therapy, and potassium serum levels as the 113 patients with uncomplicated bradyarrhythmias (Table 1). However, a disproportional percentage of patients with TdP were female (77% vs. 40%, p < 0.001). Patients with TdP more frequently required urgent temporary and permanent cardiac pacing. However, the "time at risk," which is the time from presentation to pacemaker implantation (temporary or permanent), was not different between the 2 groups (Table 1). Importantly, 4 (13%) of the patients who had TdP during bradyarrhythmia, had recurrent TdP *after* permanent pacemaker implantation. Evaluation invariably revealed that the pacemakers were implanted with their nominal settings (including a lower rate limit of 60 beats/min) (Fig. 5). Programming faster pacing rates prevented recurrent TdP.

ECG characteristics. Complete atrioventricular block and atrial flutter or fibrillation with high-degree AVB were more common among patients with TdP, whereas other bradyarrhythmias (severe sinus node dysfunction or second degree AVB) occurred with similar frequency in both groups. Yet, neither the ventricular rate nor the QRS width, measured at the time of the slowest bradyarrhythmia, distinguished between the groups. In fact, patients in the control group seemed to have a *slower ventricular rate* (with
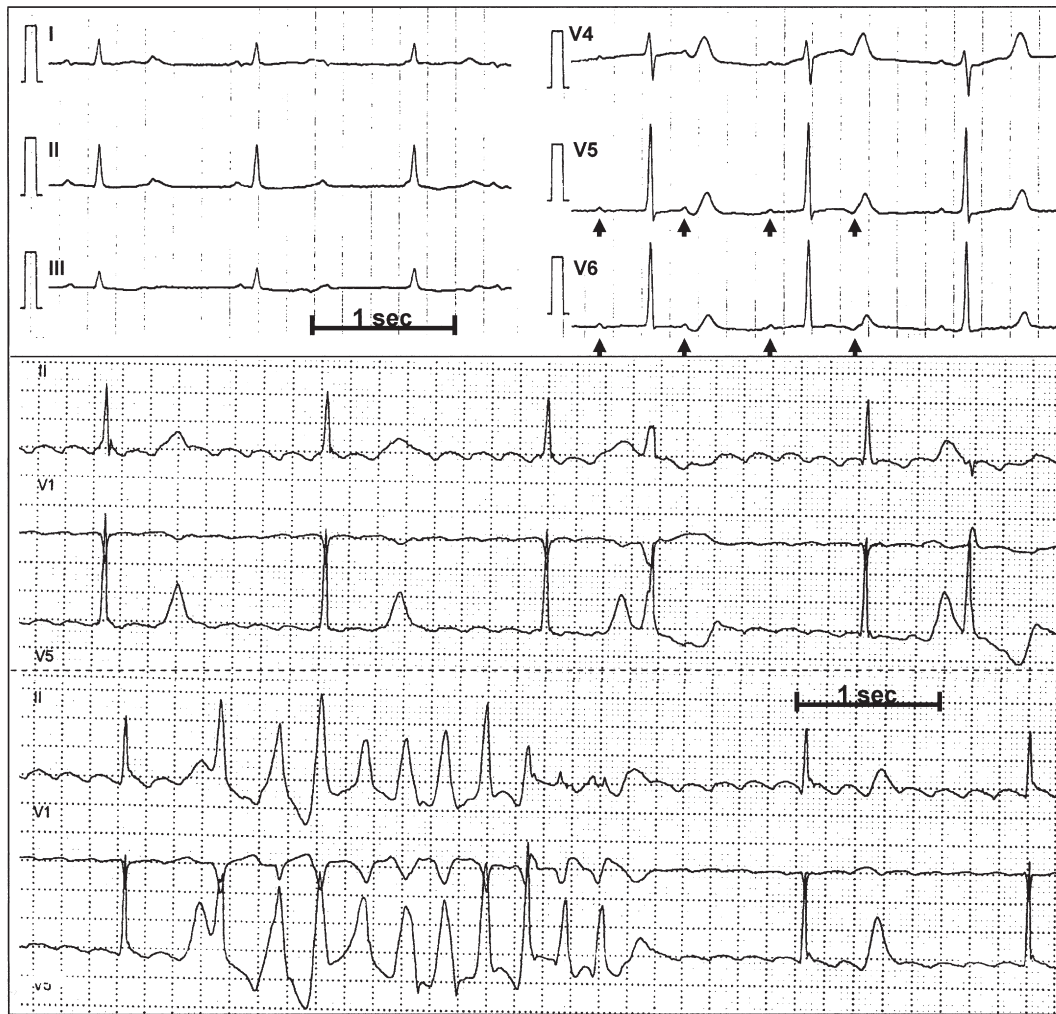
Figure 3   **Sinus Rhythm With Complete AVB (Post-Surgical AVB After Mitral Valve Replacement) Complicated by Torsade de Pointes**

The **top panel** shows sinus rhythm with complete AVB (P waves marked with **arrowheads**). Note the narrow QRS escape with a rate of 42 beats/min, suggesting AV-nodal block. Also, note the LQT3-like (small and very late T waves) morphology of the QT segment. **(Lower panel)** The same patient later developed atrial flutter with very slow ventricular rate (36 beats/min). A series of short-long sequences, due to ventricular bigeminy, culminates in torsade de pointes.

the difference not reaching statistical significance) than patients with TdP (Table 1). Also, TdP did not necessarily occur at the time of the slowest ventricular rate (Fig. 4B).

The QT interval, QTc interval, and T_{peak}–T_{end} correlated with the risk of TdP (Table 1, Fig. 6). The best single discriminator (by ROC analysis), between patients with and without TdP, was the T_{peak}–T_{end} (Table 2). The area under the curve (which is a grade of sensitivity vs. 1-specificity) was 0.994 for T_{peak}–T_{end}, 0.969 for QTc interval, and 0.952 for QT interval. Also, the positive predictive value (PPV) of QT interval and QTc interval behaved linearly, with the risk increasing gradually as the QT interval (or QTc interval) increased (Fig. 6). In contrast, the PPV of T_{peak}–T_{end} showed an S-shape curve, with a sharp increase in risk as T_{peak}–T_{end} increased above 60 ms (Fig. 6). The best cutoff values for telling apart patients with TdP from patients with

uncomplicated bradyarrhythmias appear in Table 2. Because TdP is a potentially lethal complication, one might wish to compromise on specificity to maintain 100% sensitivity. A QT interval of ≥510 ms or a QTc interval of >400 ms identified all cases of TdP. However, such values were also observed in 36% and 49% of patients *without* TdP, respectively.

QT morphology. LQT1-like and LQT3-like morphologies were rare (observed in 14% and 7% of patients, respectively) and had no predictive value. In contrast, LQT2-like changes were observed in 55% of patients with TdP but in only 3% of patients with uncomplicated bradyarrhythmias (p < 0.001). Moreover, LQT2-like morphology with T2>>T1 was seen only in patients who eventually developed TdP. The "bump-ahead" sign was observed in 59% of patients with TdP and in 18% of patients with uncompli-
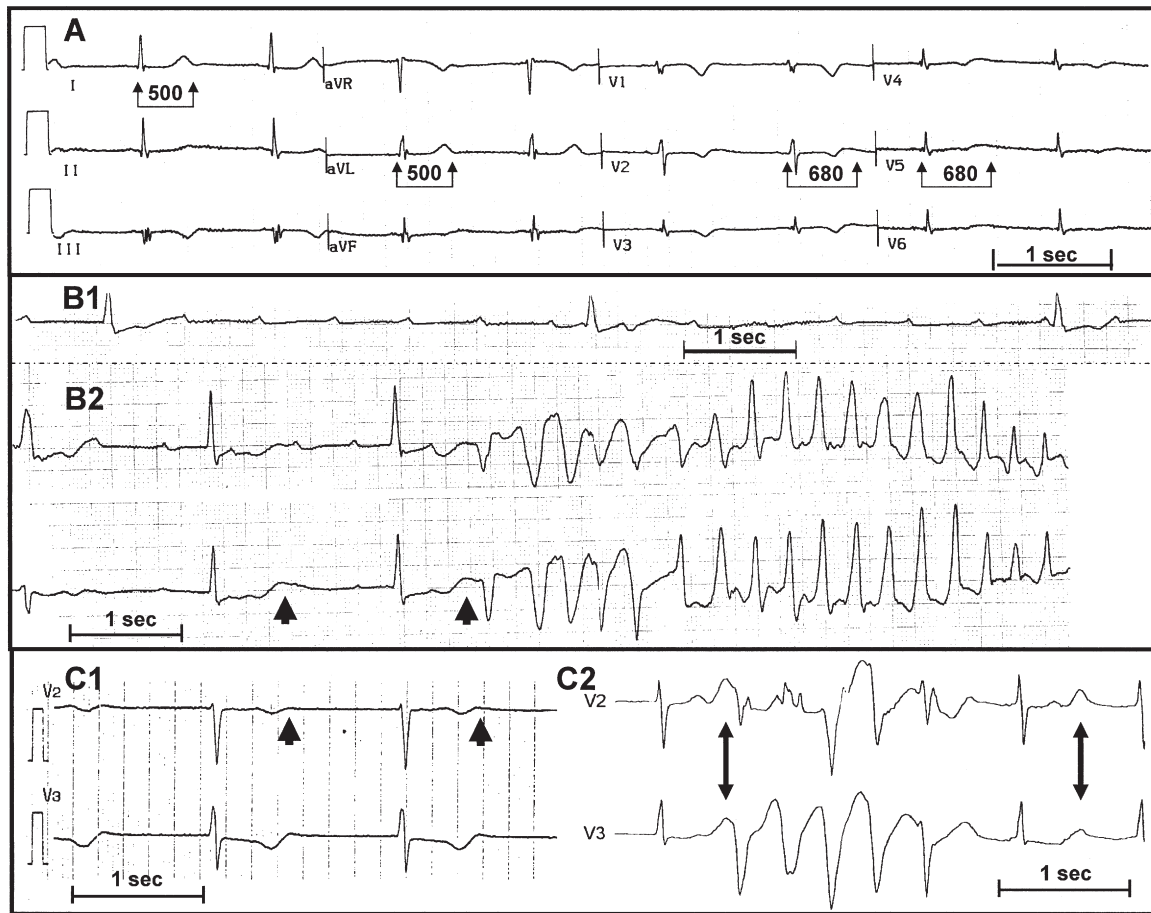
Figure 4   **Triphasic QT Interval ("Bumps-Ahead Sign") in Patients With Bradyarrhythmia-Induced Torsade de Pointes**

(A) Long-standing sinus bradycardia after MAZE operation and mitral valve replacement in a 60-year-old woman treated with low-dose beta-blockers, vasodilators, and furosemide and potassium supplements. Her potassium serum levels were 5 mEq/l. The "bumps-ahead sign" (the triphasic wave with a very late positive component) are seen in leads V_2 to V_6. Note that the QT interval in leads with clearly defined T waves (lead I and aVL) is 500 ms. In contrast, if one uses the terminal wave of the "bump sign" to calculate the QT interval, much longer values (of about 680 ms) are obtained. **(B)** An 89-year-old female patient admitted with syncope in the absence of drugs. Trace **B1** shows sinus rhythm with complete atrioventricular block (AVB) and a wide QRS escape rhythm with extremely low rate (average <15 beats/min). In trace **B2** the ventricular rate is faster (37 beats/min), but the bradyarrhythmia is complicated by torsade de pointes. **(C)** Recordings from leads V_2 to V_3 in a female patient with atrial fibrillation and slow ventricular rate (AVB related to aortic valve replacement). In traces **B2** and **C1**, **arrowheads** denote the late positive component of the triphasic "bump." The **2-way arrows** show that the amplitude of the late component of the "hump" increases just before the onset of torsade or after pauses.

cated bradyarrhythmias (p < 0.001). Inverted T waves and "deep inverted" T waves were rare and contributed no diagnostic value in addition to the QT interval.

Prediction of TdP. With multivariate logistic regression, "LQT2-like morphology" proved to be independent from the QT interval and added to the prediction of TdP. Combining QT interval or QTc interval with T_{peak}–T_{end} contributed minimally to the prediction ability of T_{peak}–T_{end} alone (area under the ROC curve for combined models: "LQT2-like morphology *and* QT" = 0.962; "LQT2-like morphology *and* QTc" = 0.971; "T_{peak}–T_{end} *and* QTc" = 0.998). Finally, the following "2 step models" can increase significantly the PPV and the specificity of QT interval alone.

If one selects the QT interval value that gives 100% sensitivity (510 ms) as cutoff value, we are left with 41 control subjects in the "positive" group (63.7% specificity, PPV = 41.4%). If one then *excludes* individuals *without* LQT2-like T waves, we are left with only 3 control subjects (97.3% specificity), and the PPV for this group is now 84.2%. *In simple terms, with a QT interval of ≥510 ms and a LQT2-like morphology, the odds for developing TdP are very high (>80%).*

By selecting the T_{peak}–T_{end} value that gives 100% sensitivity (85 ms) as cutoff value, we are left with 14 control subjects in the "positive" group (87.6% specificity, PPV = 67.4%). If one then *excludes* individuals *without* LQT2-like T waves, we are left with only 1 control (99% specificity), and the PPV is now 94%. Thus, *having a T_{peak}–T_{end} ≥85 ms with LQT2-like morphology almost surely predicted the occurrence of TdP.*

			Table 1

Table 1 — **Clinical and Electrocardiographic Characteristics of Patients With Bradyarrhythmias With and Without Torsade de Pointes**

Variable	TdP n = 30	Control n = 113	p Value
Clinical parameters			
Age (yrs)	72.5 ± 16.1	76.5 ± 10.8	0.261
Female gender	23 (76.7%)	45 (39.8%)	<0.001
Heart disease	11 (47.8%)	61 (57.5%)	0.395
Time at risk (days)*	2.9 ± 7.3	5.7 ± 9.8	0.238
Urgent pacing	13 (72.2%)	20 (18.9%)	<0.001
CAVB	21 (77.8%)	40 (36.7%)	<0.001
Atrial fibrillation	11 (40.7%)	12 (11.0%)	<0.001
RR interval (ms)	1,490 ± 480	1,540 ± 300	0.718
QRS (ms)	122 ± 22	114 ± 26	0.151
QT (ms)	684 ± 102	494 ± 68	<0.001
QTc (ms)	571 ± 73	402 ± 53	<0.001
T_{peak}–T_{end} (ms)	244 ± 95	65 ± 20	<0.001
QT morphology			
LQT1-like	4 (13.8%)	10 (8.8%)	0.426
LQT2-like	16 (55.2%)	3 (2.7%)	<0.001
LQT2 with T2>>T1	8 (27.6%)	0 (0%)	<0.001
LQT3-like	2 (6.9%)	6 (5.3%)	0.741
"Bumps-ahead sign"	17 (58.6%)	20 (17.7%)	<0.001

*Time at risk is the time lapsed from the admission due to bradycardia to the onset of torsade or (alternatively) to the time of pacemaker implantation. For definition of LQT1-, LQT2-, and LQT3-like morphologies and for definition of T2>>T1 and "bumps-ahead sign," see text.

CAVB = complete atrioventricular block; TdP = torsade de pointes.

Discussion

The LQTS caused by bradyarrhythmias has been well studied in animals (5,13–15). Such studies show that long-standing bradycardia leads to reduced messenger ribonucleic acid and protein expression of the 2 potassium channels responsible for the *slow* and the *rapid* components of the delayed-rectifier potassium current (I_{Ks} and I_{Kr}, respectively) (5,13,14). The resulting reduction in I_{Ks} and I_{Kr} currents impairs ventricular repolarization and increases the susceptibility to TdP during chronic CAVB in the dog and rabbit models (5,13,14,16). Because (genetically) defective I_{Ks} and I_{Kr} currents are also responsible for the most common types of *congenital* LQTS (LQT1 and LQT2 types), we hypothesized that T-wave abnormalities, similar to those seen in the congenital LQTS would also be a prominent feature in the *acquired LQTS* related to bradyarrhythmias. Indeed, we found that "notched" T waves, very similar to those seen in LQT2, independently predict TdP during bradyarrhythmias in humans.

Previous studies. Only 2 small case-controlled series have looked at the ECG predictors of TdP during CAVB (3,4). Both suggested that the degree of QT and/or QTc prolongation rather than the severity of bradycardia correlate with the risk of TdP (3,4). However, both series were small (each series included ≤10 patients) and had a 1:1 ratio of patients to control subjects. The larger number of patients and the 1:4 ratio of patients to control subjects in our series allowed us to identify values for QT interval, QTc interval, and T_{peak}–T_{end}

that confidently tell apart patients with uncomplicated bradyarrhythmias from those prone to develop TdP.

Type of bradyarrhythmia correlated with risk of TdP. Complete atrioventricular block or atrial fibrillation with AVB conferred a higher risk of TdP than 2:1 AVB or severe sinus node dysfunction. Yet, this was *not* due to slower heart rates in the former type of arrhythmias. In animal models, QT prolongation during bradyarrhythmia is a slowly evolving process. This might explain why CAVB, which causes more *long-lasting* bradycardia than 2:1 AVB or sinus node dysfunction, increased the risk of TdP.

Easy identifiable predictors of TdP. The Bazett formula used for correcting the QT interval for the heart rate overcorrects during bradycardia. Nevertheless, valuable cutoff values of QTc intervals were identified. For example, TdP was never seen with QTc interval values <400 ms even though such value existed in 40% of patients with bradyarrhythmias. Despite a wide range of ventricular rate in our patients, the uncorrected QT interval also proved to be of value. The T_{peak}–T_{end} interval, which represents the transmural dispersion of repolarization (17,18), was the single best predictor of TdP. Finally, 2-steps methods, looking at QT duration (or T_{peak}–T_{end}) *and* the presence of LQT2-like T waves, identified most patients with TdP.

QT morphology during bradyarrhythmias. LQT2-like "notched T waves" were common during acquired bradyarrhythmias and increased the risk for TdP. In contrast, LQT1- and LQT3-like changes were rare. The rarity of LQT3-like changes is not surprising, because upregulation of *sodium* channels has not been described in animal models of CAVB (5,13,14,16). In contrast, downregulation of I_{Ks} channels does occur during CAVB (5,13,14,16), and the rarity of LQT1-like "T waves" could be due to the following: 1) malfunction of I_{Ks} channels is expected to become clinically significant during heart rate acceleration but not during bradycardia (19,20); and 2) in the congenital LQTS due to I_{Ks} channels malfunction, T waves are often of normal morphology (12). Yet, only "broad T waves" were counted as LQT1-like in our study.

Our bradycardia patients also had complex T waves, unlike those of the congenital LQTS. Patients with congenital LQTS generally have single mutations, commonly causing malfunction of *either* I_{Ks} or I_{Kr} channels. In contrast, patients with bradyarrhythmias would be expected (on the basis of animal models) (5,13,14,16) to have *combined* I_{Kr} and I_{Ks} malfunction. In the wedge-preparation model of Antzelevitch (21), combined I_{Kr} and I_{Ks} blockade leads to complex T waves (similar to our "bump-sign") or to deep-inverted T waves, depending on the degree of blockade of each channel. Similarly, in the feline wedge preparation of sympathetic stimulation during combined I_{Kr} and I_{Ks} malfunction (22), complex deep inverted T waves were recorded. Deep inverted T waves were rare in our bradycardia patients, perhaps because pacemaker implantation was performed before sufficient downregulation of *both* I_{Kr} and I_{Ks} channels developed. Triphasic "bumps-ahead" T waves
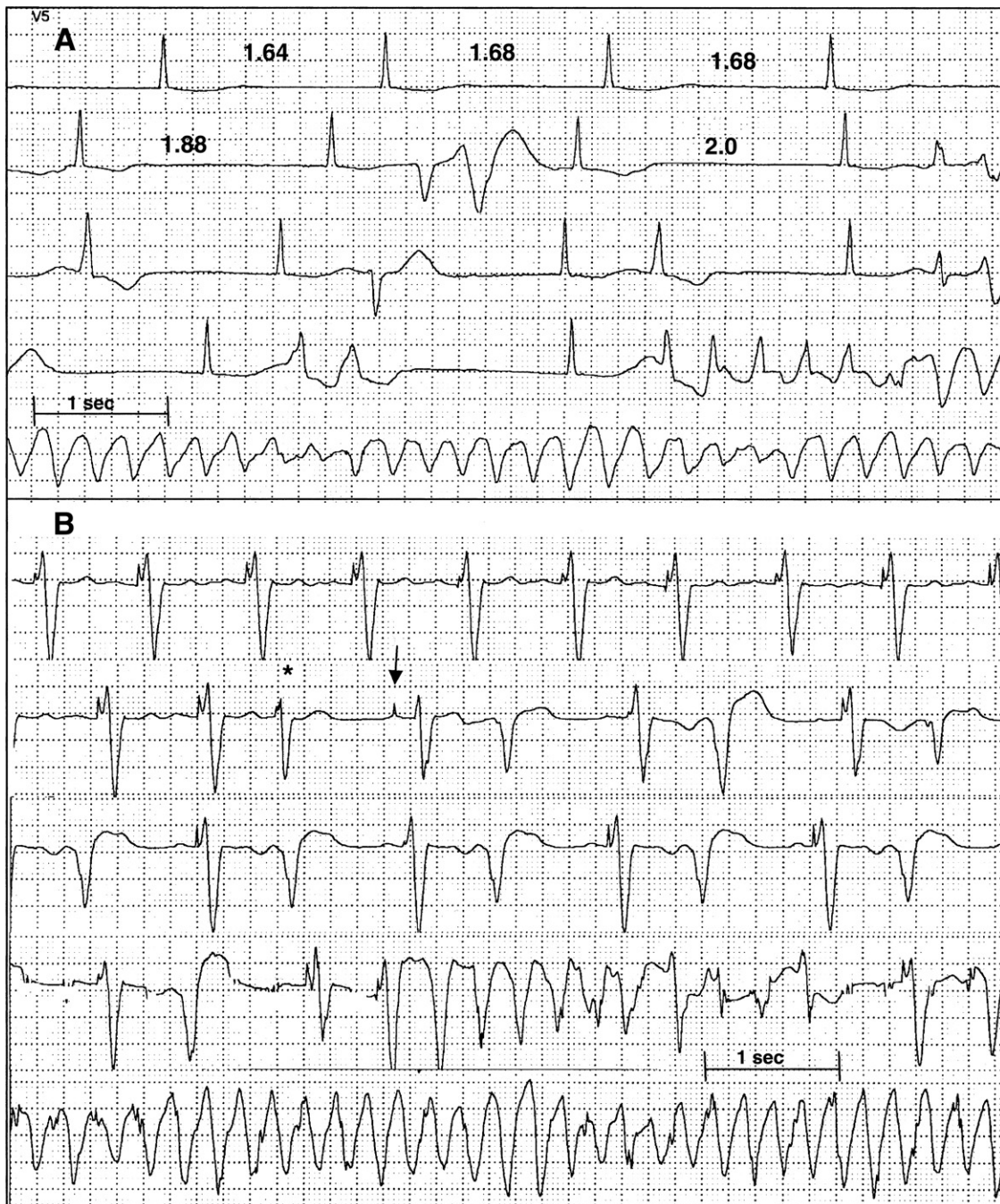
Figure 5   **Torsade de Pointes Before and After Pacemaker Implantation in a Patient With Paroxysmal Atrial Fibrillation and High-Degree Atrioventricular Block in the Absence of Drugs**

(A) Narrow QRS escape rhythm at an average rate of 36 beats/min. After a long cycle (1.88 s), a ventricular couplet, probably representing triggered activity, begins a series of short-long sequences that culminate in torsade de pointes. At the time of pacemaker implantation, sinus rhythm with 1:1 atrioventricular conduction was evident and a dual-chamber was implanted. The device was left at nominal settings (including a lower rate limit of 60 beats/min). **(B)** Several hours after pacemaker implantation the patient had recurrent torsade de pointes. The trace shows sinus rhythm (75 beats/min) with appropriate tracking and ventricular pacing. A premature complex **(*)** starts a post-extrasystolic pause that terminates with a sinus complex with atrial pseudo-fusion (the atrial pacing stimulus falls on the P-wave **[arrow]**). Ventricular bigeminy follows and culminates in torsade de pointes despite a normally functioning pacemaker. The lower rate was increased to 120 beats/min and gradually decreased during the next week to 80 beats/min. No further arrhythmias occurred.
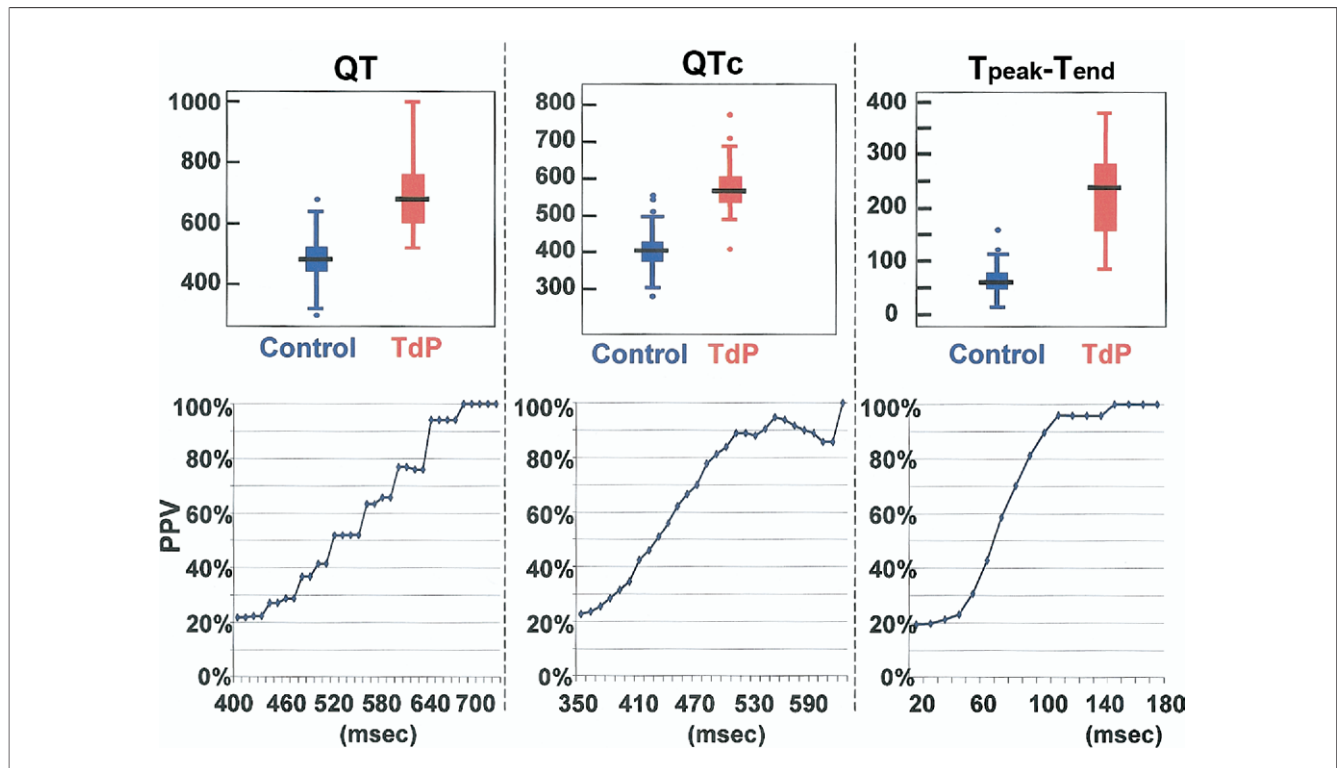
Figure 6   **Distribution of Results (in Patients and Controls) and PPV for Different Cutoff Values of QT Interval, QTc Interval, and T_{peak}–T_{end}**

(Top panels) QT interval, QTc interval, and T_{peak}–T_{end} values for patients with torsade de pointes (TdP) **(red)** and patients with uncomplicated bradyarrhythmias **(blue)**. The **horizontal black line** represents the median value, the **colored squares** represent the interquartile range (IQR). The IQR includes 50% of all values: from the 25th to the 75th percentile. The **bars** represent the range, not including outliers. Outliers, which appear as **dots**, are defined as values above or below 1.5 times the IQR. **(Lower panels)** Positive predictive value (PPV) for different cutoff values of each 1 of the 3 tests above. Note that the risk for torsade increases gradually as the QT interval or the QTc interval increase. In contrast, T_{peak}–T_{end} has an S-shape curve with a sudden increment in risk as T_{peak}–T_{end} becomes longer than 60 ms.

were common in our bradycardia patients (18%) and more so in those with TdP (59%). Moreover, whenever TdP was recorded in leads with "bump-sign" T waves, the arrhythmia invariably originated from this late wave (Figs. 1 and 4). This suggests that the late component of triphasic waves represents local early afterdepolarizations (EADs). Interestingly, triphasic T waves remarkably similar to our "bumps-sign" have been recorded in dogs undergoing vagal stimulation during I_{Kr} blockade to simulate bradycardia-dependent TdP (23). Simultaneous ECG and action potential recordings (in such dogs) suggest that the late wave of the "bump-sign" T-wave represents a "late EAD" originating in the epicar-

dium (23) (instead of the more common endocardial or M-cell origin). Of note, *epicardial* EADs also occur in the wedge-preparation models of combined I_{Kr} *and* I_{Ks} blockade by Emori and Antzelevitch (24) and by Aiba and Shimizu (22).

Study limitations. We classified "broad," "notched," and "small" T waves as LQT1-, LQT2-, and LQT3-like changes, on the basis of data from the congenital LQTS (7,11). However, more than 1 T-wave morphology might be observed in each genotype (12). Therefore, our classification of T waves during bradycardia is an oversimplification of the repolarization abnormalities that take place during CAVB. Thus, our data cannot be used as proof of downregulation of specific ion channels during bradycardia in humans. This limitation, however, does not diminish the clinical value of detecting "notched T waves" during bradycardia.

A second limitation relates to the definition of "control subjects." In the dog model, downregulation of potassium channels and QT prolongation develop gradually over the course of 4 weeks. Therefore, it is possible that some control subjects with "uncomplicated bradyarrhythmias" would have developed TdP if left untreated for longer periods. Conse-

Table 2   **Cutoff Values That Best Distinguished Patients With Bradyarrhythmias Complicated by Torsade de Pointes From Patients With Uncomplicated Bradyarrhythmias**

Parameter	Cutoff Value	Sensitivity	Specificity	PPV	NPV
T_{peak}–T_{end}	117 ms	96.6%	98.2%	93.3%	99.1%
QTc interval	480 ms	96.6%	92.0%	75.7%	99.0%
QT interval	570 ms	90.0%	86.7%	64.3%	97.0%

Values derived from receiver-operating characteristic curves.
NPV = negative predictive value; PPV = positive predictive value; QTc = corrected QT interval.

quently, the data presented here should only be use to estimate the *short-term* risk for TdP.

Clinical implications. Current AHA/ACC guidelines on cardiac pacing (6) do *not* mention "QT prolongation" as an indication for pacemaker implantation during acquired AVB or sinus node dysfunction. Our data show that patients with QT interval >510 ms, QTc interval >400, or T_{peak}–T_{end} >85 ms, especially if they also have LQT2-like "notched T waves," are at sufficiently high risk for developing TdP to justify urgent pacemaker implantation even if symptoms or additional indications are absent. The QT prolongation during bradyarrhythmias should be viewed as a channelopathy that will *not* necessarily resolve immediately upon bradycardia termination. Pacemakers implanted for AVB-induced TdP should be programmed with the precautions recommended for other forms of LQTS (25), including a pacing rate of ≥80 beats/min, until the QT interval shortens.

REFERENCES

1. Viskin S. The long QT syndromes and torsade de pointes. Lancet 1999;354:1625–33.
2. Dessertenne F. [Ventricular tachycardia with 2 variable opposing foci]. Arch Mal Coeur Vaiss 1966;59:263–72.
3. Kurita T, Ohe T, Marui N, et al. Bradycardia-induced abnormal QT prolongation in patients with complete atrioventricular block with torsades de pointes. Am J Cardiol 1992;69:628–33.
4. Strasberg B, Kusniec J, Erdman S, et al. Polymorphous ventricular tachycardia and atrioventricular block. Pacing Clin Electrophysiol 1986;9:522–6.
5. Volders PG, Sipido KR, Vos MA, et al. Downregulation of delayed rectifier K(+) currents in dogs with chronic complete atrioventricular block and acquired torsades de pointes. Circulation 1999;100:2455–61.
6. Gregoratos G, Cheitlin MD, Conill A, et al. ACC/AHA guidelines for implantation of cardiac pacemakers and antiarrhythmia devices: executive summary—a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation 1998;97:1325–35.
7. Moss AJ, Zareba W, Benhorin J, et al. ECG T-wave patterns in genetically distinct forms of the hereditary long QT syndrome. Circulation 1995;92:2929–34.
8. Malfatto G, Beria G, Sala S, Bonnazi O, Schwartz PJ. Quantitive analysis of T wave abnormalities and their prognostic implications in the idiopathic long QT syndrome. J Am Coll Cardiol 1994;23:296–301.
9. Lehmann MH, Suzuki F, Fromm BS, et al. T wave "humps" as a potential electrocardiographic marker of the long QT syndrome. J Am Coll Cardiol 1994;24:746–54.
10. Viskin S, Zelster D, Antzelevitch C. When u say "U waves," what do u mean? Pacing Clin Electrophysiol 2004;27:145–7.
11. Dausse E, Berthet M, Denjoy I, et al. A mutation in HERG associated with notched T waves in long QT syndrome. J Mol Cell Cardiol 1996;28:1609–15.
12. Zhang L, Timothy KW, Vincent GM, et al. Spectrum of ST-T-wave patterns and repolarization parameters in congenital long-QT syndrome: ECG findings identify genotypes. Circulation 2000;102:2849–55.
13. Tsuji Y, Opthof T, Yasui K, et al. Ionic mechanisms of acquired QT prolongation and torsades de pointes in rabbits with chronic complete atrioventricular block. Circulation 2002;106:2012–8.
14. Tsuji Y, Zicha S, Qi XY, Kodama I, Nattel S. Potassium channel subunit remodeling in rabbits exposed to long-term bradycardia or tachycardia: discrete arrhythmogenic consequences related to differential delayed-rectifier changes. Circulation 2006;113:345–55.
15. Vos MA, de Groot SH, Verduyn SC, et al. Enhanced susceptibility for acquired torsade de pointes arrhythmias in the dog with chronic, complete AV block is related to cardiac hypertrophy and electrical remodeling. Circulation 1998;98:1125–35.
16. Volders PG, Sipido KR, Vos MA, Kulcsar A, Verduyn SC, Wellens HJ. Cellular basis of biventricular hypertrophy and arrhythmogenesis in dogs with chronic complete atrioventricular block and acquired torsade de pointes. Circulation 1998;98:1136–47.
17. Lubinski A, Kornacewicz-Jach Z, Wnuk-Wojnar AM, et al. The terminal portion of the T wave: a new electrocardiographic marker of risk of ventricular arrhythmias. Pacing Clin Electrophysiol 2000;23:1957–9.
18. Yan GX, Antzelevitch C. Cellular basis for the normal T wave and the electrocardiographic manifestations of the long-QT syndrome. Circulation 1998;98:1928–36.
19. Shimizu W, Antzelevitch C. Cellular basis for the ECG features of the LQT1 form of the long QT syndrome. Effects of beta-adrenergic agonists and antagonists and sodium channels blockers on transmural dispersion of repolarization and torsade de pointes. Circulation 1998;98:2314–22.
20. Shimizu W, Antzelevitch C. Differential effects of beta-adrenergic agonists and antagonists in LQT1, LQT2 and LQT3 models of the long QT syndrome. J Am Coll Cardiol 2000;35:778–86.
21. Emori T, Antzelevitch C. Cellular basis for complex T waves and arrhythmic activity following combined I(Kr) and I(Ks) block. J Cardiovasc Electrophysiol 2001;12:1369–78.
22. Aiba T, Shimizu W, Inagaki M, et al. Cellular and ionic mechanism for drug-induced long QT syndrome and effectiveness of verapamil. J Am Coll Cardiol 2005;45:300–7.
23. el-Sherif N, Zeiler RH, Craelius W, Gough WB, Henkin R. QTU prolongation and polymorphic ventricular tachyarrhythmias due to bradycardia-dependent early afterdepolarizations. Afterdepolarizations and ventricular arrhythmias. Circ Res 1988;63:286–305.
24. Emori T, Antzelevitch C. Cellular basis for complex T waves and extrasystolic activity in a model of combined acquired and congenital long QT syndrome (abstr). Pacing Clin Electrophysiol 2000;23:615.
25. Viskin S. Cardiac pacing in the long QT syndrome. Review of available literature and practical recommendations. J Cardiovasc Electrophysiol 2000;11:593–600.