Giant T–U Waves Precede Torsades de Pointes in Long QT Syndrome

A Systematic Electrocardiographic Analysis in Patients With Acquired and Congenital QT Prolongation

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Objectives
This study sought to identify electrocardiographic (ECG) criteria that are associated with initiation of torsades de pointes (TdP) in patients with acquired (a-) and congenital (c-) long QT syndrome (LQTS).

Background
Electrocardiographic criteria used as risk predictors for TdP commonly rely on a prolonged QT interval but rarely consider abnormal T–U waves.

Methods
We analyzed ECG recordings with TdP from 35 LQTS patients (15 c-LQTS and 20 a-LQTS) and compared them with premature ventricular complexes (PVCs) from 40 patients with normal QT intervals and with PVCs in 24 of the 35 LQTS patients not related to TdP.

Results
Abnormal T–U waves (6.2 ± 0.9 mm) directly preceded TdP in 34 of 35 LQTS patients and were larger than T-wave amplitude (2.8 ± 0.2 mm) in control patients and larger than the largest T–U-wave in LQTS without TdP (4.7 ± 0.8 mm). The TdP-initiating beat emerged from a T–U-wave in 27 of 35 LQTS patients and in none of 40 control patients. The QRS duration of the first TdP beat (175 ± 12 ms) was longer than in control PVCs (145 ± 4 ms) and in PVCs in LQTS patients not related to TdP (138 ± 22 ms). The QRS angle was less steep before TdP than in other PVCs (all p < 0.05).

Conclusions
Abnormal, giant T–U waves separate TdP initiation in LQTS patients from PVCs in other heart disease and from other PVCs in LQTS patients. These ECG analyses suggest that early afterdepolarizations initiate TdP and, if present, may help to identify an imminent risk for TdP. (J Am Coll Cardiol 2009;54:143–9) © 2009 by the American College of Cardiology Foundation

The acquired long QT syndrome (a-LQTS) and congenital long QT syndrome (c-LQTS) predispose patients to torsades de pointes arrhythmias (TdP). The mechanisms that initiate TdP in LQTS patients are not well understood. Although abnormal prolongation of the QT interval identifies patients at increased risk for TdP (1–3), many patients tolerate marked QT prolongation without TdP. Thus, there must be other factors that cause TdP. In experimental settings, early afterdepolarizations (EADs) initiate TdP (4–6), which may be reflected by abnormal T–U waves in the electrocardiogram (ECG) (5,7,8).

A common feature of drug-induced TdP and of TdP in long QT syndrome type 2 (LQTS2) is that the TdP-initiating beat is preceded by a premature beat followed by a pause. Often, this pattern of premature beats and pauses, or short-long-short interval, repeats for several cycles in an incremental fashion, with TdP occurring when the pause has reached a critical length (9). A comprehensive publication from 2 decades ago (5) reviewed these ECG features from both experimental and clinical observations and suggested an eminent role of abnormal T–U waves in the triggering of TdP. In that and other subsequent studies, the use of monophasic action potential recordings showed that the U-wave in LQTS patients closely correlated with early EADs at the cellular level (10). This not only makes correct measurements of the QT interval more difficult but may also
in itself contain relevant information that is more directly linked to the effects that initiate TdP than QT interval analysis alone.

These considerations and occasional observations suggest that giant T–U waves in LQTS not only are an important ECG criterion for imminent TdP, but also constitute one of the actual pathophysiologic trigger mechanisms for TdP. To study the relevance and clinical usefulness of T–U waves for identification of imminent proarrhythmia, we therefore compared ECG parameters before TdP with ECG recordings before other premature ventricular complexes (PVCs).

**Methods**

**ECG data collection.** We analyzed ECG recordings in 35 patients with a- and c-LQTS and TdP (from the Academic Medical Centre, Amsterdam, collected from 1991 to 2006) and compared them with ECGs from 40 patients with normal QT intervals and PVCs on Holter or routine ECG (from University Hospital Münster) and with ECGs from 24 of the above-mentioned LQTS patients (10 c-LQTS, 14 a-LQTS) without TdP but with PVCs (Fig. 1).

**ECG analysis.** After a quality check assessing recording speed (>25 mm/s), continuous recording of the initiation of TdP or of a PVC with at least 1 normal beat before this episode, and availability of at least 2 ECG leads, all ECGs were analyzed by 2 independent observers (Fig. 1). If independently measured parameters differed (generally <5% for continuous parameters), the mean value was used for final analysis. Analysis was performed in an ECG with high-amplitude T waves. We analyzed: 1) RRprec: the RR interval preceding the last normal beat before the arrhythmia; 2) QTprec: the QT interval in the last normal beat before the arrhythmia; 3) Tprec: the T-wave amplitude in the last normal beat before the arrhythmia; 4) TUany: the largest T–U-wave amplitude in any beat of the recording strip with the exception of the beat that initiated the arrhythmia; 5) TU_{TdP}: the T–U-wave amplitude of the T–U-wave from which the arrhythmia was initiated; 6) QRS_{PVC}: the QRS duration of the first beat of the arrhythmia (TdP or PVC without TdP (as an indirect measure of propagation velocity); and 7) QRSangle: the angle of the first QRS upstroke (or downstroke) of the first beat of the arrhythmia (as a measure of premature activation velocity) (Fig. 2).

Because most recordings (often from monitor strips or in an emergency room setting) provided neither a 12-lead ECG nor voltage calibration, we compared all measurements in millimeters rather than millivolts (TU_{TdP}:wave) and also normalized TU_{TdP} to the amplitude of the “normal” T-wave (TU_{TdP}/Tprec ratio) and to the largest T- or U-wave in the entire recording (TU_{TdP}/TUany).

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**ABBREVIATIONS AND ACRONYMS**

a-LQTS = acquired long QT syndrome
c-LQTS = congenital long QT syndrome
EAD = early afterdepolarization
ECG = electrocardiogram
LQTS = long QT syndrome
PVC = premature ventricular complex
TdP = torsades de pointes

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**Figure 1** Flow Chart of Study Patients and Analysis

Shown are the electrocardiographic (ECG) tracings available for analysis and the number of ECG tracings per group used for analysis after the initial ECG quality check. See text for details. All numbers indicate numbers of patients. LQTS = long QT syndrome; PVC = premature ventricular complex; TdP = torsades de pointes.
Statistical analysis. Continuous parameters were normally distributed and compared between groups using unpaired Student $t$ tests and within groups using paired $t$ tests. No corrections were made for multiple comparisons. A 2-sided value of $p < 0.05$ was considered significant. All values depicted in bar graphs are indicated as mean with standard error of the mean.

Results

Abnormal T–U waves precede TdP. Clinical data are shown in Table 1. Figure 3A, a single-monitor lead, shows giant, abnormal T–U waves directly preceding a TdP episode. In Figure 3B, a 12-lead ECG, the TdP-initiating beat arises from the end of the giant T–U-wave complex with deep inverted T–U waves (even when the R-wave is mostly positive). The TdP-initiating beat arising from the abnormal T–U shows a slow rise velocity and wide QRS complex. The amplitude of the T–U-wave preceding TdP was more than 3 times larger in LQTS patients with TdP compared with the largest T–U-wave in LQTS patients without TdP (Fig. 4A). Control patients had no U waves or only very small ones (Figs. 2A and 4A). The T–U-wave ratios also were higher before TdP than in other recordings (Figs. 4B and 4C) (ratio of $T-U_{\text{prec}}$ divided by $T-U_{\text{any}} = 1.8 \pm 0.4$, $p < 0.05$ vs. both control groups). The T–U-wave preceding PVCs in patients with a normal QT interval was not different from other T–U waves ($T-U_{\text{prec}}/T-U_{\text{any}} = 1.0 \pm 0.3$). The T–U-wave before a PVC without TdP in LQTS patients was even smaller than other T–U waves in the same ECG recording ($T-U_{\text{prec}}/T-U_{\text{any}} = 0.4 \pm 0.1$) (Fig. 4C).

QRS duration and rise angle. One of our hypotheses was that a premature beat taking off from a U-wave (an EAD at the tissue level) should have a lower action potential
Figure 3

Examples of ECG Tracings With Giant T–U Waves and TdP

(A) A 12-lead ECG recording of a normal beat (left) and during the initiation of an episode of TdP. Arrows indicate T-wave morphology in the normal beat and the markedly larger abnormal T–U waves in leads III and aVL. The T–U-wave amplitude is higher directly before the TdP episode compared with the prior beat that initiated 2 PVCs. Both are larger than the normal T-wave. Similar changes can be found in other ECG leads. (B) Monitor strip of a patient with a-LQTS. Arrows indicate giant (negative) T–U waves in beats after a pause. The lower tracing (consecutive to the upper) shows the onset of TdP from the nadir of the giant T–U-wave. The giant T–U waves are almost as large as the abnormal T waves after ventricular paced beats. (C) The 12-lead ECG and monitor strip of 2 different patients that exemplify the slowness of the QRS rise angle of the first TdP beat arising from giant T–U-wave. RESP = respiration; other abbreviations as in Figures 1 and 2.
upstroke velocity and thus translate into a slower initial QRS rise (or descent) angle, as well as a longer QRS duration. Indeed, QRS duration of the first TdP beat was longer, and the QRS angle was lower compared with QRS duration of other PVCs. Although it may seem evident to some, the first finding has never been analyzed systematically. The second finding is, to the best of our knowledge, novel.

**Giant T–U waves initiate TdP.** Our analysis suggests that the T–U-wave plays a critical role in the precipitation of TdP. A marked increase in T–U-wave amplitude (3-fold higher amplitude compared with ECGs without TdP, 80% increase compared with the largest repolarizing wave in the entire ECG recording) was specific for imminent TdP. Often, the blinded analyzers could not differentiate between T- and U-wave in the TdP recordings. Therefore, we chose the term T–U-wave for this phenomenon that has not been systematically studied before. We believe that both an increase in T-wave amplitude and the appearance of a closely timed abnormal U-wave added up to create giant T–U waves. Abnormal U waves have been appreciated by many clinicians and investigators before (5). A similar ECG waves directly precede TdP. The first TdP beat emerges from an abnormal T–U-wave. Abnormal T–U waves are larger than any other repolarizing wave in the available ECG recording and are not found before other types of PVCs. 2) The QRS duration of the first TdP beat was longer and the QRS angle was lower compared with QRS duration of other PVCs. Although it may seem evident to some, the first finding has never been analyzed systematically. The second finding is, to the best of our knowledge, novel.

**Discussion**

**Main findings.** Our ECG analysis in a prospectively collected ECG database of LQTS patients identified several ECG characteristics before imminent TdP: 1) Giant T–U waves directly precede TdP. The first TdP beat emerges from an abnormal T–U-wave. Abnormal T–U waves are larger than any other repolarizing wave in the available ECG recording and are not found before other types of PVCs. 2) The QRS duration of the first TdP beat was longer and the QRS angle was lower compared with QRS duration of other PVCs. Although it may seem evident to some, the first finding has never been analyzed systematically. The second finding is, to the best of our knowledge, novel.

**Pause dependency of TdP?** The RR intervals and QT intervals preceding either TdP or PVC were longer in LQTS patients than RR intervals preceding PVCs in patients with other heart disease. Of note, neither RR interval nor QT interval were more prolonged before TdP than RR interval or QT interval before PVCs not inducing TdP in LQTS patients (Fig. 6).

**Figure 4** Amplitudes and Ratios of T–U Waves

(A) The T–U-wave amplitude before TdP in LQTS patients, before PVC in patients with other heart disease (control subjects), and before PVCs that did not initiate TdP in LQTS patients. The amplitude of the largest T–U-wave immediately preceding TdP was more than 3 times larger in LQTS patients with TdP when compared with the largest T–U-wave in LQTS patients without TdP. Control patients had no U waves or only very small ones. (B) The ratio of T–U-wave amplitude and T-wave amplitude and (C) ratio of T–U-wave preceding a PVC over the largest T–U-wave. This ratio is markedly higher than 1 before TdP in LQTS patients, whereas it is equal to 1 before PVCs in patients with other heart disease. Of note, the T–U-wave before PVCs not resulting in TdP is actually smaller than the preceding T–U waves (ratio <1) in LQTS patients. Color schemes reflect caliper colors in Figure 2, with mixed colors reflecting ratios of parameters. Asterisks denote significant differences of the mean of the marked versus unmarked columns at \( p < 0.05 \). The same applies to Figures 5 and 6. Abbreviations as in Figure 1.

**Figure 5** QRS Duration and Rise Angles

QRS duration (A) and QRS rise (or descent) angle (B) of the TdP-initiating beat in comparison with PVC-QRS rise angles in patients with other heart disease (control subjects) and in LQTS patients without TdP. The QRS duration was longer and the QRS angle was smaller in the first beat of a TdP episode compared with other PVCs. See Figure 4 legend for a description of the color scheme and significance of asterisks. Abbreviations as in Figure 1.
phenomenon was described as post-extrasystolic U-wave augmentation in patients who survived ventricular fibrillation in a prior ECG analysis (11). To the best of our knowledge, this is the first systematic quantification of giant T–U waves directly before TdP.

**QT interval prolongation and TdP.** The LQTS patients with a prominent prolongation of the QT interval are prone to TdP (2,12). This was confirmed in our analysis. Interestingly, the degree of QT interval prolongation in LQTS patients was not different between ECGs with TdP and ECGs with PVCs but without TdP. Hence, prolongation of the QT interval did not identify an imminent TdP episode.

**Pause dependency.** Facilitation of TdP onset by a preceding pause has been recognized previously (5,9,13). In this study, the initiation of a TdP episode was preceded by a longer RR interval than the prior beats, consistent with a previous report of the pause dependency of TdP in LQTS2 that had ECG traces that in part (some of the c-LQTS patients) overlapped with the ECGs used in this study (3). Interestingly, the RR interval was equally long before PVCs not initiating TdP and before the first TdP beat in the LQTS patient ECGs in this study (Fig. 6).

Pause dependency therefore does not discriminate imminent TdP from other types of PVCs in this set of LQTS patients.

**Normal U waves, abnormal U waves, and abnormal T–U waves before TdP.** Different types of U waves may have different relevance (5,14). Small, orthotopic U waves are a normal variant in young adults, especially in the precordial leads. These normal U waves may reflect intrinsic potential differences in the terminal part of the action potential (14) or mechanoelectrical feedback with a prolonging effect on late myocardial repolarization (15).

Abnormal U waves, for example, those found in myocardial ischemia or left ventricular hypertrophy, are less well separated from the T-wave, and often show reversed polarity compared with the T-wave (5,16). These abnormal U waves may be caused by either (but not limited to) EADs, regional contractile dysfunction and subsequent stretch-induced depolarizations, regional inhomogeneities in repolarization (e.g., during regional acute ischemia), or spontaneous activity in the Purkinje network.

Abnormal intracellular calcium release and a subsequent increased activity of the sodium–calcium exchanger may trigger early-coupled depolarizations (17–20). Given the largely epicardial potentials that are recorded in the surface ECG (21), giant T–U waves are unlikely to originate from the Purkinje network. Long QRS durations of the first TdP beat in this study also suggest an origin of the first TdP beat distant from the specialized conduction system.

**Giant T–U waves may trigger TdP in LQTS: a hypothetical mechanism.** Occasional invasive electrophysiological recordings in patients with TdP have found that EADs correspond to abnormal T–U waves at the myocardial tissue level (10,22–24). The EADs are most likely a regional phenomenon (4,25–30), hence explaining why EADs were not found in all patients. We suggest that abnormal T–U waves on the surface ECG reflect regional EADs, supported by their exclusive presence before TdP. Initiation of TdP by EADs, that is, by a slowly rising activation wave that arises in an incompletely repolarized region of the heart, is supported by the, albeit indirect, finding that QRS duration is long and QRS angle is small in the first beat of TdP.

**Study limitations.** Although we had access to a sizeable number of ECG recordings during TdP, our analysis was confined to the available ECG recordings, often monitor strips of 2-lead ECGs and occasionally 12-lead ECGs. We could not analyze longer periods (minutes to hours) before TdP. Furthermore, we did not study subtle beat-to-beat changes in the QT interval in these ECGs. Nonetheless, the T–U-wave that preceded TdP was markedly higher in amplitude than any other T–U- or T-wave found in the TdP recordings or in recordings of ECGs with PVC, either in LQTS or in control patients. Published data suggest that EADs are the underlying myocardial electric event. We cannot conclude on mechanisms of EADs nor even prove that EADs are indeed the biological event reflected by abnormal T–U waves in this study. Because of the early
take-off of the first TdP beat, we could not measure the full extent and duration of the last T–U-wave that triggered the TdP episode.

**Conclusions**

The onset of TdP is linked to abnormal giant T–U waves. Abnormal T–U waves and a slow QRS upstroke separate initiation of TdP from early PVCs in other heart diseases and in LQTS. Abnormal T–U waves support the notion that EADs are the trigger for TdP in LQTS. If found, they may be an indicator for imminent risk of TdP.

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**REFERENCES**