Prevalence of Microvolt T-Wave Alternans in Patients With Long QT Syndrome and Its Association With Torsade de Pointes

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Background—Prevalence of microvolt T-wave alternans (TWA) and the strength of its association with torsade de pointes (TdP) history have not been fully investigated in patients with long QT syndrome (LQTS).

Methods and Results—Twenty-four–hour continuous 12-lead ECGs were recorded in 10 healthy subjects (5 men; median age, 21.5 years) and 32 patients (13 men; median age, 13 years) with LQTS types 1 (n=18), 2 (n=4), 3 (n=4), and unidentified (n=6). Peak TWA was determined by the Modified Moving Average method. None of the healthy subjects had TWA ≥42 µV. All 8 (100%) LQTS patients with a history of TdP exhibited TWA ≥42 µV, whereas only 14 (58.3%) of the 24 LQTS patients without TdP history reached ≥42 µV (p=0.04). Thus, the 42-µV cut point provided 100% sensitivity and 41.7% specificity for an association with TdP history. In the 22 (68.8%) LQTS patients with TWA ≥42 µV, only 2 (median; interquartile range, 1–3) leads exhibited TWA ≥42 µV. Highest TWA levels were recorded in precordial leads (V1–V6) in 30 (93.8%) patients, most frequently in lead V2 (43.8%). A single ECG lead detected only ≤63.6% of TWA ≥42 µV episodes, whereas the combined leads V2 to V5 detected 100% of TWA ≥42 µV.

Conclusions—Microvolt TWA is far more prevalent in LQTS patients than previously reported and is strongly associated with TdP history. TWA should be monitored from precordial leads in LQTS patients. The use of a limited set of ECG leads in conventional monitoring has led to underestimation of TWA and its association with TdP.

Key Words: arrhythmias, cardiac ▪ electrocardiography ▪ heart conduction system ▪ long QT syndrome ▪ torsade de pointes ▪ T-wave alternans
performed in 27 patients at National Cerebral and Cardiovascular Center (Osaka, Japan). Twenty-six of the 27 patients were genotyped: LQT1 (n=18), LQT2 (n=4), and LQT3 (n=4). Unidentified LQTS (n=6) included 1 patient with non-1, non-2, non-3 LQTS, 1 patient awaiting genetic testing result and 4 patients who did not agree to undergo genetic testing. All unidentified LQTS patients fulfilled the diagnostic criteria for LQTS (score ≥4). Average heart rate of ≥42 μV, the sensitivity for detecting TWA ≥42 μV was evaluated in each of the 12 leads.

WHAT THE STUDY ADDS

• Automated monitoring of microvolt TWA with the Modified Moving Average method in 24-h continuous 12-lead ECGs identifies a greater prevalence of microvolt TWA episodes and a stronger association with history of torsade de pointes in LQTS patients than has been previously reported.

• Microvolt TWA is narrowly distributed in the precordial leads in LQTS patients. Thus, use of a limited set of ECG leads in conventional monitoring has led to underestimation of TWA and its association with torsade de pointes.

WHAT IS KNOWN

• Macroscopic T-wave alternans (TWA) is not only one of the diagnostic criteria for long QT syndrome (LQTS) but is also a marker of risk for cardiac events.

• Previous clinical studies on the relationship between microvolt TWA and arrhythmia risk in patients with LQTS drew negative conclusions about its significance.

Results

Patient Characteristics

The clinical characteristics of the 32 LQTS patients with types 1 (LQT1, n=18), 2 (LQT2, n=4), 3 (LQT3, n=4), and unidentified (n=6) are summarized in Table 1. The patients were divided into 2 groups: 8 patients with a history of TdP (TdP group) and 24 without (non-TdP group). The clinical characteristics of the 2 groups and healthy controls are shown in Table 2. β-Blocker use rate was significantly higher in the TdP group than in the non-TdP group (87.5% versus 41.7%; P=0.04). There were no significant differences in other clinical characteristics of LQTS patients comparing TdP and non-TdP groups at the time of microvolt TWA test. TWA ≥42 μV, which was observed in none of the healthy subjects and in all 8 LQTS patients with a history of TdP, characterized 22 (68.8%) of the 32 LQTS patients studied (Table 3).

Peak TWA Values in Healthy Subjects and Comparison With LQTS Patients

No healthy subjects exhibited visible macroscopic TWA or TWA ≥42 μV. Peak TWA values in healthy subjects were significantly lower than those in LQTS patients (median [interquartile range], 30 [26–37] versus 55 [39–73.5] μV; P<0.001).

Peak TWA Values and Hourly Distribution of Peak TWA in LQTS Patients

Peak TWA values among all of the 32 LQTS patients were the highest in lead V2 (36.5 [17.0–58.0] μV) and the second...
highest in lead $V_3$ (32.5 [19.5–41.5] $\mu$V; Figure 1A). Hourly distribution of peak TWA in a 24-hour period is shown in Figure 1B. The incidence of peak TWA was higher during daytime (8:00–20:00) than during nighttime (20:00–8:00) in LQT1 patients, whereas all the peak TWA episodes were distributed during nighttime in LQT3 patients.

### Association of TWA With TdP History in LQTS Patients

Eight (25%) of the 32 LQTS patients enrolled had a history of TdP. The association of TWA with a history of TdP in LQTS patients was assessed with receiver-operating characteristic curve analysis. The area under the receiver-operating characteristic curve was 0.61 (95% confidence interval, 0.41–0.82). The cut point TWA value of 42 $\mu$V was 15 s (interquartile range, 15–30 s; minimum–maximum, 15–45 s). One or more episodes of TWA $\geq$42 $\mu$V were observed in the same region of the heart at different times of the day in 16 (72.7%) of the 22 LQTS patients with TWA $\geq$42 $\mu$V.

Figure 2 shows representative continuous 12-lead ECGs with visible TWA in a 2-year-old boy with LQT1 (Figure 2A) and a 58-year-old woman with LQTS (Figure 2B) with a history of TdP whose LQT type could not be identified. TWA $\geq$42 $\mu$V was narrowly distributed in the precordial leads. Specifically, visible TWA of 56 $\mu$V in lead $V_3$ (Figure 2A) and of 44 and 54 $\mu$V in leads $V_5$ and $V_6$, respectively (Figure 2B), are marked with arrows.

Continuous 12-lead ECG of an 8-year-old boy with LQT3 with frequent episodes of TdP is shown in Figure 3. In this patient, a total of 112 episodes of macroscopic TWA with beat-to-beat alternating polarity of the T wave, that is, T-wave polarity alternans (TWPA), were recorded. However, all of the episodes of TWPA were overlooked because of technical problems of MARS Holter Analysis Workstation Software version 8. By visual estimation, the amplitude of TWPA was $\geq$5000 $\mu$V (Figure 3), but the peak TWA value automatically generated by MARS version 8 Software was 611 $\mu$V, a significant underestimation. In some TWPA episodes, the dynamics of TWA, that is, the time of onset, peak, and termination of the alternans, varied from region to region, suggesting that alternation in polarity is a regionally independent property of TWA (Figure 3).

At this time, 3 LQTS patients have experienced TdP since enrollment (at 28, 44, and 463 days after TWA testing, respectively), and all 3 exhibited TWA $\geq$42 $\mu$V at the time of joining the study.

### Distribution of the Lead With the Highest TWA Level in LQTS Patients

Figure 4 represents the distribution of highest lead among all 32 LQTS patients enrolled (Figure 4A) and in the 22 LQTS patients with TWA $\geq$42 $\mu$V (Figure 4B). In the group as a whole, the most frequent highest lead was $V_2$ in 14 (43.8%) LQTS patients. Highest lead was distributed in the precordial leads $V_1$ through $V_6$ and...
Table 2.  Clinical Characteristics of Healthy Controls and LQTS Groups According to TdP History

<table>
<thead>
<tr>
<th>Group</th>
<th>H (n=10)</th>
<th>T (n=8)</th>
<th>N (n=24)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Families, n (%)</td>
<td>7 (70)</td>
<td>8 (100)</td>
<td>19 (79.2)</td>
<td>0.32*</td>
</tr>
<tr>
<td>LQT1</td>
<td>NA</td>
<td>2 (25)</td>
<td>16 (66.7)</td>
<td>0.06†</td>
</tr>
<tr>
<td>LQT2</td>
<td>NA</td>
<td>1 (12.5)</td>
<td>3 (12.5)</td>
<td></td>
</tr>
<tr>
<td>LQT3</td>
<td>NA</td>
<td>1 (12.5)</td>
<td>3 (12.5)</td>
<td></td>
</tr>
<tr>
<td>Unidentified LQT type</td>
<td>4 (50)</td>
<td>2 (8.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>21.5 (11–28)</td>
<td>32.5 (12–61)</td>
<td>13 (10.5–14.5)</td>
<td>0.12*</td>
</tr>
<tr>
<td>Men, n (%)</td>
<td>5 (50)</td>
<td>3 (37.5)</td>
<td>10 (41.7)</td>
<td>0.84*</td>
</tr>
<tr>
<td>Women, n (%)</td>
<td>5 (50)</td>
<td>5 (62.5)</td>
<td>14 (58.3)</td>
<td></td>
</tr>
<tr>
<td>QTc interval (ms)</td>
<td>425 (409, 431)</td>
<td>526 (463, 538.5)</td>
<td>492.5 (472, 517.5)</td>
<td>&lt;0.001*; H&lt;T, N</td>
</tr>
<tr>
<td>Family history, n (%)</td>
<td>NA</td>
<td>2 (25)</td>
<td>15 (42.4)</td>
<td>0.23†</td>
</tr>
<tr>
<td>Sudden death</td>
<td>NA</td>
<td>1 (12.5)</td>
<td>4 (16.7)</td>
<td>&gt;0.99†</td>
</tr>
<tr>
<td>LQTS</td>
<td>NA</td>
<td>1 (12.5)</td>
<td>12 (50)</td>
<td></td>
</tr>
<tr>
<td>β-Blocker, n (%)</td>
<td>NA</td>
<td>7 (87.5)</td>
<td>10 (41.7)</td>
<td>0.04†</td>
</tr>
<tr>
<td>Propranolol (dose range, 20–60 mg)</td>
<td>NA</td>
<td>3 (37.5)</td>
<td>4 (16.7)</td>
<td>0.33†</td>
</tr>
<tr>
<td>Atenolol (dose range, 25–50 mg)</td>
<td>NA</td>
<td>1 (12.5)</td>
<td>4 (16.7)</td>
<td>&gt;0.99†</td>
</tr>
<tr>
<td>Bisoprolol (dose range, 1.25–5 mg)</td>
<td>NA</td>
<td>2 (25)</td>
<td>2 (8.3)</td>
<td>0.25†</td>
</tr>
<tr>
<td>Carvedilol (dose, 25 mg)</td>
<td>NA</td>
<td>1 (12.5)</td>
<td>0 (0)</td>
<td>0.25†</td>
</tr>
</tbody>
</table>

Values are presented as median (interquartile range). H indicates healthy control; LQTS, long QT syndrome; N, non–torsade de pointes; NA, not applicable; T, Tdp; and Tdp, torsade de pointes.

*P values compare 3 groups.
†P values compare TdP with non-TdP patients.
‡P values adjusted by the Holm method.
§P values determined by the Steel–Dwass test.

Table 3.  Association of ECG Characteristics With Torsade de Pointes

<table>
<thead>
<tr>
<th>Group</th>
<th>H (n=10)</th>
<th>T (n=8)</th>
<th>N (n=24)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average heart rate of 24-h, beats per minute</td>
<td>78 (69–86)</td>
<td>65.5 (58.5–73.5)</td>
<td>70 (65.5–76.5)</td>
<td>0.05*</td>
</tr>
<tr>
<td>Notched T wave, n (%)</td>
<td>2 (20)</td>
<td>7 (87.5)</td>
<td>13 (54.2)</td>
<td>0.02*</td>
</tr>
<tr>
<td>Peak TWA without TWPA, µV</td>
<td>30 (26–37)</td>
<td>55 (46–79)</td>
<td>53.5 (36–73.5)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>TWPA episodes, n (%)</td>
<td>0 (0)</td>
<td>2 (25)</td>
<td>2 (8.3)</td>
<td>0.19*</td>
</tr>
<tr>
<td>TWA ≥42 µV, n (%)</td>
<td>0 (0)</td>
<td>8 (100)</td>
<td>14 (58.3)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>No. of leads with TWA ≥42 µV</td>
<td>NA</td>
<td>1.5 (1–2)</td>
<td>1 (0–2)</td>
<td>0.19†</td>
</tr>
</tbody>
</table>

Values are presented as median (interquartile range). H indicates healthy control; N, non–torsade de pointes; NA, not applicable; T, Tdp; and Tdp, torsade de pointes.

*P values compare 3 groups.
†P values compare TdP with non-TdP patients.
‡P values adjusted by the Holm method.
§P values determined by the Steel–Dwass test.

V₃ in 30 (93.8%) LQTS patients (Figure 4A). Similarly, in the 22 LQTS patients with TWA ≥42 µV, the most frequent highest lead was V₂ in 11 (50%) LQTS patients. Highest lead was distributed in the precordial leads V₂ through V₄ and V₆ in 20 (90.9%) LQTS patients with TWA ≥42 µV (Figure 4B).

Sensitivity for TWA ≥42 µV Detection in Each Lead in LQTS Patients

In the 22 LQTS patients with TWA ≥42 µV, the median number of ECG leads with TWA of this level was only 2 (interquartile range, 1–3; minimum–maximum, 1–7). There was no significant difference in the number of ECG leads with TWA ≥42 µV comparing the TdP and the non-TdP groups (Table 3). The sensitivity for TWA ≥42 µV detection using a single ECG lead was the highest (63.6%) in lead V₂ (Figure 5). By contrast, combined leads V₂ through V₅ detected 100% of the TWA ≥42 µV episodes.

Discussion

In the present study, we demonstrated that TWA ≥42 µV was found in 68.8% of all LQTS patients enrolled and in 100% of LQTS patients with a history of TdP, whereas none of the healthy subjects exhibited TWA ≥42 µV. Microvolt TWA ≥42 µV is narrowly distributed in the precordial leads (median, 2 ECG leads) in LQTS patients. Indeed, the sensitivity for TWA detection using a single ECG lead was 63.6% at maximum in lead V₂, whereas the combined leads V₂ through V₅ detected 100% of the ≥42 µV TWA episodes.
Macroscopic TW A was reported to be a risk marker for cardiac events. In addition, several case reports demonstrated a direct link between macroscopic TW A and TdP, as reported in the study by Kaufman et al.21 In the present study, the duration of TW A episodes lasting <1 min were excluded from review.

Occurrence of visible, macroscopic TW A in patients with congenital LQTS has been reported to be 2.5% in standard 12-lead ECGs and 45% (5 of 11 patients) in ambulatory ECGs. Macroscopic TW A was reported to be a risk marker for cardiac events. In addition, several case reports demonstrated direct transition from macroscopic TW A to TdP, suggesting a direct link between macroscopic TW A and TdP, as reported in patients with both congenital LQTS and acquired LQTS.

The only clinical studies on the relationship between microvolt-level TW A and arrhythmia risk in LQTS patients used frequency-domain spectral analysis and drew negative conclusions about its significance. Specifically, Schmitt et al reported that none of the 10 LQTS patients with cardiac arrest or TdP exhibited a positive microvolt TW A test during monitoring of Frank orthogonal leads: X, Y, and Z during exercise, and concluded that microvolt TW A testing does not carry diagnostic value in LQTS patients. Similarly, Nemec et al reported that dobutamine-provoked microvolt TW A in leads aVF, V4, and V6 was negative in all of the 3 LQTS patients with a history of cardiac arrest and concluded that microvolt TW A does not identify high-risk subjects. Judging from our results, the regionally specific nature of TW A in LQTS patients and its narrow distribution may have led to an underestimation of TW A.

In the study by Kaufman et al.21 Later, Kaufman et al demonstrated that unsustained TW A lasting <1 min carries predictive value in patients with left ventricular dysfunction.

Furthermore, in these 3 studies, TWA testing was performed during a cardiac stress test: exercise or catecholamine-provocation. It has been reported that only 13% of cardiac events occurred during exercise in patients with LQTS 2 and 3. Moreover, only 427 of 1325 (32.2%) LQTS patients experienced their first cardiac events during acute arousal caused by exercise, swimming, emotion, or noise. In the present study, all the episodes of peak TW A in LQTS3 patients were recorded during nighttime. These facts suggest that TW A in some of the patients with LQTS3, as in the Brugada syndrome, may be rate suppressed.

These facts underscore the benefit of multilead precordial continuous ECG recordings during daily activities for TW A monitoring in LQTS patients. This approach is particularly appropriate for infants or young children, who are an important group for LQTS screening but who cannot undergo an exercise stress test. Indeed, in the study by Kaufman et al.21 more than half of the patients studied could not undergo microvolt TW A testing during exercise stress.

In the present study, we used the time-domain MMA method for continuous microvolt TW A monitoring during daily activities. The templates of superimposed complexes provided by the MMA technology allow the clinician to confirm the transient surges in TW A of 2- or 3-lead ambulatory ECG recordings in risk stratification.

Regional Specificity of TW A in LQTS Patients

Information about regional distribution of TW A in LQTS patients is sparse. In the present study, we demonstrated that the distribution of TW A is narrowly localized in a median of 2 (interquartile range, 1–3; minimum–maximum, 1–7) ECG leads and is frequently recorded in the precordial leads. Moreover, in our patient with LQTS3, TW A exhibited striking regionally independent dynamics (Figure 3).

The usefulness of microvolt TW A testing using simplified 2- or 3-lead ambulatory ECG recordings in risk stratification as a risk marker for cardiac events.
Figure 2. A, Twelve-lead electrocardiogram from a representative case (12-year-old boy) with long QT syndrome (LQTS) type 1, a history of torsade de pointes, and microvolt T-wave alternans (TWA). Left, Templates of superimposed waveforms in each lead at the time of peak TWA. Peak TWA of 56 µV was visible in lead V2 (indicated by red and blue arrows). TWA ≥42 µV could be detected only in lead V2. B, Representative 12-lead electrocardiogram exhibiting TWA in a 58-year-old women with LQTS but in whom the subtype was not identified. Left, Templates of superimposed waveforms in each lead at the time of peak TWA (54 µV) in lead V6. Red and blue arrows indicate TWA ≥42 µV detected only in leads V4 and V6.
for arrhythmic events in patients with ischemic/nonischemic cardiomyopathy has been established in several clinical studies. It is possible that patients with cardiomyopathy have widespread myocardial damage, and thus the simplified 2- or 3-lead ECG recorder is sufficient to detect TWA, which may be distributed extensively. By contrast, the regionally specific nature of TWA has been reported in the setting of acute myocardial ischemia. In this context, TWA appears in the ischemic zone, probably because myocardial damage is localized in the ischemic area, whereas the rest of the myocardium is normal. Thus, TWA may be more narrowly distributed in patients with acute myocardial ischemia than in those with cardiomyopathy.

A potential explanation for the regionally independent dynamics or narrow distribution of TWA is that the preceding diastolic interval, that is, the TQ interval, plays an important role in the initiation, maintenance, and termination of TWA. Gettes et al demonstrated that premature impulse with a diastolic interval >150 ms did not shorten the action potential duration (APD), whereas a significant abbreviation occurred when the diastolic interval lasted <150 ms in the isolated ventricular fiber of pig heart. We hypothesized that the APD of some myocardial layers in the anterior chest area may be longer than in other regions in LQTS patients. The postulated mechanism of the regional specificity of TWA in LQTS patients is illustrated in Figure 6. When an abrupt increase in heart rate occurs (beat ≈3) in site A with the shortest baseline APD, beat 3 with a sufficiently long preceding diastolic interval does not shorten the APD. On the contrary, in site C with

Figure 3. Twelve-lead electrocardiogram of a patient with the long QT syndrome showing an episode of macroscopic T-wave alternans (TWA) with regionally independent dynamics. Note that the dynamics of TWA in terms of onset, peak, and termination time varied regionally.

Figure 4. A, Distribution of highest T-wave alternans (TWA) levels in each lead in the group of 32 patients with long QT syndrome (LQTS). The most frequent highest lead was V2 in 14 (43.8%) patients. Peak TWA appeared frequently in the precordial leads in 30 (93.8%) patients. B, Distribution of highest lead in the 22 patients with microvolt TWA ≥42 µV. The most frequent highest lead was V2 in 11 (50%) patients. Highest lead was distributed in the precordial leads V2 through V6 in 20 (90.9%) patients.
the longest baseline APD, beat 3 with a very short preceding diastolic interval behaves as a premature beat and results in a shortening of the APD. This shortening, in turn, results in a prolongation of the following diastolic interval. Thus, beat 4 behaves like a nonpremature impulse and its APD returns to the baseline. This again shortens the following diastolic interval, and the process repeats until heart rate is reduced. Thereafter, APD alternans, that is, TWA, occurs only in the regions with disproportionally long APD relative to heart rate.

Medications and Microvolt TWA
β-adrenergic blocking agents were used significantly more frequently in the TdP group than in the non-TdP group. This difference may have contributed to the absence of significant differences in peak TWA values in the 2 groups. TWA amplitude is reduced by antiarrhythmic agents such as metoprolol and d,l-sotalol in patients with a history of documented or suspected ventricular tachyarrhythmias. Case reports provide evidence that β-blockade also reduces TWA in parallel with arrhythmias in LQTS patients. It will be worthwhile to evaluate in a prospective study whether these observations characterize LQTS patients as a whole.

Limitations
First, our sample size was too limited to allow multivariate analysis to determine an independent relationship between TWA and TdP history although a significant association was demonstrated. Second, the Holter Analysis Workstation Software, MARS version 8, may overlook millivolt-level TWA, which is macroscopic, including TWPA. However, it is highly possible that LQTS patients with prominent millivolt-level TWA have more frequent episodes of microvolt-level TWA, as did our patient who exhibited peak microvolt-level TWA of 611 µV, which was automatically calculated by MARS. In this patient, all episodes of prominent TWA or TWPA were preceded by microvolt-level TWA when they were initiated by gradual R–R interval shortening. Third, we derived and used a cut point of 42 µV for an association with TdP history; this level varies from the 47-µV cut point recommended for assessing arrhythmia risk in patients with cardiovascular disease and may relate to the particular genetic basis for TdP in this highly arrhythmogenic syndrome. We noted that in all 3 LQTS patients who experienced TdP after enrollment, TWA met the 42-µV cut point. Fourth, TWA testing was not performed on multiple occasions to assess reproducibility of the findings; however, multiple episodes of TWA ≥42 µV were observed in the same region of the heart at different times of day in >70% of the LQTS patients with TWA ≥42 µV. Fifth, body position might have had a non-negligible effect on the lead distribution of TWA in freely moving subjects. Finally, clinical considerations dictated initiation of β-blockade or changes in medications after TWA testing in our LQTS patients. Thus, it was not possible to determine whether in the absence of therapy, TWA would have predicted arrhythmic events in the present study.

Conclusions
Automated monitoring of microvolt TWA identifies a greater prevalence of microvolt TWA episodes and a stronger association with TdP history in patients with LQTS than has been previously reported. Microvolt TWA is narrowly distributed and more common in the precordial leads than in other leads in patients with LQTS. Multilead ambulatory ECGs including precordial leads V3 through V5 should be used to avoid underestimating TWA, which may be a risk marker for TdP. The high prevalence of TWA in the precordial leads may provide insights into mechanisms.

Disclosures
Dr Verrier receives royalty income from Georgetown University and Beth Israel Deaconess Medical Center for intellectual property on the Modified Moving Average method of T-wave alternans analysis, which has been licensed by GE Healthcare and was used in this study. The other authors report no conflicts.
References


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