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

T-wave alternans (TWA), a beat-to-beat fluctuation in T-wave morphology and ST segment, is mechanistically linked to vulnerability to life-threatening ventricular tachyarrhythmias.1,2 Macroscopic TWA has frequently been reported, sometimes accompanied by torsade de pointes (TdP), in patients with congenital3–6 and acquired7–10 long QT syndrome (LQTS). Hence, macroscopic TWA is not only one of the diagnostic criteria for LQTS11 but is also a risk marker for cardiac events.4

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Presently, microvolt-level TWA can be quantified using 24-hour continuous ECG.1,12 Ambulatory ECG recorders with 2 or 3 bipolar leads have been commonly used to monitor microvolt TWA.1 The utility of the simplified 2- or 3-lead ECG recorder to monitor TWA, however, may be limited by the regionally specific nature of the phenomenon, as in patients with acute myocardial ischemia.13–16 Indeed, we previously reported that an acquired LQTS patient exhibited regionally specific macroscopic TWA preceding the onset of TdP.10 In this patient, the precordial leads were superior to the standard telemetry lead II in terms of macroscopic TWA detection. Therefore, we hypothesized that assessment by 24-hour multilead continuous ECG would provide more complete and accurate detection of microvolt TWA in LQTS patients than would ECG recorders with fewer leads.

The goals of this study were (1) to determine the prevalence of microvolt TWA in both healthy subjects and LQTS patients using 24-hour continuous 12-lead ECGs; (2) to assess the association of microvolt TWA with TdP history; and (3) to describe the distribution of peak TWA among ECG leads.

Methods

Study Participants

We studied 10 healthy volunteers and 32 consecutive patients with LQTS. A cardiac channel gene screen for LQTS-causing mutations in KCNQ1 (LQT1), KCNH2 (LQT2), and SCN5A (LQT3) was

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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.

WHAT THE STUDY ADDS

- Automated monitoring of microvolt TWA with the Modified Moving Average method in 24-hour 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.

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 with history of torsade de pointes in LQTS patients 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 V₃ (36.5 [17.0–58.0] μV) and the second
Table 1. Patient Characteristics

<table>
<thead>
<tr>
<th>Group</th>
<th>Patients (n)</th>
<th>LQT1</th>
<th>LQT2</th>
<th>LQT3</th>
<th>Unidentified LQT Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>32</td>
<td>18</td>
<td>4</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>Families (n)</td>
<td>27</td>
<td>15</td>
<td>4</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>Age, y</td>
<td>13 (11–17.5)</td>
<td>13 (11–14)</td>
<td>11.5 (5.5–12.5)</td>
<td>21 (7.5–35.5)</td>
<td>61 (47–76)</td>
</tr>
<tr>
<td>Men, n (%)</td>
<td>13 (40.6)</td>
<td>8 (44.4)</td>
<td>1 (25)</td>
<td>2 (50)</td>
<td>2 (33.3)</td>
</tr>
<tr>
<td>Women, n (%)</td>
<td>19 (59.4)</td>
<td>10 (55.6)</td>
<td>3 (75)</td>
<td>2 (50)</td>
<td>4 (66.7)</td>
</tr>
<tr>
<td>QTc interval, ms</td>
<td>499 (472–529.5)</td>
<td>487 (466–507)</td>
<td>523 (509–535)</td>
<td>512 (440.5–603.5)</td>
<td>500 (476–542)</td>
</tr>
<tr>
<td>Symptomatic, n (%)</td>
<td>11 (34.4)</td>
<td>2 (11.1)</td>
<td>1 (25)</td>
<td>2 (50)</td>
<td>4 (66.7)</td>
</tr>
<tr>
<td>TdP (n)</td>
<td>8 (25)</td>
<td>2 (11.1)</td>
<td>1 (25)</td>
<td>1 (25)</td>
<td>4 (66.7)</td>
</tr>
<tr>
<td>Syncope (n)</td>
<td>11 (34.4)</td>
<td>3 (16.7)</td>
<td>1 (25)</td>
<td>2 (50)</td>
<td>5 (83.3)</td>
</tr>
<tr>
<td>Family history, n (%)</td>
<td>15 (46.9)</td>
<td>8 (44.4)</td>
<td>1 (25)</td>
<td>4 (100)</td>
<td>1 (16.7)</td>
</tr>
<tr>
<td>Sudden death (n)</td>
<td>5 (15.6)</td>
<td>4 (22.2)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1 (16.7)</td>
</tr>
<tr>
<td>LQTS (n)</td>
<td>13 (40.6)</td>
<td>8 (44.4)</td>
<td>1 (25)</td>
<td>4 (100)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>ICD, n (%)</td>
<td>4 (12.5)</td>
<td>1 (5.6)</td>
<td>0 (0)</td>
<td>1 (25)</td>
<td>2 (33.3)</td>
</tr>
<tr>
<td>Medication, n (%)</td>
<td>22 (68.8)</td>
<td>11 (61.1)</td>
<td>4 (100)</td>
<td>3 (75)</td>
<td>3 (50)</td>
</tr>
<tr>
<td>β-Blocker</td>
<td>17 (53.1)</td>
<td>11 (61.1)</td>
<td>2 (50)</td>
<td>1 (25)</td>
<td>3 (50)</td>
</tr>
<tr>
<td>Propranolol (dose range, 20–60 mg)</td>
<td>7 (21.9)</td>
<td>3 (16.7)</td>
<td>2 (50)</td>
<td>1 (25)</td>
<td>1 (16.7)</td>
</tr>
<tr>
<td>Atenolol (dose range, 25–50 mg)</td>
<td>5 (15.6)</td>
<td>5 (27.8)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Bisoprolol (dose range, 1.25–5 mg)</td>
<td>4 (12.5)</td>
<td>2 (11.1)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>2 (33.3)</td>
</tr>
<tr>
<td>Carvedilol (dose, 25 mg)</td>
<td>1 (3.1)</td>
<td>1 (5.6)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Mexiletine (dose range, 30–300 mg)</td>
<td>5 (15.6)</td>
<td>0 (0)</td>
<td>3 (75)</td>
<td>2 (50)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

Values are presented as median (interquartile range). ICD indicates implantable cardioverter defibrillator; LQTS, long QT syndrome; and TdP, torsade de pointes.

Assessment of TW A With TdP History in LQTS Patients

Eight (25%) of the 32 LQTS patients enrolled had a history of TdP. The association of TW A 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 TW A value of 42 μV with a sensitivity of 100% (95% confidence interval, 51.8–100) and a specificity of 41.7% (95% confidence interval, 22.1–63.4) was derived using Youden’s index. The group results for characteristics associated with TdP history including TW A ≥42 μV are shown in Table 3. There was no significant difference in peak TW A value between the TdP group and the non-TdP group. However, the TdP group exhibited a significantly higher incidence of TW A ≥42 μV than the non-TdP group (100% versus 58.3%; P=0.04). The median duration of peak TW A ≥42 μV was 15 s (interquartile range, 15–30 s; minimum–maximum, 15–45 s). One or more episodes of TW A ≥42 μV 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 TW A ≥42 μV.

Figure 2 shows representative continuous 12-lead ECGs with visible TW A 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. TW A ≥42 μV was narrowly distributed in the precordial leads. Specifically, visible TW A of 56 μV in lead V2 (Figure 2A) and of 44 and 54 μV in leads V5 and V6, respectively, were recorded. However, all of the episodes of TW A were overlooked because of technical problems of MARS Holter Analysis Workstation Software version 8. By visual estimation, the amplitude of TW A was ≥5000 μV (Figure 3), but the peak TW A value automatically generated by MARS version 8 Software was 611 μV, a significant underestimation. In some TW A episodes, the dynamics of TW A, 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 TW A (Figure 3).

At this time, 3 LQTS patients have experienced TdP since enrollment (at 28, 44, and 463 days after TW A testing, respectively), and all 3 exhibited TW A ≥42 μV at the time of joining the study.

Distribution of the Lead With the Highest TW A 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 TW A ≥42 μV (Figure 4B). In the group as a whole, the most frequent highest lead was V3 in 14 (43.8%) LQTS patients. Highest lead was distributed in the precordial leads V1 through V4 and
V6 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).

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>13 (54.2)</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>0.1†</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.

*S* 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.

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 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).

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* NA</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* H&lt;T (P=0.046‡)</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* H&lt;T (P&lt;0.001§); H&lt;N (P=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* NA</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* H&lt;T (P&lt;0.001§); H&lt;N (P=0.003‡); T&gt;N (P=0.04‡)</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† NA</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.

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 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 the highest (63.6%) in lead V2 (Figure 5). By contrast, combined leads V2 through V5 detected 100% of the TWA ≥42 µV episodes.
Microvolt TWA in Healthy Subjects

No studies exclusively in normal individuals have been performed using either the frequency-domain spectral TWA method or the time-domain MMA-based TWA method. In this study, we demonstrated that peak TWA values were significantly lower in healthy subjects than in LQTS patients, and that none of the healthy subjects exhibited macroscopic TWA.

Microvolt TWA in LQTS Patients

Occurrence of visible, macroscopic TWA 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 TWA was reported to be a risk marker for cardiac events. In addition, several case reports demonstrated direct transition from macroscopic TWA to TdP, suggesting a direct link between macroscopic TWA and TdP, as reported in patients with both congenital LQTS and acquired LQTS.

The only clinical studies on the relationship between microvolt-level TWA 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 TWA test during exercise stress test of Frank orthogonal leads: X, Y, and Z during exercise, and concluded that microvolt TWA testing does not carry diagnostic value in LQTS patients. Similarly, Nemec et al reported that dobutamine-provoked microvolt TWA in leads aVF, V3, and V4 was negative in all of the 3 LQTS patients with a history of cardiac arrest and concluded that microvolt TWA does not identify high-risk subjects. Judging from our results, the regionally specific nature of TWA in LQTS patients and its narrow distribution may have led to an underestimation of TWA. Kaufman et al reported that only 3 (17.6%) of the 17 LQTS patients with a HERG (Human Ether-a-go-go Related Gene) mutation had positive microvolt TWA test during exercise despite the use of precordial leads V5 through V6. One potential explanation is that TWA episodes lasting <1 min were excluded from review in the study by Kaufman et al. Later, Kaufman et al demonstrated that unsustained TWA 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 TWA in LQT3 patients were recorded during nighttime. These facts suggest that TWA in some of the patients with LQT3, as in the Brugada syndrome, may be rate suppressed.

These facts underscore the benefit of multilead precordial continuous ECG recordings during daily activities for TWA monitoring in LQTS patients. The 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, more than half of the patients studied could not undergo microvolt TWA testing during exercise stress.

In the present study, we used the time-domain MMA method for continuous microvolt TWA monitoring during daily activities. The templates of superimposed complexes provided by the MMA technology allow the clinician to confirm the transient surges in TWA of ≥20 μV that may disappear within 1 minute in LQTS patients and thus may be missed during routine review.

Regional Specificity of TWA in LQTS Patients

Information about regional distribution of TWA in LQTS patients is sparse. In the present study, we demonstrated that the distribution of TWA 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 LQT3, TWA exhibited striking regionally independent dynamics (Figure 3).

The usefulness of microvolt TWA testing using simplified 2- or 3-lead ambulatory ECG recordings in risk stratification...
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 woman 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 V5 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...
Relative to heart rate, TWA, occurs only in the regions with disproportionally long APD until heart rate is reduced. Thereafter, the APD alternans, that is, shortens the following diastolic interval and the process repeats until heart rate is reduced. This again shortens the following diastolic interval, and the process repeats until heart rate is reduced. 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. Therefore, 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 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. Therefore, APD alternans, that is, TWA, occurs only in the regions with disproportionally long APD relative to heart rate.

The other authors report no conflicts.
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Prevalence of Microvolt T-Wave Alternans in Patients With Long QT Syndrome and Its Association With Torsade de Pointes

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