Identification of Concealed and Manifest Long QT Syndrome Using a Novel T Wave Analysis Program

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Background—Congenital long QT syndrome (LQTS) is characterized by QT prolongation. However, the QT interval itself is insufficient for diagnosis, unless the corrected QT interval is repeatedly ≥500 ms without an acquired explanation. Further, the majority of LQTS patients have a corrected QT interval below this threshold, and a significant minority has normal resting corrected QT interval values. Here, we aimed to develop and validate a novel, quantitative T wave morphological analysis program to differentiate LQTS patients from healthy controls.

Methods and Results—We analyzed a genotyped cohort of 420 patients (22±16 years, 43% male) with either LQT1 (61%) or LQT2 (39%). ECG analysis was conducted using a novel, proprietary T wave analysis program that quantitates subtle changes in T wave morphology. The top 3 discriminating features in each ECG lead were determined and the lead with the best discrimination selected. Classification was performed using a linear discriminant classifier and validated on an untouched cohort. The top 3 features were Tpeak−Tend interval, T wave left slope, and T wave center of gravity x axis (last 25% of the T wave). Lead V6 had the best discrimination. It could distinguish 86.8% of LQTS patients from healthy controls. Moreover, it distinguished 83.33% of patients with concealed LQTS from controls, despite having essentially identical resting corrected QT interval values.

Conclusions—T wave quantitative analysis on the 12-lead surface ECG provides an effective, novel tool to distinguish patients with either LQT1/LQT2 from healthy matched controls. It can provide guidance while mutation-specific genetic testing is in motion for family members.

Key Words: diagnosis ■ electrocardiography ■ long QT syndrome ■ sudden cardiac death ■ T wave analysis ■ ventricular repolarization

Congenital long QT syndrome (LQTS) affects ≈1 in 2000 people and is an important cause of sudden cardiac death in the young.¹ There are 17 known LQTS-susceptibility genes (LQT1-17), but the most common types LQT1, LQT2, and LQT3 account for ≈75% to 80% of all congenital LQTS and over 95% of genetically proven cases.² The current diagnostic approach is based on measurement of the heart rate–corrected QT interval (QTc) and clinical factors, such as the medical and family history and clinical presentation. However, unless the QTc is repeatedly ≥500 ms without alternative acquired factors present, the QTc from the resting 12-lead ECG is insufficient for diagnosis.³ Genetic testing plays an important role in the diagnosis, risk stratification, tailoring of genotype-directed therapies and for mutation-specific confirmatory testing of appropriate relatives once the index case’s disease-causing mutation has been identified.⁴⁺⁻⁻ However, despite its excellent diagnostic yield, some genetic test results are difficult to interpret,⁶ and access to genetic testing in general can be hampered by insurance reimbursement considerations. Accordingly, there is ongoing need for more refined diagnosis and risk stratification based on readily available, noninvasive means.

The 12-lead surface ECG is an inexpensive test that is performed widely and could be used as an efficient diagnostic
WHAT IS KNOWN

- Genotype-specific patterns of T wave morphology have been well described among patients with type 1, type 2, and type 3 LQTS (LQT1, LQT2, and LQT3). However, these features are often subtle and inconsistently observed.
- Further, the QT interval, itself, is often insufficient to rule in or to exclude a diagnosis, with 25% to 50% of patients with LQTS, especially the LQTS-positive relatives, having a normal or borderline-corrected QT interval.

WHAT THE STUDY ADDS

- Quantitative T wave analysis adds important diagnostic strength to the standard 12-lead ECG in the evaluation of patients with potential LQTS.
- In both manifest and concealed LQTS cases, subtle changes in T wave architecture can help distinguish patients with LQTS from normal controls.
- This approach could streamline the evaluation of patients with suspected LQTS and direct appropriate genetic testing to individuals at higher pretest probability for the syndrome.

Methods

Study Population
We analyzed a cohort of 420 patients with either genetically confirmed LQT1 or LQT2. We then created a control cohort of age- and sex-matched (1:1) individuals with no history of cardiac disease. The LQTS cases were divided into those with electrocardiographically manifest or concealed LQTS based on the resting QTc. Concealed LQTS patients were defined as those with QTc <460 ms for women, 450 ms for men, and <440 ms for either sex ≤12 years. Asymptomatic patients were defined as those patients never experiencing an LQTS-triggered faint, seizure, or cardiac arrest. Institutional review board approval was obtained for this study.

Data Collection
We analyzed the first ECG recorded at our institution (Mayo Clinic, Rochester, MN). The 12-lead surface ECG was analyzed using our novel, proprietary T wave analysis program as previously described. Briefly, the raw, 12-lead ECG tracings (10 s duration, fs=500 samples/s) collected from the General Electric MUSE ECG management system (GE Healthcare, Waukesha, WI) were uploaded into our software tool. Preprocessing procedures were applied to enable de-noising and baseline correction. This was followed by ECG feature extraction using our automated software program. ECG features (mentioned below) from the ECG were detected by a Bayesian statistical peak delineation algorithm. Multiple beats over a 10 s ECG strip are used for analysis. Detected T waves with inconsistent locations (outliers) compared with other cardiac cycles were excluded manually from the analysis. This approach was unaware of the underlying diagnosis when analyzing the 12-lead surface ECG. The features collected for analysis are illustrated in Figure 1. The QTc was calculated (Bazett’s formula; QTc=QT/√HR) using the clinical 12-lead ECG (Marquette 12SL ECG Analysis Program, General Electric Healthcare), which measures the QT interval from the earliest detection of depolarization in any lead to the latest detection of repolarization in any lead.

ECG Feature Selection/Statistical Analysis
Our analytic approach involved 2 phases: ECG T wave feature selection for algorithm development and then subsequent validation (Figure 2). ECG T wave feature selection was performed in patients with concealed LQTS. The concealed LQT group (145 cases) and 145 matched controls were randomly divided into 3 equal cohorts: 1) a training cohort for T wave feature selection used to develop our approach, 2) a testing cohort for internal 10×10 cross validation, and 3) a validation cohort for independent validation (n=84). The features were then evaluated in a second validation phase using all manifest LQTS patients and controls (n=550).

In the training cohort, we selected the top 3 T wave features in each ECG lead that significantly distinguished cases from controls. Using a Spearman’s rank correlation coefficient of <0.3 between features, we removed ECG features that were closely correlated. We then selected a single ECG lead with the best discriminative power and evaluated the best features for this lead. We chose a single lead approach for simplicity (to avoid inclusion of related parameters from different leads) and to, potentially, facilitate the use of hand-held/mobile embodiments with automated feature detection. In the testing cohort, these features were validated using linear discriminant analysis and 10-fold cross-validation to ensure appropriate ECG feature selection. Validation was then performed in the untouched concealed validation cohort (these patients were not used in the training or testing phases of feature selection). A second external validation on an untouched cohort was then performed using the remaining patients with electrocardiographically manifest LQTS. We report the validation accuracy on the untouched cohorts.
We also evaluated the performance of these 3 features in comparison to the QTc. We also calculated the diagnostic accuracy, sensitivity, specificity, negative predictive value, and positive predictive values for these features to accurately identify the presence of LQTS.

**Missing Data**

Leads were excluded from analysis if the T wave was of low amplitude (<0.1 mV), if we were unable to interpret the T wave from a poor tracing from interference, or if the T wave was biphasic. To preserve what we would expect in an everyday ECG recording, if the lead was not interpretable, this lead was excluded from the analysis.

**Results**

In total, we analyzed 420 patients with LQTS (180 males) and 420 age- and sex-matched controls. Because of their smaller sample sizes, LQT3 patients and patients with LQT4–17 were not included in this discovery exercise. Of the 420 LQTS patients, 257 patients had LQT1 and 163 had LQT2. Baseline data are presented in Table 1.

Within the concealed cohort (145 cases, 53.1% males; 93 LQT1, 52 LQT2; 145 matched controls), the T wave selection process identified generally consistent features observed across all 12 leads, as shown in Table 2, despite having essentially identical resting QTc values. Lead V6 demonstrated the best discriminative power and had the least number of missing values/uninterpretable T wave (14 in total, 8 from training/testing cohort and 6 from validation). The top 3 features in lead V6 were T wave left slope (2863 mV/s in cases versus 3344 mV/s in controls; *P*<0.008), T wave center of gravity (COG) x axis (last 25% of the wave; 349 ms in cases versus 295 ms in controls; *P*<0.0001), and Tpeak–Tend interval (81 ms in cases versus 77 ms in controls; *P*<0.004; Table 3). When these features were examined in the entire LQTS cohort, similar values were observed: T wave left slope (2450 versus 3357 mV/s; *P*<0.0001), T wave COG x axis (last 25% of the wave; 367 versus 292 ms; *P*<0.0001), and Tpeak–Tend interval (86 versus 77 ms; *P*<0.0001) for cases versus controls, respectively (Table 3). Figure 3 illustrates these top 3

![Figure 2: Study design. The total cohort was divided into concealed (borderline or normal QTc) and manifest (prolonged QTc) long QT syndrome (LQTS) cohorts. Feature selection was performed on the concealed LQTS cohort. The concealed LQTS cohort was divided into 3 groups for (1) training (feature selection), (2) testing (10×10 cross validation), and (3) independent validation in untouched cases and controls. The manifest LQTS cohort was then used for further validation.](http://circep.ahajournals.org/)}
features on superimposed averaged tracings in lead V6 from cases and controls. There were only 10 uninterpretable ECGs in the manifest cohort (3.6%).

When applied to the validation cohort, these top features could distinguish 86.8% of LQTS patients from normal controls (Figures 4 and 5), with 83% sensitivity, 91% specificity, 90% positive predictive values, and 84% negative predictive value (Table 4 and Figure 6; Data Supplement). Even among patients with concealed LQTS, these features could distinguish 83.33% of cases from controls (Figure 4), with a sensitivity of 76%, specificity of 91%, positive predictive value of 89%, and negative predictive value of 79% (Table 4). In comparison, the QTc itself could classify LQTS status in 65.5% of the total cases and in none of the concealed cases, by definition.

**Discussion**

Using custom software, we have identified and validated T wave features that distinguish LQTS patients from normal controls with a high degree of accuracy using just a standard 12-lead ECG. Importantly, these features have discriminative power in both patients with manifest QT prolongation and in patients with completely normal resting QTc values, thereby permitting the diagnosis of LQTS in patients in whom it would be missed using the QTc alone. Given that 25% to 50% of patients with LQTS have a normal or borderline QTc, this algorithmic analysis adds important diagnostic strength to the standard ECG. Additionally, for patients with a prolonged QTc, our algorithmic analysis has superior diagnostic accuracy than the QTc itself. Our study has provided a new tool to assess the likelihood of LQTS based on the readily available surface ECG, and we anticipate that this approach may be helpful in inexpensively screening family members of LQTS probands or other patient groups with a modest pretest probability of LQTS.

Genotype-specific patterns of T wave morphology have been well described in LQTS cohorts. However, these features are subtle, inconsistently observed, and, thus, have limited applicability to routine clinical practice. Classically, LQT1 is characterized by a broad-based T waves, whereas in LQT2, a bifid or notched low-amplitude T wave can be observed. In one study, expert LQTS cardiologists could only identify LQTS patients with ≈61% and 62% sensitivity (LQT1 and 2, respectively) using these features. Takenaka et al reported the broad-based T wave in only 43% and bifid notched wave in 33% of their cohort. Similarly, Malfatto et al reported these patterns in only 15% to 40% of patients. Chorin et al demonstrated that T wave morphological changes upon standing added diagnostic value for LQT2 identification but was less helpful for LQT1 and LQT3.

**Table 2. The Top 3 Selected Features and Classification Success in Each of the ECG’s 12 Leads**

<table>
<thead>
<tr>
<th>Lead</th>
<th>Top Selected Features</th>
<th>Successful Classification, %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>LQT Cohort</td>
</tr>
<tr>
<td>I</td>
<td>Last 25% of T wave COG x axis</td>
<td>Left slope T wave</td>
</tr>
<tr>
<td>II</td>
<td>Last 25% of T wave COG x axis</td>
<td>Left slope T wave</td>
</tr>
<tr>
<td>III</td>
<td>Last 25% of T wave COG x axis</td>
<td>COG y axis</td>
</tr>
<tr>
<td>aVR</td>
<td>Last 25% of T wave COG x axis</td>
<td>Left slope T wave</td>
</tr>
<tr>
<td>aVL</td>
<td>Last 25% of T wave COG x axis</td>
<td>T wave area</td>
</tr>
<tr>
<td>aVF</td>
<td>Last 25% of T wave COG x axis</td>
<td>Left slope T wave</td>
</tr>
<tr>
<td>V1</td>
<td>T wave COG x axis</td>
<td>Last 25% of T wave COG y axis</td>
</tr>
<tr>
<td>V2</td>
<td>T wave COG x axis</td>
<td>Right slope T wave</td>
</tr>
<tr>
<td>V3</td>
<td>Last 25% of T wave COG x axis</td>
<td>Last 25% of T wave COG y axis</td>
</tr>
<tr>
<td>V4</td>
<td>Last 25% of T wave COG x axis</td>
<td>Last 25% of T wave COG y axis</td>
</tr>
<tr>
<td>V5</td>
<td>Last 25% of T wave COG x axis</td>
<td>Last 25% of T wave COG y axis</td>
</tr>
<tr>
<td>V6</td>
<td>Last 25% of T wave COG x axis</td>
<td>Left slope T wave</td>
</tr>
</tbody>
</table>

Lead V6 is given in bold to highlight the lead we selected for analysis. COG indicates center of gravity; and LQT, long QT.

**Table 3. Mean of Selected T Wave Features Observed Between Cases (LQTS) and Controls**

<table>
<thead>
<tr>
<th>T Wave Feature</th>
<th>Cases (LQTS)</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whole cohort, mean±SD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>COG x axis (last 25% of the wave), ms</td>
<td>367±50</td>
<td>292±30</td>
</tr>
<tr>
<td>Tpeak–Tend interval, ms</td>
<td>86±24</td>
<td>78±9</td>
</tr>
<tr>
<td>T wave left slope, mV/s</td>
<td>2450±1545</td>
<td>3357±1435</td>
</tr>
<tr>
<td>Overt cohort, mean±SD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>COG x axis (last 25% of the wave), ms</td>
<td>382±55</td>
<td>289±30</td>
</tr>
<tr>
<td>Tpeak–Tend interval, ms</td>
<td>89±29</td>
<td>77±8</td>
</tr>
<tr>
<td>T wave left slope, mV/s</td>
<td>2091±1339</td>
<td>3360±1472</td>
</tr>
<tr>
<td>Concealed cohort, mean±SD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>COG x axis (last 25% of the wave), ms</td>
<td>348±48</td>
<td>292±30</td>
</tr>
<tr>
<td>Tpeak–Tend interval, ms</td>
<td>81±15</td>
<td>78±10</td>
</tr>
<tr>
<td>T wave left slope, mV/s</td>
<td>2863±1679</td>
<td>3344±1402</td>
</tr>
</tbody>
</table>

COG indicates center of gravity; and LQTS, long QT syndrome.
Not only are these genotype-specific features difficult to identify, but also the QTc is often nondiagnostic, which adds to the challenge of LQTS diagnosis. To amplify phenotypic characteristics (T wave morphological changes and QTc prolongation), postural, exercise, epinephrine, and adenosine provocation testing have been proposed. However, these approaches have not been validated fully and in some cases require additional testing with drug administration. Our approach provides an opportunity for improved diagnostic yield in the unprovoked state, without any additional testing.

Using this newly developed T wave analytics tool, we were able to demonstrate that quantitative T wave changes have good sensitivity and specificity (83% and 91%, respectively) for LQTS. Similar sensitivities and specificities have been reported in other studies. A study by Viitasalo et al demonstrated that Holter data could identify LQTS cases and controls among a small cohort using QT data alone. Vaglio et al also

**Figure 3.** Superimposed average ECG tracings from cases and controls in lead V6, highlighting the top 3 features.

**Figure 4.** Flow diagram showing the outcomes of classification from our T wave analysis. LQTS indicates long QT syndrome.
used Holter data for discrimination in a small cohort.\textsuperscript{32} Kanters et al reported that the complex Hill equation applied to lead V2 could identify LQT patients with reasonable sensitivity and specificity, although the values were not reported.\textsuperscript{33} Exercise-induced QTc changes or repolarization changes have a reported sensitivity in the range of 67\% to 84\% and specificity of 33\% to 67\%\textsuperscript{24} (diagnostic accuracy not reported). Postural changes to maximal QT interval could identify LQTS with 90\% sensitivity and 86\% specificity.\textsuperscript{25} Overall, the challenge in interpreting these small studies is the complexity and subjectivity of analyses, the need for expertise in ECG interpretation in LQTS, and the potential for observer bias.

In contrast, there are many strengths of our study over the previous published literature. Aside from limiting the complexity and observer bias by providing a quantitative method, we have used a substantially larger cohort and validated this approach on an independent, untouched cohort, making this a tool with significant clinical application and potential.

### Clinical Significance and Application

Our novel T wave analytics tool uses the readily available and inexpensive surface ECG to identify individuals with possible LQTS. This approach could streamline the evaluation of patients with suspected LQTS and direct appropriate genetic testing to individuals at particularly high pretest probability of the syndrome. Although LQTS is uncommon, a significant amount of patients will undergo evaluation for borderline or nondiagnostic QT prolongation because many individuals without symptoms undergo evaluation because of affected family members. This approach could facilitate targeted genetic screening and help improve the yield and cost-effectiveness of genetic testing.\textsuperscript{35,36} Early and accurate diagnosis of LQTS is important because early drug treatment can reduce the risk of sudden cardiac death compared with a watchful waiting strategy.\textsuperscript{36} Future work describing the potential role of the ECG features in patients with Holter monitor or on exercise ECGs should be explored to determine diagnostic yield.

### Novel Analysis

Other investigators have performed notable ECG analysis for different applications and cardiac diseases. These approaches are similar in their attempt to quantify T wave morphological changes. However, there are differences compared with our novel approach in the type of ECGs used (Holter versus 12-lead surface ECG), the processing of the ECG, the type of T wave features analyzed, and identification of the T wave (manual versus automated). For example, Couderc et al have performed noteworthy analysis using software called Comprehensive Analysis of repolarization Signal (COMPAS).\textsuperscript{32,37,38} In his approach (which is largely based on Holter analysis), ECGs have to be digitally converted, they only take advantage of a single or 2 leads, and T wave calculations of left and right slope differ. Kantars et al’s,\textsuperscript{33} also noteworthy analysis, uses the mathematically complex hill equation to involve manual selection of the T wave (unlike ours which is automated).

### Study Limitations

There are several important limitations of this study. Application of this approach as a screening tool has not been assessed. This would require validation in a population with a case

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**Table 4. Validation of T Wave Analysis**

<table>
<thead>
<tr>
<th></th>
<th>Accuracy</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Manifest LQTS</td>
<td>0.86</td>
<td>0.83</td>
<td>0.91</td>
<td>0.90</td>
<td>0.84</td>
</tr>
<tr>
<td>Concealed asymptomatic LQTS</td>
<td>0.83</td>
<td>0.76</td>
<td>0.91</td>
<td>0.89</td>
<td>0.79</td>
</tr>
</tbody>
</table>

LQTS indicates long QT syndrome; NPV, negative predictive values; and PPV, positive predictive values.

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**Figure 5.** Scatter plot showing discriminative power between long QT syndrome (LQTS) cases and matched controls using 2 T wave features.
universal screening for LQTS warrant further investigation. The potential implications of this tool for diagnostic testing would be high yield and could help direct further feature could be used to identify patients in whom genetic LQTS, despite having a normal resting QTc. These T wave patients with genetically proven LQTS from matched controls V6 provides a novel diagnostic tool capable of distinguishing classification of LQT1 and LQT2 and whether variables would be more pertinent in detecting LQT1 versus LQT2.

Conclusions
Detailed quantitative analysis of T wave morphology in lead V6 provides a novel diagnostic tool capable of distinguishing patients with genetically proven LQTS from matched controls and even permits identification of over 80% of patients with LQTS, despite having a normal resting QTc. These T wave feature could be used to identify patients in whom genetic testing would be high yield and could help direct further diagnostic testing. The potential implications of this tool for universal screening for LQTS warrant further investigation.

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Disclosures
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References

Figure 6. Receiver-operator characteristic (ROC) curves of the selected ECG features in the validation data set (area under the curve [AUC] =0.858).
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Supplemental Material

Equation for classification

Equation for classification as determined by linear discriminant equation, which separates LQTs from controls, is as follows:

\[ 12.4 - 37.8 T_{\text{wave right 25\% COG x axis}} - 4.9 T_{\text{peak-end interval}} + 0.00013 T_{\text{wave left slope}} = 0, \]

where “T wave right 25\% COG x axis”, “Tpeak – Tend interval”, and “Tpeak – Tend interval” are values of particular feature.

A value <0 is suggestive of LQTS.