T Wave “Humps” as a Potential Electrocardiographic Marker of the Long QT Syndrome

MICHAEL H. LEHMANN, MD, FACC, FUMIO SUZUKI, MD, BARBARA S. FROMM, MA, DEBRA FRANKOVICH, RN, PAUL ELKO, PhD,‡ RUSSELL T. STEINMAN, MD, FACC, JULIE FRESARD, RN, JOHN J. BAGA, MD, R. THOMAS TAGGART, PhD★

Detroit, Michigan and Milwaukee, Wisconsin

Objectives. This study attempted to determine the prevalence and electrocardiographic (ECG) lead distribution of T wave “humps” (T2, after an initial T wave peak, T1) among families with long QT syndrome and control subjects.

Background. T wave abnormalities have been suggested as another facet of familial long QT syndrome, in addition to prolongation of the rate-corrected QT interval (QTc), that might aid in the diagnosis of affected subjects.

Methods. The ECGs from 254 members of 13 families with long QT syndrome (each with two to four generations of affected members) and from 2,948 healthy control subjects (age ≥16 years, QTc interval 0.39 to 0.46 s) were collected and analyzed. Tracings from families with long QT syndrome were read without knowledge of QTc interval or family member status (210 blood relatives and 44 spouses).

Results. We found that T2 was present in 53%, 27% and 5% of blood relatives with a “prolonged” (≥0.47 s), “borderline” (0.42 to 0.46 s) and “normal” (<0.41 s) QTc interval, respectively (p < 0.0001), but in only 5% and 0% of spouses with a borderline and normal QTc interval, respectively (p = 0.06 vs. blood relatives). Among blood relatives with T2, the mean ±SD maximal TIT2 interval was 0.10 ± 0.03 s and correlated with the QTc interval (p < 0.01); a completely distinct U wave was seen in 23%. T2 was confined to leads V1 and V3 in 10%, whereas V2, V5, or a limb lead was involved in 90% of blood relatives with T2. Among blood relatives with a borderline QTc interval, 50% of those with versus 20% of those without major symptoms manifested T2 in at least one left precordial or limb lead (p = 0.05). A T2 amplitude >1 mm (grade III) was observed, respectively, in 19%, 6% and 0% of blood relatives with a prolonged, borderline and normal QTc interval with T2 in at least one left precordial or limb lead. Among the 2,948 control subjects, 0.6% exhibited T2 confined to leads V2 and V3, and 0.9% had T2 involving one or more left precordial lead (but none of the limb leads). Among 37 asymptomatic adult blood relatives with QTc intervals 0.42 to 0.46 s, T2 was found in left precordial or limb leads in 9 (24%; 5 with limb lead involvement) versus only 1.9% of control subjects with a borderline QTc interval (p < 0.0001).

Conclusions. These findings are consistent with the hypothesis that in families with long QT syndrome, T wave humps involving left precordial (or especially) limb leads, even among asymptomatic blood relatives with a borderline QTc interval, suggest the presence of the long QT syndrome trait.

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available, new diagnostic criteria are needed to help determine whether an asymptomatic family member might be a carrier of the long QT genotype.

It has been appreciated that configurational abnormalities of the T wave may be observed in subjects with long QT syndrome (1,5,14). During the course of our genetic linkage studies of long QT syndrome (13), we were particularly struck by the presence of "humps" near the apex or on the descending limb of upright T waves (1) in many members of families with long QT syndrome. We hypothesized that if these electrocardiographic (ECG) deflections represent a distinct phenotypic manifestation of the long QT genotype, then the prevalence of T wave humps in family members with long QT syndrome, as well as those who have borderline QT intervals, should be greater than that expected in the general population. The present study systematically tested this hypothesis and quantitatively defined the ECG lead distribution of these abnormalities in repolarization. Our findings suggest that T wave humps might provide another indication, in addition to the QT interval, of the presence of the long QT syndrome trait.

Methods

All patients participating in this investigation were enrolled as part of an ongoing molecular genetic study of the long QT syndrome at Wayne State University School of Medicine. Twelve-lead ECGs, recorded at 25 mm/s and 0.1 mV/mm, were obtained after informed consent was given. The study was approved by the Human Investigation Committee at our institution.

Description of families with long QT syndrome. A total of 13 families with congenital long QT syndrome form the basis of this report. We measured QT intervals (to the nearest 0.01 s) from onset of the QRS complex to end of the T wave in limb lead II. Lead I, or an alternative limb lead with an upright T wave, was used if the end of the T wave was not clear in lead II. In the presence of TU fusion, the TU junction was taken as the end of the T wave. The QTc interval was calculated from the Bazett formula (QT/√RR) (4) and averaged over three consecutive cycles during stable sinus rhythm or over the three shortest cycles (consecutive when feasible) during sinus arrhythmia, according to Garson (8). All QTc values were rounded to the nearest 0.01 s. Following the convention of Keating et al. (3), family members were considered affected if they 1) had a QTc interval ≥ 0.45 s with major symptoms (i.e., syncope, seizures or cardiac arrest); or 2) had a QTc interval ≥ 0.47 s without major symptoms. For the purpose of this study, the QTc interval was considered prolonged if ≥ 0.47 s, normal if ≤ 0.41 s and borderline if ≤ 0.42 s but ≥ 0.46 s (3).

Three families had four generations of affected members, seven had three affected generations, and the remainder had two affected generations. Electrocardiograms were obtained from 210 blood relatives (94 men, 116 women; mean [±SD] age 25 ± 19 years [range 7 months to 88 years], median 20 years [range 14 to 33 years/family]) and from 44 non-blood relatives (11 male, 33 female spouses; mean age 44 ± 15 years [range 23 to 80, median 39]). The 210 blood relatives, who included probands, constituted 74% of all living blood relatives identified in the family trees that were constructed.

In all, 67 (32%) of the 210 blood relatives were affected (range 18% to 67%/family), of whom 31 (46%) were symptomatic (with 26% having had syncope, 39% seizures and 35% cardiac arrest). Sixty-two (30%) of the blood relatives (range 0% to 67%/family) had a QTc interval ≥ 0.47 s (of which 26 [42%] were symptomatic), and 73 (35%) [range 0% to 55%/family] had a QTc interval ≤ 0.41 s (of which 3 [4%] were symptomatic). Of the 75 blood relatives (35%) (range 11% to 75%/family) with a QTc interval ≤ 0.42 to 0.46 s, 10 (13%) were symptomatic. Mean QTc values (range 0.32 to 0.64 s) were 0.39 ± 0.02, 0.44 ± 0.01 and 0.50 ± 0.04 s among blood relatives with a normal, borderline and prolonged QTc interval, respectively. At the time of the index ECG, no family member was taking medication known to prolong the QT interval. All tracings were recorded during normal sinus rhythm, except for one obtained during atrial pacing.
T wave "humps": definition and grading system. For the purpose of this study, T wave humps are defined as a bulge or protuberance just beyond the apex or on the descending limb of an upright T wave. Three configurations of T wave humps can be described (Fig. 1): grade I = a perceptible bulge or protuberance that has a takeoff deflection that remains at, or falls below, the horizontal; grade II = a distinct protuberance that has a takeoff deflection that rises above the horizontal but achieves a maximal amplitude (measured from takeoff point to peak deflection height) \( \leq 1 \text{ mm (0.1 mV)} \); grade III = a distinct protuberance that has a takeoff deflection that rises above the horizontal and achieves a maximal amplitude (as for grade II) \( > 1 \text{ mm (0.1 mV)} \).

We arbitrarily termed the bulge or protuberance T2 and the immediately preceding T wave maximum T1 (Fig. 2), a nomenclature similar to that previously described (15,16).

For T2 to be considered present in a particular ECG lead, it had to be observed in at least 2 recorded hearts of that lead. To further ensure reproducibility of the finding, we required that T2 be present in at least two ECG leads. For any subject exhibiting T2, the maximal configuration grade was defined as the highest T2 grade observed among the various leads in which T2 was manifest.

Differentiation of T2 from the U wave. Differentiation was accomplished in one or more of the following ways: 1) the T wave nadir between T1 and T2 had to be \( \geq 1 \text{ mm above the baseline for T2 to be considered present (and distinct from the U wave); 2) a completely distinct wave (arising from the isoelectric line) was observed after T2, indicating the presence of three components, T1, T2, and the U wave; or 3) in the absence of a completely distinct wave after T2, the maximal T1T2 interval (see later) was \( \leq 0.15 \text{ s} \) (i.e., below the minimal expected time between the T and U waves, as extrapolated to our study patients and control subjects from previous observations in normal subjects [17]). Deflections labeled T2 or U had to clearly precede the P wave. When T1, T2 and the U wave were present in a limb lead used for determining the QT interval, the latter variable was measured from QRS onset to the T2U junction point.

The T1T2 interval was measured from the vertical line corresponding to T1 to the vertical line corresponding to the maximal amplitude of T2. When discrete T2 maxima were not clear (as sometimes occurred with grade I humps), the rightmost excursion point of T2 was used for calculation of the T1T2 interval. The maximal T1T2 interval was defined as the maximal value of all T1T2 intervals measured on a given 12-lead ECG.

Determination of the prevalence of T2 among members of families with long QT syndrome. To avoid bias, the ECG for each member of families with long QT syndrome enrolled in the study was read without knowledge of whether the family member was a blood relative or an unrelated spouse and without knowledge of age, gender, QTc interval or symptoms. The ECG leads (other than aVR and V4, excluded because of inverted T waves) were scored for the presence and configuration grade of T2, according to the criteria described earlier. Each tracing was read and classified initially by one observer (F.S.) and then reviewed by a second observer (M.H.L.), with differences resolved by consensus or, if necessary, with the aid of a third observer (R.T.S.). Disagreement requiring reclassification of T2 presence or absence occurred in only 5.5% of ECGs (specifically, in 5% of tracings classified initially as negative and in 7.7% of those classified initially as positive); reclassification of maximal T2 grade was required in only 5.2% of ECGs deemed to exhibit T2.

Determination of prevalence of T2 among ECGs from control subjects. To estimate the prevalence of T2 in the general population, we also reviewed ECGs obtained by Marquette Electronics during sinus rhythm from 3,093 volunteers known to have a history and physical examination negative for evidence of heart disease, as has been described in detail elsewhere (18). Of note, none of the volunteers was taking cardioactive medication. There remained 2,996 ECGs after excluding those with QRS duration \( \geq 0.12 \text{ s} \), left ventricular hypertrophy with repolarization abnormality or myocardial infarction. Because only eight (0.3%) ECGs were obtained from subjects <16 years old (an age cutoff used by Moss and Robinson [1]), these were excluded. Of the 2,988 remaining tracings, 26 (0.9%) were excluded on the basis of QTc interval \( \geq 0.47 \text{ s} \), because this may have indicated silent carrier status for the long QT genotype. Also excluded were an additional 14 ECGs (0.5%) representing the small opposite extremum of QTc values (\( \leq 0.38 \text{ s} \)). Consequently, we restricted our analysis to the remaining 2,948 tracings exhibiting QTc intervals in the range 0.39 to 0.46 s (from 2,376 men, 572 women; median age 32 years, range 17 to 82). These digitized ECGs were printed at a paper speed of 25 mm/s and at an amplitude scale of 0.1 mV/mm. The QTc intervals (rounded to the nearest 0.01 s) were determined by the Marquette 12SL ECG analysis program, which calculates QT intervals that differ minimally from that observed electronically. Repolarization abnormality or myocardial infarction. Because only eight (0.3%) ECGs were obtained from subjects <16 years old (an age cutoff used by Moss and Robinson [1]), these were excluded. Of the 2,988 remaining tracings, 26 (0.9%) were excluded on the basis of QTc interval \( \geq 0.47 \text{ s} \), because this may have indicated silent carrier status for the long QT genotype. Also excluded were an additional 14 ECGs (0.5%) representing the small opposite extremum of QTc values (\( \leq 0.38 \text{ s} \)). Consequently, we restricted our analysis to the remaining 2,948 tracings exhibiting QTc intervals in the range 0.39 to 0.46 s (from 2,376 men, 572 women; median age 32 years, range 17 to 82). These digitized ECGs were printed at a paper speed of 25 mm/s and at an amplitude scale of 0.1 mV/mm. The QTc intervals (rounded to the nearest 0.01 s) were determined by the Marquette 12SL ECG analysis program, which calculates QT intervals that differ minimally from that observed electronically.

Statistical analysis. Summary data are expressed as mean value \( \pm SD \), except as otherwise indicated. The unpaired Student \( t \) test was used to compare continuous variables between groups (e.g., maximal T1T2 interval between control subjects and blood relatives). Chi-square analysis or Fisher exact test, as appropriate, was used to compare categoric variables between groups (e.g., gender differences between control subjects with T2 confined to lead V2 and V3 vs. those...
with T2 involving left precordial leads). Chi-square goodness of fit was used for categoric variables to test whether the distribution in blood relatives was similar to that in control subjects. Partitioned chi-square analysis was used for subgroup comparisons of categoric variables (e.g., proportion of borderline symptomatic vs. asymptomatic blood relatives manifesting T2). The Pearson correlation coefficient was used to assess the linear relation between continuous variables (e.g., maximal TIT2 interval and age). Multiple linear regression was used to evaluate the effects of QT interval, age and gender on maximal TIT2 interval. All hypothesis tests were two sided and considered statistically significant if p < 0.05.

Results

Prevalence and characterization of T2 in blood relatives with long QT syndrome. Prevalence of T2 according to QTc group. The proportion of blood relatives with long QT syndrome manifesting T2 in at least two ECG leads was greatest in members with a prolonged QTc interval, least in those with a normal QTc interval and intermediate in those with a borderline QTc interval (Table 1). This increasing prevalence of T2 with increasing QTc interval was highly significant (p < 0.001). For those with a borderline QTc interval, the prevalence of T2 was five times that observed among spouses (p = 0.06). Voltage criteria for left ventricular hypertrophy (with ST segment depression in one subject), the only coexistent ECG abnormality, was found in three blood relatives exhibiting T2 (all women, 64 to 83 years old; two with a prolonged and one with a normal QTc interval).

Differentiation of T2 from the U wave. A completely distinct U wave, with a T2U junction at the isoelectric line, was present in 13 (23%) blood relatives manifesting T2; and an additional 26 (45%) exhibited fused T2U waves. However, T2 was still distinguishable from the U wave in 54 (95%) blood relatives with T2 on the basis of a maximal TIT2 interval ≤0.15 s. In only three blood relatives, all with a prolonged QTc interval (range 0.48 to 0.57 s), was the maximal TIT2 interval ≥0.16 s (range 0.16 to 0.20 s). For blood relatives with a QTc interval ≥0.46 s, the maximal TIT2 interval was always ≤0.12 s.

The maximal TIT2 interval (mean 0.10 ± 0.03 s) was found to correlate modestly with the QTc interval (correlation coefficient 0.38, p < 0.01) (Fig. 3). There was also modest negative correlation between maximal TIT2 interval and age (correlation coefficient -0.30, p < 0.04). No significant difference in mean maximal TIT2 interval was observed between men and women. The QTc interval and age, but not gender, were found to be statistically significant independent predictors of maximal TIT2 interval, accounting for 20% of the variability of that variable.

Electrocardiographic lead distribution of T2. Among the 57 blood relatives manifesting T2, this ECG phenomenon was confined to leads V2 and V3 in six (10%) blood relatives, whereas its presence in one or more left precordial lead (V4, V5, or V6) or limb lead (I, II, III, aVL or aVF) was noted in 51 (90%). Among the latter patients, T2 was observed in the following leads, ranked in order of decreasing prevalence: V4 (76%), V5 (76%), V6 (53%), II (51%), I (22%), aVF (18%), III (10%) and aVL (4%).

For those blood relatives with T2, a histogram of ECG lead distribution of T2 for each QTc group (Fig. 4) revealed that confinement of T2 to leads V2 and V3 occurred in 50% of four subjects with a normal QTc interval, but in only 10% of 20 with a borderline QTc interval and 6% of 33 with a prolonged QTc

Table 1. Prevalence of T2 by QTc Group

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<td>≤0.41 s</td>
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Blood relatives (n = 210) 4/73 (5%) 2/75 (27%) 33/62 (53%)
Spouses (n = 44) 0/25 (0%) 1/19 (5%) 0/0

*p = 0.06, blood relatives versus spouses. \( p < 0.001 \), comparison of QTc groups.

Figure 3. Scatterplot of the maximal TIT2 interval versus the QTc interval for 57 blood relatives with long QT syndrome with T2. The number of points is <57 owing to identical coordinates in some family members.
syndrome most closely resembling their control counterparts and compared with those of 37 blood relatives with long QT subdivided by QTc category (0.39 to 0.41 and 0.42 to 0.46 s). The two,948 control subject tracings were statistically significant (p < 0.04). The two blood relatives with a QTc interval <0.41 s and T2 in one or more left precordial (39% vs. 10%, respectively) (Fig. 5). These differences were respectively, whereas a maximal T2 grade of I was more frequent in those subjects with a QTc interval >0.47 s versus those without (3 of 168) major symptoms (p < 0.0001). However, blood relatives with a borderline QTc interval >0.47 s were more likely to manifest T2 in one or more left precordial or limb lead than those with a normal QTc interval, the remainder of this report focuses primarily on T2 not confined to leads V2 and V3.

Prevalence of T2 according to demographic and clinical features. In 12 (92%) of the 13 affected families, T2 involving one or more left precordial or limb lead was found in at least 1 blood relative (median 4 relatives/family, range 1 to 11). The prevalence in men and women was comparable (28% and 22%, respectively, p = 0.3), as was prevalence by age group (24% for both blood relatives ≥16 years old and for those <16 years old). However, blood relatives with a borderline QTc interval and a history of syncpe, seizures or cardiac arrest were more likely to manifest T2 in one or more left precordial or limb lead than their asymptomatic counterparts (p = 0.05) (Table 2). Among affected blood relatives, the prevalence of T2 in one or more left precordial or limb lead tended to be greater in those taking a beta-adrenergic blocking agent (69% vs. 48%, p = 0.17), although this trend may have reflected the much greater use of beta-blockers in those relatives with (15 of 24) versus those without (3 of 168) major symptoms (p < 0.0001).

Maximal T2 configuration grade according to QTc group. Among blood relatives manifesting T2 in one or more left precordial or limb leads, a maximal grade of III was more common in those subjects with a QTc interval ≥0.47 s versus those with a QTc interval 0.42 to 0.46 s (19% vs. 6%, respectively), whereas a maximal T2 grade of I was more prevalent in the borderline versus the prolonged QTc group (39% vs. 10%, respectively) (Fig. 5). These differences were statistically significant (p < 0.04). The two blood relatives with a QTc interval ≥0.41 s and T2 in one or more left precordial or limb lead both exhibited a maximal T2 grade of II.

Prevalence and characterization of T2 in the control population and comparison with blood relatives with long QT syndrome (Table 3). The 2,948 control subject tracings were subdivided by QTc category (0.39 to 0.41 and 0.42 to 0.46 s) and compared with those of 37 blood relatives with long QT syndrome most closely resembling their control counterparts (i.e., age ≥16 years and absence of syncpe, seizures or cardiac arrest). Only tracings with a QTc interval 0.42 to 0.46 s could be compared because T2 was not observed in asymptomatic blood relatives ≥16 years old with a QTc interval 0.39 to 0.41 s.

As evident in Table 3, the prevalence of T2 among control subjects was 13 (0.7%) of 1,940 for a QTc interval 0.39 to 0.41 s and 31 (3.1%) of 1,008 for a QTc interval 0.42 to 0.46 s (p < 0.0001), with confinement to leads V2 and V3 observed in 6 (46%) of 13 and 12 (39%) of 31 subjects in those respective QTc categories (p > 0.6). Women constituted a majority (67%) of the 18 control subjects manifesting T2 confined to leads V2 and V3 but only a minority (12%) of 26 control subjects with T2 involving left precordial leads (p < 0.001). Among control subjects (all ≥16 years old) manifesting T2, there was no significant age difference between those with T2 confined versus not confined to leads V2 and V3. There was also no significant difference in mean maximal T1T2 interval between control subjects with a normal versus borderline QTc interval, regardless of whether T2 was confined or not to leads V2 and V3. Of the eight control subjects with T2 involving lead V2 but not lead V3 or V6, the one subject with a QTc interval 0.39 to 0.41 s and three of seven subjects with a QTc interval 0.42 to 0.46 s exhibited clockwise rotation (R > S not occurring until lead V3 or V6), implying that lead V4 was not a true left precordial lead in these four subjects.

Compared with their control counterparts, asymptomatic adult blood relatives with a borderline QTc interval had a significantly greater prevalence of T2 involving leads V4, V5, or a limb lead (9 [24%] of 37 from six families vs. 1.9% in control subjects, p < 0.0001) and also proportionately fewer instances in which T2 was confined to leads V2 and V3. Among those with a borderline QTc interval and T2 not confined to leads V2 and V3, blood relatives exhibited significantly more frequent limb lead involvement (5 [56%] of 9 vs. 0 of 19, p = 0.002), a similar prevalence of maximal grade II or III (5 [56%] of 9 vs. 8 [42%] of 19, p > 0.6) and a significantly longer mean maximal T1T2 interval compared with control subjects (p < 0.005). Lead V4 was clearly left of the precordial transition.
zone in the single adult asymptomatic blood relative with a borderline QTc interval and T2 involving lead V4 but not lead V6 or V5. Among subjects in Table 3 with a borderline QTc interval and T2 involving left precordial or limb leads, concomitant nonupright T waves in lead V5 were observed in 2 of 9 asymptomatic adult blood relatives (biphasic T waves in both) and in none of the 19 adult control subjects.

### Discussion

The present study adds to a growing body of data (1,5,14) suggesting that certain T wave configurations, particularly T wave "humps" (T2), represent another phenotypic marker of the long QT syndrome, in addition to the QT interval itself. The lines of evidence from the present study in support of this hypothesis are that 1) this ECG phenomenon was found in >90% of families with long QT syndrome; 2) the proportion of blood relatives with long QT syndrome exhibiting T2, particularly those with T2 involving the left precordial or limb leads, increased progressively over the continuum of QTc categories, as one would expect if the genetic abnormality that gives rise to QT prolongation is also responsible for the altered T wave configuration; 3) T2 in left precordial or limb leads was also more prevalent among blood relatives with symptoms attributable to long QT syndrome (i.e., syncope, seizures or cardiac arrest), both among those family members with a prolonged QT as well as those with a borderline (i.e., 0.42 to 0.46 s) QTc interval; and 4) among asymptomatic adult blood relatives with long QT syndrome with a borderline QTc interval, the prevalence of T2 in left precordial or (especially) limb leads was significantly greater than that found among a large control cohort.

In the course of the present investigation, we were able to semiquantitatively describe a continuum of T2 amplitudes subdivided for simplicity into three grades, as shown in Figure 1. Although a grade I T2 lacks a discrete takeoff rising above the horizontal (seen in grades II and III), visual recognition of this more subtle end of the T2 configuration spectrum is aided by the fact that a bulge on the downsloping limb of the T wave represents a departure from the normally more brisk rate of T wave descent compared with ascent (20). We were also able to demonstrate that in nearly all subjects (except for a small minority with a clearly prolonged QTc interval), that T2 could be distinguished from a U wave, either on the basis of a distinct wave (U wave) observed after T2 or on the basis of a relatively short (<0.15 s) maximal TIT2 interval (17).

### Relation to previous studies

Previous investigators (15,21-24) have used various terms, including notched, bifid (16,25), dimpled (26) and cloven (26), to describe T wave deformities that give rise to T2. Some have emphasized that T wave flattening (21,24) or slurring of the downstroke (21), reflecting the presence of grade I humps, are related configuration variants, even though notching as such may not be visible. The terminology used in the present study, based simply on the presence and magnitude of a hump in the T wave (1), allows all the previously observed configurational manifestations to be subsumed under a single, unifying ECG taxonomy.

The presence of T2 has been noted in a minority of the general population (15,16,21,22,24), with a prevalence of 2.8% among 4,000 consecutive tracings analyzed by Watanabe et al. (16) and 3.0% of 3,980 normal subjects ≥21 years old reported by Ishikawa and Ohnuma (15). Such data are of similar order of magnitude to the 1.5% prevalence of T2 that we observed in our cohort of 2,948 control subjects, although the data are not strictly comparable given our more stringent diagnostic criteria (presence in at least 2 beats of two or more leads) and our exclusion of tracings with a QTc interval ≥0.47 s or various conditions that alter repolarization (in contrast, only 41 of the 113 ECGs of Watanabe et al. [16] showing bifid T waves were otherwise normal). Previous investigators have emphasized the
tendency of these T wave variants to occur in the right precordial or transition leads, especially in children (21,25), progressively greater left precordial involvement is observed with age (16). For subjects exhibiting T2 in our study, confinement of T2 to leads V2 and V3 among the control subjects (all ≥16 years old) was not as striking as in a previous report (16) but was still relatively more prominent than among the blood relatives with long QT syndrome (18 [41%] of 44 vs. 6 [10%] of 57, respectively, p < 0.001).

The prevalence of T2 with left precordial involvement is known to be increased under a variety of abnormal conditions (15,16,21,23-26), most commonly left ventricular hypertrophy and ischemic heart disease (15,16,21,22,24). In our series, only three blood relatives with long QT syndrome with T2 had ECG findings compatible with left ventricular hypertrophy, and none had manifestations of ischemic heart disease.

T wave humps have been described previously (1,5,14) in patients with long QT syndrome and are evident in some of the earliest published ECGs (27,28). These configuration abnormalities, especially those in the grade III category, are sometimes included as TU complexes (29,30). Malfatto et al. (14) recently showed that notched T waves were more prevalent in 53 patients with long QT syndrome than in age-matched control subjects and that these T wave abnormalities correlate with symptoms. Our detailed delineation of the configurational spectrum and ECG lead distribution of T2 in a large cohort of family members with long QT syndrome over a broad QTc range, combined with comparison data from a very large control population, confirm and extend the findings of Malfatto et al. (14).

Possible mechanisms. Early afterdepolarizations have been suspected as one of the electrophysiologic mechanisms that can give rise to ventricular tachyarrhythmias in both the congenital and acquired long QT syndrome (2,29,31). Subthreshold early afterdepolarizations conceivably could explain the occurrence of T2 in left precordial or limb leads, given the increased prevalence of major symptoms that we observed in blood relatives with a borderline (or prolonged) QTc interval with these ECG findings. However, pathologic oscillations in transmembrane voltage would seem less tenable as the basis for physiologic T2 (i.e., those confined to precordial leads V2 and V3).

An alternative, perhaps more unifying, explanation is that T2 may simply reflect asynchronous myocardial repolarization. In the absence of drugs or electrolyte disturbances, such electrical heterogeneity could reflect different anatomic regions of the heart (15,16,32) or myocardial tissues that are electrophysiologically distinct inherently (33,34) or as a result of differential autonomic stimulation (35) or disease processes (36-38). Electrocardiographic studies suggest that in the absence of heart disease, the occurrence of T2 in right precordial or transition leads reflects relatively delayed right ventricular repolarization (15,16,21,25), an impression supported by experimental observations (32).

Watanabe et al. (16) reported that in the setting of either a normal ECG or one showing left ventricular hypertrophy and ischemic features, the mean QTc interval was longer in patients with than without bifid T waves, consistent with the idea that increased dispersion of electrical recovery promotes the occurrence of T2. Analogously, we observed in our control subjects, as well as in our family members with long QT syndrome, an increased prevalence of T2 as the QTc interval lengthened and a correlation between maximal T1T2 interval and QTc interval among blood relatives. Increased dispersion of electrical recovery in the long QT syndrome has been documented by endocardial (39) and body surface mapping (40), as well as by the demonstration of action potentials of widely varying duration at different tissue layers in a papillary muscle preparation excised from a patient with long QT syndrome (41). At a cellular level, asynchrony in repolarization of contiguous myocardial tissues can give rise to electronically generated humps on the action potential that can mimic afterdepolarizations (31,34); such electrical events could summate electrocardiographically to yield T2. The existence of asynchronous and prolonged myocardial electrical recovery in long QT syndrome need not rule out, and indeed constitutes a favorable electrophysiologic milieu for the occurrence of early (or late) afterdepolarizations (31,38,43).

Study limitations. In contrast to the tracings of blood relatives, which were mixed in blinded manner with those of presumably unaffected spouses, all the control ECGs were known to derive from subjects very unlikely to carry the long QT genotype. Conceivably, this may have introduced a bias toward underdetection of T2 in the control subjects. However, 61% of control tracings deemed to exhibit T2 were found to exhibit the more subtle variety (i.e., maximal grade I [Table 3]), attesting to the careful manner in which these ECGs were read. Another methodologic issue is that QTc measurements were performed manually on a beat-to-beat basis in individual leads of family members with long QT syndrome, as opposed to the automated technique used in the control subjects that involved global measurement (over all 12 leads) of a median (i.e., representative) beat, with an RR interval derived from the average heart rate (44). Previous studies, however, have documented a high correlation between the Marquette computerized technique of QT interval measurement and manual methods, whether adopting the global 12-lead (19) or single-lead approach (45). Moreover, sinus arrhythmia was present in only a minority of the control tracings, with a difference between longest and shortest RR interval >40% (or 20%) of the average RR interval being observed in only 2% (or 14%, respectively) of ECGs. The proportion of ECGs with sinus arrhythmia were uniformly distributed over the entire range of QTc values. In the great majority of cases, therefore, average RR and single-cycle RR were essentially identical, which would be expected to yield comparable QTc intervals. Furthermore, any slight deviations between automated and manual calculations, possibly resulting in occasional overinclusion or underinclusion in different QTc categories, should have been averaged out over the nearly 3,000 control ECGs. Thus, despite some limitations, we believe that the differences observed between asymptomatic adult blood relatives with long
QT syndrome and control subjects over the borderline QTc range (Table 3) remain valid.

Implications. The present study provides strong statistical evidence that T2 occurring in nonphysiologic locations (i.e., left precordial or limb leads especially) may provide another ECG marker, in addition to QT interval prolongation, for long QT syndrome carrier status in affected families. Our findings thus support the expanded definition of long QT syndrome recently proposed by Schwartz et al. (46). Attention to the presence of T2 in two or more leads, of these 53 subjects had T2 in a single lead but confined to lead V2 or V3, in all cases.

From a mechanistic standpoint, the clear temporal distinction between T2 and U waves observed in the present study implies that disparate cardiac ionic processes, or at least functionally different variants of a similar ionic channel, are responsible for these ECG phenomena. Such a fundamental distinction tends to be obscured by the commonly used term T wave "hump," most easily misapplied in the case of a grade III T wave hump.

Finally, the fact that T2 identical to those described herein may be seen in drug-induced long QT syndrome (30,48–51) supports the hypothesis that altered cardiac ion channel function is responsible for both the congenital and acquired long QT syndromes (2,52) and argues further against the need for postulating a primary autonomic abnormality as the basis for the familial disorder (2,53).

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References