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T Wave Alternans in Idiopathic Long QT Syndrome

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Objectives. The study evaluates the association between T wave alternans and the risk of cardiac events (syncope, aborted cardiac arrest or cardiac death) in a large population of patients with idiopathic long QT syndrome.

Background. T wave alternans is an infrequently recorded electrocardiographic (ECG) finding in patients with delayed repolarization, and its clinical significance is not clear.

Methods. A total of 4,656 ECG recordings in 2,442 patients enrolled in the International Long QT Syndrome Registry were reviewed for episodes of T wave alternans. To determine the risk associated with T wave alternans, independent of corrected QT interval (QTc) duration, patients with T wave alternans were matched for QTc value (every 0.025 $s^{1/2}$) to patients with long QT syndrome without T wave alternans.

Results. T wave alternans was identified in 30 patients (25 of whom had a QTc interval >0.50 $s^{1/2}$). A strong association between QTc prolongation and T wave alternans was observed (odds ratio 1.23 per 0.01-$s^{1/2}$ unit increase in QTc, $p < 0.0001$). Conditional logistic regression analyses with adjustment for age, gender, status and QTc value revealed that T wave alternans did not make a significant independent contribution to the risk of cardiac events. The risk of experiencing a major cardiac event was primarily related to length of QTc.

Conclusions. T wave alternans, a marker of electrical instability and regional heterogeneity of repolarization, identifies a high risk subset of patients with prolonged repolarization. Patients with T wave alternans have an increased risk of cardiac events, but this risk is primarily related to the magnitude of repolarization delay (QTc prolongation). T wave alternans does not make an independent contribution to the risk of cardiac events after adjustment for QTc length.

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T wave alternans is an infrequently recorded electrocardiographic (ECG) finding with transient beat-to-beat changes in amplitude, shape and, frequently, the polarity of the T wave during sinus rhythm without concomitant QRS changes (1–3). T wave alternans was first recorded during the pioneer electrophysiologic experiments of Mines (4) in 1913 and by Taussig (5) in 1928. Thereafter, several investigators recorded episodes of T wave alternans in clinical cases, and subsequently it was suggested that this abnormality was associated with a high likelihood of torsade de pointes and ventricular fibrillation (2,6–14). Patients with marked repolarization delay resulting from primary (idiopathic long QT syndrome) or secondary (myocardial ischemia, metabolic disorders, drug induced) causes of QT prolongation are especially prone to develop T wave alternans (2,15–24). Furthermore, patients with delayed repolarization are at an increased risk of experiencing episodes of malignant ventricular arrhythmias, syncope or cardiac arrest (25,26). The purpose of this study was to determine the clinical setting and prognostic importance of T wave alternans in patients with long QT syndrome.

Methods

Study population. The identification of families with long QT syndrome in the International Long QT Syndrome Registry has been described elsewhere (26,27). The population studied included 1,171 patients with corrected QT (QTc) prolongation >0.44 $s^{1/2}$ (including 369 probands [first-identified patient with long QT syndrome in a family] and 802 affected family members [QTc >0.44 $s^{1/2}$]) and 1,271 family members with QTc ≤ 0.44 $s^{1/2}$. A 12-lead ECG was required for enrollment in the registry, and ECGs were requested at periodic intervals during follow-up. The ECGs were also requested if they were obtained at the time of a cardiac event (syncope or cardiac arrest), as identified during routine registry follow-up. There were 4,656 ECG recordings in the 2,243 subjects enrolled in the registry, and all ECGs were reviewed to identify episodes of T wave alternans. Several clinical and ECG variables (demographic data, history of symptoms, history of documented ventricular arrhythmias, deafness, ECG measures of repolarization, treatment) were

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JACC Vol. 23, No. 7
June 1994:1541–6

compared in patients with and without T wave alternans. The association between T wave alternans and cardiac events (syncope, aborted cardiac arrest, cardiac death) that occurred before or after recording of T wave alternans was also assessed.

Electrocardiographic determination of T wave alternans. The diagnosis of T wave alternans was based on the presence of beat-to-beat changes in configuration and polarity of T waves recorded during stable sinus rhythm on at least two leads of any available 12-lead ECG. Subjects with T wave alternans occurring immediately after atrial and ventricular premature beats or related to cardiac pacing were excluded. Those with T wave alternans associated with abrupt beat-to-beat sinus cycle length changes were also excluded because in such conditions, T wave abnormalities may occur even in normal subjects (28–30). Assessment of repolarization duration consisted of measurement of QT and RR intervals, with the QT interval corrected for the RR interval (QTc) using the Bazett's (31) formula.

Statistical analysis Comparisons of clinical and ECG data between patient groups were performed using nonpaired *t* tests for continuous variables, the Wilcoxon rank-sum test for nonnormally distributed data and the chi-square test or Fisher exact test, as appropriate for proportional data. The strength and significance of the association between T wave alternans and QTc length value were estimated using a logistic regression model.

To evaluate the independent clinical significance of T wave alternans in patients with prolonged QTc interval, 30 patients with T wave alternans were matched with regard to QTc value (every 0.025 $s^{1/2}$) to 583 subjects without visible T wave alternans. A conditional logistic regression analysis (32,33) was performed to determine the contribution of T wave alternans to outcome after adjustment for matching and relevant clinical variables. The odds ratios, with 95% confidence intervals express differences in outcome between patients with and without T wave alternans having the same gender and proband status and in the same age and QTc value group.

Results

Electrocardiographic patterns of T wave alternans. Episodes of T wave alternans were detected in 29 (2.5%) of 1,171 patients with a QTc interval >0.44 $s^{1/2}$ and in 1 patient among the 1,271 subjects with a QTc interval ≤0.44 $s^{1/2}$ (the QTc interval in this patient was 0.43 $s^{1/2}$). T wave alternans was found in 13 patients on the first available ECG, but in the other 17 patients it occurred on a follow-up tracing. Analysis of clinical and ECG characteristics of the 30 patients with T wave alternans (Table 1) revealed that they were usually young (77% were <20 years of age), and 17% had congenital deafness. Patients with T wave alternans had markedly prolonged repolarization (mean [±SD] QTc interval 0.60 ± 0.09 $s^{1/2}$). A documented history of malignant ventricular arrhythmias (torsade de pointes or ventricular fibrillation) was recorded in one-third of patients with T wave alternans, and aborted cardiac arrest or cardiac death occurred in 37%.

Table 1. Clinical Characteristics of Patients With Long QT Syndrome in Relation to Configuration of T Wave Alternans

		T Wave Alternans	
	Total (n = 30)	Minor (n = 9)	Marked (n = 21)
Mean age (yr)	12 ± 13	21 ± 20	9 ± 10*
<10	15 (50%)	2 (22%)	13 (62%)*
<20	23 (77%)	4 (22%)	19 (90%)†
Male/female	14/16	4/5	10/11
Probands	21 (70%)	4 (44%)	17 (81%)*
Deafness	5 (17%)	0	5 (24%)
ECG			
Mean RR interval (s)	0.95 ± 0.26	0.99 ± 0.31	0.94 ± 0.25
Mean QTc interval ($s^{1/2}$)	0.60 ± 0.09	0.54 ± 0.06	0.63 ± 0.09†
QTc interval ≥0.60 $s^{1/2}$	13 (43%)	1 (11%)	12 (57%)
U wave	19 (63%)	6 (67%)	13 (62%)
TdP/VF documented	10 (33%)	1 (11%)	9 (43%)
Therapy			
Beta-blockers	26 (87%)	7 (85%)	19 (90%)
LCTSX	6 (20%)	0	6 (29%)
Pacemaker	6 (20%)	1 (11%)	5 (24%)
Cardiac event			
Syncope >5/pt	12 (40%)	1 (13%)	11 (52%)
Cardiac death	4 (13%)	1 (11%)	3 (14%)
ACA or cardiac death	11 (37%)	1 (11%)	10 (48%)
Any event	23 (69%)	5 (56%)	18 (86%)
Mean age at 1st event (yr)	7 ± 9	12 ± 5	6 ± 9

*$p < 0.05$ and †$p < 0.01$ patients with marked versus patients with minor T wave alternans. Data presented are mean values ± SD or number (%) of patients. ACA = aborted cardiac arrest; Any event = syncope, aborted cardiac arrest or cardiac death; ECG = electrocardiogram; LCTSX = left cervicothoracic sympathectomy; pt = patient; TdP = torsade de pointes; VF = ventricular fibrillation.

Different ECG patterns were observed among the 30 subjects with T wave alternans. We divided the 30 subjects into two subsets according to the magnitude of the beat-to-beat T wave changes. Nine patients (30%) were categorized as having minor (monophasic) T wave alternans, defined as beat-to-beat changes in the shape of the T wave (notchings or bifid pattern) but without a bidirectional pattern. In the other 21 subjects (70%), marked (biphasic) T wave alternans was identified with beat-to-beat bidirectional changes in T wave polarity. Examples of minor and marked T wave alternans are demonstrated in Figures 1 and 2. The patients with marked T wave alternans were significantly younger and had a significantly longer duration of repolarization and a higher prevalence of cardiac events (86% vs. 56%, $p = 0.096$) than those with mild forms of T wave alternans (Table 1).

T wave alternans relation to QTc interval. The episodes of T wave alternans were recorded mainly in patients with a very prolonged QTc interval (25 of our 30 subjects with T wave alternans had a QTc interval >0.50 $s^{1/2}$). Figure 3 shows the prevalence of T wave alternans in our entire Long QT Syndrome Registry population in relation to the QTc length. T wave alternans was recorded in one-fifth (13 of 62)

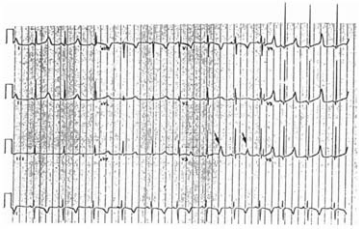

Figure 1. Minor T wave alternans in a patient with a QTc interval of 0.55 $s^{1/2}$. Beat-to-beat changes in the shape and duration of the T waves are evident (arrows), with unidirectional (monophasic) configuration of the T waves.

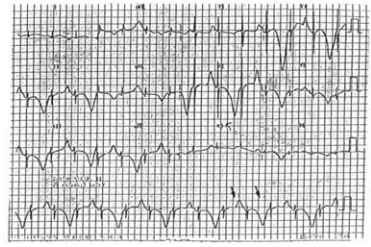

Figure 2. Marked T wave alternans in a patient with a QTc interval of 0.78 $s^{1/2}$. Beat-to-beat changes in the shape of the T waves are evident (arrows), with bidirectional (biphasic) configuration of the T waves.

of patients with a QTc interval >0.60 $s^{1/2}$. Logistic regression analysis revealed a strong and significant association between QTc interval length and T wave alternans, with an odds ratio of 1.23 per 0.01-$s^{1/2}$ unit increase in QTc length (95% confidence interval 1.18 to 1.29, $p < 0.0001$).

Clinical significance of T wave alternans. Patients with T wave alternans had a somewhat higher frequency of cardiac events than those without T wave alternans (Fig. 4). In view of the significant association between QTc length and T wave alternans, patients with T wave alternans were matched to those without visible T wave alternans on QTc length (see Methods) to determine whether T wave alternans is an independent risk factor for cardiac events. The comparative adjusted analysis did not show significant differences in clinical variables between patients with and without T wave alternans. T wave alternans did not make a significant independent contribution to the risk of cardiac events after adjustment for relevant covariates (Table 2). Analyzed separately, the risk of cardiac events in 21 patients with marked T wave alterans compared with the risk in matched control patients with long QT syndrome having the same QTc value, age, gender and status was also increased, but once again the difference was not significant.

T wave alternans in patients with a QTc interval >0.60 $s^{1/2}$. Among 1,171 enrolled patients with a QTc interval >0.44 $s^{1/2}$, 62 patients (5.3%) demonstrated a marked prolongation of QTc interval >0.60 $s^{1/2}$. Thirteen (21%) of the 62 patients had T wave alternans recorded on a 12-lead ECG. In this selected subset of 62 patients with long QT syndrome, the risk of a cardiac event was analyzed separately. Comparison of clinical data between the 13 patients with and 49 patients

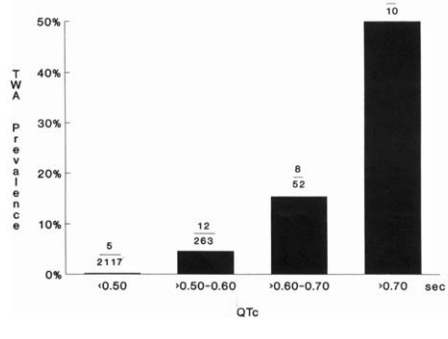

Figure 3. Frequency of T wave alternans in relation to the repolarization delay (QTc interval length). **Fractions above bars** represent the number of patients with T wave alternans (TWA) in relation to the total number of subjects in each QTc category.

JACC Vol. 23, No. 7
June 1994:1541–6

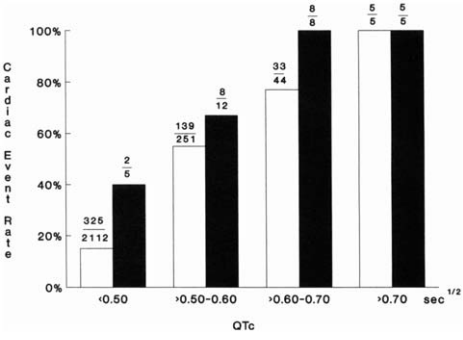

Figure 4. Cardiac event rates in patients with (**solid bars**) and without (**open bars**) T wave alternans in relation to the repolarization delay (QTc interval length). **Fractions above bars** represent the number of patients with cardiac events in relation to the total number of subjects in each QTc category.

without T wave alternans is shown in Table 3. Patients with T wave alternans were significantly younger and were more likely to develop torsade de pointes or ventricular fibrillation than those without T wave alternans (69% vs. 35%, respectively, $p = 0.027$). Patients with T wave alternans had significantly longer QTc values (0.69 ± 0.06 vs. 0.64 ± 0.04, $p = 0.013$) than those without T wave alternans. Among the 62 patients with marked QTc prolongation (>0.60 $s^{1/2}$), 13 had T wave alternans, and all 13 patients experienced cardiac events; in the 49 patients without T wave alternans 38 (78%) experienced cardiac events. This difference in event rates among those with and without T wave alternans in the subset with a QTc interval >0.60 $s^{1/2}$ was of borderline significance ($p = 0.07$). Patients with T wave alternans had a more severe clinical course with significantly more syncopal or cardiac arrest episodes per patient. Seventy-five percent of patients with T wave alternans had more than five episodes of syncope, whereas only 33% of those without T wave alternans experienced such frequent events.

Discussion

T wave alternans and repolarization delay. T wave alternans was observed on the standard 12-lead ECG in 30 patients with idiopathic long QT syndrome. This large series of patients with long QT syndrome with T wave alternans allowed us to evaluate the clinical characteristics of these patients and to estimate the prognostic significance of T wave alternans. The primary finding in our patients with T wave alternans was that they exhibited a considerable repolarization delay, with a mean QTc interval of 0.60 $s^{1/2}$. Previously reported cases of T wave alternans (2,3,6–8) also demonstrated that this phenomenon was usually seen in patients with a prolonged QTc interval, but the relation between T wave alternans and the magnitude of repolarization delay has not been explored systematically. By logistic regression analysis, the odds ratio of having versus not having T wave alternans in our population was estimated to be 1.23^x, where x is the 0.01 $s^{1/2}$ unit change in QTc interval. That is, a patient with a QTc interval of 0.60 $s^{1/2}$ would have

Table 2. Odds Ratio for Cardiac Events in Patients With Versus Without T Wave Alternans

	T Wave Alternans			Marked T Wave Alternans		
Cardiac Event	Odds Ratio*	95% CI	p Value	Odds Ratio*	95% CI	p Value
Syncope	2.34	0.69–7.93	0.17	4.00	0.79–20.13	0.09
Syncope <5/pt	1.58	0.60–4.17	0.36	2.35	0.75–7.39	0.15
Syncope or ACA	1.51	0.46–4.96	0.50	1.98	0.38–10.40	0.42
Cardiac death	1.30	0.34–4.97	0.71	1.10	0.22–5.45	0.91
Any event	1.40	0.43–4.60	0.58	1.78	0.34–9.30	0.49

*Adjusted for age, gender, status and QTc interval. 95% CI = 95% confidence interval; other abbreviations as in Table 1.

Table 3. Patients With Long QT Syndrome With a QTc Interval >0.60 $s^{1/2}$. Comparison of Clinical Characteristics of Patients With and Without T Wave Alternans

	Pts With TWA (n = 13)	Pts Without TWA (n = 49)	p Value
Mean age (yr)	8 ± 11	26 ± 19	< 0.001
Female	7 (54%)	35 (73%)	
Deafness	3 (23%)	5 (10%)	
Documented ECG findings			
Any VPBs	10 (77%)	25 (51%)	
TdP/VF	9 (69%)	17 (35%)	0.027
ECG			
Mean RR interval (s)	0.86 ± 0.25	0.96 ± 0.21	
Mean QTc interval ($s^{1/2}$)	0.69 ± 0.06	0.64 ± 0.04	0.013
Mean QT/RR interval (%)	76 ± 13	66 ± 9	0.026
Therapy			
Beta-blockers	11 (92%)	35 (76%)	
LCTSX	5 (38%)	5 (11%)	0.017
Pacemaker	3 (23%)	8 (17%)	
Cardiac events			
Syncope >5/pt	9 (75%)	14 (33%)	0.010
Any event	13 (100%)	38 (78%)	0.072
Cardiac death	3 (23%)	6 (12%)	
Age at 1st event (yr)	7 ± 11	15 ± 15	

Data presented are mean values ± SD or number (%) of patients (Pts). TWA = T wave alternans; VPBs = ventricular premature beats; other abbreviations as in Table 1.

a 22-fold greater likelihood of having T wave alternans than a patient with a QTc interval of 0.45 $s^{1/2}$ ($1.23^{15} = 22.3$). The configuration of the T wave alternans was related to the magnitude of the repolarization delay. Patients with marked (biphasic) T wave alternans had significantly longer QTc values than those with minor (monophasic) beat-to-beat changes in the configuration of the T wave.

Possible mechanisms of T wave alternans. The fundamental mechanism responsible for T wave alternans is uncertain. Published reports are replete with a variety of speculative hypotheses, including regional heterogeneity of repolarization (11,34–36), enhanced early afterdepolarization (37–40), alteration in the sympathetic nervous system (2,14,41) and shortening of the diastolic period (28–30,42). In the current study, the observed association between T wave alternans and QTc prolongation indicates a complex relation involving delayed repolarization, cycle length and the configuration of the T wave. In the normal heart, the duration of the cellular action potential (repolarization) is not absolutely uniform among the innumerable cells of the myocardium, and a certain degree of repolarization variability (heterogeneity) exists. When the action potential is prolonged, the heterogeneity of repolarization is, in all probability, increased. Interregional (endocardial-epicardial, anterior-posterior) heterogeneity of repolarization has been demonstrated previously in various experimental studies of ventricular refractoriness (36,43–47). The observed minor and marked forms of T wave alternans may be related to the extent of regional heterogeneity in myocardial repolarization, with marked (biphasic) T wave alternans reflecting more extensive regional heterogeneity in repolarization. An additional factor that may contribute to T wave alternans and cardiac arrhythmias is the level of activation of the sympathetic nervous system. Increased sympathetic tone can induce QTc prolongation, shorten the cycle length and increase the degree of repolarization heterogeneity (12,14,15,41).

T wave alternans and cardiac events. The high incidence of cardiac events (69%) in our patients with T wave alternans may suggest a common mechanism of T wave alternans and triggering of ventricular arrhythmias in patients with long QT syndrome. Results of a recent experimental study by Nearing et al. (14), who have demonstrated that the appearance of T wave alternans coincides with spontaneous occurrence of malignant ventricular tachyarrhythmias, appear to support this concept. As shown in Figure 4, T wave alternans was so strongly related to the prolongation of repolarization that the risk for experiencing cardiac events in patients with T wave alternans was mainly dominated by QTc length. Patients with T wave alternans had a somewhat higher frequency of cardiac events (odds ratios >1.3 [Table 2]) than the QTc-matched patients without T wave alternans, but these differences were not significant.

Study limitations. Patients with T wave alternans were identified from a retrospective review of 4,656 ECG recordings entered into the International Long QT Syndrome Registry. We have no reliable data as to the prevalence or incidence of T wave alternans because it is unlikely that all ECG recordings with T wave alternans were sent to the registry. The large number of enrolled patients (2,442 patients) probably minimized patient selection bias for long QT syndrome but not T wave alternans selection bias because there was no prespecified protocol for sending these recordings to the registry.

Clinical implications. In this study, the development of T wave alternans is strongly associated with the magnitude of delayed ventricular repolarization relative to the heart rate. The ECG pattern of the T wave alternans is also related to the magnitude of the repolarization delay. T wave alternans may be considered a marker for an unstable heterogeneous pattern of ventricular repolarization. Patients with long QT syndrome with T wave alternans have an augmented risk for cardiac events, but the risk is primarily associated with the QTc prolongation. Although T wave alternans in patients with long QT syndrome does not make a significant independent contribution to cardiac events, T wave alternans provides insight into a possible mechanism of electrical instability that may lead to life-threatening ventricular arrhythmias (usually torsade de pointes).

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JACC Vol. 23, No. 7
June 1994:1541–6

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