Prolonged Tpeak-to-Tend Interval on the Resting ECG Is Associated With Increased Risk of Sudden Cardiac Death

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**Background**—Early studies indicate that prolongation of the interval between the peak and the end of the T wave (Tpeak to Tend [TpTe]) on the 12-lead ECG is a marker of ventricular arrhythmogenesis. However, community-based studies have not been conducted.

**Methods and Results**—TpTe and other ECG predictors were evaluated in the ongoing Oregon Sudden Unexpected Death Study based in the Portland, Oregon, metropolitan area using a case-control design. Cases of sudden cardiac death (SCD) (n=353; mean age, 66.6 years; 95% CI, 65.1 to 68.1 years; 67% men) were compared with living controls with coronary artery disease (n=342; mean age, 64.7 years; 95% CI, 63.4 to 66.0 years; 69% men) from the same region. Analysis of TpTe and selected ECG intervals was limited to sinus rhythm 12-lead ECGs. For cases, these were obtained before and unrelated to SCD. Independent-samples *t* tests and multiple logistic regression were used. Mean TpTe was significantly greater in cases (89.4 ms; 95% CI, 87.7 to 91.2 ms; *P*<0.0001) than in controls (76.1 ms; 95% CI, 74.8 to 77.4 ms). The other ECG intervals (corrected QT interval [QTc], QRS duration [QRSD], and TpTe/QT ratio) also were significantly prolonged among cases versus controls (*P*≤0.01). TpTe remained a significant predictor of SCD after adjusting for age, sex, QTc, QRSD, and left ventricular function. Odds of SCD increased more with a 1-SD increase in TpTe (12 ms) among subjects with prolonged QRSD (odds ratio, 3.49; 95% CI, 2.06 to 5.91) than with a 1-SD increase in TpTe among subjects with normal QRSD (odds ratio, 1.96; 95% CI, 1.65 to 2.32). TpTe remained significantly associated with SCD in subjects with normal QTc.

**Conclusions**—Prolongation of the TpTe interval measured in lead V5 was independently associated with SCD, with particular utility when the QTc was normal or not measurable because of prolonged QRSD. (Circ Arrhythm Electrophysiol. 2011;4:441-447.)

**Key Words:** death sudden ■ coronary disease ■ population ■ risk factors ■ electrocardiography

Sudden cardiac death (SCD) claims 250 000 to 300 000 lives annually in the United States. The majority of SCDs are associated with significant coronary artery disease (CAD). Furthermore, SCD can be the first manifestation of CAD for many (up to 68% of younger subjects). Unfortunately, overall survival after out-of-hospital cardiac arrest remains <5%, even in countries with advanced first-responder systems. Therefore, innovations in interventional cardiology and device technology are ineffective for the majority of patients who do not reach the hospital alive. It is crucial to enhance the risk stratification methodology for SCD, and because the annual incidence is 53/100 000 population, it becomes necessary to investigate SCD in the general community.

**Clinical Perspective on p 447**

We and others have previously highlighted the significant association between prolonged ventricular repolarization (measured as the corrected QT interval [QTc]) and risk of SCD in the community. However, these findings are not uniformly observed for all subjects who experience SCD (some have normal QTc), and on occasion, the QTc is not measurable because of the presence of intraventricular conduction delay (IVCD) or block.

The interval from the peak of the T wave to the end of the T wave (Tpeak to Tend interval [TpTe]) on 12-lead ECG is a measure of transmural dispersion of repolarization in the left ventricle (LV), with prolongation of this interval representing a period of potential vulnerability to reentrant ventricular arrhythmias. Prolonged TpTe has been associated with increased risk of mortality in congenital and acquired long-QT syndromes, in hypertrophic cardiomyopathy with troponin I mutations, and in patients undergoing primary percutaneous coronary intervention for myocardial infarction. However, there is no information available regarding the potential predictive ability of TpTe for SCD in the general population.
population. We evaluated the association between TpTe and risk of SCD in the general population. We also hypothesized that TpTe is an effective risk marker among subjects with SCD with normal QTc or unmeasurable QTc.

Methods

Study Participants

The Oregon Sudden Unexpected Death Study prospectively identifies cases of SCD from out-of-hospital cardiac arrests occurring among residents of the Portland, Oregon, metropolitan region (population ~1 million).\(^8,18-22\) SCD cases were identified from the emergency medical response system (EMS), the coronal examiner office, and local emergency departments. SCD was defined as a sudden, unexpected, pulseless condition of likely cardiac origin; subjects surviving SCD also were included. If unwitnessed, subjects who were found dead within 24 hours of having last been seen alive and in a normal state of health were included. A diagnosis of SCD was based on a review of available medical records, circumstances of cardiac arrest, and autopsy records when available. Patients with terminal illness, such as cancer, and known noncardiac causes of death, such as pulmonary embolism, cerebrovascular accident, and drug overdose, were excluded. Cases of SCD were compared to controls with CAD from the same geographical area in the same time frame (2002 to 2009). We restricted the analysis to cases and controls aged ≥18 years with availability of resting 12-lead ECGs in sinus rhythm.

Subjects were categorized as having CAD if they had a ≥50% stenosis of a major coronary artery or history of myocardial infarction, coronary artery bypass graft surgery, or percutaneous coronary intervention. Because ≥80% of subjects with SCD have been demonstrated to have significant CAD on autopsy,\(^5\) the control group was required to have significant CAD but no history of SCD. To include controls over the broad spectrum of CAD, these tests also were required to be performed before and unrelated to the cardiac arrest. ECG readers were blinded to case status. The study was approved by the Institutional Review Boards of Cedars-Sinai Medical Center, Oregon Health and Science University, and all participating hospitals and health systems.

Statistical Analysis

SPSS and SAS version 9.1 statistical software were used. Independent-samples t tests and Pearson \(\chi^2\) tests were used for univariate case-control comparisons of continuous and categorical variables, respectively. Additional, exploratory univariate analyses were conducted for 2 clinically relevant subgroups: (1) subjects with normal QTc according to the Rotterdam criteria (men, QTc ≤430 ms; women, QTc ≤450 ms) and (2) subjects with prolonged QRSD due to IVCD. The rationale for these additional analyses was that the QTc value is normal in 1 group and not measurable in the other (because QRSD forms part of the QTc); we hypothesized that TpTe measurement is helpful for these 2 subgroups. Unadjusted odds ratio (OR) estimates were determined for the ECG intervals as well as for LV systolic function. Multiple logistic regression models were used to estimate ORs for SCD associated with TpTe interval, adjusted for variables that were significant in the univariate analyses. ORs presented for TpTe are the estimated increase in odds of SCD associated with a 1-SD increase in the interval, using the SD among controls. To assess the predictive value of TpTe among subjects with normal versus abnormal QTc and among subjects with or without IVCD, we evaluated possible interactions between TpTe and binary variables of QTc and QRSD. Because LV function values were available for approximately half the subjects, this variable was categorized as normal, severe LV systolic dysfunction (ejection fraction ≤35%), and LV function unknown. In addition, a receiver operating characteristic (ROC) curve was produced for each ECG parameter for the entire group to compare the parameter’s ability to predict SCD. Models adjusted for comorbidities (diabetes, obesity, hypertension, and sleep apnea) also were run. Finally, we modeled the ECG parameters as categorical variables (prolonged TpTe >85 ms, QRSD >120 ms, and QTc >430 ms for men and >450 ms for women), adjusting for LV systolic dysfunction and comorbidities. For all analyses, \(P<0.05\) was considered significant.

Results

Univariate Analysis

All Subjects

Among the total 353 cases and 342 controls that met criteria for analysis, age, sex, and history of comorbidities were not significantly different (Table 1). TpTe was significantly associated with SCD, with mean TpTe significantly prolonged in cases compared to controls (\(P<0.0001\)) (Figure 1A, Table 1). Evaluation of the distribution of TpTe in cases versus controls (Figure 1B) demonstrates that beyond a TpTe of ≥85 ms, 72% of subjects were cases, and of ≥95 ms, ≥80% were cases. QTc, QRSD, and TpTe/QT ratio also were significantly prolonged in cases compared to controls (Table 1). Unadjusted OR estimates of significant factors are shown in Table 2.

Subjects With Normal QTc

Among subjects with a normal QTc by Rotterdam study criteria\(^9\) (145 cases and 236 controls), age, sex, and presence of comorbidities were not significantly different between cases and controls (\(P=0.12\)). In this subgroup, TpTe was significantly greater in cases versus controls (83.8 [95% CI, 81.4 to 86.1] versus 74.5 [95% CI, 72.9 to 76.0] ms;
Subjects With IVCD
Among subjects with IVCD (61 cases and 44 controls), all ECG parameters (TpTe, QTc, QRSD, and TpTe/QT ratio) were significantly prolonged in cases versus controls (P=0.0005). TpTe was significantly greater in cases versus controls (98.6 [95% CI, 94.3 to 102.9] versus 79.0 [95% CI, 75.5 to 82.6] ms; P<0.00001). Age, sex, and prevalence of comorbidities were not significantly different (P=0.13).

Multivariable OR Estimates
In a multiple logistic regression model for all cases and controls (n=695), TpTe, QTc, QRSD, and LV systolic dysfunction were included. There was no significant interaction between normal versus prolonged QTc and TpTe (P=0.71). The interaction between normal versus prolonged QRSD and TpTe was statistically significant (P=0.04), and the respective OR of a 1-SD increase in TpTe among these subgroups are presented in Table 3. Lack of significant interaction between TpTe and binary QTc shows that TpTe remains significantly associated with SCD in subjects with normal as well as prolonged QTc. With a 1-SD increase in the TpTe interval, the increase in odds of SCD among subjects with IVCD (OR, 3.49; 95% CI, 2.06 to 5.91) was greater than the increase in odds associated with a 1-SD increase in TpTe among subjects with normal QRSD (OR, 1.96; 95% CI, 1.65 to 2.32) (Table 3). Prolonged QTc (OR, 2.08; 95% CI, 1.45 to 2.96) and severe LV dysfunction (OR, 3.83; 95% CI, 1.88 to 7.78) were strongly associated with SCD in this group.

Sensitivity Analyses
Although diabetes, obesity, hypertension, and sleep apnea were not strongly associated with SCD risk in univariate comparisons, we conducted additional analyses to determine whether they were potential confounders of the association between ECG parameters and SCD risk. TpTe remained a significant predictor of SCD after adjustment for all comorbidities listed in Table 1 (OR, 2.03; 95% CI, 1.70 to 2.42). In addition, we evaluated the predictive ability of TpTe using a cut point of 85 ms (prolonged TpTe). In this separate model using the ECG intervals as categorical variables, a prolonged TpTe increased the risk of SCD (OR, 3.53; 95% CI, 2.41 to 5.18) in all subjects.

ROC Curves
We examined the predictive ability of each ECG parameter separately by plotting ROC curves (Figure 2). The area under the ROC curve for TpTe was 0.73 (95% CI, 0.69 to 0.77), which was significantly better (P=0.042) than the area under the ROC curve for QTc (0.68; 95% CI, 0.64 to 0.72), although these differences were observed at moderate sensitivity and specificity. The ROC curve for QRSD was not significantly different from 0.5, indicating that QRSD did not improve prediction of SCD beyond chance alone (0.53; 95% CI, 0.49 to 0.57).

Discussion
In this population-based study of SCD, TpTe on the resting 12-lead ECG was prolonged in SCD cases compared to controls and was significantly associated with SCD independently of age, sex, QTc, QRSD, and LV dysfunction. Furthermore, TpTe was significantly associated with risk of SCD when QTc could not be used for risk assessment (ie, among SCD cases with normal QTc or prolonged QRSD because of IVCD/block). It is important to recognize that significant differences in the TpTe interval were identified between 2 groups of subjects who had significant heart disease (controls also were required to have significant CAD).

There are findings from the bench that link TpTe to mechanisms of ventricular arrhythmia. Using a canine myocardial wedge preparation model, Antzelevitch and coworkers26,27 explored the genesis of TpTe as well as the potential mechanisms that link TpTe prolongation to increased risk of
ventricular arrhythmogenesis. There are 3 electrophysiologically distinct cell types identifiable in the ventricular myocardium: the endocardial, epicardial, and subendocardial M cells (Masonic midmyocardial Moe cells). During bradycardia or because of a repolarization-prolonging insult, the action potential of the M cells is more vulnerable to prolongation compared with the other 2 cell types,12 likely because of larger late-sodium and sodium/calcium exchange currents and a weaker, slowly activating delayed rectifier current.28 TpTe corresponds with transmural dispersion of repolarization in the ventricular myocardium, a period during which the epicardium has repolarized and is fully excitable, but the M cells are still in the process of repolarization and are vulnerable to the occurrence of early afterdepolarizations.29,30 If conditions are favorable, these early afterdepolarizations can lead to reentry and its perpetuation, resulting in polymorphic ventricular tachycardia or ventricular fibrillation. Hence, a prolonged TpTe likely corresponds to an extended vulnerable period and given the right conditions, could increase risk of ventricular arrhythmogenesis.13,31–33 Others have suggested that abnormal transmural dispersion of repolarization underlies ventricular arrhythmogenesis in Brugada syndrome,34 in patients undergoing primary percutaneous intervention for acute myocardial infarction,17 in hypertrophic cardiomyopathy with troponin I mutations,16 and in short-QT and long-QT syndromes.15,35 Lubinski et al16 observed that patients with CAD and inducible ventricular tachycardia had a higher TpTe (74±14 versus 63±16 ms; P<0.004) and TpTe/QT ratio

Figure 1. A, Box plot of the distribution of TpTe among cases and controls. B, Bar diagram of the distribution of TpTe among cases and controls showing relative clustering of cases toward the higher values of TpTe; above the interval range of 95 to 104.9 ms of TpTe, ≥80% are cases. TpTe indicates Tpeak-to-Tend interval.
expressed as a percentage (21±4% versus 17±3%; P=0.02) than those who survived myocardial infarction without inducible ventricular tachycardia. To our knowledge, the association between prolonged TpTe and SCD among subjects in the community is a novel finding.

What absolute value of TpTe should be considered abnormally prolonged? TpTe values >100 ms during acute myocardial infarction and >113 ms in the setting of acquired bradyarrhythmias have been reported previously as “high risk” in the literature. In the present study, the majority (90.4%) of subjects with a TpTe value >100 ms were cases. Our findings are comparable with a smaller study of patients with acute myocardial infarction that evaluated overall mortality (not SCD) in which 10 of 11 patients who died had TpTe >100 ms. However, mean TpTe in the present cases was lower at 89.4±16.9 ms (95% CI, 87.7 to 91.2). In our study, TpTe value of ≥100 ms had a specificity of 97% but a sensitivity of only 27%. Hence, the cutoff for TpTe for SCD risk prediction in the community may be lower than values published earlier. This fact is supported from data by Lubinski et al, who reported that the mean TpTe observed in subjects with CAD and inducible ventricular tachycardia was relatively low (74±14 ms). However, further studies are needed for establishing cutoffs for patients at risk of SCD in the community.

A disproportionate increase in transmural dispersion of repolarization relative to the total duration of repolarization (the TpTe/QT ratio) also has been found to have proarrhythmic effects. TpTe/QT stays relatively constant in a narrow range of 0.17 to 0.23 across several species from guinea pig to the cow, may play a role in electric stability of the myocardium, and could be especially useful in eliminating effects of heart rate as well as interindividual variations in QT interval. In healthy adults, average TpTe/QT is 0.21 in the precordial ECG leads and has been proposed as a marker of arrhythmogenesis for long-QT syndrome and hypertrophic cardiomyopathy with K183del mutation in the cTnI gene. In the present study, mean TpTe/QT was significantly greater among cases than among controls in the entire study population and the subgroups analyzed.

Limitations
As is the case for QTc, the difficulty in locating Tend when the T-wave morphology is flat or multiphasic may affect TpTe measurements. However, readers were blinded, so any such errors would be unrelated to case status. Therefore, any bias introduced by this error would be unlikely to affect the validity of the findings. LV function assessment was available only in a subset. This is not unexpected for a community-based study because 40% to 50% of patients experience SCD as an unfortunate first manifestation of their illness and are unlikely to have undergone cardiac investigations. Finally, because we conducted subgroup analyses, it is possible that our family-wise type I error was somewhat inflated.

Conclusions
TpTe was significantly and independently associated with increased odds of SCD among subjects with CAD. TpTe measurement may extend the value of repolarization beyond the QTc, particularly in situations where QTc is
either normal or not valid because of prolongation of QRS duration. Prolonged TpTe has potential for enhancement of either normal or not valid because of prolongation of repolarization time in the intact heart? Repolarization gradients in the intact heart.


**CLINICAL PERSPECTIVE**

The interval from the peak to the end of the T wave (TpTe) on the 12-lead ECG is a measure of transmural dispersion of repolarization in the left ventricle and a possible marker of ventricular arrhythmogenesis. We evaluated the association between TpTe and risk of sudden cardiac death (SCD) in the general population. TpTe interval was significantly prolonged in cases compared to controls. Cases of SCD also had a longer QRS duration and corrected QT interval than controls. TpTe remained a significant predictor of SCD after adjustment for age, sex, other ECG intervals, and left ventricular systolic dysfunction. The predictive value of TpTe was higher among subjects with unmeasurable QT because of prolongation of QRS duration compared to subjects with normal QRS duration. Furthermore, TpTe was associated with the risk of SCD in subjects with a normal QT interval. TpTe is likely to be a novel marker of SCD in the community, with particular utility when the corrected QT interval cannot be measured. These findings are likely to contribute to the enhancement of SCD risk stratification and merit evaluation in additional populations.
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