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Tpeak-to-Tend interval corrected for heart rate: A more precise measure of increased sudden death risk?:

Towards an improved sudden death risk prediction

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Abstract

Background—The Tpeak-to-Tend interval (Tpe) on the 12-lead electrocardiogram (ECG) predicts increased risk of sudden cardiac arrest (SCA). There is controversy on whether Tpe would be more useful if corrected for heart rate (Tpec).

Objective—We evaluate if the predictive value of Tpe for SCA improves with heart rate correction and determine an optimal cut-off value for Tpec in the context of SCA risk.

Methods—Cases of SCA (n=628; mean age 66.4±14.5years; 66.2% males) from the Oregon Sudden Unexpected Death Study with an archived ECG available prior and unrelated to the SCA event, were analyzed. Comparisons were made with control subjects (n=819; mean age 66.7±11.5years; 68.2% males). The Tpe interval was corrected for heart rate using Bazett (TpecBa) and Fridericia (TpecFd) formulae, and the predictive value of Tpec for SCA was evaluated in logistic regression models.

Results—The area-under-curve (AUC) for Tpec predicting SCA improved with both correction formulae. Tpec using the Bazett and Fridericia formulae were shown to have an AUC of 0.695 and 0.672 respectively compared to a baseline of 0.601 with an uncorrected Tpe. TpecBa >90ms was predictive of SCA independent of age, gender, comorbidities, QRS duration, QTc and severely reduced left ventricular ejection fraction [LVEF 35%; OR 2.8 (95% CI, 1.92 to 4.17; p<0.0001)].

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Conclusion—Correcting the Tpe for heart rate, using either the Bazett or Fridericia formulae, improved the independent predictive value of this marker for assessment of SCA risk. Prolongation of TpecBa beyond 90ms was associated with a nearly 3-fold increased risk of SCA.

Keywords

Death; sudden cardiac; cardiac arrest; risk; stratification; prediction; prevention

Introduction

Sudden cardiac arrest (SCA) remains a difficult clinical conundrum. It is the leading cause of death in the United States, accounting for up to 50% of cardiovascular deaths with an estimated global burden of 4–5 million per year.¹ Our best preventive strategy to date remains the implantable cardioverter-defibrillator (ICD) for which, based on current guidelines, only a fraction of SCA victims are eligible and an even smaller proportion of them actually receive the device.² More importantly, among those with an ICD, a substantial number will never receive an appropriate therapy.³ Hence the ability to improve SCA risk stratification based on simple clinical tools such as the 12-lead electrocardiogram (ECG) could be of significant importance.

Repolarization abnormalities on the resting 12-lead ECG have garnered considerable interest, and the Tpeak-to-Tend interval (Tpe) has been shown to be a useful SCA risk predictive tool especially when the QRS duration (QRSD) is prolonged.⁴ Prolonged Tpe reflects abnormal dispersion of ventricular repolarization, and is associated with increased risk of ventricular arrhythmogenesis.^{5–7} This marker has been associated with increased risk of cardiovascular morbidity and mortality in the general population as well as other subsets of patients.^{9–12} There are differing opinions regarding whether the Tpe is rate-dependent.^{13,14} In this regard, studies have shown the corrected Tpe (Tpec) to be superior to the Tpe in predicting cardiovascular outcomes among patients with systolic cardiomyopathy^{10,11} but there is a lack of information regarding the specific association of Tpec with increased SCA risk.

The objective of this study was to evaluate whether correcting Tpe for heart rate would improve the predictive value of this marker for increased SCA risk in the community. If this was the case, we also sought to determine the optimal method of correction and cut-off value.

Methods

We identified study subjects from the Oregon Sudden Unexpected Death Study (Oregon SUDS) which prospectively identifies cases of sudden cardiac arrest (SCA) from out-of-hospital cardiac arrests in the Portland, Oregon, metropolitan region (population of approximately 1 million). The details of our methodology have been published previously.^{15–16} SCA cases were identified from multiple sources, including emergency medical services, the medical examiner's office and local emergency departments. A comprehensive process of in-house adjudication by 3 physicians is then carried out to determine cases meeting criteria for SCA. SCA was defined as a sudden, unexpected,

pulseless condition of likely cardiac origin, including survivors. If unwitnessed, subjects had to be last seen alive in their usual state of health. Control subjects are ascertained from the same geographic region and the majority (~80%) have significant coronary artery disease (CAD). Enrolling a large proportion of control subjects with prevalent CAD allows for efficient control for history of CAD in analysis, making any differences that are identified, more specific for SCA. Subjects were categorized as having CAD if they had a ≥50% stenosis of an epicardial coronary artery or history of myocardial infarction (MI), coronary bypass graft surgery or percutaneous coronary intervention. Controls with CAD were identified from patients undergoing coronary angiography at one of the region's major participating health systems, from patients transported by the region's EMS system with symptoms suggestive of coronary ischemia, and from patients with and without stable CAD enrolled in a regional health maintenance organization.

For the current analysis, SCA cases and controls ascertained from February 2002 till January 2015 were examined. The analysis was restricted to cases and controls aged ≥18 years with availability of an archived resting 12-lead ECG. For cases, this archived ECG had to be performed prior and unrelated to the SCA event and for controls, the ECG was obtained at the time of the study enrollment visit or from clinic or hospital visits unrelated to the study. 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.

Electrocardiographic measurements

A standard 12-lead ECG tracing at 25 mm/s paper speed and 10 mm/mV amplitude was used for analysis. Heart rate and QRS duration were obtained from the automated ECG report. Measurements of the QT, RR and Tpe intervals were conducted using digital semi-automated onscreen software (DataIn Measure; DataInf GmbH; Tübingen, Germany). Only subjects with sinus rhythm on the ECG were included in this analysis.

Two trained physicians performed separate, blinded measurements on a subset of ECGs and we have previously demonstrated high intra-class correlation coefficients for the intervals measured.¹⁶ Tpe was measured in milliseconds from the peak of the T wave to the end of the T wave in V5, followed by leads V4 and V6 if lead V5 was not suitable.^{4,12,17} If the T-wave amplitude was <1.5 mm in a particular lead, that lead was excluded from analysis. The QT interval was measured in milliseconds from the earliest onset of the QRS complex to the end of the T wave. The end of the T wave was defined as the return of the descending limb to the TP baseline when not followed by a U wave or if distinct from the following U wave. If there was a terminal low-amplitude signal interrupting the terminal portion of the T wave, the downslope of the T wave was extended by drawing a tangent to the steepest proportion of the downslope until it crosses the TP segment to determine the end of the T wave.^{18,19} The QT interval was then corrected for heart rate using the Bazett formula²⁰ (QT/RR) (QT_c) while the Tpe interval was corrected using both the Bazett and Fridericia²¹ ($QT/RR^{1/3}$) (Tpe_c) formulae. The RR interval was measured in seconds and taken as the immediate RR interval preceding the Tpe from the same lead in which the Tpe interval was measured. For the sake of simplicity, we have taken the units of Tpe_c to be ms since its

correction parallels that of QTc which has been widely accepted as ms¹⁸, recognizing that these may not be mathematically equivalent.

Prolonged QTc was defined as ≥ 450 ms for men and ≥ 460 ms for women and prolonged QRSD was defined as ≥ 120 ms.¹⁸ Conduction abnormalities including left bundle branch block (LBBB), right bundle branch block (RBBB), incomplete LBBB (ILBBB), incomplete RBBB (IRBBB) and nonspecific intraventricular conduction disturbance (NIVCD) were defined based on published criteria.²²

LVEF was obtained from echocardiograms, left ventricular angiograms or multi-gated acquisition scans that were performed before and unrelated to the SCA event. LVEF was categorized as severely reduced if this measurement was $\leq 35\%$.

Statistical analysis

All analyses were performed using SAS 9.2 (SAS Institute Inc., Cary, NC). Independent-samples *t* tests and Pearson χ^2 tests were used for univariate case-control comparisons of continuous and categorical variables, respectively. For variables with missing values, proportions and *P* values were calculated using the available sample size as the denominator. Multiple logistic regression models were used to estimate the odds ratios for SCA. Several models including all potentially associated variables were analyzed. Values were presented as *n* (%) or mean $\pm$ standard deviation (SD) and a *P* value of ≤ 0.05 was considered significant for all analyses. Receiver operating characteristic (ROC) curves were generated and the area under the curve (AUC) was calculated to compare the performance of the Tpe, TpecBa and TpecFd. The Youden index, calculated as sensitivity + specificity – 1, is a statistical index often used in conjunction with the ROC analysis to compare the diagnostic performance of test values²³. This index was used to determine the optimal cut-off value for TpecBa.

Results

A total of 628 cases and 819 controls were included in this analysis. Cases and controls were comparable in terms of age and gender (mean age of 66.4 ± 14.5 years vs 66.7 ± 11.5 years and with proportion of males at 66.2% vs 68.2%). Their baseline characteristics, comorbidities and ECG parameters are shown in Table 1. The cases had a higher burden of comorbidities such as hypertension and diabetes mellitus compared to controls and were more likely to have conduction abnormalities (44.0% vs 36.1%, $p=0.02$), a higher heart rate (78.0 ± 18.0 bpm vs 67.6 ± 14.4 bpm, $p<0.0001$), a wider QRS duration (101.7 ± 21.1 ms vs 97.9 ± 21.0 , $p=0.002$) and a longer QTc (458.2 ± 41.3 ms vs 427.1 ± 32.9 ms, $p<0.0001$). There were also significantly more subjects with severely reduced LVEF ($\leq 35\%$) as compared to controls (27.0% vs 9.7%, $p<0.0001$). The Tpe and Tpec using either Bazett's (TpecBa) or Fridericia's (TpecFd) formula were all significantly longer in cases compared to controls.

On univariate analysis, Tpe (OR 1.2; 95% CI 1.15–1.31; $p<0.0001$), TpecBa and TpecFd were significantly associated with an increased risk of SCA. For every 10ms increase in TpecBa or TpecFd, there was a 40% increase in the risk of SCA (TpecBa: OR 1.4; 95% CI

1.34–1.52; $p < 0.0001$ and TpecFd: OR 1.4; 95% CI 1.31–1.50; $p < 0.0001$). These results are presented in Table 2.

Using the ROC curve analysis shown in Figure 1, TpecBa demonstrated the highest AUC value associated with SCA in comparison to TpecFd and Tpe (0.695 vs 0.672 vs 0.601 respectively). The cut-off value for TpecBa with the highest Youden index that maximized the combined sensitivity and specificity was 90ms (sensitivity 63.5%, specificity 67.5%).

TpecBa value > 90 ms was significantly associated with an increased risk of SCA independent of age, gender, comorbidities such as hypertension, diabetes mellitus, coronary artery disease, QRSD, QTc and severely reduced LVEF in a multivariate model (OR 2.8; 95% CI 1.92–4.17; $p < 0.0001$) (Table 3).

Discussion

In this community-based study of SCA, prolonged TpecBa or TpecFd was significantly associated with an increased risk of SCA. Correcting the Tpe for heart rate using either the Bazett's (n/RR) or Fridericia's ($n/\sqrt[3]{RR}$) formula improved predictive value for SCA with the TpecBa faring marginally better than TpecFd in this regard. (AUC: TpecBa 0.695; TpecFd 0.672; Tpe 0.601).

The T wave, in large part, is created by currents that flow down voltage gradients that are present on either side of the “M region” (deep subendocardium–midmyocardium) of the left ventricular wall, during phase 2 and phase 3 of the ventricular action potential. The peak of the T wave coincides with full repolarization of the epicardial action potential, and the end of the T wave with repolarization of the M cells. Therefore the Tpe reflects transmural dispersal of repolarization and observed to be a more precise representation of ventricular repolarization as compared to the QT interval^{24–26}; and especially useful in the presence of prolonged QRSD.⁴ An abnormal dispersion of ventricular repolarization denoted by a prolonged Tpe is postulated to represent vulnerable myocardial substrate with varying degrees of refractoriness leading to an increased potential for re-entrant ventricular arrhythmias.^{6–8}

It is interesting to postulate why the Tpec may be a better risk marker for SCA compared to Tpe. One possible explanation may be found in the relationship of resting heart rate and SCA risk. We have previously published,²⁷ and also confirmed in the present analysis, the finding that higher resting heart rate is independently associated with increased risk of SCA (OR 1.3 per 10bpm increase; 95% CI 1.22–1.41, $p < 0.0001$, $n = 1447$). Accounting for heart rate-related risk may contribute to the improved risk prediction observed with Tpec.

Several formulae have been proposed to correct the QT interval for heart rate. Although our findings support the use of the Bazett's formula for adjustment of Tpe, it is important to consider that this most widely used formula was derived from only 39 young patients.²⁰ Furthermore, the Bazett's formula leaves a strong positive residual correlation ($r = 0.32$) while the Fridericia's formula leaves a negative correlation ($r = -0.26$ to -0.32) with heart rate, hence the adjusted QT values may be erroneous at extremes of heart rates.^{29,30} Other correction formulae proposed by Framingham³⁰ and Hodges³¹ have been published to

reduce the effect of rate dependency but since these were studied in a linear regression model for the QT interval, it did not seem logical for them to be used for the correction of Tpe.

It is challenging to determine a meaningful cut-off value for the Tpec. As with any continuous variable that is positively correlated with outcomes, a higher cut-off would be more specific and less sensitive and vice versa for a lower cut-off. An uncorrected Tpe cut-off of 110ms has been recommended from the Women's Health Initiative (WHI) for non-African-American women³²⁴ while other studies looking at a general population or post myocardial infarction patients have suggested a cut-off at 100ms.^{4,33} In the WHI study, the mean TpecBa among the subjects was found to be $85 \pm 11.2\text{ms}$.³² Other authors have found that a TpecBa value of 104ms maximizes the sensitivity and specificity in predicting cardiovascular outcomes in a systolic cardiomyopathy cohort.^{10,11} However, it is important to realize that since this value is derived from a group of patients with cardiomyopathy who may have a higher prevalence of repolarization abnormalities, it may be an over-estimate for utilization in the general population. In addition, the value was determined from an automated ECG analysis program which generates a global Tpe that is often longer than an actual measured Tpe.¹⁸ In our study, Tpe intervals were methodically measured manually and a ROC analysis showed an optimal cut-off value for TpecBa to be 90ms.

Employing this cut-off value, a TpecBa >90ms remained significantly associated with an increased risk of SCA independent of age, gender, hypertension, diabetes mellitus, coronary artery disease, QRSD, QTc and severely impaired LVEF. When we dichotomized QTc (< 450ms for men and < 460ms for women was defined as prolonged), TpecBa >90ms remained associated with an increased SCA risk (OR 3.2; 95% CI 2.16–4.66; $p < 0.001$; $n=657$). A prolonged QTc (OR 3.9; 95% CI 2.61–5.82; $p < 0.0001$) and severely reduced LVEF (OR 3.2; 95% CI 1.90–5.40; $p < 0.0001$) remained positively correlated with the risk of SCA. These results indicate the potential value of using a TpecBa cut-off of >90ms in an SCA risk prediction model.

Limitations

There are several limitations of our study, especially those inherent in community-based studies, which should be considered when interpreting our findings. Clinical data was not universally available among all our study subjects. This is because approximately 40% of subjects who suffer SCA have this condition as the first manifestation of cardiac disease and hence may not have had any prior medical evaluations. For instance, information on LVEF was available in 657 (48.7%) subjects with ECG data available and this reduced the power of our analysis when we included this variable in our model.

As an individual marker, the effect size of Tpec on prediction of SCA risk is modest. However, recent studies clearly indicate that any individual marker (even the left ventricular ejection fraction) is likely to have a modest role, and any real impact on SCA risk stratification will be made via cumulative risk stratification using a combination of multiple markers.^{34,35} In addition, although TpecBa fared marginally better than TpecFd, we cannot determine which method is superior based on our analysis.

We analyzed the ECGs that were available prior and unrelated to the SCA event but did not evaluate sequential ECGs which could have characterized the progression of such repolarization changes. Hence we cannot comment on the temporal effects of a prolonged TpeakBa, and this warrants further investigation.

Conclusion

Correcting the Tpeak-to-Tend interval using the Bazett's formula improved the predictive value of this marker for SCA risk and a cut-off of >90ms was associated with an increased risk of SCA independent of age, gender, comorbidities, QRSD, QTc and severely reduced LVEF. This simple ECG interval can potentially enrich SCA risk stratification and should be prospectively evaluated in risk prediction models.

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Figure 1.

Receiver operating characteristic (ROC) curve comparing Tpe, TpecBa, TpecFd

Tpe denotes Tpeak-to-Tend interval; TpecBa, corrected Tpe using Bazett's formula; TpecFd, corrected Tpe using Fridericia's formula.

Table 1

Baseline characteristics

Baseline characteristics	Cases (n=628)	Controls (n=819)	P value [†]
Age, years	66.4 ± 14.5	66.7 ± 11.5	0.66
Males	416 (66.2%)	559 (68.2%)	0.42
Hypertension	467 (74.4%)	553 (67.5%)	0.005
Diabetes mellitus	255 (40.6%)	209 (25.5%)	<0.0001
Conduction abnormalities	276 (44.0%)	296 (36.1%)	0.02
- LBBB	43 (6.8%)	36 (4.4%)	
- RBBB	24 (3.8%)	41 (5.0%)	
- NIVCD	117 (18.6%)	114 (13.9%)	
- ILBBB/IRBBB	14 (2.2%)	10 (1.2%)	
- Others	78 (12.6%)	95 (11.6%)	
Heart rate, bpm	78.0 ± 18.0	67.6 ± 14.4	<0.0001
QRS duration, ms	101.7 ± 24.1	97.9 ± 21.0	0.002
QTc, ms [‡]	466.1 ± 45.5	432.5 ± 36.3	<0.0001
Tpe, ms	88.3 ± 18.1	82.5 ± 15.6	<0.0001
TpecBa, ms [§]	99.9 ± 20.7	86.9 ± 17.7	<0.0001
TpecFd, ms [§]	96.0 ± 19.0	85.4 ± 16.5	<0.0001
Severely reduced LVEF [¶]	87 (27.0%)	45 (9.7%)	<0.0001

Data are presented as n (%) or mean ± SD.

Bpm denotes beats per minute; ILBBB, incomplete left bundle branch block; IRBBB, incomplete right bundle branch block; LBBB, left bundle branch block; NIVCD, nonspecific intraventricular conduction disturbance; RBBB, right bundle branch block; Tpe, Tpeak-to-Tend interval; TpecBa, corrected Tpeak-to-Tend interval using Bazett's formula ($Tpe/ \sqrt{RR}$); TpecFd, corrected Tpeak-to-Tend interval using Fridericia's ($Tpe/ \sqrt[3]{RR}$) formula; QTc denotes corrected QT interval using Bazett's ($QT/ \sqrt{RR}$) formula.

Conduction abnormalities including LBBB, RBBB, ILBBB, IRBBB and NIVCD were defined based on published criteria. Other conduction abnormalities included first-degree AV block, left anterior or posterior fascicular block or bifascicular block.

[†]Pvalue was derived from Pearson χ^2 for categorical variables and *t* test for continuous variables.

For variables with missing values, proportions and P values were calculated using the non-missing data as the denominator.

[‡]Information on QTc was available in 561 cases and 754 controls.

[§]Information on TpecBa and TpecFd was available in 588 cases and 762 controls.

[¶]Information on LVEF was available in 322 cases and 475 controls; Severely reduced LVEF was defined as $\leq 35\%$

Table 2

Univariate analysis for Tpe, TpecBa and TpecFd

	OR (95% CI)[†]	P value
Tpe	1.2 (1.15–1.31)	<0.0001
TpecBa [‡]	1.4 (1.34–1.52)	<0.0001
TpecFd [‡]	1.4 (1.31–1.50)	<0.0001

Tpe denotes Tpeak-to-Tend interval; TpecBa, corrected Tpe using Bazett's formula; TpecFd, corrected Tpe using Fridericia's formula.

[†]OR (95% CI) presented for every 10ms increase in the interval of interest

[‡]Information on TpecBa and TpecFd was available in 588 cases and 762 controls.

Table 3

Multivariable analysis for TpecBa

	TpecBa[†]	P value	TpecBa >90ms	P value
Model 1 [‡]	1.4 (1.34–1.52)	<0.0001	3.7 (2.90–4.63)	<0.0001
Model 2 [§]	1.3 (1.18–1.36)	<0.0001	2.5 (1.91–3.25)	<0.0001
Model 3 [¶]	1.3 (1.21–1.48)	<0.0001	2.8 (1.92–4.17)	<0.0001

TpecBa denotes corrected Tpeak-to-Tend interval using Bazett's formula

[†]OR (95% CI) presented for every 10ms increase in TpecBa

[‡]Model 1 (n=1350) covariates: age, sex, hypertension, diabetes mellitus and coronary artery disease

[§]Model 2 (n=1220) covariates: age, sex, hypertension, diabetes mellitus, coronary artery disease, QRS duration (QRSD) and corrected QT (QTc)

[¶]Model 3 (n=657) covariates: age, gender, hypertension, diabetes mellitus, coronary artery disease, QRSD, QTc and severely reduced left ventricular ejection fraction (LVEF <35%)