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RESEARCH ARTICLE

A NOVEL ELECTROCARDIOGRAPHIC ENIGMA: THE MEASUREMENT TECHNIQUE, INTERPRETATION OF THE TP-E/QT RATIO AND ITS DIAGNOSTIC USE IN MAKING CLINICAL DECISIONS

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ABSTRACT

In recent years, many ventricular repolarization markers on 12-derivation body surface ECGs have started to be used in various clinical conditions to predict malignant ventricular arrhythmias. Currently, QT dispersion is still the most commonly used evaluation method among these parameters. The failure to accurately identify the QRS complex and the T wave due to a variety of reasons has led to a search for different methods of assessing the repolarization period. However, the dispersion analyses of these new repolarization parameters failed to provide a more accurate diagnostic value than typical QT dispersion, and in some cases, it was not even found to be correlated with QT dispersion. Recent studies have shown that the Tp-e/QT ratio provides more accurate predictive data about ventricular arrhythmias than the measurement of QT, QTc, and the Tp-e interval and that it is not influenced by the variability of the heart rate. This review attempted to perform a thorough evaluation of the Tp-e/QT ratio that has started to be used more frequently in recent years.

INTRODUCTION

The markers of ventricular repolarization heterogeneity that are calculated electrocardiographically are appealing diagnosis and assessment methods for clinicians because they are relatively easy to use, cheap, and also non-invasive. The failure to accurately identify the QRS complex and the T wave has led to a search for different methods to assess the repolarization period (1). In this review, the measurement techniques and problems associated with the ECG parameter QT dispersion that has inspired the most clinical research to this day, the Tp-e/QT ratio that has started to be used more frequently in recent years, and the clinical areas it has started to be used in have been discussed.

The Definition of QT Dispersion and Its Measurement Methods

It is known that ventricular repolarization may differ between the basal electrocardiography (ECG) derivations and that the difference between the repolarization durations on derivations called QT dispersion (QTD) could predict the risk for arrhythmia in patients with increasing QT dispersion (1,2). QT dispersion (QTD) (the maximum QT interval-minimum QT interval) is regarded as a crude and approximate measurement of abnormalities of ventricular repolarization (3). It has been reported that increased QT dispersion is associated with severe arrhythmias and a risk for sudden death in many patients and disease groups such as patients with organic heart diseases when compared to healthy individuals, and that it has a prognostic importance (2-4,5).

The difference between the longest QT (Qtmax) interval and the shortest QT (QTmin) interval calculated on 12-derivation ECG is called QT dispersion (3). Increased QTd; is an indicator of significantly increased ventricular repolarization variability, it is a true risk for arrhythmia and can cause sudden death (6). The QT interval is measured on the derivation with the longest QT interval among the derivations where the end of the T wave is distinct. The most accurate results are obtained from derivations DII, V5, and V6 (7). If the T-wave is followed by a U wave, wide U waves that joined the T wave (> 1mm) should also be included in the calculation. Small U waves separate from T waves should be excluded. The maximum slope intercept method is used to identify the end of the T wave (8) (Figure 1).

The QT interval is defined as the interval between the start of the QRS complex and the end of the T wave. The maximum slope intercept method takes the end of the T wave as the interception of the isoelectric line and the tangent line drawn from the maximum down slope (Figure 1).

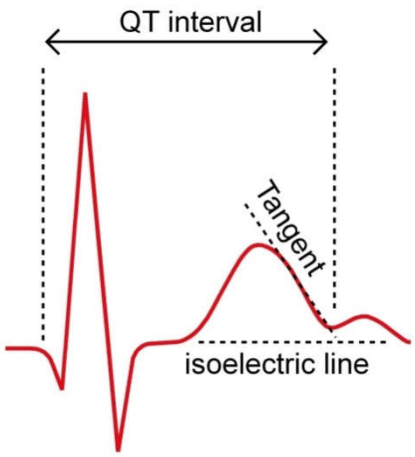

Figure 1 Maximum Slope Intercept Method

In the presence of a notched T wave , the QT interval is calculated using the tangent line drawn on top of the interception point of the start of QRS and the isoelectric line and the maximum slope of the second notch (Figure 2).

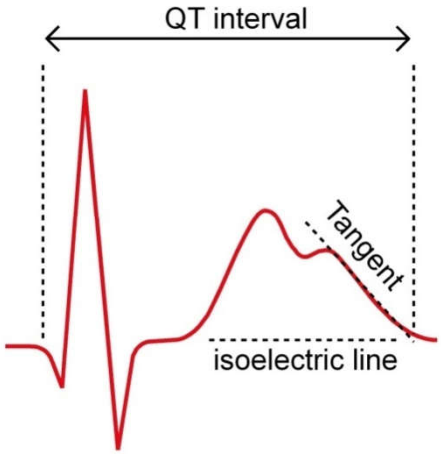

Figure 2 Maximum Slope Intercept Method In the Presence of a Notched T Wave

Before calculating QTd the corrected QT (QTc) distance should be measured. The most common formula used for this is the Bazzett's Formula: QTc = QT /√ R-R interval (7) (Figure 3).It is most useful in correcting heart rates higher than 100/min, and least useful in heart rates under 60/min, but it provides adequate correction for heart rates between 60 - 100/min (8).

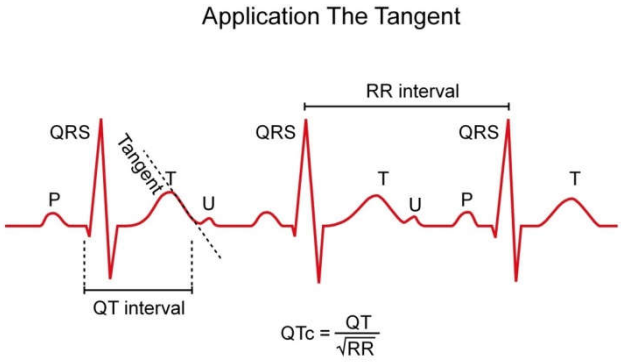

Figure 3 Bazzett's Formula

The other formulas used to calculate the QTc interval other than the Bazzett's formula are (7, 9, 10):

- The Framingham Formula: QTc= QT + 0.154X[(1-RR(second)].
- The Fridericia Formula: QTc= QT / $^{3}\sqrt{}$ R-R).
- The Hodges Formula: QTc= QT + 1.75 X (Heart rate-60)
- Strength Equation Formula: QTc = 453.65 × RR/3.02
- The Van de Water Formula: QTc = QT - 0.087 (RR - 1000)
- The Matsunaga Formula: QTc = log(600) QT/(logRR)
- The Kawataki Formula: QTc = QT/RR ($^{0.25)}$
- The Mayeda Formula: QTc = QT/RR × 0.604
- The Larsen and Skulason Formula: QTc = QT + 0.125 × [1 – RR(second)]
- Schlamowitz Formula: QTc = QT + 0.205 × [1 – RR(second)]
- The Wohlfart Formula: QTc = QT + 1.23 × (HR - 60)
- The Boudolas Formula: QTc= QT + 2.0 × (HR - 60)
- The Sagie Formula: QTc = QT + 0.154 × [1 – RR(second)]
- The Malik Formula: QTc = QT/RR × 0.371
- The Lecocq Formula: QTc = QT/RR $^{(0.314)}$
- The Sarma Formula: QTc= QT (RR)$^{1/2}$

If the heart rate is outside the range of 60-100/min the Frederica and the Framingham formulas are the most appropriate and they should be used (8). However, the Hodges Formula has the best approximation during sleep (9).

The QTc values regarded as normal, borderline, and prolonged in men and women are presented in Table 1 (7).

Table 1

	Female (ms)	Male (ms)
Normal	<450	<430
Borderline	451-470	431-450
Prolonged	>470	>450

QT dispersion can be defined as a parameter proposed as an indicator of the spatial dispersion of ventricular recovery times that was suggested to differentiate a myocardium that manifests non-homogeneous conduction from a myocardium that manifests homogeneous conduction (11). It is difficult to determine the normal and abnormal ranges of QT dispersion with certainty. The most important reason behind this can be shown as the wide range of normal values identified in numerous studies (10-71,7 millisecond) and the overlap with values regarded as abnormal (3,12). Surawicz B. has reported that the upper limit of QT dispersion is 65 ms in normal healthy individuals (13). Çelik T. *et al*. have reported that QT dispersion is a crude and approximate measurement of myocardial repolarization abnormalities and that all the values proposed as the upper limit in healthy individuals are unreliable, and that therefore it is possible that only the abnormal QT dispersion values (> 100 millisecond) outside the error margin of calculations could have clinical importance in showing repolarization abnormality (11).

The failure to identify electrocardiographic parameters adequately and reach a consensus about the values identified due to a variety of reasons have led to a search for a different assessment method for the repolarization period (1). JT (the interval between the end of the QRS complex and the end of the T wave), QTapex (the interval between the start of the QRS complex and the apex of the T wave), Tend (the interval between the apex of the T wave and the end of the T wave), T

wave area (the total area below the J point and the end of the T wave) can be presented as examples of this search (14). However, these novel repolarization parameters were not more accurate than conventional QT dispersion in assessing dispersion and in some cases, they did not correlate with QT dispersion (14, 15).

In recent studies, it has been suggested that the Tp-e/QT ratio provides more accurate predictive data about arrhythmias than the measurement of QT, QTc and the Tp-e intervals and that it is not influenced by heart rate variables (16). In this review, we attempted to analyze the measurement technique, interpretation of the Tp-e/QT ratio and its diagnostic use in making clinical decisions in different diseases where the Tp-e/QT ratio is used as an indicator of arrhythmia.

Cellular basis of T wave and Tp-e interval

It is now well recognized that ventricular myocardium is electrically a heterogeneous structure, comprised of 3 distinct myocardial cell types-epicardial, endocardial, and midmyocardial M cells. The M cells—Masonic Midmyocardial Moe cells-are located in subendocardial layer and characterized by the ability of their action potential to prolong more than that of epicardial or endocardial cell in response to slowing of rate or in response to agents that prolong the action potential(16). Despite the fact that these myocytes are morphologically similar, they exhibit different electrophysiological characteristics. Midmyocardial M cells have typically the longest action potential duration(APD) followed by endocardial and epicardial cells. The ionic basis for the features of M cells that distinguish them from the epicardium and endocardium includes the presence of a smaller slowly activating delayed rectifier inward potassium current (I_{Ks}) but a larger late inward sodium I_{Na}. On the other hand, rapidly activating delayed rectifier inward potassium current (I_{Kr}), the ionic target by most APD-prolonging agents, is similar in density across the ventricular wall. Therefore, the difference in the I_{Ks}:I_{Kr} ratio among three transmural cell types plays an important role in transmural dispersion of repolarization(TDR)(17). The earliest completion of repolarization occurs in the epicardial cells. The peak of T wave represents the end of the epicardial action potential, and the end of T wave represents the end of the midmyocardial action potential. Therefore, Tp-e interval is a reflection of TDR(18). Also, some studies have reported that an increase in the Tp-e interval could become a major index for predicting ventricular tachyarrhythmia and cardiovascular mortality(19-22).

Measurement Methods and Definition of the Tp-e/QT Ratio

It has been claimed that the ratio of the Tp-e interval to the QT interval is not influenced by fluctuations in the heart rate and that it is more reliable than calculating QT, QTc, and the Tp-e interval in showing ventricular repolarization dispersion and therefore the predisposition to arrhythmia (16, 23). Gupta *et al*. reported that not only the QT interval but also the Tp-e interval increases linearly with the increase in body mass and this observation strongly suggests that as the body weight increases, there is an increase in TDR. However, despite of the dynamic changes in this parameters, the Tp-e/QT ratio remains relatively constant, within a very narrow range of values from 0.17 to 0.23(16). Besides this, changes in heart rate(HR) may alter the Tp-e interval. At a different HR, the changes in Tp-e and QT interval occur in a proportional and parallel fashion to the effect that the Tp-e/QT ratio remains constant. However, despite the changes in HR, the Tp-e/QT ratio remained relatively constant between a narrow range of values between 0.15 to 0.25 with a median of 0.21 and a mean of 0.21 ± 0.003(16).

The Tp-e is obtained from the difference between QT interval and QT peak interval; measurement is from the beginning of the QRS until the peak of the T-wave (Figure 4). In case of negative or biphasic T waves, QT peak is measured to the nadir of the T-wave. T waves smaller than 1.5 mm in amplitude are not measured.

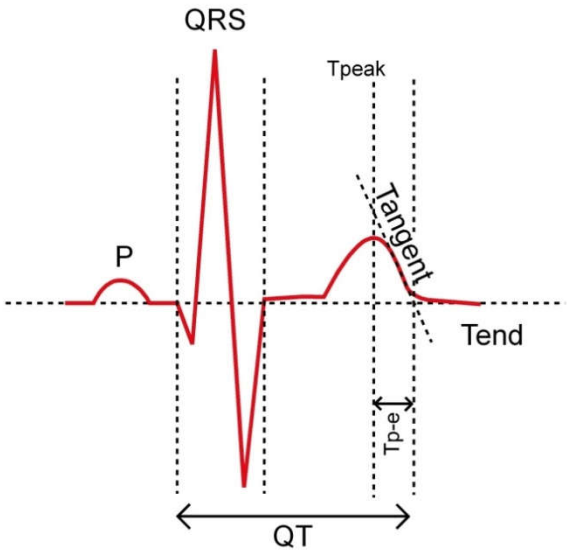

Figure 4 The Schematic Presentation of the Measurement of the Tp-Te and QT intervals

Clinical conditions where the Tp-Te/QT Ratio Can Be Used as a Predictor of Ventricular Arrhythmia:

Cardiovascular Diseases: Day *et al*. were the first to report that the increase of QT dispersion indicates risk for arrhythmia (2). Van de Loo A *et al*. have reported that QT dispersion increases in acute myocardial infarction and that patients with relatively higher QT dispersion have a higher risk of ventricular fibrillation within the first 24 hours (24). It has been reported that the Tp-Te/QT measurements are observed high in patients with organic cardiac disorders such as acute myocardial infarction in addition to diseases with a high risk for arrhythmias such as long QT syndrome, short QT syndrome and Brugada syndrome and that these values can reliably predict predisposition to malignant ventricular arrhythmias (16). In parallel, there are studies reporting that the Tp-Te/QT ratio is higher in cases with coronary slow flow, coronary artery ectasia, or cardiac syndrome X that are regarded as variants of ischemic heart disease than it is in the normal population, and that these values can be used as a novel electrocardiographic index of arrhythmogenicity (25-27).

It was reported that the Tp-Te/QT ratio was significantly increased in mitral valve prolapse cases by Yontar OC *et al*. and in aortic stenosis cases by Yayla C *et al*., they also stated that the Tp-Te/QT ratio was positively correlated with the increase in the average aortic gradient and that Tp-Te/QT is an independent predictor of severe aortic stenosis (28, 29).

It has been reported that the Tp-Te/QTc values were calculated high and that a predisposition to ventricular arrhythmia was identified in cases with arrhythmogenic right ventricular dysplasia where myocytes in the right ventricular wall are

gradually replaced by fibrous and adipose tissue and malignant arrhythmias occur frequently and in asymptomatic patients with arrythmogenic right ventricular dysplasia (30, 31). Letsas KP *et al*. demonstrated that cases with early repolarization syndrome are prone to malign ventricular arrhythmias by measuring high Tp-e/QT values on V2 (32).

Diabetes Mellitus and Metabolic Syndrome: Tokatli A *et al*. observed high Tp-Te/QT values in patients with diabetes mellitus, and based on these findings they reported that type II diabetes mellitus increases the predisposition to ventricular arrhythmogenicity (18). It has been reported that higher Tp-Te/QT ratios are observed in patients with metabolic syndrome in comparison to the control group and that these patients could potentially be at higher risk in terms of ventricular arrhythmias (33). Karaagac K *et al*. calculated the effect of the blood pressure rhythm on the Tp-Te/QT ratio in metabolic syndrome patients in cases with dipper and non-dipper hypertension on the basis of the decrease in nocturnal blood pressure values and identified that both parameters were higher in patients with non-dipper hypertension (34).

Cigarette Smoking: In recent years, studies have reported that the Tp-Te/QTc ratio is high in chronic smokers, that these values are directly proportional to the number of cigarettes smoked, and that there also is a positive correlation between being a smoker and inhomogeneous ventricular repolarization (35, 36). Besides this, Ari H. *et al*. have reported that the Tp-Te/QTc values increase in chronic smokers after the administration of the partial α4-β2 nicotinic acetylcholine receptor (nAChR) agonist varenicline which is one of the agents used for smoking cessation and that these values did not change in non-smokers (37).

Obstetrics and Gynecology: Karaagac K *et al*. have reported that the Tp-Te/Qt ratio which can also show autonomic dysfunction is independent of changes in the heart rate is observed high in patients with polycystic ovary syndrome and that it could predict the heterogenicity of cardiac repolarization (38). Tanindi A *et al*. calculated the Tp-Te/QT ratio in pregnant cases and they reported that these values increased during the third trimester and that this could predict predisposition to ventricular arrhythmia (39).

Obstructive Sleep Apnea: A study conducted on cases of obstructive sleep apnea has demonstrated that the Tp-Te/QTc ratio of moderate and severe cases was measured high and that these values were positively correlated with the apnea-hypopnea index (40).

Sepsis: In another recent study, the Tp-Te/QTc values were measured higher in pediatric intensive care patients being followed for sepsis than in the control group, and it was determined that these ECG parameters are valuable instruments for predicting mortality among sepsis patients in intensive care (41).

Chronic Kidney Diseases: Karaagac K *et al*. have reported that Tp-Te/QTc can be used to identify ventricular electrical instability in chronic renal failure (CFR) patients that receive hemodialysis and that the Tp-e/QT ratio is calculated higher in this population than it is in the control group (42).

Psychiatric Disorders: By calculating the Tp-e, QT, and QTc intervals and the Tp-e/QT ratio, Yontar OC *et al*. assessed the effect of olanzapine a second-generation antipsychotic used in the treatment of schizophrenia because it is less likely to trigger arrhythmias than first-generation antipsychotics and reported that olanzapine usage did not alter the QT and QTc values, but that it increased the Tp-e/QT measurements substantially and that it could be an indicator of the risk for arrhythmia in this patient group (43). It appears that studies that evaluate the risk for arrhythmia using the Tp-e/QT ratio in cardiac and non-cardiac fields will increasingly continue to be conducted. However, on the other hand, determining the predisposition to ventricular arrhythmias in cardiovascular or systemic diseases using body surface ECG, and also basing the management of treatment on these findings has become no more than an interesting research topic. Studies that clinicians have conducted so far using the Tp-e/QT ratio have mostly contributed to the reliability of this new method rather than enlightening its status as an indicator of ventricular arrhythmia in clinical conditions previously shown to be predisposed to arrhythmias by different methods. Besides this, it is needed to reliably establish the predictive value of this ECG parameter for it to become a non-invasive method used to reduce morbidity and mortality and to provide useful information about the effectiveness of treatment in some cardiovascular or systemic diseases that are known to or are suspected to predispose to ventricular arrhythmias by means of wide-scope and long-term studies.

RESULT

Malignant ventricular arrhythmias are among the most common causes of death. In healthy asymptomatic individuals, it may occur isolated or together with pathologies of other systems. It is possible to predict future ventricular arrhythmias using body surface ECGs by using ventricular repolarization markers. These parameters could be useful for forming a more adequate basis for patient risk classification and medical management. Assessments performed so far using the QT dispersion especially have yielded beneficial results in predicting predisposition to arrhythmia in some clinical conditions, however, due to technical problems, specialists were unable to reach a consensus. Besides this, it has been claimed that the Tp-e/QT ratio is not altered by fluctuations in the heart rate and that it is more reliable in demonstrating predisposition to ventricular arrhythmia than other known calculations (16, 23). Gupta P *et al*., standardized the Tp-e/QT ratio as 0.21± 0.03 based on measurements obtained from the V6 derivation that reflects the left ventricle transmural axis best in healthy individuals (16). However, the overlap of normal Tp-e/QT ratios (0.17 ± 0.02 - 0.27 ± 0.06 ms) and pathological values (0.20 ± 0.03 - 0.30 ± 0.06 ms) has raised questions about this ECG measurement technique (18, 26, 33, 35, 36, 44). Gupta selected the V6 lead which was considered to represent the transmural dispersion ideally for measurements in the group, and claimed that Tp-e / QT ratio of any cycle of would be the TDR of the whole ECG, considering that the ratio would remain constant. However, as any value in the 0.15-0.25 interval, which was defined by Gupta as a narrow range, can be observed in any cycle of 12-lead ECG trace of a healthy individual, it can also be observed in any cycle of the ECG trace of another individual who was considered to have increased TDR. Considering the facts that the measured values are in terms of milliseconds (ms) and the values obtained in numerous studies and accepted as normal and pathological overlap, it can be said with ease that the Tp-e / QT ratio of the provided numbers cannot meet the expectation of normal value standardization. It is obvious that whether the QT and Tp-e distances measured for every beat

will not increase or decrease at the same rate, that even the ratio of Tp-e / QT between beats in the same lead would differ and that this situation needs a further formulation encompassing all derivations (at least all chest derivations) and all QRS complexes. In addition, to overcome reliability issues that may develop related to this measurement technique and to increase its applicability, the normal values should be determined and standardized in comprehensive studies on healthy individuals and professional athletes in relation to gender, high altitudes, race, age and the body-mass index.

Despite the problems discussed, it seems as though the Tp-e/Qt ratio that has started to be used in literature as a new electrocardiographic marker by clinicians that are looking for a simple and rapid method to identify predisposition to malignant ventricular arrhythmias will continue to keep the cardiology society busy.

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