REVIEW DERLEME

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Tpeak-Tend Interval and its Derivatives as Indices of Repolarization Dispersion and Arrhythmic Risk: Traditional Review

Repolarizasyon Dağılımı ve Aritmik Risk Göstergeleri Olarak Tpeak-Tend Aralığı ve Türevleri: Geleneksel Derleme

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ABSTRACT Development of life-threatening ventricular arrhythmias is often associated with an increase in the dispersion of ventricular repolarization (DOR), which can be detected by electrocardiographic (ECG) methods. For several decades, there was an active search for ECG markers reflecting the magnitude of DOR and the associated arrhythmic risk. The interval from the peak to the end of the T-wave (Tpe) was found to be the most accurate measure of DOR and a reliable marker of arrhythmic risk in various cardiac disorders. In addition to Tpe interval itself, its derivatives-Tpe dispersion and Tpe/QT ratiowere proposed as arrhythmic risk markers. In this review, several aspects regarding Tpe and its derivatives are discussed: (1) physiological rationale for relationship to DOR and arrhythmic risk, (2) clinical significance for predicting ventricular arrhythmias, and (3) clinical limitations. Based on the experimental, clinical and simulation studies, the review demonstrates that Tpe, dTpe and Tpe/QT ratio are informative concerning both the global and the local DOR. They are significant predictors of arrhythmias associated with increased DOR, and the overall mortality. Besides, Tpe magnitude showed itself as a simple, non-invasive, inexpensive and quick indirect assessment of hemodynamic and volumetric ventricular parameters, the extent and severity of coronary artery stenosis, therapy response and the expected hospital stay. However, the lack of consensus in measurements led to large variations of cut-off values reported by different researchers. The inclusion of Tpe in routine ECG analysis requires further research based on the more unified measurements, including machine learning and artificial intelligence tools.

Keywords: Repolarization dispersion; arrhythmic risk; Tpeak-Tend interval; Tpeak-Tend dispersion; Tpeak-Tend/QT ratio

ÖZET Hayatı tehdit eden ventriküler aritmilerin gelişimi, genellikle elektrokardiyografik (EKG) yöntemlerle tespit edilebilen ventriküler repolarizasyon dispersiyonundaki [dispersion of ventricular repolarization (DOR)] bir artışla ilişkilidir. Onlarca yıl boyunca, DOR'un büyüklüğünü ve ilgili aritmik riski yansıtan EKG belirteçleri için aktif bir araştırma yapılmıştır. T-dalga zirvesinden sonuna kadar olan aralık (Tpe), DOR'un en doğru ölçüsü ve çeşitli kardiyak bozukluklarda güvenilir bir aritmik risk belirteci olarak bulunmuştur. Tpe aralığının kendisine ek olarak, türevleri - Tpe dispersiyonu ve Tpe/QT oranı- aritmik risk belirteçleri olarak önerilmiştir. Bu derlemede, Tpe ve türevlerine ilişkin çeşitli yönler tartışılmaktadır: (1) DOR ve aritmik risk ile ilişki için fizyolojik gerekçe, (2) ventriküler aritmilerin öngörülmesinde klinik önem ve (3) klinik kısıtlamalar. Deneysel, klinik ve simülasyon çalışmalarına dayanarak, bu derleme, Tpe, dTpe ve Tpe/QT oranının hem küresel hem de lokal DOR hakkında bilgilendirici olduğunu göstermektedir. Bunlar, artmış DOR ile ilişkili aritmilerin ve genel mortalitenin önemli öngörücüleridir. Ayrıca Tpe büyüklüğü hemodinamik ve volümetrik ventriküler parametrelerin, koroner arter stenozunun kapsamı ve şiddeti, tedaviye yanıtın ve beklenen hastanede kalış süresinin basit, invaziv olmayan, ucuz ve hızlı bir dolaylı değerlendirmesi olarak kendini göstermiştir. Ancak ölçümlerde fikir birliği olmaması, farklı araştırmacılar tarafından bildirilen eşik değerlerinde büyük farklılıklara yol açmıştır. Tpe'nin rutin EKG analizine dâhil edilmesi, daha birleşik ölçümlere dayanan, makine öğrenimi ve yapay zekâ araçlarını içeren daha fazla araştırma gerektirmektedir.

Anahtar Kelimeler: Repolarizasyon dispersiyonu; aritmik risk; Tpeak-Tend aralığı; Tpeak-Tend dispersiyonu; Tpeak-Tend/QT oranı

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One of the key factors of arrhythmogenic substrate formation is the increased dispersion of ventricular repolarization (DOR), which can be detected by electrocardiographic (ECG) methods.[1] For several decades, a search for ECG markers reflecting the magnitude of DOR and the associated arrhythmic risk remains a major challenge in modern day electrocardiology.

To date, the interval from the peak to the end of ECG T-wave (Tpe) was suggested to be the most accurate measure of DOR and a reliable ECG predictor of arrhythmic risk and cardiovascular death.[2] Besides Tpe interval itself, its derivatives such as Tpe/QT ratio and Tpe dispersion were found to be useful instruments for prognosis of arrhythmias.[3-5]

In this review based on the results of experimental, clinical and simulation studies, the following aspects regarding Tpe and its derivatives are discussed: (1) physiological rationale for relationship to DOR and arrhythmic risk, (2) clinical significance for predicting ventricular arrhythmias, and (3) clinical limitations.

TPE: PHYSIOLOGICAL RATIONALE

A quarter of century ago, *in vitro* studies by Yan and Antzelevitch performed using arterially-perfused canine ventricular wedge preparations showed that repolarization of epicardium (the shortest action potentials) coincided with the peak of the T-wave, and the repolarization of the M-cells (midmyocardial myocites with longest action potentials) coincided with the end of the T-wave, so that Tpe interval reflected the magnitude of the transmural DOR.[6] In the same study, the increase in the transmural DOR and Tpe interval under the QT prolonging drugs administration was associated with extrasystoles and the development of torsade de pointes.[6] Thereby, Tpe interval was introduced by Yan and Antzelevitch as a measure of transmural DOR and as a potential ECG predictor of arrhythmic risk.[6]

In the whole heart, M-cells were poorly detected, and along with the transmural, the anterior-posterior, left-to-right and apicobasal repolarization gradients with the magnitudes exceeding the magnitude of the transmural one were revealed.[7,8] *In vivo* and *in silico* studies showed that in the whole heart T-wave peak coincides not with full epicardial repolarization but rather with the most earlier end of repolarization, whereas T-wave end coincides with the most late end of repolarization, so that *in vivo* Tpe is an index for the global DOR (Figure 1).[7-9]

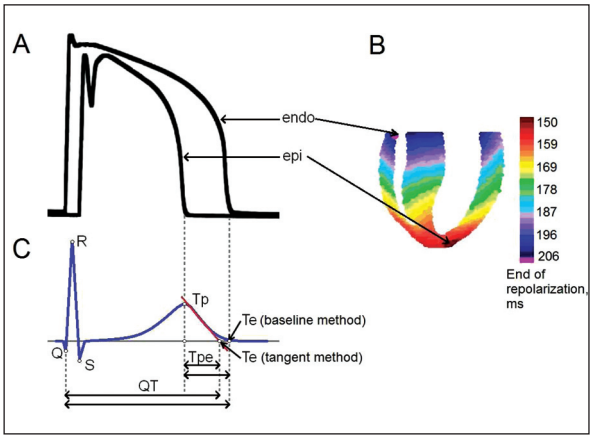

FIGURE 1: The schematic relationship between ventricular action potentials, the end-of-repolarization sequence and T-wave morphology.
A, the morphology and the relationship in time between the shortest (epicardial, epi) and the longest (endocardial, endo) ventricular transmembrane action potentials. B, the end-of-repolarization sequence of the heart ventricles (frontal projection) reconstructed from experimental data, with the transmural and the apicobasal gradients: the earliest end-of-repolarization was detected in the apical subendocardium, and the latest one-in the subendocardium of the right ventricle's base. C, the body surface electrocardiographic. The peak (Tp) and the end (Te) of the T-wave correspond to the earliest and the latest end-of-repolarization in the heart ventricles, correspondingly. When using the tangent method, QT and Tpe intervals are shorter than those determined by the baseline (tail) method.[9]

TPE DISPERSION: PHYSIOLOGICAL RATIONALE

Tpe dispersion (dTpe) means the difference between the maximum and minimum Tpe interval among the measured ECG leads during a single beat. dTpe was suggested as an index of local variations in transmural DOR among different ventricular regions.[3] This suggestion was based on that ECG leads primarily reflect the local cardiac events in the nearest ventricular region (especially the precordial ones), resulting in lead-to-lead variations in Tpe magnitude. An increase in DOR over a short distance comparable to the thickness of ventricular wall results in a steep local repolarization gradient, so it is more proarrhythmic than a large but evenly distributed global DOR.[1]

TPE/QT RATIO: PHYSIOLOGICAL RATIONALE

Based on the analysis of ECG measurements performed in humans and some animals species, Gupta et al. reported that in healthy humans, in the wide range of heart rhythm values (from 60 to 100 beats per minute), the Tpe/QT ratio in 12-lead ECG remains relatively constant between a narrow range of values from 0.15 to 0.25 with a median value of 0.21; moreover, Tpe/QT ratio is approximately the same (0.17-0.23) across the species of various body sizes and action potential durations.[4]

Regarding the physiological significance of Tpe/QT, Gupta et al. hypothesized that since Tpe/QT ratio remains relatively constant across evolutionarily different species, it may be a unifying parameter that probably serves to maintain electrical stability of an excitable medium such as the heart; the disproportionate amplification of the transmural or the global DOR relative to QT interval disrupts the electrical stability of the heart and has a pronounced arrhythmic effect.[4]

In silico studies showed that Tpe/QT reflects the relationship between the longest and the shortest APD values in the heart ventricles: to maintain this ratio at the same level, the longest (endocardial) and the shortest (epicardial) action potentials should change at different rates; thereby, the increased Tpe/QT magnitude means a "disbalance" between the longest and the shortest ventricular action potentials.[10]

TPE AND ITS DERIVATIVES: CLINICAL SIGNIFICANCE

Coronary artery desease: In patients with coronary atherosclerosis, whether in the form of stable coronary artery disease, chronic total occlusion, slow flow, or acute coronary obstruction, Tpe and Tpe/QT values were significantly higher than in healthy subjects, and in men higher than in women.[11-14] In myocardial infarction, Tpe and Tpe/QT were significantly higher in patients with non-obstructive coronary artery disease comparing to the stable out-patients without significant lesions in their coronary arteries.[15]

Tpe magnitude significantly correlated with both the extent and severity of coronary artery stenosis: it was the longest in multivessel disease, followed by double vessel disease, single vessel disease, and stenosis-free groups.[16] At hypertension, higher Tpe and Tpe/QT values correlated with the degree of the left ventricular hypertrophy, endothelial dysfunction, arterial stiffness, impaired coronary perfusion, and accelerated arterial aging.[17,18]

The increased values of Tpe and Tpe/QT distinguished the patients with higher risks of arrhythmic or mortality outcomes [ventricular tachycardia (VT)/ ventricular fibrillation (VF), sudden cardiac death, cardiovascular death, and all-cause mortality] in hypertension, ischemic heart desease, in the acute phase of myocardial infarction.[4,19-22] In myocardial infarction, Tpe/QT ratio was a more sensitive arrhythmic risk predictor than Tpe interval itself.[4]

The increase in DOR associated with coronary artery disease was reversible. In patients with chronic total occlusions, significant decreases in Tpe intervals and Tpe/QT ratio were observed after successful percutaneous coronary intervention.[23] In myocardial infarction, the prolonged Tpe and Tpe/QT values decreased after the reperfusion, in stable coronary artery disease patients-under ranolazine therapy (an antianginal drug which exhibits antiarrhythmic effect by affecting action potential time, refractory period, and repolarization reserve).[24,25] Therefore, the dynamical Tpe changes may serve as a surrogate measure of treatment success.

Heart failure: The systematic review and meta-analysis by Tse et al. showed that in patients with heart failure, increased Tpe value was a significant predictor of arrhythmic outcomes (VT/VF), cardiovascular and all-cause mortality.[19] This was true both for decompensated chronic heart failure and after the treatment.[26,27] In heart failure patients treated with implantation of cardiac resynchronization therapy defibrillator, in addition to predicting ventricular arrhythmias and all-cause mortality in post-implantation period, Tpe was correlated with the rate of the left ventricular reverse remodeling being an independent predictor of a favorable therapy response.[28,29]

Other cardiac disorders: Over the past two decades, multiple clinical studies have been identified Tpe and its derivatives as reliable indices for predicting the development of adverse cardiac events (syncope, ventricular arrhythmias or sudden cardiac death) and all-cause mortality in a wide range of congenital cardiac disorders, including long QT syndrome, short QT syndrome, Brugada syndrome.[3,30-33] It is noteworthy that in some Brugada syndrome patients who had recurrent VF, Tpe value (the symbol of global DOR) was not beyond the normal range, while dTpe (the symbol of local DOR) was increased.[3] In congenital and acquired channelopathies and Takotsubo syndrome, Tpe/QT ratio was more sensitive arrhythmic risk predictor than Tpe interval.[4]

In addition to the prediction of arrhythmias and mortality, Tpe magnitude was associated with hemodynamic and volumetric parameters of the ventricles. In patients with arrhythmogenic right ventricular cardiopathy (ARVC), Tpe was associated with RVFAC, and the prolonged Tpe interval distinguished ARVC patients from those with idiopathic VT arising from the right ventricular outflow tract.[34,35] In Takotsubo syndrome, increased Tpe/QT ratio predicted a high risk of major adverse cardiovascular events during hospitalization and was associated with ejection fraction.[36] In the patients with wide QRS, after the left bundle branch area pacing, the post-implant Tpe was associated with the echocardiographic response.[37]

Non-cardiac disorders: Repolarization abnormalities reflecting in the increased Tpe, dTpe and Tpe/QT values, were observed in a lot of non-cardiac disorders: in coronavirus disease-2019 (even asymptomatic), *autoimmune hepatitis*, *Type 2 diabetes mellitus*, in *epilepsy* under anti-epileptic drugs (especially by valproic acid) administration.[38-41] In *chronic kidney disease* patients, Tpe, Tpe/QT and Tpe/QTc were significantly higher in the predialysis group than in patients receiving hemodialysis or underwent successful transplantation.[42]

Along with prediction of arrhythmic and mortality risk, the values of Tpe and its derivatives were related to the other clinical indices and the severity of the disease. In patients with *rheumatoid arthritis*, there was a direct relationship between Tpe, inflammatory cytokines and autonomic dysfunction.[43] In drug-free patients with *major depressive disorder*, Tpe/QTc was significantly and inversely correlated with the duration of illness.[44] In systemic sclerosis, the prolonged Tpe and Tpe/QT values correlated with clinical severity score.[45] Similarly, in human immunodeficiency virus infection and acquired immune deficiency syndrome, the prolonged Tpe and Tpe/QT correlated with the severity of the disease.[46]

All-cause mortality: Meta-analysis of 29 observational studies involving 23,114 patients showed that Tpe interval was significantly associated with all-cause mortality, and this association was not affected by the heart rate correction.[47] It is important that not only the increased but also the decreased Tpe magnitudes were associated with the high risk of sudden cardiac death and all-cause mortality.[48]

LIMITATIONS

The major clinical limitation of the use of Tpe and its derivatives as arrhythmia predictors is that arrhythmogenesis mechanisms are complex and involve not only repolarization abnormalities.[49] This limitation also applies to the indices based solely on conduction. A possible solution to this problem are the combined indices based on both de- and repolarization, such as an index of cardiac electrophysiological balance, given by QT/QRSd (where QRSd is QRS duration), a surrogate of excitation wavelength, and its modification [Tpe/QRSd and Tpe/(QT×QRSd)] by Tse and Yan, who replaced QT with Tpe, based on that Tpe and Tpe/QT were superior to the QT in arrhythmic risk stratification.[5,50] In addition, recent studies suggest that any single ECG index is likely to be inferior to cumulative risk stratification using a combination of multiple markers.[51,52]

Another important limitation is the lack of consensus in Tpe measurements, while its magnitude depends significantly on numerous factors: (a) it varies from lead to lead, and Tpe measured from a single

lead will differ from the average or maximum values calculated from several leads; (b) its magnitude and predictive power concerning arrhythmias depends on the method used for T-wave end detection-the *baseline* ("*tail"*), or the *tangent*; (c) age (it increases with age); (d) gender (in men it is higher than in women); (e) whether it was rate-corrected or not (in some cases, rate-correction improves arrhythmic risk stratification); (f) breathing; and (g) body position during ECG recording (Figure 1).[3,53-56]

Different measurement approaches result in large variations in the normal and cut-off Tpe values reported by different researchers. Particularly, the reported cut-off values vary in a wide range: from 85 ms to 116 ms for Tpe, from 15.1 ms to 58.8 ms for dTpe, and from 0.22 to 0.29 for Tpe/QT ratio.[12,48,57-60]

One more limitation is that Tpe and its derivatives are not currently involved in routine ECG analysis. However, modern technologies make it possible to develop friendly applications (including those for mobile devices) for automatically calculating indices and evaluating the degree of arrhythmic risk.

CONCLUSION

In vivo, *in vitro* and *in silico* experimental studies demonstrated that Tpe interval (its "global" or maximum value) is a measure of the global DOR in the heart ventricles; dTpe is a measure of the local DOR; and Tpe/QT ratio, the proportion between the duration and the dispersion of repolarization, reflects the dynamically changes in the longest (subendocardial) and the shortest (subepicardial) ventricular action potentials.

Numerous clinical studies showed that Tpe, dTpe and Tpe/QT ratio are useful predictors of arrhythmias associated with repolarization abnormalities, and the overall mortality. Besides, Tpe magnitude has a potential as a simple, non-invasive, inexpensive and quick indirect assessment of hemodynamic and volumetric ventricular parameters, the extent and severity of coronary artery stenosis, therapy response and the expected hospital stay. However, the inclusion of Tpe in routine ECG analysis requires further research based on the more unified measurement approach, including machine learning and artificial intelligence tools.

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Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

This study is entirely author's own work and no other author contribution.

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