Journal of Geriatric Cardiology (2017) 14: 776–779

Letter to the Editor · **Open Access** ·

Meta-analysis of T-wave indices for risk stratification in myocardial infarction

Gary Tse[1,2,*], Cheuk Wai Wong[3], Meng–Qi GONG[4], Lei MENG[4], Konstantinos P Letsas[5], Guang–Ping LI[4], Paula Whittaker[6], Aishwarya Bhardwaj[7], Abhishek C Sawant[7], William KK Wu[8], Sunny Hei Wong[1,2], Jayaprakash Shenthar[9], Lap Ah Tse[10], Martin CS Wong[10], Adrian Baranchuk[11], Gan–Xin YAN[12,13], Tong LIU[4,*], International Health Informatics Study (IHIS) Network

[1] *Department of Medicine and Therapeutics, Faculty of Medicine, Chinese University of Hong Kong, Hong Kong, China*
[2] *Li Ka Shing Institute of Health Sciences, Faculty of Medicine, Chinese University of Hong Kong, Hong Kong, China*
[3] *Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong, China*
[4] *Tianjin Key Laboratory of Ionic-Molecular Function of Cardiovascular disease, Department of Cardiology, Tianjin Institute of Cardiology, Second Hospital of Tianjin Medical University, Tianjin, China*
[5] *Second Department of Cardiology, Laboratory of Cardiac Electrophysiology, "Evangelismos" General Hospital of Athens, Athens, Greece*
[6] *Division of Population Health, Health Services Research and Primary Care, School of Health Sciences, University of Manchester, United Kingdom*
[7] *Division of Cardiology, Department of Internal Medicine, State University of New York at Buffalo, USA*
[8] *Department of Anaesthesia and Intensive Care, State Key Laboratory of Digestive Disease, LKS Institute of Health Sciences, The Chinese University of Hong Kong, Hong Kong, China*
[9] *Electrophysiology Unit Sri Jayadeva Institute of Cardiovascular Sciences and Research B G Road, 9th Block, Jayanagar, Bangalore, India*
[10] *JC School of Public Health and Primary Care, The Chinese University of Hong Kong, Hong Kong, China*
[11] *Division of Cardiology, Kingston General Hospital, Queen's University, Kingston, Ontario, Canada*
[12] *Lankenau Institute for Medical Research and Lankenau Medical Center, Wynnewood, Pennsylvania, USA*
[13] *Beijing Anzhen Hospital, Capital Medical University, Beijing, China*

J Geriatr Cardiol 2017; 14: 776–779. doi:10.11909/j.issn.1671-5411.2017.12.009

Keywords: Myocardial infarction; Repolarization; Sudden death; Tpeak-Tend; Tpeak-Tend/QT

Ventricular tachy-arrhythmias are the commonest cause of sudden cardiac death in patients with ischemic heart disease.[1] It is estimated that up to 20% patients with acute myocardial infarction suffer from these arrhythmias.[2] There is a growing need for developing tools for risk assessment for sudden cardiac death (SCD) in this population. Several ECG indices have been proposed for risk stratification and for prognostication after myocardial infarction (MI).[3–5] These can divided broadly into those based on repolarization, conduction or both, as reviewed recently.[3] Repolarization indices include QT interval, QT dispersion, T_{peak}-T_{end} interval, T_{peak}-T_{end}/QT ratio, JT_{peak}/JT, (T_{peak}-T_{end})/JT_{peak} and T_{peak}/JT ratios. Conduction indices include QRS duration and QRS dispersion. Conduction-repolarization indices are exemplified by index of Cardiac Electrophysiological Balance (iCEB: QT/QRS),[6] and QRS-T angle, amongst others.[7–9]

Of the repolarization markers, T_{peak}-T_{end} interval, the difference between the peak and the end of the T wave, and T_{peak}-T_{end}/QT ratio, represent the dispersion of repolarization.[10] A meta-analysis recently published by our group demonstrated its predictive value in several cardiac conditions that included Brugada syndrome, heart failure and myocardial infarction.[11] Other investigators have proposed dividing T_{peak}-T_{end} by the QT interval. This yields the T_{peak}-T_{end}/QT ratio, which has a relatively constant normal range between 0.17 and 0.23.[12] Theoretically, increases in this ratio represent a higher dispersion of repolarization, which should promote ventricular arrhythmogenesis, however its value for predictive arrhythmic or mortality risk after MI remains controversial. Thus, three studies also did not demonstrate differences in this ratio between high and low risk groups.[13–15] Therefore, we performed a systematic review and meta-analysis to examine whether T_{peak}-T_{end} interval and T_{peak}-T_{end}/QT ratio can distinguish patients with MI who are at high risk of arrhythmic or mortality events from those free from these events.

A total of 42 and 95 entries were retrieved from Pubmed and Embase, respectively, of which 10 studies met the inclusion criteria and were therefore included. A total of 1967 MI patients were included in this meta-analysis. The pa-

***Correspondence to:** tseg@cuhk.edu.hk (Tse G) & liutongdoc@126.com (LIU T)

tients had a mean age of 68 and 78% were male with a mean follow-up period of 15 ± 12 months. We found that T_{peak}-T_{end}/QT ratios were significantly higher in high risk patients compared to the low risk group (mean difference: 0.06, standard error 0.02, $P < 0.01$; $I^2 = 88\%$; Figure 1). The Cochran's Q value was greater than the degrees of freedom (58 *vs.* 7), indicating that the true effect size was different between studies. I^2 was 88%, which indicates the presence of substantial heterogeneity. Begg and Mazumdar rank correlation analysis demonstrated that Kendall's Tau took a value of -0.1 with $P > 0.05$, which suggests no significant publication bias. Egger's test demonstrated no significant asymmetry (intercept 2.2, *t*-value 2.1; $P > 0.05$). To identify the source of the heterogeneity, sensitivity analysis was performed by removing one study at a time, but this did not significantly influence the mean difference. This suggests that none of the studies was singly responsible for the heterogeneity observed. ORs/HRs were available for five studies and are shown in Figure 2. In terms of risk quantification, all five studies reported a positive association between increased T_{peak}-T_{end}/QT and increased risk of VT/VF or mortality (two studies used multivariate analysis and three studies used univariate analysis). The pooled meta-analysis demonstrated that a higher T_{peak}-T_{end}/QT ratio is associated with approximately 3.16 times higher risk of these endpoints (95% CI: 1.13 to 8.82; $P < 0.05$). The Cochran's Q value was greater than the degrees of freedom (21 *vs.* 4), indicating the true effect size were different among different studies. I^2 of 81% suggested substantial heterogeneity. Begg and Mazumdar rank correlation analysis demonstrated that Kendall's Tau took a value of 0 with $P > 0.05$, which suggests no significant publication bias. Egger's test demonstrated significant asymmetry (intercept 2.2, *t*-value 5.0; $P < 0.05$). To identify the source of the heterogeneity, sensitivity analysis was performed by removing one study at a time, but this did not significantly influence the mean difference. This suggests that none of the studies was singly responsible for the heterogeneity observed.

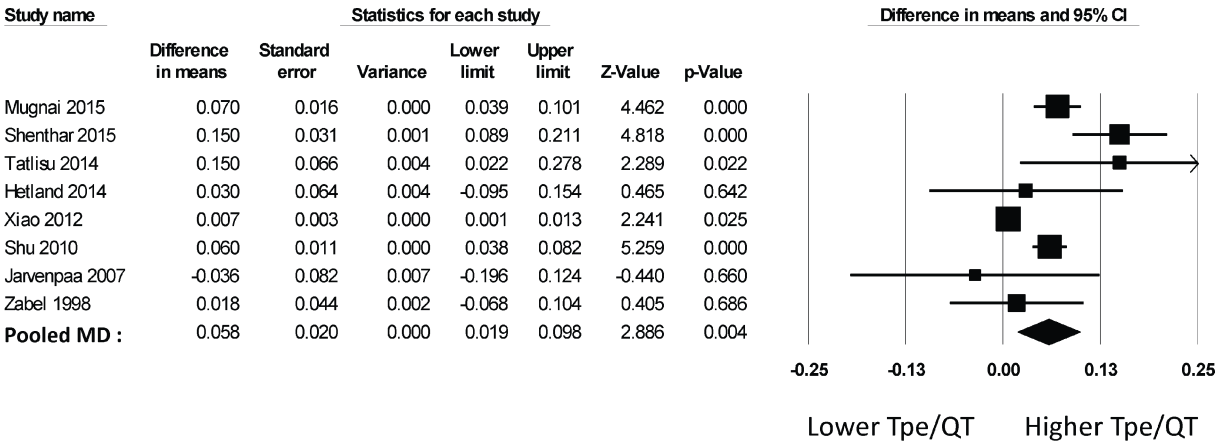

Figure 1. Flow diagram of the study selection process for studies investigating T_{peak}-T_{end} interval and T_{peak}-T_{end}/QT ratio in myocardial infarction patients. CI: confidence inervals; MD: Mean difference.

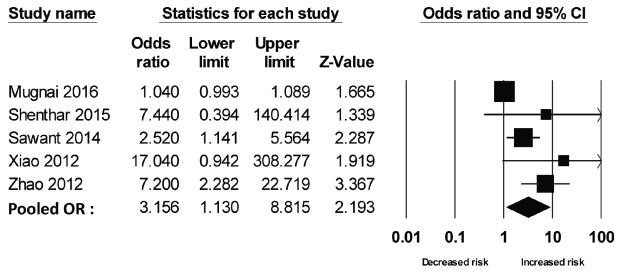

Figure 2. Forest plot demonstrating the mean differences for between T_{peak}-T_{end}/QT ratios obtained in event-positive and event-negative groups. CI: confidence inervals; OR: odds ratio.

Our study is the only meta-analysis that evaluates the role of Tpeak-Tend/QT ratio for prognostication in 1967 patients with prior MI. The main findings are: (1) T_{peak}-T_{end}/QT ratio is higher by 0.06 in patients who suffered from malignant ventricular arrhythmias and/or death compared to those who were free from these events; (2) a higher T_{peak}-T_{end}/QT ratio with a mean cut-off of 0.26 are associated with 3.16-fold increase in the risk of ventricular arrhythmias and/or death, respectively. T_{peak}-T_{end} is the interval between the peak and the end of the T-wave on the ECG, which is a reflection of the dispersion of repolarization.[10] As this interval varies with heart rate,[12] dividing it by the QT interval yields the T_{peak}-T_{end}/QT ratio, which has a relatively constant normal range between 0.17 and 0.23.[12] Theoretically, higher values of both indices reflect increased dispersion of repolarization, which is expected to increase arrhythmogenicity.[16] Pre-clinical experiments conducted in

coronary-perfused, canine wedge preparations showed that the end of action potential (AP) repolarization at the epicardium coincided with the T_{peak} and end of AP repolarization at the M-cell coincided with T_{end}.[17] In other words, T_{peak}-T_{end} can be used as a surrogate marker of transmural dispersion of repolarization (TDR). Increases in TDR are pro-arrhythmic owing to the increased likelihood of developing unidirectional conduction block and therefore to re-entry. Increased TDR is also thought to underlie phase 2 reentry in Brugada syndrome.[16] T_{peak}-T_{end} is lead-dependent as the dispersion of repolarization varies with cardiac regions.[18] This interval can be determined generally using two methods, the tangent method and the tail method. This is important because one study reported that T_{peak}-T_{end} interval, when determined using the tangent method, was not significantly between high risk and low risk groups.[13] However, using the tail method, T_{peak}-T_{end} interval was significantly prolonged in high risk MI patients compared to the low risk cohort.[13]

Recently, our group conducted a comprehensive systematic review with meta-analysis into the value of T_{peak}-T_{end} interval in predicting arrhythmic and mortality outcomes in different clinical conditions.[11] However, it did not examine the relationship between T_{peak}-T_{end}/QT ratio and adverse outcomes. Therefore, the present study goes on to investigate the mean differences in T_{peak}-T_{end}/QT ratio in a cohort of myocardial infarction patients. The central hypothesis is that higher T_{peak}-T_{end}/QT ratios increase arrhythmic risk due to an exacerbation of the transmural or global dispersion of repolarization, and that measures that reduce this exacerbation would reduce arrhythmic risk.[3] The results of this meta-analysis clearly show that prolongations do indeed distinguish high risk patients from patients who did not suffer from adverse cardiac events. It should be noted that three studies reported no value of this ratio in risk stratification.[13–15] There are several reasons why this might have been the case. Firstly, in normal hearts, a degree of transmural repolarization heterogeneity ensures the normal unidirectional conduction of the cardiac impulse through the heart. Normally the endocardium depolarizes first and repolarizes last whereas the epicardium depolarizes last and repolarizes first. Disturbances in this activation and recovery sequence could potentially lead to arrhythmogenesis.[19] Decreases in transmural dispersion of repolarization, reflected by shorter T_{peak}-T_{end} intervals, may also be pro-arrhythmic. Indeed, this notion is supported by a study published by Porthan and colleagues demonstrating that a reduction in this interval was associated with a higher likelihood of ventricular arrhythmic events in the general population.[20] Other studies found no significant difference in T_{peak}-T_{end} intervals[15] or in T_{peak}-T_{end}/QT ratios[13–15] between high and low risk groups. These findings suggest that increased transmural dispersion of repolarization is only one mechanism through which arrhythmogenesis takes place. Other electrophysiological abnormalities, such as reduced conduction velocity and increased dispersion of conduction are also important, as suggested previously.[11]

In conclusion, this meta-analysis shows that T_{peak}-T_{end}/QT ratio is a significant predictor of ventricular tachy-arrhythmias and/or death in myocardial infarction. Our study adds to growing body of evidence supporting utility of repolarization abnormalities seen on a standard electrocardiogram for prognostication and risk stratification in patients with prior myocardial infarction. These indices are should be utilized in clinical practice to aid risk stratification.

Acknowledgements

Gary Tse thanks the Croucher Foundation of Hong Kong for the support his clinical assistant professorship.

References

1 Bayes de Luna A, Coumel P, Leclercq JF, *et al*. Ambulatory sudden cardiac death: mechanisms of production of fatal arrhythmia on the basis of data from 157 cases. *Am Heart J* 1989; 117: 151–159.
2 Henkel DM, Witt BJ, Gersh BJ, *et al*. Ventricular arrhythmias after acute myocardial infarction: a 20-year community study. *Am Heart J* 2006; 151: 806–812.
3 Tse G, Yan BP. Traditional and novel electrocardiographic conduction and repolarization markers of sudden cardiac death. *Europace* 2017; 19: 712–721.
4 Gimeno-Blanes FJ, Blanco-Velasco M, Barquero-Pérez Ó, *et al*. Sudden cardiac risk stratification with electrocardiographic indices—a review on computational processing, technology transfer, and scientific evidence. *Front Physiol* 2016; 7: 82.
5 Abdelghani SA, Rosenthal TM, Morin DP, *et al*. Surface electrocardiogram predictors of sudden cardiac arrest. *Ochsner J* 2016; 16: 280–289.
6 Lu HR, Yan G-X, Gallacher DJ, *et al*. A new biomarker – index of cardiac electrophysiological balance (iCEB) – plays an important role in drug-induced cardiac arrhythmias: beyond QT-prolongation and Torsades de Pointes (TdPs). *J Pharmacol Toxicol Methods* 2013; 68: 250–259.
7 Tse G. (Tpeak-Tend)/QRS and (Tpeak-Tend)/(QT x QRS): novel markers for predicting arrhythmic risk in the Brugada syndrome. *Europace* 2017; 19: 696.
8 Tse G. Novel conduction-repolarization indices for the stratification of arrhythmic risk. *J Geriatr Cardiol* 2016; 13: 811–812.
9 Tse G. Both transmural dispersion of repolarization and of refractoriness are poor predictors of arrhythmogenicity: a role for iCEB (QT/QRS)? *J Geriatr Cardiol* 2016; 13: 813–814.

10 Xia Y, Liang Y, Kongstad O, *et al*. Tpeak-Tend interval as an index of global dispersion of ventricular repolarization: evaluations using monophasic action potential mapping of the epi- and endocardium in swine. *J Interv Card Electrophysiol* 2005; 14: 79–87.
11 Tse G, Gong M, Wong WT, *et al*. The Tpeak – Tend interval as an electrocardiographic risk marker of arrhythmic and mortality outcomes: a systematic review and meta-analysis. *Heart Rhythm* 2017; 14: 1131–1137.
12 Gupta P, Patel C, Patel H, *et al*. T(p-e)/QT ratio as an index of arrhythmogenesis. *J Electrocardiol* 2008; 41: 567–574.
13 Hetland M, Haugaa KH, Sarvari SI, *et al*. A novel ECG-index for prediction of ventricular arrhythmias in patients after myocardial infarction. *Ann Noninvasive Electrocardiol* 2014; 19: 330–337.
14 Järvenpää J, Oikarinen L, Korhonen P, *et al*. Changing capacity of electrocardiographic ventricular repolarization in post-myocardial infarction patients with and without nonfatal cardiac arrest. *Am J Cardiol* 2007; 99: 295–299.
15 Zabel M, Klingenheben T, Franz MR, *et al*. Assessment of QT dispersion for prediction of mortality or arrhythmic events after myocardial infarction: results of a prospective, long-term follow-up study. *Circulation* 1998; 97: 2543–2550.
16 Yan GX, Antzelevitch C. Cellular basis for the normal T wave and the electrocardiographic manifestations of the long-QT syndrome. *Circulation* 1998; 98: 1928–1936.
17 Antzelevitch C, Shimizu W, Yan GX, *et al*. The M cell: its contribution to the ECG and to normal and abnormal electrical function of the heart. *J Cardiovasc Electrophysiol* 1999; 10: 1124–1152.
18 Bieganowska K, Sawicka-Parobczyk M, Bieganowski M *et al*. Tpeak-tend interval in 12-lead electrocardiogram of healthy children and adolescents tpeak-tend interval in childhood. *Ann Noninvasive Electrocardiol* 2013; 18: 344–351.
19 Tse G, Lai ET, Lee AP, *et al*. Electrophysiological mechanisms of gastrointestinal arrhythmogenesis: lessons from the heart. *Front Physiol* 2016; 7: 230.
20 Porthan K, Viitasalo M, Toivonen L, *et al*. Predictive value of electrocardiographic T-wave morphology parameters and T-wave peak to T-wave end interval for sudden cardiac death in the general population. *Circ Arrhythm Electrophysiol* 2013; 6: 690–696.