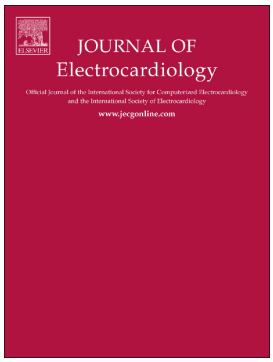

Meta-analysis of Tpeak–Tend and Tpeak–Tend/QT ratio for risk stratification in congenital long QT syndrome

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Meta-analysis of $T_{peak} - T_{end}$ and $T_{peak} - T_{end}$/QT ratio for risk stratification in congenital long QT syndrome

Short title: T_{peak}-T_{end} indices in congenital long QT syndrome: a meta-analysis

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Abstract

Background and Objectives: Congenital long QT syndrome (LQTS) predisposes affected individuals to ventricular tachycardia/fibrillation (VF/VF), potentially resulting in sudden cardiac death. The $T_{peak} - T_{end}$ interval and the $T_{peak} - T_{end}$ / QT ratio, electrocardiographic markers of dispersion of ventricular repolarization, were proposed for risk stratification but their predictive values in LQTS have been controversial. A systematic review and meta-analysis was conducted to examine the value of $T_{peak} - T_{end}$ intervals and $T_{peak} - T_{end}$ / QT ratios in predicting arrhythmic and mortality outcomes in congenital LQTS.

Method: PubMed and Embase databases were searched until 9th May 2017, identifying 199 studies.

Results: Five studies on long QT syndrome were included in the final meta-analysis. $T_{peak} - T_{end}$ intervals were longer (mean difference [MD]: 13 ms, standard error [SE]: 4 ms, P = 0.002; I^2 = 34%) in congenital LQTS patients with adverse events [syncope, ventricular arrhythmias or sudden cardiac death] compared to LQTS patients without such events. By contrast, $T_{peak} - T_{end}$ / QT ratios were not significantly different between the two groups (MD: 0.02, SE: 0.02, P = 0.26; I^2 = 0%).

Conclusion: This meta-analysis showed that $T_{peak} - T_{end}$ interval is significant higher in individuals who are at elevated risk of adverse events in congenital LQTS, offering incremental value for risk stratification.

Keywords: Tpeak – Tend; Tpeak – Tend / QT; dispersion of repolarization; risk stratification; ventricular arrhythmia; sudden cardiac death

Introduction

Congenital long QT syndrome (LQTS) increases the risk of ventricular tachycardia/fibrillation (VT/VF), potentially leading to sudden cardiac death (SCD). However, patients with prolonged QT intervals are heterogeneous in that only a subset develop these adverse events, and risk stratification in this condition remains difficult. Traditional electrocardiographic markers for risk prediction have largely focused on abnormal repolarization, of which the archetypal examples are QT [1] and QT_c [2]. Other markers [3], such as QT dispersion (QT_d) [4, 5], interval from the peak to the end of the T wave [6] ($T_{peak} - T_{end}$ interval) and $T_{peak} - T_{end}$ / QT ratio [7] were developed to improve risk stratification.

Prolongation in the $T_{peak} - T_{end}$ interval increases arrhythmic risk because increased dispersion of repolarization predisposes to the occurrence of unidirectional block and therefore reentry [8-11]. However, $T_{peak} - T_{end}$ varies with different species and heart rate, has significant inter-individual variability [12]. It was found that dividing it by the QT interval yielded a parameter, $T_{peak} - T_{end}$ / QT ratio, that had a relatively constant normal range between 0.17 and 0.23 [12]. Much of the work on dispersion of repolarization were conducted by Yan and Antzelevitch in animal models and electrocardiographic correlates of repolarization dispersion were subsequently used for risk stratification in humans [12]. However, the predictive value of $T_{peak} - T_{end}$ interval or $T_{peak} - T_{end}$ / QT ratio in LQTS remains controversial. A recent meta-analysis examined the prognostic value of $T_{peak} - T_{end}$ interval by pooling together the odds or hazard ratios for arrhythmic or mortality outcomes when this interval is prolonged, but it did not examine the absolute values of this index, nor did it investigate LQTS in the subgroup analyses [13]. Thus, many studies have reported $T_{peak} - T_{end}$ interval or $T_{peak} - T_{end}$ / QT ratio in LQTS. For $T_{peak} - T_{end}$ interval, three studies did not report a significant difference in duration between

LQTS patients who suffered from adverse events compared to those who did not [14, 15]. For $T_{peak} - T_{end}$ / QT ratio was a significant predictor of *torsade de pointes* in univariate analysis, but lost its significance in multivariate analysis [16]. By contrast, $T_{peak} - T_{end}$ / QT ratio was not significantly higher in LQTS patients who suffered from ventricular arrhythmias compared to LQTS patients without such events. Given these conflicting findings, the aim of this study is to conduct a systematic review with meta-analysis into the association between $T_{peak} - T_{end}$ interval and $T_{peak} - T_{end}$ / QT ratio and arrhythmic and/or mortality endpoints in LQTS.

Methods

Search strategy, inclusion and exclusion criteria

This systematic review and meta-analysis was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISM) statement [17]. PubMed and Embase were searched for studies that investigated the association between $T_{peak} - T_{end}$ or $T_{peak} - T_{end}$ / QT with arrhythmic or mortality endpoints in long QT syndrome. The following search terms were used for both databases: [“Tpeak–Tend” OR “Tp-Te” OR “Tpeak-end” OR “Tp-e” OR "T(peak)-T(end)" OR "T wave peak-to-end" OR "T peak-T end" OR “Tpe” "TPEc" OR "T-peak to T-end" OR "Tpeak-to-Tend" AND "long QT"]. The search period was from the beginning of the database through to 9th May 2017 without language restrictions. The following inclusion criteria were used: i) the study was conducted on humans, ii) $T_{peak} - T_{end}$ intervals or $T_{peak} - T_{end}$ / QT ratios were provided; iii) endpoint events [appropriate implantable cardioverter-defibrillator therapy (ICD), ventricular tachycardia/fibrillation (VT/VF), sudden cardiac death (SCD), cardiovascular death (CVD), major adverse cardiac events (MACE) or all-cause mortality were reported.

The quality assessment of these studies included in our meta-analysis was performed using the Newcastle–Ottawa Quality Assessment Scale (NOS) [18]. The point score system evaluated the categories of study participant selection, comparability of the results, and quality of the outcomes. The following characteristics were assessed: a) representativeness of the exposed cohort; b) selection of the non-exposed cohort; c) ascertainment of exposure; d) demonstration that outcome of interest was not present at the start of study; e) comparability of cohorts based on study design or analysis; f) assessment of outcomes; g) follow-up periods that were sufficiently long for outcomes to occur; and h) adequacy of follow-up of cohorts. This scale varied from zero to nine stars, which indicated that studies were graded as poor quality if the score was <5, fair if the score was 5 to 7, and good if the score was >8. Studies with a score equal to or higher than six were included. The details of the NOS quality assessment are shown in **Supplementary Tables 1 and 2**. No studies were excluded based on the quality score.

Data extraction and statistical analysis

Data from the different studies were entered in pre-specified spreadsheets in Microsoft Excel. All potentially relevant studies were retrieved as complete manuscripts and assessed fully to determine whether they met the inclusion criteria. In this meta-analysis, the extracted data elements consisted of: i) publication details: last name of first author, publication year and locations; ii) study design; iii) endpoint(s); iv) the quality score; and v) the characteristics of the population including sample size, gender, age and number of subjects. Two reviewers (GT and CW) reviewed each included study independently. Disagreements were resolved by adjudication with input from a third reviewer (TL).

The endpoints of the studies are occurrences of ventricular arrhythmias (VT/VF), sudden cardiac death, cardiovascular death, major adverse cardiac events (MACE) or all-cause mortality. If more than one endpoint is described, then SCD is preferentially used for analysis, followed by cardiovascular death and all-cause mortality. Mean differences with 95% confidence interval (CI) for $T_{peak} - T_{end}$ interval and $T_{peak} - T_{end}$/QT ratio were extracted from each study and subsequently pooled.

The heterogeneity between studies was determined using Cochran's Q value, the weighted sum of squared differences between individual study effects and the pooled effect across studies, and the I^2 statistic from the standard chi-square test, which describes the percentage of the variability in effect estimates resulting from heterogeneity, rather than sampling error. $I^2 > 50\%$ was considered to reflect significant statistical heterogeneity. A fixed effects model was used if no significant heterogeneity was found. The random-effects model using the inverse variance heterogeneity method was used with $I^2 < 50\%$. To locate the origin of the heterogeneity, sensitivity analysis excluding one study at a time, and subgroup analyses based on different disease conditions and different endpoints were performed. Funnel plots, Begg and Mazumdar rank correlation test and Egger's test were used to assess for possible publication bias.

Results

Figure 1 shows a flow diagram detailing the above search terms with inclusion and exclusion criteria. A total of 97 and 116 entries were retrieved from Pubmed and Embase, respectively. Five studies were relevant for congenital long QT syndrome (LQTS) and were included in our final meta-analysis [14, 15, 19-21]. In this meta-analysis, a total of 388 patients were

included (mean age 35 years old, range from 7 to 38; 37% male). **Table 1** shows the baseline characteristics of these studies and of the study populations.

Regarding $T_{peak} - T_{end}$ intervals, two studies reported longer values in event-positive group compared to event-negative groups, whilst the remaining three studies demonstrated no significant prolongation (**Figure 2**). The $T_{peak} - T_{end}$ intervals for event-negative and event-positive groups were 96 ± 8 and 114 ± 11, respectively, with a significant mean difference of 13 ± 4 ms (P = 0.002). The Cochran's Q value was greater than the degrees of freedom (6 vs. 4), indicating that the true effect size was different between studies. I^2 took a value of 34%, suggesting a low level of heterogeneity. A funnel plot plotting standard errors against differences in means is shown in **Supplementary Figure 1**. Begg and Mazumdar rank correlation analysis demonstrated that Kendall's Tau took a value of 0.2 with P = 0.62, which suggests no significant publication bias. Egger's test demonstrated no significant asymmetry (intercept 1.5, t-value 1.2; P = 0.32). To identify the source of the heterogeneity, sensitivity analysis was performed by removing one study at a time. However, this did not significantly influence the mean difference (**Supplementary Figure 2**), suggesting that no single study was responsible for the heterogeneity observed in this meta-analysis.

For $T_{peak} - T_{end}$ / QT ratio**,** none of the four studies included in the analysis reported any significant difference between event-positive and event-negative groups (**Figure 3**). The $T_{peak} - T_{end}$ / QT ratio for event-negative and event-positive groups were 0.19 ± 0.01 and 0.21 ± 0.01, respectively, with no significant difference between the groups (mean difference: 0.02 ± 0.02; P = 0.26). The Cochran's Q value was less than the degrees of freedom (0.2 vs. 3), indicating that the true effect size was not significantly different between the included studies. I^2 took a value of 0%, suggesting no heterogeneity. A funnel plot plotting standard errors against differences in

means is shown in **Supplementary Figure 3**. Begg and Mazumdar rank correlation analysis demonstrated that Kendall's Tau took a value of 0 with P = 1.00, which suggests no publication bias. Egger's test demonstrated no significant asymmetry (intercept 0.1, t-value 0.3; P = 0.81). To identify the source of the heterogeneity, sensitivity analysis was performed by removing one study at a time to calculate the pooled OR. However, this did not significantly influence the mean difference (**Supplementary Figure 4**), suggesting that no single study was responsible for the heterogeneity observed in this meta-analysis.

Discussion

Our main findings are that $T_{peak} - T_{end}$ intervals are longer and $T_{peak} - T_{end}$ / QT ratios are higher, in congenital LQTS patients suffering from adverse events compared to those who without these events.

Pre-existing heterogeneities in the heart are crucial for ensuring unidirectional spread of action potentials conducted through the cardiac conduction system [22, 23]. These are due to differences in repolarization times of the different cell types, which are responsible for inscription of the T-wave on the electrocardiogram (ECG) [24, 25]. However, exacerbation of these heterogeneities has been linked to ventricular arrhythmogenesis in a variety of conditions. These include congenital ion channelopathies such as LQTS and Brugada syndrome [26-28], acquired causes of LQTS [29] and short QT syndrome [30], as well as other diseases such as diabetes mellitus, hypertension and myocardial infarction [31-34]. These heterogeneities can occur locally or across the myocardial wall [35], potentially causing arrhythmias by inducing unidirectional conduction block and therefore circus-type or spiral wave re-entry [36, 37]. Pre-clinical experiments have

associated higher degrees of transmural dispersion of repolarization (TDR) with arrhythmogenesis observed in long QT and Brugada syndromes [38, 39].

A number of electrocardiographic indices have been developed for risk stratification [40, 41]. The $T_{peak} - T_{end}$ interval was first proposed by Yan and Antzelevitch as an electrocardiographic surrogate marker of TDR [24, 42-44]. This was based on observations in coronary-perfused wedge preparations, in which the end of repolarization of the epicardium coincided with the T_{peak} and end of repolarization of M-cells coincided with T_{end} [45]. Subsequent experiments in pigs suggest that T_{peak} coincided with the *earliest* end of repolarization and T_{end} coincided with the *latest* end of repolarization. However, given that the U-wave also represents the repolarizing current, T_{end} will likely reflect the majority of repolarization [46-48]. Together, $T_{peak} - T_{end}$ is a surrogate marker for global dispersion of repolarization [6, 9, 49, 50].

In clinical studies, an increase in $T_{peak} - T_{end}$ interval has been associated with ventricular arrhythmias in LQTS type 1 and type 2 [51, 52], Brugada syndrome [53] and other cardiac conditions such as myocardial infarction [54]. $T_{peak} - T_{end}$ interval can be normalized to the QT interval, yielding $T_{peak} - T_{end}$ / QT ratio, which is equivalent to heart rate correction by Bazett's formula, with a relatively constant range of 0.17 to 0.23 [12]. This is thought to be a more sensitive index of arrhythmia risk than $T_{peak} - T_{end}$ interval, as it provides an estimate of dispersion of repolarization relative to total duration of repolarization, which would eliminate the confounding effects of heart rate and QT interval variability. Despite several studies have demonstrated the predictive value of $T_{peak} - T_{end}$ / QT ratio [12, 16, 32, 51, 55-57], three studies failed to demonstrate its value in LQTS and SQTS [16, 58, 59]. Only one of the included studies compared the performance of $T_{peak} - T_{end}$ intervals to traditional repolarization markers. Firstly, Samol and colleagues reported a sensitivity of 83% and a specificity of 73% at a cut-off value of 87ms with an area

under the curve (AUC) of 0.80±0.07) for the prediction of adverse clinical events by $T_{peak} - T_{end}$ [20]. This compared to a comparable sensitivity of 82% but lower specificity of 68% with AUC of 0.86 ± 0.07 for QTc with a cut-off of 488 ms. It would appear that $T_{peak} - T_{end}$ has a higher specificity with similar sensitivity of discriminating high-risk patients when compared to QT_c. These need to be confirmed by larger studies. More complex derivations of these repolarization intervals have been proposed [60, 61], but whether these provide incremental value for risk stratification is controversial [62, 63].

However, incorporating conduction parameters into repolarization indices would likely improve risk stratification, since the likelihood of re-entry depends on both conduction velocity and refractory period, together determining the wavelength of excitation [64]. This can be estimated electrocardiographically [40, 65, 66]. Moreover, dispersion of conduction can predispose to unidirectional block. This can be observed as fragmentation in the QRS complex, whose prognostic value has been confirmed in Brugada syndrome [67]. Fragmented QRS has been observed in LQTS [68, 69], but whether it will be useful as a risk marker remains to be evaluated prospectively.

Limitations

The following strengths should be noted. Firstly, this is the only meta-analysis to date analyzing the predictive of $T_{peak} - T_{end}$ intervals and $T_{peak} - T_{end}$ / QT ratios for adverse clinical outcomes in congenital LQTS. Secondly, only a small degree of heterogeneity for the meta-analysis on mean difference of $T_{peak} - T_{end}$ intervals between event-positive and event-negative groups in congenital LQTS. This was despite different sub-types of congenital LQTS being included, suggesting that $T_{peak} - T_{end}$ intervals may be universally applicable regardless of the

underlying ion channel that is mutated. However, some limitations remain. Firstly, the percentage of male patients and age differed between the studies. As this was a study-level meta-analysis, it was not possible to ascertain the impact of these factors on $T_{peak} - T_{end}$ intervals. Secondly, $T_{peak} - T_{end}$ intervals vary with lead positions and therefore measurement of these intervals from different leads can introduce a source of heterogeneity. Thirdly, their methods of determination, such as measurement from a single T-wave, averaged values of T-waves or median complexes, also differ. Fourthly, the definition of T_{end} also differs between studies. Three studies used the tangent method by taking the intersection of a tangent to the steepest downslope of the dominant repolarization wave with the isoelectric line, one study used the point at which the T-wave crossed the isoelectric line, and one study did not specify the method of T_{end} determination. Fifthly, there is considerable inter-observer variability. Interestingly, a previous study noted that for patients with LQTS, more than 80% of arrhythmia experts but less than 50% of cardiologists and less than 40% of non-cardiologists calculated the QTc correctly, and that interobserver agreement was excellent among QT experts, but moderate among arrhythmia experts and low among cardiologists and non-cardiologists [70]. It also demonstrated underestimation of the QTc for LQTS patients and overestimation of this interval for healthy patients [70]. Finally, recall bias may have been present in the retrospective studies, which could have also contributed to some of the heterogeneity observed. Nevertheless, the aim of this study is to determine the prognostic value of $T_{peak} - T_{end}$ intervals, which we have confirmed in our meta-analysis.

Conclusions

This meta-analysis shows that $T_{peak} - T_{end}$ interval and $T_{peak} - T_{end}$ / QT ratio can distinguish high-risk patients with congenital LQTS from those who are at low-risk of adverse cardiac events. Further prospective studies with similarly definition of $T_{peak} - T_{end}$ interval from the same observers are needed to elucidate whether these indices provide additional value for risk stratification when compared to traditional repolarization indices such as the QTc interval.

References

[1] Priori SG, Schwartz PJ, Napolitano C, Bloise R, Ronchetti E, Grillo M, Vicentini A, Spazzolini C, Nastoli J, Bottelli G, Folli R, Cappelletti D: Risk stratification in the long-QT syndrome. N Engl J Med 2003; 348:1866-1874.

[2] Surawicz B: The QT interval and cardiac arrhythmias. Annu Rev Med 1987; 38:81-90.

[3] Tse G, Yan BP: Traditional and novel electrocardiographic conduction and repolarization markers of sudden cardiac death. Europace 2017; 19:712-721.

[4] Elming H, Holm E, Jun L, Torp-Pedersen C, Kober L, Kircshoff M, Malik M, Camm J: The prognostic value of the QT interval and QT interval dispersion in all-cause and cardiac mortality and morbidity in a population of Danish citizens. Eur Heart J 1998; 19:1391-1400.

[5] Linker NJ, Colonna P, Kekwick CA, Till J, Camm AJ, Ward DE: Assessment of QT dispersion in symptomatic patients with congenital long QT syndromes. Am J Cardiol 1992; 69:634-638.

[6] Xia Y, Liang Y, Kongstad O, Holm M, Olsson B, Yuan S: 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.

[7] Castro Hevia J, Antzelevitch C, Tornes Barzaga F, Dorantes Sanchez M, Dorticos Balea F, Zayas Molina R, Quinones Perez MA, Fayad Rodriguez Y: Tpeak-Tend and Tpeak-Tend dispersion as risk factors for ventricular tachycardia/ventricular fibrillation in patients with the Brugada syndrome. J Am Coll Cardiol 2006; 47:1828-1834.

[8] Gilmour RF, Jr.: Restitution, heterogeneity and unidirectional conduction block: New roles for old players. Heart Rhythm 2009; 6:544-545.

[9] Opthof T, Coronel R, Wilms-Schopman FJ, Plotnikov AN, Shlapakova IN, Danilo P, Jr., Rosen MR, Janse MJ: Dispersion of repolarization in canine ventricle and the electrocardiographic T wave: Tp-e interval does not reflect transmural dispersion. Heart Rhythm 2007; 4:341-348.

[10] Wiegerinck RF, van Veen TA, Belterman CN, Schumacher CA, Noorman M, de Bakker JM, Coronel R: Transmural dispersion of refractoriness and conduction velocity is associated with heterogeneously reduced connexin43 in a rabbit model of heart failure. Heart Rhythm 2008; 5:1178-1185.

[11] Coronel R, Wilms-Schopman FJ, Opthof T, Janse MJ: Dispersion of repolarization and arrhythmogenesis. Heart Rhythm 2009; 6:537-543.

[12] Gupta P, Patel C, Patel H, Narayanaswamy S, Malhotra B, Green JT, Yan GX: T(p-e)/QT ratio as an index of arrhythmogenesis. J Electrocardiol 2008; 41:567-574.

[13] Tse G, Gong M, Wong WT, Georgopoulos S, Letsas KP, Vassiliou VS, Chan YS, Yan BP, Wong SH, Wu WKK, Ciobanu A, Li G, Shenthar J, Saguner AM, Ali-Hasan-Al-Saegh S, Bhardwaj A, Sawant AC,

Whittaker P, Xia Y, Yan GX, Liu T: 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.

[14] Couderc J, Xia J, Xu X, Kaab S, Hinteeser M, Zareba W: Static and Dynamic Electrocardiographic Patterns Preceding Torsades de Pointes in the Acquired and Congenital Long QT Syndrome. Computing in cardiology 2010; 37:357-360.

[15] Couderc JP, Xia X, Peterson DR, McNitt S, Zhao H, Polonsky S, Moss AJ, Zareba W: T-wave morphology abnormalities in benign, potent, and arrhythmogenic I(kr) inhibition. Heart Rhythm 2011; 8:1036-1043.

[16] Yamaguchi M, Shimizu M, Ino H, Terai H, Uchiyama K, Oe K, Mabuchi T, Konno T, Kaneda T, Mabuchi H: T wave peak-to-end interval and QT dispersion in acquired long QT syndrome: a new index for arrhythmogenicity. Clin Sci (Lond) 2003; 105:671-676.

[17] Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart LA, Group P-P: Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Systematic Reviews 2015; 4:1.

[18] Marshall SC, Molnar F, Man-Son-Hing M, Blair R, Brosseau L, Finestone HM, Lamothe C, Korner-Bitensky N, Wilson KG: Predictors of driving ability following stroke: a systematic review. Top Stroke Rehabil 2007; 14:98-114.

[19] Krych M, Biernacka EK, Poninska J, Kukla P, Filipecki A, Gajda R, Hasdemir C, Antzelevitch C, Kosiec A, Szperl M, Ploski R, Trusz-Gluza M, Mizia-Stec K, Hoffman P: Andersen-Tawil syndrome: Clinical presentation and predictors of symptomatic arrhythmias - Possible role of polymorphisms K897T in KCNH2 and H558R in SCN5A gene. J Cardiol 2017; 70:504-510.

[20] Samol A, Gones M, Zumhagen S, Bruns HJ, Paul M, Vahlhaus C, Waltenberger J, Schulze-Bahr E, Eckardt L, Monnig G: Improved Clinical Risk Stratification in Patients with Long QT Syndrome? Novel Insights from Multi-Channel ECGs. PLoS One 2016; 11:e0158085.

[21] Kanters JK, Haarmark C, Vedel-Larsen E, Andersen MP, Graff C, Struijk JJ, Thomsen PE, Christiansen M, Jensen HK, Toft E: T(peak)T(end) interval in long QT syndrome. J Electrocardiol 2008; 41:603-608.

[22] Nerbonne JM, Kass RS: Molecular physiology of cardiac repolarization. Physiol Rev 2005; 85:1205-1253.

[23] Nerbonne JM, Guo W: Heterogeneous expression of voltage-gated potassium channels in the heart: roles in normal excitation and arrhythmias. J Cardiovasc Electrophysiol 2002; 13:406-409.

[24] Antzelevitch C: Heterogeneity and cardiac arrhythmias: an overview. Heart Rhythm 2007; 4:964-972.

[25] Chen Q, Kirsch GE, Zhang D, Brugada R, Brugada J, Brugada P, Potenza D, Moya A, Borggrefe M, Breithardt G, Ortiz-Lopez R, Wang Z, Antzelevitch C, O'Brien RE, Schulze-Bahr E, Keating MT, Towbin JA, Wang Q: Genetic basis and molecular mechanism for idiopathic ventricular fibrillation. Nature 1998; 392:293-296.

[26] Antzelevitch C, Yan GX, Ackerman MJ, Borggrefe M, Corrado D, Guo J, Gussak I, Hasdemir C, Horie M, Huikuri H, Ma C, Morita H, Nam GB, Sacher F, Shimizu W, Viskin S, Wilde AA: J-Wave syndromes expert consensus conference report: Emerging concepts and gaps in knowledge: Endorsed by the Asia Pacific Heart Rhythm Society (APHRS), the European Heart Rhythm Association (EHRA), the Heart Rhythm Society (HRS), and the Latin American Society of Cardiac Pacing and Electrophysiology (Sociedad Latinoamericana de Estimulacifin Cardiaca y Electro fi siologia [SOLAECE]). Europace 2017; 19:665-694.

[27] Liu T, Zheng J, Yan GX: J Wave Syndromes: History and Current Controversies. Korean Circ J 2016; 46:601-609.

[28] Tse G, Chan YW, Keung W, Yan BP: Electrophysiological mechanisms of long and short QT syndromes. Int J Cardiol Heart Vasc 2017; 14:8-13.
[29] Tse G, Tse V, Yeo JM: Ventricular anti‐arrhythmic effects of heptanol in hypokalaemic, Langendorff‐perfused mouse hearts. Biomed Rep 2016; 4:313-324.
[30] Tse G, Sun B, Wong ST, Tse V, Yeo JM: Anti-arrhythmic effects of hypercalcemia in hyperkalemic, Langendorff-perfused mouse hearts. Biomed Rep 2016; 5:301-310.
[31] Erikssen G, Liestol K, Gullestad L, Haugaa KH, Bendz B, Amlie JP: The terminal part of the QT interval (T peak to T end): a predictor of mortality after acute myocardial infarction. Ann Noninvasive Electrocardiol 2012; 17:85-94.
[32] Tokatli A, Kilicaslan F, Alis M, Yiginer O, Uzun M: Prolonged Tp-e Interval, Tp-e/QT Ratio and Tp-e/QTc Ratio in Patients with Type 2 Diabetes Mellitus. Endocrinol Metab (Seoul) 2016; 31:105-112.
[33] Jani Y, Kamberi A, Xhunga S, Pocesta B, Ferati F, Lala D, Zeqiri A, Rexhepi A: The influence of type 2 diabetes and gender on ventricular repolarization dispersion in patients with sub-clinic left ventricular diastolic dysfunction. American journal of cardiovascular disease 2015; 5:155-166.
[34] Tse G, Lai ET, Tse V, Yeo JM: Molecular and electrophysiological mechanisms underlying cardiac arrhythmogenesis in diabetes mellitus. J Diabetes Res 2016; 2016:2848759.
[35] Dogan M, Yiginer O, Degirmencioglu G, Un H: Transmural dispersion of repolarization: a complementary index for cardiac inhomogeneity. Journal of Geriatric Cardiology : JGC 2016; 13:99-100.
[36] Shaw RM, Rudy Y: The vulnerable window for unidirectional block in cardiac tissue: characterization and dependence on membrane excitability and intercellular coupling. J Cardiovasc Electrophysiol 1995; 6:115-131.
[37] Tse G, Wong ST, Tse V, Lee YT, Lin HY, Yeo JM: Cardiac dynamics: Alternans and arrhythmogenesis. J Arrhythm 2016; 32:411-417.
[38] Tse G, Wong ST, Tse V, Yeo JM: Restitution analysis of alternans using dynamic pacing and its comparison with S1S2 restitution in heptanol-treated, hypokalaemic Langendorff-perfused mouse hearts. Biomed Rep 2016; 4:673-680.
[39] Shimizu W, Aiba T, Kamakura S: Mechanisms of disease: current understanding and future challenges in Brugada syndrome. Nat Clin Pract Cardiovasc Med 2005; 2:408-414.
[40] Robyns T, Lu HR, Gallacher DJ, Garweg C, Ector J, Willems R, Janssens S, Nuyens D: Evaluation of Index of Cardio-Electrophysiological Balance (iCEB) as a New Biomarker for the Identification of Patients at Increased Arrhythmic Risk. Ann Noninvasive Electrocardiol 2016; 21:294-304.
[41] Robyns T, Lu HR, Gallacher DJ, Garweg C, Ector J, Willems R, Janssens S, Nuyens D: Evaluation of Index of Cardio-Electrophysiological Balance (iCEB) as a New Biomarker for the Identification of Patients at Increased Arrhythmic Risk. Ann Noninvasive Electrocardiol 2016.
[42] Shimizu W, Antzelevitch C: Cellular and ionic basis for T-wave alternans under long-QT conditions. Circulation 1999; 99:1499-1507.
[43] Emori T, Antzelevitch C: Cellular basis for complex T waves and arrhythmic activity following combined I(Kr) and I(Ks) block. J Cardiovasc Electrophysiol 2001; 12:1369-1378.
[44] 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.
[45] Antzelevitch C, Shimizu W, Yan GX, Sicouri S, Weissenburger J, Nesterenko VV, Burashnikov A, Di Diego J, Saffitz J, Thomas GP: 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.
[46] Postema PG, Ritsema van Eck HJ, Opthof T, van Herpen G, van Dessel PF, Priori SG, Wolpert C, Borggrefe M, Kors JA, Wilde AA: IK1 modulates the U-wave: insights in a 100-year-old enigma. Heart Rhythm 2009; 6:393-400.
[47] Morita H, Zipes DP, Morita ST, Wu J: Mechanism of U wave and polymorphic ventricular tachycardia in a canine tissue model of Andersen-Tawil syndrome. Cardiovasc Res 2007; 75:510-518.

[48] Ritsema van Eck HJ, Kors JA, van Herpen G: Dispersion of repolarization, myocardial iso-source maps, and the electrocardiographic T and U waves. J Electrocardiol 2006; 39:S96-100.
[49] Xia Y, Liang Y, Kongstad O, Liao Q, Holm M, Olsson B, Yuan S: In vivo validation of the coincidence of the peak and end of the T wave with full repolarization of the epicardium and endocardium in swine. Heart Rhythm 2005; 2:162-169.
[50] Opthof T, Coronel R, Janse MJ, Rosen MR: A wedge is not a heart. Heart Rhythm 2007; 4:1116-1119.
[51] Takenaka K, Ai T, Shimizu W, Kobori A, Ninomiya T, Otani H, Kubota T, Takaki H, Kamakura S, Horie M: Exercise stress test amplifies genotype-phenotype correlation in the LQT1 and LQT2 forms of the long-QT syndrome. Circulation 2003; 107:838-844.
[52] Watanabe H, Makiyama T, Koyama T, Kannankeril PJ, Seto S, Okamura K, Oda H, Itoh H, Okada M, Tanabe N, Yagihara N, Kamakura S, Horie M, Aizawa Y, Shimizu W: High prevalence of early repolarization in short QT syndrome. Heart Rhythm 2010; 7:647-652.
[53] Zumhagen S, Zeidler EM, Stallmeyer B, Ernsting M, Eckardt L, Schulze-Bahr E: Tpeak-Tend interval and Tpeak-Tend/QT ratio in patients with Brugada syndrome. Europace 2016; 18:1866-1872.
[54] Tse G, Wong CW, Gong M, Meng L, Letsas KP, Li G, Whittaker P, Bhardwaj A, Sawant AC, Wu WKK, Wong SH, Shenthar J, Tse LA, Wong MCS, Baranchuk A, Yan GX, Liu T: Meta-analysis of T-wave indices for risk stratification in myocardial infarction. . Journal of Geriatric Cardiology 2017.
[55] Letsas KP, Charalampous C, Korantzopoulos P, Tsikrikas S, Bramos D, Kollias G, Efremidis M, Sideris A: Novel indexes of heterogeneity of ventricular repolarization in subjects with early repolarization pattern. Europace 2012; 14:877-881.
[56] Zhao X, Xie Z, Chu Y, Yang L, Xu W, Yang X, Liu X, Tian L: Association between Tp-e/QT ratio and prognosis in patients undergoing primary percutaneous coronary intervention for ST-segment elevation myocardial infarction. Clin Cardiol 2012; 35:559-564.
[57] Ozdemir R, Isguder R, Kucuk M, Karadeniz C, Ceylan G, Katipoglu N, Yilmazer MM, Yozgat Y, Mese T, Agin H: A Valuable Tool in Predicting Poor Outcome due to Sepsis in Pediatric Intensive Care Unit: Tp-e/QT Ratio. J Trop Pediatr 2016.
[58] Samol A, Gönes M, Zumhagen S, Bruns H-J, Paul M, Vahlhaus C, Waltenberger J, Schulze-Bahr E, Eckardt L, Mönnig G: Improved Clinical Risk Stratification in Patients with Long QT Syndrome? Novel Insights from Multi-Channel ECGs. PLOS ONE 2016; 11:e0158085.
[59] Giustetto C, Schimpf R, Mazzanti A, Scrocco C, Maury P, Anttonen O, Probst V, Blanc JJ, Sbragia P, Dalmasso P, Borggrefe M, Gaita F: Long-term follow-up of patients with short QT syndrome. J Am Coll Cardiol 2011; 58:587-595.
[60] 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.
[61] Tse G, Yan BP: Novel arrhythmic risk markers incorporating QRS dispersion: QRSd x (Tpeak - Tend)/QRS and QRSd x (Tpeak - Tend)/(QT x QRS). Ann Noninvasive Electrocardiol 2017; 22.
[62] Robyns T, Lu HR, Gallacher DJ, Garweg C, Ector J, Willems R, Janssens S, Nuyens D: Response of Robyns to the Tse's letter to editor. Ann Noninvasive Electrocardiol 2017; 22.
[63] Zumhagen S, Stallmeyer B, Eckardt L, Schulze-Bahr E: (Tpeak - Tend)/QRS and (Tpeak - Tend)/(QT x QRS) as risk markers in Brugada syndrome: authors' reply. Europace 2017; 19:696-697.
[64] Tse G: Novel conduction-repolarization indices for the stratification of arrhythmic risk. J Geriatr Cardiol 2016; 13:811-812.
[65] 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.
[66] Lu HR, Yan GX, Gallacher DJ: 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.

[67] Meng L, Letsas KP, Baranchuk A, Shao Q, Tse G, Zhang N, Zhang Z, Hu D, Li G, Liu T: Meta-analysis of Fragmented QRS as an Electrocardiographic Predictor for Arrhythmic Events in Patients with Brugada Syndrome. Front Physiol 2017; 8:678.
[68] Moss AJ: Fragmented QRS: the new high-risk kid on the block in acquired long QT syndrome. Heart Rhythm 2010; 7:1815-1816.
[69] Haraoka K, Morita H, Saito Y, Toh N, Miyoshi T, Nishii N, Nagase S, Nakamura K, Kohno K, Kusano KF, Kawaguchi K, Ohe T, Ito H: Fragmented QRS is associated with torsades de pointes in patients with acquired long QT syndrome. Heart Rhythm 2010; 7:1808-1814.
[70] Viskin S, Rosovski U, Sands AJ, Chen E, Kistler PM, Kalman JM, Rodriguez Chavez L, Iturralde Torres P, Cruz FF, Centurion OA, Fujiki A, Maury P, Chen X, Krahn AD, Roithinger F, Zhang L, Vincent GM, Zeltser D: Inaccurate electrocardiographic interpretation of long QT: the majority of physicians cannot recognize a long QT when they see one. Heart Rhythm 2005; 2:569-574.

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Additional information

No conflicts of interest declared.

Tables

Table 1 Characteristics of the ten studies included in this meta-analysis

First author / Year	Study design	Population	Lead for $T_{peak} - T_{end}$ measurement	Method of T_{end} measurement	Sample size (n)	Age	% Male	Endpoints	No. of patients with any positive events	Syncope	Ventricular arrhythmia	SCA / SCD	Reference
Krych 2017	Retrospective	Congenital LQT7 (KCNJ2)	V2 or V3	Not specified	25	30	52	Syncope, CA, PVC > 2000 / 24 hours, PVT, BiVT	14	-	-	-	[19]
Samol 2016	Prospective	Congenital LQT1 (KCNQ1), 2 (KCNH2),8 (CACNA1c) and unknown subtype	V1	Tangent method	34	31	32	Syncope, TdP, SCA	12	12	7 (TdP)	4 (SCA)	[20]
Couderc 2011	Retrospective	Drug-induced and congenital LQTS (KCNH2)	II	Tangent method	143	38	39	SCA, SCD	74	77	-	11 (SCA), 3 (SCD)	[15]
Couderc 2010	Retrospective	Drug-induced and congenital LQTS (subtypes not described)	All 12 leads	Tangent method	8	7	63	TdP	5	-	5	-	[14]
Kanters 2008	Retrospective	Congenital LQT1 (KCNQ1), 2 (KCNH2), 3 (SCN5A)	V5	The point at which T-wave crosses isoelectric line	95	37	34	Syncope	45	45	-	-	[21]

Abbreviations: LQT: long QT; CA: cardiac arrest; SCA: sudden cardiac arrest; SCD: Sudden cardiac death; ICD: implantable cardioverter-defibrillator; PVC: premature ventricular complex; VT: Ventricular tachycardia; PVT: polymorphic VT; BiVT: bidirectional VT;

Figures

Figure 1. Flow diagram of the study selection process.

Figure 2. Forest plot demonstrating the mean differences for between $T_{peak} - T_{end}$ intervals obtained from event-positive and event-negative groups in LQTS.

Figure 3. Forest plot demonstrating the mean differences for between $T_{peak} - T_{end}$/QT ratios from in event-positive and event-negative groups in LQTS.

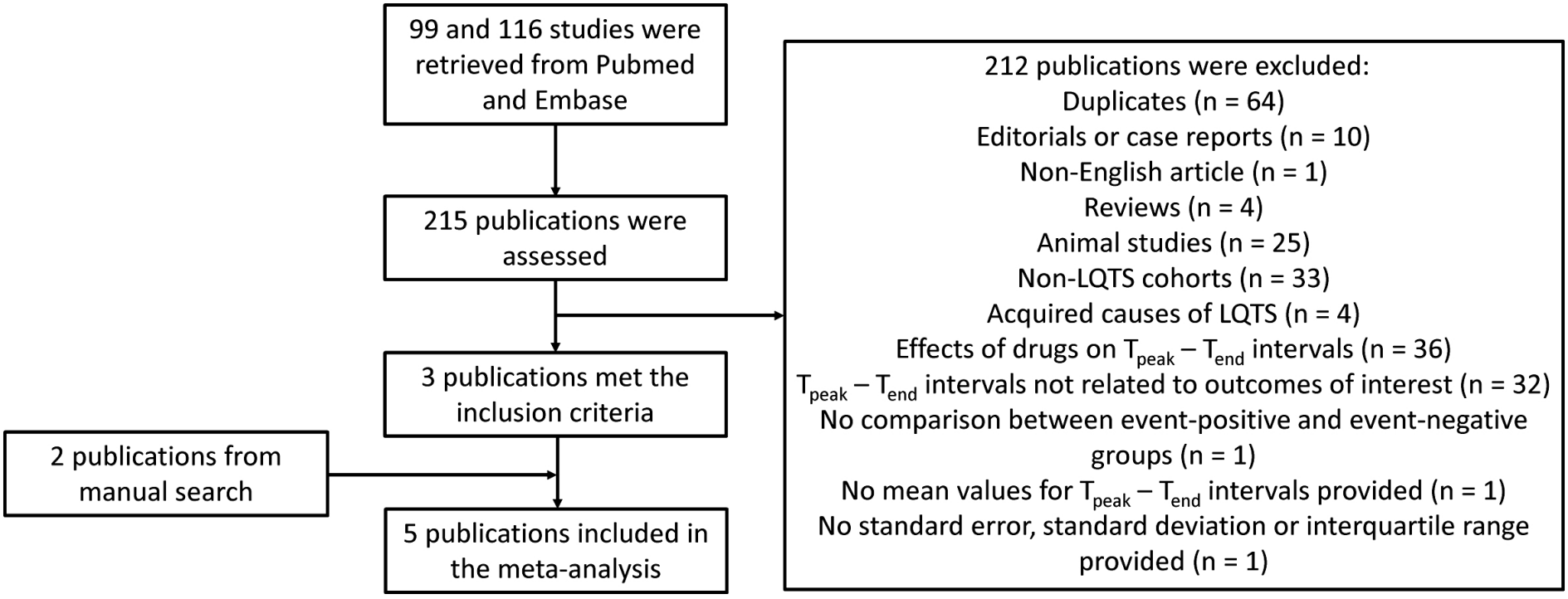
99 and 116 studies were retrieved from Pubmed and Embase
215 publications were assessed
3 publications met the inclusion criteria
2 publications from manual search
5 publications included in the meta-analysis
212 publications were excluded:
Duplicates (n = 64)
Editorials or case reports (n = 10)
Non-English article (n = 1)
Reviews (n = 4)
Animal studies (n = 25)
Non-LQTS cohorts (n = 33)
Acquired causes of LQTS (n = 4)
Effects of drugs on $T_{peak} – T_{end}$ intervals (n = 36)
$T_{peak} – T_{end}$ intervals not related to outcomes of interest (n = 32)
No comparison between event-positive and event-negative groups (n = 1)
No mean values for $T_{peak} – T_{end}$ intervals provided (n = 1)
No standard error, standard deviation or interquartile range provided (n = 1)

Figure 1

$T_{peak} - T_{end}$

Study name	Difference in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
			Statistics for each study				
Krych 2017	29.000	10.690	114.281	8.047	49.953	2.713	0.007
Samol 2016	19.900	9.099	82.789	2.067	37.733	2.187	0.029
Couderc 2011	3.000	5.824	33.917	-8.415	14.415	0.515	0.606
Couderc 2010	14.000	32.391	1049.167	-49.485	77.485	0.432	0.666
Kanters 2008	19.000	10.248	105.031	-1.087	39.087	1.854	0.064
	12.779	4.056	16.451	4.830	20.729	3.151	0.002

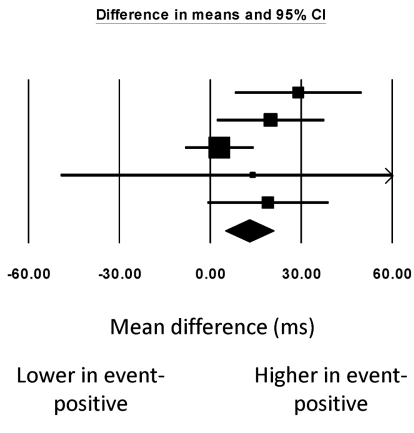

Figure 2

$T_{peak} - T_{end}$ / QT ratio

Study name	Difference in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
			Statistics for each study				
Krych 2017	0.056	0.087	0.008	-0.114	0.226	0.645	0.519
Samol 2016	0.018	0.018	0.000	-0.017	0.053	1.017	0.309
Couderc 2011	0.009	0.058	0.003	-0.104	0.123	0.164	0.870
Couderc 2010	-0.008	0.221	0.049	-0.441	0.424	-0.038	0.970
	0.019	0.017	0.000	-0.014	0.051	1.119	0.263

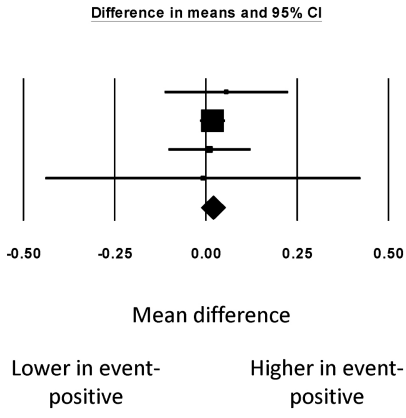

Figure 3