Indian Pacing and Electrophysiology Journal 19 (2019) 205–210

Contents lists available at ScienceDirect

Indian Pacing and Electrophysiology Journal

journal homepage: www.elsevier.com/locate/IPEJ

Markers of ventricular repolarization as an additional non-invasive electrocardiography parameters for predicting ventricular tachycardia/fibrillation in patients with Brugada Syndrome – A systematic review and meta-analysis

Raymond Pranata [a, *], Emir Yonas [b], Rachel Vania [a], Ian Huang [a]

[a] Faculty of Medicine, Universitas Pelita Harapan, Tangerang, Indonesia
[b] Faculty of Medicine, Universitas YARSI, Jakarta, Indonesia

ARTICLE INFO

Article history:
Received 11 April 2019
Accepted 21 June 2019
Available online 22 June 2019

Keywords:
TpTe interval
Tpe dispersion
TpTe interval/QT ratio
QTc interval
Brugada syndrome

ABSTRACT

Background: Controversies surrounded the management of asymptomatic Brugada syndrome. Prognostication using electrophysiology study (EPS) is disputable. Non-invasive parameters may be a valuable additional tool for risk stratification. We aim to evaluate the use markers of ventricular repolarization including Tpeak-to-Tend (TpTe), Tpe Dispersion, TpTe/QT ratio, and QTc interval as additional non-invasive electrocardiography parameters for predicting ventricular tachycardia/fibrillation in patients with Brugada syndrome.

Methods: We performed a comprehensive search on TpTe, Tpe Dispersion, TpTe/QT ratio, and QTc interval as a predictor for ventricular tachycardia(VT)/fibrillation(VF)/aborted sudden cardiac death/appropriate ICD shock in patients with Brugada syndromes up until October 2018.

Results: We included ten studies in the qualitative synthesis and eight studies in meta-analysis. There were a total of 2126 subjects from ten studies. We found that TpTe interval (mean difference 11.97 m s [5.02–18.91]; $p < 0.001$; I^2 80% possibly on ≥80–100 m s and maximum QTc interval (mean difference 11.42 m s [5.90–16.93], $p < 0.001$; I^2 28%) were the most potential ECG parameters to predict VT/VF/AT/SCD. Tpe dispersion and TpTe/QT ratio have a high heterogeneity. Upon sensitivity analysis, there is no single study found to markedly affect heterogeneity of Tpe dispersion and TpTe/QT ratio. Removal of a study reduced maximum QTc interval heterogeneity to 0%.

Conclusions: Measurement of TpTe interval, Tp-e dispersion, TpTe/QT ratio, and QTc interval on ECG emerge as a promising prognostication tool which needs further investigations with a more standardized method, outcome, and cut-off points. As for now, only maximum QTc interval has a reliable result with low heterogeneity sufficiently reliable for prognostication.

1. Introduction

Brugada syndrome is a genetically determined channelopathy leading to syncope and ventricular tachyarrhythmia causing sudden death in those without evident structural heart disease [1]. The established predictor of sudden cardiac death includes spontaneous type 1 electrocardiography (ECG) and aborted sudden cardiac death (SCD) or syncope of arrhythmic origin [2,3]. This warrants the implantation of an implantable cardioverter defibrillator (ICD). However, controversies surround the management of asymptomatic Brugada syndrome as the only established predictor in this patient is spontaneous type 1 ECG which is deemed insufficient [4]. The value of ventricular inducibility on electrophysiology study (EPS) remains controversial [2,5,6].

Other new non-invasive parameters may be a valuable additional tool for risk stratification. Recent studies evaluated the use of additional ECG/signal-averaged ECG parameters such as fragmented QRS complexes, QRS width, lead aVR sign, early repolarization, late potentials, and T-wave alternans [7–18]. Tpeak-to-Tend

* Corresponding author. Faculty of Medicine, Universitas Pelita Harapan, Tangerang, Banten, Indonesia.
E-mail addresses: raymond_pranata@hotmail.com (R. Pranata), E_yonas@windowslive.com (E. Yonas), Rachel.vania@gmail.com (R. Vania), ianhuang2108@gmail.com (I. Huang).

Peer review under responsibility of Indian Heart Rhythm Society.

https://doi.org/10.1016/j.ipej.2019.06.003

(TpTe), TpTe/QT ratio, and Tpe Dispersion which are the interest of this systematic review are also touted to have prognostic value for predicting sudden cardiac death [19–21]. If these less established parameters acquired sufficient evidence for their use in clinical practice may be used to formulate new risk stratification criteria without having to order additional invasive tests for the patient.

This systematic review will evaluate the markers of ventricular repolarization which includes TpTe, Tpe Dispersion, TpTe/QT ratio, and QTc interval as additional non-invasive electrocardiography parameters for predicting ventricular tachycardia/fibrillation/aborted sudden cardiac death/appropriate ICD shocks in patients with Brugada syndrome.

2. Methods

2.1. Search strategy

We performed a comprehensive search on topic that assesses TpTe, Tpe Dispersion, TpTe/QT ratio, and QTc interval as a predictor for ventricular tachycardia(VT)/fibrillation(VF)/aborted sudden cardiac death/appropriate ICD shocks from inception up until October 2018 through PubMed, EuropePMC, EBSCOhost, Cochrane Central Database, and ClinicalTrials.gov. A broad strategy to maximise the initial scope of research with keyword [tpeak tend and Brugada syndrome] and its related synonym to ensure largest amount of records searched. The records were then systematically evaluated using inclusion and exclusion criteria. We also snowballed from references of the included studies and abstracts from conference proceedings. Two researchers (R.V and I.H) independently performed an initial search, discrepancies were resolved by discussion. (A Preferred Reporting Items for Systematic Reviews and Meta-Analyses flowchart of the literature search strategy of studies investigating the ablation index was presented in Fig. 1.

2.2. Selection criteria

The inclusion criteria for this study is all prognostic studies that assess TpTe, Tpe Dispersion, TpTe/QT ratio, and QTc interval as a predictor for VT/VF/aborted sudden cardiac death/appropriate ICD shocks in patients with Brugada syndrome. We include all related clinical researches/original articles and exclude case reports, and review articles.

2.3. Data extraction

Data extraction and quality assessment were done by two independent authors (R.P and E. Y) using standardized extraction form which includes authors, year of publication, study design, sample size, VT, VF, aborted SCD. Appropriate ICD shocks, TpTe interval, Tpe dispersion, TpTe/QT ratio, and Max QTc interval.

2.4. Statistical analysis

To perform a meta-analysis, we used RevMan version 5.3. We used mean difference and its standard deviation as a pooled measure for the continuous data. Inconsistency index (I [2]) test which ranges from 0 to 100% was used to assess heterogeneity across studies. A value above 50% or $p < 0.05$ indicates statistically significant heterogeneity. We used the Inverse Variance method with a fixed-effect model for meta-analysis and random-effects model was used in case of heterogeneity. All P values were two-tailed with a statistical significance set at 0.05 or below.

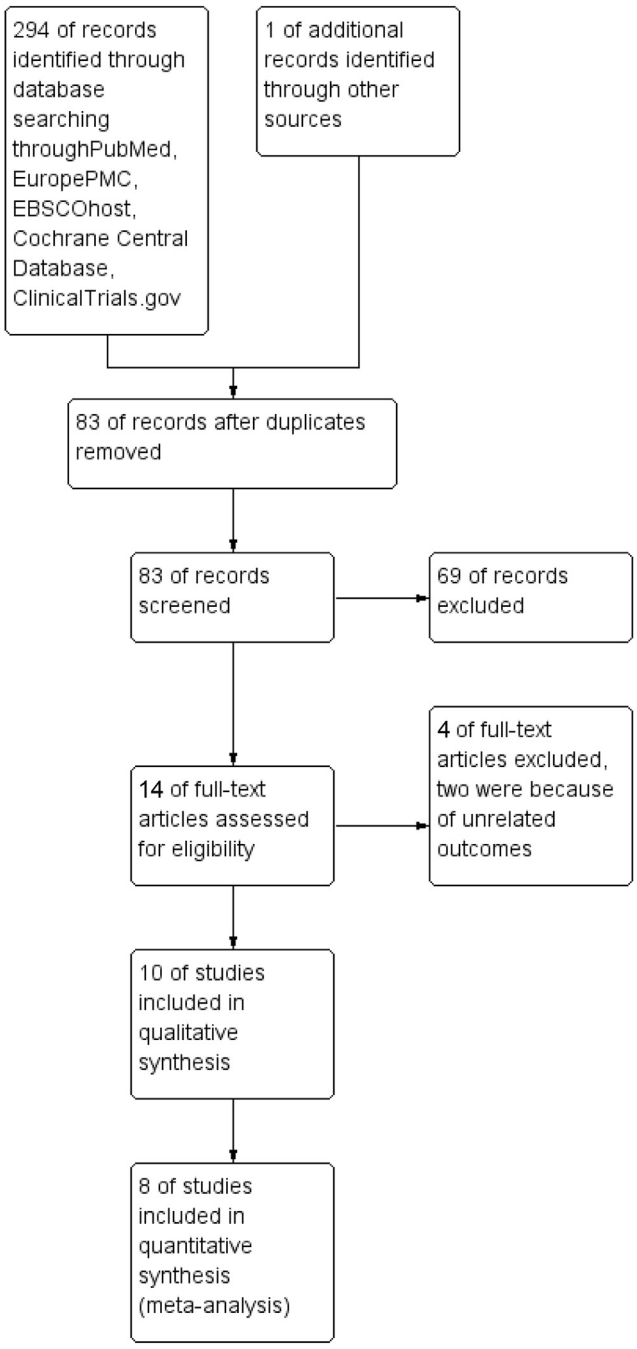

Fig. 1. Study flow diagram.

3. Results

We found a total of 294 results and acquired one additional record from snowballing. 83 were relevant titles/abstract. After assessing 14 full-text for eligibility; we excluded four studies because of unrelated outcomes. We included ten studies in the qualitative synthesis and eight studies in meta-analysis [19–27]. (Fig. 1) Four studies are prospective cohort, one cross-sectional, and five are case-control studies. There were a total of 2126 subjects from ten studies (Table 1). We exclude two studies from meta-analysis because the Letsas et al. uses VT/VF inducibility as the outcome and there is insufficient data in Hevia et al.

Table 1
Summary of the key findings of this systematic review.

Study	Study Design	Samples	Subjects	Outcome of Interest	Results
Morita 2018	Case-Control	62	Brugada-type ECG	Initial VF	1. TpTe → OR of difference Tpe interval (V1) ≥ +10 m s: 11.0, CI: 2.6–46.1, p = 0.001. Mean 108 ± 33 m s vs 78 ± 18 m s; p < 0.01. 2. Tpe Dispersion → No Data 3. TpTe/QT ratio → No Data 4. Max QTc → Mean 411 ± 52 m s vs 371 ± 33 m s; p < 0.01.
Morita 2017	Retrospective Cohort	471	Brugada Syndrome	VF (but also included syncope)	1. TpTe → TpTe V2 ≥ 95 → HR 3.03 1.26–9.01 0.0143. Mean 86 ± 25 m s vs 81 ± 23 m s; p = 0.04. 2. Tpe Dispersion → No Data 3. TpTe/QT ratio → No Data 4. Max QT (not corrected) → Mean 399 ± 41 m s vs 385 ± 34 m s; p < 0.0003.
Zumhagen 2016	Case-Control	78	Brugada Syndrome	VT/VF/Aborted SCD	1 TpTe → ≥ 77 m s, 63.6% & 74.1%; AUC 0.675. Mean 87 ± 30 m s vs 71 ± 21 m s 2 Tpe Dispersion → No Data 3 TpTe/QT ratio → ≥ 0.205, 72.7% & 68.5%; AUC 0.673. Mean 0.24 ± 0.09 m s vs 0.19 ± 0.05 m s 4 Max QTc → not statistically significant
Maury 2015	Case-Control	325	Brugada Syndrome	SCF/Appropriate ICD Shocks	1. TpTe → Max Tpe >100 m s OR of 9.61 (95% CI 3.13–9.41) (p < 0.0001). Sensitivity 84% & Specificity 68%, PPV 19%, NPV 98%. Mean 85 ± 18 m s vs 67 ± 22 m s; p < 0.001 2. Tpe Dispersion → Mean 47 ± 27 m s vs 30 ± 17 m s; p = 0.005 3. TpTe/QT ratio → Mean 0.21 ± 0.04 vs 0.17 ± 0.05; p < 0.0001 4. Max QTc → No Data 5. AUROC: 0.789
Mugnai 2017	Cohort	448	Brugada Syndrome	VT/VF/SCD/ Appropriate ICD Shocks	1 TpTe → Not statistically significant 2 Tpe Dispersion → Not statistically significant 3 TpTe/QT ratio → Not statistically significant 4 Max QTc → not statistically significant
Kawazoe 2016	Case-Control	143	Brugada Syndrome	VF	1. TpTe → mean 124 ± 33 m s vs 104 ± 22 m s; p = 0.001 2. Tpe Dispersion → Mean 59 ± 29 m s vs 35 ± 23 m s; p = 0.0001. Tpe Dispersion was an independent predictor of VF, adjusted OR 1.069 (1.03–1 .10), p = 0.001. 3. TpTe/QT ratio → No Data. 4. Max QTc → Mean 401 ± 32 m s vs 386 ± 37 m s; p = 0.33. 5. Tpe Dispersion AUROC 0.869
Letsas 2010	Case-Control	23	Brugada Syndrome	VT/VF Inducibility	1 TpTe → TpTe V2 (88.82 ± 15.70 m s vs. 78.33 ± 4.08 m s, P = 0.02) and V6 (mean 76.33 ± 10.08 m s vs 66.66 ± 5.16 m s, P = 0.04). 2 Tpe Dispersion → Not statistically significant. 3 TpTe/QT ratio → Greater Tpeak–Tend/QT ratio in lead V6 (0.214 + 0.028 vs 0.180 + 0.014, P = 0.009). 4 Max QTc → Not statistically significant.
Hevia 2006	Cohort	29	Brugada Syndrome	VT/VF	1. TpTe → TpTe Cut-off point >100 m s; Sensitivity 77.8% & specificity 70%; AUC 0.7861. TpTe was significantly prolonged in patients with recurrences versus patients without events (mean 104.4 m s vs 87.4 m s; p = 0.006). 2. Tpe Dispersion → Tp-e dispersion Cut-off point >20 m s; Sensitivity 66.7% & Specificity 90%; AUC 0.7722. Tp-e dispersion was significantly prolonged in patients with recurrences versus patients without events (mean 35.6 m s vs 23.2 m s; p = 0.03). 3. TpTe/QT ratio → No Data 4. Max QTc → QTc >460 m s in V2, was associated with VT/VF recurrence; p = 0.03
Calo 2016	Cohort	347	Brugada Syndrome	VF/SCD	1. TpTe → TpTe HR 1.028 [1.013–1.042]; <0.0001 (cut-off unknown). Mean 90 ± 25 m s vs 72 ± 22 m s; p = 0.044. 2. Tpe Dispersion → No Data 3. TpTe/QT ratio → No Data 4. Max QTc → Not statistically significant
Juntilla 2008	Cross-Section	200	Brugada Syndrome	Syncope/VT/VF/ SCD	1. TpTe → Not statistically significant 2. Tpe Dispersion → No Data 3. TpTe/QT ratio → No Data 4. Max QTc → Not statistically significant

Description: TpTe = Tpeak-Tend interval; SCD=Sudden Cardiac Death; ICD=Implantable Cardioverter Defibrillator; VF=Ventricular Fibrillation; VT=Ventricular Tachycardia. Results of the systematic review of the role of Tpeak-Tend, Tpeak-Tend/QT ratio, and Tpe Dispersion as Additional Non-Invasive Electrocardiography Parameters for Predicting Ventricular Tachycardia/Fibrillation in Patients with Brugada Syndrome.

3.1. Tpeak-Tend interval

A total of eight studies showed that TpTe is reliable in predicting VT/VF/aborted SCD/appropriate ICD shocks, cut-off points varied between precordial leads from ≥80 m s to ≥100 m s in which two studies reported a sensitivity 77.8–84% & specificity 68–70%; PP 19%, NPV 98%, OR 9.61 (95% CI 3.13–9.41) (p < 0.0001), AUC 0.7861 with ≥100 m s. Kawazoe et al. and Maury et al. demonstrated the association of longer TpTe interval and VF/SCD/Appropriate ICD Shocks (mean 124 ± 33 m s vs 104 ± 22 m s and 85 ± 18 m s vs 67 ± 22 m s respectively). Morita-1 et al. and Zumhagen et al. demonstrated (mean 108 ± 33 vs 78 ± 18 and 87 ± 30 m s vs 71 ± 21 m s respectively). According to Mugnai et al. and Juntilla et al. TpTe is not a statistically significant predictor of VT/VF/SCD/ Appropriate ICD Shocks. Morita-1 et al. study indicated that the progression of Tpe >10 m s on repeat ECG correlates with OR 11.6 (p = 0.001). Calo et al. showed that longer TpTe interval (Mean 90 ± 25 m s vs 72 ± 22 m s) was associated with VF/SCD HR 1.028 [1.013–1.042]; <0.0001 (cut-off unknown). Morita-2 et al. showed that longer TpTe interval was associated with VF + syncope than asymptomatic subjects HR 3.03 1.26–9.01 0.0143, mean 86 ± 25 m s vs 81 ± 23 m s. Hevia et al. showed that TpTe was significantly prolonged in patients with recurrence VT/VF versus patients without events (mean 104.4 m s vs 87.4 m s). Calo et al. revealed a longer TpTe interval in those experiencing VF/SCD (mean 90 ± 25 m s vs 72 ± 22 m s). Letsas et al. demonstrated that patient that is VT/VF inducible had a longer TpTe interval (Lead V_2: 88.82 ± 15.70 m s vs 78.33 ± 4.08 m s, P = 0.02). Our meta-analysis

showed significant difference in Tpeak-Tend interval (mean difference 11.97 m s [5.02–18.91]; p < 0.001, high heterogeneity I [2] 80%; p < 0.001) between groups experiencing VT/VF/AT (Appropriate ICD Shock)/Aborted SCD compared to those without VT/VF/AT/Aborted SCD (Fig. 2A).

3.2. Tpe Dispersion

Kawazoe et al. and Maury et al. reported that Tp-e dispersion was associated with VT/VF (mean 59 ± 29 vs 35 ± 23 and 47 ± 27 vs 30 ± 17 respectively). Kawazoe et al. also reported that Tpe Dispersion was an independent predictor of VF, adjusted OR 1.069 (1.03–1 0.10), p = 0.001. Hevia et al. of which reported Cut-off point >20 m s; Sensitivity 66.7% & Specificity 90%; AUC 0.7722. Only Mugnai et al. demonstrated the non-significant relation of the parameters above and VT/VF. Letsas et al. showed no difference between Tpe dispersion and ventricular inducibility upon EP study. Our meta-analysis demonstrated no significant difference in Tpe dispersion between groups experiencing VT/VF/AT/Aborted SCD compared to those without VT/VF/AT/Aborted SCD (Fig. 3A). The fixed-effect model yields a statistically significant result, but not the random-effect model.

3.3. Tpeak-Tend/QT ratio

Zumhagen et al. showed that TpTe/QT ratio is reliable in predicting VT/VF in which a ratio of ≥0.205 has sensitivity 72.7% & specificity 68.5%; AUC 0.673. Letsas et al. indicate that TpTe and greater Tpeak–Tend/QT ratio in lead V6 is related to VT/VF inducibility, but the latter was not related to the arrhythmic outcome. The data for a direct association with the arrhythmic outcome was unavailable. Maury et al. demonstrated that patients with sudden death/appropriate ICD shocks have a higher TpTe/QT Ratio (Mean 0.21 ± 0.04 vs 0.17 ± 0.05). However, Mugnai et al. showed no association between TpTe/QT Ratio and VT/VF/SCD/Appropriate ICD Shocks. Hence, two studies are in favour of its use but one is against, and one lacks direct association to the outcome. Our meta-analysis revealed no significant difference in TpTe/QT Ratio between groups experiencing VT/VF/AT/Aborted SCD compared to those without VT/VF/AT/Aborted SCD (Fig. 3B). The fixed-effect model yields a statistically significant result, but not the random-effect model.

3.4. Maximum QTc interval

Kawazoe et al. and Morita-1 et al. demonstrated a higher maximum QTc interval in patients with VT/VF/Aborted SCD (mean 401 ± 32 m s vs 386 ± 37 m s and 411 ± 52 m s vs 371 ± 33 m s respectively). Mugnai et al., Calo et al., Juntilla et al. and Zumhagen et al. showed no association between maximum QTc interval and VT/VF/SCD/Appropriate ICD Shocks. Also, Morita-2 et al. showed max QT (not corrected) had a mean 399 ± 41 m s vs 385 ± 34 m s in VF + syncope group compared to asymptomatic subjects. Hevia et al. stated that QTc >460 m s in V2 was associated with VT/VF recurrence; p = 0.03. Our meta-analysis demonstrated a significant difference in maximum QTc interval (mean difference 11.42 m s [5.90–16.93]; p < 0.001, low heterogeneity I [2] 28%; p = 0.23) between groups experiencing VT/VF/AT/Aborted SCD compared to those without VT/VF/AT/Aborted SCD (Fig. 2B).

3.5. Sensitivity analysis

We performed a sensitivity analysis by removing one study at a time in an attempt to reduce heterogeneity. We found that no single study markedly affected the summary estimate or p values

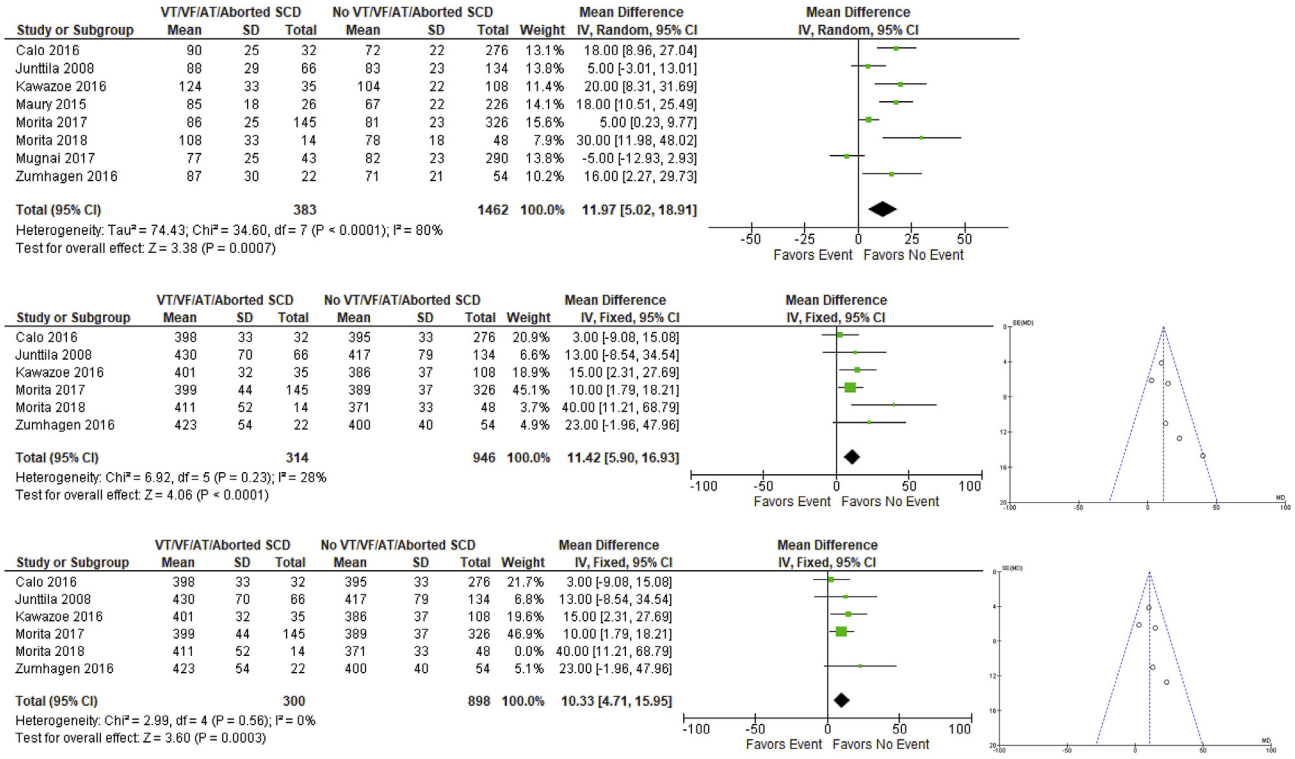

Fig. 2. Mean Difference of Tpeak-Tend interval and Max QTc interval between VT/VF/AT/Aborted SCD group and those without.
Mean Difference of Tpeak-Tend interval (Fig. 2A) and Max QTc (Fig. 2B) interval between VT/VF/AT/Aborted SCD group and those without. Fig. 2C showed a heterogeneity of 0% after removal of Morita 2018 et al. study upon sensitivity analysis. Description: AT = Appropriate ICD Shock, SCD=Sudden Cardiac Death, VF=Ventricular Fibrillation, VT=Ventricular Tachycardia.

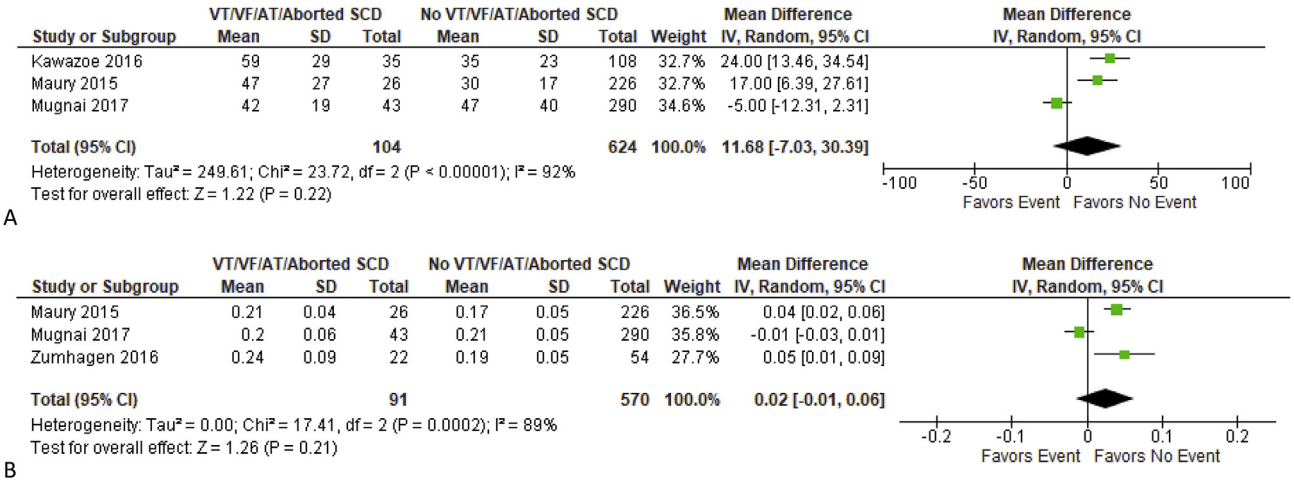

Fig. 3. Mean Difference of Tpe Dispersion and TpTe/QT ratio between VT/VF/AT/Aborted SCD group and those without.
Mean difference of Tpe Dispersion (Fig. 3A) and TpTe/QT ratio (Fig. 3B) between VT/VF/AT/Aborted SCD group and those without. Description: AT = Appropriate ICD Shock, SCD=Sudden Cardiac Death, VF=Ventricular Fibrillation, VT=Ventricular Tachycardia. The fixed-effect model yields a statistically significant result, but not the random-effect model.

for heterogeneity in Tpeak-Tend duration. Heterogeneity for Tpe Dispersion and TpTe/QT ratio decreased to 0% upon removal of Mugnai et al. study to become an MD of 20.52 [13.04–28.00], $p < 0.001$ and 0.04 [0.03–0.06], $p < 0.001$ upon fixed-effect model, but the removal of these Mugnai et al. study left only two studies left in the pooled analysis. Removal of Morita 2018 et al. study from the pooled analysis for Max QTc reduced heterogeneity from I [2] 28% into 0% with MD of 10.33 [4.71–15.95], $p < 0.001$ (Fig. 2C).

4. Discussion

Eight studies showed that TpTe interval might be prolonged in those with VT/VF/AT/Aborted SCD with a cut-off point possibly on ≥80–100 m s, it was not statistically significant in a study. Three studies demonstrate that Tpe dispersion is a statistically significant predictor of VT/VF/AT/Aborted SCD and one study found no association. Two studies showed that a higher TpTe/QT interval ratio was associated with VT/VF/AT/Aborted SCD and one study found no association. One study found a cut off ≥0.205, 72.7% & 68.5%; AUC 0.673. A longer maximum QTc interval was statistically significant for VT/VF/AT/Aborted SCD in three studies evaluating QTc and one studies that evaluate uncorrected QT; although the cut-off point is unclear. It was statistically not significant in three studies. Based on our meta-analysis TpTe interval (mean difference 11.97 m s [5.02–18.91]; $p < 0.001$, high heterogeneity I [2] 80%; $p < 0.001$) and maximum QTc interval (mean difference 11.42 m s [5.90–16.93]; $p < 0.001$, low heterogeneity I [2] 28%; $p = 0.23$) were the most potential ECG parameters to predict VT/VF/AT/SCD. However, the cut-off for maximum QTc interval is unclear and needs further research. Meta-analysis of Tpe dispersion and TpTe/QT ratio on the fixed-effect model showed significant results but not on the random-effect model. We used a random-effect model due to high heterogeneity. Further research to increase the pooled sample size may shed a more certain light on this topic.

This meta-analysis involved studies regarding results of electrocardiography. Several studies used a computer algorithm to determine the exact point of observation while others utilized cardiologists who are blinded to the patient's clinical history. A particular study employs two cardiologists who examined ant interpreted ECG tracings using a magnifying glass, disputes of clinical interpretations of the ECG above were resolved by consensus [28]. This poses a risk to interobserver variability, which is assessed internally in this study using kappa statistic and proportion agreement. Several other studies involved in this meta-analysis also used the interpretation of ECG done by a cardiologist. One study reported an acceptable rate of interobserver variability, however, no specifics were disclosed [24]. One study was done by Kawazoe et al. explicitly stated the implementation of Automated T wave end detection method using the Tangent method [25]. It is interesting to note that the results of this study do not differ significantly from other studies, except for a study by Mugnai et al. Mugnai et al. utilize manual measurements to identify TpTe, TpTe/QTc ratio, The dispersion, and QT interval. This study, however, showed results which are contradictory to other studies included in this meta-analysis [20].

Another consideration lineated by a study mentioned that, in regards to Brugada syndrome, Arrhythmia inducibility was a major deciding factor in treatment and risk prediction of patients with Brugada syndrome. However, not all of the studies involved in this meta-analysis utilized VT/VF inducibility to be assessed with new emerging diagnostic indicators such as the TpTe, TpTe/QTc Ratio, Tpe dispersion, or QT interval.

Tpe dispersion showed a great potential to be used as a diagnostic/risk stratification tool, this is further emphasized by results of Area under the receiver operating characteristic curve (AUROC) across studies. TpTe showed AUROC of (0.789 by Maury et al., 0.786 by Hevia et al. and 0.869 by Kawazoe et al.) respectively [13,21,25]. AUROC analysis was performed to assess the possibility of using these novel parameters as a prediction/diagnosis modality. The overwhelming value of AUROC that exceeds 0.5 shows a great potential to be used as a prediction tool. However, not all of the studies included in this meta-analysis displayed AUROC values.

Another aspect of being considered is the fact that studies used in this meta-analysis commonly collected patient data from a single medical institution. With few exceptions such as; study done by Juntilla et al. which pooled 200 patients worldwide [11], a study by Maury et al. which collected data from 2 medical centers [24], a study by Kawazoe et al. which was done using data from 3 medical centers in Japan [25], and a study by Calo et al. which collected data from 4 medical institutions in France [28].

Limitation in this systematic review include the different type of study design; there are cohort and case-control studies. The studies have different cut-off points, and many of them did not have one. The studies also lack data required to conduct a meta-analysis to

create a pooled estimate of the odds ratio, sensitivity, and specificity on a more uniformed cut-off point. One study included syncope as the equivalent outcome of VF and hence, cannot be used in the meta-analysis. One study also used VT/VF inducibility as their outcome. VT/VF inducibility itself was not associated with future arrhythmic events in this study. To address these issues, further multicentre studies with a more standardized method of measurement, outcome measured, and cut-off points need to be conducted. Our study also showed a high heterogeneity in TpTe interval, Tpe dispersion, and TpTe/QT ratio. Tpe dispersion and TpTe/QT ratio reduced with the removal of a study but was limited by the number of studies (only two after removal). Only QTc interval has potential, with 28% heterogeneity before removal of one study and 0% heterogeneity after.

5. Conclusion

Measurement of TpTe interval, Tp-e dispersion, TpTe/QT ratio, and QTc interval on ECG emerge as a promising prognostication tool which needs further research, especially with a multicentre prospective cohort design with a more standardized method, outcome, and cut-off points. Based on our study TpTe interval possibly on $\geq$80–100 m s and maximum QTc interval were the most potential ECG parameters to predict VT/VF/AT/SCD. However, TpTe interval is limited due to high heterogeneity. As for now, only maximum QTc interval has a reliable result with low heterogeneity sufficiently reliable for prognostication. However, it did not have specific cut-off points. Controversies surrounding EPS in risk stratification which was fuelled by a negative finding in one of the study indicates that a combination of non-invasive parameters in addition to the traditional history taking and possibly EPS may help in risk stratification of Brugada syndrome. Further investigations with a more standardized method of measurement, outcome measured, and cut-off points need to be conducted.

Authors contribution

Raymond Pranata conceived and designed the study, interpreted the data, and drafted the manuscript. Ian Huang and Rachel Vania acquired the data and drafted the manuscript. Raymond Pranata and Emir Yonas interpreted the data. Raymond Pranata performed meta-analysis. All authors contributed to the writing of the manuscript.

Conflicts of interest

The authors declare that they have no conflict of interests.

References

[1] Antzelevitch C, Yan G-X, Ackerman MJ, et al. J-Wave syndromes expert consensus conference report: emerging concepts and gaps in knowledge. J Arrhythmia 2016;32(5):315–39. https://doi.org/10.1016/j.joa.2016.07.002.
[2] Priori SG, Wilde AA, Horie M, et al. HRS/EHRA/APHRS expert consensus statement on the diagnosis and management of patients with inherited primary Arrhythmia syndromes. Heart Rhythm 2013;10(12):1932–63. https://doi.org/10.1016/j.hrthm.2013.05.014.
[3] Priori SG, Blomström-Lundqvist C, Mazzanti A, et al. 2015 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death. Eur Heart J 2015;36(41):2793–867. https://doi.org/10.1093/eurheartj/ehv316.
[4] Letsas KP, Asvestas D, Baranchuk A, et al. Prognosis, risk stratification, and management of asymptomatic individuals with Brugada syndrome: a systematic review. Pacing Clin Electrophysiol 2017;40(12):1332–45. https://doi.org/10.1111/pace.13214.
[5] Sieira J, Ciconte G, Conte G, et al. Asymptomatic brugada syndrome. Circ Arrhythmia Electrophysiol 2015;8(5):1144–50. https://doi.org/10.1161/CIRCEP.114.003044.
[6] Kamakura S, Ohe T, Nakazawa K, et al. Long-term prognosis of probands with brugada-pattern ST-elevation in leads V 1 –V 3. Circ Arrhythmia Electrophysiol 2009;2(5):495–503. https://doi.org/10.1161/CIRCEP.108.816892.
[7] Priori SG, Gasparini M, Napolitano C, et al. Risk stratification in brugada syndrome. J Am Coll Cardiol 2012;59(1):37–45. https://doi.org/10.1016/j.jacc.2011.08.064.
[8] Take Y, Morita H, Toh N, et al. Identification of high-risk syncope related to ventricular fibrillation in patients with Brugada syndrome. Heart Rhythm 2012;9(5):752–9. https://doi.org/10.1016/j.hrthm.2011.11.045.
[9] Sakamoto S, Takagi M, Tatsumi H, et al. Utility of T-wave alternans during night time as a predictor for ventricular fibrillation in patients with Brugada syndrome. Heart Vessel 2016;31(6):947–56. https://doi.org/10.1007/s00380-015-0692-y.
[10] Morita H, Kusano KF, Miura D, et al. Fragmented QRS as a marker of conduction abnormality and a predictor of prognosis of brugada syndrome. Circulation 2008;118(17):1697–704. https://doi.org/10.1161/CIRCULATIONAHA.108.770917.
[11] JUNTTILA MJ, BRUGADA P, HONG K, et al. Differences in 12-lead electrocardiogram between symptomatic and asymptomatic brugada syndrome patients. J Cardiovasc Electrophysiol 2008;19(4):380–3. https://doi.org/10.1111/j.1540-8167.2007.01050.x.
[12] Adler A, Rosso R, Viskin D, Halkin A, Viskin S. What do we know about the “malignant form” of early repolarization? J Am Coll Cardiol 2013;62(10):863–8. https://doi.org/10.1016/j.jacc.2013.05.054.
[13] Maury P, Rollin A, Sacher F, et al. Prevalence and prognostic role of various conduction disturbances in patients with the brugada syndrome. Am J Cardiol 2013;112(9):1384–9. https://doi.org/10.1016/j.amjcard.2013.06.033.
[14] Viskin S, Adler A, Rosso R. Brugada burden in Brugada syndrome: the way to go in risk stratification? Heart Rhythm 2013;10(7):1019–20. https://doi.org/10.1016/j.hrthm.2013.04.010.
[15] Kasanuki H, Ohnishi S, Ohtuka M, et al. Idiopathic ventricular fibrillation induced with vagal activity in patients without obvious heart disease. Circulation 1997;95(9):2277–85. https://doi.org/10.1161/01.CIR.95.9.2277.
[16] Nademanee K, Veerakul G, Nimmannit S, et al. Arrhythmogenic marker for the sudden unexplained death syndrome in Thai men. Circulation 1997;96(8):2595–600. https://doi.org/10.1161/01.CIR.96.8.2595.
[17] Ikeda T, Takami M, Sugi K, Mizusawa Y, Sakurada H, Yoshino H. Noninvasive risk stratification of subjects with a brugada-type electrocardiogram and no history of cardiac arrest. Ann Noninvasive Electrocardiol 2005;10(4):396–403. https://doi.org/10.1111/j.1542-474X.2005.00055.x.
[18] Tokioka K, Kusano KF, Morita H, et al. Electrocardiographic parameters and fatal arrhythmic events in patients with brugada syndrome. J Am Coll Cardiol 2014;63(20):2131–8. https://doi.org/10.1016/j.jacc.2014.01.072.
[19] Zumhagen S, Zeidler EM, Stallmeyer B, Ernsting M, Eckardt L, Schulze-Bahr E. Tpeak-Tendinterval and Tpeak-Tend/QT ratio in patients with Brugada syndrome. Europace 2016;18(12):1866–72. https://doi.org/10.1093/europace/euw033.
[20] Mugnai G, Hunuk B, Hernandez-Ojeda J, et al. Role of electrocardiographic tpeak-tend for the prediction of ventricular arrhythmic events in the brugada syndrome. Am J Cardiol 2017;120(8):1332–7. https://doi.org/10.1016/j.amjcard.2017.07.014.
[21] Castro Hevia J, Antzelevitch C, Tornés Bárzaga F, et al. 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(9):1828–34. https://doi.org/10.1016/j.jacc.2005.12.049.
[22] Junttila MJ, Brugada P, Hong KUI, et al. Differences in 12-lead electrocardiogram between symptomatic and asymptomatic brugada syndrome patients. 2007. p. 380–3. https://doi.org/10.1111/j.1540-8167.2007.01050.x.
[23] Letsas KP, Weber R, Astheimer K, Kalusche D, Arentz T. Tpeak-Tend interval and Tpeak-T end/QT ratio as markers of ventricular tachycardia inducibility in subjects with Brugada ECG phenotype. Europace 2010;12(2):271–4. https://doi.org/10.1093/europace/eup357.
[24] Maury P, Sacher F, Gourraud JB, et al. Increased Tpeak-Tend interval is highly and independently related to arrhythmic events in Brugada syndrome. Heart Rhythm 2015;12(12):2469–76. https://doi.org/10.1016/j.hrthm.2015.07.029.
[25] Kawazoe H, Nakano Y, Ochi H, et al. Risk stratification of ventricular fibrillation in Brugada syndrome using noninvasive scoring methods. Heart Rhythm 2016;13(10):1947–54. https://doi.org/10.1016/j.hrthm.2016.07.009.
[26] Morita H, Watanabe A, Kawada S, et al. Identification of electrocardiographic risk markers for the initial and recurrent episodes of ventricular fibrillation in patients with Brugada syndrome. J Cardiovasc Electrophysiol 2018;29(1):107–14. https://doi.org/10.1111/jce.13349.
[27] Morita H, Miyamoto M, Watanabe A, et al. Progression of electrocardiographic abnormalities associated with initial ventricular fibrillation in asymptomatic patients with Brugada syndrome. Heart Rhythm 2018;15(10):1468–74. https://doi.org/10.1016/j.hrthm.2018.06.035.
[28] Calo L, Giustetto C, Martino A, et al. A new electrocardiographic marker for sudden death in brugada syndrome. JACC 2016;67(12):1427–40.