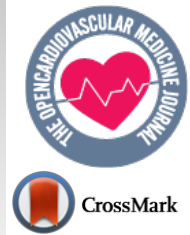




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EDITORIAL

Electrocardiographic T Wave Peak-T Wave End Interval: In Pursue of Improving Risk Factors for the Prediction of Cardiac Arrhythmic Events in Brugada Syndrome

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The Brugada syndrome has been linked to abnormalities in the cardiac sodium channel and associated to life threatening ventricular arrhythmias in previously asymptomatic patients. The Brugada syndrome is responsible for 4-12% of all sudden deaths and at least 20% of deaths in patients with structurally normal hearts. Re-entry is thought to be the predominant mechanism underlying increased arrhythmogenicity, and less commonly triggered activity. The risk stratification of Brugada syndrome patients still remains to be the most challenging task. There is no definite consensus for the asymptomatic patients and the therapeutic management depends on evaluation of different clinical parameters. Therefore, it is very important to keep looking for certain parameters that may improve risk stratification in these patients. Several electrocardiographic parameters have been proposed for stratification of arrhythmic or mortality risk. The Tpeak-Tend of the T wave was found to correlate with an increased risk for malignant arrhythmic events in the Brugada syndrome. However, their sensitivity, specificity and predictive accuracy are relatively low with limited prognostic value. In addition, a great amount of the evidence came from retrospective data and meta-analysis which may have higher degrees of bias. Risk stratification scores comprising multiple and different clinical factors, genetic status, conventional 12-leads ECG parameters, ECG imaging and, invasive electrophysiological mapping studies may provide more accurate risk stratification. Further prospective studies may be needed to establish a more definite diagnostic model in order to identify high risk patients with Brugada syndrome.

Brugada syndrome is a hereditary ion channel disorder characterized electrocardiographically by a coved-type ST-segment elevation in leads V1 to V3 and associated with ven-

tricular arrhythmias and Sudden Cardiac Death (SCD) in structurally normal hearts. It has been linked to cardiac sodium channel abnormalities and associated with life-threatening ventricular arrhythmias in asymptomatic patients [1 - 5]. The Brugada syndrome is responsible for 4-12% of all sudden deaths and at least 20% of deaths in patients with structurally normal hearts [4]. Pathogenic mutations in other ion channels have also been described. Re-entry is thought to be the predominant mechanism underlying increased arrhythmogenicity, and less commonly triggered activity [3]. There are 2 main mechanisms forming the pathophysiologic basis of the Brugada syndrome. The depolarization hypothesis emphasizes that the delayed depolarization of the right ventricular outflow tract creates a potential difference between this mentioned zone and regions of the right ventricle. The repolarization hypothesis is related to the higher level of transmural dispersion of repolarization involved in local and transmural repolarization alterations leading to phase-2 re-entry in the right ventricular epicardium [6 - 11].

Regardless of the underlying mechanism for re-entry, the transmural dispersion of repolarization can be quantified electrocardiographically by the interval from the peak to the end of the T wave. The differences in repolarization times of myocardial cells are responsible for the generation of the T-wave on the electrocardiogram (ECG) [12 - 14]. However, the exacerbation of such differences in electrophysiological heterogeneities has been associated with ventricular arrhythmias in different conditions generating a pro-arrhythmic phenotype [15]. These heterogeneities can occur locally or across the myocardial wall, potentially causing re-entrant ventricular arrhythmias by inducing conduction delay and unidirectional block [15 - 17]. In addition, a greater transmural repolarization time difference may increase the propensity of phase-2 re-entry, which is suggested to generate premature ventricular contractions that may act as triggers of ventricular tachycardia

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and fibrillation in the Brugada syndrome [18 - 20].

Risk stratification of Brugada syndrome patients remains a challenging task. There is no definite consensus for the asymptomatic patients and therapeutic management depends on the evaluation of different clinical parameters. Therefore, it is important to look for certain parameters that may improve risk stratification. Several electrocardiographic parameters have been proposed for the stratification of arrhythmic or mortality risk [20 - 23]. For example, QRS-fragmentation was found to be an independent predictor for ventricular arrhythmias in Brugada syndrome and was associated with a 3.9-fold increase in the risk of future arrhythmic events [24, 25]. Moreover, the presence of late potentials detected by signal-averaged ECG is associated with an increased risk of arrhythmic events. These late potentials had 92% sensitivity but only 46% specificity for the endpoint of sudden death or ventricular tachyarrhythmias. Nevertheless, late potentials alone in both symptomatic and asymptomatic patients showed limited prognostic value [26, 27]. In addition, it was shown that the presence of an inferolateral early repolarization pattern triples the risk of future arrhythmic events in patients with Brugada syndrome [28].

We will focus on the Tpeak-Tend interval. Antzelevitch and Yan [12 - 14] were the first to propose the use of the difference between the peak and the end of the T-wave (the Tpeak-Tend interval) as a measure of transmural dispersion of repolarization. The following parameters from the conventional 12 lead electrocardiogram (ECG) can be obtained, namely, Tpeak-Tend interval, Tpeak-Tend/QT ratio, and Tpeak-Tend dispersion [24 - 26]. In the context of studying these indices, Mugnai *et al.* [29] conducted a retrospective study to analyse the role of electrocardiographic Tpeak-Tend interval for the prediction of ventricular arrhythmic events in the Brugada syndrome. They included a total of 448 patients with spontaneous or drug-induced type 1 Brugada pattern. The authors found no significant difference in all the above-mentioned indices between asymptomatic subjects and patients with syncope and malignant arrhythmias. Another study with similar findings [30] found no significant difference in Tpeak-Tend intervals in 471 patients comparing those with syncope or VT/VF with those who were asymptomatic. The effects of the autonomous nervous system play an important role on the findings and are considered when analysing the T wave intervals. Increased activity of the parasympathetic nervous system may reduce Tpeak-Tend intervals, which may also be pro-arrhythmic [31]. On the other hand, exercise can exacerbate pre-existing heterogeneities by increasing sympathetic activity developing conduction slowing and increasing dispersion of repolarization [32].

In contrast to the above evidence, Tse *et al.* [33] found contrasting results in a meta-analysis. They extracted and pooled odds or hazard ratios looking for the relationship between Tpeak-Tend intervals and cardiac arrhythmias, and/or mortality outcomes in several clinical entities, including Brugada syndrome. They demonstrated that a prolonged Tpeak-Tend interval was associated with an increased risk of ventricular arrhythmias and SCD in Brugada Syndrome. The same authors [18] performed another systematic review and

meta-analysis on T wave indices for risk stratification in Brugada syndrome including more patients in their study. They used a cut-off value of 88 ms for the T-peak-Tend interval in this study. They included 1597 patients with Brugada syndrome and demonstrated that Tpeak-Tend intervals, as well as, Tpeak-Tend/QT ratio, and Tpeak-Tend dispersion are higher in patients with Brugada syndrome with adverse cardiac events when compared with asymptomatic Brugada subjects. The adverse cardiac events consisted of ventricular tachyarrhythmias and SCD. Similarly, Maury *et al.* [20] showed that the Tpeak-Tend interval is highly related to arrhythmic events in Brugada syndrome patients. The authors reported that an increased dispersion and prolongation of the Tpeak-Tend interval were significantly higher in patients with SCD and appropriate ICD therapies [20]. Additionally, Zumhagen *et al.* [21] reported that the Tpeak-Tend interval and the Tpeak-Tend/QT ratio in V1 were higher in high-risk Brugada syndrome patients than in those patients with lower risk [21].

Bachmann *et al.* [22] observed a U-shaped relationship between Tpeak-Tend intervals and increased cardiovascular morbidity and mortality in their Copenhagen ECG epidemiological study. Several researchers measured Tpeak-Tend intervals from different leads. Some measured it from all 12 leads and took the mean values, while others only used leads V1 to V3. There is no consensus about which leads are most appropriate for measurement. Although measuring the T wave intervals from all 12 leads is time-consuming, it derives the maximum, the minimum, and the dispersion of the Tpeak-Tend interval. However, in order to simplify Tpeak-Tend interval determination, Tse *et al.* [18] proposed measuring from the right precordial leads, given that the Brugada syndrome is primarily a right ventricular disorder. While it may be shown that the difference in Tpeak-Tend interval between high-risk and low-risk Brugada patients was only small (about 12 ms) it should be emphasized that increased transmural dispersion of repolarization is only one mechanism by which re-entrant arrhythmogenesis is generated. Other mechanisms include reduced conduction velocity, increased dispersion of conduction, and steep action potential restitution. In this setting, alterations in the Tpeak-Tend interval, Tpeak-Tend/QT ratio, or Tpeak-Tend dispersion may be observed, and they also contribute to arrhythmogenesis in Brugada syndrome [18]. Therefore, better risk stratification scores will need to incorporate a combination of repolarization and conduction indices. Moreover, some of these dynamic changes may not be detectable on the ECG and may require additional tests such as non-invasive ECG imaging, or stressful test conditions such as exercise testing [32].

In conclusion, several ECG parameters related to the Tpeak-Tend of the T wave were found to correlate with an increased risk for malignant arrhythmic events in the Brugada syndrome. However, their sensitivity, specificity and predictive accuracy are relatively low with limited prognostic value. In addition, considerable evidence came from retrospective data and meta-analysis, which may have a risk of bias. Risk stratification scores comprising multiple and different clinical factors, genetic status, conventional 12-lead ECG parameters, ECG imaging and, invasive electrophysiological mapping studies may provide more accurate risk stratification. Further

prospective studies in genotyped cohorts of patients who are phenotypically evaluated may be needed to establish a more definite diagnostic model in order to identify high-risk patients with Brugada syndrome. In addition, there is a need to establish to what extent mutations in the SCN5A gene influence the electrocardiographic parameters of ventricular repolarization.

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