

Review Article

Research Progress in Formation and Application of Tp-Te Interval

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Abstract: Tp-Te interval refers to the duration from the peak to the end time points of T wave in electrocardiogram. Tp-Te interval is an electrocardiogram index reflecting malignant ventricular arrhythmia, while Tp-Te interval mainly reflects ventricular transmural repolarization dispersion. The increase of ventricular transmural repolarization dispersion makes it easy to appear depolarization after repolarization, and forms functional conduction block between different regions, which leads to malignant arrhythmias. In this review we discuss how these markers have demonstrated to be effective to predict malignant arrhythmias in medical conditions such as long and short QT syndromes, Brugada syndrome and so on. However, the same results have not been found in all conditions. Further studies are needed to reach a global consensus in order to incorporate these VR parameters in risk stratification of these patients.

Keywords: Electrocardiographic Predictor, Ventricular Repolarization Markers, Ventricular Fibrillation, Sudden Cardiac Death, Tp-Te Interval

1. Introduction

An electrocardiogram (ECG) represents one of the most common medical tools used by physicians in clinical practice. Its adequate interpretation makes the possibility for diagnosing and predicting multiple cardiac diseases. Sudden cardiac death (SCD) causes approximately 800000 deaths each year in the world [1]. And it is often produced by malignant ventricular arrhythmias (MVA). MVA which may result in SCD frequently occur in sick hearts but around 15%-20% occur in healthy hearts [2]. Many people who develop MVA have a previous disease that may be the cause of this condition. It is often possible to predict the development of ventricular cardiac arrhythmias by ECG analysis in these patients. That is feasible by analysing several ventricular repolarization (VR) markers such as Tp-Te interval. The aim of this manuscript is to review the usefulness of Tp-Te interval to predict SCD in several conditions such as long and short QT syndromes, Brugada syndrome, early

repolarization syndrome, acute myocardial ischemia, heart failure, hypertension, diabetes mellitus, obesity and high trained athletes and the possible mechanisms involved in order to encourage their clinical use to improve patients' risk evaluation.

1.1. The Tp-Te Interval Definition

Tp-Te interval is a part of QT interval. The time interval between the peak of T wave and the end point of T wave, representing the end of cardiac repolarization from the end of heart repolarization to the end of middle M cell repolarization [3].

1.2. The Tp-Te Interval Formation Theory

1.2.1. The Theory of Temperature Difference and Pressure Difference

The epicardial membrane is surrounded by fat and the temperature is higher. In addition, compared with endocardium, the epicardial myocardium is subjected the less

reaction when the ventricular began to contract and eject, so the epicardial membrane is faster than the endocardium during the repolarization. That is probably why ventricular muscle depolarization is from endocardium to epicardium in physiological state. The difference of time in the repolarization process is the foundation of the formation of Tp-Te interval.

1.2.2. The Theory of Ventricular Transmural Repolarization Dispersion

From Noble in 1970s to Antzelevitch in 1990s then to Yan in 1998, it was concluded that the Tp-Te interval is from the end of the cardiomyocyte repolarization of the epicardium to the end of the repolarization of the M cell, which reflects the level of myocardial repolarization dispersion. That is the theory of ventricular transmural repolarization. Based on that, Tp-Te interval is regarded as a quantitative index of ventricular transmural repolarization dispersion.

1.2.3. The Recent Findings

Recent studies suggest that the Tp-Te interval is a reflection of the total spatial dispersion of the cardiac repolarization. Therefore, the mechanism of the Tp-Te interval formation is not only related to the ventricular transmural repolarization dispersion, but also to the whole heart repolarization dispersion. However, the exact electrophysiological mechanism of the Tp-Te interval is still unclear [4].

2. The Clinical Application of the Tp-Te Interval

Although the Tp-Te interval cannot be equated with ventricular transmural repolarization dispersion, but it can reflect the cardiac transmural repolarization and the global repolarization dispersion. The increase of the ventricular transmural repolarization dispersion is an important mechanism of the ventricular arrhythmias. Many studies have shown that it is an important predictor of the malignant ventricular arrhythmias. Previous studies have suggested that the time of the Tp-Te interval is an effective noninvasive index for the acute myocardial infarction, the long QT syndrome and the Brugada syndrome [5-7]. Application of Tp-Te interval to predict MVA in some diseases is discussed below.

2.1. The Tp-Te Interval and the Ventricular Arrhythmia

The Tp-Te interval is equal to the relative refractory period of the ventricle, and the excitability of ventricular myocytes varies greatly, and easily form the reentrant. Then the risk of malignant ventricular arrhythmias was significantly increased. Therefore, the predictive value of the Tp-Te interval in ventricular arrhythmias has received wide attention. A study showed that the Tp-Te interval of 191 normal children with malignant arrhythmia was significantly higher than that of normal children [8]. A study in 2015 [9] analysed 305 patients with a left ventricular ejection fraction (LVEF) < 35% who were initially prevented by ICD implantation. The results showed that even after controlling for a variety of univariate

predictors, the Tp-Te interval also independently predicted the combined endpoints of MVA and / or death, and clarified the relationship of them. A meta-analysis of 155,856 patients carried out by Tse et al. [10] in 2017 found a positive correlation between the prolongation of Tp-Te interval and the increased risk of MVA or SCD. And it also found that the prolonged Tp-Te interval also predicted the occurrence of MVA or SCD in the general population.

2.2. The Long QT Syndrome

Long QT syndrome is an arrhythmogenic channelopathy characterized by severe alterations in ventricular repolarization. Long QT syndrome can be congenital or acquired. The risk of malignant ventricular arrhythmias in the long QT syndrome was significantly increased, and the main mechanism was the increase of ventricular transmural repolarization dispersion. Some studies have found that Tp-Te interval may be the best predictor of the risk of ventricular tachycardia in patients with long QT syndrome. Yamaguchi et al [11] also found that, Tp-e/QT ratio in V5 exceeding 0.28 was also associated with the risk to develop Torsades de Pointes.

2.3. The Short QT Syndrome

Congenital short QT syndrome is a rare channelopathy which increases the incidence of paroxysmal atrial fibrillation, ventricular tachycardia and/or fibrillation [12-14]. The results of the short QT syndrome showed that the prolongation of Tp-Te interval in short QT syndrome can also reflect the increase of ventricular transmural repolarization dispersion and the tendency of reentry, resulting in ventricular tachycardia or ventricular fibrillation. Short QT syndrome should be studied further like other conditions which are associated with genetic mutations and several clinical presentation forms.

2.4. The Brugada Syndrome

The Brugada syndrome is a familial genetic disorder of ion channel gene, characterized by ventricular tachycardia or ventricular fibrillation. Castro Hevia et al [15] found an increased risk for ventricular arrhythmias in patients with Brugada syndrome than healthy controls. The increase of T wave peak end interval and T wave peak end interval to QT interval is an effective predictor of fatal arrhythmia in patients with Brugada syndrome [16]. Zumhagen et al [16]. found that the increase of Tp-Te/QT is an effective predictor of fatal arrhythmia in patients with Brugada syndrome. In addition, univariate analysis of Morita et al [17] showed that spontaneous type 1 electrocardiogram, Tp-Te interval ($\geq 95\text{ms}$), high ST level ($\geq 0.52\text{mV}$) and fQRS were common predictors of ventricular fibrillation in asymptomatic and symptomatic groups.

2.5. The Tp-Te Interval and the Coronary Slow Flow

During coronary angiography, the time for contrast agent to reach the distal vessel is longer than three cardiac cycles,

so the coronary blood flow velocity is considered to be slower. Coronary slow flow is characterized by delayed opacity of the coronary artery in the absence of obstructive coronary artery disease in coronary angiography [18]. The clinical manifestation is angina pectoris or acute coronary syndrome. Studies have shown that there is a significant correlation between inflammatory markers and coronary blood flow velocity [19]. This phenomenon is associated with the increased risk of ventricular arrhythmias and sudden cardiac death. Erhan et al [20] found that the QTd, Tp-Te interval and Tp-Te / QT ratio were prolonged in patients with slow flow coronary artery. It is suggested that the measurement of Tp-Te interval and Tp-Te / QT ratio can be used to predict the risk of adverse cardiovascular events associated with coronary slow flow.

2.6. The Tp-Te Interval and the Organic Heart Disease

2.6.1. The Myocardial Infarction

The acute myocardial infarction is a common cardiovascular disease with high mortality. The results showed that the excitability of the sympathetic nerve was significantly increased during acute myocardial ischemia and the degree of the excitation of the ventricular sympathetic fibers was different. So the myocardial transmural repolarization dispersion was increased and the Tp-Te interval was prolonged. Some studies have shown that prolonged Tp-Te interval before PCI in patients with acute ST segment elevation myocardial infarction may increase the overall mortality rate [21]. Prolongation of Tp-Te interval is an independent predictor of the malignant arrhythmia and independent of left ventricular ejection fraction after the acute myocardial infarction [22]. Shenthar et al. [23] found that Tp-Te interval > 100 ms and Tp-Te / QT > 0.3 could predict the occurrence of MVA in patients with acute ST segment elevation myocardial infarction within 24 hours.

2.6.2. The Hypertrophic Cardiomyopathy

Hypertrophic cardiomyopathy (HCM) is a common hereditary heart disease characterized by ventricular hypertrophy and myocardial fibrosis, which is significantly associated with the high risk of fatal ventricular arrhythmia events. Previous studies have suggested that increased Tp-Te interval is a risk factor for unsustainable ventricular tachycardia in patients with hypertrophic cardiomyopathy [24]. The latest study by Akbog et al [25] in 2017 Found that Tp-Te interval and Tp-Te / QT can be independent predictors of ventricular arrhythmias in HCM patients. A study by Chinese experts on hypertrophic cardiomyopathy (Tp-Te) confirmed that The Tp-Te interval was significantly shortened after chemoablation. It has been proved that ventricular arrhythmia and sudden death have been significantly reduced after chemoablation. Therefore, the shortening of Tp-Te interval may mean the reduction of the happence of ventricular vulnerability, ventricular reentry, ventricular arrhythmia and sudden death.

2.7. The Heart Failure

Heart failure is the end stage of many organic heart diseases. It is easy to trigger ventricular arrhythmia and even lead to sudden death. There is a certain correlation between Tp-Te interval and cardiac insufficiency. Studies have shown that ventricular diastolic dysfunction is associated with prolongation of Tp-Te interval in both resting and exercise induced states, suggesting that prolongation of Tp-Te interval is an independent predictor of heart failure in male patients [26]. Xue C et al found that the incidence of ventricular tachycardia and ventricular fibrillation decreased in patients with heart failure after one year of cardiac resynchronization [27]. Tp-Te interval is an independent predictor of ICD efficacy after ICD implantation. Rosenthal et al [28] thought that Tp-Te interval is an independent predictor of VT/VF events and 1-year overall mortality in patients undergoing ICD implantation for primary prevention of systolic dysfunction.

3. The Conclusions and Perspectives

It is well known that malignant ventricular arrhythmia is an important cause of sudden cardiac death. Current clinical studies suggest that Tp-Te interval is associated with malignant ventricular arrhythmias, which is of great significance in predicting the occurrence and risk of malignant ventricular arrhythmias. In conclusion, Tp-Te interval plays an important role in predicting the occurrence of malignant arrhythmia and sudden death, which should be paid more attention to in clinical practice. The Tp-Te interval extends our alternative for arrhythmias' prediction. It is necessary to continue medical studies in this field with the aim to clarify some aspects discussed above and to achieve a global consensus which would result in better management of our patients.

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