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Research Paper

Tpeak-Tend interval as a new risk factor for arrhythmic event in patient with Brugada syndrome

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Abstract

Objective: To evaluate Tpeak-Tend (Tp-e) interval in surface standard ECG as a new risk factor for arrhythmic event in patient with Brugada syndrome. **Methods**: 23 male patients with Brugada syndrome and 20 male patients with paroxysmal supraventricular tachycardia (PSVT) as the control group were investigated in this study. Tp-e interval in surface standard ECG was compared between BrS and PSVT patients. **Results**: Tp-e interval in BrS patients was significantly longer than that in PSVT patients (109.57±22.86 ms vs. 88.50±13.08ms, $P<0.05$). There was significant difference in Tp-e interval between 16 BrS patients with arrhythmic events (including syncope, clinical ventricular fibrillation [VF] and programmed electrical stimulation [PES]-induced VF) and 7 BrS patients without arrhythmic events and PSVT patients (118.12±20.40ms vs. 90.00±15.27ms, $P<0.05$; 118.12±20.40ms *vs.* 88.50±13.08ms, $P<0.05$). However, Tp-e interval was similar in BrS patients without arrhythmic events and PSVT patients (90.00±15.27ms vs 88.50±13.08ms, $P>0.05$). **Conclusion**: The prolongation of Tp-e interval could serve as a new noninvasive event predictor for arrhythmic events in patients with Brugada syndrome.

Keywords: Brugada syndrome; Tpeak-Tend; risk factors

INTRODUCTION

The Brugada syndrome (BrS) has been recognized as a major cause of idiopathic ventricular fibrillation in structurally normal hearts since its first description in 1992 [1]. BrS is characterized by a coved-type ST-segment elevation, in leads V1 to V3 of the electrocardiogram (ECG), recurrent syncope and sudden death. Among the recently reported risk factors associated with ventricular tachycardia (VT)/ventricular fibrillation (VF) in BrS patients was a spontaneous coved-type ST-segment elevation. These risk factors have been reported as well as a male gender history of syncope or aborted sudden death, and programmed electrical stimulation (PES)-induced VT/VF [2]. However there is still some controversy surrounding some of these risk factors for the prediction of arrhythmic events in BrS patients[3,4]. This present study was designed to examine the Tpeak-Tend (Tp-e) interval as a new risk factor for arrhythmic events in BrS patients.

MATERIALS AND METHODS

Subjects

Between December 2002 and July 2006, 23 patients with syncope, aborted sudden cardiac death, spontaneous Brugada ECG wave and family sudden death history (death attributable to an acute cardiac episode) were referred to our hospital for clinical evolution. These were all male, mean age 44.91 ± 10.02 years having being diagnosed with Brugada syndrome based on the second consensus conference about Brugada syndrome endorsed by the Heart Rhythm Society and the European Heart Rhythm As-

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sociation in 2005 [2]. To compare the Tp-e interval with normal people, 20 patients(all male, mean age 42.05 ± 9.86 years) with paroxysmal supraventricular tachycardia(PSVT) were employed as the control group.

Tab 1 showed the clinical characteristics of 23 BrS patients. There were 16 (mean age 45.93 ± 10.69 years) BrS patients with arrhythmic events including syncope, documented VF and inducible VF in EP lab and 7 BrS patients(mean age 42.57 ± 8.54 years) without arrhythmic events. All BrS patients underwent the physical examination including echocardiogram, chest X-ray and coronary angiography. These showed normal results and excluded patients with organic heart disease. If the standard 12 leads ECG was insufficient for diagnosing Brugada syndrome, a novel precordial 42 leads system[5] were performed to raise the sensitivity of the diagnostic method. Pharmacological challenge with intravenous ajmaline [6] (1 mg/kg body weight) or propafenone [7](initiated at 1 mg-1.5 mg/kg body weight, after 20 minutes 0.5 mg/kg body weight) was performed in 18 BrS patients. PES was carried out in 16 patients:three cycle length basic (600, 430 and 330) and three extra stimuli from the right ventricular apex and right ventricular outflow tract until to the ventricular refractory period or induce arrhythmia[8].

Tab 1 **Clinical characteristics of 23 BrS patients**

No	Age(yrs)	Syncope	family history	ECG	novel precordial lead system	Pharmacological challenge	Cli VF	PES VF	Tp-e(ms)
1	34	+	+	−	+	+	+	+	120
2	38	+	+	−	+	+	+	+	120
3	37	+	+	+	+	+	+	−	160
4	40	+	−	−	+	+	+	−	160
5	31	+	+	−	+	+	+	+	120
6	50	+	−	+	+	+	−	+	90
7	44	+	−	+	−	−	+	−	120
8	64	+	−	+	+	+	+	+	120
9	48	+	−	−	+	+	−	−	80
10	55	+	+	−	+	+	+	−	120
11	54	+	−	−	+	N	−	−	120
12	57	+	−	+	+	N	−	−	120
13	48	+	+	−	+	−	−	−	110
14	37	+	−	+	+	N	−	+	100
15	64	+	−	+	+	+	−	−	110
16	34	−	−	+	+	−	−	+	120
17	32	−	−	−	+	−	−	N	90
18	48	−	−	−	+	+	−	N	80
19	32	−	+	−	+	+	−	N	80
20	53	−	−	−	+	+	−	N	80
21	41	−	−	+	+	N	−	N	80
22	51	−	−	+	+	+	−	N	120
23	41	−	−	+	+	N	−	N	100

Cli VF=clinical syncope with documented VF; PES VF=PES-induced VF; (+)= Positive; (−)=Negative; (Y)=Yes; (N)=No

All PSVT patients had received electrophysiologic test and radiofrequency catheter ablation (RFCA),8 of them were atrioventricular nodal reentrant tachycardia and 12 were atrioventricular reentrant tachycardia (all PSVT patients were concealed atrioventricular bypass tract in order to eliminate the preexcitation effect on ventriclar repolarization).

Tp-e interval was manually measured by using hand-held calipers[17,18]. Electrocardiogram was recorded with a GE Marquette MAC 1200 machine using screen speed of 25 mm/sec. As the maximal Tp-e interval is often used as a noninvasive estimate for the dispersion of ventricular repolarization [9], we selected the maximal Tp-e interval measured from the peak of the T-wave until the end of the T-wave in each precordial lead(V1-V6) as our parameter(***Fig 1***). In the case of negative or biphasic T wave, the Tp-e interval was measured to the nadir of the T wave. T waves smaller than 1.5 mm in amplitude were not measured. The end of the T-wave was defined as the intersection between a tangent to the terminal slope of the T-wave and the PR baseline. If a U-wave was present, the intersection between the T-wave and U-wave was utilized as end of the T-wave [11-13].

Statistical Analysis

All measurements were performed by two inde-

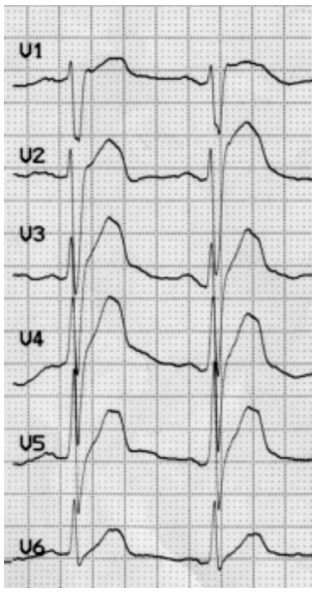


Fig 1 Precordial leads of the electrocardiogram (ECG) of a BrS patient(40 years old)with clinical syncope, clinical VF, no family history of sudden death,novel precordial lead system(+), ajmaline challenge(+),Tp-e interval was 160 ms.

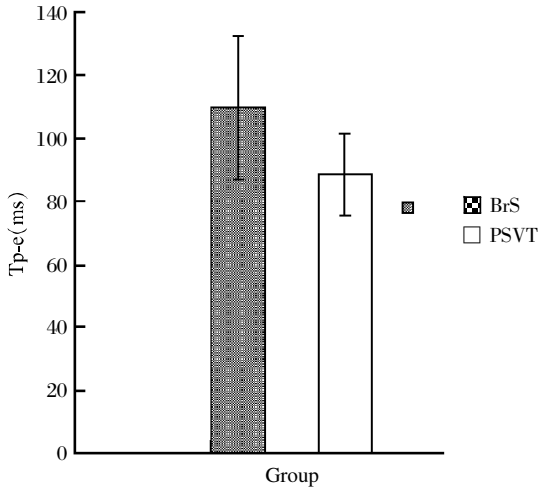
pendent observers, if the interobserver discrepancy was more than 20 msec, the final decision was made by a third observer. Categorical variables were compared using chisquared test. Continuous data were expressed as mean ± SD. The mean values were compared by using the one way ANOVA test. A value of $P<0.05$ was considered statistically significant.

RESULTS

There was a significant difference in Tp-e interval between BrS patients and PSVT patients (109.57 ± 22.86 ms *vs.* 88.50 ± 13.08 ms,$P<0.05$,***Fig 2***). There were no age and gender difference between BrS patients and PSVT patients. Tp-e interval in 16 BrS patients with arrhythmic events was significantly longer than 7 BrS patients without arrhythmic events and PSVT patients (118.12 ± 20.40 ms vs. 90.00 ± 15.27 ms,$P<0.05$;118.12 ± 20.40 ms vs. 88.50 ± 13.08 ms,$P<0.05$,***Fig 3***), but Tp-e interval was similar in BrS patients without arrhythmic events and PSVT patients(90.00 ± 15.27 ms *vs.* 88.50 ± 13.08 ms, $P > 0.05$, ***Fig 3***).

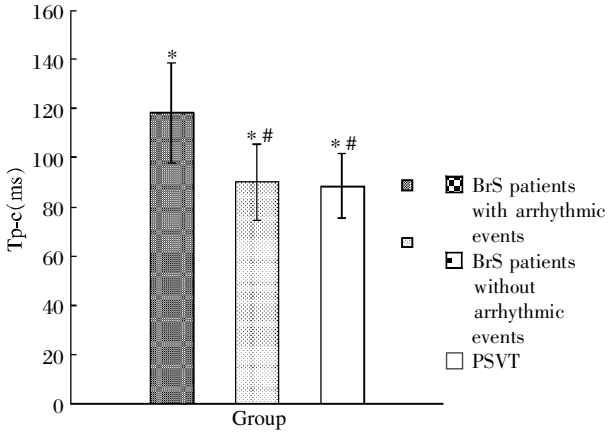
DISCUSSION

Transmural dispersion of the Repolarization(TDR) within the ventricular myocardium has been suggested to underlie arrhythmogenesis in Brugada, short QT, and long QT Syndromes[10]. Three electrophysiologically distinct cells had been identified in the ventricular myocardium:endocardial, epicardial and M cell. In1991, Sicouri *et al* [14]first found that M cells in ventricular myocardium have special electrophysiological characteristics, which provided theoretical foundation for the concept of ventricle repolarization heterogeneity and its subsequent quantifying studies. The ununiformed repolarization of different transmural myocardium has lead to the heterogeneity of ventricular repolarization. Its quantification index is TDR, which is the maximal minus the minimal value of the action potential between different layers transmural myocardium. In pathological conditions, electrical heterogeneity among the three layers of ventricular myocardium is increased. The



There was significant difference in Tp-e interval between BrS patients and PSVT patients.

Fig 2 Tp-e interval compared between BrS and PSVT patients



Tp-e interval in BrS patients with arrhythmic events was significantly longer than BrS patients without arrhythmic events and PSVT patients ($^{*}P < 0.05$),However, Tp-e interval was similar in BrS patients without arrhythmic events and PSVT patients($^{\#}P > 0.05$)

Fig 3 Tp-e interval compared between BrS patients with arrhythmic events, BrS patients without arrhythmic events and PSVT patients

increase of TDR leads to more frequent after-depolarization phenomenon when the myocardium undergoing repolarization, which could result in ventricular arrhythmia. *In vitro* myocardium experiment [15] has proved that the peak of the T-wave was shown to coincide with epicardial repolarization and the end of the T-wave with repolarization of the M cells, so that Tp-e interval provides a measurement of TDR.

Tp-e interval and QT dispersion are defined as two distinct values, QT dispersion reflects the variance of QT interval between different ECG leads, hence it represents the repolarization difference and dispersion in myocardium at different sites. On the other hand, Tp-e interval reflects the repolarization dispersion between endocardium and epicardium, towards the electrode. Evidence in support of this hypothesis, that the prolongation of Tp-e interval associated with arrhythmic events has been provided by hypertrophic cardiomyopathy, congenital analysis and the appearance of a long QT segment[16]. To our knowledge, there has been little research to evaluate Tp-e interval as a risk factor in patients with BrS.

Our study showed that Tp-e interval was significantly different in BrS patients *vs.* PSVT patients. Also, it was different from BrS patients with arrhythmic events vs. BrS patients without arrhythmic events. The Tp-e interval however was similar in BrS patients without arrhythmic events *vs.* PSVT patients. This outcome coincided with previous result that augmentation of the TDR was related to arrhythmic events. Among 16 BrS patients with arrhythmic events, the proportion of BrS patients with arrhythmic events (whose Tp-e interval was more than 120 ms was 68.75%,11/16). The Tp-e interval $\geqslant$120 ms was found in all patients (8/8) who had documented VF, and in 71.43% patients who had PES-induced VF. In contrast, among BrS patients without arrhythmic event and PSVT patients, the proportion of Tp-e interval $\geqslant$120 ms was 14.29% (1/7) and 10.00%(2/20) respectively. Jesus *et al*[17] had conducted a similar study involving 29 patients with BrS pattern ECG. In that study, all BrS patients with Tp-e $\geqslant$100 ms had cardiac events during 60 months of follow-up, while, only 30% of BrS patients with Tp-e < 100 ms had events in the same period.

In BrS patients, a reduction in the density of the sodium channel current (as occurs with the SCN5A gene mutation) is known to shift the balance of currents leading to loss of the action potential dome at some epicardial sites [19]. Loss of the action potential dome in epicardium but not endocardium results in the development of a marked transmural dispersion of repolarization, which is responsible for the development of a vulnerable window during which an extrasystole can induce a reentrant arrhythmia such as VT or VF. Because of the increase of TDR in BrS patients, the Tp-e interval is prolonged in surface standard ECG.

It is commonly acknowledged that risk stratification in BrS patient is controversial, especially the use of PES for patients with a Brugada ECG. In June 2006, Anil K *et al*[20] reported a Meta-Analysis about risk stratification of individuals with Brugada electrocardiogram involving 1545 patients. They found that (male) patients with a history of syncope or SCD and patients with a spontaneous Type Ⅰ Brugada ECG had a 3-to 4-fold increased risk of arrhythmic events. The risk of cardiac events was not significantly increased in BrS patients inducible at PES, and it was also found that neither a family history of SCD nor the presence of a mutation in the SCN5A gene increased the risk of events. The author presumed the heterogeneity found in the use of PES for risk stratification may be due to methodological differences in the stimulation protocols used for PES or in the criteria used for a positive or negative PES. Because of this heterogeneity, it was difficult to decide that whether an asymptomatic patient with a Brugada ECG should undergo PES to assist in selection for ICD implantation. Our study proposed that if the Tp-e interval in a patient suspected of BrS is more than 120 ms, this may have a high prediction value for a positive PES. If the PES result is positive in the patient with Tp-e interval $\geqslant$120 ms, the patient should receive ICD implantation, even if the PES result is negative, as this kind of patient is belongs to high risk population who must receive close clinical follow-up. This is essential for the diagnosis and management of BrS patient.

Our study suggested a significant correlation between Tp-e interval and life-threatening arrhythmic events in BrS patients, suggesting that the prolongation of the Tp-e interval could serve as a new noninvasive risk factor for arrhythmic event in patients with Brugada syndrome.

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