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Original Article

The role of right precordial intrinsicoid deflection time in determining the conversion of Type 2 Brugada ECG pattern to Type 1 Brugada ECG pattern on 12-lead electrocardiogram with ajmaline test

Orcun Ciftci[1], Casit Olgun Celik[1], Volkan Camkiran[2], Ilyas Atar[3], Bulent Ozin[1]

[1]Department of Cardiology, Faculty of Medicine, Baskent University, Ankara, Turkey
[2]Clinic of Cardiology, Memorial Hospital Bahcelievler Hospital, Istanbul, Turkey
[3]Clinic of Cardiology, Guven Hospital, Ankara, Turkey

Abstract

Aim: Brugada syndrome is a genetic disorder associated with fatal ventricular arrhythmias. Type 1 (cove-type) ECG pattern is diagnostic for Brugada syndrome while Type 2 (saddle-type) ECG pattern requires ajmaline test to convert it to Type 1 ECG pattern to make the diagnosis. However, this test may cause ventricular arrhythmias and death. Intrinsicoid deflection time (IDT) is an ECG parameter reflecting intraventricular conduction delay, which is one of the pathophysiological mechanisms for Brugada syndrome. We examined IDT for conversion of type 2 Brugada pattern to type 1 Brugada pattern in ajmaline test.

Materials and Methods: This retrospective study involved patients with Type 2 ECG pattern that was converted to Type 1 ECG pattern with ajmaline test (Group 1) and an age- and sex-matched control group with a normal ECG (Group 2). IDT was digitally measured in the lead V2, from the onset of the QRS complex to the peak of the R wave and compared between the study groups. A ROC curve was drawn to test the predictive ability of IDT for conversion to Type 1 ECG pattern.

Results: There were 28 subjects (21 men, 7 women) in Group 1 and 28 subjects (21 men, 7 women) in Group 2. Group 1 had a significantly greater IDT than Group 2 (28 (17.1-78.0) msec vs 21 (16.0-36.9) msec; $p<0.05$). In ROC analysis, IDT significantly predicted conversion to Type 1 ECG pattern, and a cut-off value of 25 msec for IDT had a sensitivity of 55.6% and a specificity of 81.5% for predicting conversion to Type 1 ECG pattern.

Conclusion: IDT was significantly longer in patients with Type 2 ECG pattern converted to Type 1 ECG pattern by ajmaline compared with the control subjects. IDT has a good specificity and a modest sensitivity for prediction of conversion to Type 1 ECG pattern.

Keywords: Brugada syndrome; ajmaline test; intrinsicoid deflection time

INTRODUCTION

First described in 1992 (1), Brugada syndrome is a genetic disease of cardiac sodium channels characterized by an increased incidence of sudden cardiac death secondary to ventricular arrhythmias among individuals free of an overt structural heart disease. It has a worldwide prevalence of 5-20 per 10.000 people (1-6). It has been shown that Brugada syndrome is responsible for 5-40% of all sudden cardiac deaths among people younger than 40 years of age who are free of any overt structural heart disorder. Similar to other primary arrhythmia syndromes, sudden cardiac death may occur as the first manifestation of Brugada syndrome (7). The general electrocardiographic phenotypic characteristics of Brugada syndrome may occur by different pathophysiological mechanisms. There are in excess of 300 different sodium channel gene SCN5A mutations causing a defect in sodium channels and affecting phase 0 (rapid depolarization) of the cardiac myocyte action potential (8-10). Brugada syndrome is characterized by an atypical right bundle branch block pattern and ST segment elevation in right precordial leads (most commonly V1 and V2, and sometimes V3). While Type 1 ECG pattern (cove-type ST elevation) is diagnostic of the disorder, Type 2 ECG pattern (saddle-type ST elevation) is not diagnostic but suggestive of the disorder, and ajmaline or other sodium channel blockers

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Corresponding Author: Orcun Ciftci, Department of Medical Genetic, Faculty of Medicine, Ankara Yildirim Beyazit University, Ankara, Turkey, **Email:** orucun@yahoo.com

are typically necessary to convert Type 2 ECG pattern to Type 1 ECG pattern.

Although the pathophysiology of Brugada sybdrome has not been fully understood, several hypotheses have focused on depolarization and repolarization abnormalities in Brugada syndrome. According to the depolarization hypothesis, slowed conduction in the right ventricular outflow tract (RVOT) plays a primary role in the genesis of arrhytmogenic and electrocardiographic changes in Brugada syndrome (11). Indeed, slowed electrical conduction in RVOT demonstrated by electrophysiological studies performed with endocardial (12), epicardial (13), and body mapping (14) in patients with Brugada syndrome corroborate the depolarization hypothesis. Nademanee et al. showed that the elimination of the epicardial arrhythmogenic region by radiofrequency ablation disrupted fractionated bipolar electrocardiograms and late potentials and significantly reduced arrhythmia susceptibility and ST segment elevation (15).

Intrinsicoid deflection time (IDT), also known as R peak time, reflects time from QRS onset to the peak of R or R' wave in unipular lateral precordial leads V5 and V6, and represents the complete myocardial depolarization time underlying those leads (16). R peak time is an ancillary diagnostic parameter in the diagnosis of conditions characterized by left ventricular concentric hypertrophy and hypertrophic cardiomyopathy. QRS duration is prolonged in left ventricular concentric hypertrophy, and a QRS duration of more than 110 ms is considered abnormal among individuals older than 16 years of age. Prolongation of QRS duration is typically associated with an increased R peak time (>50 msec) in V5 and V6. This increase is the net result of an increased left ventricular wall thickness or prolonged endo-apicardial transmural conduction associated with intramural fibrosis.

Right-sided IDT is a marker of transmural depolarization time in right precordial leads (V1-V2) and is usually between 15 msec and 35 msec. Right-sided IDT is typically prolonged in right bundle branch block (RBBB) and right ventricular hypertrophy. It has also been reported to be prolonged in mitral stenosis (MS), pulmonary hypertension, and asthma (16). Brugada syndrome may give rise to prolonged IDT in right precordial leads as a result of delayed depolarization underlying them. Therefore, we aimed herein to investigate if delayed right ventricular depolarization and hence a delayed conduction time in Brugada syndrome brings about an increase in IDT and whether it predicts patients with Type 2 ST elevation on 12-lead ECG that is converted to a Type 1 ST elevation upon ajmaline drug challenge.

MATERIALS and METHODS

This retrospective study was approved by Başkent University Medical and Health Sciences Research Committee (Project No: KA19/220) and funded by Başkent University Research Fund. The patient group (Group 1) consisted of patients having incomplete right bundle branch block (IRBBB) with Type 2 ST elevation on 12-lead ECG that was converted to Type 1 ST elevation upon ajmaline challenge performed after the patients' admission to Başkent University Faculty of Medicine, Department of Cardiology between 01.01.2010 and 01.01.2013 with complaints of palpitations, unexplained syncope, and sudden cardiac death, or with a family history of Brugada syndrome in first degree relatives. The control group (Group 2) consisted of subjects who presented to Başkent University Faculty of Medicine Department of Cardiology for various cardiac reasons but had no palpitations, unexplained syncope, sudden cardiac death, or a family history of Brugada syndrome in first degree relatives. The control subjects had no Type 1 or Type 2 ST elevation on 12-lead ECG, and 8 (28.6%) had IRBBB but 20 (71.4%) did not. The exclusion criteria included severe pulmonary hypertension, right ventricular hypertrophy, right ventricular enlargement, severe mitral stenosis, severe pulmonic stenosis or regurgitation, arrhytmogenic and right ventricular dysplasia.

In patients with Type 1 ST elevation, ajmaline test was performed intravenously by the protocol recommended by the Brugada consensus conference reports issued in 2002 and 2005 (2,17). A maximum dose 1mg/kg ajmaline was infused intravenously over a period of 5-10 minutes while continuous 12-lead ECG monitorization and recording were undertaken. An external defibrillator was kept ready on stand-by mode. Ajmaline infusion was stopped when a diagnostic type I ECG pattern with ST elevation greater than 0.2 mV was formed in at least two right precordial leads, premature ventricular depolarizations or ventricular tachycardia (VT) developed, QRS duration increased by more than 130% of the baseline duration, or high grade atrioventricular (AV) block developed. After ajmaline infusion was stopped, monitorization continued for either at least 60 minutes or until after ST elevations returned to baseline (18). Intrinsicoid deflection time was measured with the help of a magnifier, from the onset of the QRS complex to the peak of the proceeding R wave of the lead V2; and it was reported in milliseconds (16). All measurements were separately performed by two independent researchers (ÇOÇ, OÇ), and a third measurement was done when the two observers disagreed. All echocardiographic examinations were performed by expert echocardiographers of the Institution, using aGE Vivid 7 (Horten, Norway) echocardiography device; all echocardiographic examinations were done and all echocardiographic measurements were taken with the patients lying in supine and left lateral decubitis position, from the parasternal long axis, parasternal short axis, apical four chamber, and subcostal positions.

Statistical analysis

All statistical analyses were performed using SPSS v. 21.0 statistical software (IBM Inc, USA). The descriptive statistics were reported as mean±standard deviation, median (minimum-maximum), and number (percentage).

As the quantitative variables did not show normal distribution, they were compared using Mann Whitney–U test; categoric data were compared using Chi-square test or Fisher's exact test. The intrinsicoid deflection times, echocardiographic, and demographic variables of both groups were compared. The predictive power of IDT for Brugada syndrome was tested by drawing a Receiver Operating Curve (ROC), and its sensitivity and specificity were calculated. All statistical comparisons were considered significant for p<0.05.

RESULTS

Group 1 consisted of 28 patients, 21 (75%) males and 7 (25%) females, with a median age of 32 years (min 24-max 44); Group 2 consisted of 28 subjects, 21 (75%) males and 7 (25%) females, with a median age of 33 years (min 19-max 46). Both groups were statsitically similar in terms of age and sex distribution. They did not show anysignificant difference regarding the demographic and echocardiographic parameters (Table 1). Group 1 had a median IDT of 28 (17.1-78.0) mec while the control group 21 (16.0-36.9) msec in lead V2 (p<0.05). A ROC analysis to determine IDT's predictive value for the development of Type 1 Brugada pattern revealed an area under the curve (AUC) of 0.72 (%95 CI 0.58-0,89; p<0.05). For a cut-off value of 25 msec, IDT could predict conversion to Type 1 Brugada pattern with a sensitivity of 55.6%, specificity of 81.5%, positive predictive value of 75%, and negative predictive value of 64.7% (Figure 1 and Figure 2).

Table 1. Comparison of IDT, demographic, and echocardiographic parameters between the study groups

Parameter median (min-max) or n (%)	Group 1 (n=28)	Group 2 (n=28)	p
Age (years)	32 (24-44)	33 (19- 46)	NS*
Sex (male)	21 (75%)	21 (75%)	NS**
Smoking	6 (21.4%)	7 (25.0%)	NS**
Diabetes mellitus	0 (0%)	1 (3.6%)	NS**
Hypertension	3 (10.7%)	4 (14.3%)	NS**
Coronary artery disease	1 (3.6%)	1 (3.6%)	NS**
Heart failure	1 (3.6%)	0 (0%)	NS*
LVEF (%)	55 (25-62)	57 (49-66)	NS*
TAPSE (mm)	21 (18-26)	23 (19-26)	NS*
PAP (mmHg)	35 (30-50)	32 (25-45)	NS*
A4B RVD (mm)	33 (28-42)	31 (21-44)	NS*
A4C RVT (mm)	3.6 (3.2-5.1)	3.8 (2.9-5.4)	NS*
A4B RAD (mm)	26 (19-38)	24 (21-29)	NS*
QRS duration (msec)	104 (96-112)	102 (99-109)	NS*
Heart Rate (beats/minute)	77 (56-92)	72 (61-89)	NS*
V2 IDT (msec)	28 (17.1-78.0)	21 (16.0-36.9)	<0.05*

*Mann Whitney-U test, ** Chi-Square test; NS: Non-significant; A4C: Apical 4 chamber, RVD: Right ventricular diameter, RVT: Right Ventricular wall thickness, RAD: Right atrial diameter, TAPSE: Tricuspid annular plane systolic excursion, PAP: Pulmonary artery pressure, LVEF: Left ventricular ejection fraction, IDT: Intrinsicoid deflection time

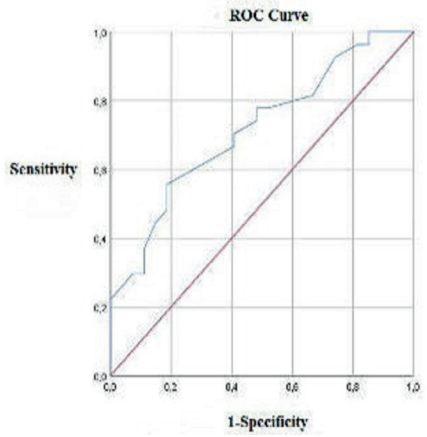

Figure 1. ROC curve of IDT to determine its predictive power for the determination of conversion of Type 2 Brugada pattern to Type 1 Brugada pattern

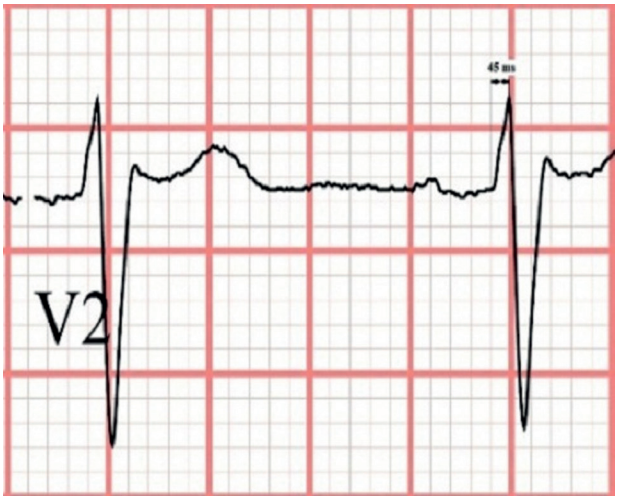

Figure 2 A. 12-lead ECG recordings of a patient with conversion of Type 2 Brugada pattern to Type 1 Brugada pattern in lead V2 with ajmaline testing (A), and a control subject without Type 2 or Type 1 Brugada pattern in lead V2

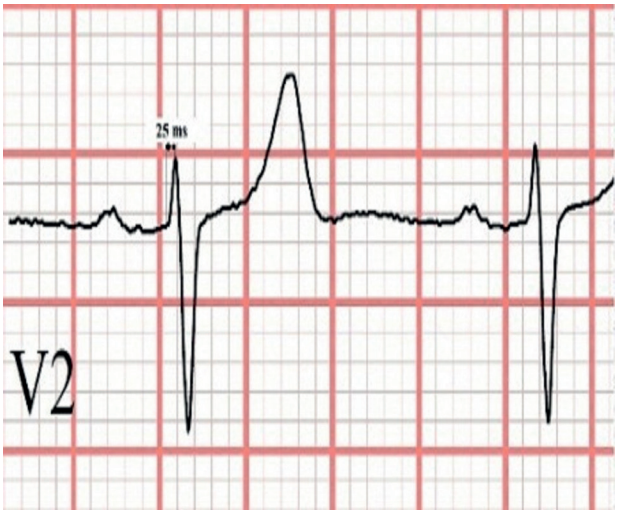

Figure 2 B. Please note that IDT in lead V2 is significantly prolonged in the patient with Type 2 Brugada pattern than that in the control subject (45 msec vs 25 msec, respectively)

DISCUSSION

Brugada syndrome is a genetic arrhythmic syndrome characterized by a defect in cardiac sodium channels and fatal arrhythmias. The majority of patients who die are young, and the fatal incidents appear to occur more commonly under certain conditions such as sleeping, fever, increased body temperature such as showering with hot water, and when taking certain sodium blocking medications. Brugada syndrome is diagnosed on the basis of the typical ECG pattern with a right bundle branch block-like pattern and the typical cove-shaped ST elavation in leads V1 and V2 (Type 1 Brugada ECG pattern). The other variant, Type 2 Brugada ECG pattern is the so-called saddle-type ST elevation in V1-V2, which is not diagnostic but suspective of the disease. Patients with Type 2 ECG who suffer palpitations, unexplained syncope, aborted sudden cardiac death or ventricular fibrillation, or those with Type 2 ECG and a family history of Brugada syndrome, unexplained sudden death especially at an earlier age, or Type 1 Brugada pattern in first degree relatives should be tested for Brugada syndrome. Such testing is performed by infusion of ajmaline, a class 1 antiarrhythmic and a sodium channel blocker among others, to unmask a potential Type 1 ECG by further blocking of cardiac sodium channels, resulting in the conversion of Type 2 pattern to Type 1 pattern. Ajmaline is administered with continuous infusion using some established protocols, and this should be done under close electrical rhythm monitoring and a defibrillator and other resuscitation equipments should be kept immediately available (2,17). However, ajmaline and other sodium channel blockers given for this purpose are not free of side effects, and some lethal arrhythmias including aventricular premature complexes, tachycardia, or fibrillation, atrioventricular block, pulseless electrical activity, and death may occur during their infusion (18). Therefore, ajmaline testing should be selectively performed in suitable candidates, which is important to reduce complications and unwanted side effects, and to cut costs and hospital admissions. Hence, it is of paramount importance to predict patients with Type 2 Brugada pattern that are likely to convert to Type 1 Brugada pattern. It is best accomplished with non-invasive tools such as 12-lead surface ECG.

Intrinsicoid deflection time (IDT) is a parameter that can be measured from the onset of QRS complex to the peak of the proceding R or R' wave; it reflects the time of electrical stimulus propagation from endocardium to epicardium of both ventricles (16). IDT greater than 50 msec in V5-V6 and greater than 35 msec in V1-V2 has been shown to be correlated to depolarization delay caused by left and right ventricular hypertrophy, left and right bundle branch block, and intramural conduction delay. IDT is expected to prolong in disorders primarily characterized by concentric remodeling affecting lef tor right ventricle (16). Apart from that, left-sided prolonged IDT has been linked to left ventricular dysfunction and progression to heart failure (19), prediction of sudden cardiac death (20), and determination of the response to cardiac resynchronization therapy (21); right-sided IDT, on the other hand, has been correlated toright bundle branch block (16), diagnosis of right ventricular hypertrophy secondary to mitral stenosis (16), and diagnosing pulmonary embolism and determination its severity (22).

There are three hypotheses for the pathogenesis of Brugada syndrome, which are the reploarization hypothesis, the depolarization hypothesis, and the flow/load imbalance hypothesis. According to the depolarization hypothesis, slowing of the ascending limb of phase 0 of the action potential and the eventual decrease in action potential conduction velocity is responsible for arrhythmogenesis (23). Supporting this hypothesis, an excessively slowed electrical stimulation primarily affecting RVOT has been shown by endocardial and eipcardial mapping techniques in patients with Brugada syndrome suffering electrical storm (12-24). In this regard, it may be useful to demonstrate regional transmural conduction delay among patients with suspected Brugada syndrome (saddle type ST elevation pattern in leads V1 and V2) in order to predict conversion to Type 1 Brugada pattern and, possibly, to diagnose Brugada syndrome. Indeed, our study revealed that IDT in V2 facing the right ventricle was significantly longer in patients with Type 2 Brugada pattern at baseline that was converted to Type 1 Brugada pattern in ajmaline test compared to controls. We believe that this finding is consistent with the depolarization hypothesis proposed for Brugada syndrome. Another finding of our study is that IDT, a t a cut-off level of 25 msec, could predict conversion to Type 1 Brugada pattern with good specificity but a modest sensitivity. This result suggests that right-sided IDT is a satisfactorily specific albeit not very sensitive predictor of conversion of Type 2 Brugada pattern to Type 1 Brugada pattern. In other words, although IDT >25 msec is specific for conversion of Type 2 Brugada pattern to Type 1 Brugada pattern, conversion to Type 1 Brugada pattern is still possible when IDT is smaller than 25 msec. Conversion to Type 1 Brugada pattern in the absence of right-sided IDT prolongation may suggest that other factors than depolarization abnormalities including the repolarization hypothesis may be responsible for Brugada syndrome, as has been previously reported. A high specificity may imply that, in the absence of any other abnormality causing the prolongation of right ventricular intramural depolarization in any healthy appearing individual, a prolonged IDT would indicate Brugada syndrome with a high probability.

Limitations

The limitations of the present study include its retrospective design, a relatively low number of patients, and the lack of enrollment of patients with type 2 Brugada pattern that did not convert to Type 1 brugada pattern in ajmaline testing.

CONCLUSION

Right-sided IDT was significantly longer in patients with type 2 Brugada ECG pattern that evolved to Type 1 ECG pattern than the controls without Type 1 or Type 2 ECG

patterns. Additionally, IDT could predict conversion of Type 2 Brugada ECG pattern to Type 1 ECG pattern with a good specificity and a modest sensitivity. In order to determine whether this parameter may reduce the need for ajmaline testing, additional studies should be performed to compare patients with Type 2 ECG pattern that is converted to Type 1 ECG pattern and patients with Type 2 ECG pattern that is not converted to Type 1 ECG pattern with ajmaline testing.

Competing interests: The authors declare that they have no competing interest.

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