T Wave Alternans Does not Assess Arrhythmic Risk in Patients with Brugada Syndrome

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Background: Brugada syndrome is associated with a risk for sudden death, but the arrhythmic risk in an individual Brugada syndrome patient is difficult to predict. Pathologic changes in the early repolarization phase of the ventricular action potential probably constitute part of the arrhythmogenic substrate in Brugada syndrome. Microvolt T wave alternans (TWA) assesses dynamic beat-to-beat changes in repolarization and has been suggested as a marker for repolarization-related sudden death. We therefore tested whether TWA is an indicator for arrhythmias in Brugada syndrome with a focus on right precordial ECG leads.

Methods: We assessed TWA in nine symptomatic, inducible patients with established Brugada syndrome and in seven healthy controls. TWA was assessed at rest and during exercise using both standard methods and an algorithm that assesses TWA in the early ST segment and the right precordial leads.

Results: None of the Brugada patients developed TWA in this study irrespective of analysis at rest or during exercise, neither using standard methods nor when the early ST segment was included in the analysis. When the early ST segment was included in the analysis, nonsustained TWA was found in three out of seven, and sustained TWA in one control.

Conclusion: T wave alternans is not an appropriate test to detect arrhythmic risk in patients with Brugada syndrome.

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Brugada syndrome; sudden arrhythmic death; T wave alternans; risk stratification; non-invasive tests; repolarization

Reversible ST segment elevation in the right precordial leads is the paramount sign of Brugada syndrome.[1,2] Patients with Brugada syndrome are at risk for sudden cardiac death, and it has been recommended to implant a defibrillator in these patients.[2] Some data, however, suggest that only a subgroup of patients may benefit from device implantation,[3] and the incidence of arrhythmic events appears low in the first year following defibrillator implantation.[3,4] Furthermore, some patients show ECG changes suggestive of Brugada syndrome but may not be at arrhythmic risk.[5,6] Given the invasive procedure needed to implant a defibrillator, additional methods are needed to better identify Brugada syndrome patients who would benefit from a defibrillator.

T wave alternans measures microvolt beat-to-beat changes in T-wave amplitude and morphology caused by corresponding alternans of ventricular repolarization.[7,8] T wave alternans is a risk marker for arrhythmic death in patients with coronary artery disease and heart failure.[9–11] The Brugada syndrome causes transient alterations in the right ventricular action potential.[12] Microvolt T wave alternans therefore appears to be a promising technique to detect such changes, especially when right ventricular leads and the early ST segment are analyzed.

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We therefore studied whether T wave alternans can be detected in patients with Brugada syndrome who are at high risk for sudden death and fine-tuned the method to detect changes in early repolarization in the right precordial chest ECG leads.

METHODS

Patient Selection

For this study, we prospectively included patients with (1) documented incomplete right bundle branch block and ST-segment elevation in the right precordial leads during administration of slowly dissociating sodium channel blockers; (2) inducible polymorphic ventricular arrhythmias during electrophysiological testing, and (3) a history of syncope or aborted sudden death. All patients who consented to participate in the study underwent measurement of T wave alternans at rest and during exercise. Follow-up visits at the Department of Cardiology, University Hospital Münster (n = 7), or at other hospitals (n = 2) included regular interrogation of the implanted defibrillator. The control group consisted of seven persons without a history of ventricular arrhythmias or syncope. One control subject underwent radio frequency ablation in the inferior region of the AV node to cure AV nodal reentrant tachycardia. The other patients had no arrhythmia history. None of the control subjects had a history of syncope or sudden death. All patients gave informed consent.

Measurement of T Wave Alternans

T wave alternans (TWA) was assessed on a computerized bicycle ergometer system (Cambridge Heart 2000). The system for recording of T wave alternans has been described in detail previously.[7,9] Data were continuously acquired at rest for a period of 3–7 minutes, during exercise with increasing work load (1W increase/5 sec) until the patients reached a heart rate of >115 beats/min, and after cessation of exercise until heart rate had dropped below 90 beats/min.

Data Analysis

The entire recording period was assessed. T wave alternans was measured using two different methods. Primarily, standard criteria for significant T wave alternans (TWA) were used.[7,9] In a second analysis, the early ST segment (from 20 ms after the J point) was included in the interval used to compute T wave alternans, and the right precordial leads (V1–V3) were scrutinized for occurrence of TWA (TWA–J20). Presence of TWA was defined by published criteria.[7,9] All analyses were performed by a single experienced investigator and confirmed by a second investigator who was unaware of the subject's diagnosis.

RESULTS

All patients showed typical right precordial ST segment elevation, either transiently during a resting ECG or during challenge with ajmaline (1 mg/kg maximal dose). In the Brugada patients, males outnumbered females by 6:3 (66% male). All patients presented with either syncope (n = 6) or aborted sudden arrhythmic death requiring defibrillation (n = 3). One Brugada patient complained of palpitations and was found to have AV nodal reentrant tachycardia during electrophysiological

Table 1. Clinical Characteristics of the Study Patients

	Brugada Patients	Controls
Male sex	6/9	4/7
Median age	46 years	31 years
Syncope	6/9	0/7
Survived SCD	3/9	0/7
Supraventricular tachycardias	1/9 AVNRT	1/7 AVNRT
Family history of SCD	2/9	0/7
Defibrillator implanted	9/9	0/7
pVT/VF inducible during programmed stimulation	9/9 (7 by two extra stimuli, 2 by three extra stimuli)	–

Numbers indicate number of patients. The abbreviations indicate: SCD = sudden cardiac death, AVNRT = AV nodal reentrant tachycardia, pVT = polymorphic ventricular tachycardia, VF = ventricular fibrillation.

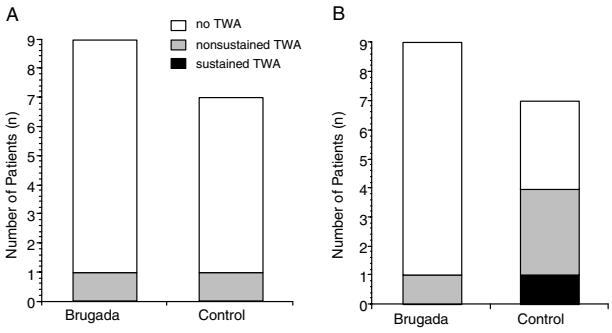

Figure 1. (A). Proportion of individuals with T wave alternans (% TWA, y-axis) in Brugada patients (Brugada, left column) and control subjects (Control, right column) using standard TWA analysis. (B). Proportion of individuals with TWA when the early ST segment was included in the T wave analysis. White bars indicate no presence of TWA, gray bars indicate presence of nonsustained TWA, and black bars indicate presence of sustained TWA.

testing.[13] Echocardiography and angiography including right heart catheterization were normal in all patients.

Measurement of T Wave Alternans

The exercise protocol was well tolerated in all patients, and all patients reached a heart rate >115 beats/min. Sustained TWA was not detected in any of the study patients using standard criteria for TWA measurement. Nonsustained TWA was present in one control individual by standard definition, and in none of the Brugada patients (Fig. 1A). When the early ST segment was included in the TWA analysis (TWA–J20), one of the Brugada patients showed nonsustained TWA–J20 (Fig. 1B). In the control group, three individuals were found to have nonsustained TWA–J20. One control subject, a young male with incomplete right bundle branch block but without a history or family history of arrhythmias, syncope, or sudden death, had sustained TWA–J20 (Fig. 1B).

Follow-up

All Brugada syndrome patients received an implantable defibrillator. During a median follow-up of 34 months, one of the Brugada patients developed a rapid polymorphic ventricular tachycardia that was adequately terminated by the implantable defibrillator (Fig. 2). In this patient, T wave alternans had not been detected, neither at rest nor during exercise.

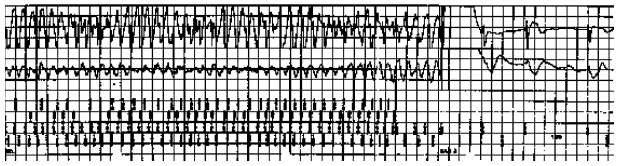

Figure 2. Intracardiac electrograms recorded by the implanted defibrillator in a Brugada patient without detectable T wave alternans who developed a rapid polymorphic ventricular tachycardia during follow-up. The upper panel shows the intracardiac bipolar electrogram, the middle panel shows the far field electrogram (coil versus can), and the lower panel shows the marker channel. On the right part of the recording, the defibrillator delivers a shock that successfully restores sinus rhythm. Note that the early ST segment is elevated after the ICD shock.

DISCUSSION

In this study of symptomatic Brugada syndrome patients at high risk for arrhythmic death, we found no microvolt T wave alternans at rest or during exercise. Alternans of the early ST segment in the right precordial leads, the portion of the surface ECG showing the characteristic ECG changes associated with Brugada syndrome, was also not detected. T wave alternans does not identify Brugada syndrome patients at high risk for sudden death.

Patient Characteristics

All of the patients studied had an established diagnosis of Brugada syndrome, as demonstrated by typical ECG changes, a history of syncope or aborted sudden cardiac death, and by ventricular arrhythmias during electrophysiologic testing.[1,14] One patient received adequate defibrillator shocks terminating polymorphic ventricular tachycardia during the follow-up period. According to all currently available risk stratification parameters, this patient group therefore represents Brugada syndrome patients at high risk for sudden death.[1–4]

T Wave Alternans in Brugada Syndrome

T wave alternans could be adequately measured in all patients studied.[7] Despite the clinical and electrophysiological indicators for a high risk of sudden cardiac death, there was no sustained T wave alternans in any of the Brugada patients studied. Even when the early ST segment and the right precordial leads were included in the analysis, sustained T wave alternans was not found. Thus, although cardiac repolarization is altered in Brugada

syndrome as demonstrated by the reversible ST segment changes, there was no beat-to-beat T wave alternans in the early ST segment of symptomatic Brugada syndrome patients. Our data concur with another previously published study on T wave alternans in Brugada syndrome.[15] This study extends that report in two ways: First, this study demonstrates that T wave alternans cannot be detected in Brugada patients at high risk for sudden death. Second, analysis of T wave alternans in the predominant locations of ECG changes in Brugada syndrome, i.e., in the early ST segment and in the right ventricular precordial leads, does also not identify high risk Brugada syndrome patients.

T wave alternans identifies patients with structural heart disease who are at risk for sudden arrhythmic death, including patients with heart failure,[7] patients with inducible ventricular arrhythmias during electrophysiological testing,[16] patients with dilated cardiomyopathy,[11] and patients with hypertrophic obstructive cardiomyopathy.[17] Unlike these diseases, exclusion of structural heart disease is part of the diagnosis of Brugada syndrome.[1,3] The syndrome is associated with mutations in the sodium channel SCN5A in some cases, or an altered function of Ito.[2,14,18–20] Its value in structural heart disease notwithstanding, our data suggest that T wave alternans may not be as valuable in patients with primary electrical disease such as the Brugada syndrome.

CONCLUSIONS

T wave alternans is not an adequate method to identify Brugada syndrome patients who are at high risk for arrhythmic death. T wave alternans might not be an ubiquitous phenomenon in patients at high risk for ventricular arrhythmias and could be related to arrhythmic risk in patients with structural heart disease.

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