Cardiovascular Innovations and Applications

INVITATION

An Open Invitation to Join the International Brugada Electrocardiographic Indices Registry

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Abstract

Background: The Brugada Electrocardiographic Indices Registry is a comprehensive data registry composed of patients with Brugada patterns on the electrocardiogram (ECG). The aim is to test the hypotheses that (i) ECG indices combining both depolarization and repolarization abnormalities can better predict spontaneous ventricular arrhythmias than existing ECG markers in Brugada syndrome and (ii) that serial ECG measurements will provide additional information for risk stratification, especially in asymptomatic patients.

Methods: Patients with both Brugada pattern ECGs and Brugada syndrome are eligible for inclusion in this registry. Baseline characteristics and ECG variables reflecting depolarization and repolarization will be determined. The primary outcome is spontaneous ventricular tachycardia/ventricular fibrillation or sudden cardiac death. Secondary outcomes are inducible ventricular tachycardia/ventricular fibrillation and syncope.

Results: As of November 15, 2019, 39 investigators from 32 cities in 18 countries had joined this registry. As of December 15, 2019, 1383 cases had been enrolled.

Conclusions: The Brugada Electrocardiographic Indices Registry will evaluate the disease life course, risk factors, and prognosis in a large series of Brugada patients. It will therefore provide insights for improving risk stratification.

Keywords: Sudden cardiac death; Brugada syndrome; risk stratification; electrocardiogram indices; BEIR consortium.

Introduction

Sudden cardiac death (SCD) is a significant problem globally, and is frequently due to ventricular tachyarrhythmias [1]. Brugada syndrome (BrS) is a genetic ion channelopathy that predisposes affected individuals to SCD. Different methods of risk stratification have been developed; however, it remains difficult to determine which patients are most at risk of developing these malignant arrhythmias. Traditionally, repolarization markers such as the corrected QT interval (QTc) have been widely used for the risk stratification of SCD [2]; however, they have low sensitivity and specificity [3] because ventricular arrhythmias have been observed in the presence of a normal or even reduced QT interval [4]. Other markers that have been proposed include QT dispersion [5, 6], the interval from the peak to the end of the T wave [7] ($T_{peak}-T_{end}$, reflecting transmural dispersion of repolarization [8]), the ($T_{peak}-T_{end}$)/QT ratio [9], and $T_{peak}-T_{end}$ dispersion [10]. However, they largely ignore a contribution from abnormal conduction in cardiac arrhythmogenesis [11]. In this scheme, reduced conduction velocity (CV) and is reflected electrocardiographically as a prolonged QRS duration [12, 13]. Reduced CV increases the probability of ventricular arrhythmias via reentry by shortening the excitation wavelength, λ (CV times refractory period). The challenge is that λ must be determined invasively during an electrophysiological study. Thus, it would be advantageous to identify noninvasive markers that reflect both conduction and repolarization processes and evaluate their relation to arrhythmic events and SCD.

To address the risk stratification problem in BrS, we have established the international Brugada Electrocardiographic Indices Registry (BEIR). This will enable two main hypotheses to be tested, which are (i) that electrocardiogram (ECG) indices combining both depolarization and repolarization abnormalities can better predict spontaneous ventricular arrhythmias than existing ECG markers in BrS and (ii) that serial ECG measurements will provide additional information for risk stratification, especially in asymptomatic patients. The BEIR Consortium currently comprises investigators from 18 countries (Figure 1). As of December 15, 2019, 1383 cases had been enrolled. The target is to recruit 2000 cases.

Methods

Study Design and Patient Inclusion Criteria

This is a retrospective registry including patients with type 1 or type 2 ECG Brugada pattern recorded from the right precordial leads V_1 and V_2 in the second, third, or fourth intercostal space [14]. Type 1 (coved pattern) is defined as ascending and high takeoff of 2 mm of more at the end of the QRS duration, followed by a coved or rectilinear downward-sloping ST segment and a negative
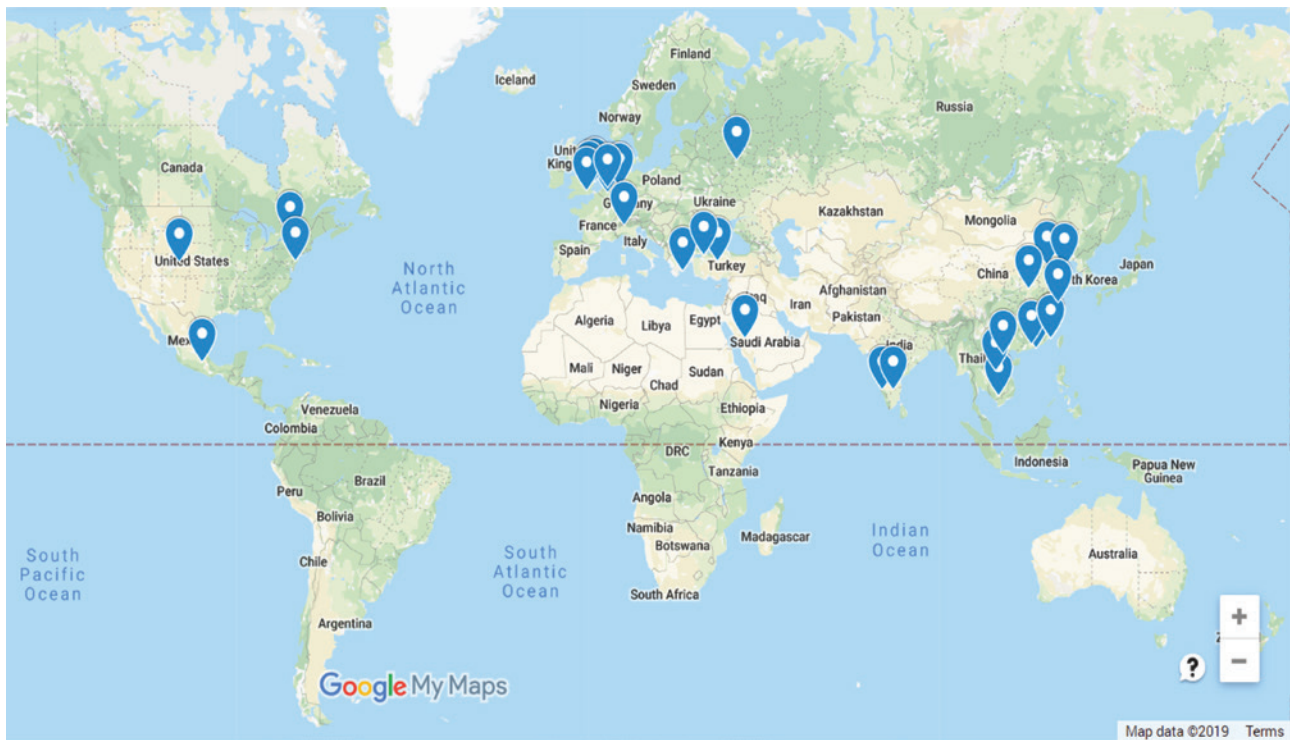
Figure 1: The Brugada Electrocardiographic Indices Registry is an International Collaborative Effort, which Currently Comprises 39 Investigators from 32 Cities in 18 Countries.

symmetric T wave in one or more right precordial leads (V_1 and V_2). Type 2 (saddleback pattern) is defined as high-takeoff r′ of 2 mm or more, followed by convex ST elevation remaining at more than 0.5 mm relative to the isoelectric line and a positive T wave in V_2 ($T_{peak} > ST_{minimum}$) or a T wave of variable morphology in V_1.

Patient Details and Characteristics

The following patient data will be collected: city and country of origin, ethnicity, sex, age at first presentation of Brugada pattern (earliest documented by ECG or case notes), current age or age at death, date of birth, date of the first Brugada pattern (earliest date documented by ECG or case notes), initial type of ECG Brugada pattern (type 1 or type 2), fever-induced type 1 pattern, family history of BrS, family history of ventricular fibrillation (VF) or SCD, family history of VF or SCD in family members younger than 35 years, documented atrial fibrillation, sinus node dysfunction, syncope, spontaneous ventricular tachycardia (VT)/VF, and SCD. Information on antiarrhythmic agents, their doses, their prescription durations, and any side effects should be obtained.

The following will be noted: outcome of drug challenge tests and electrophysiological study details, including the date of the procedure, the number of extrastimuli used, and positive outcome during electrophysiological study, defined as sustained VF or VT lasting more than 30 s or requiring termination because hemodynamic compromise was induced. Additional results from Holter monitoring, genetic tests, exercise tolerance tests, and echocardiography will be analyzed, if available.

Electrocardiographic Variables

The following ECG variables will be obtained: type of Brugada pattern, beta angle [15], PR interval, RR interval, QRS duration, JT_{peak} (J point to peak of T wave), $T_{peak}-T_{end}$ (peak of T wave to end of T wave), QT duration, QTc duration by Bazett's formula, QT dispersion, $T_{peak}-T_{end}/QT$, $T_{peak}-T_{end}/QTc$, fragmented QRS complexes [16], terminal r wave in a VR lead, concomitant right bundle branch block, first-degree atrioventricular block (PR duration 200 ms or more), early repolarization pattern (≥1 mm (0.1 mV) elevation of the QRS-ST junction (J point) in two or more contiguous inferior

(II, III, and aVF) and/or lateral (I, aVL, V_5, and V^6) leads) [17], and right ventricular outflow tract delayed conduction signs [18].

Follow-up Data and Outcomes

The primary outcome is spontaneous VT/VF or SCD. Secondary outcomes include inducible VT/VF and syncope. Death information, including date of death, age at death, cause of death, and underlying cause of death, will be collected. The follow-up duration (months) is defined as the time between the date of the first Brugada ECG and the date of death, or the censor date of the study, whichever is earlier. Data from implantable cardioverter defibrillators (ICDs) include the device insertion date, the number of appropriate shocks, any atrial pacing or ventricular pacing, VT/VF before ICD implantation, episodes of VT/VF after the first ICD implantation, ICD type, the number of inappropriate shocks, the reason for inappropriate shocks, and complications, such as lead malfunction, lead dislocation, or infection.

Statistics

Data will be expressed as median values (quartile 1 to quartile 3). Patients will be divided into different study groups on the basis of symptoms (asymptomatic, syncope, VT/VF/SCD) and type of Brugada pattern at initial presentation. Categorical data will be analyzed by Fisher's exact test. Differences between study groups will be tested by the Kruskal-Wallis test. $P < 0.05$ will be considered statistically significant. Cox regression will be used to identify significant predictors of primary and secondary outcomes. Those variables with $P < 0.10$ will be included in a multivariate model. Receiver operating characteristic curve analysis will be used to evaluate the discriminative value of continuous variables. Risk scores based on logistic regression will be developed.

Discussion

We have described the rationale for and the design of the BEIR, an international collaborative effort designed to bring together investigators from different countries to create a comprehensive database that will facilitate research in Brugada patients. To date many publications are based on cohorts from Western populations. However, there are relatively fewer studies on patients from other geographical regions. Moreover, risk stratification, especially in asymptomatic patients, remains difficult. By inclusion of both Brugada pattern and BrS patients, data from this registry will enable comparisons of outcomes between asymptomatic, syncope, and VT/VF/SCD groups, and evaluation of the predictive value of different ECG risk markers [19, 20].

We are grateful to *Cardiovascular Innovations and Applications* for this opportunity to make an open invitation to investigators from China and beyond to join our study. The BEIR differs from other registries in three major respects. Firstly, we are taking an all-inclusive stance, and welcome contributions from any interested investigators with relevant cases to join our project. Secondly, junior researchers are particularly encouraged to join our project. Thirdly, we have recruited investigators from different disciplines, such as preclinical electrophysiology, data science, clinical cardiology and electrophysiology, and epidemiology, to facilitate collaboration and cooperation. In doing so, this collaboration will achieve the goal of using complex and higher-dimensional analyses to facilitate risk prediction.

We hope that you will consider joining this effort. Further details are available at https://sites.google.com/view/beir/home. For a copy of the protocol and template for data input or further information, please contact us at gary.tse@doctors.org.uk.

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