Twelve-lead ambulatory electrocardiographic monitoring in Brugada syndrome: Potential diagnostic and prognostic implications

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BACKGROUND Patients with Brugada syndrome (BrS) are diagnosed and risk stratified on the basis of a spontaneous or drug-induced type 1 electrocardiographic (ECG) pattern, often at single time points not accounting for variation throughout the day.

OBJECTIVES The purpose of this study was to prospectively assess the overall burden of type 1 Brugada ECG changes using 12-lead 24-hour Holter monitoring and evaluate association with cardiac events.

METHODS From July 1, 2013 to December 31, 2015, patients with BrS were recruited from 3 Australian centers and the Australian Genetic Heart Disease Registry. All patients underwent clinical review, baseline ECG, and 12-lead 24-hour Holter assessment with precordial leads placed in the left and right second, third, and fourth intercostal spaces. The frequency, temporal, and spatial burden of type 1 BrS ECG pattern were analyzed and assessed for association with cardiac events.

RESULTS A total of 54 patients with BrS were recruited (n=44, 81% men; mean age 44 ± 13 years); the mean follow-up was 2.3 ± 2.5 years. Eleven of 32 patients (34%) initially classified as "drug-induced BrS" demonstrated a spontaneous type 1 pattern at least once over 24 hours. Patients with cardiac events had a significantly higher temporal burden of type 1 ST-segment elevation in the 24-hour monitoring period (total area under the curve 21% vs 15%; $P = .008$), being most pronounced between the hours of 1600 and 2400 ($P = .027$).

CONCLUSION Patients with BrS traditionally classified as drug-induced can exhibit spontaneous ECG changes with longer-term monitoring, particularly in the evening. Temporal burden on 12-lead Holter monitor was associated with cardiac events. Ambulatory 12-lead ECG monitoring may have potential utility in the diagnosis and risk stratification of patients with BrS.

KEYWORDS Brugada syndrome; 12-Lead Holter monitoring; Diagnosis; Risk stratification; Brugada burden

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Introduction

Brugada syndrome (BrS) is an inherited arrhythmia syndrome characterized by coved-shaped ST-segment elevation in the right precordial leads on the 12-lead electrocardiogram (ECG) with associated sudden cardiac death (SCD) due to ventricular fibrillation.[1] BrS is diagnosed in the presence of a spontaneous or drug-induced type 1 Brugada ECG pattern (≥2 mm ST-segment elevation with type 1 morphology in ≥1 right precordial lead V_1 or V_2 in either second, third, or fourth intercostal space [ICS]) independent of symptoms.[2]

The presence of a spontaneous type 1 pattern has consistently been demonstrated to be associated with a higher risk of arrhythmic events in BrS.[3–8] However, it is known that the Brugada ECG pattern may fluctuate over time[9] and the utility of prolonged ECG monitoring in this context has recently been highlighted.[10] A proportion of patients who are initially be classified as lower risk "drug-induced" BrS on the basis of non-diagnostic baseline ECG demonstrate a

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"spontaneous type 1 pattern" at other times.[10] A study of 34 patients with BrS suggested the "burden" of type 1 Brugada ECG changes using 3-lead 24-hour Holter monitoring to be more prevalent in symptomatic patients.[11] Shimeno et al[12] demonstrated increased diagnostic sensitivity with higher intercostal lead placement in 12-lead ECGs and prolonged Holter monitoring as did a recent study correlating ECG lead position with anatomical location of the right ventricular outflow tract on cardiac magnetic resonance imaging.[13]

This study sought to prospectively assess the overall frequency, spatial, and temporal burden of Brugada ECG changes using 12-lead 24-hour Holter monitoring with high precordial lead placement and correlation with clinical events.

Methods

Patient selection and baseline assessment

From July 2013 to December 2015, patients with BrS were recruited from the Genetic Heart Disease Clinics at Royal Prince Alfred Hospital, Concord Repatriation General Hospital, and Blacktown Hospital, in Sydney, Australia, as well as the Australian Genetic Heart Disease Registry.[14] Any patient with a type 1 Brugada ECG pattern observed either spontaneously or after infusion of type 1 antiarrhythmic medication was included (either flecainide 2 mg/kg [maximum of 150 mg] over 10 minutes or ajmaline 1 mg/kg over 5 minutes),[2,15] as were concealed mutation-positive patients. Patients underwent baseline review with comprehensive history, physical examination, and baseline ECG with right precordial leads placed in the standard position (fourth ICS) as well as second and third ICSs. Fragmentation of the QRS was defined as $\geq$4 spikes in 1 lead or $\geq$8 spikes in all leads V_1-V_3.[16] Family history of SCD was defined as any SCD event (including aborted cardiac arrest [ACA]) in a family member younger than 45 years. Research-based genetic testing involved 100–176 cardiac arrhythmia panel in 19 patients (35%), whole exome sequencing in 16 patients (30%), Brugada panel in 1 patient (2%), *SCN5A* testing alone in 1 patient (2%), and predictive testing in 8 patients (15%) with known familial pathogenic variants in BrS genes. All studies were conducted with approval and in strict accordance with the Sydney Local Health District Ethics Review Committee, Australia.

Holter assessment

All patients underwent 12-lead 24-hour Holter assessment with precordial leads placed in the left and right parasternal regions of the second, third, and fourth ICSs (Figure 1A) using the following Holter recording systems (GE SEER 12 2013, GE, Chicago, IL and Mortara H12+, Mortara, Milwaukee, WI) and review systems (GE MARS software version 8.0 and Mortara H-Scribe version 4.34). The 12-lead Holter data were manually reviewed with a 10-second window recorded at 5-minute intervals over the 24-hour period. The degree of ST-segment elevation was quantified for each lead at each time point. Diagnostic ST-segment elevation on Holter monitoring was defined as $\geq$2 mm type 1 Brugada pattern ST-segment elevation in any precordial lead followed by a negative T-wave as per ECG criteria (Figures 1B and 1C).[2] Degree of ST-segment elevation was measured at the J point (inflection between the end of the QRS complex and the ST segment) using published criteria (Supplemental Figure 1).[18,19] In ECGs with a prominent R′ wave, the measurement was taken from the end of the R′ wave where there was a clear inflection point between the end of the QRS complex (using simultaneous leads) and the onset of the ST segment. In cases of dispute, the ECG was reviewed by 2 cardiologists using additional criteria.[20–22] Spatial burden was calculated by the number of precordial leads demonstrating diagnostic ST-segment elevation. Temporal burden was calculated by the number of 5-minute time points demonstrating diagnostic ST-segment elevation. Total time burden was defined as the total time duration (in minutes) with type 1 pattern over the 24-hour period. The global burden of type 1 BrS pattern on Holter monitoring was then quantified as a *Global Burden Index* defined as the product of the amplitude of ST-segment elevation (in millimeters), the number of leads, and the duration of ST-segment elevation (in minutes). Holter heart rate variability data were recorded. Fifteen Holter monitors were randomly selected for analysis by an independent observer (P.K.), with 98% agreement in the evaluation. A different random subset of 15 patients underwent second 24-hour Holter monitoring to assess intrapatient variability.

Clinical events

Clinical events were defined as ACA, sustained ventricular arrhythmia, and/or arrhythmic syncope. Events that had occurred before patient recruitment as well as prospective events occurring during follow-up were included as defined in Table 1. All patients with suspected arrhythmic syncope underwent careful history by 2 independent physicians (B.G. and R.W.S.). Where available, electrograms from implantable cardioverter-defibrillator interrogation were used to confirm arrhythmic events.

Statistical analysis

Statistical analyses were carried out using SAS 9.3 (SAS Institute Inc., Cary, NC). Plots were produced in SPSS version 21 (IBM Corporation, Armonk, NY), Sigmaplot 12.5 (Systat Software Inc), Stata 12.1 (StataCorp LLC, College Station, TX), and GraphPad Prism 6 (La Jolla, CA). Continuous variables were assessed for having a normal distribution, and those not normally distributed were summarized with medians and interquartile ranges and compared using the Wilcoxon test. Box plots were produced in Stata that uses Tukey's hinges for the box limits. Categorical variables were compared using the χ^2 and Fisher exact tests. The data over all time points were summarized into 1 observation per patient and compared using the Wilcoxon test. The area under the curve was calculated as the average percentage over all time points and compared using a generalized linear