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Original article

Paradoxical nocturnal elevation of sympathetic tone and spontaneous ventricular fibrillation in Brugada syndrome

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ABSTRACT

Background: Nocturnal dominance of the incidence of spontaneous ventricular tachyarrhythmias has been reported in patients with Brugada syndrome (BrS). The purpose of the present study is to analyze the QT dynamics and autonomic balance as well as their diurnal variations in BrS patients.
Methods: Of the 33 consecutive patients with BrS included in the study, 14 had a history of cardiopulmonary arrest due to spontaneous ventricular fibrillation (VF) episodes (VF-BrS) and 19 had asymptomatic BrS (A-BrS). QT dynamics and heart rate variability were analyzed using 24-h Holter electrocardiogram recordings.
Results: Of the total 14 first cardiopulmonary arrest episodes due to spontaneous VF, 11 (79%) occurred in VF-BrS patients during the nighttime or at rest. The QT/RR slope during daytime was significantly steeper than that during nighttime in the A-BrS patients ($p = 0.031$), but not in the VF-BrS patients ($p = 1.0$). There were significant diurnal differences pertaining to the high-frequency (HF) and low-frequency (LF)/HF ratios in the A-BrS patients ($p = 0.019$ and $p = 0.019$, respectively), but not in the VF-BrS patients ($p = 1.0$ and $p = 1.0$, respectively). The VF-BrS patients were characterized by relatively high LF/HF ratios, whereas the A-BrS patients were characterized by relatively low LF/HF ratios throughout the daytime and nighttime. Furthermore, the LF/HF ratios during the nighttime in the VF-BrS patients were significantly higher than those in the A-BrS patients ($p = 0.021$).
Conclusions: Most first episodes of spontaneous VF in the VF-BrS patients occurred during the nighttime or at rest. The autonomic imbalance of paradoxical nocturnal elevation of the sympathetic tone along with an underlying persistent sympathetic tone throughout the day may play a key role for spontaneous VF initiation in BrS patients.

Introduction

Brugada syndrome (BrS) is characterized by a coved-type ST-segment elevation in the right precordial leads [1], and cardiac events such as spontaneous ventricular fibrillation (VF) episodes are often documented at rest, particularly during nighttime sleep and at dawn [2], or during the postprandial period [3,4]. Therefore, a dominance of vagal tone has been reported to be associated with the occurrence of J-wave augmentation and spontaneous VF in BrS patients [5]. Heart rate variability (HRV) determined using Holter electrocardiogram (ECG) recordings is a noninvasive and representative parameter that reflects the autonomic balance and its modulation. QT dynamics, expressed as the QT/RR slope, relate to the evaluation of repolarization and autonomic balance. Although some previous studies [6–9] have analyzed Holter ECG recordings in BrS patients, to the best of our knowledge, no previous study has analyzed the differences in QT dynamics and HRV during the daytime and nighttime between BrS patients with a history of cardiopulmonary arrest due to spontaneous VF (VF-BrS patients) and those without any cardiac symptoms (A-BrS patients). Therefore, the aim of the present study was to clarify the clinical and electrocardiographic characteristics and autonomic balance associated with BrS and to understand how to prevent spontaneous VF in BrS patients.

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Methods

Study subjects and diagnosis of BrS

From December 1998 to August 2013, 35 consecutive survivors of cardiopulmonary arrest episodes with documented spontaneous VF without any apparent structural heart disease were referred to the Department of Cardiology at Fukuoka University Hospital for assessment and treatment. All patients were examined noninvasively using echocardiography, exercise stress test, chest radiography, and ECG. Some patients were examined invasively using coronary angiography with an ergonovine provocation test. Of the 35 patients, 14 were diagnosed with BrS based on the presence of a coved-type ST-segment elevation (type 1) of more than 2 mm in more than 1 lead from V1 to V3, placed in the standard or a superior position (up to the second intercostal space), either spontaneously or after a pilsicainide infusion (1 mg/kg). On the basis of the resting ECG, exercise test, and catecholamine (isoproterenol and/or epinephrine) provocation test, no short QT syndrome or catecholaminergic polymorphic ventricular tachycardia was detected in any of the patients. For comparison, we included 19 consecutive patients with A-BrS, i.e. BrS without any symptoms such as faintness and/or syncopal attacks. None of the subjects took any drugs that would influence the autonomic balance, including beta-blockers or stimulants. The ethics committee of Fukuoka University Hospital approved this study, and written informed consent was obtained from each patient prior to participation.

Resting 12-lead ECG recordings

The 12-lead ECG during sinus rhythm was recorded in the supine position at a paper speed of 25 mm/s with a 1 cm/mV standardization. The heart rate (HR), QT interval, QT interval corrected using the Bazett's formula (QTc), and the T-wave peak-to-end (Tp-e) interval were measured by two investigators who were blinded to the clinical condition of the patients. Early repolarization in inferolateral leads (ERIL) was defined as a J-point elevation of at least 1 mm (0.1 mV), either notched or slurred, in at least two inferior or lateral leads [10].

Holter ECG recordings and HR variability (HRV)

Twenty-four hour Holter ECG recordings using a 2-channel (NASA and CM5 leads) recorder (Cardiomemory RAC-3103; Nihon Kohden Co., Ltd., Tokyo, Japan) were obtained for all 19 A-BrS patients and for 9 of the 14 VF-BrS patients about a month after their spontaneous VF episode. To evaluate the influence of actual sleep at night on the 24-h Holter ECG recordings, a log was maintained to indicate each patient's time of sleep during the nighttime period from 18:00 h to 06:00 h. The HR and QT interval were automatically measured using an analysis system (CardioREV DSC-3300; Nihon Kohden Co., Ltd.). HRV for the analysis time and frequency domain indices included the following: the average HR, standard deviation of the beat-to-beat interval (SDNN), and low-frequency (LF: 0.04–0.15 Hz) and high-frequency (HF: 0.15–0.40 Hz) components. The LF and HF components were quantified as the square root of the areas under respective power spectra using an analysis software (MemCalc Chiram; GMS Co., Ltd., Tokyo, Japan). The HF component was used to assess the parasympathetic nerve activity, and LF/HF ratio was used to assess the sympathetic nervous activity. The QT dynamics were calculated using the least-squares method as the linear-regression slope of the QT intervals plotted against the RR intervals in the CM5 lead (the QT/RR slope). These data were compared between a 6-h non-sleep period (daytime, from 12:00 h to 18:00 h) and a 6-h actual sleep period (nighttime), and were recorded in a detailed log maintained by each patient.

Statistical data analyses

The statistical data analyses were performed using the statistical analysis system (SAS) software package (Ver. 9.4, SAS Institute Inc., Cary, NC, USA) at Fukuoka University (Fukuoka, Japan). Two sets of comparisons were made: between the VF-BrS and A-BrS patients and between the VF-BrS patients in whom the first episode of spontaneous VF occurred at daytime or during effort and those in whom the episode occurred at nighttime or during rest. Categorical variables were compared using the chi-square analysis or Fisher's exact test. Differences in the continuous variables, including the QT interval, QTc interval, Tp-e interval, QT/RR slope, HR, SDNN, HF, LF/HF ratio, were evaluated using the Wilcoxon rank-sum test. Variances between groups were compared using the Ansari–Bradley test. Changes in the QT/RR slope, HR, SDNN, HF, and LF/HF during daytime and nighttime were examined using the Wilcoxon signed-rank test. The relationships between continuous variables were examined using the Spearman correlation analysis. The ability of using daytime LF/HF, nighttime LF/HF, or the daytime/nighttime ratio of LF/HF to distinguish between VF-BrS and A-BrS patients was examined using the logistic regression analysis. The Youden Index (YI) was used to determine the optimum threshold (cut-off point) (Gonen M. Analyzing receiver operating characteristic curves with SAS. Cary, NC, USA: SAS Institute Inc.; 2007.). The distribution of VF-BrS and A-BrS patients among groups determined according to the combined strata of daytime LF/HF and nighttime LF/HF or of daytime LF/HF and the daytime/nighttime ratio of LF/HF were examined using the Fisher's exact test. Data are presented as the mean ± standard deviation (SD), and statistical significance was considered to be $p < 0.05$ unless indicated otherwise.

Results

Clinical characteristics of the BrS patients

As shown in Table 1, there were no significant differences in age, gender, or family history of sudden cardiac death between the VF-BrS and A-BrS patients. Among the total 14 episodes of a first cardiopulmonary arrest due to spontaneous VF in the VF-BrS patients, 11 (79%) were detected during nighttime or at rest (6 while sleeping, 4 in the postprandial period, and 1 during the administration of anesthesia). The remaining 3 episodes occurred at daytime or during effort (1 during desk work, 1 during cleaning, and 1 during outside activity). There were no significant differences in age, gender, or family history of sudden cardiac death between the VF-BrS patients experiencing their first episode of spontaneous VF in the daytime or during effort and those experiencing their first episode at nighttime or during rest. An implantable cardioverter defibrillator (ICD) was implanted in 13/14 (93%) of the VF-BrS patients for secondary prevention. Five VF-BrS patients (mean follow-up period: 133 ± 19 months) had documented episodes of spontaneous VF after the ICD implantation. In 2 of these patients, episodes of VF storm (more than 3 episodes of spontaneous VF in a day) were documented. Typical examples of spontaneous VF episodes were obtained after ICD implantation in 1 of the VF-BrS patients; Fig. 1 shows a spontaneous VF episode in a stored ECG from the ICD. This episode occurred at nighttime during rest.

Resting ECG parameters

As shown in Table 2, there were no significant differences in HR, QT interval, QTc interval, Tp-e interval, incidence of ERIL, or amplitude of ERIL between the VF-BrS and A-BrS patients. ERILs in the resting 12-lead ECG were detected in 7/14 (50%) of