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Original article

Deterioration of the circadian variation of heart rate variability in Brugada syndrome may contribute to the pathogenesis of ventricular fibrillation

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ABSTRACT

Aims: Abnormal sympathetic innervation triggers ventricular fibrillation (VF). We examined the circadian variation of autonomic nervous system and its relevance to risk stratification of VF in patients with Brugada syndrome (Brs).
Methods: We enrolled 12 male Brs patients with documented VF (Brs-S; mean age, 42 ± 4 years), 17 without documented VF (Brs-N; mean age 48 ± 4 years), and 16 age- and gender-matched controls. The clinical data, 12-lead electrocardiography (ECG), signal-averaged ECG, electrophysiological study (EPS), and heart rate variability from 24 h Holter ECG were compared between the groups.
Results: The low frequency components (LF) in Brs-S and Brs-N and high frequency components (HF) in Brs-S patients were significantly lower than in the controls (409.8 ± 128.6 ms^2, 329.5 ± 108 ms^2 vs. 945.3 ± 111.3 ms^2; 135.1 ± 73.8 ms^2 vs. 391.8 ± 63.9 ms^2, respectively). The circadian variation of the LF and LF/HF decreased in the Brs patients, the standard deviation (SD) of LF/HF (<2.5) and SD of LF (<400 ms^2) had sufficiently high sensitivity (96.6%) and specificity (92.9%) for the diagnosis of Brs. Most of the Brs-S patients (83.3%) were located under the line formed by the SD/mean of HF = SD/mean of LF in the scatter plots.
Conclusion: Lack of the circadian variation of autonomic function occurs in Brs, and this may contribute to the pathogenesis of VF.

Introduction

Many reports have documented the role of abnormal sympathetic innervation as a trigger of ventricular fibrillation (VF) [1–6]. Brugada syndrome (Brs) is one of the major causes of VF and a significant circadian peak from midnight to early morning in VF has been reported in patients with Brs [7]. Presynaptic sympathetic abnormalities of the heart in patients with Brs have been documented using positron emission tomography and [^{123}I]*m*-iodobenzylguanidine-single-photon emission computed tomography [8,9]. A predominance of a vagal tone has also been reported in patients with Brs using the head-up tilt test [10,11]. With regard to the heart rate variability (HRV), some studies have reported decreased HRV in patients with Brs. However, most of those reports dealt with asymptomatic patients and there are only a few reports with various results discussing differences in the HRV between symptomatic and asymptomatic Brs [10,12,13]. There are many reports discussing the risk stratification of VF in Brs [14–23]. However, these parameters were inadequate and the risk stratification of VF in Brs remains controversial. The relationship between the autonomic nervous system and VF in Brs patients remains to be fully elucidated.

We investigated the circadian variations in autonomic nervous system using the HRV from 24-hour Holter electrocardiography (24-h ECG) in patients with Brs. Furthermore, we investigated whether an abnormal autonomic nervous system was related to the pathogenesis of a higher incidence of lethal ventricular arrhythmias associated with Brs.

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Methods

Subjects

We enrolled 12 male patients with documented VF (Brs-S group; mean age, 42 ± 4 years), 17 without documented VF (Brs-N group; mean age, 48 ± 4 years), and 16 age- and gender-matched controls (mean age, 43 ± 4 years) without structural heart disease, arrhythmias, and diseases affecting the autonomic nervous system. Among the enrolled patients, seven had a family history of sudden cardiac death. Noninvasive examinations revealed normal cardiac structure and function in all patients. Brs was definitively diagnosed when a type 1 ST-segment elevation was observed in >1 right precordial lead (V_1 to V_3) in the presence or absence of a sodium channel-blocking agent and in conjunction with one of the criteria of the Brs consensus conference [11]. A baseline examination revealed a spontaneous type 1 Brugada ECG pattern in 27 patients and type 2 Brugada ECG pattern at baseline in 2 patients who underwent a pharmacological challenge test with a pilsicainide injection (1 mg/kg body weight/10 min), which subsequently converted to a type 1 ECG pattern in more than one right precordial lead.

We retrospectively compared the following parameters in the Brs-S and Brs-N groups: (1) a history of syncope and family history of sudden cardiac death; (2) occurrence rate of paroxysmal atrial fibrillation; (3) 12-lead ECG parameters and type of Brugada ECG; (4) signal-averaged ECG findings; (5) electrophysiological study (EPS) parameters and induction of VF/ventricular tachycardia (VT) with burst pacing and triple paired extrastimuli from the right ventricular apex and right ventricular outflow tract; and (6) genetic analysis for the SCN5A gene which encodes for the α-subunit of the human cardiac sodium channel (hNav1.5).

We thoroughly investigated the HRV and also compared the power and fluctuation in the time and frequency domains of the HRV in the Brs-S, Brs-N, and controls.

The study was approved by Ethical Review Committee of our institution.

Twelve-lead ECG findings

The 12-lead ECG was recorded at a speed of 25 mm/s and an amplification of 1 cm/mV. We measured the RR, PQ, QRS, and corrected QT (QTc) intervals in lead V_6 and the J-point amplitude in leads V_1 and V_2 (STJ). We classified the Brugada ECG patterns into types 1–3, according to the criteria of the Brs consensus conference [11]. Because the ST configurations in the right precordial leads are known to show a day-to-day variation, more than five ECGs were recorded on different days for each patient. When a spontaneous type 1 Brugada ECG pattern was recorded at least once from a patient with Brs, that patient was identified as having a type 1 ECG pattern.

Signal-averaged ECG findings

Late potentials were analyzed using an FP-705LP system (Fukuda Denshi, Tokyo, Japan). The ECG was recorded using Frank X, Y, and Z leads during sinus rhythm, and the signals from 300 beats were amplified, digitized, averaged, and filtered with backward and forward filters at a high band-pass frequency of 40 Hz. The filtered QRS duration (f-QRS), root mean square voltage of the terminal f-QRS segment (RMS 40), and duration of low-amplitude signals <40 μV in the terminal f-QRS segment (LAS 40) were calculated. Late potentials were identified as being present when two of the following criteria were satisfied: f-QRS >114 ms, RMS 40 <20 μV, or LAS 40 >38 ms [24].

Heart rate variability

Each subject underwent 24-h ECG monitoring, and we analyzed the total heart beats, minimum, maximum, and mean heart rate during 24 h. We obtained heart beats without premature beats and other arrhythmias, and used them for the analysis of the HRV (SCM-6600™, Fukuda Denshi or MARS™, Ambulatory ECG system ver.8, GE Medical Systems, Milwaukee, WI, USA). We performed time domain and frequency domain analyses (Fast Fourier transformation) with the data. The time domain indices were as follows: the standard deviation (SD) of normal sinus RR intervals (SDNN), SD of the average normal sinus RR intervals every 5 min (SDANN), average SD of normal sinus RR intervals every 5 min (ASDNN), and root mean square of successive normal sinus RR interval difference (rMSSD). The frequency domain indices were as follows: very low frequency component (VLF): 0.003–0.04 Hz; low frequency component (LF): 0.04–0.15 Hz that reflects the modulation of the sympathetic and parasympathetic tone by baroreflex activity; high frequency component (HF): 0.15–0.4 Hz that reflects the modulation of the vagal tone; and the ratio of the LF to HF [25]. The method of normalizing is [Normalized LF] = (LF − [mean of LF])/[SD of LF]. The data were normalized to have mean = 0 and variance = 1. LF* is the moving average of the LF. Here, the LF* at time t is given as the average of the LFs at time t, $t-1$ hour and $t+1$ hour. None of the subjects took any antiarrhythmic agent and we confirmed all of the subjects with implantable cardioverter defibrillators were in regular sinus rhythm without pacing during recording the 24-h ECG monitoring.

EPS and VT/VF induction

After informed consent was obtained from the patients and their families, an EPS was performed in all patients. Three 5 French-quadripolar electrode catheters with 5-mm inter-electrode spacing were positioned in the high right atrium, bundle of His, and right ventricular apex. Programmed ventricular stimulation was performed in all patients with burst pacing [up to 230 beats per min (bpm)] and up to triple extrastimuli at two different drive cycle lengths (400 and 600 ms) from the right ventricular apex and right ventricular outflow tract. The shortest coupling interval of premature beats was limited to 200 ms.

Sequence analysis of SCN5A using genomic DNA

Peripheral blood samples were obtained from all patients, and the genomic DNA was extracted from leukocytes according to the standard protocol using a QIAamp DNA Blood Maxi Kit (QIAGEN, Hilden, Germany). All *SCN5A* exons and their splice sites were amplified by a polymerase chain reaction from 2.5 ng of genomic DNA with GO Taq DNA polymerase (Promega, Madison, WI, USA). The samples were resequenced using the 64 sense and antisense primers (approximately 300 bp each) of *SCN5A* with an ABI PRISM 310 Genetic Analyzer (Applied Biosystems, Foster City, CA, USA).

Statistical analyses

Statistical analysis was performed using commercially available software (JMP 8.0.2 Software, SAS Institute Inc., Cary, NC, USA). Values are presented as the mean ± standard error (SE). A Mann–Whitney U test was used to compare the continuous variables between two groups. The continuous variables among the three different groups were analyzed using Kruskal–Wallis and Steel–Dwas tests. The χ^2 test and Fisher's exact test were used to evaluate the differences in the categorical variables between the subgroups. We used a repeated measures of ANOVA with a Friedman's Test to evaluate the HF, LF, and LF/HF every hour in the three