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Comparison of circadian, weekly, and seasonal variations of electrical storms and single events of ventricular fibrillation in patients with Brugada syndrome

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ABSTRACT

In patients with Brugada syndrome (BS), VF occurred predominantly during the nocturnal period. Some patients also developed ESs. In addition to the circadian rhythm, patients showed weekly and seasonal patterns. The patients with ESs had peak episodes of VF on Saturday and in the winter and spring, while episodes of VF in patients with single VF events occurred most often on Monday with smaller seasonal variation. Except for age, there was no difference in the clinical or ECG characteristics between the patients with ESs and those with single VF episodes.

1. Introduction

Circadian, weekly, and seasonal variations are known to exist with fatal ventricular tachyarrhythmias (VTAs), as well as sudden death in patients with structural heart disease. In such patients, cardiac events peak during the morning hours, on Monday, and during the winter [1–4]. In contrast, ventricular fibrillation (VF) in patients with Brugada syndrome (BS), an inherited arrhythmic syndrome generally lacking structural abnormalities, occurs at night [5]. A percentage of the patients with BS may develop electrical storms (ESs) due to VF. Recently, we reported a high prevalence of early repolarization in patients with BS who develop ESs [6]. Subsequently, we analyzed the rhythmic occurrence of ESs in a large sample of patients with BS with a history of ESs. The aim of this study was to identify the characteristic patterns of ESs in patients with BS to understand the pathogenesis underlying ESs in these patients and to ensure proper clinical management of this disorder.

2. Methods

2.1. Study population

We recruited 23 patients with Brugada syndrome and a history of ESs and 21 patients with Brugada who had only single VF events as a comparison group from multiple centers. The latter patients were recruited from 3 institutions during the last 7 years. ESs or VF occurred before or after the implantation of an implantable cardioverter defibrillator (ICD). BS was diagnosed according the published criteria [5].

Abbreviations: BS, Brugada syndrome; CRBBB, complete right bundle branch block; ECG, electrocardiogram; ES, electrical storm; ICD, implantable cardioverter defibrillator; IVF, idiopathic ventricular fibrillation; MRI, magnetic resonance imaging; SD, standard deviation; VF, ventricular fibrillation; VT, ventricular tachycardia.

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After admission, patients were placed under intensive care and monitored for episodes of VF. Isoproterenol was administered to control recurrent VF[6–8]. After informed consent was obtained from the patients and family members, an ICD was implanted before discharge. To control for possible recurrence of VF, antiarrhythmic drugs were prescribed based on the clinical judgment of the attending cardiologists.

2.2. ECG analysis

At the time of the first hospital admission, the ECGs were analyzed for the RR, PR and QT intervals, and the QT interval was corrected by Bazett's formula. When J waves were present, the type (notch or slurring), distribution pattern, and morphology of the ST segment following the J waves were determined [7,8]. The ECGs were read by two cardiologists. When there was disagreement regarding the J waves, they discussed the results together to reach an agreement.

2.3. Data analysis

The ECG and other clinical features were compared between the patients with ESs and those with single episodes of VF. The exact time and day of the onset of the ES were obtained from the medical charts or ICD records, and the rhythmicity of the episodes of VF was analyzed and compared between the two patient groups. The acute and long-term clinical outcomes were also compared between the two groups.

2.4. Definitions

Patients with BS included in this study met the following inclusion criteria [5]: a typical coved type Brugada ECG pattern (≥0.2 mV elevation of the J point with a type 1 ST elevation in ≥1 right precordial lead) occurring spontaneously or after provocation with a sodium channel blocker [9]; normal cardiac structure and function confirmed by echocardiography, MRI or catheterization; negative serology for inflammatory disease and an absence of electrolyte imbalances.

Coronary spasms were excluded by a provocation test using either acetylcholine or ergonovine maleate when informed consent was obtained [10]. An ES was defined as ≥3 separate episodes of VF/24 h. For any early repolarization, J waves were diagnosed by the following criteria: 1) a notch or slur in the terminal portion of the QRS complex and 2) an amplitude of $_amp_$gt;0.1 mV above the isoelectric line in at least two contiguous leads [11–14].

As for the rhythmicity, VF occurring between 0:00 and 6:00 was defined as nocturnal, and VF occurring between 20:00 and 8:00 was defined as nighttime. Spring, summer, autumn and winter were defined as March to May, June to August, September to November, and December to February, respectively.

2.5. Statistical analysis

The continuous data are presented as the mean ± standard deviation (SD), and the categorical variables are expressed as absolute numbers or percentages. The statistical comparisons among the groups were made using a t-test or Mann–Whitney U-test for continuous variables and Pearson's chi-square test for categorical variables. The statistical analyses were performed with SPSS (Statistical Package for the Social Sciences), version 12.0 software (SPSS Inc., Chicago, IL, USA). A two-sided p of $_amp_$lt;0.05 was considered statistically significant.

Written informed consent was obtained from all patients at each institution before the invasive procedures. This study was approved by the Ethics Committee of Keio University School of Medicine.

3. Results

3.1. Patient characteristics

Forty-four patients who met the inclusion criteria were enrolled in this study. ESs developed in 23 patients, and 21 patients experienced single VF events. The mean age was significantly younger in the ES group (38 ± 13 vs. 48 ± 16 years, P = 0.004). Two patients in the ES group and one from the non-ES group had a family history of sudden cardiac death or Brugada syndrome (Tables 2 and 3). All episodes of ES and all single VF episodes occurred outside the hospital and were successfully defibrillated by an external defibrillator or ICD. The average number of VF events occurring in the ES patients was 4.8 ± 5.7 (Tables 1 and 2, P $_amp_$lt; 0.0001). Fig. 1 shows the onset of VF triggered by frequent premature ventricular complexes (patient no. 14, Table 2).

A spontaneous type 1 pattern was observed in 78.3% of patients in the ES group and in 52.4% of patients in the non-ES group (P = 0.069). The remaining patients underwent a provocation test for BS using pilsicainide, a class Ic drug, and the results were uniformly positive. The prevalence of J waves, the ST morphology following the J waves and their distribution patterns did not differ. There was no difference in the other ECG parameters, including the RR, PR, QRS, QT, or QTc intervals between the patients with ESs and those with single VF events, but complete right bundle branch block (CRBBB) was observed more frequently in the ES group (P = 0.043, Table 1). None of the patients developed any chest pain suggestive of myocardial ischemia prior to the onset of VF or an ES. There was no evidence of significant stenosis or coronary spasms in the patients who underwent a provocation test: 10 in the ES group and 20 in the non-ES group. Inflammatory disease and electrolyte imbalances were also ruled out by serological tests and blood chemistry.

3.2. Circadian pattern of the VF occurrence

Fig. 2 shows the circadian distributions of the timing of VF events in 37 patients. Similar percentages of ESs and VF events occurred between 0:00 and 6:00 (nocturnal) in 10/20 (50.0%) vs. 8/17 (47.1%), and between 20:00 and 8:00 (nighttime) in 15/20 (75.0%) vs. 13/17 (76.5%), respectively (Fig. 2A and B). None of the patients who experienced these episodes were nighttime workers. Except for two patients who

Table 1
Comparison of the clinical parameters between patients with ES vs. a single VF events.

	Overall (n = 44)	ES (n = 23)	Single VF (n = 21)	P value
Age	42 ± 16	38 ± 13	48 ± 16	0.004
Male sex, %	42 (95.3)	23(100)	19 (90.5)	0.080
Family history, %	5 (11.4)	2 (8.7)	3 (14.3)	0.559
Number of VF	3.0 ± 4.5	4.8 ± 5.7	1 ± 0	0.004
Spontaneous type 1	29 (65.9)	18 (78.3)	11(52.5)	0.069
J wave	9 (27.3)	6 (26.1)	3 (14.3)	0.328
ECG parameters				
RR (s)	0.91 ± 0.2	0.86 ± 0.2	0.92 ± 0.2	0.367
PR (ms)	161 ± 22	161 ± 22	160 ± 23	0.586
QRS (ms)	104 ± 14	104 ± 14	100 ± 12	0.062
QT (ms)	394 ± 35	394 ± 35	396 ± 39	0.309
QTc ($ms^{1/2}$)	410 ± 26	410 ± 26	410 ± 29	0.939
CRBBB, %	3 (6.8)	3 (13.0)	0 (0)	0.043
Recurrence	17 (38.6)	11 (47.8)	6 (28.6)	0.188
Time to recurrence, y	2.1 ± 3.0	1.2 ± 1.6	4.3 ± 4.2	0.061
Treatment for VF				
Bepridil, %	12 (27.3)	8 (34.8)	4 (19.0)	0.060
RFCA, %	2 (4.5)	1 (4.3)	1 (4.8)	0.948

CRBBB: complete right bundle branch block. RFCA: radiofrequency catheter ablation.