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Autonomic Imbalance and QT Dynamics in Idiopathic Ventricular Fibrillation

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Abstract

Introduction: The incidence of early repolarization in the inferior and /or lateral leads (ILER) is reported to have a relatively high prevalence in patients with idiopathic ventricular fibrillation (IVF). However, its clinical, electrocardiographic, and autonomic characteristics are not fully understood.

Subjects and Methods: The present study included 18 patients with IVF and 21 normal subjects without structural heart disease and cardiac symptoms as Controls. The clinical and electrocardiographic characteristics in idiopathic VF patients were evaluated and the QT dynamics and heart rate variability were analyzed using 24-hour Holter ECG recordings obtained during daytime and nighttime.

Results: No family history of sudden cardiac death (0/18, 0%) or ILER (8/18, 44%) were detected in 18 IVF patients. Of the total 18 first cardiopulmonary arrest episodes due to spontaneous VF in each patient, 10/18 (56%) episodes were detected during nighttime or at rest. The QT/RR slope during daytime was significantly steeper than that during nighttime in the Control subjects (0.19±0.14 vs. 0.13±0.09, P=0.012), but not in the IVF patients. There were significant diurnal differences in the high-frequency (HF) and low-frequency (LF)/HF ratios in the Control subjects (238.6±276.2 vs. 506.4±524.8 ms^2, P=0.001 and 3.8±1.8 vs. 2.4±1.6, P=0.027, respectively), but not in the IVF patients. The LF/HF ratios during nighttime in the IVF patients were significantly higher than in the Control subjects (3.7±2.3 vs. 2.4±1.6, P=0.048).

Conclusion: More than half of the first cardiopulmonary arrest episodes occurred during nighttime or rest in IVF patients. The elevated nocturnal sympathetic tone may play an important role in the occurrence of VF in these patients.

Key words: Autonomic tone; Idiopathic ventricular fibrillation; QT dynamics

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Introduction

Early repolarization in the inferior and /or lateral leads (ILER) has been thought to be a benign ECG finding in the general population. Based on the results of a basic study using arterially perfused canine ventricular wedge preparations [1], the pathogenesis of the J-waves, consisting of early repolarization, is manifested by an electrical gradient caused by a prominent action potential notch in the epicardium, but not in the endocardium. An increase in the net repolarizing current, due to either a decrease in the inward currents or augmentation of the outward currents, accentuates the notch leading to the augmentation of the J-wave. The patients with idiopathic ventricular fibrillation (IVF) who do not have Brugada syndrome characteristics such as a coved type ST-segment elevation in the right precordial leads at baseline or under the use of sodium channel blockers, and who have at least a history of spontaneous VF, have been reported to be associated with a high incidence of ILER [2,3]. The nocturnal increase in the J-wave amplitude and depolarization abnormalities have also been reported in IVF patients [4,5]. However, the conditions around the spontaneous onset of VF and the electrocardiographic and autonomic characteristics remain unclear. Therefore, the present study aimed to clarify the clinical, electrocardiographic, and autonomic characteristics in IVF patients.

Methods

Study Subjects

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 an assessment and treatment. All patients were examined by noninvasive studies, including echocardiography, exercise stress tests, chest radiography, and an ECG. Invasive studies including coronary angiography with an ergonovine provocation test were performed in some patients. Among the 35 patients, 3 with long QT syndrome and 14 with Brugada syndrome were excluded. Based on 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. The remaining 18 patients were diagnosed with IVF including 8 with or 10 without ILER. For a comparison, we included 21 normal subjects without any cardiac symptoms or structural heart disease (Control, 11/21 [52%] with ILER), who were randomly and consecutively selected from relatively young patients in which echocardiography and Holter ECG recordings were performed during the preoperative state of an orthopedic surgery. 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 at a paper speed of 25 mm/sec with a 1cm/mV standardization in the supine position. The heart rate (HR), QT interval, QTc interval (QT interval corrected by Bazett's formula), and Tp-e (peak to the end of the T-wave) interval were measured by two investigators who were blinded to the clinical condition of the patients. ILER 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 [2].

Twenty-four Hour Holter ECG Recording and Heart Rate Variability

Twenty-four hour Holter ECG recordings were performed in 14 of 18 IVF and in the 21 Control subjects and on a 2-channel (NASA and CM5 leads) recorder (Cardiomemory; RAC 3103 Nihon Kohden Co., Ltd.). To evaluate the influence of actual sleep at night on the 24-hour Holter ECG recordings, a log was maintained to indicate the time of sleep in each patient during the nighttime period from 6PM to 6AM. The heart rate and QT interval were automatically measured by an analysis system (CardioREV, DSC-3300 Nihon Kohden Co Ltd.). The heart rate variability (HRV) for the analysis time and frequency domain indices included the following: the average HR, standard deviation of the beat-to-beat interval (SDNN), low-frequency (LF: 0.04–0.15 Hz) and high-frequency (HF: 0.15–0.40 Hz) components. The LF and HF were quantified as the square root of the area under the respective power spectrum using analysis software (MemCalc Chiram; GMS Co., Ltd.). The HF components were used to assess the parasympathetic nerve activity, and the LF/HF ratios were used to assess the sympathetic nervous activity. The QT dynamics as a linear-regression slope of the QT intervals plotted against the RR intervals in the CM5 lead (QT/RR slope) were calculated using the least-squares method. These data were compared between the 6-hour daytime

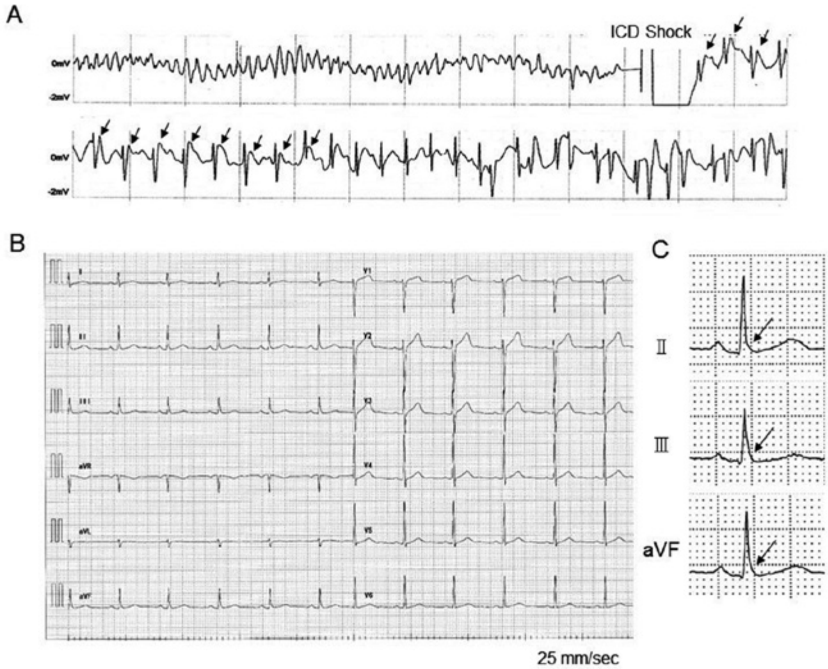

Figure 1. A spontaneous ventricular fibrillation episode during sleep and the recovery of sinus rhythm after a shock from an implantable cardioverter defibrillator. The arrows indicate the augmentation of the coved-type ST-segment elevation immediately after the defibrillation (A). A resting 12-lead ECG (B) showing a slurred QRS in the inferior leads (C) in a male patient with idiopathic VF with early repolarization.

non-sleep period (daytime: 6 hours from 12:00 to 18:00) and 6-hour 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 SAS (Statistical Analysis System) Software Package (Ver. 9.4, SAS Institute Inc., Cary, NC, USA) at Fukuoka University (Fukuoka, Japan). The differences in continuous variables, including the HR, QT, QT interval, QTc interval, Tp-e, QT/RR slope, SDNN, HF and LF/HF ratios, etc., between the IVF patients and Control subjects were examined by an unpaired *t*-test and Wilcoxon rank-sum test. The QT/RR slope, HR, SDNN, HF, and LF/HF during the daytime and nighttime were compared using the paired *t*-test and Wilcoxon signed-rank test. Data are presented as means ± standard deviations, and the significance level was considered to be less than 0.05 unless indicated otherwise.

Results

Clinical Characteristics in IVF Patients and Control Subjects

As shown in Table 1, there were no significant differences in the age, gender, incidence of ILER or maximal amplitude of the J-waves between the IVF patients and Control subjects. Among a total of 18 patients (13 males) with IVF, the mean age was 46 ± 16 years old. No family history of sudden cardiac death and 8 patients with ILER (44%) were detected. The average max amplitude of the ILER was 0.21±0.06 mV. Among 18 first episodes of spontaneous VF, 10 episodes (10/18, 56%) occurred at nighttime or during rest. A typical example of spontaneous VF episodes was obtained after the implantation of an ICD for secondary prevention in an IVF patient (Figure 1). Figure 1 shows the J-wave augmentation immediately after the defibrillation of spontaneous VF in a stored ECG on an implantable cardioverter defibrillator.

Table 1. Clinical Characteristics of the IVF Patients and Control Subjects

	IVF (n=18)	Control (n=21)	P value
Age (y)	46 ± 16	44 ± 18	0.93
Male (%)	13 (72%)	17 (81%)	0.52
Family history of SCD (%)	0 (0%)	0 (0%)	
ILER (%)	8 (44%)	11 (52%)	0.62
Max ILER amplitude (mV)	0.21 ± 0.06	0.21 ± 0.10	0.80
First episode of spontaneous VF			
Nighttime or during Rest (%)	10 (56%)	–	
Daytime or during Effort (%)	8 (44%)	–	

VF=ventricular fibrillation; IVF=Idiopathic VF; SCD=sudden cardiac death; ILER=early repolarization in the inferolateral leads.

Resting ECG Parameters

As shown in Table 2, there were no significant differences in the HR, QT interval, QTc interval, or Tp-e interval among the IVF and Control patients.

Table 2. Parameters of the Resting ECG in the IVF Patients and Control Subjects

	IVF (n=18)	Control (n=21)	P value
HR (bpm)	68 ± 15	69±11	0.89
QT (ms)	389 ± 32	400±25	0.30
QTc (ms)	422 ± 27	424±19	0.76
Tp-e (ms)	88 ± 23	79±15	0.33

VF=ventricular fibrillation; IVF=idiopathic ventricular fibrillation; HR=heart rate; QT=QT interval, QTc= corrected QT interval; Tp-e=interval of the peak to the end of the T-wave.

QT Dynamics

The QT/RR slope was analyzed in 14 of the 18 IVF patients and all 21 Control subjects. As shown in Figure 2, although the QT/RR slopes during the daytime were significantly steeper than those during the nighttime in the Control subjects (0.19 ± 0.14 vs. 0.13 ± 0.09, P=0.012), there were no significant differences in the QT/RR slope between the daytime and nighttime in the IVF patients (0.17 ± 0.10 vs. 0.16 ± 0.08, P=0.18).

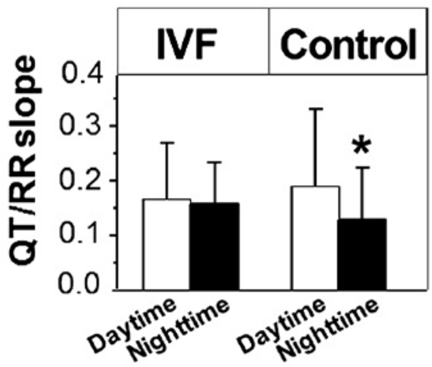

Figure 2. The QT/RR slope during the daytime and nighttime in the IVF patients and Control subjects.
*P<0.05, vs. daytime in the same group

Autonomic Balance Using Heart Rate Variability

The average HR, SDNN, HF, and LF/HF ratio are shown in Figure 3. The average HR during the nighttime was significantly slower than that during the daytime in the IVF patients (66 ± 12 vs. 78 ± 13 bpm, P<0.0001) and Control subjects (63 ± 10 vs. 78 ± 9 bpm, P<0.0001). While these differences were not statistically significant, the SDNN during the nighttime was shorter than that during the daytime in the IVF patients (91.2 ± 35.9 vs. 100.6 ± 32.2 ms, P=0.18) and Control subjects (98.4 ± 41.7 vs. 113.7 ± 33.4 ms, P=0.08).

The HF during the nighttime was significantly higher than that during the daytime in the Control subjects (506.4 ± 524.8 vs. 238.6 ± 276.2 ms^2; P=0.001), but not in the IVF patients (248.2 ± 416.5 vs. 114.7 ± 95.2 ms^2; P=0.18). The LF/HF ratios during the nighttime were significantly lower than those during the daytime in the Control subjects (2.4 ± 1.6 vs. 3.8 ± 1.8, P=0.027), but not in the IVF patients (3.7 ± 2.3 vs. 4.1 ± 1.8, P=0.18). The LF/HF ratio during the nighttime in the IVF patients was significantly higher than that in the Control subjects (3.7 ± 2.3 vs. 2.4 ± 1.6, P=0.048).

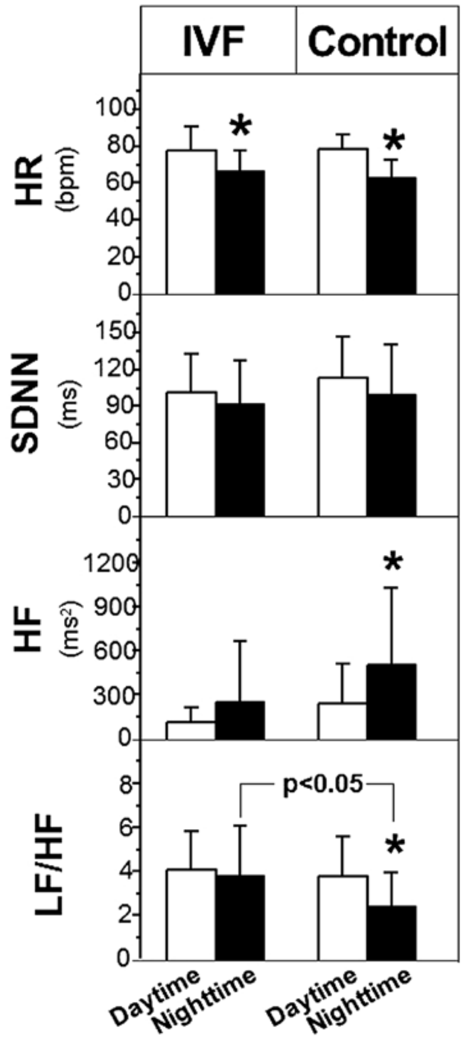

Figure 3. The parameters of the heart rate variability during the daytime and nighttime in the IVF patients and Control subjects. HR=average heart rate, SDNN=standard deviation of the beat-to-beat interval, HF= high-frequency component, LF/HF= ratio of the low-frequency component and high-frequency component.
*P<0.05, vs. daytime in the same group

Discussion

Major Findings

No family histories of sudden cardiac death were detected in 18 IVF patients. The differences in QT dynamics (QT/RR slope) between daytime and nighttime in the IVF patients were attenuated compared to those in the Control subjects. Significant differences in the sympathetic and parasympathetic tone between daytime and nighttime were detected in the Control subjects, but not in the IVF patients. The sympathetic tone during the nighttime significantly elevated in the IVF patients, compared to that in the Control subjects. This autonomic imbalance with an elevation in the nocturnal sleep-related sympathetic tone might be associated with spontaneous VF episodes in the IVF patients.

QT Dynamics

The disturbance in temporal dynamics of ventricular repolarization have been reported in long QT syndrome [6]. The present study indicated that the QT/RR slopes during daytime were significantly steeper than those during nighttime in the Control subjects, but not in the IVF patients. Thus, unlike that observed in the Control, the attenuation of the diurnal difference between daytime and nighttime for repolarization dynamics, may affect the occurrence of VF in the IVF patients.

Autonomic Imbalance

The elevation of the vagal tone has been thought to amplify the occurrence of J-waves before and after spontaneous episodes of VF in patients with IVF [2]. On the other hand, the amplitude of the J-waves in ILER is often attenuated during provocation tests with sodium channel blockers [7, 8]. Therefore, there are similarities and differences between the pathophysiological mechanisms of J-waves between the ILER and right precordial leads in BrS patients. The present study was performed in IVF patients that experienced cardiopulmonary arrest episodes due to spontaneous VF, and compared them to subjects with similar electrophysiological characteristics including ILER, but who did not have any cardiac symptoms or episodes of faintness, syncope or VF. The HRV analysis in the present study clarified the autonomic imbalances associated with the elevation in the sympathetic tone during nocturnal sleep and at nighttime in IVF patients. The possible explanations for these results are the tonic effects of autonomics, observed in patients with neutrally mediated syncope, and an accentuated antagonism [9, 10], where the vagal tone more efficiently affects the HR during periods of sympathetic activation. Therefore, this underlying nocturnal elevation in the sympathetic tone may cause an abrupt shift toward a vagal predominance that may lead to a subsequent spontaneous VF onset in IVF patients.

Study Limitations

Since the present study was retrospective and included a small patient series at a single center, larger studies will be required to confirm these findings, and prospective studies will be required to evaluate the clinical impact of the suppression of sympathetic tone and the prevention of spontaneous VF on the patient outcome.

Conclusion

The IVF patients had attenuated diurnal differences between daytime and nighttime in both the sympathetic and parasympathetic tone compared to normal control subjects and a paradoxical elevation in the nocturnal sympathetic tone, which may play an important role in the onset of spontaneous VF. This autonomic imbalance may be a therapeutic target for the prevention of spontaneous primary VF.

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