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The circadian pattern of the development of ventricular fibrillation in patients with Brugada syndrome

K. Matsuo, T. Kurita, M. Inagaki, M. Kakishita, N. Aihara, W. Shimizu, A. Taguchi, K. Suyama, S. Kamakura and K. Shimomura

Division of Cardiology, Department of Internal Medicine, National Cardiovascular Center, Osaka, Japan

Aims Brugada syndrome is considered to be a distinctive subgroup of idiopathic ventricular fibrillation. Identification of the circadian pattern of ventricular fibrillation would contribute to the elucidation of its underlying pathophysiology, but this pattern remains unknown in patients with Brugada syndrome.

Methods and Results A total of 12 consecutive Brugada syndrome patients (46 ± 14 years, all male) who underwent implantation of an implantable cardioverter–defibrillator were studied. The distribution of the time of ventricular fibrillation detection was examined and classified into four 6-hour time periods of the day. The mean follow-up period following implantation was 777 ± 535 days. In six out of the 12 patients, ventricular fibrillation occurred during follow-up. The data logs revealed that ventricular fibrillation was detected 30 times (range, 3–9). Ventricular fibrillation was observed more frequently at night (1800 h to 0600 h) than in the day (0600 h to 1800 h) (93·3% [28/30] vs 6·7% [2/30], $P<0·001$), and during sleep than while awake (86·7% [26/30] vs 13·3% [4/30], $P<0·001$). Ventricular fibrillation occurred most frequently between midnight and 0600 h in patients with ventricular fibrillation episodes during sleep (76·9% [20/26] vs 23·1% [6/26], $P<0·01$).

Conclusion These results suggest that increased nocturnal vagal activity and withdrawal sympathetic activity may play an important role in the arrhythmogenesis of the Brugada syndrome.
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Key Words: Idiopathic ventricular fibrillation, circadian pattern, implantable cardioverter–defibrillator.

See page 401 for the Editorial comment on this article

Introduction

In 1992, Brugada and Brugada[1] described a form of idiopathic ventricular fibrillation with right bundle branch block and persistent ST segment elevation in a 12-lead electrocardiogram (ECG) during sinus rhythm. (This became known as the Brugada syndrome.) Identification of the circadian pattern of ventricular fibrillation may contribute to the elucidation of the underlying pathophysiology of this syndrome. It is well known that the incidence of sudden death is highest in the daytime in patients with organic heart disease, including old myocardial infarction[2,3], whereas the circadian pattern of the development of ventricular fibrillation remains unknown in patients with Brugada syndrome. Late-generation implantable cardioverter–defibrillators have the ability to record the time and date of each tachycardia incidence, accurately enabling the patterns of ventricular fibrillation occurrence to be analysed [4,5]. Therefore, we prospectively investigated the circadian pattern of ventricular fibrillation by analysing the data stored in implantable cardioverter–defibrillators of patients with Brugada syndrome.

Methods

Subjects

A total of 12 consecutive Brugada syndrome patients (46 ± 14 years, all male) who underwent implantation of an implantable cardioverter–defibrillator were studied. All of the patients met the following criteria; (1) a

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Correspondence: Kiyotaka Matsuo, MD, Third Department of Internal Medicine, Nagasaki University School of Medicine, 1-7-1 Sakamoto, Nagasaki 852-8501, Japan.

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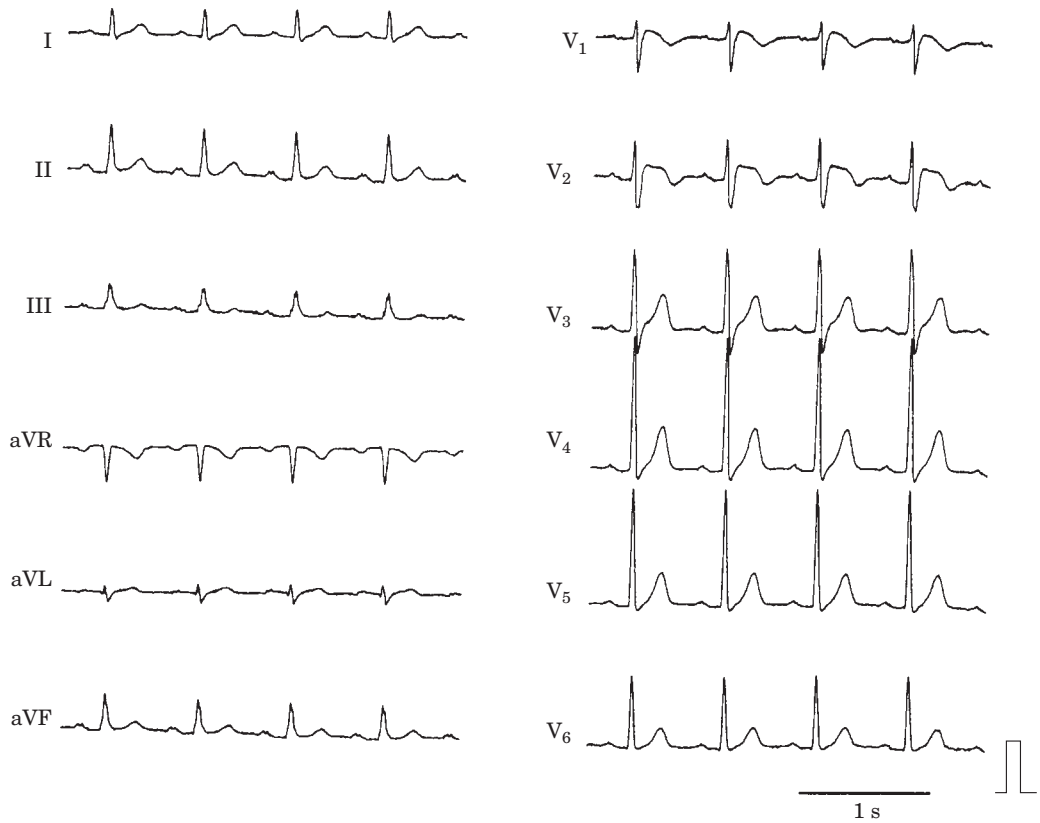

Figure 1 **Twelve-lead electrocardiogram obtained from a representative Brugada syndrome patient (patient 6) during sinus rhythm. An incomplete right bundle branch block pattern and ST segment elevation with a coved type in leads V_1 and V_2 and with a saddle-back type in lead V_3 can be seen.**

history of cardiac arrest or aborted sudden cardiac death with or without ventricular fibrillation documentation, (2) some degree of right bundle branch block and ST segment elevation (a coved or saddle-back type) in leads V_1 to V_2/V_3 during sinus rhythm (Fig. 1), (3) a normal QTc interval $\leq 0{\cdot}44\ ms^{1/2}$ (corrected by Bazett's formula: $QTc = QT/\ [RR]^{1/2}$), (4) normal laboratory values, including serum electrolytes, (5) no significant organic stenosis and no spasm inducible by an intracoronary injection of ergonovine or acetylcholine in coronary arteriography, (6) normal right and left ventricular size and function, as assessed by echocardiography or ventriculography and (7) induction of ventricular fibrillation or non-sustained polymorphic ventricular tachycardia by right ventricular programmed stimulation with up to triple extrastimuli under no medication. Ventricular fibrillation was defined as polymorphic ventricular tachyarrhythmia with an R-R interval of ≤ 200 ms (≥ 300 beats . min^{-1}) and haemodynamic decompensation requiring cardioversion for termination if the arrhythmia was sustained ≥ 10 s. Non-sustained polymorphic ventricular tachycardia was defined as polymorphic ventricular tachyarrhythmia sustained ≥ 5 beats but terminated < 10 s spontaneously.

Protocol

Written informed consent to participate in this study was obtained from all patients. After implantation, each patient was followed-up at our implantable cardioverter–defibrillator clinic, where the data obtained from the patients was confirmed every 3 months. In each implantable cardioverter–defibrillator used in this study, the ventricular fibrillation heart rate setting was programmed from 180 to 200 beats . min^{-1} in order to prevent undersensing of ventricular fibrillation. None of the patients took any antiarrhythmic drug during the follow-up period. However, an oral beta-blocker (propranolol) was administered to four patients to prevent an inappropriate shock during sinus tachycardia and/or atrial fibrillation. During the follow-up period, six of the 12 patients had recurrence of ventricular fibrillation after implantable cardioverter–defibrillator implantation.

(1) We divided the study patients into two groups; patients with recurrences (n=6) and patients without recurrences (n=6) (Table 1). Between the two groups, clinical and electrophysiological characteristics were compared. (2) We investigated the time and data of ventricular fibrillations from the date of the implantable cardioverter–defibrillator implantation to 31 December

Table 1 Clinical characteristics and follow-up data of the study male patients

Patient number	Age (years)	FH	EPS induction		ICD generator	Follow-up period (days)	Total VF detection number (times)	First VF detection interval (days)	Drug (mg . day^{-1})
			VF	NSPVT					
Patients with recurrences									
1	46	—	—	+	Ventak PRX-II	1384		676	—
2	29	—	+	—	Ventak PRX-II	1351	5	823	—
3	57	—	—	+	Jewel Plus	861	4	293	—
4	47	—	—	+	Ventak PRX-II	713	9	111	—
5	32	—	+	—	Ventak P	554	5	331	Propranolol (60)
6	63	—	+	—	Micro Jewel	278	3	242	—
	46 ± 13*					857 ± 440*	5 ± 2	413 ± 275	
Patients without recurrences									
7	63	—	+	—	Ventak P	1981	0	NA	Propranolol (30)
8	47	+	+	—	Ventak MINI	617	0	NA	—
9	19	—	—	+	Ventak MINI	565	0	NA	Propranolol (60)
10	61	—	—	+	Ventak P	502	0	NA	—
11	51	—	+	—	Micro Jewel	321	0	NA	Propranolol (60)
12	37	—	+	—	PCD	201	0	NA	—
	46 ± 16					698 ± 648			

EPS=electrophysiologic study; FH=family history of aborted sudden cardiac death; First VF detection interval=interval between the implantation of the implantable cardioverter–defibrillator and the first ventricular fibrillation detection; ICD=implantable cardioverter–defibrillator; NA=not assessed; NSPVT=non-sustained polymorphic ventricular tachycardia; Total VF detection number=total number of ventricular fibrillation after implantable cardioverter–defibrillator implantation; VF=ventricular fibrillation; *=not significant vs patients without recurrences.

1997 in six patients with recurring ventricular fibrillation. Four different types of implantable cardioverter–defibrillators were implanted in the six study patients: Ventak P (n=1) and Ventak PRX-II (n=3) (Cardiac Pacemaker, Inc., St. Paul, MN, U.S.A.), and Jewel Plus (n=1) and Micro Jewel (n=1) (Medtronic, Inc., Minneapolis, MN, U.S.A.). The Ventak PRX-II, Jewel Plus and Micro Jewel systems have extensive retrievable data-logging capabilities, including storage of the time, date and cycle length of the tachycardia, and the response by the defibrillator on detection of the tachycardia. The time and date of recorded events are provided by reference to time calibrations from the respective programmers. Because these three models also have electrocardiographic storage capacity, each detection of ventricular fibrillation could be checked to see whether the shock was appropriate or not. However, the Ventak P, implanted in patient 5, was only able to confirm the number of shocks, and could not provide the time or date of the shock or the number of electrocardiograms during ventricular fibrillation. Nevertheless, because the total number of shocks identified by the defibrillator was compatible with the patients' symptoms and/or the witnessed events, reliable rough information of the time and date of episodes of VF was considered available. The distribution of the time of ventricular fibrillation detection was examined prospectively and classified into four 6-h periods: midnight to 0600 h, 0600 h to noon, noon to 1800 h, and 1800 h to midnight. The last follow-up day was 31 December 1997, in all patients except for patient 4, in whom 2 May, 1996 was used as the last follow-up day, because he received oral amiodarone to prevent frequent ventricular fibrillation attacks from that time.

Statistics

Quantitative data are presented as means ± SD, and were analysed by a two-tailed Student's t-test. Categorical data are presented as absolute and percentage frequencies, and were analysed by the chi-square test. The level of significance was set at $P<0{\cdot}05$.

Results

(1) Patients characteristics and ventricular fibrillation recurrence

The clinical and electrophysiological characteristics of the 12 study patients are shown in the Table 1. One of the 12 had a family history of aborted sudden cardiac death. Other family members of the remaining patients had no symptoms. There was no significant difference between the clinical and electrophysiological characteristics (age, family history, inducibility of ventricular tachyarrhythmias, follow-up period and medication) in patients with and without ventricular fibrillation recurrences.

(2) The circadian pattern of ventricular fibrillation onset after implantable cardioverter–defibrillators implantation

Of the 31 ventricular fibrillation detected from the six patients with recurrences, a total of 30 were available (range, 3–9 detections; mean, 5·0 detections). One

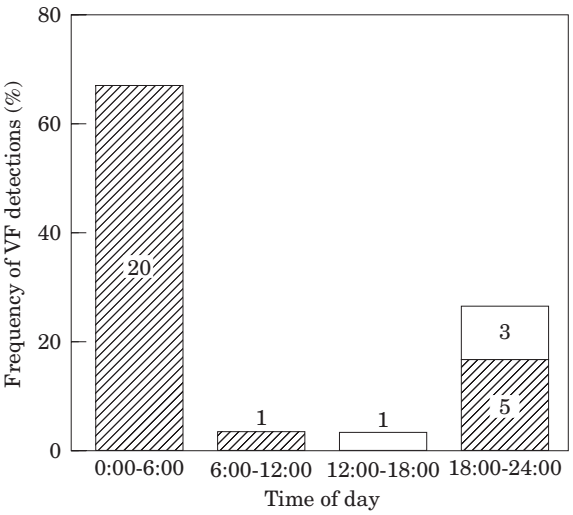

Figure 2 **The circadian pattern of all six study patients. Each detected ventricular fibrillation (VF) was classified into one of four 6-h time periods of the day: midnight to 0600 h (0:00–6:00), 0600 h to noon (6:00–12:00), noon to 1800 h (12:00–18:00), and 1800 h to midnight (18:00–24:00). The numbers inside the bars indicate the absolute number of ventricular fibrillations detected. Ventricular fibrillation occurred most frequently between midnight and 0600 h during sleep. See text for details. □=while awake; ▨=during sleep.**

episode was excluded because it was due to an inappropriate shock for sinus tachycardia. Each of the detected ventricular fibrillation was definitely terminated by the first shock of the implantable cardioverter–defibrillator. Unsuccessful shocks were not detected during the follow-up period. The mean period between implantation and the first ventricular fibrillation detection was 413 ± 275 days. A total of 28 episodes of ventricular fibrillation were detected at (1800 h–0600 h), whereas only two episodes of ventricular fibrillation were detected in the day (0600–1800 h). Ventricular fibrillations were detected significantly more frequently at night than during the day (93·3% vs 6·7%, $P<0·001$). A total of 26 episodes of ventricular fibrillation were detected during sleep, whereas only four were detected while awake. Ventricular fibrillations were detected significantly more frequently during sleep than while awake (86·7% vs 13·3%, $P<0·001$). Ventricular fibrillation occurred most frequently between midnight and 0600 h in patients with episodes of ventricular fibrillation during sleep (76·9% [20/26] vs 23·1% [6/26], $P<0·01$). (Fig. 2). The recurrence of attacks of ventricular fibrillation was detected during the night without any symptoms in four of the six patients (Fig. 3).

Discussion

We found certain circadian patterns of spontaneous ventricular fibrillation onset after implantable cardioverter–defibrillator implantation in patients with Brugada syndrome. Regarding 24 h periodicity, ventricular fibrillation was most frequently detected in the midnight-to-early morning period during sleep.

In the clinical characteristics, we found a family history of aborted sudden death in only one of the 12 study patients, which was reported previously[6]. A long-term follow-up is necessary because the ECG findings in asymptomatic patients with Brugada syndrome change during follow-up and symptoms may occur in the future[7]. A half of the study patients had no attacks of ventricular fibrillation after the implantable cardioverter–defibrillator implantation during the mean follow-up period of 777 days, which is consistent with the rate of recurrence of arrhythmic events in Brugada syndrome patients, as recently reported[8]. Furthermore, none of the previous clinical data predicted recurrence of ventricular fibrillation after the implantable cardioverter–defibrillator implantation. Thus, all patients with Brugada syndrome should be followed-up with an implantation because no drug, including amiodarone and beta-blockers, prevent recurrences of ventricular fibrillation[8].

In previous epidemiological studies[2,3], the incidence of sudden death was frequent in the morning and rare at midnight. Similarly, it was demonstrated that the occurrence rate of malignant ventricular tachyarrhythmias was highest in the late morning to afternoon and lowest in the middle of the night, according to data obtained from implantable cardioverter–defibrillators in patients with organic heart disease[4,5]. It has been proposed that the mechanism responsible for the circadian pattern of ventricular tachyarrhythmias is the physical and mental stress after wakening, and endogenous variables, e.g. plasma epinephrine and platelet aggregability[9–11]. This circadian pattern seems to be in contrast to our result. The discrepancy may be attributable to the difference in the underlying heart diseases, i.e. myocardial infarction or cardiomyopathy in the previous studies vs structurally normal hearts in the present study. However, Belhassen *et al.*[12] reported five idiopathic ventricular fibrillation patients with a normal 12-lead ECG, who were awake just before their cardiac arrest. In contrast, ventricular fibrillation occurred most frequently during sleep in our patients with right bundle branch block and persistent ST segment elevation in a 12-lead ECG, suggesting that Brugada syndrome may have a pathophysiology different from the idiopathic ventricular fibrillation reported previously.

Sudden unexpected death syndrome is characterized by sudden death at night among healthy young adults, most of whom were males in Southeast Asia[13,14]; this syndrome is known as 'Lai Tai', meaning death in sleep in Northeast Thailand[15,16], 'Bangungut', meaning sudden death with moaning during sleep in the Philippines[17], and 'Pokkuri disease', meaning sudden nocturnal unexpected death in Japan[18–20]. Although prolongation of the QT interval[21] and hypokalaemia[22] are suspected as causes of sudden unexpected death syndrome, the exact mechanism of sudden death has not been established. In the present study, the corrected QT

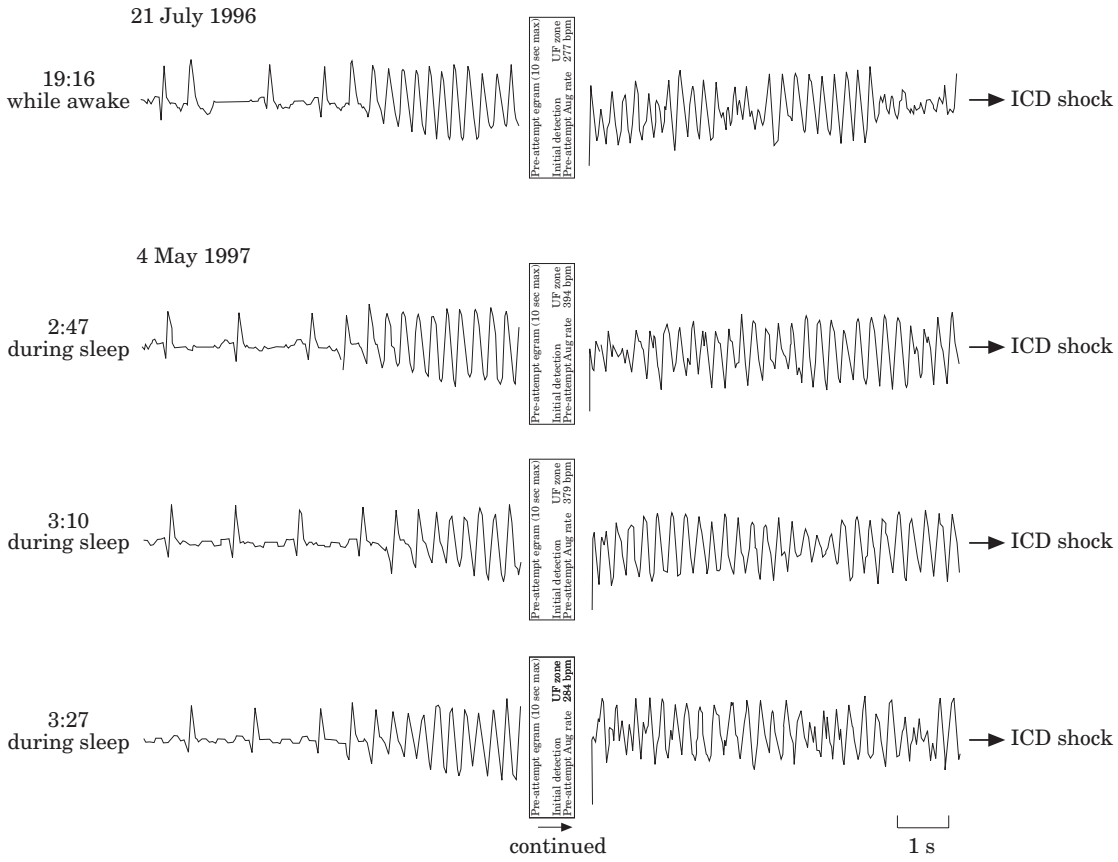

Figure 3 **The stored electrocardiograms from patient 2. Four ventricular fibrillation episodes were detected on two different days about 8 months apart. All episodes occurred at night, and three of the four ventricular fibrillation episodes were clustered within only 40 min in the middle of the night (2:47 to 3:27). Due to the implantable cardioverter–defibrillator (ICD) the patient was unaware that he had suffered three shocks during sleep.**

interval and serum potassium level were normal in all 12 of the patients. In the previous studies of sudden unexpected death syndrome, right bundle branch block and ST segment elevation were not noted except in a few cases[14,19]. Nademanee *et al.*[23] recently reported that right bundle branch block and precordial ST elevation in V_1 through V_3 was the arrhythmogenic marker for sudden unexpected death syndrome in Thai men. In contrast, the present Japanese patients with ECG findings typical of Brugada syndrome (right bundle branch block and ST segment elevation in leads V_1 to V_2/V_3) showed a circadian pattern of the development of ventricular fibrillation similar to that in patients with sudden unexpected death syndrome. These findings suggest that Brugada syndrome and sudden unexpected death syndrome have an identical ventricular fibrillation mechanism and that these two syndromes in fact belong to the same group of idiopathic ventricular fibrillation.

Kasanuki *et al.*[24] reported a sudden increase of vagal activity just before the episodes of ventricular fibrillation in a patient with Brugada syndrome, which was represented by heart rate variability patterns during Holter monitoring. Miyazaki *et al.*[25] showed the effects of autonomic receptor stimulation on ST segment elevation in Brugada syndrome. During beta-adrenoceptor stimulation by isoproterenol, the ST segment elevation was eliminated, whereas it was augmented by muscarinic stimulation with intravenous edrophonium. In an experimental study, Litovsky and Antzelevitch[26] demonstrated that acetylcholine facilitates loss of the action potential dome by suppressing the calcium current and/or augmenting the potassium current, which accentuates ST segment elevation. In the present study, the circadian pattern established by the analysis of implantable cardioverter–defibrillator storage data also suggests that an increase in nocturnal vagal activity and withdrawal of sympathetic activity may play an important role in arrhythmogenesis in Brugada syndrome. Recently, we reported a significant direct relationship between the preceding RR interval and ST segment elevation just after a ventricular fibrillation episode in a patient with Brugada syndrome[27]. This is consistent with the results of an experimental study in which decreased J point elevation at short RR intervals is due to slow recovery of the prominent transient outward current from inactivation[28]. Under these circumstances, high rate pacing might have a beneficial effect by preventing ventricular fibrillation during sleep at night.

Limitations

There are several limitations in the present study. (1) The electrocardiograms before the onset of ventricular fibrillation were stored by the implantable cardioverter–defibrillators in five of the six patients. However, we could not analyse the heart rate variability because the interval of the stored electrocardiograms was too short to investigate the autonomic balance. (2) We could not clarify the circadian pattern of ventricular fibrillation episodes before the implantable cardioverter–defibrillators implantation because the data of the time of the episodes before the implantation is rough, and multiple episodes might be influenced by delayed termination of ventricular fibrillation and/or by acute therapy during cardiopulmonary resuscitation.

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