Mode of Onset of Ventricular Fibrillation in Patients With Brugada Syndrome Detected by Implantable Cardioverter Defibrillator Therapy

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OBJECTIVES
We sought to demonstrate the mode of spontaneous onset of ventricular fibrillation (VF) in patients with Brugada syndrome.

BACKGROUND
The electrophysiologic mechanisms ofVF in Brugada syndrome have not been fully investigated.

METHODS
Nineteen patients (all male, mean age 47 ± 12 years) with Brugada syndrome were treated with an implantable cardioverter defibrillator (ICD). The implanted devices were capable of storing electrograms during an arrhythmic event. We investigated the mode of spontaneous onset of VF according to the electrocardiographic features during the episode of VF, which were obtained from stored electrograms of ICDs and/or electrocardiographic (ECG) monitoring.

RESULTS
During a follow-up of 34.7 ± 19.4 months (range 14 to 81 months), 46 episodes of spontaneous VF attacks were documented in 7/19 (37%) patients. The event-free period between ICD implantation and the first spontaneous occurrence of VF was 14.6 ± 12.1 months (range 3.7 to 27.4 months). We investigated 33/46 episodes of VF, for which electrocardiographic features (10 to 20 s before and during VF) were obtained from ICDs and/or ECG monitoring in five patients. A total of 22/33 episodes of VF were preceded by premature ventricular contractions (PVCs), which were almost identical to the initiating PVCs of VF. Furthermore, in three patients who had multiple VF episodes, VF attacks were always initiated by the same respective PVC. The coupling interval of the initiating PVCs of VF was 388 ± 28 ms.

CONCLUSIONS
Spontaneous episodes of VF in patients with Brugada syndrome were triggered by specific PVCs. These findings may provide important insights into the pathophysiological mechanisms causing VF in Brugada syndrome. (J Am Coll Cardiol 2000;36:1646–53) © 2000 by the American College of Cardiology

Ventricular fibrillation (VF) is a major cause of out-of-hospital sudden death. As there is no demonstrable structural heart disease in 5% to 10% of these patients, this form of VF has been recognized as idiopathic VF (1–4). Recent interest has focused on one distinctive subgroup of idiopathic VF, so-called Brugada syndrome (5). This intriguing syndrome is characterized by right bundle branch block, normal QT interval, persistent ST segment elevation in precordial leads V1 to V2 or to V3 and sudden death. Owing to the high recurrence rate of VF in this syndrome (18% to 37% during a follow-up of one to three years), an implantable cardioverter defibrillator (ICD) is the generally accepted mode of therapy, improving the long-term prognosis in these patients (1,6–9). However, the electrophysiologic mechanisms of VF in Brugada syndrome have not yet been fully investigated.

Analysis of electrocardiographic manifestations during an episode of ventricular arrhythmia is an effective method of clarifying the episode's mechanism. We investigated the mode of spontaneous onset of VF in patients with Brugada syndrome using ICDs, which provide extensive storage of endocardial electrograms during episodes of arrhythmia.

METHODS
Patients. We studied 19 patients (all male; mean age 47 ± 12 years) with Brugada syndrome who underwent implantation of an ICD. Written informed consent to participate in this study was obtained from all patients. The ICDs were implanted between July 1992 and February 1998. Clinical follow-up was obtained until March 1999. The presence of structural heart disease or coronary artery disease was excluded in all patients by noninvasive and invasive tests, such as normal laboratory tests, including enzymatic and electrolytic profile; no significant stenosis and no spasm inducible in coronary angiography; normal right and left ventricular size and function, as assessed by echocardiography, nuclear scintigraphy, and ventriculography of both ventricles; and normal right ventricular endomyocardial biopsy findings.

All patients had right bundle branch block pattern and
persistent ST segment elevation in right precordial electrocardiographic (ECG) leads (Fig. 1). The PR, QT and QTc intervals were within normal limits. Episodes of VF or sudden death were documented before ICD implantation. During electrophysiologic study, VF or polymorphic ventricular tachycardia was induced by programmed electrical stimulation in all patients. In Holter ECG, all patients had few PVCs outside of the VF episodes.

In 12 of the 19 patients in this study, we have recently reported the circadian pattern of the development of ventricular fibrillation in Brugada syndrome (10).

The device. Six different types of ICDs were implanted in the study patients: the Ventak P (n = 3), Ventak PRX-II (n = 3) and Ventak Mini (n = 2) (Cardiac Pacemaker, Inc., St. Paul, Minnesota), and the PCD (n = 1), Jewel Plus (n = 2) and Micro Jewel (n = 8) (Medtronic, Inc., Minneapolis, Minnesota). All ICDs except for the Ventak P and PCD have extensive retrievable data-logging capabilities, including storage of the time, date, pre- and post-therapy R-R intervals, tachycardia cycle length and the ICD response to tachycardia detection. The Ventak PRX-II, Ventak Mini and Micro Jewel are capable of storing electrograms 10 to 20 s before, during and after an arrhythmic event. In the Ventak PRX-II and Ventak Mini, the stored electrograms are recorded between the distal spring electrode in the right ventricle and the proximal spring electrode in the high right atrium to the superior vena cava. The Micro Jewel was programmed to record the electrograms between the distal spring electrode in the right ventricle and the precordial can. The stored electrograms obtained from these systems provide a more global visualization of myocardial activity. The Ventak P is able only to confirm the number of shocks, and cannot provide the time or date of the shock or electrograms during VF. However, because the total number of shocks identified by the ICD was compatible with the patient’s memory of symptoms and/or the witnessed events, reliable rough information concerning the time and date of the VF episodes was considered to be available.

We investigated the mode of spontaneous onset of VF according to the electrocardiographic features before and during VF, which were obtained from stored electrograms of ICDs and/or ECG monitoring. “Preceding PVCs” was defined as PVCs recorded shortly before the episode of VF. “Initiating PVCs” was defined as the first complex of the VF episode.

Statistical analysis. The event-free survival curve was obtained using the Kaplan–Meier method. Quantitative data are expressed as mean ± SD.

RESULTS

During a follow-up of 34.7 ± 19.4 months (range 14 to 81 months), all patients survived, and 46 episodes of spontaneous VF attacks were detected in 7 (37%) of the 19 patients (1 to 23 episodes per patient) (Fig. 2). At the time of VF detection, two patients were on beta-blocker to prevent inappropriate shocks during supraventricular tachycardia. The remaining patients did not take any antiarrhythmic drug during the follow-up period. The event-free period between ICD implantation and the first spontaneous occurrence of VF was 14.6 ± 12.1 months (range, 3.7 to 27.4 months). Follow-up data of the patients with VF recurrence after ICD implantation are shown in Table 1. In 43 of the 46 episodes of VF, defibrillation was successful on the first shock; the second shock was necessary in the remaining

![Figure 1](image.png)

Figure 1. Twelve-lead electrocardiogram of Patient 4 with Brugada syndrome during sinus rhythm. An incomplete right bundle branch block and ST segment elevation with a coved type in leads V1 and V2 were observed.
three episodes. Electrocardiographic features obtained from stored electrograms of ICDs and/or ECG monitoring were available for 33 of the 46 episodes of VF ("documented" episodes) in 5 patients. In Patient 5, in whom a Ventak P was implanted, we were able to document electrocardiographic manifestations during VF on ECG monitoring, because he had a VF attack during his stay in our hospital. In Patients 6 and 7, we were only able to analyze the date and number of VF attacks due to limited memory function of the late-generation ICD.

Mode of onset of VF.

1. Before the onset of VF, frequent preceding PVCs were recorded in 22 of the 33 VF episodes (Fig. 3 and 4). In all these events, the morphology of the preceding PVCs was almost identical (according to the stored electrogram) to the initiating PVCs of VF.

2. Multiple VF episodes were stored in the devices of three patients (Patients 1–3). Analysis of these events revealed that different VF episodes in the same patients were initiated by PVCs of similar morphology (Fig. 5). Although no preceding PVC was observed in the remaining 11 VF episodes, the morphology of initiating PVC was similar to that of preceding and initiating PVCs during different VF episodes (Fig. 6).

3. Three patients (Patients 1–3) underwent implantation of the same ICD systems (Ventak PRX-II combined with Endotak lead). Thus, we were able to compare the morphology of the PVCs initiating VF in different patients (Fig. 3). The morphology of PVCs in Patient 1 was strikingly similar to that of the PVCs of Patient 3. This finding indicates that the initiating PVC originated from the particular common ventricular focus in these patients.

4. According to the R-R intervals stored for 39 VF episodes in 6 patients, the PVCs initiating all VF episodes arose from the terminal part of the T wave: the coupling interval of the initiating PVC was 388 ± 28 ms (range 336 to 453 ms) and the QT interval was normal. Of note, a long-short sequence initiated VF in only 1 patient (Patient 1) and in only 25% (5 of 21) of his VF episodes. Thus, pause-dependent arrhythmias were rare in VF episodes in Brugada syndrome.

DISCUSSION

In this study we demonstrated that (a) many spontaneous episodes of VF in patients with Brugada syndrome were preceded by frequent PVCs, (b) preceding and initiating PVCs of a single and different VF episodes in the same patient showed the same pattern of QRS morphology and (c) the QRS patterns of PVCs in two different patients (Patients 1 and 3) were very similar to each other.

The relationship of PVCs and VF. Although, in patients with Brugada syndrome, very few PVCs were observed on Holter monitoring at the remote phase of VF episodes, these tended to occur more frequently before the onset of VF. This finding suggests that there is a close relationship between PVCs and the occurrence of VF. Furthermore, another clinical study demonstrated progressive ST segment elevation in right precordial leads immediately before VF onset (11). Therefore, it is strongly suggested that the series of electrocardiographic phenomena in this syndrome (ST elevation, frequent PVC and VF) derives from a common electrophysiologic mechanism. Antzelevitch et al. induced
Figure 3. Stored intracardiac electrograms of the initiation ofVF obtained from Patients 1, 2 and 3 with implantation of Ventak PRX-II. All VF episodes were preceded by the PVCs (asterisk), which were almost identical to the initiating beats of VF. Only Patient 1 demonstrated long-short R-R sequences before the onset of VF.
ST segment elevation similar to that in Brugada syndrome by producing a transmural voltage gradient during repolarization, which was provoked by a loss of action potential dome in epicardium but not endocardium. This sole electrophysiologic mechanism properly accounts for the ST segment elevation, the PVC (phase 2 reentry) and the substrate for VF (increased dispersion of repolarization) in Brugada syndrome (12–14).

The identity of the PVCs. Preceding and initiating PVC of VF episodes in our patients showed a similar pattern of QRS morphology, which suggests that the PVCs originating from the peculiar ventricular sites may relate to electrophysiologic mechanism of VF in Brugada syndrome.

Because the stored electrograms in the present study were obtained from endocardial sites and were single-channel recordings, we cannot assess the origin of the PVCs exactly. However, several clinical and experimental studies suggest that the specific ventricular sites (e.g., right ventricular free wall) can be the most possible foci for triggering PVC (11,15–20). The ST segment elevation in leads V1 to V3 can be the most possible foci for triggering PVC (11,15–20). The ST segment elevation in leads V1 to V3 suggests electrophysiologic abnormality in the right ventricular free wall, because the area may influence the right precordial ECG leads. If marked shortening of action potential duration is the mechanism of ST elevation, PVC firing from the area with shorter action potential duration owing to phase 2 reentry is most likely to induce VF (21,22).

The coupling interval of the initiating PVC. PVC firing at the most vulnerable period of the ventricle (near the peak of T wave) may lead to the genesis of reentry. Actually, in several clinical settings, short-coupled PVC (about 250 to 300 ms) has been demonstrated to occur before episodes of VF or polymorphic ventricular tachycardia (23,24). However, the coupling interval of the first PVC of VF in the present study was 388 ms, and therefore, its onset was close to the end of T wave. Kasanuki et al. (11) also reported a >300 ms coupling interval of the first PVC during VF episode in Brugada syndrome. During the electrophysiologic study at the remote phase of the VF episode, multiple extrastimuli with very short coupling intervals (<200 ms) were found to be necessary to induce VF in Brugada syndrome. However, at the spontaneous onset of VF, it is obvious that only single- and longer (>300 ms) coupled PVCs are able to provoke VF. These facts indicate the importance of the site-specificity of the PVC focus and the acutely increased vulnerability of the ventricle before spontaneous VF episodes.

Post-extrasystolic pause generated by PVCs may be associated with the ST segment elevation and the development of ventricular arrhythmia. Several clinical studies reported that the longer preceding cycles after a PVC augmented the J wave and ST segment elevation (25,26). These findings are consistent with the experimental data showing that premature stimulation restored the loss of the action potential dome due to the slow reactivation kinetics of Ito (12,14). Although the long-short initiating sequence may enhance the electrophysiologic mechanism of VF in Brugada syndrome, pause-dependent PVC and/or first beat of VF was demonstrated in only one patient.

Study limitations. It has been considered that increased vagal activity is related to the development of VF in Brugada syndrome (11). Analysis of heart rate variability using stored electrograms and/or R–R logs in ICD may help to prove a role of vagal activity. However, the data stored in the ICDs were too short to analyze the heart rate variability before the onset of VF. Moreover, because intracardiac electrograms were recorded by digital signal and single endocardial lead systems, we could not precisely investigate the coupling interval, PVC morphology or level of ST segment. In this study, although VF attacks were detected in 7 patients, electrocardiograms were available for only 5 (26%) of the 19 patients.
**Patient 1**

**June 14, 1995**

**Episode: 4**

Date: 14-JUN-95   Time: 17:03   Type: Spontaneous

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**April 30, 1996**

**Episode: 7**

Date: 30-APR-96   Time: 02:15   Type: Spontaneous

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**November 19, 1996**

**Episode: 32**

Date: 19-NOV-96   Time: 05:09   Type: Spontaneous

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**Figure 5.** Stored intracardiac electrograms at the onset of VF obtained from Patient 1 with Ventak PRX-II. A total of 23 episodes of VF occurred within several years. Three episodes are presented. Ventricular fibrillation episodes were initiated by the PVC (asterisk), with the same pattern of QRS morphology.
Figure 6. Stored intracardiac electrograms at the onset of VF obtained from Patient 2 with Ventak PRX-II. Frequent PVCs were seen before the onset of VF on January 23, 1996, but not during the other episodes. Preceding PVCs (asterisk) and initiating PVCs (arrow) show the similar QRS morphology.
patients. In Patients 6 and 7, we were unable to obtain the stored electrogram of ICD because of limited ICD memory function, and ECG monitoring was impossible because the VF episodes occurred out of hospital. Therefore, all VF events in the present patients were not fully investigated, and several exceptions might be present.

Clinical implications. Patients with Brugada syndrome are at high risk of sudden death. At the present time, ICD is the generally accepted mode of therapy. However, no preventive therapy for VF in Brugada syndrome has yet been established. Because VF appears to be initiated by a particular PVC, it is possible that VF could be avoided by (radiofrequency) ablation targeting the initiating PVCs (27,28).

Conclusions. Spontaneous episodes of VF in patients with Brugada syndrome were triggered by specific PVCs. These findings may provide important insights into the pathophysiological mechanisms causing VF in Brugada syndrome.

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REFERENCES