Surface ECG Characteristics of Ventricular Tachyarrhythmias Before Degeneration Into Ventricular Fibrillation in Patients With Brugada-Type ECG

Kimiie Ohkubo, MD, Ichiro Watanabe, MD, Yasuo Okumura, MD, Sonoko Ashino, MD, Masayoshi Kofune, MD, Masakatsu Ohta, MD, Toshiko Nakai, MD, Satoshi Kunimoto, MD, Yuji Kasamaki, MD, and Atsushi Hirayama, MD

Summary

This study was designed to evaluate whether the right ventricular outflow tract (RVOT) is the arrhythmogenic focus in Brugada syndrome. We enrolled 45 patients with Brugada-type ECG who underwent programmed ventricular stimulation and inducible ventricular fibrillation (VF). In 25 of these 32 patients, repetitive VT was observed before degeneration into VF. The QRS morphology of surface ECG and intracardiac electrograms were evaluated to determine the origin of the ventricular tachycardia (VT) that degenerated into VF. The VT morphology was a left bundle branch block pattern with an inferior axis in 22 of 28 VTs and the intracardiac conduction sequence during VT revealed activation from the RVOT to the RV apex in these 22 VTs. The majority of the patients with Brugada syndrome showed repetitive VT originating from the RVOT that degenerated into VF. The RVOT may be an arrhythmogenic focus in patients with Brugada syndrome. (Int Heart J 2009; 50: 477-487)

Key words: Brugada syndrome, Electrophysiologic study, Ventricular tachycardia, Ventricular fibrillation

BRUGADA syndrome is an idiopathic VF of uncertain etiology. Recent papers described mutation in the sodium channel $\alpha_1$ subunit (SCN5A) gene, $\beta_1$ subunit (SCN1B) gene, glycerol-3-phosphate dehydrogenase 1-like gene, and cardiac L-type calcium channel gene. In experimental and clinical studies, pathogenesis of the Brugada syndrome has been reported to be depression or loss of the action potential dome in the right ventricular (RV) epicardium that creates a transmural voltage gradient possibly responsible for the ST-segment
elevation and that also induces extrasystolic activity due to phase 2 reentry.\textsuperscript{7-10} However, the existence of a conduction delay at the RVOT has been suggested in many reports.\textsuperscript{11-14} In addition, several clinical studies have also suggested that spontaneous episodes of VF are triggered by premature ventricular contractions (PVCs) originating mainly from the RVOT.\textsuperscript{15-17} We previously reported that low-amplitude fragmented and delayed potentials were recorded in the RVOT in patients with Brugada syndrome and that these electrograms showed more fractionation and disorganization with programmed ventricular stimulation that led to VF.\textsuperscript{14} In addition, several reports have shown a high incidence of ventricular late potentials,\textsuperscript{18,19} high rate of induction of ventricular fibrillation (VF) by programmed ventricular stimulation,\textsuperscript{20-24} and that inducibility of VF is increased more by programmed stimulation from the RVOT than from the RV apex in Brugada syndrome.\textsuperscript{25,26} The aim of this study was to investigate the characteristics of the induced ventricular tachycardia (VT) that degenerates to VF to evaluate whether the RVOT is the arrhythmogenic focus in Brugada syndrome in a retrospective manner.

**Methods**

**Patients:** We included 45 patients (44 men, 1 woman; age: 52.0 ± 12.5 years, range, 24-76 years) with Brugada type ECG who were admitted to Nihon University Hospital for electrophysiologic study from 1996 through 2008 in a retrospective manner. These 45 patients were referred to Nihon University Hospital for an ECG abnormality detected by their family doctor or during an annual health check-up, evaluation of syncope, or an aborted sudden cardiac death (Table I). The mean age of the symptomatic patients was 54.5 ± 11.7 years old and that of the asymptomatic patients was 51.4 ± 12.6 years old (not statistically significant). The diagnosis of Brugada-type ECG was based on typical electrocardiographic patterns: persistent or transient right precordial ST-segment elevation with or without atypical right bundle branch block.\textsuperscript{27} In accordance with the first consensus on the Brugada syndrome conducted in Europe, the ECG was classified as Brugada-type 1, 2, or 3.\textsuperscript{27} Two patients had an episode of aborted cardiac arrest, 10 patients had episodes of syncope, and 33 patients were asymptomatic. Five patients had a family history of sudden cardiac death (Table I). Routine studies, including cardiac echocardiography, coronary angiography, and right and left ventriculography showed no evidence of structural heart disease.

**Electrophysiologic study:** All patients gave informed consent for participation in the study, which was approved by the Clinical Research Committee of Nihon University Hospital. All patients were studied in the fasting, drug-free state, and were sedated with midazolam and fentanyl. Programmed ventricular stimula-
tion (PVS) was performed as reported previously.\textsuperscript{28} One quadripolar catheter and one octapolar catheter were percutaneously inserted through the left femoral vein and advanced under fluoroscopic guidance, initially to the right atrial appendage and to the His-bundle region, respectively. An octapolar catheter was inserted through the right internal jugular vein and advanced to the coronary sinus. One steerable electrode catheter was inserted through the right femoral vein and advanced to the RV apex (RV A). The electrophysiologic study included basal measurement of conduction intervals and programmed ventricular stimulation (PVS). The atrio-His interval and the His-ventricular interval were measured during sinus rhythm. The protocol used included two sites of ventricular stimulation (RV A and RVOT) at a pulse width of 2 ms and output of twice the diastolic thresholds, two basic cycle lengths (600 and 400 ms), and 1 and 2 ventricular premature beats (S2 down to the effective refractory period and S3 down to 180 ms). At each basic cycle length, programmed stimulation was performed in the RVA first. A patient was considered to be inducible if a sustained ventricular arrhythmia (VF, polymorphic VT, or monomorphic VT lasting > 30 seconds or requiring emergency intervention) was induced. In patients in whom sustained ventricular arrhythmia was induced, PVS was conducted again from RVA and RVOT during recording of electrograms from the free wall of the RVOT, HBE recording site, RVA, and coronary sinus. Repetitive monomorphic VT was defined as VT ≥ 5 beats of same morphology and cycle length ≥ 180 ms. Surface 12-lead ECG morphology and local electrograms during sinus rhythm and the

<table>
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<tr>
<th>VT induction (+)</th>
<th>VT induction (-)</th>
<th>P</th>
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<td>58.8 ± 9.4</td>
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<td>QRS duration (ms)</td>
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<td>113.8 ± 23.8</td>
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<td>QRS duration (ms)</td>
<td>113.2 ± 16.5</td>
<td>113.8 ± 23.8</td>
<td>NS</td>
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VT indicates ventricular tachycardia; AH, atrio-his; HV, his-ventricular; RVA, right ventricular apex; RVOT, right ventricular outflow tract; ERP, effective refractory period; and BCL, basic cycle length.

Table I. Patient Characteristics
monomorphic VT rhythm that degenerated into VF were compared. Self-terminating polymorphic VT was ruled out from the analysis because reproducibility was poor.

**Statistical analysis:** Data are expressed as the mean ± SD for continuous variables and were compared by Student’s unpaired t-test. Categorical variables were summarized as percentages, and group comparisons were based on Fisher’s exact probability test. A logistic regression model was used to determine the predictors of VF induction during programmed stimulation. A $P$ of < 0.05 were considered statistically significant.

The statistical software StatView 5.0 (SAS Institute Inc.) was used.

**RESULTS**

**Patients characteristics:** VF was induced in 32 (71.1%) of the 45 study patients (VF (+) group), and VF was not induced in the remaining 13 patients (28.9%), (VF (-) group). The baseline characteristics of the two groups are summarized in Table I. There were no differences in the sex or familial history between the two groups. The patients in whom VF was induced by PVS were significantly younger than the patients without inducible VF (50.0 ± 12.6 years versus 58.8 ± 9.4 years, $P < 0.02$). In addition, the prevalence of symptomatic patients tended to be greater in the VF (+) group than that of the asymptomatic patients ($P = 0.13$). After adjusting for age and a history of symptoms, age (odds ratio 0.91: 95% CI 0.85-0.98, $P = 0.013$) and a history of symptoms (odds ratio 11.54: 95% CI 1.06-125.34, $P = 0.045$) remained the marginal predictors of VF induction.

<table>
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<th>Initial VT Morphology</th>
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<th>10 VF by RVA pacing</th>
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<tr>
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<td>3</td>
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<tr>
<td>LBBB, Nor</td>
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VF indicates ventricular fibrillation; VT, ventricular tachycardia; RVOT, right ventricular outflow tract; RVA, right ventricular apex; LBBB, left bundle branch block; Inf, inferior axis; Sup, superior axis; and Nor, normal axis.
Electrocardiographic characteristics: ECG data are shown in Table I. The patients were classified into the Brugada-type 1 ECG group (n = 20, 44.4%), Brugada-type 2 ECG group (n = 11, 24.4%), and Brugada-type 3 ECG group (n = 14, 31.1%). The ECG of all 11 type 2 and 14 type 3 patients changed to type 1 ECG after pilsicainide administration (1 mg/kg, iv). Baseline type-1 ECG did not differ between VF (+) patients (46.9%) and VF (-) patients (38.7%). Mean QRS duration was 113.2 ± 16.5 ms in the VF (+) group and 113.8 ± 23.8 ms in the VF (-) group (NS).

Electrophysiologic characteristics: The electrophysiologic data are shown in Table I. 1) AH, HV intervals and ERPs: The atrio-His interval was 100.1 ± 19.7 ms in the VF (+) group and 100.2 ± 17.2 ms in the VF (-) group (NS) and the His-ventricular interval was 52.1 ± 13.3 ms in the VF (+) group and 48.3 ± 9.2 ms in the VF (-) group (NS), respectively. The effective refractory period of the RVA at a cycle length of 600 and 400 ms did not differ between the VF (+) and VF (-) groups (215.8 ± 19.6 ms; VF (+) versus 215.0 ± 16.9 ms; VF (-) / 600 ms; 198.7

Figure 1. Twelve-lead ECG of induced ventricular tachycardia (VT) in patient 42. Note that double ventricular premature stimuli from the right ventricular apex induced rapid VT of left bundle branch block (LBBB) and inferior axis configuration.
± 22.0 VF (+) versus 188.8 ± 9.9 ms VF (-) / 400 ms. The effective refractory period of the RVOT at a cycle length of 600 and 400 ms did not differ between the VF (+) and VF (-) groups (212.0 ± 20.6 ms; VF (+) versus 210.0 ± 17.6 ms; VF (-) / 600 ms; 194.4 ± 15.5 VF (+) versus 193.6 ± 19.6 ms VF (-) / 400 ms).

2) Incidence and induction site of VF: VF was induced by PVS in 32 of the 45 patients (71.1%). VF was induced by 2 extrastimuli from the RVA in 10 patients, from the RVOT in 19 patients, and from both RVA and RVOT in 3 patients.

3) VT morphology: Programmed stimulation from the RVOT induced left bundle branch block, inferior axis repetitive monomorphic VT (≥ 5 beats, cycle length ≥ 180 ms) before degenerating into VF in 16 patients, left bundle block, noninferior axis VT in 2 patients, and VF without initial VT in 4 patients. On the other hand, programmed ventricular stimulation from the RVA induced left bundle block, inferior axis VT in 6 patients, left bundle block, noninferior axis VT in 4 patients, and VF without initial VT in 3 patients (P < 0.05 versus RVOT).

The mean number and cycle length of the VT before degenerating into VF was 6.6

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**Figure 2.** Intracardiac electrograms of the induced ventricular tachycardia (VT) in the patient shown in Figure 1. Note that highly disorganized activation of the right ventricular outflow tract (RVOT) preceded that in the right ventricular apex (RVA) and the left ventricular activation recorded in the coronary sinus (CS) electrograms occurred after RVA activation. Arrows indicate local activation conducting from RVOT to RVA during VT. P indicates proximal electrode pair of the electrode catheter; and d, distal electrode pair of the electrode catheter.
 ± 1.3 beats and 205.3 ± 14.6 ms. Morphology of the VT showed a left bundle branch block pattern with an inferior axis in 22 of 28 VTs (78.5%, Table II, Figure 1 and Figure 3), and the intracardiac conduction sequence during the VT revealed activation from the RVOT to the RVA in these patients irrespective of the stimulation site (Figure 2). Morphology of the VT showed a left bundle branch block pattern and normal axis in 3 VTs (10.7%) and a superior axis in 3 VTs (10.7%). There were no clinical, electrocardiographic, or electrophysiologic differences between patients with and without initial VT phase.

**Therapy and follow-up:** The mean follow-up period was 59.9 ± 38.4 months. An implantable cardioverter defibrillator (ICD) was implanted in 19 patients, antiarrhythmic drugs were administered in 7 patients (1; cibenzoline + amiodarone, 5; amiodarone, and 1; cibenzoline), and the remaining 19 patients had no therapy. We used amiodarone in 6 of the early cases (from 1996) because ICDs were not covered by insurance and the efficacy of amiodarone was still controversial during the early phase. During the follow-up period, one patient who rejected an ICD implantation died suddenly 1 month after an electrophysiologic study, but the remaining 44 patients had no episodes of syncope, aborted sudden death, or ICD discharges.

**Figure 3.** Twelve-lead ECG of induced ventricular tachycardia (VT) in patient 31. Note that double ventricular premature stimuli from the right ventricular outflow tract induced rapid VT of left bundle branch block (LBBB) and inferior axis configuration.
In the present study, we showed that 1) a previous history of aborted sudden death or syncope was a marginal predictor of VF induction, 2) the age of VF (+) patients was younger than VF (-) patients, 3) prevalence of the baseline type-1 ECG did not differ between VF (+) patients and VF (-) patients, and 4) monomorphic VT (mainly RVOT origin) preceded VF by programmed ventricular stimulation. A previous study demonstrated that age and baseline coved-type ECG did not differ among the patients with aborted sudden death, syncope, and asymptomatic patients with Brugada syndrome, but the rate of VF induction was higher in symptomatic patients compared with asymptomatic patients, however, no previous report assessed the value of age for risk stratification of VF induction with Brugada syndrome. In this study, the inducibility of VT/VF was higher than that reported in Europe. In this study, the inducibility of VT/VF in symptomatic patients was 92% and 64% in asymptomatic patients. Brugada, et al reported that inducibility of VF in symptomatic patients was 73% and 33% in asymptomatic patients. Priori, et al reported that the inducibility of VT/VF was 65% in symptomatic patients and 68% in asymptomatic patients. Eckerd, et al reported that inducibility of VT/VF was 63% in symptomatic patients and 39% in asymptomatic patients. There have been 2 multicenter studies on Brugada syndrome in Japan (unpublished observation). Kamakura, et al (2008) reported that VT/VF inducibility was 87% (n = 162) in symptomatic patients and 64% (n = 308) in asymptomatic patients. Aonuma, et al (2003) reported that VT/VF inducibility was 80% (n = 51) in symptomatic patients and 76% (n = 25) in asymptomatic patients. It is not clear why VT/VF inducibility in asymptomatic patients was higher in these Japanese populations. We showed that PVS reproducibly induced repetitive VT that degenerated into VF in 25 of 32 VF (+) patients (78%) with Brugada syndrome. The morphology of the repetitive VT showed a left bundle branch block pattern with inferior axis in 22 of the 28 VTs (78.6%), and the intracardiac conduction sequence during the VT revealed a conduction pattern from the RVOT to the RV in these patients. The other 6 VTs showed a left bundle branch block pattern and a normal axis or a superior axis. Morphology of the induced VT was related to the stimulation site; ie, stimulation from the RVOT induced left bundle block, inferior axis VT in 16 of 18 VTs (89%), but stimulation from the RVA induced left bundle branch block, inferior axis VT in 6 of 10 VTs (60%). Murakoshi, et al also reported that the majority of their patients with Brugada syndrome had repetitive VT induced by PVS originating from the RVOT that degenerated into VF. Recent reports indicated an overlap between Brugada syndrome and arrhythmogenic RV cardiomyopathy, and electron-beam CT and magnetic resonance imaging in patients with
Brugada syndrome have revealed localized RV morphologic abnormalities and fat infiltration.\textsuperscript{36,37} Furthermore, recent articles reported histopathologic changes such as myocarditis, hypertrophy, fibrosis, and fatty infiltration in the RV.\textsuperscript{38-40} An animal study also found that mutation in the gene encoding SCN5A in mice resulted in impairment of atrial and ventricular conduction associated with myocardial rearrangement and fibrosis.\textsuperscript{41} Furthermore, we have reported more steeply sloped action potential duration restitution kinetics in the RVOT in patients with Brugada syndrome than in control patients.\textsuperscript{42} Thus, repetitive monomorphic VT originating mainly from the RVOT that degenerates into VF may be related to both abnormal depolarization and repolarization properties of the RVOT, leading to local reentry in the RVOT by programmed ventricular stimulation in patients with Brugada syndrome.

**Study limitations:** First, the number of the patients in the present study was small, and 74.4\% of the patients were asymptomatic. Second, our study was limited to VT induced by PVS, and we did not study spontaneous episodes of VT that degenerate into VF because it is very difficult to obtain a 12-lead ECG during spontaneous onset of VT/VF. However, Kakishita, \textit{et al}\textsuperscript{43} reported that spontaneous episodes of VF obtained from stored electrograms of an implantable cardioverter defibrillator and/or electrocardiographic monitoring in patients with Brugada syndrome were triggered by specific PVC. Furthermore, Morita, \textit{et al}\textsuperscript{16} demonstrated that 8 of 10 patients with pilsicainide-induced PVCs had a QRS morphology of left bundle branch block with inferior axis suggesting RVOT origin. Third, the activation sequence from RVOT to RVA during rapid VT is difficult to decide during rapid VT by 2 catheters. However, all VT with LBBB and an inferior axis demonstrated an activation sequence was directed from the RVOT to RVA, then LV that was determined from CS electrograms, at least the first 3 to 5 beats of VT.

**Conclusion:** In the present study, the majority of the patients with Brugada syndrome showed repetitive VT originating from the RVOT that degenerated into VF. The RVOT may be an arrhythmogenic focus in patients with Brugada syndrome.

**References**

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20. Ohkubo K, Watanabe I, Takagi Y, et al. Electrocardiographic and electrophysiologic characteristics in patients with Brugada type electrocardiogram and inducible ventricular fibrillation: single center expe-