Abnormal Action Potential Duration Restitution Property in the Right Ventricular Outflow Tract in Brugada Syndrome

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Background: Although patients with Brugada syndrome (BS) are at risk of ventricular fibrillation (VF) and ensuing death, the action potential duration (APD) restitution properties of the right ventricular outflow tract (RVOT) in patients with BS remain undetermined.

Methods and Results: Endocardial monophasic action potentials (MAPs) were obtained from 16 patients with BS and 17 control patients. MAPs were recorded from the RVOT in all patients. The MAP duration at 90% repolarization (MAPD₉₀), effective refractory period (ERP), and maximum slope of the APD restitution curve were obtained. VF was induced with up to 3 extrastimuli from the RV apex or RVOT. There was no difference in MAPD₉₀ between the 2 groups, but the ERP was significantly shorter in patients with BS than in control patients (210.7±10.5 vs 223.8±13.4 ms, $P=0.008$). MAPD at the shortest diastolic interval was significantly shorter in patients with BS than in control patients (149.9±19.9 vs 179.8±13.7 ms, $P<0.001$). The maximum slope of the APD restitution curve was steeper in patients with BS than in control patients (2.90±1.29 vs 1.38±0.41, $P<0.001$).

Conclusions: The shorter ERP, shorter MAPD at the shortest diastolic interval and steeply sloped APD restitution curve in the RVOT appear to be related to the inducibility of VF in patients with BS. (*Circ J* 2010; **74**: 664–670)

Key Words: Action potential duration restitution; Brugada syndrome; Monophasic action potential; Ventricular fibrillation; Ventricular refractory period

Brugada syndrome (BS) is characterized electrocardiographically by a right bundle branch block pattern and ST-segment elevation in precordial leads V_{1–3}, and also by a propensity for sudden cardiac death because of ventricular fibrillation (VF).¹ Several studies have linked BS to 1 or more gene mutations;^{2–4} however, the mechanisms of arrhythmogenesis remain controversial. Animal studies suggest that the ECG “Brugada sign” reflects loss of the action potential dome in the epicardium but not in the endocardium, allowing extra beats (from phase 2 reentry) to interact with transmembrane repolarization dispersion to initiate reentry (repolarization disorder) and/or conduction delay in the right ventricular (RV) outflow tract (OT).^{5–7} However, the factors that cause degeneration into VF and continuation of the fibrillatory activities, perhaps providing the background for inducible sustained VF during electrophysiologic study (EPS), have not been elucidated. The electrical restitution property of the myocardium has been shown to play an important role in determining the susceptibility of the heart to fibrillation. Evidence from experimental^{8–10} and clinical studies^{11,12}

indicates that the maximum slope of the ventricular action potential duration (APD) restitution curve, which portrays the relation between the local APD and the preceding diastolic interval, reflects the propensity for VF. If the slope of the restitution function at a short diastolic interval exceeds unity, small changes in the diastolic interval can produce large fluctuations in the APD and refractoriness,^{9,13} which may lead to functional gradients in repolarization that may promote conduction block and the wavebreak of re-entrant wavefronts.¹⁴ Two groups of investigators have documented that the maximum slope of the APR restitution curve in the RV apex (RVA) is greater than that in the RVOT.^{15,16} However, we showed repetitive ventricular tachycardia (VT) originating from the RVOT and degenerating into VF in a majority of patients with BS.¹⁷ We also reported a case in which monophasic action potentials (MAPs) recorded from the RVOT at a basic cycle length (CL) of 400 ms showed MAP alternans, and VF was induced only when extrastimuli were applied after a decrease in the MAP duration (MAPD) of the alternans.¹⁸ Thus we hypothesized that the RVOT contributes to

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the inducibility of VF in patients with BS undergoing programmed ventricular stimulation. To examine this hypothesis, we recorded MAPs from the RVOT to calculate the repolarization restitution slope during programmed ventricular stimulation.

Methods

Subjects and Clinical Data Collection

BS Patients Sixteen patients diagnosed with BS between 2004 and 2008 comprised the BS group. Clinical data, including age at diagnosis, sex, family history of sudden death, documented VF, episodes of syncope, and implantable cardioverter-defibrillator (ICD) implantation, were obtained for all patients. Structural heart disease was ruled out in each case on the basis of the patient's clinical history and by extensive evaluation, including non-invasive and invasive procedures (echocardiography, coronary angiography, and left and right ventriculography). A family history of sudden death was defined as sudden death of unknown cause in a family member at less than 50 years of age. Thirteen patients showed a typical type 1 Brugada pattern as previously defined.¹⁹ In the remaining 3 patients with a type 2 (n=1) or 3 (n=2) Brugada pattern, 1 mg/kg of pilsicainide (a pure sodium channel blocker) was administered intravenously for 10 min with continuous monitoring, and it was confirmed that the Brugada pattern changed to type 1. Fourteen of the 16 patients provided informed consent for investigation of SCN5A gene mutation, but no mutation was found.

Control Patients Seventeen age-matched patients who underwent catheter ablation for tachyarrhythmia but did not have a Brugada-type ECG comprised the control group. Structural heart disease was ruled out in all cases on the basis of the patient's clinical history and by extensive evaluation, including non-invasive and invasive procedures (echocardiography, coronary angiography, and left and right ventriculography).

This single-center study complied with the guidelines of the Declaration of Helsinki and was approved by the institutional ethics committee.

EPS

Comprehensive EPS was performed in all BS and control patients after written informed consent was given. The EPS was conducted with subjects in a fasting, drug-free, and non-sedated state. After access to the right femoral vein was obtained at 2 sites, 2 steerable quadripolar catheters (6F) with an interelectrode distance of 2–5–2 mm (Biosense-Webster, Diamond Bar, CA, USA) were positioned in the RV. Endocardial potentials were filtered to recording frequencies of 30–500 Hz and recorded on a BARD computer system. Programmed electrical stimulation from the RVA and RVOT was performed at twice the diastolic threshold strength and a pulse of 2-ms duration with a pulse generator (BC-02, Fukuda Denshi Co, Tokyo, Japan). An S₁–S₂ interval was applied after 8 beats of drive pacing (S₁) at basic CLs of 600 ms and 400 ms. The S₁–S₂ interval was decreased in 10-ms steps until the effective refractory period (ERP) of the RV was reached. When VF that lasted >10 s and required DC shock was not induced with a single premature beat, up to 3 extrastimuli (S₁S₂ until the ERP was reached, S₂S₃ and S₃S₄ to 180 ms) were delivered. Patients with polymorphic VT or VF that terminated spontaneously within 10 s were not included in this study.

A 7F MAP recording/pacing catheter (Franz[®] catheter, EP Technologies Inc, San Jose, CA, USA) was inserted through

the right femoral vein and positioned in the RVOT at 20 min after DC shock for patients with BS or after successful ablation in control patients. MAP signals were amplified at a filter setting of 0.05–500 Hz. Ventricular pacing was performed from the proximal electrode pair of the Franz catheter at twice the diastolic threshold strength and a pulse of 2-ms duration. The MAPD was measured as the interval along a line horizontal to the diastolic baseline from the steepest part of the MAP upstroke to the level of 90% repolarization (MAPD₉₀).²⁰

Construction of the APD Restitution Curve

Restitution of the MAPD₉₀ was determined by using a single S₂ delivered after every 12th S₁ at a basic CL of 600 ms. The S₁S₁ interval was started at 600 ms and was decreased in 20-ms steps until an S₁S₂ of 400 ms was reached. It was decreased in 10-ms steps until an S₁S₂ of 300 ms was reached, and then in 5-ms steps until ventricular capture failed. After each S₂, S₁ pacing was interrupted for 1.5 s. No VT/VF was induced by single ventricular extrastimulus from the MAP recording/pacing catheter. The APD restitution curve was constructed by plotting the MAPD₉₀ of S₂ vs the preceding diastolic interval, which was obtained by subtracting the MAPD₉₀ of the 11th S₁ from the S₁S₂ interval and adding the latency (stimulus–tissue delay) after S₂. The time course of restitution obtained by S₁S₂ was fitted by using the mono-exponential equation with the use of Origin 7.0 software (OriginLab Corp, Northampton, MA, USA), and the maximum slope of the APD restitution curve was obtained by the maximum value of the first derivative of the mono-exponential equation fitting curve.^{15,21,22}

Statistical Analysis

Continuous data are presented as mean ± SD. Differences in continuous clinical variables were analyzed by two-tailed t-test. Differences in repolarization and conduction parameters were analyzed by Mann-Whitney U test. A P value <0.05 was considered statistically significant. StatView 5.0 software (SAS Institute, Cary, NC, USA) was used for analysis.

Results

Patient Characteristics

Left ventricular ejection fraction did not differ between the BS and control patients (67.8 ± 5.9% vs 67.6 ± 6.4%, respectively) nor did the left atrial diameter (31.3 ± 5.1 mm vs 31.2 ± 5.0 mm, respectively). The BS patients were all probands. None of the patients in this study were members of the same family. Aborted sudden cardiac death occurred in 1 patient, episodes of syncope occurred in 1 patient, and another 2 patients had a family history of unexplained sudden death (Table 1). A spontaneous type 1 ECG pattern was observed in 13 of the 16 patients with BS. The control group consisted of 4 patients with concealed Wolf-Parkinson-White syndrome, 11 patients with atrioventricular nodal reentrant tachycardia, and 2 patients with premature ventricular contraction of RVOT origin.

EPS

A type 1 ECG pattern was observed in 13 of the 16 patients with BS during the EPS. There was no significant difference between the groups in terms of the AH interval (103.3 ± 25.0 ms in BS patients vs 93.0 ± 12.6 ms in control patients, P=0.358) or the HV interval (48.4 ± 11.5 ms in BS patients vs 43.1 ± 5.2 ms in control patients, P=0.242) (Table 2). One-to-one conduction of the atrioventricular node did not differ

Table 1. Clinical Characteristics Per Study Group			
	Brugada (n=16)	Control (n=17)	P value
Clinical data			
Age (years)	51.2±13.2	54.2±11.9	0.497
Sex ratio (M/F)	16/0	8/9	<0.001
Spontaneous type 1 ECG	13	0	
Family history of sudden death	2	0	
Syncopal episode	1	0	
Documented VF	1	0	
Echocardiographic data			
Left atrial diameter (mm)	31.3±5.1	31.2±5.0	0.955
LVEF (%)	67.8±5.9	67.6±6.4	0.926

Number of patients is shown unless otherwise indicated.
VF, ventricular fibrillation; LVEF, left ventricular ejection fraction.

Table 2. Electrophysiologic Characteristics Per Study Group			
	Brugada (n=16)	Control (n=17)	P value
AH interval (ms)	103.3±25.0	93.0±12.6	0.358
HV interval (ms)	48.4±11.5	43.1±5.2	0.242
Wenckebach cycle length (ms)	409.6±51.8	381.5±68.3	0.320
ERP of the RVOT (ms)	211.9±11.2	233.8±13.4	0.008
MAPD ₉₀ of the RVOT (ms)	226.6±15.5	233.9±15.9	0.192
MAPD ₉₀ at the shortest DI (ms)	149.9±19.9	179.8±13.7	<0.001
Maximum MAPD ₉₀ slope	2.90±1.28	1.38±0.91	<0.001
VF induction during EP study	16/16	NA	

ERP, effective refractory period; RVOT, right ventricular outflow tract; MAPD₉₀, 90% repolarization of the monophasic action potential; DI, diastolic interval; NA, not appropriate. Other abbreviation see in Table 1.

Figure 1. Right ventricular MAP recordings at the shortest DI in a control patient. Effective refractory period of the RVOT of this patient was 220ms. MAP, monophasic action potential; RVOT, right ventricular outflow tract; DI, diastolic interval.

significantly between the BS and control patients (409.6±51.8ms vs 381.5±68.3ms, P=0.320). The ERP-RVOT at a basic CL of 600ms was significantly shorter in the BS group than in the control group (211.9±11.2ms vs 233.8±13.4ms, P=0.008), but there was no statistically significant difference

between the 2 groups in the RVOT MAPD₉₀ (226.6±15.5ms vs 233.9±15.9ms). The RVOT MAPD₉₀ at the shortest diastolic interval was significantly shorter in the BS group (Figures 2,4) than in the control group (Figures 1,3) (149.9±19.9ms vs179.8±13.7ms, P<0.001). The maximum slope of

Figure 2. Right ventricular MAP recordings at the shortest DI in a patient with Brugada syndrome. Effective refractory period of the RVOT of this patient was 205 ms. RVOT, right ventricular outflow tract, MAP, monophasic action potential; DI, diastolic interval.

Figure 3. Electrical restitution curve at the RVOT in the control patient shown in Figure 1. According to a single linear plot, the maximum slope was 1.4. RVOT, right ventricular outflow tract; MAPD₉₀, monophasic action potential duration at 90% repolarization.

the RVOT MAPD₉₀ restitution curve was significantly greater in the BS group than in the control group (2.90 ± 1.28 [1.0–4.6] vs 1.38 ± 0.41 [1.0–2.4], $P < 0.001$) (Figures 3, 4; Table 2). Polymorphic VT or VF lasting >10 s requiring DC shock was induced in all 16 patients with BS (Table 3). Because all patients had spontaneous type 1 ECG and/or syncopal episode, family history of sudden death, documented VF, and inducible VF, we recommended implanting an ICD, which 12 of the 16 patients (75.0%) did receive; 4 patients refused. Patients with BS were followed-up in the outpatient clinic every 6 months for 40.6 ± 19.2 months (11–65 months).

No sudden cardiac death or appropriate ICD shock was noted during the follow-up period.

Discussion

Repolarization Properties and the Inducibility of Ventricular Arrhythmias

The present study compared the ERP and MAPD₉₀, MAPD₉₀ at the shortest diastolic interval, and steepness of the maximum APD restitution slope of the RVOT between BS patients and control patients. We showed that the ERP-RVOT and

Table 3. Electrophysiologic Characteristics Per Patient	
Patient no.	VF induction (ms)
1	RVOT: 600/230/220
2	RVOT: 600/230/200/200
3	RVOT: 400/250/190
4	RVOT: 600/230/200
5	RVOT: 600/250/230
6	RVOT: 600/230/220
7	RVOT: 400/220/210
8	RVOT: 400/270/270/200
9	RVOT: 600/250/200
10	RVA: 600/230/210
11	RVOT: 400/220/200
12	RVA: 400/230/200
13	RVOT: 600/270/250
14	RVA: 600/270/200
15	RVA: 600/220/220
16	RVA: 400/210/200

RVA, right ventricular apex. Other abbreviations see in Tables 1,2.

MAPD₉₀ at the shortest diastolic interval were significantly shorter, and the maximum RVOT APD restitution slope was significantly steeper, in patients with BS. Recent studies have shown that the maximum slope is steeper in patients with inducible VT^{21,23} and that these patients had a greater risk of sudden cardiac death than did those without.²³ Furthermore, recent studies have examined the repolarization restitution properties in patients with BS. Narayan et al reported that the RV MAPD restitution slope was steeper in the RVA than in the RVOT in a patient with inducible VF,¹⁶ and Hayashi et al reported that the maximum activation recovery interval restitution slope in the RVA, but not the RVOT, was steeper in BS patients with inducible VF than in those without.¹⁴ In a reported case of short-coupled torsades de pointes, the patient's MAPD was significantly shorter at the RVA than at the RVOT, and the maximum slope of the MAPD restitution

curve was much steeper at the RVA than at the RVOT.²²

Previously, we recorded low-amplitude fragmented and delayed potentials at the RVOT in BS patients with inducible VF,²³ and we found that a majority of patients with BS showed repetitive VT originating from the RVOT that degenerated into VF.¹⁷ Moreover Park et al reported that the maximum slope of the APD restitution curve in BS patients with inducible VF was 2.1 at the RVOT and significantly greater than that at the RVA (1.1).²⁴ To our knowledge, we provide the first description of the detailed APD restitution properties in BS. Theoretically, if the APD restitution slope exceeds unity, the wavelength oscillations self-amplify and the diastolic interval becomes too short for the wave to propagate, resulting in conduction block and wavebreak.^{13,14} In the present study, the maximum APD restitution slope was shown to be steeper in BS patients with inducible VF, and a slope >1 in the RVOT was observed in 94.4% of the patients. Abrupt shortening of the APD in premature beats close to the refractory period is the primary reason for a steep repolarization restitution slope. In the earliest premature responses, a less-negative initial membrane voltage, resulting from incomplete sodium channel activation diminishes the following L-type calcium activity, which is responsible for the action potential plateau, and foreshortens the APD.²⁵ In BS, mutations in the cardiac sodium channel gene SCN5A have been found and shown to result in a loss of the channel function,² and several experimental studies^{26,27} have revealed a significantly more delayed “slow” inactivation in the cells with a mutant SCN5A channel than in those without. In BS, in the case of premature beats preceded by very short diastolic intervals, the degree of curtailment of the action potential plateau would be related to the severity of reduced sodium channel activity. Another possibility for the steep repolarization slope in BS is the excessive activation of the transient outward current. We reported that intravenous administration of quinidine inhibited the induction of VF by programmed ventricular stimulation, and that the mechanism was related to the increase in the shortest APD and decrease in the restitution slope after quinidine administration.²⁸

Experimental BS models have shown that a local re-excitation called phase 2 reentry captures the vulnerable windows and triggers a circus movement reentry.^{5,6,29} We assessed the repolarization restitution property and showed that the maximum restitution slope in the RVOT of BS patients with inducible VF is significantly steeper than that of control patients, which indicates that the RVOT region may play an important role in the degeneration into sustained VF in patients with BS. Previous studies have also revealed the importance of the RVOT in the development of VF in BS, based on the presence of delayed potentials in the RVOT,³⁰ the presence of initial repetitive VT originating from the RVOT before degeneration into VF,¹⁷ and development of spontaneous premature contractions triggering VF mainly in the RVOT.³¹ Transmural dispersion of repolarization in the RVOT has been shown to contribute to initial repetitive excitation during VT in experimental BS models.^{5,6,29} Previous studies have shown the presence of spatial heterogeneity of APD restitution properties in patients with BS and a short-coupled variant of torsades de pointes.^{15,16,22} However, a previous study in the explanted Langendorff-perfused heart from a patient with BS at heart transplantation failed to show steep APD restitution and the importance of slow conduction in the right ventricle.³² In vivo human heart studies also have shown broad restitution of propagation in patients with BS.^{15,16,33,34} A recent report showed that the critical parameter for differentiating between the occurrence of reentry and the mere occurrence of a line of activation block between 2 myocardial regions (and no reentry) was not the magnitude of the premature activation wave at the distal side of the premature beat proximal to the line of block, but rather the restitution characteristics of the tissue with shorter action potential, in combination with the time of arrival of the premature wavefront at the distal end side of the line of block, determines the occurrence of reentry.³⁵ We observed a case of BS in which VF was induced by a single premature ventricular stimulus from a MAP catheter (**Figure 5**). Following a very short MAP induced by an extrastimulus, a premature ventricular beat occurred, preceded by an MAP from the same recording site, leading to VF.

The value of the maximal slope of the repolarization restitution curve in clinical studies using MAPD varies. Pak et al showed that the mean maximum slopes of the RVOT and RVA in control patients measured at a basic CL of 600ms were 1.9 ± 1.1 and 1.7 ± 1.1 , respectively.²¹ Yamazaki et al showed that the mean maximum slopes in the RVOT and RVA in control patients measured at a basic CL of 600ms were 1.26 ± 0.66 and 1.27 ± 0.51 , respectively,²² comparable to values shown in our control patients. Pak et al reported that the mean maximum slopes of the RVOT and RVA in inducible VT group patients measured at a basic CL of 600ms were 3.7 ± 2.1 and 2.3 ± 2.7 , respectively.²¹ Park et al also reported that the mean maximum slopes of the RVOT and RVA in BS patients with inducible VF were 2.1 and 1.1, respectively,²⁴ also comparable to values shown in our BS patients with inducible VF.

Our study might have been limited by the fact that the MAP catheter records electrical activity from multiple cells in close proximity to the recording electrodes.^{20,36} The amplitude of

the MAP recording declines gradually over the study.³⁷ However, the APD restitution curve recorded with the MAP electrode closely resembles the APD restitution curve obtained by the microelectrode technique.³⁸ A second limitation is that only APD restitution from the RVOT was measured, making determination of spatial heterogeneity of APD restitution inapplicable. Third, comparison of APD restitution between BS patients with and without documented VT/VF and between those with and without inducible VT/VF was not done. Fourth, restitution of propagation was not measured in the present study. Finally, there was a significant difference in the sex ratio between the BS group and the control group in the present study, but there was no significant difference in the ERP-RVOT (219.4 ± 14.5 ms vs 227.8 ± 11.8 ms, $P=0.173$), MAPD₉₀-RVOT (227.4 ± 4.6 vs 239.7 ± 5.5 ms, $P=0.101$), shortest MAPD₉₀-RVOT (175.8 ± 4.4 vs 183.4 ± 4.8 ms, $P=0.308$), or maximum slope of the the MAPD₉₀-RVOT restitution curve (1.19 ± 0.006 vs 1.544 ± 0.166 , $P=0.115$) between males and females in the control group. Recent studies have shown that propagation restitution, in addition to steep APD restitution, is important in determining myocardial electrical instability.^{16,39} Further studies should use epicardial as well as endocardial mapping to better define the role of repolarization, conduction, and transmural dispersion in BS-related arrhythmogenesis.

Results of the present study suggest that the repolarization restitution property may relate to the propensity for VF in BS. The maximum APD restitution slope in the RVOT was

steeper in BS patients with inducible VF than in control patients. Further studies are needed to record MAPs from multiple sites within the RV and to simultaneously measure propagation restitution to better define the role of repolarization, spatial dispersion of repolarization, and conduction in BS-related arrhythmogenesis.

Disclosures

The authors have no conflict of interests to disclose. The study was supported by departmental resources only.

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