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MINI-FOCUS ISSUE: BRUGADA SYNDROME

Ventricular Repolarization Restitution Properties in Patients Exhibiting Type 1 Brugada Electrocardiogram With and Without Inducible Ventricular Fibrillation

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Objectives This study aimed to elucidate the contribution of the repolarization restitution property to the sustained ventricular fibrillation (VF) in Brugada syndrome.

Background Although phase 2 re-entry develops as the trigger of VF, the other precipitating factors have remained unclear.

Methods Twenty-one patients with a type 1 Brugada electrocardiogram underwent programmed electrical stimulation. Before the VF induction, single extrastimuli were delivered at 3 basic drive cycle lengths (BCLs) (400 ms, 600 ms, and 750 ms) from the right ventricular apex (RVA) and outflow tract (RVOT), and the activation recovery interval (ARI) was measured at 5-mm vicinity of the pacing site. The maximum ARI restitution slope was determined using the overlapping least-squares linear segments.

Results We found that VF was inducible in 10 patients. A repeated-measure analysis of variance revealed that the slope in the RVA was steeper in patients with inducible VF than in those without but that in the RVOT was similar. The slope was steeper at longer BCLs and also steeper in the RVA than RVOT at BCLs of 600 and 750 ms. In patients with inducible VF, the percentage of patients exhibiting a slope >1 was 0%, 20%, and 75% in the RVA and 0%, 0%, and 14% in the RVOT at BCLs of 400 ms, 600 ms, and 750 ms, respectively. No patients without inducible VF had a slope >1.

Conclusions These results suggest the repolarization restitution property is a contributing factor to the propensity for VF in Brugada syndrome and, regarding this property, the RVA plays more important role than the RVOT. (J Am Coll Cardiol 2008;51:1162–8) © 2008 by the American College of Cardiology Foundation

Brugada syndrome is characterized by ST-segment elevation in the right precordial leads and a high incidence of sudden death because of ventricular fibrillation (VF) in patients with no demonstrable structural heart disease (1,2).

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Experimental studies indicate that phase 2 re-entry leads to the development of a closely coupled extrasystole capable of triggering a circus movement re-entry (3,4); however, the factors degenerating it into VF and maintaining the fibrillatory activities, which also may be the background making sustained VF inducible during electrophysiologic study, have not been fully 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 (5–7) or clinical studies (8,9) indicates that the maximum slope of the ventricular action potential duration (APD) restitution curve, which portrays the relationship between the local APD and preceding diastolic interval (DI), reflects the propensity for VF. If the slope of the restitution function at a short DI exceeds the unity, small changes in the DI can produce large fluctuations in the APD and refractoriness (6,10), which may lead to functional gradients in the repolarization that may promote conduction block and wavebreak of re-entrant wavefronts (11).

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To our knowledge, no prior clinical study has systemically examined the clinical relevance of the repolarization restitution property to sustained VF in patients with Brugada syndrome. The purpose of this prospective study was to test the hypothesis that a steep repolarization restitution slope would contribute to the inducibility of sustained VF in patients with a Brugada-type electrocardiogram undergoing programmed electrical stimulation (PES). To examine this hypothesis, we used the activation recovery interval (ARI) determined by the unipolar electrogram, which has been shown to be closely correlated with the monophasic action potential recordings (12,13), as a substitution for the APD.

Methods

Study population. The present study included 21 patients (19 men, mean age 43 ± 9 years) with suspected Brugada syndrome because of the ST-segment elevation in the right precordial leads, who were referred for arrhythmia risk stratification (14,15). Table 1 shows clinical and electrocardiographic characteristics in each of the 21 patients. No patients experienced aborted sudden cardiac death. Two patients had had syncopal events. A type 1 Brugada electrocardiogram characterized by a coved type ST-segment elevation displaying a J-wave amplitude or ST-segment elevation of ≥0.2 mV (15) was observed spontaneously in 16 patients and after an intravenous administration of ajmaline in 5 patients. Written informed consent was obtained in all patients prior to the electrophysiologic study.

Electrophysiologic study. The electrophysiologic study was performed in a fasting state, without using any drugs. Two 6-F quadripolar catheters were positioned in the right atrium and right ventricle under fluoroscopic guidance. The intracardiac electrocardiograms along with the 12-lead body-surface electrocardiograms were continuously recorded with a Prucka Cardio Lab system (GE Medical Systems, Houston, Texas). Unipolar and bipolar electrograms were filtered at a band-pass of 0.05 to 500 Hz and that of 30 to 500 Hz, respectively. PES was performed with a cardiac stimulator (UHS20, Biotronik, Germany) by use of a 2-ms rectangular impulse at twice the late diastolic pacing threshold. PES to assess the ARI restitution was at first performed, and then, PES to induce VF was delivered from the right ventricular apex (RVA) and right ventricular outflow tract (RVOT), consisting of an 8-beat drive train at 2 different cycle lengths (600 and 400 ms) followed by up to 3 ventricular extrastimuli delivered at progressively premature coupling intervals down to 200 ms or until the ventricular refractory period was reached.

ARI restitution. Activation recovery interval restitution was measured at the RVA in all patients and also at the RVOT in the last 17 patients. Constant pacing was performed for 2 min at cycle lengths of 750 ms, 600 ms, and

Abbreviations and Acronyms

ANOVA = analysis of variance
APD = action potential duration
ARI = activation recovery interval
BCL = basic drive cycle length
DI = diastolic interval
PES = programmed electrical stimulation
RVA = right ventricular apex
RVOT = right ventricular outflow tract
VF = ventricular fibrillation

Table 1 Clinical and Electrocardiographic Characteristics of the Study Population

Patient #	Age, yrs	Gender	Syncopal History	Family History of SCD	Spontaneous Type 1 ECG	Maximum ST-Segment Elevation, mV
1	36	Male	No	No	Yes	0.2
2	56	Male	No	Yes	No	0.1
3	59	Male	No	No	Yes	0.4
4	40	Male	No	Yes	Yes	0.2
5	50	Female	Yes	No	No	0.3
6	39	Male	No	No	Yes	0.4
7	19	Male	No	Yes	Yes	0.2
8	55	Male	No	No	Yes	0.2
9	58	Male	No	No	Yes	0.2
10	47	Male	No	No	Yes	0.2
11	41	Male	No	No	No	0.1
12	44	Male	No	No	Yes	0.3
13	42	Male	No	Yes	Yes	0.4
14	31	Female	Yes	No	No	0.1
15	39	Male	No	No	Yes	0.3
16	38	Male	No	No	Yes	0.3
17	36	Male	No	No	Yes	0.5
18	48	Male	No	Yes	No	0.1
19	49	Male	No	No	Yes	0.3
20	39	Male	No	No	Yes	0.4
21	44	Male	No	Yes	Yes	0.3

ECG = electrocardiogram; SCD = sudden cardiac death.

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400 ms. A basic drive cycle length (BCL) of 750 ms could not, however, be delivered in 6 patients because of faster sinus rate. After a steady state had been established, an extrastimulus (S2) was introduced after a 10-beat drive train (S1). The coupling interval of the S1 to S2 was decremented by 10 ms every cycle from the steady state until refractoriness. The stimulation was delivered using the distal pair of a quadripolar catheter, and the third electrode, with an interelectrode distance of 5 mm from the second electrode, was used to record the unipolar electrogram used for measuring the ARI.

The unipolar recording data were extracted digitally to a personal computer with 1,000-Hz temporal and 0.01-mV amplitude resolutions, and a derivative plot of the electrograms was obtained using commercially available spreadsheet software (Microsoft Excel 2003, Seattle, Washington). The ARI was measured between the time of the minimum dV/dt of the QRS and minimum dV/dt of the positive T wave or maximum dV/dt of the negative T wave (alternative method) (Figs. 1A to 1C) (12). The DI between S1 and S2 was defined as the interval from the end of the ARI of S1 to the beginning of the ARI of the succeeding S2. At shorter S1-S2 coupling intervals, the DI cannot be directly measured because the S2 obscures the assessment of the ARI of S1. In such a case, the ARI of the preceding S1 of the drive train was used to calculate the DI (16). The ARIs of the S2 after an abrupt shortening of the S2 coupling interval were plotted against the preceding DI as restitution curves (Fig. 1D). For each ARI restitution curve, the slopes were determined using a least-squares linear fit to the overlapping 40-ms segments of the DI commencing from the shortest DI range that contained data points. This stepwise linear-fit method was described in detail by Taggart et al. (9) and is considered to be more robust than fitting a single function such as an exponential, polynomial, or sigmoid. The maximum ARI restitution slopes at each pacing site and BCL were compared between the patients with and without inducible VF.

Paced-QRS duration. Paced-QRS duration during premature stimulation was measured from the 12-lead surface electrocardiogram using digital on-screen calipers of Prucka Cardio Lab system at a speed of 100 mm/s and compared between the premature beat with the longest and shortest ARI constituting the data points of the maximum ARI restitution slopes (points C and A in Fig. 1D).

Statistical analysis. The data are expressed as the mean ± standard deviation for continuous variables and as the frequency for categorical variables. Differences between the patients with and without inducible VF were compared with an unpaired *t* test for continuous variables and by the Fisher exact test for categorical variables. Differences in the restitution slope at a BCL of 750 ms, however, were compared with the Mann-Whitney *U* test because of the small number of patients. Differences in the continuous data over each of the 3 constant BCLs were compared with an analysis of variance (ANOVA) for repeated measures. The paired *t* test was used to compare the steepness of the restitution slope in the RVA with that in the RVOT. All tests were 2-sided, and a p value <0.05 was considered statistically significant. The statistical analysis was conducted using StatView 5.0 (SAS Institute Inc., Cary, North Carolina).

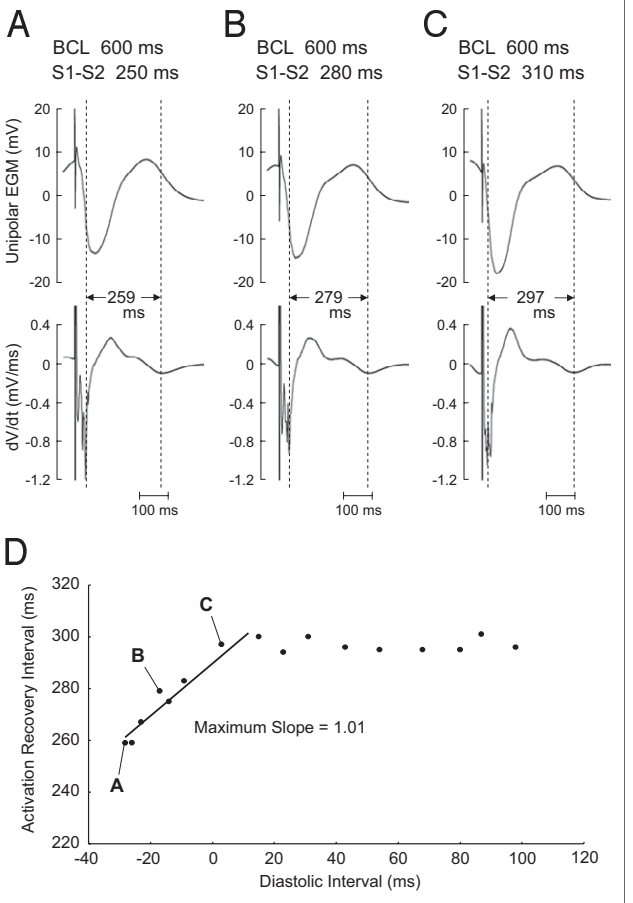

Figure 1 **Measurement of ARI and Maximum Slope of Repolarization Restitution Curve**

(A to C) Unipolar electrograms (EGMs) and their first derivatives (dV/dt) of the S2 at S1 to S2 intervals of 250 ms, 280 ms, and 310 ms with a basic drive cycle length (BCL) of 600 ms are shown. The activation recovery interval (ARI) is the interval between the minimum dV/dt of the QRS and minimum dV/dt of the T wave (between the **two dashed lines**). **(D)** The ARI restitution curve is constructed by plotting the ARIs of the S2 against the preceding diastolic intervals. The least-squares linear fit to the 40-ms diastolic interval with the maximum slope is shown. **A, B, and C** of the curve correspond to the ARIs in **A**, **B**, and **C**, respectively.

Results

The ARI in the RVA and RVOT. In all the patients, the unipolar electrogram at the recording site demonstrated a positive T-wave morphology as shown in Figures 1A to 1C. Table 2 shows the ARI of the S1 and S2 at the shortest S1-S2 coupling intervals at the 2 right ventricular sites at each of the 3 BCLs. The ARI was prolonged along with the increase in the BCL (p = 0.001). The ARI measured at the

Table 2 The ARI of the S1 and S2 at the 2 Right Ventricular Sites

	S1			S2 at the Shortest S1-S2 Interval		
	BCL 400	BCL 600	BCL 750	BCL 400	BCL 600	BCL 750
ARI at RVA, ms	265 ± 19	286 ± 19	309 ± 21	218 ± 16	240 ± 18	255 ± 19
ARI at RVOT, ms	263 ± 18	286 ± 18	311 ± 19	223 ± 17	242 ± 22	255 ± 14

ARI = activation recovery interval; BCL = basic drive cycle length; RVA = right ventricular apex; RVOT = right ventricular outflow tract.

2 right ventricular sites was similar at each BCL for both S1 and S2.

Inducibility of VF. Among all 21 patients, VF was induced in 10 (48%). No difference was observed in the clinical background between the patients with and without inducible VF (Table 3). The degree of the maximum ST-segment elevation in the right precordial leads before pacing showed a nonsignificant trend toward higher values in the patients with inducible VF.

Restitution slopes for the patients with and without inducible VF. Figure 2 compares the maximum ARI restitution slope between the patients with and without inducible VF at each BCL and pacing site. The slope obtained from the RVA was significantly steeper in the patients with inducible VF than in those without at BCLs of 600 ms (0.88 ± 0.12 vs. 0.73 ± 0.12; p = 0.01) and 750 ms (1.02 ± 0.15 vs. 0.78 ± 0.07; 2-tail Mann-Whitney *U* test, p = 0.01) but was similar at a BCL of 400 ms (0.69 ± 0.19 vs. 0.61 ± 0.14; p = 0.29) (Fig. 2A). The maximum slope in the RVOT was similar between the 2 groups at BCLs of 400 ms (0.61 ± 0.11 vs. 0.55 ± 0.12; p = 0.31) and 600 ms (0.72 ± 0.12 vs. 0.66 ± 0.14; p = 0.32) but was significantly steeper in the patients with inducible VF at a BCL of 750 ms (0.91 ± 0.13 vs. 0.71 ± 0.12; 2-tail Mann-Whitney *U* test, p = 0.04) (Fig. 2B).

A repeated measure ANOVA including maximum slopes of all 21 patients at BCLs of 400 and 600 ms in the RVA revealed that the slope was significantly steeper in patients with inducible VF than in those without (p = 0.03). The same analysis including the slopes of 15 patients who underwent PES at all 3 BCLs in the RVA also revealed that the slope was significantly steeper in patients with inducible VF (p = 0.002). On the other hand, a repeated-measure ANOVA including maximum slopes of 17 patients at BCLs of 400 and 600 ms in the RVOT showed that the slope was similar between the patients with and without inducible VF (p = 0.27), and the same analysis including the slopes of 11 patients who underwent PES at all 3 BCLs in the RVOT also showed the similar results (p = 0.16). All of these 4 analysis showed that the maximum slope was significantly steeper at longer BCLs (p < 0.001).

In the patients with inducible VF, a slope >1 in the RVA was observed in none, 2 of 10 patients (20%), and 6 of 8 patients (75%) at BCLs of 400 ms, 600 ms, and 750 ms, respectively, whereas a slope >1 in the RVOT was observed in none at BCLs of 400 and 600 ms and in 1 of 7 patients (14%) at a BCL of 750 ms (Fig. 2). No patient without inducible VF had a slope >1 at any of the BCLs and pacing sites.

Spatial heterogeneity in the restitution slopes. The maximum ARI restitution slope was significantly steeper in the RVA than RVOT at a BCLs of 600 ms (0.82 ± 0.13 vs. 0.69 ± 0.13; p = 0.01) and 750 ms (0.93 ± 0.18 vs. 0.84 ± 0.16; p = 0.02), but the difference did not reach a statistical significance at a BCL of 400 ms (0.66 ± 0.17 vs. 0.58 ± 0.11; p = 0.08). Conversely, the dispersion of the maximum restitution slope, defined as the absolute difference in the slope between the RVA and RVOT, was not different between the patients with and without inducible VF at any of the BCLs.

Table 3 Clinical and Electrocardiographic Characteristics of the Patients With and Without Inducible VF

	VF Inducible (n = 10)	VF Noninducible (n = 11)	p Value
Age, yrs	44 ± 7	43 ± 12	0.91
Male gender	9 (90%)	10 (91%)	1.00
Syncopal history	1 (10%)	1 (9%)	1.00
Family history of sudden cardiac death	2 (20%)	4 (36%)	0.64
Spontaneous type 1 electrocardiogram	9 (90%)	7 (64%)	0.31
Maximum ST-segment elevation in V_1 to V_3, mV	0.31 ± 0.10	0.22 ± 0.12	0.07
PQ interval, ms	182 ± 18	175 ± 15	0.35
QRS duration, ms	108 ± 8	104 ± 11	0.33
Corrected QT interval, ms	416 ± 12	425 ± 13	0.12
HV interval, ms	48 ± 8	49 ± 7	0.71

VF = ventricular fibrillation.

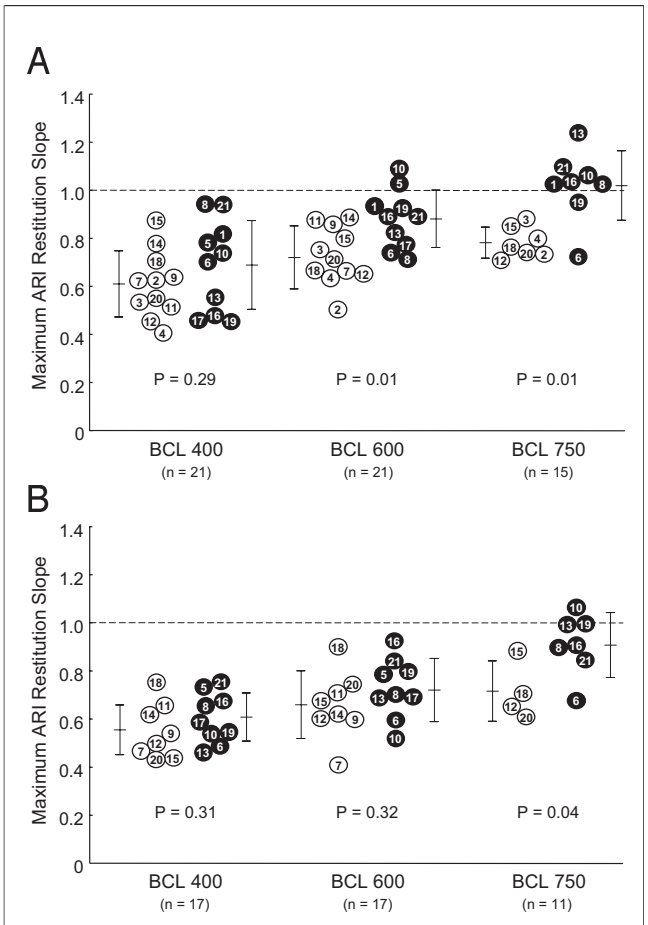

Figure 2 Comparison of Maximum ARI Restitution Slopes

The maximum activation recovery interval (ARI) restitution slopes at each of the 3 basic drive cycle lengths (BCLs) in the right ventricular apex **(A)** and outflow tract **(B)** are compared between the patients with **(filled circles)** and without inducible ventricular fibrillation **(unfilled circles)**. The number written in the circle corresponds to the patient number in Table 1. The **dashed line** indicates the ARI of the unity.

Prolongation of paced-QRS duration. Table 4 shows paced-QRS duration of the premature beats with the longest and shortest ARI used to draw the maximum restitution slope, in the RVA. The prolongation of QRS duration observed when shortening the S1-S2 interval was significantly greater in the patients with inducible VF than in those without at BCLs of 600 and 750 ms.

Discussion

Repolarization restitution slopes and the propensity for ventricular arrhythmias. The present study compared the steepness of the maximum ARI restitution slope between the patients exhibiting a type 1 Brugada electrocardiogram with and without inducible VF. The results showed that the inducibility of VF was associated with steeper repolarization restitution properties. Recent studies (8,9,16–18) have examined the repolarization restitution slope in the clinical setting, and some of those have shown that the steepness of the maximum slope was greater in the patients with inducible ventricular tachycardia (16,17) or had a more significant risk for sudden cardiac death (16) than in those without. To date, no study has systemically compared the repolarization restitution slope in the patients with spontaneous or inducible VF.

Theoretically, if the APD restitution slope exceeds the unity, the wavelength oscillations are self-amplifying and the DI becomes too short for the wave to propagate, resulting in conduction block and wavebreak (10,11). In the present study, the maximum ARI restitution slope was shown to be steeper at longer BCLs, and a slope >1 in the RVA was observed in 75% of the patients with inducible VF at BCL = 750 ms. Conversely, Xie et al. (19) reported that an APD restitution slope >1 might not always be necessary to produce wave break under the condition that a spatial heterogeneity of those slopes exists. In the present study, the dispersion between the two right ventricular sites was not different between the patients with and without inducible VF. However, other regions, including the left ventricle, might demonstrate a greater heterogeneity of the restitution slope (18,20).

Mechanism of VF in Brugada syndrome. Experimental Brugada syndrome models have demonstrated that a local re-excitation called phase 2 re-entry captured the vulnerable window and triggered a circus movement re-entry (3,4). It, however, has remained unclear whether this circus movement re-entry degenerates into sustained VF without any specific factors. Although an autonomic imbalance, fever, hypokalemia, and some drugs are thought to be precipitating factors for VF in Brugada syndrome (15), it has not been clarified whether they actually contribute to the degeneration into VF and its maintenance or merely increase the

Table 4 QRS Duration at Premature Beats in the RVA

	VF Inducible			VF Noninducible		
	QRS Duration (ms)			QRS Duration (ms)		
	At the Longest ARI	At the Shortest ARI	QRS Prolongation	At the Longest ARI	At the Shortest ARI	QRS Prolongation
BCL 400	154 ± 16	167 ± 16	13 ± 5	147 ± 10	157 ± 11	10 ± 5
BCL 600	153 ± 12	170 ± 14	17 ± 5	152 ± 11	161 ± 13	10 ± 6*
BCL 750	157 ± 10	178 ± 14	21 ± 8	154 ± 7	167 ± 7	13 ± 6*

*$p < 0.05$ versus VF inducible.

ARI = activation recovery interval; BCL = basic drive cycle length; VF = ventricular fibrillation; other abbreviations as in Table 2.

chance of the initial trigger. On the other hand, electrophysiological studies are widely performed in patients with Brugada syndrome (15), and the inducibility of sustained VF is reported to be a strong predictor of sudden cardiac death or spontaneous VF (14). This result indicates that the background leading a repetitive ventricular response provoked by PES into sustained VF also might be responsible for the degeneration of the spontaneous circus movement re-entry into sustained VF. We assessed the repolarization restitution property directly before the induction of VF, and demonstrated that the maximum restitution slope in the RVA is significantly steeper in the patients with inducible VF. Further, the slope was steeper in the RVA than RVOT. These results may indicate that the RVA region plays an important role for the degeneration into sustained VF in the Brugada syndrome, although spontaneous premature contractions triggering circus movement re-entry mostly develop in the RVOT (21). It is noteworthy that steep maximal repolarization restitution slope has been recently reported in a patient exhibiting type 1 Brugada electrocardiogram with inducible VF (22).

Transmural dispersion of repolarization in the RVOT has been shown to contribute to initial repetitive excitations during ventricular tachycardia (VT) in an experimental Brugada syndrome model (3,4). However, the 2 mechanisms are not necessarily exclusive and it is tempting to hypothesize that functional re-entrant substrate due to dispersion of repolarization lead to polymorphic VT/VF but that perpetuation may depend on other ventricular properties such as ventricular restitution properties.

Steeper restitution slope in Brugada syndrome with inducible VF. 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-positive initial membrane voltage resulting from incomplete sodium channel activation diminishes the following L-type calcium channel activity, which is responsible for the action potential plateau, and foreshortens the APD (23). In Brugada syndrome, mutations in the cardiac sodium channel gene SCN5A have been found and shown to result in a loss of the channel function (24), and several experimental studies (25,26) have demonstrated a significantly more delayed recovery of the sodium channel after a short DI because of a enhanced "slow" inactivation in the cells with a mutant SCN5A channel than in those without. In Brugada syndrome, in case of premature beats with a very short DI, the degree of the curtailment of the action potential plateau would be related to the severity of reduced sodium channel activity. In our data, we observed a larger QRS duration prolongation when decreasing the S1 to S2 coupling interval in patients with inducible VF than in those without. It is thus tempting to speculate that the difference in the maximum repolarization restitution slope in the patients with and without inducible VF in the present study might be directly or indirectly related to the difference in the degree of the reduced sodium channel activity. In addition, we found a nonsignificant trend toward a greater ST-segment elevation in the patients with inducible VF than in those without. This difference in the degree of the ST-segment elevation during sinus rhythm might reflect the difference in degree of a reduced sodium channel activity. There was, however, not correlation between ST elevation and restitution slope (data not shown).

Methodological considerations for the steepness of the repolarization restitution slope. The value of the maximum slope of the repolarization restitution curve in the clinical studies varies, and the discrepancy seems attributable to methodological differences. Yue et al. (18) showed that the mean slope in the right ventricle measured at a BCL of 400 ms was 0.65 ± 0.26 in the patients with a normal cardiac function, which is consistent with that of the present study. Selvaraj et al. (16) reported a mean slope of 0.59 ± 0.19 at a BCL of 500 ms in the patient group considered at low risk for sudden cardiac death, which also is comparable with that shown in our patients without inducible VF. In these two studies, the ARI measured by the alternative method (12) was used as a substitution for the APD, and the maximum slope was determined by means of a least-squares linear fit to the overlapping 40-ms segments of the DI, both of which were adopted in the present study. On the other hand, 2 studies (17,20) observed a mean slope >1 in the right ventricle at a BCL of 600 ms in the patients without ventricular tachyarrhythmias. These studies used a monoexponential equation to decide the maximum restitution slope, which is not always considered suitable for modeling the cardiac restitution data (9). Further, the authors in one of these studies (20) used the Wyatt method for measuring the ARI, which has been shown to underestimate the ARI and exhibit a greater difference from the monophasic APD than the alternative method (12,13).

Study limitations. This study has several limitations. First, we recorded the electrograms at only 2 right ventricular sites. The regional differences in the repolarization restitution slopes have been demonstrated by mapping of the entire cardiac chamber using a noncontact balloon array (18) or multielectrode epicardial sock (20). The patients in the present study, however, just required PES for the risk stratification regarding Brugada syndrome, in which a high resolution spatial mapping system was inapplicable. Second, no clinical follow-up data was shown in the present study. Although it might provide information about the prognostic value of the repolarization restitution slope, it is not the purpose of the present study which aimed to elucidate the contribution of the repolarization restitution property in sustained VF.

Conclusions

The present study suggested that the repolarization restitution property is a contributing factor to the propensity for VF in Brugada syndrome. The maximum ARI restitution slope in the RVA was steeper in the patients with inducible VF than in

those without, but the slope in the RVOT was similar. A slope >1 was observed in none of the patients without inducible VF, but in 70% of the patients with inducible VF. Regarding the repolarization restitution property, the RVA may play more important role than the RVOT.

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