Right Ventricular Histological Substrate and Conduction Delay in Patients With Brugada Syndrome

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SUMMARY

The reported pathogenesis of Brugada syndrome is phase 2 reentry resulting from shortening of the epicardial action potential duration at the right ventricular outflow tract (RVOT). However, several studies have revealed a high incidence of ventricular late potentials and high rate of ventricular fibrillation (VF) induced by programmed ventricular stimulation (PVS). The aim of the present study was to evaluate the role of slow conduction at the RVOT for the initiation of VF by PVS and any underlying pathological conditions in Brugada syndrome. Endocardial mapping of the RVOT and endomyocardial biopsy of the right ventricle were performed in 25 patients with Brugada syndrome with inducible VF. Late potentials were positive in 11 of the 25 (44%) patients. Low-amplitude fragmented and delayed electrograms were recorded at the RVOT in 13 of 18 (72.2%) patients. Histologic examination of the biopsy samples revealed fatty tissue infiltration, interstitial fibrosis, lymphocyte infiltration, and/or myocyte disorganization in 13 patients. Slow conduction at the RVOT may contribute to the induction of VF by PVS in Brugada syndrome. Various pathomorphologic changes may contribute to slow conduction at the RVOT. (Int Heart J 2010; 51: 17-23)

Key words: Brugada syndrome, Electrophysiologic study, Delayed potential, RV biopsy

Since its identification as a clinical entity, Brugada syndrome has gained worldwide recognition as an important cause of sudden death.^{1,2)} SCN5A gene, which encodes the cardiac sodium channel, has been proven to be involved in 20-30% of cases, and the disease is inherited in an autosomal dominant fashion.^{3,4)} Its signature is ST segment elevation in right precordial ECG leads and predisposition to malignant ventricular tachyarrhythmias. The two hypotheses on the mechanism of Brugada syndrome that currently receive the widest support from clinical and experimental studies are 1) heterogeneous abbreviation of right ventricular epicardial action potentials (“repolarization disorder”)⁵⁾ and 2) conduction delay in the right ventricular outflow tract (“depolarization disorder”).⁶⁻¹⁰⁾ Moreover, recent studies suggest that other derangements may contribute to the pathophysiology of Brugada syndrome, in particular right ventricular structural derangements.¹¹⁾

The aim of this study was to determine whether concealed cardiac abnormalities are present in patients with Brugada syndrome by identifying pathological findings from right ventricular endomyocardial biopsy specimens obtained from patients with the syndrome.

METHODS

Subjects: Twenty-four men and 1 woman (age, 51.0 ± 13.7

years, range, 27 - 73 years) with Brugada syndrome who were admitted to Nihon University Hospital for electrophysiologic study between 1996 and 2007 were enrolled in the study. All had inducible ventricular fibrillation (VF). The diagnosis of Brugada syndrome was based on typical electrocardiographic patterns (persistent or transient right precordial ST-segment elevation with or without atypical right bundle branch block).¹²⁾ Nine patients had episodes of syncope or aborted sudden cardiac death, and 16 were asymptomatic. Three patients had family history of sudden cardiac death (Table I). Routine studies, including cardiac echocardiography and radionuclide imaging, showed no evidence of structural heart disease in any patient.

Signal-averaged electrocardiography: A ventricular signal-averaged electrocardiogram (ART 1200 EPX signal-averaged ECG apparatus, Arrhythmia Research Technology Inc., Austin, TX, USA; noise level $< 0.3 \mu\text{V}$, a bidirectional 4-pole Butterworth high pass filter 40 Hz) was recorded in all patients. A positive late potential (LP) characterizing Brugada syndrome is defined in our institution as a root mean square voltage of the last 40 msec $< 20 \mu\text{V}$.^{13,14)}

Cardiac catheterization: All patients underwent cardiac catheterization, coronary angiography, and left and right ventricular angiography.

Electrophysiologic study: All patients gave informed consent for participation in the electrophysiologic study and for endomyocardial biopsy, which were approved by the

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Table I. Patient Characteristics

Patient	Age (years)	Sex	FH	ECG Type	Symptom	LP
1	27	M	+	I	-	+
2	39	M	-	III	Syncope	-
3	45	M	-	I	-	-
4	54	M	-	II	-	-
5	42	M	-	III	Syncope	-
6	53	M	-	III	Syncope	+
7	68	M	+	II	Syncope	-
8	33	M	-	I	-	+
9	54	M	-	I	Syncope	+
10	66	M	-	I	-	-
11	53	M	+	I	Syncope	-
12	29	M	-	II	-	+
13	50	F	-	I	-	-
14	73	M	-	II	-	-
15	64	M	-	III	-	-
16	54	M	-	II	-	-
17	43	M	-	III	CPA	+
18	43	M	-	III	CPA	+
19	61	M	-	III	-	+
20	45	M	-	III	-	+
21	28	M	-	II	-	-
22	65	M	-	II	-	-
23	58	M	-	I	-	+
24	76	M	-	I	Syncope	+
25	52	M	-	I	-	-

FH indicates family history of sudden death; LP, late potential; and CPA, cardiopulmonary arrest.

Table II. Electrophysiologic Data

Patient	VF induction	RV endo-cardial DP	Therapy	F/U (months)
1	RVA	(+)	None	1*
2	RVOT	(-)	Cib, Amio	131
3	RVOT	(+)	Amio	126
4	RVOT	(+)	Amio	107
5	RVOT	(-)	Amio	89
6	RVA	(+)	Amio	89
7	RVOT	(-)	ICD	87
8	RVA	(-)	Amio	78
9	RVA, RVOT	(+)	None	69
10	RVA, RVOT	(+)	None	67
11	RVOT	(-)	ICD	63
12	RVA	NA	None	89
13	RVOT (S4)	NA	None	67
14	RVOT (S4)	(+)	None	58
15	RVOT (S4)	NA	None	55
16	RVOT (S4)	(+)	None	58
17	RVOT	(+)	ICD	61
18	RVOT (S4)	NA	ICD	49
19	RVOT	NA	None	49
20	RVOT	(+)	ICD	46
21	RVOT	NA	ICD	53
22	RVOT	(+)	ICD	41
23	RVOT	(+)	None	47
24	RVOT	(+)	ICD	35
25	RVOT	NA	None	32

DP indicates delayed potential; Cib, cibenzoline; Amio, amiodarone; and F/U, follow-up. *means sudden cardiac death.

Clinical Research Committee of Nihon University Hospital. All studies were conducted with patients in the fasting, drug-free state and sedated with midazolam and fentanyl, and programmed electrical stimulation was performed with conventional intracardiac recording and stimulation.¹⁵⁾ A quadripolar catheter and an octapolar catheter were inserted percutaneously through the right femoral vein and advanced under fluoroscopic guidance, initially to the right atrial appendage and the His-bundle region. One steerable catheter was inserted through the left femoral vein and advanced to the right ventricular apex (RVA). Electrophysiologic study included basal measurement of the conduction interval and programmed ventricular stimulation (PVS). The atrio-His interval and the His-ventricular interval were measured during sinus rhythm. The protocol specified 2 sites of ventricular stimulation (the RVA and RVOT), 2 basic cycle lengths (600 and 400 ms), and 1 to 3 ventricular premature beats (S2 down to an effective refractory period and S3 and S4 down to a minimum of 190 ms). At each basic cycle length, programmed stimulation at the RVA was performed first. Ventricular arrhythmia was considered inducible if a sustained ventricular arrhythmia (VF, polymorphic ventricular tachycardia, or monomorphic ventricular tachycardia lasting > 30 seconds or requiring emergency intervention) resulted. A local bipolar electrogram with a 30-500-Hz bandwidth at the right ventricular endocardium was mapped to record delayed potentials (DPs) during sinus rhythm in 18 patients with the use of a quadripolar 6F deflectable catheter (EP Technologies, San Jose, CA, USA) by moving the catheter that had been placed at the right atrial appendage. DPs were defined as fragmented local electrograms lasting more than

30 ms after termination of the QRS complex.

Endomyocardial biopsy: Endomyocardial biopsy samples were obtained from the upper septal region of the right ventricle (1 to 3 samples per patient). Myocardial specimens were fixed in 10% buffered formalin and embedded in paraffin for histologic analysis. Five micron-thick sections were stained with haematoxylin and eosin and examined by light microscopy. Fatty infiltration and interstitial fibrosis were examined at $\times 30$ magnification, myocyte hypertrophy, myocyte degeneration, and arrangement disorder were examined at $\times 100$ magnification, and inflammatory cell infiltration was examined at $\times 250$ and $\times 400$ magnifications.

Statistical analysis: All values are expressed as the mean $\pm$ standard deviation (SD). A *P* value of less than 0.05 was considered statistically significant. StatView 5.0 software (SAS Institute, Cary, NC, USA) was used for data analysis.

RESULTS

Electrocardiographic characteristics: Clinical characteristics of the patients are summarized in Table I. The ECG patterns of all patients were diagnostic for Brugada syndrome: spontaneous type 1 ECG pattern, 10 patients (40%); type 2 ECG pattern, 7 patients (28%); and type 3 ECG pattern, 8 patients (32%).¹²⁾ In the 7 patients with a type 2 ECG pattern and 8 patients with a type 3 pattern, the ECG changed to a typical type 1 pattern after intravenous administration of pilsicainide (1 mg/kg in 10 minutes).¹⁶⁻¹⁸⁾ The mean QRS duration was 110.8 ± 21.6 ms. No patient had any features of arrhythmogenic right ventricular cardiomyopathy such

as T wave inversion in V1-V3, ventricular ectopy of right ventricular origin, ventricular tachycardia, family history of heart failure, or heart block.

Signal-averaged ECG: According to signal-averaged ECGs, late potentials were positive in 11 (44%) of the 25 patients.

Cardiac catheterization and angiography: No left or right ventriculographic abnormality was found in any patient and the coronary angiography findings were normal in all patients.

Electrophysiologic characteristics: Electrophysiologic data are shown in Table II. The atrio-His and His-ventricular intervals during sinus rhythm were 97.0 ± 18.1 ms (70 -131 ms) and 53.8 ± 13.9 ms (30 -100 ms), respectively. VF was induced by 2 extrastimuli from the RVA in 4 patients in whom RVOT programmed pacing was not performed, from both the RVA and RVOT in 2 patients, and only from the RVOT in 14 patients, and by 3 extrastimuli from the RVOT in 5 patients. DPs were recorded from the RVOT in 13 of 18 patients (72.2%) (Figure 1). Late potentials were positive in 7 of the 13 patients with positive DPs (53.8%) and in 1 of the 5 patients without DPs (20.0%).

Histology: Histopathologic data are summarized in Table III. Moderate (++) to severe (+++) fatty infiltration, myocyte degeneration, fibrosis, and mild (+) lymphocyte infiltration were considered to be abnormal findings. Moderate (++) to severe (+++) fatty infiltration was observed in 5 patients (Figure 2). Other pathologic changes such as myocyte degeneration (++) , fibrosis (++) , and lymphocyte infiltration (+) were observed in 4, 4, and 4 patients, respectively (Figures 3, 4, and 5), but we did not detect inflammatory tissue changes. We were unable to find any correlation between

clinical phenotype (syncope, aborted sudden death) and electrophysiologic characteristics (ECG type, inducibility of VF, right ventricular endocardial DP) of Brugada syndrome and endomyocardial biopsy findings. However, 1 patient (patient 1) with a family history of sudden death, Brugada type 1 ECG, positive late potential, and endocardial DPs

Figure 1. Surface electrocardiographic leads II and V1, intracardiac electrograms from free wall side of the right ventricular outflow tract (RVOT), right ventricular inflow tract, and right ventricular apex (RVA) of patient 1 during sinus rhythm. Note the delayed potentials recorded from the RVOT.

Table III. Histologic Findings

Patient	Myocyte hypertrophy	Myocyte degeneration	Arrangement disorder	Fatty infiltration	Interstitial fibrosis	Inflammatory cell infiltration
1	+	++	++		++	
2		+	+	++	++	
3		+				
4	+	+	+		++	
5	+	+	+		+	
6		++	+		++	
7		+	+		+	
8	+	++	++		+	+
9		++	++	+	+	
10	+	+	+	+		
11		+	+	++		
12		+	++	++	+	
13		+	+	+++	+	
14		+	++		+	+
15		+	+		+	
16				+		
17				+	+	
18	+	+				
19	+	+				
20		+	+		+	+
21						
22		+		++	+	
23	+	+				
24				+		
25	+				+	+

+ indicates mild change; ++, moderate change; and +++, severe change.

Patient 11

Figure 2. Histopathologic section of the right ventricular septum of patient 11. Haematoxylin and eosin stain ($\times 20$). Note the moderate fatty infiltration.

Patient 4

Figure 4. Histopathologic section of the right ventricular septum of patient 4. Haematoxylin and eosin stain ($\times 20$). Note the marked fibrosis of the myocardium.

Patient 1

Figure 3. Histopathologic section of the right ventricular septum of patient 1. Haematoxylin and eosin stain ($\times 40$). Note the myocyte hypertrophy, myocyte degeneration, interstitial fibrosis, and disordered arrangement.

in the RVOT died suddenly. His endomyocardial biopsy specimen showed myocyte degeneration (++), arrangement disorder (++), and moderate interstitial fibrosis (++) (Figures 1 and 3).

Treatment and follow-up: Eight patients received an implantable cardioverter defibrillator (ICD), 6 patients were treated with antiarrhythmic drugs, and 11 patients did not receive any antiarrhythmic treatment (Table II). Patients were followed-up by physical examination, resting electrocardiography, Holter monitoring, 2D echocardiography, and ICD data (for arrhythmic events) retrieval monthly for the first 6 months and every 3 months thereafter. At a median follow-up time of 61.0 months and interquartile range of 39.0 months (range, 1 to 131 months), ICD data retrieval revealed no major arrhythmic event in any patient. One pa-

Patient 8

Figure 5. Histopathologic section of the right ventricular septum of patient 8. Haematoxylin and eosin stain. (A) shows myocardial fiber disarray ($\times 40$), and (B) shows mononuclear cell infiltration ($\times 400$).

tient who refused an ICD died suddenly during the follow-up period, whereas no major arrhythmic event occurred in any of the other patients who did not receive an ICD. In 3 symptomatic patients (patients 2, 5, 6) and 3 asymptomatic patients (patients 3, 4, 8), amiodarone was used for treatment because these patients refused an ICD and the usefulness of quinidine treatment was not well recognized.¹⁹⁾

DISCUSSION

Main findings: In this study, cardiac myocyte hypertrophy ($\geq ++$), myocyte degeneration ($\geq ++$), disordered myocyte arrangement ($\geq ++$), fatty infiltration ($\geq ++$), interstitial fibrosis ($\geq ++$), or inflammatory cell infiltration ($\geq +$) were found from biopsy samples taken in the right ventricular septum in 13 of 25 (52%) patients with Brugada syndrome, and LPs were positive in 6 of 13 (46%) of these patients. However, LPs were positive in 5 of 12 (42%) patients with mild histologic findings. DPs were positive in 7 of 10 (70%)

patients with abnormal histologic findings, but DPs were positive in 6 of 8 (75%) patients with mild histologic findings.

Histology: We have reported that clinically recognized Brugada syndrome may not be a single disease entity and that arrhythmogenic right ventricular cardiomyopathy-like fatty tissue infiltration was seen in at least 30% of cases in a multicenter study.²⁰⁾ Several studies also revealed histologic abnormalities (fatty infiltration, fatty replacement, fibrofatty replacement) in the right ventricle and suggested an overlap between Brugada syndrome and arrhythmogenic right ventricular cardiomyopathy.^{6,21-27)} Recently, Coronel, *et al*¹⁰⁾ reported on the histopathologic and electrophysiologic characteristics of the heart of a 44-year-old man with genetically proven Brugada syndrome who underwent heart transplantation because of untreatable VF storms. Activation slowing and fractionated electrograms were recorded in the region of the RVOT where histopathologic examination showed epicardial fatty infiltration and extensive fibrosis. Moreover, Frustaci, *et al*²⁸⁾ examined the histopathologic substrate in patients with the clinical phenotype of Brugada syndrome by analyzing biventricular endocardial biopsy samples and found prevalent or localized right ventricular myocarditis with detectable viral genomes, right ventricular fibrofatty infiltration, and cardiomyopathic changes. Zumhagen, *et al* uncovered moderate but uncharacteristic cardiac abnormalities in patients with Brugada syndrome.²⁹⁾ In the present study, at least one of the following was observed in almost all cases; myocardial hypertrophy, myocyte degeneration, arrangement disorder, fatty infiltration, interstitial fibrosis, and lymphocyte infiltration. However, we were unable to find any correlation between the clinical phenotype and electrophysiologic characteristics of Brugada syndrome and endomyocardial biopsy findings. Neither were Frustaci, *et al* able to correlate the clinical, ECG, and arrhythmic characteristics with histological abnormalities.²⁸⁾ However, they showed that in 3 of 4 patients who were carriers of the SCN5A gene mutation, myocyte cytoplasm degeneration was present upon histologic examination. Furthermore, histopathological examination of the autopsied heart or heart explanted due to cardiac transplantation in patients with Brugada syndrome or right bundle branch block, right precordial ST-segment elevation revealed marked fatty infiltration in the RVOT or right ventricular anterior wall.^{10,30-32)} In previous animal studies, aged heterozygous SCN5A-knock-out mice showed impaired atrioventricular conduction, delayed intramyocardial conduction, increased ventricular refractoriness, and ventricular tachycardia associated with myocardial rearrangements and fibrosis.^{33,34)} These studies provided evidence that a monogenic ion channel defect can lead progressively to myocardial structural anomalies. With regard to the possible mechanisms that link sodium channel loss of function to cellular damage, it is well established that intracellular sodium homeostasis has a relevant role in myocardial function, because through the action of sodium-hydrogen and sodium-calcium exchangers,³⁵⁾ it may influence the regulation of both intracellular pH and calcium homeostasis,^{35,36)} thus impairing excitation-contraction coupling and energy production mechanisms.

Electrophysiologic abnormalities in the RVOT: There is growing clinical evidence for electrophysiologic/structural

RVOT abnormalities in patients with Brugada syndrome. A high proportion of patients with Brugada syndrome have ventricular tachyarrhythmia inducible only from the RVOT, pointing to the importance of the RVOT as a possible site of origin of ventricular tachyarrhythmias.³⁷⁾ The electrical abnormality is localized in the free wall of the RVOT, as suggested by the frequent origin or induction of ventricular arrhythmia from this region,³⁸⁻⁴¹⁾ and Haissaguerre, *et al*⁴²⁾ showed the importance of focal premature ventricular beats, originating mainly from the RVOT, in triggering VF in patients with Brugada syndrome. Several studies based on noninvasive techniques have shown right ventricular abnormalities in patients with the clinical phenotype of Brugada syndrome. Takagi, *et al*^{43,44)} and Sato, *et al*⁴⁵⁾ revealed right RVOT and right ventricular inferior wall motion abnormalities in patients with Brugada syndrome by means of electron beam computed tomography or magnetic resonance imaging. Alix, *et al*⁴⁶⁾ and Papavassiliou, *et al*⁴⁷⁾ showed regional dyskinesia and adipose tissue infiltration in the right ventricle by means of magnetic resonance imaging. Nagahara, *et al*⁴⁸⁾ reported frequent detection of myocardial abnormalities in the right ventricle by means of right ventricular myocardial scintigraphy (RV-SPECT) and showed that the arrhythmogenic substrate detected by RV-SPECT can contribute to focal repetitive firing, which degenerates nonself-terminating VF induced by PVS. Furthermore, Tukkie, *et al*⁸⁾ demonstrated, using tissue Doppler echocardiography, that the occurrence of a positive response (coved-type ST elevation) after administration of the class Ic antiarrhythmic drug flecainide coincides with delayed onset of right ventricular contraction, that the extent of the delay correlates with the magnitude of ST elevation, and that right ventricular ejection time shortens as the Brugada ECG pattern emerges. Invasive cardiac studies, including coronary and biventricular angiography with endomyocardial biopsy and 3-dimensional electroanatomical mapping may provide relevant diagnostic information but are rarely applied systematically in patients with the clinical phenotype of Brugada syndrome. Corrado, *et al*⁴⁹⁾ and Postema, *et al*⁵⁰⁾ revealed a low-voltage area with fractionated electrograms in the RVOT by 3-dimensional electroanatomic voltage mapping.

Study limitations: We obtained endomyocardial biopsy samples only from the septal region of the right ventricle. Previous postmortem histopathologic studies in sudden death victims who had right precordial ST-segment elevation, either isolated or associated with right bundle branch block, revealed predominant fibrofatty replacement in the right ventricular free wall.^{20,21)} Moreover, Coronel, *et al*¹⁰⁾ conducted morphometric analysis of intramyocardial adipose tissue and fibrosis from an explanted heart in a patient with Brugada syndrome who underwent cardiac transplantation and showed that intramyocardial fibrosis and adipose tissue content were greater in the RVOT and lateral wall of the right ventricle than in the left ventricle and septal myocardium. Our findings are consistent with theirs. We did not compare electrophysiologic characteristics of the RVOT and endomyocardial biopsy in patients with Brugada syndrome without inducible VF and control patients. However, it was very difficult to obtain endomyocardial biopsy from "control" patients. We did not analyze the genotypes of SCN5A

mutations in this study, however, since SCN5A mutations are reported to be involved in 20-30% of cases of Brugada syndrome, it might be difficult to correlate the genotype mutation, and electrophysiologic and histological findings.

Conclusions: We have provided evidence that symptomatic or asymptomatic patients with Brugada syndrome in whom VF can be induced by PVS despite an apparently normal heart upon clinical, echocardiographic, and angiographic examination have concealed structural abnormalities in the right ventricle. Thus, structural abnormalities in the right ventricle may be the cause of positive late potentials on the signal-averaged ECG and delayed and fragmented potentials recorded from the RVOT.

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