

Underlying Cardiomyopathy in Patients With ST-Segment Elevation in the Right Precordial Leads

Hyungseop Kim, MD; Yongkeun Cho, MD; Yonghwi Park, MD; Hyunsang Lee, MD;
Hyunjae Kang, MD; Deuk-Young Nah, MD*; Taein Park, MD**;
Dong Heon Yang, MD; Hun Sik Park, MD

Background Ventricular fibrillation (VF) and sudden death (SD) may occur in patients with ST-segment elevation in the right precordial leads. The mechanism of such events is unclear, so the aim of the present study was to assess whether there is an underlying morphological or pathological abnormality in these patients.

Methods and Results Fourteen consecutive patients (44±10 years old, all male) with ST-segment elevation of more than 2 mm in the right precordial leads underwent a cardiac evaluation, including right ventriculography and endomyocardial biopsy. The ST-segment changes after the administration of sodium-channel blockers were also evaluated. Two patients survived documented VF, 11 patients had chest pain or tightness, and another patient had a history of syncope. Only 1 patient had a family history of premature SD. The coronary angiograms were normal in all the patients. VF was induced in 5 patients (36%). Wall motion abnormalities of the right ventricle were detected in 4 patients (29%) and endomyocardial biopsy revealed features of cardiomyopathy in 7 patients (50%). In total, 9 (64%) of 14 patients exhibited wall motion abnormalities and/or pathologic findings.

Conclusions Underlying cardiomyopathy was present in more than half of the present patients with ST-segment elevation in the right precordial leads. (Circ J 2006; 70: 719–725)

Key Words: Cardiomyopathy; Electrocardiography; Right precordial leads; ST-segment elevation

Right bundle branch block (RBBB) and ST-segment elevation in the right precordial leads are known to be associated with sudden death (SD) from idiopathic ventricular fibrillation (VF), later called Brugada syndrome.¹ Structural abnormalities of the heart have not been found to date, so the etiology of this syndrome is suggested to be functional.¹ However, even before the first report of Brugada syndrome, Martini et al reported that some patients with idiopathic VF had RBBB pattern on ECG and structural abnormalities of the right ventricle.² A few years ago, Corrado et al also reported that a subgroup of young victims of SD from arrhythmogenic right ventricular cardiomyopathy (ARVC) had typical ECG features of Brugada syndrome.³ Some imaging studies have described structural abnormalities in a subpopulation of patients with Brugada syndrome, which suggested that they may have underlying organic heart disease rather than a primary electrical disease.⁴ These suggestions are strongly supported by recent reports of histologic abnormalities in typically symptomatic patients⁵ and localized conduction slowing with fibrosis in a patient with Brugada syndrome.⁶ We have previously reported that many patients with ARVC died during sleep or at rest,⁷ which is similar to the clinical manifestation of Brugada syndrome. However, as the study

populations of these studies were small and some showed a different clinical course to that of typical Brugada syndrome, the relationship between underlying organic heart disease and the Brugada-type ECG pattern remains unclear.

This study was designed to determine the presence of morphological and/or histological abnormalities in patients with ST-segment elevation in the right precordial leads.

Methods

Study Population

Between January 2002 and December 2005 patients referred for further evaluation of ST-segment elevation of more than 2 mm in the right precordial leads were prospectively included after giving written informed consent. The study protocol was approved by the institutional ethics committees. After obtaining a history and performing a physical examination, patients underwent 12-lead ECG and 2-dimensional (D) echocardiography. Fifteen patients with the Brugada-type ECG pattern were initially evaluated, but 1 patient was excluded from further studies because of typical ECG changes after induced coronary spasm. In total, 14 patients were analyzed.

Signal-Averaged ECG (SAECG)

SAECG was performed with bidirectional high-pass filters (40 Hz), and the low-pass cutoff frequency was fixed at 250 Hz. Late potentials were considered to be present with the usual criteria⁸

Electrophysiologic Study (EPS)

An EPS was performed in the baseline state and during a 2 µg/min infusion of isoproterenol (Korea United Pharm, Korea). Programmed electrical stimulation was performed

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Division of Cardiology, Department of Internal Medicine, Kyungpook National University, Taegu, *Division of Cardiology, Department of Internal Medicine, Dongguk University, Gyeongju and **Department of Pathology, Kyungpook National University, Taegu, Korea
Mailing address: Yongkeun Cho, MD, PhD, Department of Internal Medicine, Kyungpook National University Hospital, 50 Samduck 2-Ga, Chung-Ku, Taegu 700-721, Korea. E-mail: choyk@mail.knu.ac.kr

Table 1 Clinical Characteristics of 14 Patients With ST-Segment Elevation in the Right Precordial Leads

Patient no.	Sex	Age (years)	Family history of premature sudden death	Symptoms	Documented VF	ECG findings during sinus rhythm			
						QRS duration in lead V ₂ (ms)	QTc (ms)	ST elevation (max, mm)	Type ¹⁷
1	Male	36	–	Chest pain	–	96	405	V ₁₋₂ (3.5)	2
2	Male	49	–	Cardiac arrest	+	108	433	V ₁₋₃ (6.0)	1
3	Male	44	+	Chest pain	–	110	438	V ₁₋₂ (7.4)	1
4	Male	64	–	Chest pain	–	97	404	V ₂₋₃ (5.0)	2
5	Male	31	–	Chest tightness	–	108	413	V ₁₋₂ (5.5)	1
6	Male	43	–	Chest tightness	–	86	344	V ₁₋₂ (4.0)	2
7	Male	41	–	Chest pain	–	91	367	V ₁₋₂ (5.0)	1
8	Male	45	–	Chest tightness	–	112	405	V ₁₋₂ (3.6)	1
9	Male	42	–	Cardiac arrest	+	115	403	V ₁ (2.0)	1
10	Male	40	–	Chest pain	–	101	381	V ₁ (2.6)	2
11	Male	25	–	Chest tightness	–	123	409	V ₁₋₂ (2.7)	2
12	Male	49	–	Syncope	–	84	388	V ₁₋₃ (8.2)	1
13	Male	53	–	Chest tightness	–	117	430	V ₁₋₃ (7.5)	1
14	Male	35	–	Chest tightness	–	118	443	V ₂ (2.7)	2

VF, ventricular fibrillation.

Table 2 Results of the Studies in 14 Patients With ST-Segment Elevation in the Right Precordial Leads

Patient no.	Inducible VF	Na ⁺ channel blockers	Wall motion abnormality	Late potentials	Coronary angiogram	Biopsy findings
1	–	– (Pils)	–	+	Normal	Normal
2	–	+ (Pils)	–	ND	Normal	Normal
3	+	ND	–	–	Normal	ARVC
4	+	ND	+	–	Normal	ARVC
5	–	– (Pils)	–	+	Normal	Normal
6	–	– (Proc)	+	ND	Normal	Normal
7	+	– (Proc)	–	+	Normal	Cardiomyopathy
8	+	– (Proc)	–	ND	Normal	Normal
9	–	+ (Proc)	–	+	Normal	Cardiomyopathy
10	–	– (Proc)	–	+	Normal	Cardiomyopathy
11	–	ND	–	+	Normal	Cardiomyopathy
12	+	ND	+	+	Normal	Cardiomyopathy
13	–	– (Pils)	–	+	Normal	Normal
14	–	– (Pils)	+	+	Normal	Normal

VF, ventricular fibrillation; Pils, pilsicainide; ND, not done; ARVC, arrhythmogenic right ventricular cardiomyopathy; Proc, procainamide.

using up to double extrastimuli at the right ventricular apex and right ventricular outflow tract (RVOT). The coupling intervals of the extrastimuli were kept at more than 200 ms. The endpoint was either the reproducible induction of VF or completion of the pacing protocol.

Drug Challenge Test

Sodium channel blockers, 10 mg/kg of procainamide (Sabex Pharm, Canada), or 0.5 mg/kg of pilsicainide (Suntory Pharm, Japan), were intravenously administered to investigate the ST-segment changes.

Right Ventriculography (RVG) and Coronary Angiography (CAG)

RVG was performed with a 6 Fr pigtail catheter (Boston Scientific, USA) and Ultravist 370 (Schering, Germany) at end-inspiration. We used anteroposterior and lateral projections (30 frames/s, 512×512 matrix).

Coronary spasm during CAG was induced with intracoronary administration of up to 0.2 mg of ergonovine maleate (Jeil Pharm, Korea) in patients with chest pain or tightness.

Endomyocardial Biopsy

Endomyocardial biopsies were performed from the right

side of the interventricular septum and RVOT using 5.5 Fr forceps (Biopsy-forceps, Cordis, USA) until approximately 5–7 specimens of adequate size were obtained.

Treatment With Follow-up

We recommended implantation of a cardioverter defibrillator (ICD) for high-risk patients and observation only was scheduled for low-risk patients. All the patients regularly visited the outpatient clinic and were followed-up.

Results

Clinical Characteristics

Tables 1 and 2 show the clinical characteristics of the 14 patients (mean age 44±10 (range 25–64); all male). Eight patients had the type 1 coved pattern and 6 had the type 2 saddle-back pattern. Eleven patients had a history of atypical chest pain or tightness and 2 (Nos. 2 and 9) had survived cardiac arrests that had occurred while they were at rest. Another patient had a history of agonal respirations with an altered mentality at midnight (No. 12). Only 1 patient (No. 3) had a family history of premature SD. None of the patients had abused drugs or were taking any medication at the time of the study. The physical examinations were normal in all patients, with no evidence of cardiac or

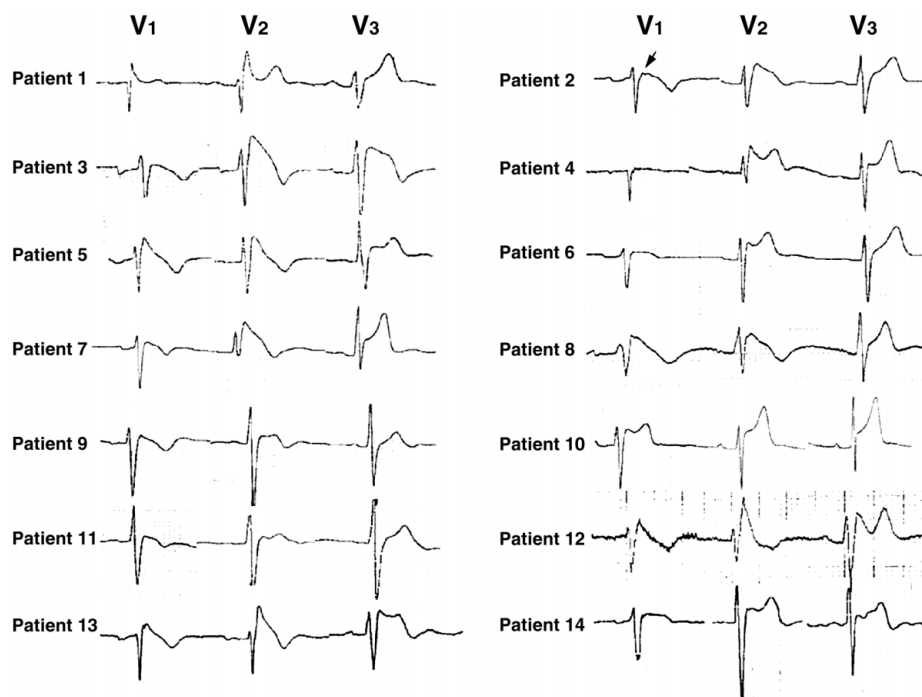


Fig 1. Routine ECGs from the 14 patients. ECG from patient No.2 shows an epsilon wave (arrow).

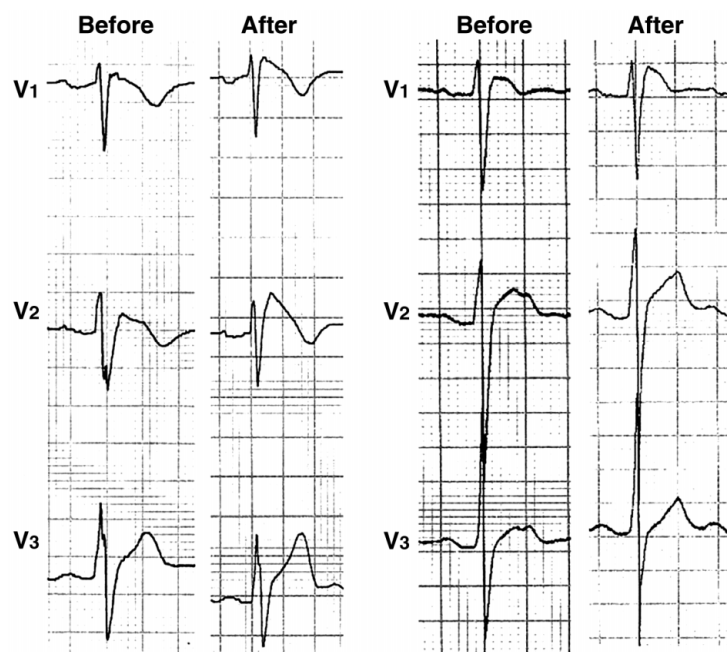


Fig 2. Changes in ST-segment in the right precordial leads after administration of sodium-channel blockers in (Left) patient No.2 and (Right) patient No.9.

extracardiac disease. The chest X-ray, routine laboratory and thyroid tests were normal in all patients.

Twelve-Lead ECG and Drug Challenge Test

The 12-lead ECGs (Fig 1) revealed sinus rhythm in all the patients. The PR interval, QT interval, and rate-corrected QT interval were all within normal limits. The ECG from patient No.2 showed an epsilon wave in lead V1. Four patients (Nos. 1–3 and 12) had intermittent RBBB with ST-segment elevation in the right precordial leads during follow-up. In addition, the ECG of patients Nos.2 and 9 exhibited augmentation of the ST elevation after the administration of sodium-channel blockers (Fig2).

CAG

CAG with and without intracoronary administration of ergonovine was normal in all patients.

EPS and SAECG

VF was induced in 5 patients (36%), 9 patients (82%) had positive late potentials, and 2 patients (Nos.7 and 12) had both induced VF and positive late potentials.

Morphological and Pathological Abnormalities

Routine 2-D echocardiography was normal in all patients, but RVG was abnormal in 4 patients (29%) (Fig3). On endomyocardial biopsy 7 patients (Nos.3, 4, 7, 9–12)

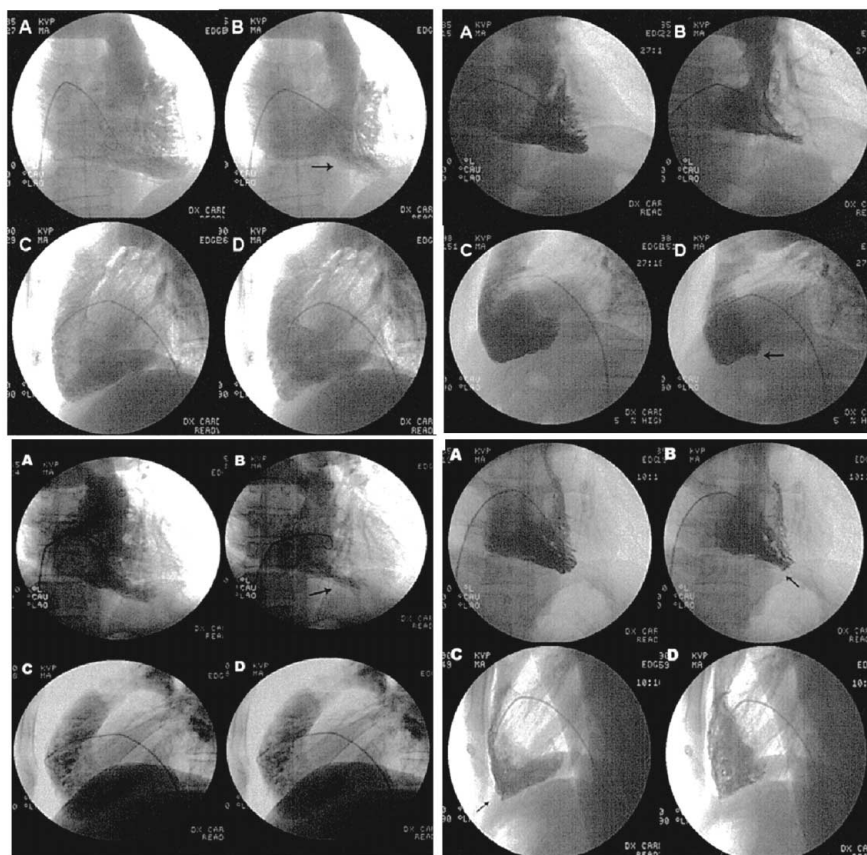


Fig 3. Right ventriculograms showing wall motion abnormalities (arrow) in (Left upper) patient No. 4, (Right upper) patient No. 6, (Left lower) patient No. 12 and (Right lower) patient 14.

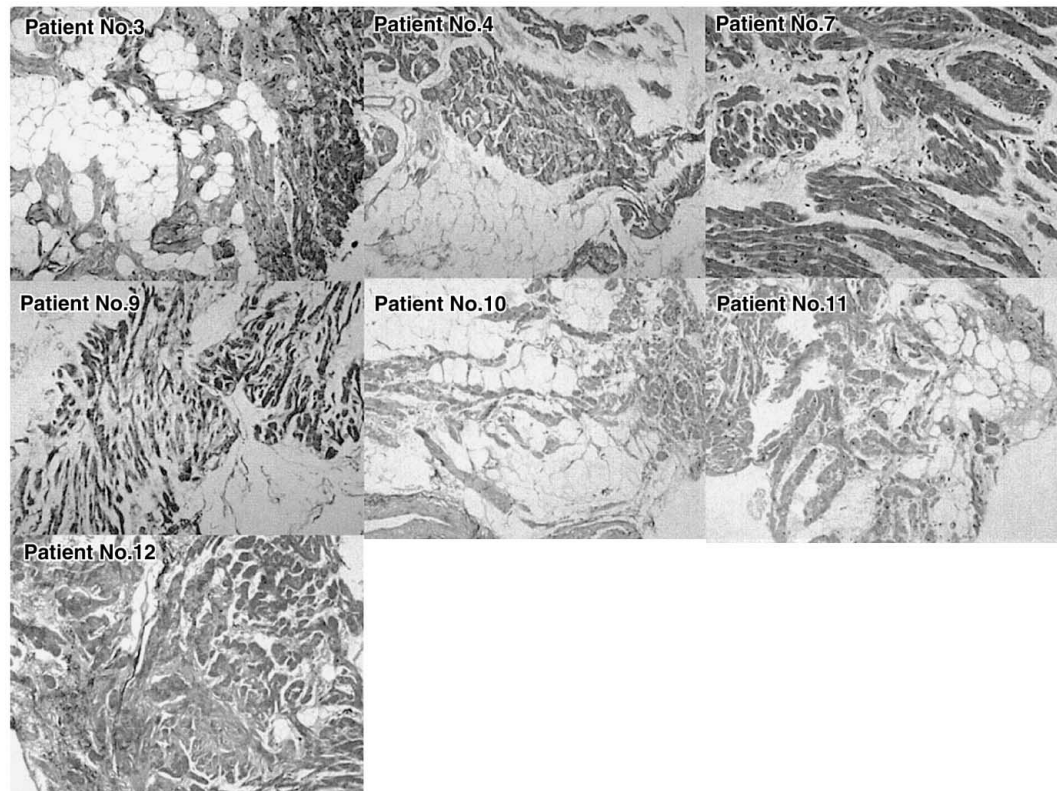


Fig 4. Endomyocardial biopsy specimens obtained from the right interventricular septum and right ventricular outflow tract myocardium show myocyte degeneration and fibrosis (blue) with and without fatty infiltration consistent with cardiomyopathy (Mason's trichrome stain).

ICD Model: Maximo VR 7232
Serial Number: PRN608625S

Dec 08, 2005 17:28:19
9979 Software Version 1.0
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Episode Lists Report

Page 1

Last Interrogation: Dec 08, 2005 10:45:24
Episodes Last Cleared: Jul 28, 2005 09:59:39

VT/VF Episodes

ID#	Date/Time	Type	V. Cycle	Last Rx	Success	Duration
12	Dec 04 17:07:47	VF	150 ms	VF Rx 1	Yes	10 s
11	Nov 28 16:56:02	VF	150 ms	VF Rx 1	Yes	9 s
10	Nov 27 20:39:08	VF	180 ms	VF Rx 1	Yes	10 s
9	Nov 27 20:07:29	VF	180 ms	VF Rx 1	Yes	11 s
8	Nov 21 19:30:36	VF	170 ms	VF Rx 1	Yes	8 s
7	Nov 21 18:50:09	VF	210 ms	VF Rx 1	Yes	10 s
6	Nov 21 17:31:52	VF	190 ms	VF Rx 1	Yes	10 s
5	Nov 20 18:00:07	VF	220 ms	VF Rx 1	Yes	11 s
4	Nov 20 17:26:24	VF	230 ms	VF Rx 1	Yes	11 s
3	Nov 13 15:31:03	VF	180 ms	VF Rx 1	Yes	10 s

-----Last Session (Nov 11, 2005)-----

(Data prior to last session has not been interrogated.)

SVT/NST Episodes

ID#	Date/Time	V. Cycle	Duration	Reason
2	Nov 21 19:30:33	190 ms	12 beats	Non-Sustained

-----Last Session (Nov 11, 2005)-----

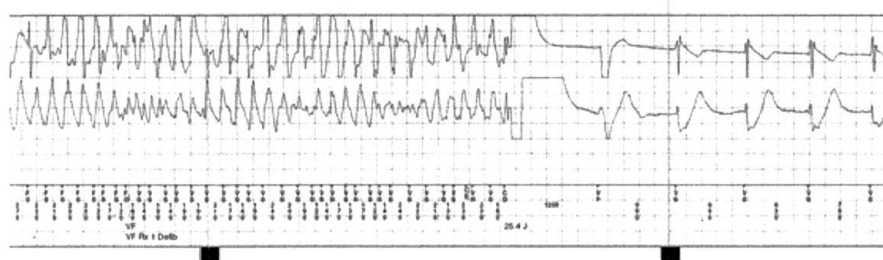


Fig 5. Stored episode lists and intracardiac electrogram from the implantable cardioverter-defibrillator in patient No. 12 show 10 episodes of ventricular fibrillation that were successfully defibrillated. VT, ventricular tachycardia; VF, ventricular fibrillation; SVT, supraventricular tachycardia; NST, non-sustained ventricular tachycardia.

showed nonspecific myocyte degeneration with inflammatory cell infiltration suggesting cardiomyopathy. In particular, 2 patients (Nos. 3 and 4) showed marked fatty and fibrofatty replacement consistent with ARVC (Fig 4).

Treatment With Follow-up

The 3 patients (Nos. 2, 9 and 12) who presented with cardiac arrest or syncope were recommended for ICD, but only 1 underwent the procedure (No. 12); the other 2 refused. Of the patients with atypical chest pain or tightness, those with induced VF by EPS were treated with β -blockers and those without inducible VF were followed up without medication. All except 2 patients (Nos. 1 and 12) had a regular follow-up without events. One patient (No. 1) died of an unrelated accident and another (No. 12) had 10 episodes of VF with appropriate ICD shocks (Fig 5).

Discussion

In 1992, the Brugada brothers described 8 patients with typical ST-segment elevation in the right precordial leads and cardiac arrest from idiopathic VF, which is now known as Brugada syndrome.^{1,9} Because the ST-segment elevation and VF in those patients could not be explained by electrolyte disturbances, ischemia or structural heart disease, a pure electrical disease was suggested as the mechanism. A cardiac sodium-channel gene mutation found in some of these patients further supported that concept.¹⁰ However, in most series the assumption of structurally normal hearts in those patients has not been based on a detailed pathological examination, but rather on the clinical features and routine

cardiac imaging modalities.^{1,9} Some studies even demonstrated fibrofatty replacement of the right ventricular myocardium.^{2,3,11} Recently, histologic abnormalities have been detected in patients with Brugada syndrome,⁵ and right ventricular fibrosis with localized conduction delay was found in the explanted heart of a patient with Brugada syndrome.⁶ However, despite these repeated suggestions of structural abnormalities, the relationship between the typical ECG pattern and the pathologic changes is still unclear because the study populations have been small and some have shown a different clinical course to that of typical Brugada syndrome.¹² Both Brugada syndrome and ARVC are not rare in Korea^{7,13} and our previous study⁷ showed that many patients with ARVC died during their sleep or at rest, which is similar to Brugada syndrome. Therefore, we wanted to assess whether there is underlying organic heart disease in patients with Brugada-type ECGs.

In the present study there were histologic abnormalities in a substantial number of patients with ST-segment elevation in the right precordial leads. Two patients (Nos. 2 and 9) had documented VF with cardiac arrest and a Brugada type 1 ECG, with a positive drug provocation test, and 1 patient (No. 12) with a type 1 ECG had a clinical history of agonal respirations associated with altered consciousness and documented VFs on stored electrograms in the ICD during follow-up. Therefore, these 3 patients could be diagnosed as definite cases of Brugada syndrome. However, the endomyocardial specimens from 2 of them (Nos. 9 and 12) showed underlying cardiomyopathy, which is similar to the results from a previous study.² Another thing to consider is that the ECG of patient No. 2 showed an epsilon wave,

which is attributed to the presence of delayed activation in the RV and is observed in up to 30% of patients with ARVC.¹⁴ Other 5 patients with insufficient ECG findings and/or history to be diagnosed with Brugada syndrome also had wall motion and/or histologic abnormalities. Although Tada et al failed to reveal any abnormalities on endomyocardial biopsy,¹¹ we found histologic abnormalities in 50% of the cases. We obtained samples from many areas of the myocardium, which may have influenced the results. The recent study by Frustaci et al showed abnormal histologic findings in all of their typically symptomatic patients.⁵ These differences in results may be partly explained by the small number of typically symptomatic patients in the present study.

Some patients with Brugada syndrome are positive for late potentials,¹⁵ which are regarded as representative of delayed conduction, but their cause in this electrical disease has not been easy to explain. Recently, Nagase et al demonstrated an 'epicardial abnormality' in the RVOT, which may help to explain late potentials in Brugada syndrome,¹⁶ but in the present study 9 of 11 patients who underwent SAECG had late potentials, and 5 of those 9 had an 'endocardial abnormality' on the endomyocardial biopsy. This difference in results suggests that both epicardial and endocardial abnormalities may be involved in the pathogenesis of the ST-segment elevation in the right precordial leads, an hypothesis that is supported by Coronel et al who showed that localized epicardial conduction delay in the RVOT was associated with ST-segment elevation in the right precordial leads.⁶ Our results also suggest that positive late potentials fulfilling all 3 parameters strongly reflect underlying pathological changes. Among the 9 patients who satisfied all 3 parameters of late potentials, 5 had wall motion abnormalities and/or pathologic findings on endomyocardial biopsy. VF was induced in 5 patients and 2 (Nos. 3 and 4) of them had fibrofatty infiltration of the myocardium suggesting ARVC. Of the 3 patients with documented VF or syncope, VF was inducible in 1, and late potentials were positive in 2. Only 1 patient (No. 12) had all the abnormal findings: positive history, inducible VF, positive late potentials, and pathologic findings compatible with cardiomyopathy.

Traditionally, wall motion abnormalities have been regarded as evidence of organic heart disease. Previous studies have reported wall motion abnormalities in patients with ST-segment elevation in the right precordial leads,^{2-4,11} although routine 2-D echocardiography may fail to detect the subtle wall motion abnormalities in such patients. In our study, we detected wall motion abnormalities in 4 (29%) of 14 patients by RVG, but 2-D echocardiography did not reveal these abnormalities in any of the patients, confirming the well-known limitation of 2-D echocardiography to detect subtle abnormalities in the right ventricle.⁵

The Brugada-type ECG pattern is classified as type 1, 2 or 3 according to the ST-T configuration and ST-segment elevation.¹⁷ Patients with the type 1 pattern are considered to be at high risk for an adverse prognosis, whereas those with a type 2 or 3 pattern are likely to have a more benign course. In our study, 1 (No. 12) of 3 patients who have experienced cardiac arrest or syncope was treated with an ICD. In addition to spontaneous ST-segment elevation and a history of syncope, the change in the ST-segment in the right precordial leads from a nondiagnostic to typical coved-type pattern after a sodium-channel blockade has been reported to be helpful for diagnosing and risk stratification for

Brugada syndrome in survivors of cardiac arrests and their relatives.¹⁸⁻²⁰ However, more recently it has been shown that the drug provocation test may be negative in up to 80% of asymptomatic patients with normal resting ECG²⁰ and the response to sodium-channel blockade would not be specific for the Brugada syndrome but could be positive in other conditions such as cardiomyopathy and myocarditis.⁵ In the present study, even with this limitation, the drug provocation tests in patients Nos. 2 and 9 revealed an augmented ST-segment elevation of more than 1 mm from the baseline ECG and we were able to obtain a pathological confirmation in 1 of them (No. 9).

The endomyocardial specimens from patients Nos. 3 and 4 showed fibrofatty infiltration suggesting ARVC. Patient No. 4 had both an aneurysm in the right ventricle and fibrofatty infiltration of the myocardium, which were enough to make a diagnosis of ARVC according to the Task Force Criteria.²¹ However, patient No. 3 could not satisfy the Task Force Criteria although the biopsy specimens showed typical fibrofatty infiltration and there was a family history of premature SD. Tada et al reported that ARVC might underlie the cardiac manifestation of Brugada syndrome.¹¹ The Brugada-like ECG pattern with wall motion abnormalities reported here could not be explained by other causes, such as ischemia or conduction abnormalities, as suggested by Brugada et al.²²

The present study was designed to demonstrate wall motion and histologic abnormalities in both typically and atypically symptomatic patients with ST-segment elevation in the right precordial leads. Our findings suggest that ST-segment elevation in the right precordial leads may reflect an underlying pathologic process in the right ventricle and that some pathological process may also exist in patients who have been diagnosed as so-called Brugada syndrome. Therefore, it is prudent to exclude all other organic heart diseases before making a diagnosis of Brugada syndrome. Further studies are needed to enhance our understanding of this complex syndrome.

Study Limitations

The major limitation was the lack of typical symptoms in most of the patients. Second, a genetic analysis was not available. However, sodium-channel mutations have been identified in only a small portion of patients¹⁸ and these mutations per se may not exclude an underlying organic heart disease.^{5,23}

Conclusion

Wall motion and/or histologic abnormalities of the right ventricle were found in more than half of the patients with ST-segment elevation in the right precordial leads, which suggests that the Brugada-type ECG pattern may reflect underlying cardiomyopathy.

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