ORIGINAL

^{123}I-metaiodo-benzylguanidine myocardial scintigraphy in the Brugada-type ECG

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Abstract : The degree of ST-segment elevation and amplitude of J waves, which may change in patients with the Brugada-type electrocardiogram (ECG) over time, are influenced by autonomic nervous activity and the administration of antiarrhythmic drugs. In the present study, we evaluated whether the shape of ST-segment elevation in patients with a Brugada-type ECG might alter the parameters of an ^{123}I-MIBG myocardial scintigraphy and body surface signal-averaged ECG (SAECG). The subjects consisted of 12 patients with a Brugada-type ECG and 15 healthy volunteers (N group). The patients with a Brugada-type ECG were classified into the following 2 groups based on the type of ST-segment elevation: 6 patients with the coved type ST-segment elevation (C group), and 6 patients with the saddle-back type ST-segment elevation (S group). Planar and SPECT images were obtained 15 minutes (early images) and 3 hours (delayed images) after the administration of ^{123}I-MIBG, respectively. In addition, the washout rate (% WR) of ^{123}I-MIBG was obtained in a bull's eye map of the SPECT image. There were no significant differences in the early H/M ratio between the C and S groups. In the C group, however, there were some patients who showed a decreased accumulation or defect of ^{123}I-MIBG in the planar and SPECT images. Furthermore, in contrast to the N and S groups, the C group showed a decreased delayed H/M ratio and increased % WR. SAECG did not show any significant differences between the S and C groups. These results of the present study suggest that the shape of ST-segment elevation may be associated with myocardial autonomic nervous function. In addition, the electric heterogeneity of the action potential in the right ventricular epicardial myocardium, which is frequently influenced by autonomic nervous activity, is closely associated with the development of Brugada syndrome.
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Keywords **:** *Brugada syndrome, ST-segment, ^{123}I-MIBG myocardial scintigraphy, SAECG*

INTRODUCTION

Brugada *et al*.(1) reported 8 cases of idiopathic ventricular fibrillation demonstrating J waves at the end of the QRS complex and ST-segment elevation in the right chest leads of a standard 12-lead ECG during a non-attack period as Brugada syndrome. Various issues concerning this syndrome have been

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clarified, though many problems remain to be solved. An experimental evaluation at the cellular level demonstrated that changes in the ST segment and the development of ventricular fibrillation were caused by a repolarization abnormality in this syndrome(2, 3). Clinically, however, ventricular late potentials were frequently detected by SAECG in some patients with Brugada syndrome who developed ventricular fibrillation, in addition to recordings of a prolonged His-Purkinje (HV) interval in a His bundle electrogram and fragmented potentials in epicardial mapping (4 -7). Therefore, a great deal of attention has been paid to the association of a depolarization abnormality in this syndrome. During a standard 12-lead ECG, the degree of ST-segment elevation increases over an intercostal recording or after the administration of sodium channel blockers(8 -11). In addition, ventricular fibrillation is frequently induced by programmed ventricular stimulation. However, these findings are also obtained in asymptomatic patients with a Brugada-type ECG alone. Therefore, the significance of risk classification in Brugada-type ECG remains unclear.

Syncopal attacks in Brugada syndrome are induced by ventricular fibrillation, and a ventricular premature beat with short R-R intervals triggers the conversion from polymorphic ventricular tachycardia to ventricular fibrillation. Such an attack of ventricular fibrillation frequently occurs at night or during sleep, suggesting the involvement of parasympathotonia and elimination of sympatheticotonia (12). However, patients with such ECG findings do not always develop ventricular fibrillation, and many of them show the Brugada-type ECG alone. Therefore, predicting the development of ventricular fibrillation is clinically important.

The degree of ST-segment elevation and amplitude of the J waves, which may be influenced by autonomic nervous activity and the administration of antiarrhythmic drugs, serially change in the Brugada-type ECG (12). In the present study, we evaluated whether cardiac sympathetic nervous function is influenced by the shape of ST-segment elevation in patients with the Brugada-type ECG, using ^{123}I-metaiodobenzylguanidine (MIBG) myocardial scintigraphy to confirm the possibility of conducting an evaluation based on the level of risks.

SUBJECTS AND METHODS

1) Subjects

The subjects consisted of 12 patients who were diagnosed with the Brugada-type ECG demonstrating patterns of right bundle branch block (RBBB) and persistent ST-segment elevation in their right chest leads (Brugada group), and 15 healthy volunteers (N group). Patients with the Brugada-type ECG were classified into the following 2 groups based on the type of ST-segment elevation:6 patients with the coved type ST-segment elevation (C group : 4 men and 2 women, mean age, 46.5 ± 6.3 years) and 6 patients with the saddle-back type ST-segment elevation (S group, 5 men and 1 woman, mean age, 49.2 ± 5.3 years). In 2 patients in the C group, ventricular fibrillation was induced by an electrophysiological study.

The healthy volunteers did not have any particular history of cardiopulmonary diseases, and showed normal findings upon physical examination, including a standard 12-lead ECG and chest X-ray. Patients with hypertension or diabetes mellitus and those who had been treated with autonomic nervous drugs within 1 month before the initiation of the present study were excluded.

2) ^{123}I-MIBG myocardial scintigraphy

Both planar and SPECT images were obtained 15 minutes (early images) and 3 hours (delayed images) after intravenous injection of 111 MBq of ^{123}I-MIBG via the cubital vein. A 3-head rotating gamma camera (Prism 3000, Picker Inc., Ohio, U. S. A.) with a low-energy all-purpose collimator was used for imaging. The planar images were collected in a 256×256 matrix for 2 to 3 minutes. The collection time was 30 seconds per frame, and 360-degree data were taken using 72 image steps (5 °step; 24 directions×3 heads) for SPECT imaging, and a data-processing super computer (ODYSSEY, Shimadzu Corporation, Kyoto, Japan) was used to analyze the SPECT data.

On the anterior planar images, the number of pixels in the regions of interest (ROIs) and mean counts of the upper mediastinum (M) and heart (H) were calculated for both the early and delayed images. The H/M ratio of MIBG in the initial and delayed images were calculated.

A bull's eye map was used for the SPECT imaging. Myocardial segments visualized by SPECT imaging (bull's eye map) were divided into 4 segments (anterior wall, septum, lateral wall, and posterior wall), and the %WR in each myocardial segment was calculated using the following formula :

%WR of SPECT image = [(mean counts for the initial image-mean counts for the delayed image)/(mean counts for the initial image)]×100 (%)

3) Body surface signal-averaged electrocardiography (SAECG)

The body surface SAECG was recorded using VCM-3000 (Fukuda Denshi Co., Ltd. Tokyo, Japan), and using the vector magnitude method reported by Simson *et al.*, (13) signals obtained by bipolar leads corresponding to the 3 axes of the X, Y, and Z leads of the Flank leads were averaged to obtain values for $(X^2+Y^2+Z^2)^{1/2}$. Signals from 256 heart beats were averaged using a high-cut filter (300 Hz) and a low-cut filter (40 Hz). The following three parameters were measured: 1) the filter-QRS (f-QRS) duration, 2) root mean square (RMS) voltage of the terminal 40 msec of the f-QRS waveform (RMS-40), and 3) amplitude over the last 40 msec under the 40 μV duration (LAS40) (14).

4) Statistical analysis

All values were expressed as the mean ± standard deviation (SD), and statistical analysis was performed using StatView 5.0(SAS Institute Inc., USA). Values were compared between the two groups using the paired t-test, and $p<0.05$ were regarded as significant.

RESULTS

1) Planar images of ^{123}I-MIBG myocardial scintigraphy in healthy volunteers and patients with Brugada-type ECG

Figure 1 shows examples of planar images of ^{123}I-MIBG myocardial scintigraphy in a healthy subject (a) and in patients with the saddle-back type (b) and coved type ST-segment elevations (c). In a healthy subject (a), the H/M ratios in the early and delayed images were 1.83 and 2.11, respectively. In a patient with the saddle-back type ST-segment elevation (b), the H/M ratios in the early and delayed images were 1.85 and 2.02, respectively. However, one patient with the coved type ST-segment elevation (c) showed H/M ratios of 1.33 and 1.56 in the early and delayed images, respectively. Compared to the healthy subject (a) and the patient with the saddle-back type ST-segment elevation, the patient with the coved type ST-segment elevation showed a lower H/M ratio.

2) SPECT images of ^{123}I-MIBG myocardial scintigraphy in healthy subjects and patients with the Brugada-type ECG

Figures 2 and 3 shows examples of SPECT and

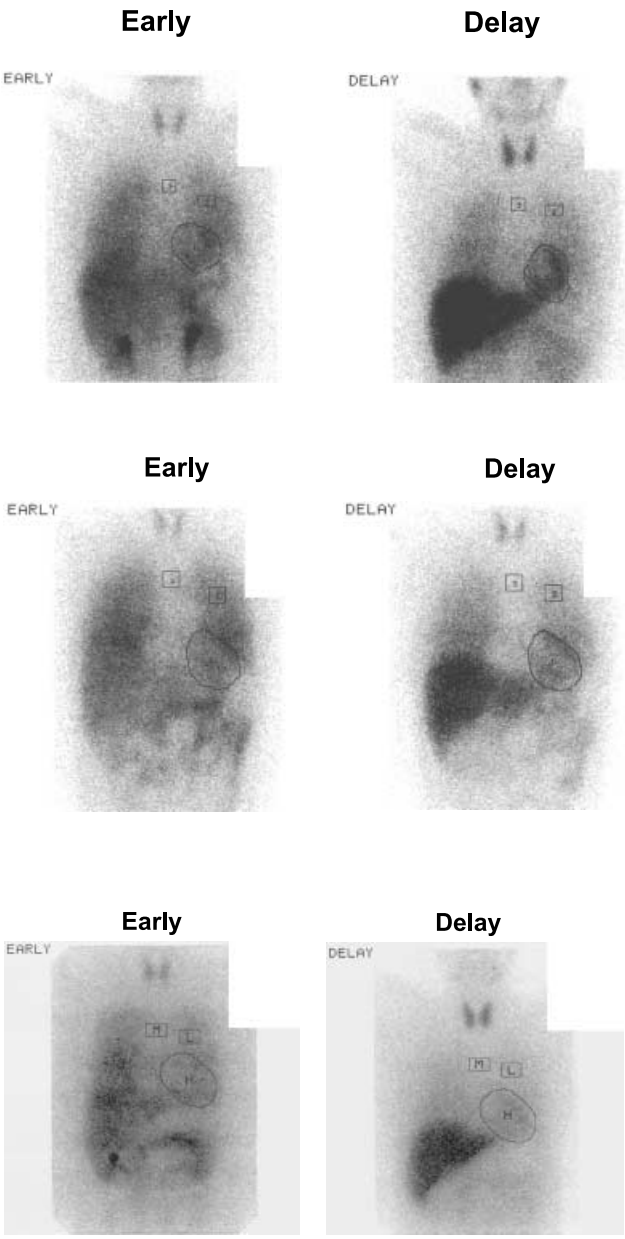

Fig. 1. Examples of planar images of ^{123}I-MIBG myocardial scintigraphy in a healthy subject (a), and in patients with saddle-back type ST-segment elevation (b) and coved type ST-segment elevation (c).
Panel a : H/M ratios in the early image (1.83) and delayed image (2.11).
Panel b : H/M ratios in the early image (1.85) and delayed image (2.02).
Panel c : H/M ratios in the early image (1.33) and delayed image (1.56). Compared to Panels a and b, Panel c shows a lower H/M ratio.

bull's eye images of ^{123}I-MIBG myocardial scintigraphy in patients with the saddle-back type (Figure 2) and the coved type ST-segment elevations (Figure 3). In a patient with the saddle-back type ST-segment elevation (Figure 2 a), neither the initial nor delayed images showed any significant decreased accumulation or defect of the ^{123}I-MIBG SPECT images of the short

and vertical long axes (Figure 2b). In the bull's eye images of this patient, the %WR at the anterior wall, septum, inferior wall, and lateral wall was 5.9 %, 9.5 %, 13.1 %, and 8.9 %, respectively (Figure 2c). In a patient with the coved type ST-segment elevation (Figure 3 a), however, both the initial and delayed SPECT images along the short and vertical long axes showed decreased accumulation and a defect of ^{123}I-MIBG between the inferior and posterior walls and at the apex (Figure 3b). In the bull's eye images of this patient, %WR at the anterior wall, septum, inferior wall, and lateral wall was 8.9 %, 9.1 %, 32.1 %, and 7.8 %, respectively, and the values of the inferior segment were higher than those in the patient with the saddle-back type ST-segment elevation (Figure 3 c).

3) Delayed H/M ratios and %WR among N, S, and C groups

Figure 4 shows a comparison of the delayed H/M ratios and %WR among the N, S, and C groups. The delayed H/M ratio was significantly lower in the C group than in the N and S groups. In the bull's eye images, although the %WR in the inferior wall was significantly higher in the C group than in the N and S groups, those of the other segments did not significantly differ among these 3 groups. However, the mean value of the %WR in all segments was significantly higher in the C group than in the N and S groups.

3) Body surface SAECG in the N, S, and C groups

Figure 5 shows a comparison of the respective parameters of the body surface SAECG (f-QRS, RMS-40, and LAS-40) among the N, S, and C groups. Both f-QRS and LAS 40 were significantly higher, and RMS-40 was significantly lower, in the S and C groups than in the N group. However, these parameters did not significantly differ between the S and C groups.

DISCUSSION

Among patients with the Brugada-type ECG, those with the coved type ST-segment elevation may have

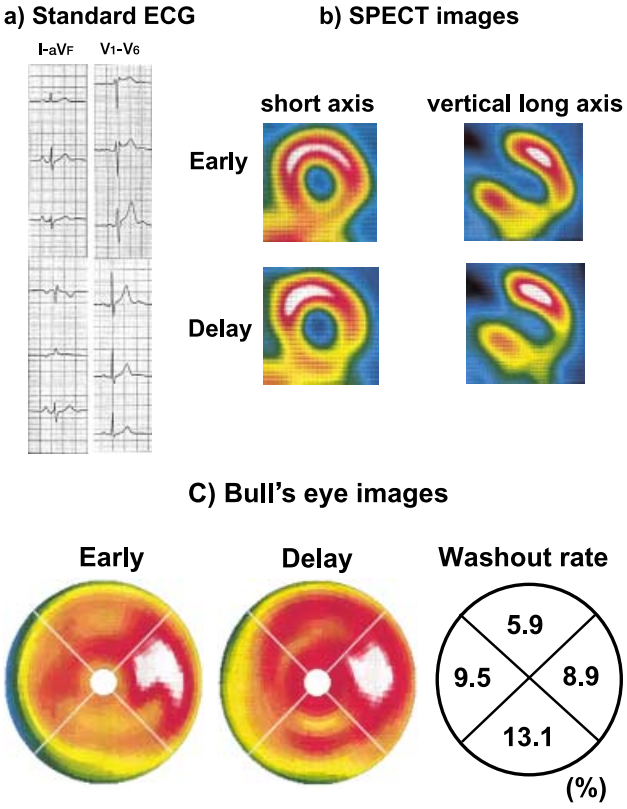

Fig. 2. Examples of standard 12-lead ECG (a), SPECT image (b) and bull's eye image (c) of ^{123}I-MIBG myocardial scintigraphy in patients with saddle-back type ST-segment elevation
Panel b : Neither the initial nor delayed images showed any significant decreased accumulation or defect.
Panel c : %WR at the anterior wall (5.9%), septum (9.5%), inferior wall (13.1 %), and lateral wall (8.9%).

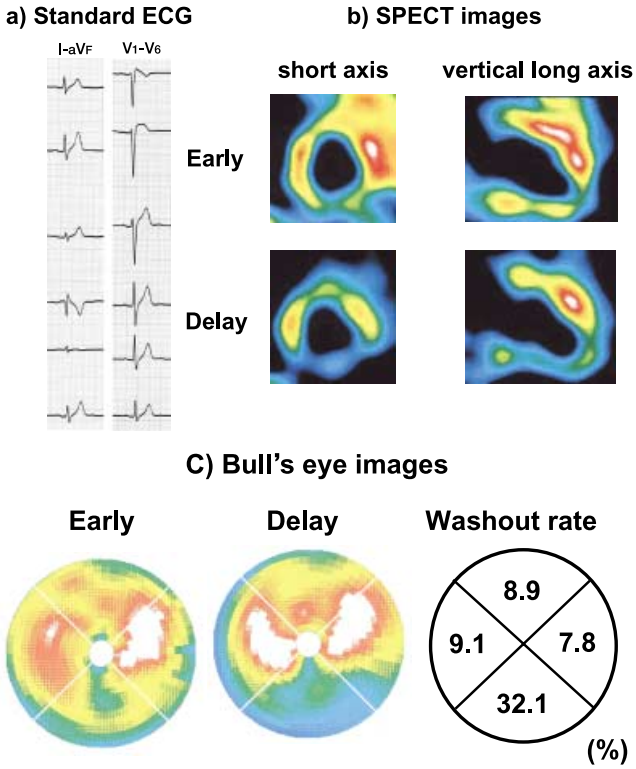

Fig. 3. Examples of standard 12-lead ECG (a), SPECT image (b) and bull's eye image (c) of ^{123}I-MIBG myocardial scintigraphy in patients with coved type ST-segment elevation.
Panel b : Initial and delayed SPECT images along the short and vertical long axes showed decreased accumulation and a defect of ^{123}I-MIBG between the inferior and posterior walls and at the apex.
Panel c : %WR at the anterior wall (8.9%), septum (9.1%), inferior wall (32.1 %), and lateral wall (7.8 %).

a higher risk of ventricular fibrillation (15). In the present study, patients with the coved type ST-segment elevation showed a decreased delayed H/M ratio and increased %WR. Therefore, the shape of ST-segment elevation may be associated with cardiac sympathetic nervous function. The results of the present study suggested that patients with the coved type ST-segment elevation had abnormal autonomic nervous activity, even when they did not have syncopal attacks. Therefore, careful observation and appropriate treatment may be required in such patients.

1) Relationship between autonomic nervous activity and the Brugada-type ECG

Among patients with idiopathic ventricular fibrillation that causes sudden death despite the absence of organic heart disease, there were some patients who showed a combination of marked ST-segment elevation in their right chest leads ($V_{1,2}$) and RBBB patterns (16). In 1992, Brugada reported that 8 patients with prodromal symptoms of sudden death such as repeated syncopal attacks commonly showed characteristic ECG findings during a non-attack period, as described below (1). Attention was focused on the etiology of Brugada syndrome. In 1998, Chen *et al.* (17) reported that some cases of this syndrome were caused by abnormalities of the gene encoding sodium channels in the myocardial cell membrane. Although approximately 25% of patients with Brugada syndrome reportedly showed alteration of the myocardial sodium channels, not all such patients have these genetic abnormalities (18).

In general, an attack of ventricular fibrillation accompanied by underlying diseases is closely associated with increased sympatheticotonia ; however, increased vagotonia is closely associated with the development of ventricular fibrillation in patients with Brugada syndrome (12). These findings are important in considering the etiology and treatment of ventricular fibrillation in Brugada syndrome. That is, patients with Brugada syndrome frequently develop ventricular fibrillation during sleep at night or at rest in the early morning, but rarely during exercise (19, 20). In addition, electrocardiographic ST-segment elevation and RBBB patterns also show within-day or day-to-day variations, which are inhibited by exercise and the administration of β-stimulators and vagal blockers or enhanced by the administration of β-blockers, hyperventilation, and parasympathotonia (21). Therefore, electrophysiological abnormalities and changes in autonomic nervous activity might play important roles in the etiology of Brugada syndrome. However, few studies have investigated the Brugada-type ECG

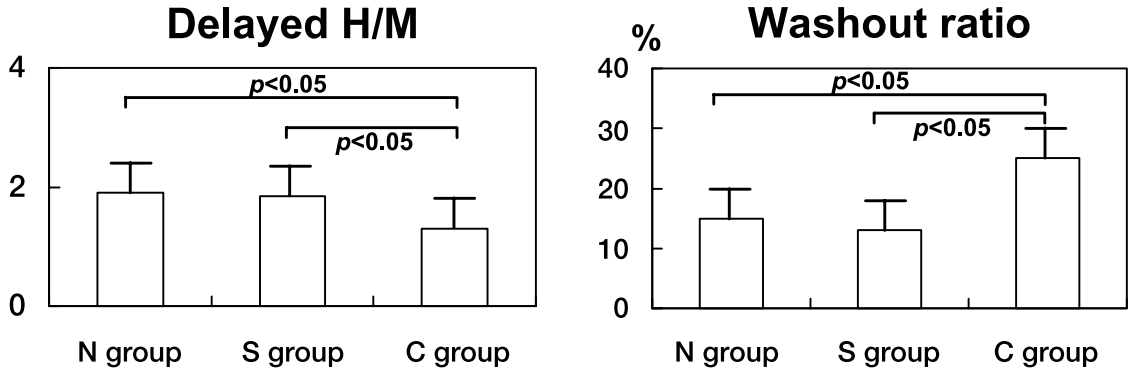

Fig. 4. Comparison of delayed H/M ratios and %WR among N, S, and C groups.
The delayed H/M ratio was significantly lower in the C group than in the N and S groups. In the bull's eye images, the %WR in the inferior wall was significantly higher in the C group than in the N and S groups.

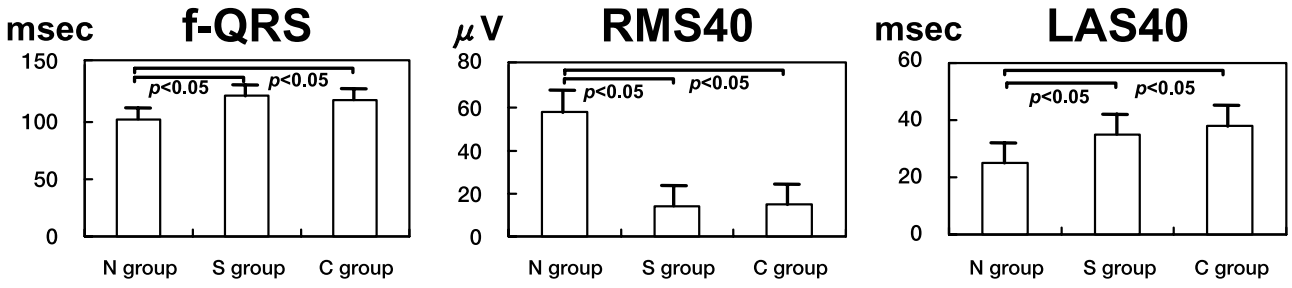

Fig. 5. Comparison of the respective parameters of body surface SAECG (f-QRS, RMS-40, and LAS-40) among the N, S, and C groups.
f-QRS and LAS 40 were significantly higher, and RMS-40 was significantly lower, in the S and C groups than in the N group.

using ^{123}I-MIBG myocardial scintigraphy to evaluate cardiac autonomic nervous activity (22-24).

A number of sympathetic nerves are distributed over the heart, and both cardiac sympathetic and parasympathetic nerves play important roles in the circulatory control by the autonomic nervous system. ^{123}I-MIBG is used for myocardial scintigraphy visualizing the distribution of sympathetic nerves in the myocardium and the state of chatecholamine storage at the sympathetic nerve endings in patients with myocardial infarction, ischemic heart diseases, or cardiomyopathy (25, 26). In particular, ^{123}I-MIBG myocardial scintigraphy facilitates the detection of abnormalities in patients with cardiac autonomic dystonia caused by Shy-Drager syndrome or diabetes mellitus (27). In addition, ^{123}I-MIBG myocardial scintigraphy is routinely used to directly visualize and diagnose autonomic dystonia in patients with Parkinson's syndrome or familial amyloid polyneuropathy (28, 29).^{123}I-MIBG is an analogue of guanidine, a sympathetic nerve blocker, which accumulates in the sympathetic nerve endings after being taken into the myocardium. Therefore, ^{123}I-MIBG facilitates visualization of the local distribution and function of cardiac sympathetic nerves.

In 1998, Chen *et al.*(17) observed a mutation of the gene (SCN5A) that encodes for the sodium channel in myocardial cells. Gussak and Antzelevitch *et al.* (30, 31) administered sodium channel blockers such as flecainide, ajmaline, and procainamide in patients with the atypical ECG findings of Brugada syndrome, and such atypical ECG findings were unmasked and converted to the typical Brugada-type ECG, suggesting that the ECG findings in Brugada syndrome may be caused by abnormalities in the sodium channels. In this report, the loss of the dome of the action potential in the right ventricular epicardial myocardium induced ST-segment elevation in the right chest leads, and the presence of such myocardial segments also induced electric heterogeneity, resulting in the induction of a ventricular premature beat with short R-R intervals via a phase 2 reentry mechanism. Subsequently, the development of a ventricular premature beat may induce ventricular tachycardia and ventricular fibrillation. In addition, inward Ca currents may also play an important role in dome formation. Such Ca currents are easily controlled by autonomic nerves, and activation of the sympathetic nerves increases the Ca currents. In addition, increased parasympatheticotonia inhibits Ca currents, probably resulting in the manifestation of marked ST-segment elevation.

Among patients with the Brugada-type ECG used in the present study, ^{123}I-MIBG myocardial scintigraphy showed decreased accumulation and defect of ^{123}I-MIBG in patients with the coved type ST-segment elevation, demonstrating that ^{123}I-MIBG myocardial scintigraphy facilitates the detection of abnormal autonomic nervous activity. However, patients with the Brugada syndrome demonstrating the saddle-back type ST-segment elevation did not show any abnormality in ^{123}I-MIBG myocardial scintigraphic findings, as in the healthy subjects. Thus, it is considered that ^{123}I-MIBG myocardial scintigraphy is useful for evaluating the presence or absence of cardiac autonomic nervous abnormalities in patients with the Brugada-type ECG.

2) Relationship between the Brugada-type ECG and SAECG

Detection of ventricular late potentials suggests the presence of slow conduction that causes reentry. Ventricular late potentials are frequently observed in patients with persistent ventricular tachycardia accompanied by underlying diseases such as myocardial infarction and ventricular aneurysm, though they are rarely observed in those with idiopathic ventricular tachycardia (32). However, many previous studies have indicated the usefulness of detecting ventricular late potentials in patients with Brugada syndrome (33). In the present study, ventricular late potentials were frequently observed in the Brugada-type ECG, but the relationship with ventricular tachycardia remained unclear.

The detection of ventricular late potentials also means the presence of local slow conduction, and is associated with reentry and triggered automaticity without the development of ventricular tachycardia (34). Since patients with the Brugada-type ECG also show patterns of incomplete RBBB, f-QRS and LAS 40 obtained by SAECG were prolonged in almost all such patients. Therefore, the relationship between local slow conduction and reentry and triggered automaticity may be limited. In addition, since patients with Brugada syndrome more frequently develop ventricular fibrillation rather than ventricular tachycardia, the relationship with late potentials may also be limited. Furthermore, although the relationship between ventricular fibrillation and QT dispersion has been suggested, many previous studies have reported the absence of QT dispersion in patients with Brugada syndrome (35).

Electric heterogeneity in the action potential in the right ventricular epicardial myocardium, which is frequently influenced by autonomic nervous activity, is closely associated with the development of Brugada

syndrome. Therefore, early detection of autonomic nervous abnormalities may be more useful for predicting a high-risk group for Brugada syndrome than the detection of late potentials.

LIMITATION

For the evaluation of autonomic nervous function in patients with Brugada type ECG, time courses in the same patients both having coved and saddle back type are essential, but these evaluations were not studied because few patients were collected in the present study. In the future study, new knowledge of prognosis in these patients would become clear by detail study of the autonomic nervous function in the same patient both having coved and saddle back type ECG.

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