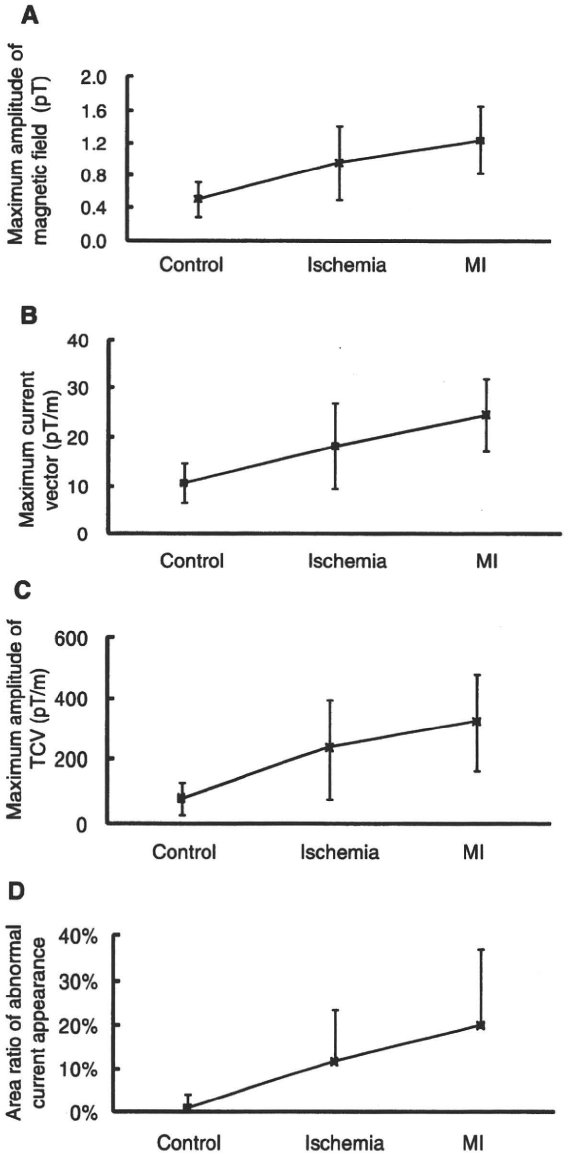

Figure 6. Relationships among control, ischemia, and myocardial infarction. (A) Maximum amplitude of magnetic field, (B) maximum current vector, (C) maximum amplitude of total current vector, (D) area ratio of abnormal current vector appearance.

time point, namely, the last 1 milliseconds in 1001 milliseconds, was used to superpose the normalized Tpeak-Tend waveform on the normalized ST-Tpeak waveform. On the other hand, 1000 milliseconds was chosen for easy calculation of the normalization ratio, and 1000 milliseconds must be sufficiently longer than a general ST-Tend time in order to obtain a positive normalization ratio. The authors, therefore, consider that 1000 milliseconds is adequate time for making the template waveform.

The subtracted ST-T peak of normal subjects is significantly decreased in Figure 2B, while that of a CHD patient (Fig. 3B) has a higher amplitude. The difference between the peaks indicates that a normal electrical-current vector with the same direction exists in the ventricular area. It is, therefore, considered that the subtracted waveforms of the CHD patients are produced by the abnormal residual currents (which indicate an ischemic area).

The increase in each MCG parameter in Figure 4 and the abnormal area in Figure 5, according to the increase in lesion sites, indicates that the increase in lesion areas enhances the residual electrical components or degrades normal electrical activities. The subtraction method is, therefore, helpful for estimating the lesion area easily.

On the other hand, a stenosis site in the coronary arteries was not found in the CAM of the subtracted waveform of each patient. This may be because the occupied area of each coronary artery becomes complementary in the ventricular muscle[22] and the individual variation of coronary-artery shape results in difficulties in identifying it.

Detection of Abnormalities in CHD Patients

Other groups have detected abnormalities in CHD patients by using magnetic field parameters (MFPs), which are calculated from the MCG data in the ventricular repolarization phase.[10,11] In particular, it has been reported that the four MFPs are the most sensitive indicators for diagnosing CHD patients,[10] and the detection sensitivity (86.4%) and specificity (82.5%) possible by using the MFPs is higher than our results (sensitivity: 74.6%; specificity: 84.1%). However, quoting the same patients' data, our previous report clarified the decrease in MFP sensitivity and specificity compared with the results obtained with our current-distribution parameters (CDPs).[16] We consider that CDP is the most important parameter for detecting CHD. Although the sensitivity and specificity obtained with CDPs are also high, the correlation between abnormal score and lesion area is not good. In this study, we assumed that abnormal current distribution depending on CHD is extracted by subtraction of normal electrical-current activities, and

we found a good correlation between the number of lesion sites and the magnitude of subtracted waveforms.

Furthermore, as for the subtraction MCG method, the highest values of MCG parameters of patients with MI areas, as shown in Figure 6, reflect the lack of electrical activation (depending on the infarction area). The difference between MI and ischemia, therefore, shows that ischemic status can be evaluated with this method. Consequently our proposed CHD-evaluation method using subtracted MCG ST-T waveforms makes it possible to estimate sizes of infarctions and coronary-artery lesions.

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LIMITATION OF THIS STUDY

This study has the following limitations. First, CHD patients were identified in terms of coronary artery stenosis only; therefore, the status such as ischemia, MI, and stable/unstable angina of all patients were not distinguished. Second, the subtraction method may be insufficient in the case of MI patients with a low-amplitude T wave whose T-wave peak cannot be identified because the subtraction method needs a correct T-wave peak as a reference point.

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Classification and assessment of computerized diagnostic criteria for Brugada-type electrocardiograms

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BACKGROUND Although a Brugada-type electrocardiogram (ECG) is occasionally detected in mass health screening examinations in apparently healthy individuals, the automatic computerized diagnostic criteria for Brugada-type ECGs have not been established.

OBJECTIVE This study was performed to establish the criteria for the computerized diagnosis of Brugada-type ECGs and to evaluate their diagnostic accuracy.

METHODS We examined the ECG parameters in leads V1 to V3 in patients with Brugada syndrome and cases with right bundle branch block. Based on the above parameters, we classified the ECGs into 3 types of Brugada-type ECGs, and the conditions for defining each type were explored as the diagnostic criteria. The diagnostic effectiveness of the proposed criteria was assessed using 548 ECGs from 49 cases with Brugada-type ECGs and the recordings from 192,673 cases (36,674 adults and 155,999 school children) obtained from their annual health examinations.

RESULTS The Brugada-type ST-segment elevation in V1 to V3 was classified into 3 types, types 1, 2/3, and a suggestive Brugada ECG (type S). The automatic diagnostic criteria for each type were established by the J-point amplitude, ST-segment elevation with its amplitude and configuration, as well as the T-wave morphology in leads V1 to V3.

CONCLUSION The proposed criteria demonstrated a reasonable accuracy (type 1: 91.9%, type 2/3: 86.2%, type S: 76.2%) for diagnosing Brugada-type ECG in comparison to the macroscopic diagnosis by experienced observers. Moreover, the automatic criteria had a comparable detection rate (0.6% in adults, 0.16% in children) of Brugada-type ECGs to the macroscopic inspection in the health screening examinations.

KEYWORDS Brugada syndrome; J wave; ST-segment elevation; Coved-type ST-segment elevation; Saddleback-type ST-segment elevation; Computerized diagnosis; Health screening examination

ABBREVIATIONS **ECG** = electrocardiogram; **NPV** = negative predictive value; **PPV** = positive predictive value; **RBBB** = right bundle branch block; **SCD** = sudden cardiac death; **VF** = ventricular fibrillation; **VT** = ventricular tachycardia

(Heart Rhythm 2010;7:1660–1666)

Brugada syndrome is characterized by unique electrocardiographic (ECG) changes and carries a high risk for sudden cardiac death (SCD) due to ventricular fibrillation (VF) in patients without major structural heart disease.[1–8] The hallmark for diagnosing Brugada syndrome is ST-segment elevation in leads V1 to V3, but similar ECG changes are seen in various normal and abnormal conditions.[1–6]

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The consensus reports by the subgroup of the Heart Rhythm Society and European Heart Rhythm Association have proposed the diagnostic ECG criteria for Brugada syndrome.[5,6] According to the consensus reports, there are 3 ECG patterns, type 1, type 2, and type 3. Type 1 is regarded as a diagnostic sign for Brugada syndrome, and a final diagnosis can be made when at least 1 of the following conditions are also present: documented VF and/or polymorphic ventricular tachycardia (VT), a family history of sudden cardiac death at <45 years old, coved-type ECGs in family members, induction of VT/VF with programmed electrical stimulation, syncope, or nocturnal agonal respiration.

Although the 3 types of ECG waveforms are occasionally detected in mass health screening examinations, which mostly utilize computerized ECG machines, there have been no detailed methods for quantitatively discriminating waveforms similar to Brugada syndrome. Another issue related to the difficulty in the ECG diagnosis is that VF or SCD has occasionally been observed in cases of Brugada syndrome with ECG patterns not included in the 3 types in the consensus report.[7–13,16] In this study we sought to establish computerized diagnostic criteria for the detection of the Brugada-type ECG. We further assessed the diagnostic accuracy of the proposed criteria for the differentiation of ECG patterns in patients with Brugada syndrome, or right bundle branch block (RBBB), and in apparently healthy adults and school children.

Methods

Data acquisition and analysis of the ECG waveforms

A 12-lead ECG was recorded in all individuals using conventional and commercially available computerized ECG machines at a paper speed of 25 mm/s. The ECG records were acquired simultaneously, at least 6 limb or precordial leads. All ECG parameters were automatically acquired and calculated during 2 cardiac cycles. The following definitions and data acquisition were used: The J point in leads V1 to V3 was defined as the timing of the J point in lead V5 with simultaneous recordings in V1 to V6. The J-wave amplitude was automatically measured as the height from the isoelectric line. The positive peak deflection after the R wave was defined as the STmax, the timing after 40 ms of the STmax as STmax40 and that after 80 ms as STmax80. The STmax was identical to the R′ (or r′) wave of RBBB in conventional ECG terminology. The minimum point of the ST-segment elevation and positive peak amplitude of the T wave were detected. Two morphologies of the ST-segment elevation, a coved type and a saddleback type, were other conditions for defining the diagnosis of a Brugada-type ECG.[3,4] Brugada-type ST-segment elevation was divided into type 1, type 2/3, and type S. Type 1 was defined as a coved-type ST-segment elevation with a J-point amplitude ≥0.2 mV and negative or flat T wave. This type was equivalent to type 1 of the consensus report.[5,6] Type 2/3 was defined as a saddleback-type ST-segment elevation with a J-wave amplitude ≥0.2 mV and positive or biphasic T waves, which would be included in type 2 and type 3 in the consensus report.[5,6] Type S, as abbreviated terminology for suggestive, was defined as a coved-type ST-segment elevation with J-wave amplitude ≥0.1 mV and <0.2 mV.

For a comparison to an automatic diagnosis, manual measurements in a macroscopic inspection were performed by 2 independent and experienced observers without any knowledge of the clinical background of the subjects.

The subjects included 32 patients with Brugada syndrome who were diagnosed according to the diagnostic criteria of the consensus report.[5,6] The ECGs from 118 cases with RBBB were diagnosed by macroscopic inspections from the stored records of previous health examinations in workers. The ECG data from the annual health examinations in 36,674 workers and 155,999 school children with ages between 8 and 18 years were used for an exploration of the diagnostic accuracy of the proposed criteria.

Diagnostic assessment of the proposed automatic criteria for a Brugada-type ECG

The conditions and waveforms for defining type 1, type 2/3, and type S ST-segment elevation were proposed and explored by their diagnostic accuracy to differentiate the ECG recordings in 57 leads (V1 to V3) displaying a coved-type ST-segment elevation from 32 patients with Brugada syndrome (Brugada group) and 151 leads displaying an rSR′ pattern (V1 to V3) in 118 cases with RBBB (RBBB group).

Then, 3 conditions for defining type 1, type 2/3, and type S were proposed as diagnostic criteria for a Brugada-type ECG, and their diagnostic effectiveness was assessed in 548 ECGs from 49 patients with a Brugada-type ECG by a macroscopic inspection. Type 1 ECG was classified when type 1 ST-segment elevation was observed in at least 1 of the 3 leads (V1 to V3). Type 2/3 ECG was defined when only type 2/3 or type 2/3 and type S ST-segment elevation was recorded in any of leads V1 to V3. Type S ECG was defined when type S ST-segment elevation alone was seen in any of leads V1 to V3.

We next examined the accuracy of how the proposed diagnostic criteria could differentiate Brugada-type ECGs using the recordings from 192,673 cases (36,674 workers and 155,999 school children) in their annual health examinations. The effectiveness of the automatic diagnosis was assessed in the ECGs retrieved from our cohorts by a macroscopic inspection.

Statistical analysis

The chi-square test was used to evaluate the differences in categorical variables between the 2 groups. A P value <.05 was considered significant.

Results

Classification and conditions of Brugada-type ECGs for the diagnostic criteria

There were 2 morphologies of the ST-segment elevation in leads V1 to V3, a coved type and a saddleback type, in

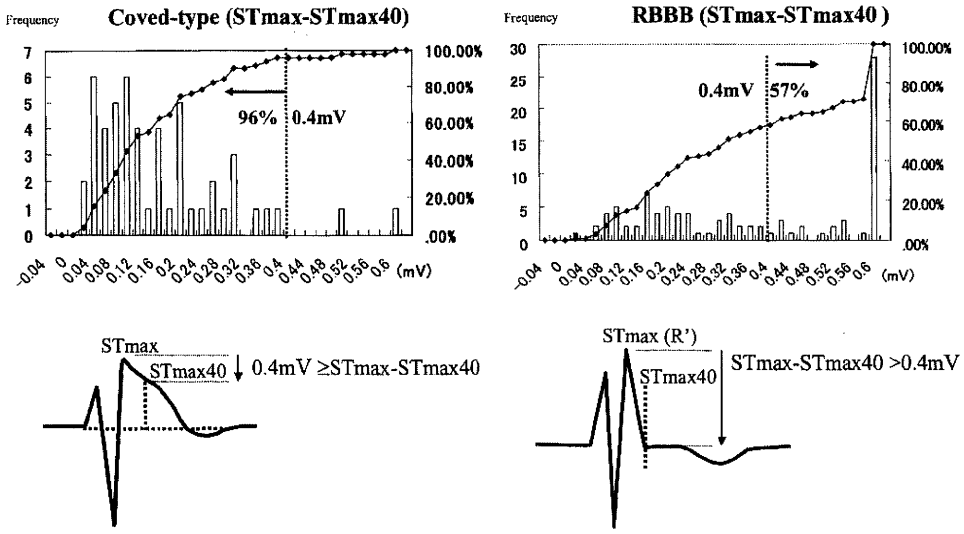

Figure 1 Distinction of a coved-type ST-segment elevation in Brugada syndrome (Brugada) and the ST-segment in right bundle branch block (RBBB). The histogram of the gradients between the amplitude of the STmax and STmax40 (STmax – STmax40) in 51 leads showing coved-type ST-segment elevation (Brugada group) is shown on the left and in 97 leads showing an rSR′ pattern with RBBB (RBBB group) on the right. See the detailed explanation in the text.

patients with Brugada syndrome and suspected cases.[3,4] We sought to establish the conditions for distinguishing the 2 morphologies of the ST-segment elevation with J-wave amplitude of ≥0.2 mV. In addition, we added a third condition of a coved-type ST-segment elevation and J-wave amplitude ≥0.1 mV and <0.2 mV, which was not included in the criteria by the consensus report,[5,6] but this type of ST-segment elevation might be seen in suspected cases of Brugada syndrome.[7–9] Based on the morphologies and amplitude of the ST-segment elevation, we classified the Brugada-type ECG into type 1, type 2/3, and type S. The ECG conditions for distinguishing the 3 types were further explored.

Type 1 ST-segment elevation

The ECG waveforms with a J-wave amplitude ≥0.2 mV and ST-segment elevation were automatically detected by the computerized ECG machines. For defining the coved-type ST-segment elevation, similar to the gradually descending ST-slope in the consensus report, we adopted the condition of STmax > STmax40 > STmax80 as the first step. Because coved-type ST-segment elevation with a J or STmax wave could be seen not only in patients with Brugada syndrome (Brugada group) but also in subjects with RBBB (RBBB group), we tested whether the combination of the 2 conditions (J wave amplitude ≥0.2 mV and STmax > STmax40 > STmax80) could discriminate the 2 groups. The combined conditions could be detected in 45 of 57 leads (V1 to V3) satisfying the condition from 32 patients in the Brugada group, which was macroscopically diagnosed by the 2 experienced observers. The same condition could also be detected in 2 (1.3%) of 151 leads (V1 to V3) with an rSR′ pattern from 118 cases in the RBBB group.

To improve the discrimination of the waveforms in the Brugada group from those in the RBBB group, the histograms of the gradient between the amplitude of the STmax and STmax40 in the 2 groups were explored (Figure 1). We adopted a condition of a voltage gradient within 0.4 mV between the amplitude of the STmax and STmax40 (0.4 mV ≥ STmax − STmax40) to discriminate between the 2 groups because this condition could detect the majority of patients (96%) in the Brugada group and 43% of those in the RBBB group ($P < .01$). Consequently, the 3 combined conditions (J-point amplitude ≥0.2 mV, STmax > STmax40 > STmax80, and 0.4 mV ≥ STmax − STmax40) could detect 97.8% of those (44 of 45 leads) in the Brugada group but only 1 (0.6%) of 151 leads in the RBBB group ($P < .01$). In addition, a negative or isoelectric T wave was adopted as the condition for defining type 1. Figure 2 shows an example of an ECG recording automatically diagnosed by the proposed criteria for type 1 using the above conditions.

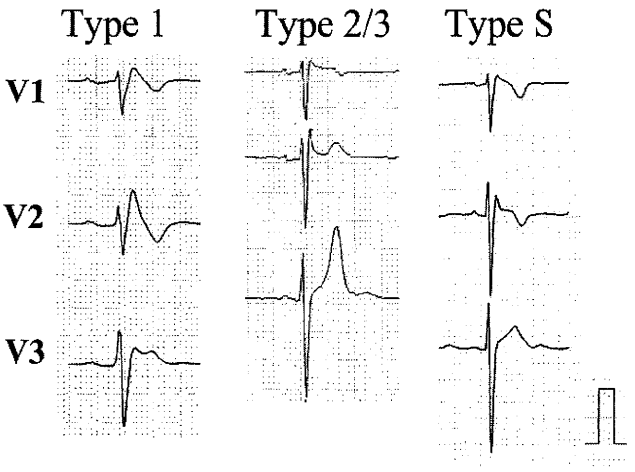

Figure 2 Electrocardiographic records of the 3 types diagnosed by the proposed criteria. **Left:** Type 1. **Middle:** Type 2/3. **Right:** Type S.

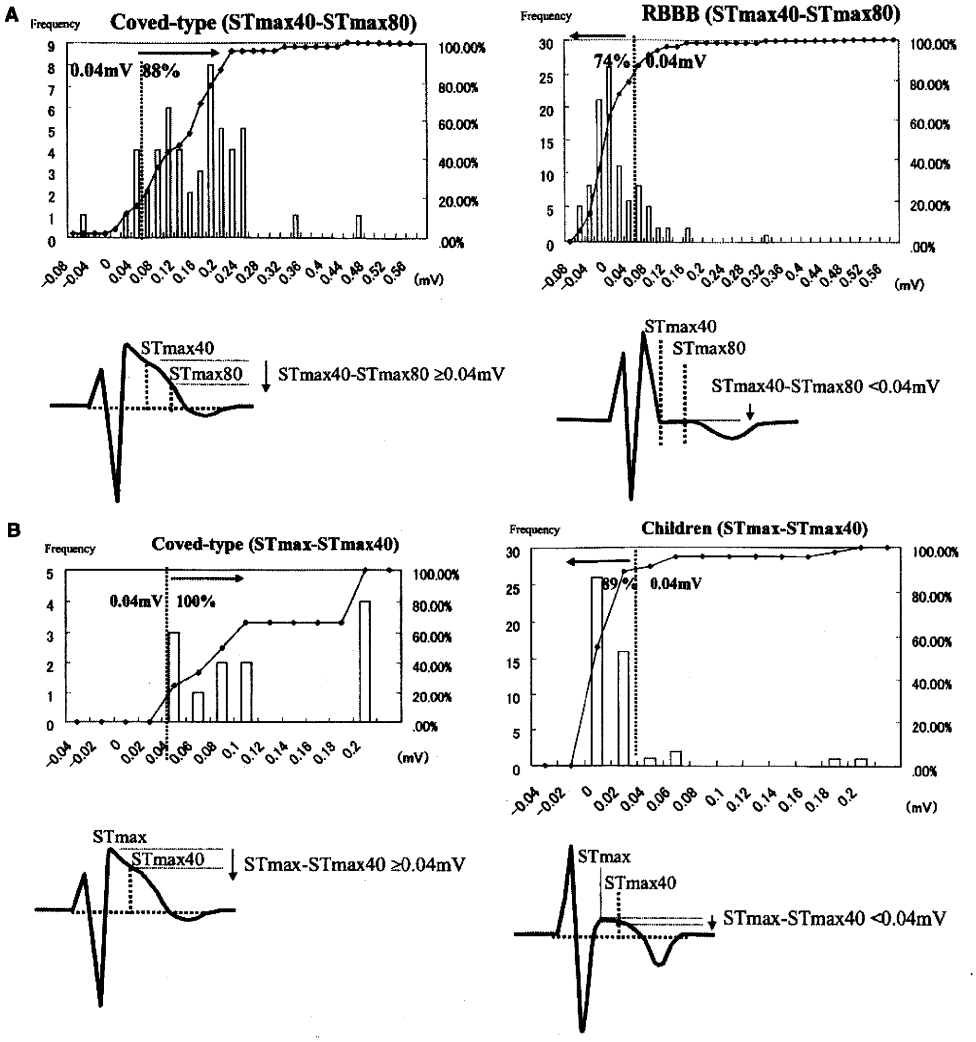

Figure 3 A histogram of the gradients between the amplitude of the STmax40 − STmax80 **(top)** and STmax − STmax40 **(bottom)** in the 2 groups (Brugada and RBBB groups). **Top:** Using the criteria of STmax40 − STmax80 ≥ 0.04 mV, the majority (88%) of the patients in the Brugada group were included, whereas 74% were excluded in the RBBB group. **Bottom:** Using an additional condition of STmax − STmax40 ≥ 0.04 mV, all of the leads in the Brugada group met the criteria and 42 of 47 electrocardiograms in RBBB children were excluded. Abbreviations as in Figure 1.

Type 2/3 ST-segment elevation

To define the saddleback-type ST-segment elevation, we adopted the conditions of the J-wave amplitude > the minimum point of the ST-segment (STmin), as well as the peak of the T wave (Tpeak) > STmin > 0 mV. The condition of the Tpeak > STmin > 0 mV could also define a positive or biphasic T wave. Thus, the conditions matching J-wave amplitude ≥0.2 mV, J amplitude > STmin, and Tpeak > STmin > 0 mV were determined as the criteria for type 2/3. Figure 2 represents an example of a type 2/3 ECG detected by this diagnostic criteria.

Type S ST-segment elevation

We adopted the parameter of J-wave amplitude ≥0.1 mV and < 0.2 mV, and other parameters similar to type 1 (STmax > STmax40 > STmax80, and 0.4 mV ≥ STmax − STmax40) for defining type S. The conditions combined by the above 3 parameters could be detected in 12 of 57 leads from 32 patients in the Brugada group and could also diagnose 6 of 151 leads with an rSR′ pattern in the RBBB group as type S. Therefore, we searched for other conditions to precisely differentiate the Brugada-type ECGs from those with RBBB. To this end, we applied a similar method as shown in Figure 1.

As for the STmax40 − STmax80 parameter, the histograms of the gradients between the amplitudes in the 2 groups are shown at the top in Figure 3. Applying the condition of an STmax40 − STmax80 ≥ 0.04 mV, the majority (88%) of the Brugada group patients were included, whereas 74% of the RBBB group were excluded ($P < .01$). Adding the condition of an STmax40 − STmax80 ≥ 0.04 mV to 0.4 mV ≥ STmax − STmax40, the remaining 2 leads in the RBBB group were still included, but the numbers of type S in the Brugada group remained unchanged ($P < .01$).

Another group to be differentiated from type S appeared to be that with incomplete RBBB and mild ST-segment

Type 1 : (coved-type ST-segment elevation)
① J point ≥0.2mV
② STmax >STmax40 >STmax80
③ T wave: under or on the isoelectric line
④ 0.4mV ≥STmax-STmax40

Type 2/3 : (saddleback-type ST-segment elevation)
① J point ≥0.2mV
② J point >STmin
③ Tpeak >STmin >0mV

Type S : (mild coved-type ST-segment elevation)
① 0.2mV >J point ≥0.1mV
②③: same criteria as Type 1
④ 0.4mV ≥STmax-STmax40 ≥0.04mV
⑤ STmax40-STmax80 ≥0.04mV

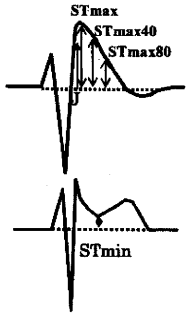

Figure 4 Classification and waveforms of Brugada-type electrocardiograms. See the detailed explanation in the text.

elevation in leads V1 to V3, often seen in healthy children. Therefore, we evaluated the reliability of the proposed conditions of STmax > STmax40 > STmax80, 0.4 mV ≥ STmax − STmax40 and STmax40 − STmax80 ≥ 0.04 mV in 47 leads showing mild ST-segment elevation in 37 children with incomplete RBBB. A close inspection of the ECG recordings with type S by a macroscopic diagnosis and those with incomplete RBBB suggested a difference in the steepness at the early portion of the ST-segment comparable to the STmax − STmax40 interval with a lesser degree in type S than in type 1. So, the parameter of the STmax − STmax40 was modified and the conditions with a new parameter were further evaluated by a similar method as shown in the case of type 1 (Figure 1). The histograms of the gradients between the amplitude of the STmax − STmax40 in 47 leads in the 37 ECGs from children were compared (Figure 3, bottom). The condition of STmax − STmax40 ≥ 0.04 mV could exclude 42 of 47 leads in the incomplete RBBB group. Three of the remaining 5 ECGs detected by this condition had the same recordings as type S by the macroscopic diagnosis. Therefore, we modified the conditions defining type S as J-wave amplitude ≥0.1 mV and <0.2 mV, STmax > STmax40 > STmax80, 0.4 mV ≥ STmax − STmax40 ≥ 0.04 mV, and STmax40 − STmax80 ≥ 0.04 mV. Consequently, the above conditions could exclude all 151 leads from the 118 ECGs with RBBB from type S, and detect type S in 12 of 57 leads from the Brugada group that agreed with the macroscopic diagnosis (Figure 3, bottom). An example of type S ECG detected by the automatic diagnostic criteria is shown in Figure 2. The automatic diagnostic criteria of type 1, type 2/3 and type S for Brugada-type ECGs are summarized in Figure 4.

Diagnostic accuracy of the automatic diagnostic criteria for Brugada-type ECGs

The recordings from 548 ECGs obtained in 49 cases with Brugada-type ECGs were diagnosed by the proposed criteria into type 1, type 2/3 and type S ECG. The results were compared with a macroscopic diagnosis by experienced observers (Table 1). Nearly 92% of the macroscopic diagnoses of type 1 ECGs by the experienced observers matched the automatic diagnosis (sensitivity 91.8%, specificity 96.8%, positive predictive value [PPV] 92.9%, negative predictive value [NPV] 96.3%). An additional 2.3% matched the automatic diagnosis of type 2/3 and type S ECGs, revealing 94.2% accuracy in total. The macroscopic diagnosis of a type 2/3 ECG had an 86.2% accuracy matched to the automatic diagnosis (sensitivity 86.2%, specificity 98.4%, PPV 99.0%, NPV 79.5%); 76.2% of type S ECG by the automatic diagnosis matched the macroscopic inspection (sensitivity 76.2%, specificity 99.4%, PPV 84.2%, NPV 99.0%).

The mass screening ECG recordings from 192,673 individuals undergoing annual health checkups for adult workers and school children were diagnosed into type 1, type 2/3 and type S ECGs by the proposed criteria (Table 1). The numbers detected by the automatic criteria for type 1, type 2/3 and type S ECGs were 20 (0.05%), 161 (0.44%), and 40 cases (0.11%), respectively, in the adult cases. Those in the children were 13 (0.008%), 154 (0.099%), and 89 cases (0.057%), respectively. The overall detection for the 3 types of Brugada ECGs was 221 cases (0.6%) in the adults and 256 (0.16%) in the children.

Table 1 Diagnostic accuracy using the proposed criteria for Brugada-type ECGs

	Brugada-type ECGs* 49 cases, n (%)			Random ECGs† 192,673 cases, n (%)	
	Macroscopic diagnosis			Adults	Children
Automatic diagnosis	Type 1 172 ECGs	Type 2/3 355 ECGs	Type S 21 ECGs	36,674 cases	155,999 cases
Type 1 ECG	158 (91.9)	11 (3.1)	1 (4.8)	20 (0.05)	13 (0.008)
Type 2/3 ECG	3 (1.7)	306 (86.2)	0 (0)	161 (0.44)	154 (0.099)
Type S ECG	1 (0.6)	2 (0.6)	16 (76.2)	40 (0.11)	89 (0.057)
Total	162 (94.2)	319 (89.9)	17 (81.0)	221 (0.6)	256 (0.16)

ECG = electrocardiogram.

*The automatic diagnosis using the proposed criteria was compared with the diagnosis made by experienced observers in a macroscopic inspection in a total of 548 ECGs from 49 cases with a Brugada-type ECG. The numbers in the columns are the automatically diagnosed numbers of cases and the percentage (%) relative to the macroscopic diagnosis.

†Incidence of a Brugada-type ECG diagnosed by the proposed criteria automatically in the mass screening examinations of 192,673 adults and school children.

We assessed the accuracy of the automatic diagnosis of ECGs retrieved from our cohorts by a comparison with the macroscopic inspection by the 2 experts. The experts reviewed 14 of 20 cases with type 1 ECGs by the automatic diagnosis, 146 of 161 with type 2/3, and 28 of 40 with type S in the adult cases. They diagnosed 10 of 13 cases with type 1, 144 of 154 with type 2/3, and 44 of 89 with type S in children.

Consequently, 78.5% (11 of 14 cases) of the automatic diagnoses of type 1 matched the macroscopic diagnosis by the 2 experts in adult cases (sensitivity 78.5%, specificity 98.8%, PPV 84.6%, NPV 98.2%). An additional 14.2% (2 of 14 cases) matched a macroscopic diagnosis of type 2/3 and type S, revealing a 92.8% accuracy in total. The automatic diagnosis of type 2/3 had a 95.2% (139 of 146 cases) agreement with the macroscopic diagnosis (sensitivity 95.2%, specificity 97.6%, PPV 99.2%, NPV 85.4%). Type S was 75% (21 of 28 cases) agreement with the macroscopic diagnosis (sensitivity 75.0%, specificity 98.7%, PPV 91.3%, NPV 95.7%). In children, 80% (8 of 10 cases) of the automatic diagnoses of type 1 matched the macroscopic diagnosis (sensitivity 80.0%, specificity 100%, PPV 100%, NPV 98.9%). An additional 10% (1 of 10 cases) matched the macroscopic diagnosis of type S, revealing 90% (9 of 10 cases) agreement in total. The automatic diagnosis of type 2/3 had 94.4% accuracy to the macroscopic diagnosis (sensitivity 94.4%, specificity 100%, PPV 100%, NPV 87.0%). Type S of the automatic diagnosis showed 77.2% agreement with the macroscopic diagnosis (sensitivity 77.2%, specificity 99.3%, PPV 97.1%, NPV 93.8%).

Discussion

In the present study, we established the automatic criteria for the computerized diagnosis of Brugada-type ECGs. The waveforms of the Brugada-type ECG were divided into 3 types, type 1, type 2/3, and type S. For the establishment of the diagnostic criteria, conditions for differentiating each type were determined and evaluated by comparing the ECG recordings from cases with Brugada syndrome and RBBB. Then, we examined the diagnostic usefulness of the criteria in a discrimination of 192,673 recordings of the ECGs from annual health checkups for workers and school children. The results yielded a reasonable rate of the recognition of Brugada-type ECGs in 0.6% of the adults and 0.16% of the children.

Although the 2 waveforms of the ST-segment elevation have been recognized in cases with Brugada syndrome,[3,4] the consensus report divided them into 3 types, type 1, type 2, and type 3.[5,6] Type 1 was assumed to be diagnostic of Brugada syndrome.[5,6] Although the initial report indicated persistent ST-segment elevation as a characteristic ECG finding of Brugada syndrome,[1] the fluctuating nature of the ST-segment elevation over time was recognized as a general feature of this syndrome.[3,4] The development of a spontaneous type 1 ECG was regarded as an important clinical sign for predicting cardiac events and the prognosis in patients with Brugada syndrome,[14] but other reports did not support this notion.[15,16] These findings may indicate that the detection of type 1 ECG as a diagnostic sign proposed by the consensus report may not always be applicable and can be missed in certain cases due to inconsistent appearance of a specific ST-segment elevation. Another diagnostic problem could emerge regarding the prognostic variables for Brugada syndrome with respect to the types of ST-segment elevation because the long-term prognosis of patients with Brugada syndrome in the non–type 1 group was similar to that in the type 1 group.[16] There was a missing form of ST-segment elevation among the 3 types in the consensus report: a coved-type ST-segment elevation with J-wave amplitude $\geq$0.1 mV and $<$0.2 mV. Therefore, we divided the Brugada-type ECGs into 3 types depending on morphologies of ST-segment elevation and J-wave amplitude. Type 1 had a coved-type ST-segment elevation with the J-wave amplitude $\geq$0.2 mV, which was equivalent to type 1 in the consensus report.[5,6] Type 2/3 had a saddleback-type ST-segment elevation with J-wave amplitude $\geq$0.2 mV. Type S represented a coved-type ST-segment elevation with J-wave amplitude $\geq$0.1 mV and $<$ 0.2 mV. We included type S because of the occasional association of an increased risk of VF or SCD in Japanese cases with Brugada syndrome.[7–9,11–13,16]

Automatic diagnostic criteria for the Brugada-type ECG

To define the waveforms of type 1, type 2/3, and type S, the conditions corresponding to each type were sought and formulated by the J-point amplitude, ST-segment elevation with amplitudes and morphology, as well as the T-wave morphology in leads V1 to V3 from the ECGs between the patients with Brugada syndrome and cases with RBBB. For defining the conditions of the coved-type and saddleback-type ST-segment elevation, the voltage amplitudes of the STmax, STmax40, and STmax80 as well as STmin, T-wave amplitude, and morphology were shown to be essential factors from the analysis of the ECGs in Brugada syndrome and RBBB cases, which shared a similarity in the ST-segment in leads V1 to V3. By choosing these parameters, each condition for defining the waveforms of type 1, type 2/3, and type S was shown a reasonable accuracy for diagnosing Brugada-type ECGs and the criteria for a computerized diagnosis were proposed.

Diagnostic accuracy of the proposed automatic criteria and prevalence of Brugada type ECGs in the mass screening examinations

The diagnostic accuracy of the proposed criteria was then evaluated in a large-scale mass screening of ECG recordings in workers and school children. The overall detection of a Brugada-type ECG was 0.6% in the adults and 0.16% in the school children. A Brugada-type ECG was reported to be detected with an incidence of 0.05% to 0.7% from the health screening examinations in Japan, which was mostly diagnosed by a macroscopic inspection.[7–9,11–13] Therefore,

the present results have a comparable diagnostic accuracy to those of the previous reports in Japan.

Among the 3 types of ECG criteria, type 2/3 was the highest frequency, followed by an order of type S and type 1 in both the adults and school children. The incidence of type S in the school children was nearly equivalent to that in the adults, which might reflect a prominent negativity of the T wave in V1 to V3 leads in this age group. This result may pose a need for special care in differentiating between Brugada syndrome and normal variants in children. These findings suggest that the automatic criteria were useful for detecting Brugada-type ECGs in the mass health screening examinations in adults and school children.

Study limitations

Although ST-segment elevation in V1 to V3 is an important sign of the Brugada phenotype, its presence is not necessarily diagnostic; the final diagnosis can be made through careful evaluation of various conditions including clinical symptoms, a family history, and other electrophysiological examinations. The present criteria for the automatic diagnosis, therefore, cannot be applied as a definite diagnosis for Brugada syndrome. Further, the clinical significance of the presentation of type 2/3 and type S has not been explored, except for cases in Japanese patients.[16] Therefore, the clinical significance of type 2/3 and type S must be further evaluated in Brugada patients of other ethnic groups.

For the diagnosis of Brugada syndrome, type 1 with drug provocation and higher lead placement were considered diagnostic.[5,6] Because the present study did not examine the ECG recordings during drug provocation tests or with a higher lead placement, our estimation of the diagnostic criteria might have missed those cases in which provocation would change a normal ECG into a type 1 ECG or those that would show a type 1 ECG with a higher lead placement.

Various drugs, including not only the ones used for the provocation tests but also those of different classes to be avoided by Brugada syndrome patients, were recommended because of occasional and unexpected developments of Brugada-type ST-segment elevation.[17] We could not obtain any information on these drug uses in our cohorts.

Although the diagnosis of RBBB is traditionally made in the presence of an S wave in the left precordial leads, we differentiated the Brugada-type ECG from RBBB by the J-point amplitude and the voltage amplitudes of the STmax, STmax40, and STmax80, as well as the T-wave morphology in the right precordial leads (V1 to 3). Therefore, RBBB may be more easily excluded from the Brugada-type ECGs by adding the condition of an S wave in the left precordial leads to these criteria.

Conclusion

The automatic diagnostic criteria for type 1, type 2/3, and type S were established to detect Brugada-type ECG in leads V1 to V3. The criteria could differentiate Brugada-type ECGs from those with RBBB. The 3 criteria had a comparable detection rate of Brugada-type ECGs to the macroscopic inspection by experienced observers in the health screening examinations in adults and school children.

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Editorial

Is Early Repolarization Syndrome Different from Brugada Syndrome?

Early repolarization (ER) had been considered an innocuous finding in healthy young individuals. In 2008, Haïssaguerre et al reported that patients with idiopathic ventricular fibrillation (VF) had a high incidence of the ER pattern, a J-point elevation $\geq$0.1 mV with either a notch or slur, in at least two leads other than V1-V3.[1] Since then, the ER syndrome in the inferolateral leads has become a hot topic in the field of arrhythmia as a new entity of sudden cardiac death syndrome, like Brugada syndrome with coved ST elevation in the right precordial leads.

The ER syndrome is identified in 3–6% of the general population.[1,2] Patients are mainly male, have shorter QT intervals, and have high-amplitude J waves at the onset of premature ventricular contractions and VF, which originate from the ventricular myocardium or Purkinje tissue concordant with the location of repolarization abnormalities with a short coupling interval of 260–400 msec. Twenty-seven percent have multiple episodes of VF, which are unresponsive to beta-blockers, but respond to isoproterenol infusion followed by quinidine administration.[3] In spite of these clinical features similar to Brugada syndrome, the incidence of sudden death during sleep and the inducibility of VF by electrophysiological testing are much lower in Brugada syndrome. In addition, the mechanism of VF and the genetic background of ER syndrome are also still unknown. Therefore, ER syndrome is presently considered to be different from Brugada syndrome, although these syndromes may share ionic abnormality and arrhythmogenicity.

Recently, Kamakura et al indicated that inferolateral ER coexisted in 10% of patients with Brugada-pattern ECGs as a predictor of fatal arrhythmic events, and that Brugada patients with Non-Type 1 ECGs were possibly included in the ER syndrome. They also reported the good prognosis of asymptomatic Brugada patients (annual arrhythmic death rate: 0.5%) in their prospective follow-up study.[4] Tikkanen et al reported that the ER pattern in the inferior leads, but not in the lateral leads, was associated with an increased risk of death and that patients with inferior ER $\geq$ 0.2 mV, which was present in 0.3% of all subjects, died from arrhythmia at a rate of 0.8%/year in their retrospective analysis of death certificates in Finland.[2] This rate of death and the prevalence of patients with inferior ER $\geq$ 0.2 mV are interestingly similar to those of asymptomatic Brugada patients, which have been shown by Kamakura et al and previous epidemiologic studies in Japan.

Surveys of cellular and ionic abnormalities as well as prospective follow-up studies, with a predefined and precise definition of the cause of death, are needed to clarify the mechanism and outcome of ER syndrome, which may enable us to determine whether these two syndromes are distinct entities and whether a patient requires the placement of an implantable defibrillator.

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特集　特発性心室細動―病態から治療まで

特発性心室細動類縁疾患*

Brugada症候群

鎌倉史郎[1]

はじめに

Brugada症候群とは12誘導心電図で右脚ブロック様波形と，V_1-V_3誘導におけるcoved型またはsaddleback型のST上昇を呈し，主として若年～中年男性が夜間に心室細動(VF)を引き起こして突然死する疾患である．本症候群にはVFや失神などの症状を伴う有症候群と，心電図異常を有するが症状のない無症候群がある．本疾患は遺伝性不整脈疾患であり，心筋のNaチャネルの*SCN5A*遺伝子変異の他，L型Caチャネル遺伝子の変異など，これまでに計7つの原因遺伝子が同定されている．

本稿ではBrugada症候群が特発性VFのなかで独立した疾患として認められるようになった経緯，成因，治療，問題点などについて述べる．

Brugada症候群の歴史

Brugada症候群の歴史は，1992年11月にBrugada PとBrugada Jが，特異な心電図学的特徴と突然死を呈する8症例をJ Am Coll Cardiol誌に報告したことに始まる[1]．Brugadaらはこの論文のなかで，「8例中6例は男性で，全例で基礎心疾患を認めず，電解質異常やQT延長もない．12誘導心電図では全例が右脚ブロックであり，V_1-V_3誘導で0.1 mV以上のST上昇を伴う．突然死の原因はVFであり，電気生理学検査(EPS)では全例で多形性心室頻拍やVFが誘発される」と述べている．

しかしながら，これと同様な心電図波形は1953年にOsherらにより報告されている[2]．著者らは論文のなかで，この波形は正常人に認められ，急性心筋傷害様ではあるが，記録時期により少しずつ変化しながら継続して認められると述べている．その後，この心電図波形が注目されることはなかったが，1989年になってMartiniが6例のVF例を報告し，そのなかの1例で，右脚ブロックを伴った典型的なcoved型ST上昇を有する心電図を提示した[3]．おそらくこれがVFとBrugada波形との関連を示した最初の論文と思われるが，Martiniはこの波形に関しては特に言及していないうえに，本例を含む6例のVFの原因を右室の器質的心疾患に求めている．

日本においても，1990年に元木らがポックリ病におけるV_1，V_2誘導の異常なST上昇を[4]，相原らが特発性VF例と非特異的なST上昇との関係を報告している[5]．このなかで元木らは4枚の典型的なcoved型ST上昇を示す12誘導心電図を経時的に示しているが，残念ながら“ポックリ”の原因をVFなどの不整脈に求めておらず，

* Idiopathic Ventricular Fibrillation and Related Diseases: Brugada Syndrome

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相原らもcoved型ST上昇とVFとの関連性に言及していなかった．一方，宮沼らは両者の関係に気付いたが，その症例報告の論文(呼吸と循環)が発行されたのはBrugadaらが報告した少し後であった[6]．

Brugadaらが報告した一連の疾患群は，当初特発性VFのサブグループと考えられ，Brugada症候群という呼称も用いられていなかった．しかしながら，その後，本疾患の独特の臨床病態が判明し，J波の発生機序が解明されるにつれて，1996年頃から徐々に症候群と呼ばれるようになった[7]．また，1998年には原因遺伝子の一部が解明され[8]，現在ではBrugada症候群はQT延長症候群と同様に，独立した遺伝性不整脈疾患の一つとして扱われるに至っている．

Brugada症候群の成因

1．原因遺伝子

Brugada症候群では現在7つの原因遺伝子が同定されている．1998年にNaチャネルαサブユニットをコードする*SCN5A*遺伝子の変異(B1)が報告された後[8]，しばらく新しい原因遺伝子の発見がなかったが，2007年になり*GPD1L*遺伝子変異(B2)と[9]，L型Caチャネルのα_1サブユニットの*CACNA1C*遺伝子(B3)，およびβ_2bサブユニットの*CACNB2b*遺伝子の変異(B4)が報告された[10]．2008年にはNaチャネルβ_1サブユニットをコードする*SCN1B*変異(B5)[11]とKチャネルβサブユニットをコードする*KCNE3*変異(B6)[12]とが報告され，2009年になってNaチャネルβ_3サブユニットの*SCN3B*変異由来のBrugada症候群(B7)の存在が確認された[13]．これら7つの遺伝子変異のうち*SCN5A*，*GPD1L*，*SCN1B*，*SCN3B*ではNa電流を減少させるloss of functionが，*CANA1C*と*CANB2b*ではL型Ca電流を減少させるloss of functionが，*KCNE3*ではI_{to}電流を増加させるgain of functionがBrugada症候群の成因となっている．

ただ，Brugada症候群のうちでこれらの遺伝子変異が見つかるのは15～30%程度に過ぎず，それ以外の症例にどのような遺伝子異常があるかは未だ不明である．このため，今後，Brugada症候群ではQT延長症候群と同様に種々の原因遺伝子が同定されると考えられている．

一方，遺伝子変異ではなく，遺伝子多型により軽症のBrugada症候群がもたらされる可能性が指摘されている．Bezzina，Shimizuらは*SCN5A*の転写領域に3つの組み合わせ(ハプロタイプ)で連鎖する6つの多型を同定した．このうち，ハプロタイプBがアジア人にのみ存在し，転写活性や心臓の興奮伝導能を*SCN5A*変異例ほどではないが，低下させていることを報告した[14]．このハプロタイプはBrugada症候群の直接原因ではないが，本症候群がアジア人に多いという人種差を説明しうるものと考えられている．

2．ST上昇と心室細動の発生機序

Brugada症候群では遺伝子変異を背景として，右室流出路心外膜側で内向きのNa電流やCa電流などが減少する結果，I_{to}など相対的な外向き電流が増加して，活動電位第1相のnotchが大きくなり，心外膜-心内膜間に電位勾配が生じる．それによりJ波の増大に引き続いてST上昇が起こる．さらに相対的な内向き電流が減少すると，第2相のdome形成が遅延し，心内膜側より心外膜側で再分極が遅れて，ST上昇に加えT波の陰転が生じることが動物実験で証明されている．

この相対的な内向き電流がさらに減少すると心外膜側でdomeが消失し，周囲との間に大きな電位勾配が生じるために，domeの消失した心筋において再脱分極が起こる．これはphase 2リエントリーと呼ばれ，VFの起源であると考えられている．ただ，このphase 2リエントリーによる1発目の心室期外収縮(PVC)は，domeの消失だけでは発生せず，心外膜側の局所的な再分極のばらつきが必要になる．またPVCが持続し，VFが持続するためには，再分極異常だけでは説明できず，軽度の脱分極が必要であることがAibaらの報告で指摘されていた[15]．

最近Lambiaseらは，Ensiteのマッピングシステムを用いて，早期刺激時の右室心内膜局所の伝導特性，再分極特性を種々の指標を用いて解析し，さらに電気刺激によるVF発生部位と伝導遅延部位との相関を検討した[16]．その結果，

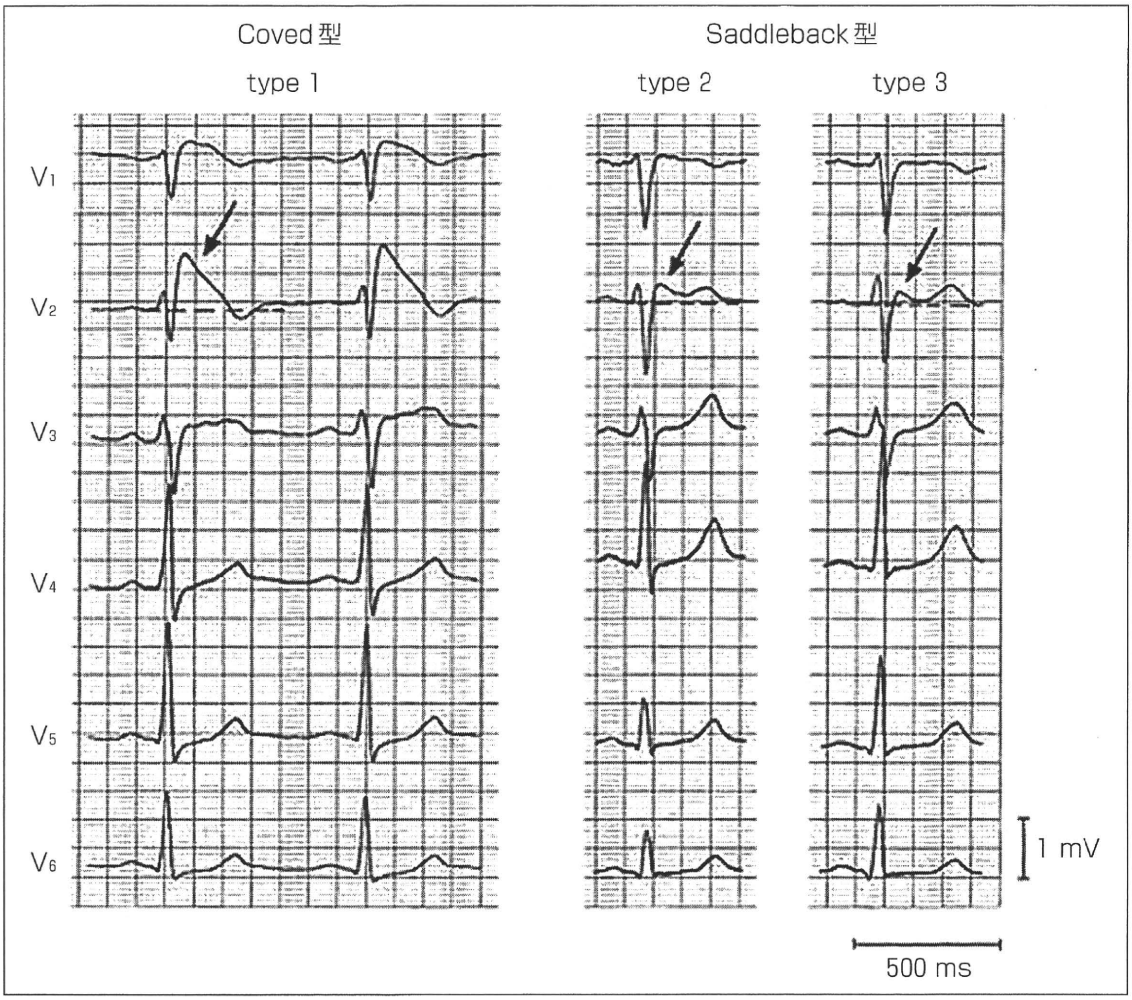


図1　Heart Rhythm学会のBrugada症候群心電図分類

Brugada症候群では短い連結期での刺激で右室前壁に著明な伝導遅延が生じるとともに，空間的な再分極のばらつきと，回復曲線に急峻な傾斜が生じ，伝導遅延と伝導ブロックが生じた部位からVFが発生することを確認した．彼らは，VFは局所の伝導遅延と再分極異常の両方の機序に基づいて発生するとし，重要なのは局所の伝導遅延であると主張している．

これまでBrugada症候群例では，貫壁性および心外膜層内で再分極時間のばらつきが生じて，phase 2リエントリーからVFが発生するという，“再分極仮説”が主流となっていた．一方，右室局所の伝導遅延に原因を求める“脱分極仮説”も少数意見として支持されていた．本研究では，Ensiteを用いて仮想の心内膜単極電位からisochrone mapを構築しているため，伝導遅延と再分極の評価に問題を残し，かつ自然発生のPVCでない点が限界といえる．しかしながら，VF発生時には再分極異常だけでなく脱分極異常が必要であることが改めてヒトで証明されたともいえる．

心電図所見

1．心電図分類

米国および欧州Heart Rhythm学会はV_1-V_3誘導のST異常を3つのタイプに分類し，いずれもJ点で0.2 mV以上の上昇があるが，coved型でT波が陰転しているものをType 1，ST終末部が0.1 mV以上上昇していてsaddleback型を呈し，T波が陽性または2相性のものをType 2，ST終末部の上昇が0.1 mV未満で，saddleback型またはcoved型で，かつT波が陽

A型：①J点≧0.2 mV
②R′>R′40>R′80　R′: Peak R′（R′40, R′80：R′点より40 msec, 80 msec後）
③T波：陰性か基線上
④R′-R′40点≦0.4 mV
B型：①J点≧0.2 mV
②J点>ST min　ST min：ST部分の最下点（終末部）
③ST min>0 mV
④T波>ST min
⑤T波：陽性；ST min>0 mV
2相性；ST min ≧0.1 mV
C型：① 0.2 mV>J点≧0.1 mV
②③④はAと同一条件
⑤R′-R′40≧0.04 mv
⑥R′40-R′80≧0.04 mv

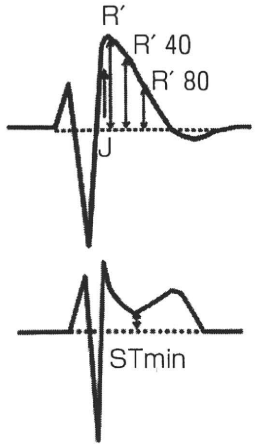


図2　日本心電学会が提唱するBrugada症候群の心電図自動診断基準

性のものをType 3と定義している(図1)[17]．ただ，Type 1波形が自然の状態で，またはピルジカイニドなどのNaチャネル遮断薬による薬物負荷後に認められる場合はBrugada型心電図としてもよいが，負荷後においてもType 2やType 3にとどまる場合はBrugada型とは断定できないとする意見が主流である．

しかしながら，Type 2またはType 3であっても高位肋間(1〜2肋間上方)でV_1-V_3誘導を記録すると，Type 1心電図を示す場合があり，その予後は通常部位でType 1を示す例と変わらないことが示されている[18]．また，Type 1，2，3に合致しないBrugada様心電図波形(例えばJ点波高が0.1-0.2 mVのもの)も数多く認められる．さらにType 3波形は，Type 1またはType 2波形に付随している場合が多く，V_1-V_3誘導でType 3波形だけが認められる例は極めて少ない(数%以下)のが事実である．

このため，2006年に日本心電学会からBrugada症候群の心電図に関する自動診断基準が提唱されている[19]．本基準のA型はType 1にT波陰転のないcoved型を含み，B型はType 2，3を包括した分類であり，かつC型はJ点で1 mm以上で2 mm未満のcoved型を含む．これらBrugada波形は，正確には右脚ブロック様波形と表現するのが正しく，本基準で通常の右脚ブロックによるV_1，V_2誘導のR'をJ点と取り間違えないような工夫が加えられている点でも，より優れたタイプ分類法といえる(図2)．

右側胸部誘導でのBrugada様心電図変化は，催不整脈性右室心筋症(ARVC)，心筋梗塞，狭心症，心筋炎，肺血栓塞栓症などでも認められる．しかしながら，何らかの器質的心疾患に基づいてST上昇が生じている場合，または12誘導心電図の他の誘導にST低下などが認められる場合はBrugada症候群とはしないのが通常である．

2．有病率，発症率

Type 1心電図に限れば，日本人学童の有病率は0.005%程度，成人の有病率は0.1〜0.2%程度で，加齢とともにその比率は増加する．発症率は年間0.014%程度であり[20]，30歳台から40歳台に発症のピークがあって，その平均発症年齢は45歳である．

3．心電図変化をもたらす薬剤，病態

前述のごとく，Naチャネル遮断薬投与後や，自然の状態で，2 mm以上のcoved型ST上昇(Type 1)が認められるものをBrugada症候群とするというのが従来の見解であるが，コントロール時に1 mm以上のcoved型，またはsaddle-back型のST上昇を有する症例をBrugada症候群に含むと，50〜70%の症例がNaチャネル遮断薬でType 1波形に変化する．このように

Brugada症候群にST上昇をもたらすものとして，Naチャネル遮断薬の他，Ca拮抗薬，β遮断薬，狭心症薬，向精神薬，麻酔薬，低K血症，発熱などが指摘されている[17]．このうち，実際に突然死が複数例で報告されているのは，プロポフォールなどの麻酔薬と発熱であり，いずれもNa電流の低下に由来すると考えられている[21]．一方，Brugada症候群では，運動負荷中やイソプロテレノール投与中にはST上昇が改善するが，運動負荷後や投与後には再上昇することが多い．

4．合併する心電図所見

Naチャネルをコードする*SCN5A*遺伝子変異を原因とする疾患はBrugada症候群の他にQT延長症候群，家族性心臓ブロック，洞不全症候群，乳幼児突然死症候群など多数あり，それぞれが独立した疾患でなく，互いにオーバーラップすることが知られている．このため，Brugada症候群ではQT延長や徐脈が合併する例が少なくない．なかでもLQT 3とのオーバラップでは，その4割がE 1764 Kという同一の変異に由来することがMakitaらにより報告されている[22]．

一方，L型Caチャネルの*CACNA1C*遺伝子と*CACNB2B*遺伝子の変異ではQT短縮が約半数で指摘されている[10]．実際に委託研究の登録例でBrugada症候群全体におけるQT短縮合併の頻度を検討したところ，360 msec以下のQT短縮が約5%に認められた．

病　態

1．性　差

Brugada症候群は男性に多く発症することが知られており，家系例を多く含む欧米の研究では，男性が全体の7～8割を占めると報告されている．しかしながら，主として発端者を集積した本邦の報告ではほとんどが男性であり，女性は5%にすぎない．このようにBrugada症候群に男性が多いのは，右室心外膜細胞でI_{to}密度が高く，第1相のnotchが深いために*SCN5A*などの遺伝子変異や種々の外的要因によるイオン電流の影響を受けやすいうえに，男性ホルモン(テストステロン)の関与が示唆されている．テストステロンはI_{Ks}，I_{Kr}，I_{K1}などの外向きK電流を増強させ，逆にL型Ca電流などの内向き電流を減少させることが知られているが，Brugada症候群例では血中テストステロンレベルが有意に高いことが報告されている[23]．

2．家族歴

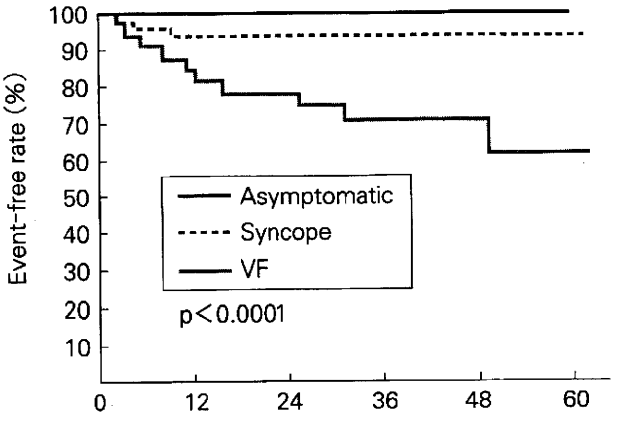
45歳未満での突然死，またはBrugada症候群の家族歴を有する症例の比率も，欧米と日本の報告とでは大きく異なる．欧米の報告は家系例を多く含むため，必然的に突然死の家族歴を有する症例が多く，その比率は25～55%にのぼる[24~26]．一方，本邦で発端者だけを対象として検討すると，突然死の家族歴を有するものは14%にとどまる[27]．この数値はPrioriらが発端者の集団で認めた20%とほぼ一致する[25]．

3．心室細動

Brugada症候群では副交感神経刺激により，L型Ca電流が減少してST上昇を引き起こす．また，徐脈によりI_{to}電流が増加して，STをさらに上昇させる．このため，Brugada症候群では副交感神経の緊張時，または交感神経の緊張低下時にVF発作が生じやすい．失神は安静時または夜間睡眠中に生じやすいのが特徴で，その際，約半数でPVCが認められる[27]．PVCは*SCN5A*遺伝子に変異のない例ではほとんどが右室流出路起源であるが，変異例では左室起源PVCが多く存在すると報告されている[28]．EPSでは2連発または3連発の心室早期期外刺激で50～80%の例にVFや多形性VTが誘発され，その誘発率は無症候群よりも有症候群で有意に高い[27]．

4．心房細動，その他

心房細動(AF)は15～30%の症例に合併しており，その多くは発作性AFであるが，有症候群，特にVF群で合併頻度が高いことが報告されている．また，*SCN5A*変異例ではEPSでAFが有意に誘発されやすいが，臨床的なAF発生とは関係しないと報告されている[29]．これに加えてBrugada症候群では冠攣縮性狭心症，神経調節性失神の合併が，それぞれ20～30%の症例に認められる．



Months	Inclusion	12	24	36	48	60
Asymptomatic	82	81	69	45	26	1
Syncope	51	45	40	33	21	3
VF	33	28	24	18	10	2

図3 J-IVF研究での登録症例全体の症状別の累積心事故回避率(文献[30]より引用)

検査とその意義

1. 非侵襲的検査

Brugada症候群が疑われる時に行う非侵襲的検査として，12誘導心電図(高位肋間でのV_1-V_3誘導記録を含む)，運動負荷心電図，薬物負荷心電図，加算平均心電図，TWA(T波オルタナンス)，遺伝子検査などがある．12誘導心電図では，V_1-V_3誘導のST上昇，J波，QRS幅(r-J時間を含む)[30]，PQ時間，Tpe時間，Tpe dispersion，QRS波fragmentation[31]などが検討され，運動負荷心電図では運動中または運動後のV_1-V_3誘導におけるST変化が解析の対象となる．また，薬物負荷心電図ではピルジカイニドなどのNaチャネル遮断薬投与後のV_1-V_3誘導のST上昇の有無を確認する必要がある．ただ，運動負荷と薬物負荷はType 1心電図(J点で2 mm以上のcoved型ST上昇)を顕在化することを主目的とした検査でもあり，明らかなType 1 ST上昇が過去に記録されている場合は必ずしも施行しなくてよいとする意見もある．一方，加算平均心電図やTWAは，Brugada症候群の予後の予測に有用との報告[32]があり，運動負荷や薬物負荷でのST上昇形式も，今後，予測指標になる可能性が指摘されている．

遺伝子検査はBrugada症候群の診断において最も信頼できる検査法といえる．しかしながら，遺伝子検査を施行できる施設は限定されており，*SCN5A*などの遺伝子変異が検出される確率が全症例の30%以下にとどまる点が今ひとつの限界でもある．この他，Brugada症候群の診断に有用な検査として糖負荷試験，満腹テスト，CT，MRIなどの画像検査などが挙げられる．しかしながら，これまでに述べたほとんどの指標は大規模登録研究において，長期予後との関係が未だ証明されていないという事実も存在する．

2. 電気生理学検査(EPS)

Brugada症候群の侵襲的検査としてはEPSがある．本検査は，1998年頃からBrugadaらが予後予測に有用と報告しはじめ，2005年のsecond consensus報告[17]における治療指針にも記載されたため，最近まで無症候例のICD適応決定に必須の検査と考えられていた．しかしながら，その後，本検査の意義に関して否定的な見方が強まっている．Paulらは，EPS施行例の予後をメタ解析した結果，EPSでのVF誘発性は心事故を予測する有意な指標でなかったと述べている[33]．

これまでEPSが有用であると報告したのはBrugadaだけであるが，Brugadaらの報告は右室心尖部1カ所から誘発し，最小期外刺激間隔は200 msec以上である[24]．一方，他の多くの報告では右室の2カ所から誘発し，期外刺激間隔も一定していない．この誘発法の差異が結果に影響した可能性は否定できないが，Brugadaらの報告には後ろ向きに集積した症例が多く含まれ，バイアスが存在する可能性が指摘されている．現在，特発性心室細動研究会では，統一したプロトコールでEPSを施行した症例の経過観察がなされており，数年後にはEPSの意義に関して結論が導き出されると思われる．

予後

これまでBrugada症候群においては，J点で2 mm以上の電位を有するcoved型ST上昇(Type 1心電図)例だけを対象として登録研究が

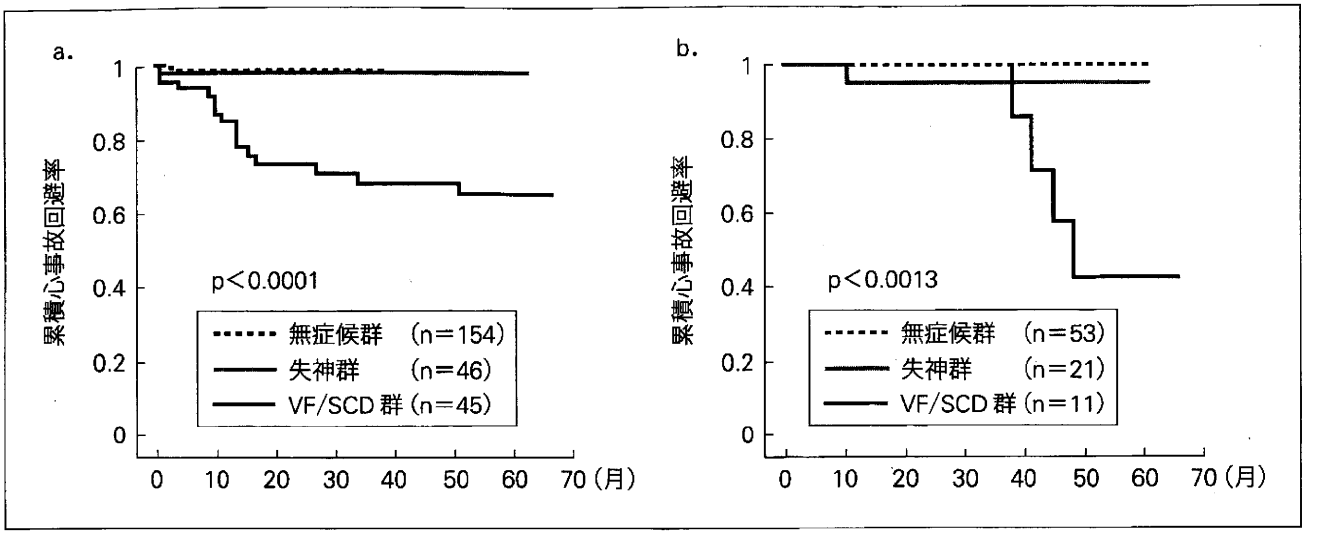


図4　循環器病委託研究の登録例(発端者)の予後
a. Type 1群の症状別の累積心事故回避率，**b.** 非Type 1群の症状別の累積心事故回避率

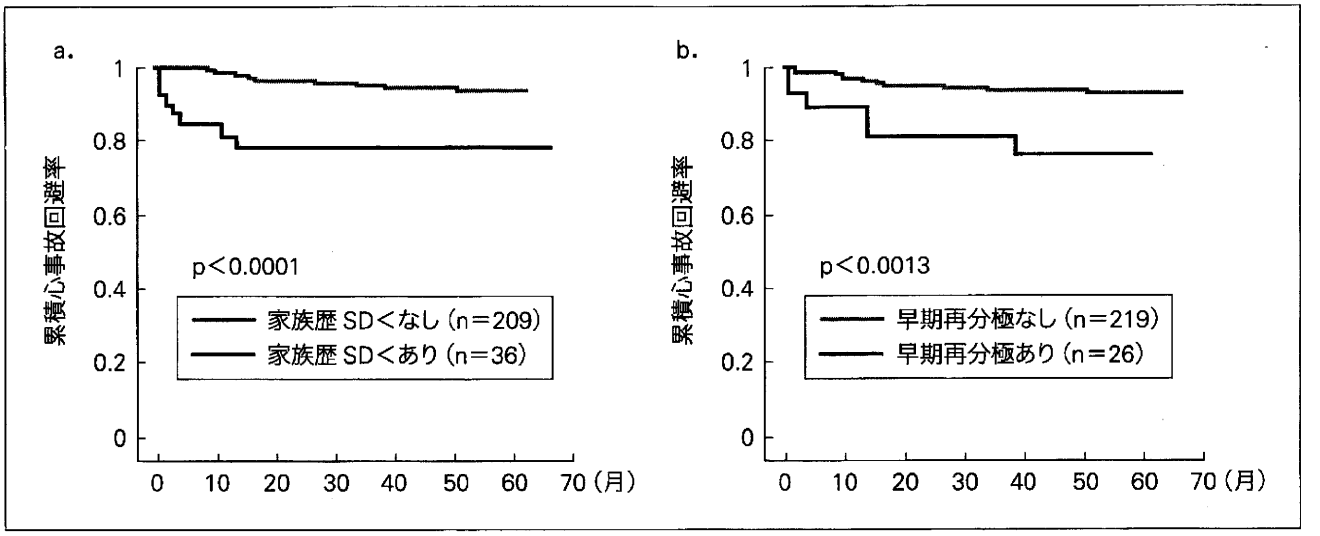


図5　循環器病委託研究のType 1群における指標別の予後
a. 突然死家族歴を有する例と有さない例の累積心事故回避率，**b.** 早期再分極を有する例と有さない例の累積心事故回避率

なされ，その予後が検討されてきた．しかしながら，無症候群を含めて，全ての症例の予後が悪いという結果と，全ての予後は良好であるという，全く相反する結果が報告され，果たしていずれが正しいのかが不明であった[24~26]．また，それらの結果に基づいて治療ガイドラインが報告されていたが[17]，それが日本人に適しているかは疑問であった．このため，2001年から厚生労働省の循環器病委託研究と，特発性心室細動研究会によるJ-IVF研究が開始され，Brugada症候群の予後が前向きで検討された[27,30]．

その結果，いずれの研究においても無症候群と失神群の予後は良好で，VF群の予後は不良であった(図3，4)．委託研究では非Type 1心電図(Type 2，Type 3，J点で1 mm以上2 mm未満のcovedまたはsaddleback型ST上昇)を有する症例の予後も検討された．それによると，非Type 1群もType 1群と同様な予後を示し，VF既往例では約10%/年の頻度で心事故を生じていた(図4)．

クラスⅠ:
心停止・心蘇生例，自然停止するVF/多形性VTが確認されている例
クラスⅡ:
Brugada型心電図を有する例(薬物負荷，1肋間上の心電図記録例も含む)で，失神，家族歴，VF誘発のうち，2つ以上の指標があればⅡa，1つだとⅡbとする

	Coved(type 1)型(自然or薬物)						
失神	+	+	+	+	−	−	−
突然死家族歴	+	+	−	−	+	+	−
VF誘発	+	−	+	−	+	−	+
クラス分類	Ⅱa	Ⅱa	Ⅱa	Ⅱb	Ⅱa	Ⅱb	Ⅱb

図6 QT延長症候群(先天性・二次性)とBrugada症候群の診療に関するガイドラインにおけるBrugada症候群のICD植込み適応(文献[38]より引用)

心事故予測因子

1．無症候群と失神群の予測因子

これまで欧米では男性，失神，自然の状態でType 1心電図が記録される例，EPSでのVF/多形性VT誘発例が，無症候群と失神群における不良な予後を予測する因子とされている[24~26,34]．一方，突然死の家族歴は予測因子とされていなかった．これは欧米の報告が家系例を多く含むために，家族歴を有する例と有さない例の間に差がでなかったと考えられる．J-IVF研究では無症候群と失神群において心事故を予測しうる因子は見つからなかったが，委託研究では70歳未満における突然死の家族歴が心事故の独立した予測因子であった[27]．一方，無症候群と失神群において従来報告された因子(失神，自然のType 1心電図，EPSでのVF/多形性VT誘発)は，本邦では予測に有用ではなかった．

2．全ての群における予測因子

VF群を含めた全症例の多変量解析に関しては，委託研究では，突然死の家族歴と，下後壁誘導での早期再分極の合併が不良な予後の独立した予測因子であり(**図5**)[27]，Type 1群では，突然死の家族歴と早期再分極合併が，非Type 1群では突然死の家族歴が有意な心事故予測因子であった．一方，J-IVF研究では，AFの既往例で心事故発生率が高く，またV_2誘導でのr-J間隔≧90 msec以上と，V_6誘導でのQRS幅≧90 msecが心事故の有意な予測因子であった[30]．

性差については，本邦では女性例が極めて少ないことから評価不能であった．最近Benitoらは，単変量解析において女性は男性に比べ有意に予後が良く，PR時間の延長した例に心事故が生じやすかったが，多変量解析では性差は独立した予測因子でなかったと報告している[35]．彼らの報告には従来の欧米の報告と同様に家系例が多数含まれている．そのため，性差が真の予後予測因子か否かは，発端者のみを集積した，より長期間の大規模観察研究での解明が必要と思われる．

Brugada症候群が遺伝性疾患であることから，遺伝子変異が予後に影響する可能性は高い．これまで*SCN5A*変異を有する例では，ない例に比べてPQ時間，HV時間が延長しており，加齢とともにPQ時間とQRS時間が延長する[36]．また，変異例では心房内伝導時間が有意に長く，AF誘発率も高いと報告されている[29]．さらにQRS内の複数のspike(fragmentation)を有する例では，ない例より*SCN5A*遺伝子が陽性の傾向が強く，予後が悪いとも報告されている[31]．しかしながら，遺伝子変異が予後の予測に関して有用であるとの報告は未だなされていない．この原因として，Brugada症候群の変異例における浸透率の低さが挙げられている．遺伝子変異と予後との関係に関しても，性差と同様に，多数の発端者における検討が今後必要となろう．

治　療

1．非薬物治療

本邦における予後調査結果から，Brugada症候群でVFの既往がある場合は，心電図波形に関係なくICD植込みが必要と考えられる．

一方，欧米のガイドラインでは，失神例，VTを有する例もICD植込みの適応(クラス2a)とされており[37]，無症候群に関しても，かつてはEPSによるVF誘発例でのICD植込みの必要性が強調されていた[17]．しかしながら，夜間の心肺停止を伴うような失神はVFと同様に扱ってもよいが，それ以外の失神は真に不整脈由来か否かの鑑別が難しい．現に本邦の調査研究では失神群の予後は極めて良好であった．また，Brugada症候群で認められるVTは，多形性VTではなく，

特発性の流出路起源の単形性非持続性VTである場合が多く，予後との関連も不明である．さらにEPSによるVF誘発は近年ではその意義が疑問視されている．以上より本邦では欧米とは異なる治療基準が必要と考えられている．

このため，2007年12月に発表された日本循環器学会の診療ガイドライン[38]では，失神群，無症候群においては，VF誘発や失神をICD植込み条件を満たす単独の指標とはせず，失神，突然死家族歴，EPSでのVF誘発のうち2つ以上を満たす場合をクラス2a，それ以外は2bの適応としている．本ガイドラインは現時点で最も妥当な指針と思われるが，一方で対象をType 1例に限定していることと，失神例の取り扱いやEPSの意義に関して，若干議論の余地を残している(図6)．

2．薬物治療

VF多発時の薬物治療としてはイソプロテレノールの持続点滴が有用である．VF予防の経口薬としては，これまでβ刺激薬や，I_{to}チャネル遮断作用のある薬物(キニジン，ベプリジルなど)，Ca電流を増加させるシロスタゾールが有効と報告されている．しかしながら，これらの薬剤はVFを完全に抑制するまでには至らないため，無症候群の一次予防には用いられていない．

一方，Brugada症候群でAFや冠攣縮性狭心症，神経調節性失神を伴うことが少なくない．この際，Naチャネル遮断薬やCa拮抗薬，β遮断薬，向精神薬などが使用される可能性があるが，これらの薬剤では心筋のイオン電流を変化させて，STを上昇させることが報告されている．このすべてがBrugada症候群例にVFを発生させるわけではないが，治療の際にはその選択に十分な留意が必要となろう．

Brugada症候群と早期再分極症候群との類似点

特発性VFでは，V_1-V_3誘導でのST上昇はないが，II，III，aVF誘導またはV_3-V_6誘導でJ波が存在～増高していたり，saddleback型に近いST上昇の見られる例が報告されていた．また，J波増高とBrugada型(coved)心電図の両方が，異なった時期の異なった誘導部位で認められる例もあり，それらはBrugada症候群の亜型であるか，またはVFの基質がBrugada症候群とは異なる部位にある可能性が示唆されていた．

近年，Haïssaguerreらは特発性VF 206例を集積し，V_1-V_3誘導を除く下後壁誘導(II，III，aVF，I，aVL，V_4-V_6)で0.1 mV以上のJ波増高を伴う早期再分極例の臨床的特徴を報告した[39]．その詳細は別稿に譲るが，病態，予後ともにBrugada症候群に類似し，軽症のBrugada症候群と言うべき臨床像を呈していた．

HaïssaguerreらはV_1-V_3誘導でのType 1心電図例を除外しているため，本疾患群はBrugada症候群とは異なる新しい概念と考えられている．しかしながら，非Type 1心電図を呈するBrugada症候群がこのなかに含まれている可能性を否定できない．今後Brugada症候群との類似性を含めて，真の早期再分極症候群の病態の解明が望まれる．

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