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

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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

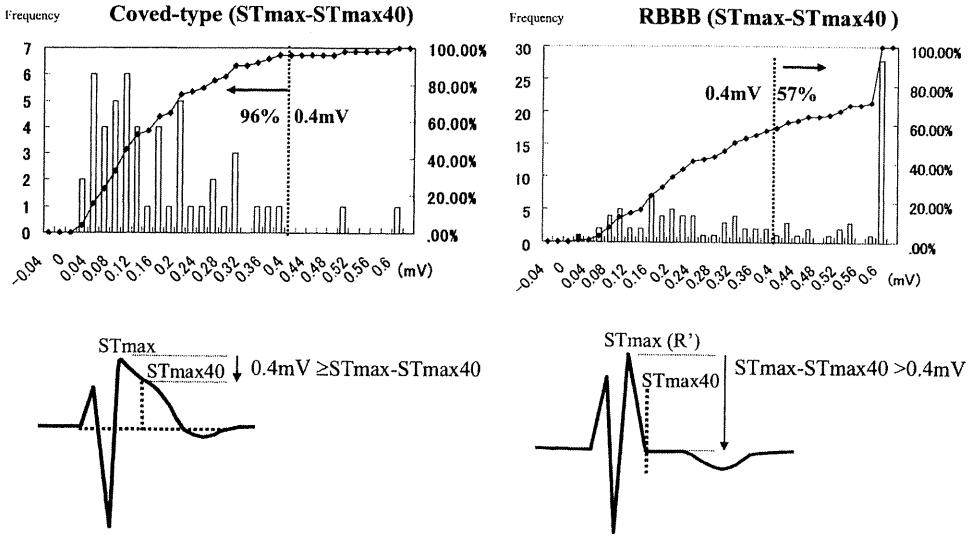

Figure 1 Distinction of a coved-type ST-segment elevation in Brugada syndrome (Brugada) and the ST-segment in right bundle branch block (RBBB). The histogram of the gradients between the amplitude of the STmax and STmax40 (STmax – STmax40) in 51 leads showing coved-type ST-segment elevation (Brugada 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.

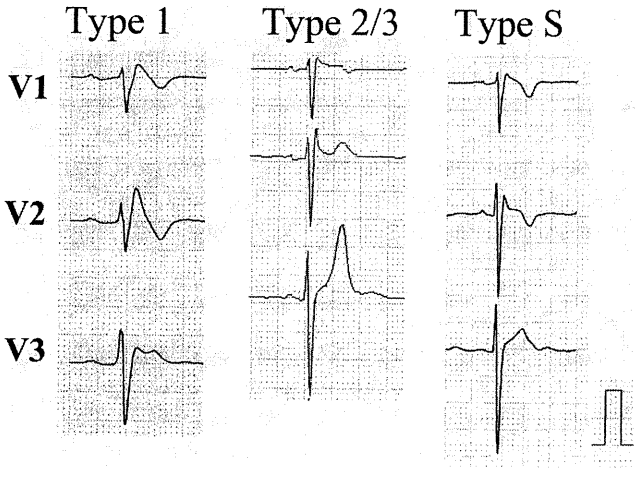

Figure 2 Electrocardiographic records of the 3 types diagnosed by the proposed criteria. **Left:** Type 1. **Middle:** Type 2/3. **Right:** Type S.

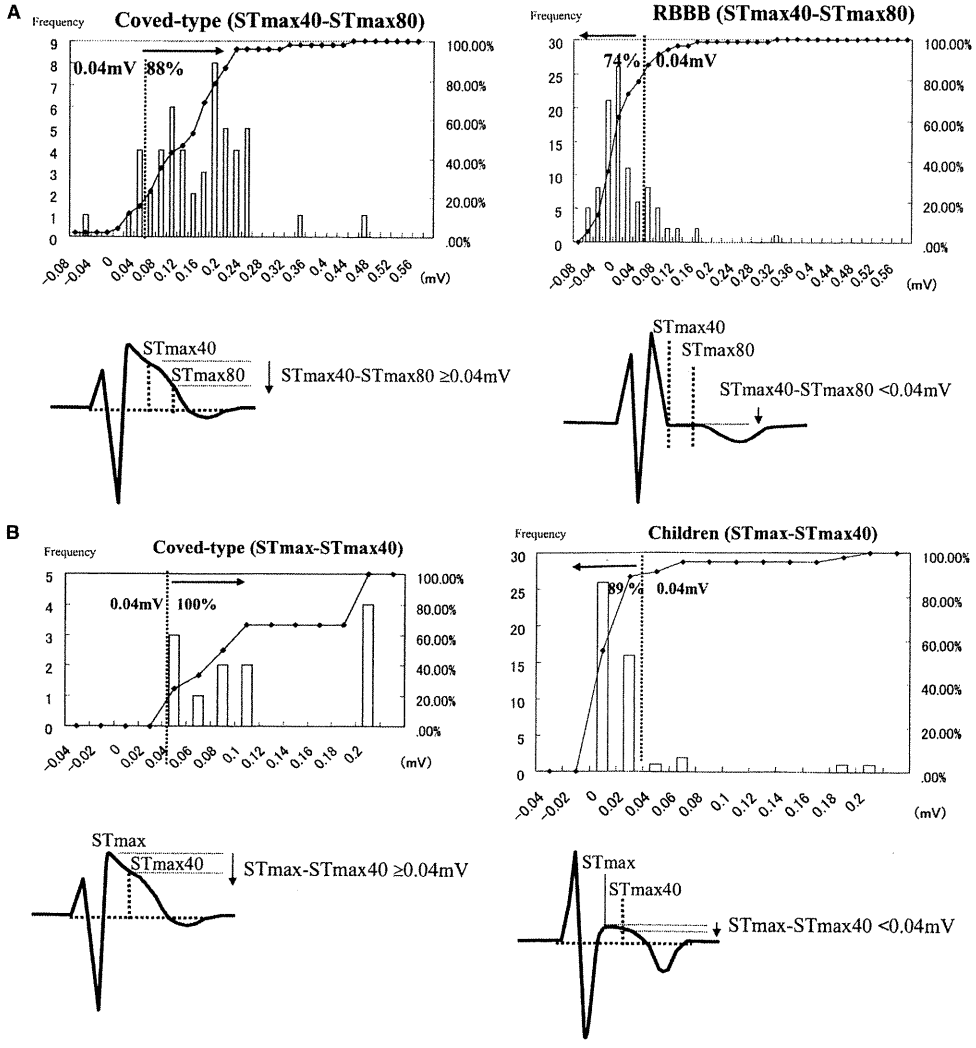

Figure 3 A histogram of the gradients between the amplitude of the STmax40 − STmax80 **(top)** and STmax − STmax40 **(bottom)** in the 2 groups (Brugada and RBBB groups). **Top:** Using the criteria of STmax40 − STmax80 ≥ 0.04 mV, the majority (88%) of the patients in the Brugada group were included, 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

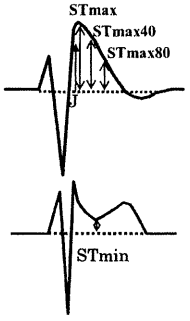

Figure 4 Classification and waveforms of Brugada-type electrocardiograms. See the detailed explanation in the text.

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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一般住民検診におけるBrugada型心電図の長期予後調査

Brugada症候群の長期予後調査研究班
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Brugada症候群は右側胸部誘導におけるST上昇を特徴とし，致死性心室性不整脈による突然死をきたす可能性を有する症候群である．無症候性Brugada症候群は比較的突然死の危険性が低いと考えられているが，一般住民における長期予後に関する報告は少なく，明らかではない．われわれは，日本人の一般住民検診での循環器リスク疫学研究(Circulatory Risk of Communities Study：CIRCS)におけるBrugada型心電図の罹患率・長期予後を調査した．1983～1986年に住民検診を施行し，CIRCSに登録された40～65歳までの4，113名の健康成人(男性1,768名，女性2,345名)のうち，心疾患の既往を有する81例，および追跡調査不能の147例を除外し，3,885例を最終対象者とした．12誘導心電図を読影し，V_1～V_3誘導でJ点が0.2 mV以上の上昇とST部分がcoved型を示すものを典型的Brugada症候群(type 1)，type 2，type 3およびV_1～V_3誘導でJ点が0.1 mV以上の上昇とST部分がcoved型/saddleback型を示すものをまとめて非典型的Brugada型心電図(atypical)群，それ以外を対照(control)群と分類した．2004年までの最長22年間にわたる追跡調査を行い，24時間以内の突然死の発生をエンドポイントとした．7例(0.18%)の典型的Brugada症候群，83例(2.1%)の非典型的Brugada型心電図を認め，3,795例(97.7%)は対照群に分類された．22年間にわたる予後調査で，対照群では58例(1.5%)の突然死が認められたのに対し，典型的Brugada症候群では0例(0.0%)，非典型的Brugada型心電図群では4例(4.8%)の突然死が認められた．突然死した非典型的Brugada型心電図群のうち4症例中3症例で，下壁誘導または側壁誘導にノッチまたはスラーを認めた．V_1～V_3誘導で0.1 mV以上のJ点の上昇を有し，ST部分がcovedあるいはsaddleback型ST上昇を示す非典型的Brugada型心電図例で，突然死のリスクが高い可能性が示唆された．

Keywords
- Brugada症候群
- 突然死
- 早期再分極症候群

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Circulatory Risk in Communities Study (CIRCS)
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Ⅰ．はじめに

現在，本邦では年間約5～10万例もの心臓突然死が発生していると推定されるが，そのうち約10～20％は原因不明の突然死症候群として扱われている．Brugada症候群は右側胸部誘導におけるST上昇という特徴的な心電図所見を有し，心室細動による突然死をきたしうる症候群である[1]．アジア人男性に多く発症し，本邦における突然死症候群のなかで最も頻度が高いと考えられている．心室細動や心停止から蘇生された例，すなわち症候性Brugada症候群は高率に突然死や心室細動を再発する危険性を有し，予防的治療として植込み型除細動器(ICD)の絶対的な適応である[2]．しかし，無症候性Brugada型心電図症例は診断基準があいまいであること，一般住民における長期予後調査が十分に行われていないことから，治療・管理をどのようにすればよいのか十分に示されていない．われわれは，1969年から5地域で定期的に実施している循環器リスク疫学研究(Circulatory Risk in Communities Study : CIRCS)で得られた心電図の再解析を行うとともに，本邦の一般住民における無症候性Brugada症候群の疫学的実態を評価し，有病率・新規発症率・臨床背景・長期の自然予後を把握することを目的とした観察研究を実施した．

Ⅱ．研究対象と方法

研究対象として，筑波大学大学院人間総合科学研究科社会環境医学教室，大阪大学大学院医学系研究科公衆衛生学教室および愛媛大学大学院医学系研究科医療環境情報解析学で1969年から30年間以上継続して行われているCIRCSの登録症例を用いた．今回の研究では，1982～1986年に茨城県K町の住民健診を受診した40歳以上65歳未満の4,113名(男性1,768名，女性2,345例)のうち，心疾患の既往を有する81例，および追跡調査不能の147例を除外し3,885例を最終対象者とした．各年度の心電図を読影し，米国不整脈学会および欧州不整脈学会による2 nd consensus report[1]に基づき，V_1～V_3誘導におけるJ点の0.2 mV以上の上昇と上に凸型(coved型)のST上昇を認めるものを典型的Brugada症候群(type 1)と診断した．Type 2(0.2 mV以上のJ点上昇および0.1 mV以上のsadddleback型ST上昇を認めるもの)，type 3(0.2 mV以上のJ点上昇および0.1 mV未満のsadddleback型ST上昇を認めるもの)，およびJ点の0.1 mV以上の上昇とcoved型あるいはsaddleback型ST上昇が認められるものをまとめて，非典型的Brugada型心電図(atypical)と分類した．J点の0.1 mVを超える上昇がないものを対照(control)とした．

2004年まで22年間にわたる追跡調査を行い，転出者，死亡者を特定した．死因は死亡診断書(死亡票)，アンケート調査，救急搬送記録，診療記録などによって特定した．突然死は症状出現から24時間以内の原因不明の死と定義した．Type 1，atypical，control各群の突然死発生率を算出した．

Ⅲ．研究結果

表1に各群の背景・予後を示す．典型的Brugada症候群(type 1群)は7例(0.18%)，非典型的Brugada型心電図(atypical群)は83例(2.1%)に認められた．両群とも85％以上が男性であり，有意に年齢が高く，body mass index (BMI)が低いという特徴が認められた．

22年間の予後調査期間中の突然死発症率を，control群 3,885例中58例(1.5%)と比較したところ，type 1群7例中0例(0.0％)，atypical群83例中4例(4.8%)で，atypical群に突然死が多く認められた．

突然死を起こしたatypical群の4症例の背景を表2に，心電図を図1に呈示する．

症例1は64歳で突然死した男性で，V_2誘導で0.2 mVを超えるJ点上昇と0.1 mVを超えるsaddleback型ST上昇を認めたtype 2のBrugada型心電図である．aV_L誘導でスラーが，V_1誘導でノッチが認められた．

表1　対照群，典型的Brugada症候群，非典型的Brugada型心電図群の背景と突然死

	対照群 (control)	典型的Brugada症候群 (type 1)	非典型的Brugada型心電図群 (atypical)	p値
対象者数(n)	3,795	7	83	—
全対象者数における割合(%)	97.7	0.18	2.14	—
年齢(年)	54.8	57.1	58.1	0.004
性別(%, 男性)	42.4	85.7	85.5	<0.001
BMI(kg/m²)	23.5	21.5	22.5	0.004
収縮期血圧(mmHg)	136	124	134	0.18
拡張期血圧(mmHg)	80	72	80	0.14
左室高電位(%)	15	21	16	0.91
突然死(n)	58	0	4	—
突然死発症率(%)	1.5	0.0	4.8	—

表2　突然死した4症例

	症例1	症例2	症例3	症例4
年齢·性別	64歳男性	60歳男性	63歳男性	74歳男性
J点波高(mm)	6.0	3.8	1.7	1.6
T波形	陽性	陽性	陽性	陽性
ST-T波形	saddlebach	saddlebach	saddlebach	saddlebach
ST部波高(mm)	2.0	0.8	1.4	1.2
分類	type 2	type 3	J point elevation	J point elevation
ノッチ	−	+	+	−
スラー	+	−	−	−

症例2(60歳男性)は，0.2 mVを超えるJ点上昇を有するが，ST上昇が0.1 mVを超えておらず，type 3のBrugada型心電図である．Ⅱ，Ⅲ，aV_F誘導でS波に重なるノッチが，aV_L誘導でスラーが認められた．

63歳および74歳で突然死を起こした症例3，症例4は，いずれもJ点の上昇が0.1 mV以上0.2 mV未満であり，本研究ではatypical群に分類される．症例3ではⅢ誘導にS波に重なるノッチが認められた．

Ⅳ．考　　察

今回の長期にわたる一般住民を対象とした観察研究により，以下の知見が得られた．第一に，22年間の追跡期間中，type 1群の7例で突然死は1例も認めなかった．第二に，control群と比較し，type 2·type 3を含むatypical群では突然死の頻度が高かった．第三に，atypical群のなかで突然死をきたした例では，下壁側壁誘導の早期再分極所見が多く認められた．

本研究におけるBrugada症候群の罹患率はtype 1群で0.18%であり，これまでの報告とほぼ一致していた．Brugadaらの報告[3]によると，無症候性Brugada症候群190例中，約2年(平均27ヵ月)のフォローアップで，突然死または心室細動をきたした例は8%であったのに対し，Prioriらの報告[4]では，約3年(平均33ヵ月)のフォローアップ期間内に，無症候性Brugada症候群30例中，突然死・心室細動をきたした例は1例もなかった．また本邦でも，KamakuraらのBrugada研究班は，平均48ヵ月の追跡調査にて，無症候性Brugada症候群は予後が比較的良好であったと報告[5]している．特発性心室

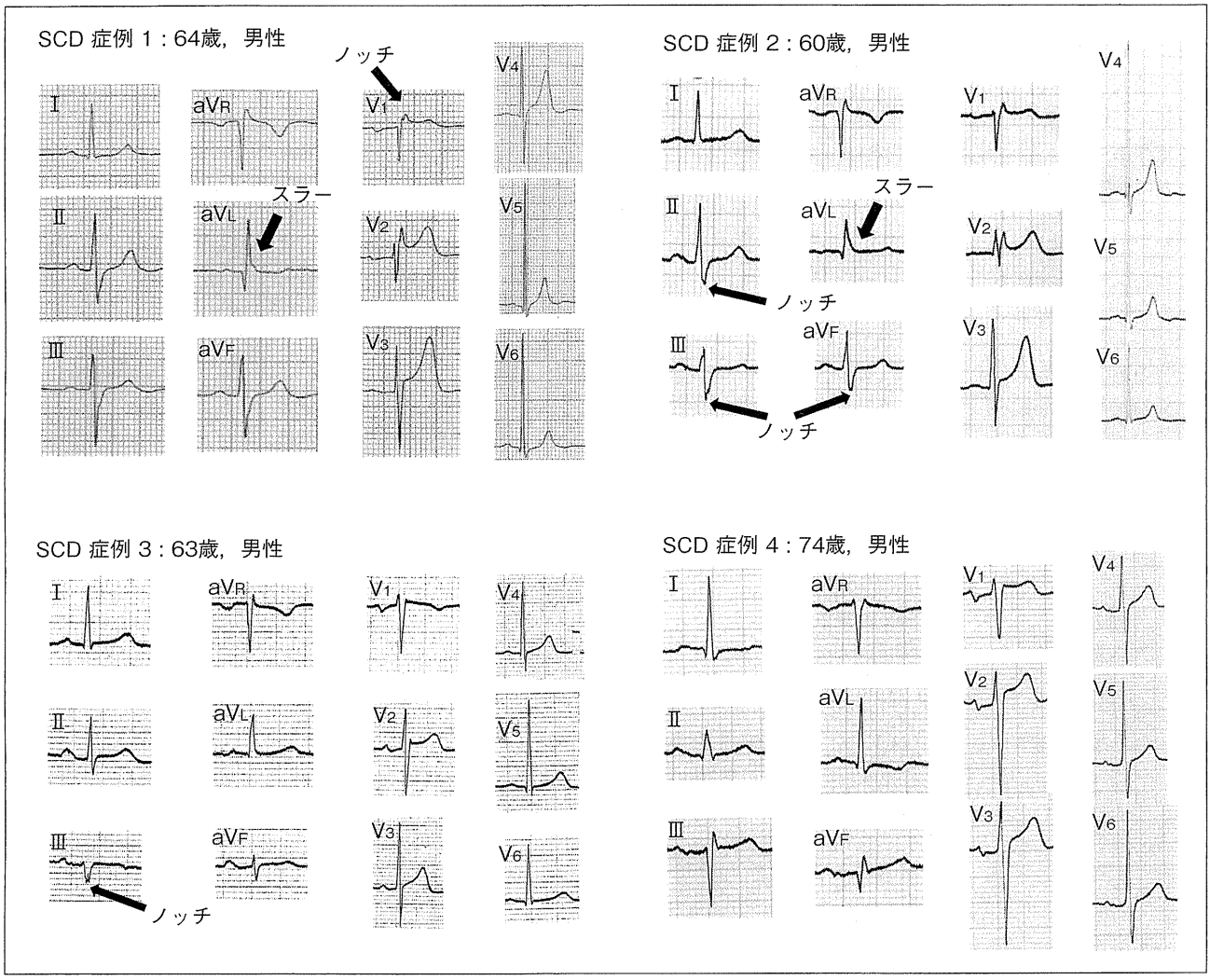

図1　突然死した4症例の心電図

細動研究会(J-IVFS)の調査でも，無症候性Brugada症候群98例の平均37ヵ月のフォローアップ期間中，突然死・心室細動をきたした例はなかった[6]．今回の長期の追跡研究の結果はこれらの報告とほぼ一致しており，無症候性Brugada症候群の長期予後は比較的良好である可能性が示唆された．ただし，Brugada症候群では心電図の時間的変化が認められることが知られており，今後は心電図の経時的な解析が必要と考えられる．また，本研究ではtype 1群が7例と少なかったため，さらなる症例の蓄積が必要である．

従来，健康若年男性に多く認められる早期再分極は一般的に良性と考えられてきたが，近年，下壁誘導あるいは側壁誘導にJ点上昇を認めるいわゆる早期再分極症候群(early repolarization syndrome；J wave syndrome)が突然死と関連していることが報告[7]され注目を集めている．本研究では，これまでの報告にある下壁側壁誘導のみならず，前胸部誘導における0.1 mV以上のJ点上昇が認められた群で突然死のリスクが高い可能性が新たに示された．さらに，atypical群のなかで突然死をきたした症例では，下壁側壁誘導における早期再分極の合併頻度が高いことが示された．Kamakuraらの報告[5]では，本研究の分類同様，type 2，type 3，およびV_1～

V_3誘導における0.1～0.2 mVのJ点上昇をnon-type 1と分類しているが，non-type 1群の長期予後はtype 1群とほぼ同等，すなわち心停止・心室細動蘇生例は予後不良なのに対し，無症候性のnon-type 1群は予後が比較的良好であった．この報告のなかで，Brugada型心電図例での予後不良の予測因子として，若年の突然死の家族歴および下壁誘導での早期再分極所見の存在があげられている．本研究の結果とあわせ，type 1群でなくとも，非典型的なBrugada型心電図に下壁誘導でのJ点上昇が合併する症例で，突然死のリスクが高い可能性が強く示唆された．しかし，突然死の真の高リスク群を同定するためには，今後さらに症例を集積し，詳細な検討と長期にわたる追跡調査が必要である．

V．結　　論

約3,800例の20年以上にわたる長期予後解析の結果から，非典型的Brugada型心電図を認める例に突然死のリスクが高い可能性が示唆された．

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Early Repolarization is an Independent Predictor of Occurrences of Ventricular Fibrillation in the Very Early Phase of Acute Myocardial Infarctions

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Early Repolarization is an Independent Predictor of Occurrences of Ventricular Fibrillation in the Very Early Phase of Acute Myocardial Infarctions

Running title: *Naruse et al.; Early repolarization and VF during an AMI*

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Abstract:

Background - Recent evidence has linked early repolarization (ER) to idiopathic ventricular fibrillation (VF) in patients without structural heart disease. However, no studies have clarified whether or not there is an association between electrocardiographic ER and the VF occurrences after the onset of an acute myocardial infarction (AMI).

Methods and Results - This study retrospectively included 220 consecutive patients with an AMI (57 female; mean age, 69±11 years) in whom the 12-lead ECGs before the AMI onset could be evaluated. The patients were classified based on a VF occurrence within 48 hours after the AMI onset. Early repolarization was defined as an elevation of the QRS-ST junction of >0.1 mV from baseline in at least 2 inferior or lateral leads, manifested as QRS slurring or notching. Twenty-one (10%) patients experienced a VF occurrence within 48 hours of the AMI onset. A multivariate analysis revealed that ER (odds ratio [OR]=7.31; 95% confidence interval [CI]=2.21–24.14; p<0.01), a time from the onset to admission of less than 180 minutes (OR=3.77; 95% CI=1.13–12.59; p<0.05), and a Killip class of greater than I (OR=13.60; 95% CI=3.43–53.99; p<0.001) were independent predictors of VF occurrences. As features of the ER pattern, a J-point elevation in the inferior leads, greater magnitude of the J-point elevation, notched morphology of the ER, and ER with a horizontal/descending ST-segment, all were significantly associated with a VF occurrence.

Conclusions - The presence of ER increased the risk of VF occurrences within 48 hours after the AMI onset.

Clinical Trial Registration Information: http://www.umin.ac.jp; Identifier: UMIN000005533.

Key words: ECG; myocardial infarction; ventricular fibrillation; early repolarization

Early repolarization (ER), characterized by an elevation of the QRS–ST junction (J point) in leads other than V1 through V3 on the 12-lead ECG, has historically been regarded as an innocuous finding in healthy, young persons.[1,2] While considered benign, the potential role of ER in arrhythmogenicity has been suggested in experimental studies.[3] Recently, several case reports have called our attention to the association of idiopathic ventricular fibrillation (VF) to J-point elevation (with or without ST-segment elevation).[4-8] In addition, recent evidence has linked ER to idiopathic VF in patients with no structural heart disease[9-15] and to life threatening ventricular arrhythmias associated with chronic coronary artery disease.[16]

Death from VF in the setting of an acute myocardial infarction (AMI) has historically been one of the most frequent causes of sudden cardiac death.[17] Prior investigators have evaluated the clinical and angiographic features and outcomes associated with VF in patients with an AMI.[18-22] In those patients, ER might be related to the VF occurrence after the AMI. However, no studies have attempted to clarify whether or not ER is associated with VF occurrences within 48 hours after the onset of an AMI. Accordingly, the purpose of this study was to clarify this point.

Methods

Study population

Between April 2006 and August 2010, 964 consecutive Japanese patients with an AMI (239 women; mean age, 67±12 years) who underwent percutaneous coronary intervention in Tsukuba University Hospital, Tsukuba Medical Center Hospital, and Ibaraki Prefectural Central Hospital were retrospectively enrolled. Patients were eligible if they were 18 years or older and presented within 24 hours of the onset of the symptoms associated with an AMI. Every patient

was asked for ECGs recorded well before the index event. Maximal effort was taken to collect such ECGs, from which the presence of ER was evaluated. Six hundred eighty seven patients in whom no ECGs recorded before the onset of the AMI were available were excluded from this study. Furthermore, 3 patients had a type 2 (n=2) or type 3 (n=1) Brugada ECG pattern,[23] and 31 had a QRS complex duration of $\geq$120 msec before the onset of the AMI. Another 23 experienced a prior AMI. After excluding those patients, the remaining 220 patients were finally included in this study. The mean duration from the baseline 12-lead ECG recording to the AMI onset was 5±3 months (range, 1–12).

The primary endpoint of this study was the occurrence of sustained VF within 48 hours after the onset of the AMI. The patients were classified based on the occurrence of sustained VF within 48 hours after the onset of the AMI. The demographic and clinical data were analyzed in both study groups. The data collection covered the age, gender, cardiovascular risk factors, culprit artery, number of diseased coronary arteries, time from the symptom onset to arrival at the emergency room, Killip class on admission, and infarct size (based on a peak creatine kinase rise). Hypertension, hypercholesterolemia, and diabetes mellitus were scored on the basis of the previous diagnosis and initiation of therapy. Ethical approval was obtained from the institutional review committee of each participating hospital, and all patients gave their written informed consent before participation.

An AMI was defined as a rise in the MB fraction of the creatine kinase of above the 99th percentile of the upper reference limit together with symptoms of ischemia, ECG changes indicative of new ischemia (new ST-T changes or new left bundle branch block), and/or development of pathologic Q waves on the ECG.[24] An ST elevated myocardial infarction (STEMI) was defined as an AMI with new ST elevation at the J-point in two contiguous leads

with the following cut-off points: ≥0.2 mV in men or ≥0.15 mV in women in leads V2-V3 and/or ≥0.1 mV in the other leads.[24] Sustained VF was defined as that lasting longer than 30 seconds or that requiring electrical cardioversion.

ECG analysis

To blind the ECG interpreters from the clinical characteristics and patient grouping, all tracings were scanned and coded. The early repolarization patterns were stratified according to the degree of the J-point elevation (≥0.1 mV) that was either slurred (a smooth transition from the QRS segment to the ST segment) or notched (a positive J deflection inscribed on the S wave) in at least 2 consecutive inferior leads (II, III, and aVF), lateral leads (I, aVL, and V4 to V6), or both (Figure 1).[1,2,10] The J-point amplitude was measured at the QRS-ST junction in case of slurred J waves or the peak J point in the case of notched J waves, and relative to the QRS onset in order to minimize any baseline wandering effect.[16] We analyzed the inferior and lateral J-point elevation independently to clarify the significance of the localization, and used two predefined cutoff points (≥0.1 mV and ≥0.2 mV) to assess the significance of the amplitude of the J-point elevation from baseline. The morphologic characteristics of the ER (notching or slurring) were also analyzed independently.[9,13] The anterior precordial leads (V1 to V3) were excluded from the analysis of the ER in order to avoid the inclusion of patients with right ventricular dysplasia or Brugada syndrome.[23,25] We also analyzed the ST-segment pattern after the J-point independently to clarify the significance of the ST-segment characteristics according to the criteria proposed by Tikkanen:[12] An upsloping ST-segment was defined as an elevation of the ST segment of ≥0.1 mV within 100 msec after the J-point or a persistently elevated ST segment of ≥0.1 mV throughout the ST-segment (Figure 2).[12] A horizontal/descending ST-segment was defined as an elevation of the ST segment of <0.1 mV within 100 ms after the

J-point (Figure 3).[12] We assessed the prevalence, localization, amplitude, morphology, and ST-segment of the ER in both patient groups. Two trained investigators independently evaluated the baseline 12-lead ECGs for the presence of ER without any knowledge of the other observer's judgment or the clinical information. A third observer was consulted in the case of disagreement. All ECGs containing an ER pattern were double-checked and the grading was established by consensus. The interobserver variability was assessed in all patients. In 50 randomly selected patients, one observer evaluated a new arbitrary judgment on a separate occasion to determine the intraobserver variability.

Statistical analysis

The continuous variables were expressed as the mean±SD. The comparisons between 2 groups were tested by an unpaired t-test. We used the Log-transformed peak creatine kinase levels and time from the symptom onset to arrival at the emergency room as is conventionally done. All categorical variables were presented as the number and percent in each group and were compared by a chi-square analysis or Fisher's exact test. An overall chi-square test for a 2 x n table was constructed when comparisons involved >2 groups. A univariable of the patient characteristics was compared between the VF occurrence group and no VF occurrence group, and a logistic regression analysis was performed to detect any independent significant predictors by adjusting with multi-variables (reported as odds ratios [OR] with 95% confidence intervals [95% CIs]). The intraobserver and interobserver variability was investigated by Kappa statistics. A p value <0.05 was considered statistically significant.

Results

Demographic and clinical characteristics of all AMI patients

Among the 220 patients in whom the 12-lead ECGs prior to the AMI onset were obtained, 21

(10%) patients experienced an episode of VF within 48 hours after the onset of the AMI, and the remaining 199 (90%) did not. VF occurred before catheterization in 13 patients, during catheterization in 7, and after catheterization but within 48 hours after the onset of the AMI in the remaining patient. There was no significant difference in the age or prevalence of cardiovascular risk factors between these 2 groups (Table 1). However, the patients with VF had a greater prevalence of a male gender ($p<0.05$) and shorter duration from the symptom onset to the arrival at the emergency room ($p<0.001$) than those without (Table 1). Although the culprit artery, peak creatine kinase level, or prevalence of an STEMI did not differ between the 2 groups, the patients with VF had a greater number of diseased coronary arteries ($p<0.05$) and Killip class on admission ($p<0.001$) than those without (Table 1). Furthermore, with the analysis of the 12-lead ECG recorded before the AMI, ER was found in 10 (48%) of the patients with VF, which was more prevalent than in those without (12%; $p<0.001$; Table 1).

Predictors of VF occurrence during an AMI

A multivariate logistic regression analysis revealed that a time from the symptom onset to the arrival at the emergency room of less than 180 minutes (OR, 3.77; 95%CI, 1.13 to 12.59; $p<0.05$), Killip class greater than I (OR, 13.60; 95%CI, 3.43 to 53.99; $p<0.001$), and the presence of ER (OR, 7.31; 95%CI, 2.21 to 24.14; $p<0.01$) were associated with the occurrence of VF within 48 hours after the onset of the AMI (Table 2). A male gender, the peak creatine kinase level, and the presence of ST-segment elevation or multi-vessel disease were not associated with the occurrence of VF within 48 hours after the AMI onset (Table 2).

Detailed characteristics of early repolarization for predicting VF

Distribution

Among the 34 patients who had ER, the J-point elevation was in the inferior leads in 26 (76%)