Life-Threatening Ventricular Arrhythmia and Brugada-Type ST-Segment Elevation Associated With Acute Ischemia of the Right Ventricular Outflow Tract

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Background: Brugada-type ECG (Br-ECG) is occasionally observed during acute myocardial ischemia of the right ventricular outflow tract (RVOT). No studies have explored, however, the association of ventricular tachyarrhythmia and development of Br-ECG due to acute ischemia of the RVOT.

Methods and Results: The study included 13 consecutive patients with acute ischemia of the RVOT during coronary catheterization. Patients were divided into 2 groups: those with Br-ECG (group B) and those without (group N). The proportion of male patients was higher in group B than in group N (100% vs. 25%, P<0.01), and VT/VF developed in only patients with Br-ECG (group B). In group B, VT/VF was observed in patients without pre-existing organic change in the conus/right ventricular (RV) branch of the right coronary artery and no VT/VF was seen in patients with organic coronary stenosis despite Br-ECG.

Conclusions: Acute myocardial ischemia of the RVOT caused Br-ECG predominantly in male patients and subsequent development of VT/VF in some patients. VT/VF was seen in patients without any obstructive lesion but arrhythmic events were not observed in RVOT ischemia in the case of pre-existing coronary occlusion or stenosis of the conus or RV branch, suggesting the effects of precondition.

Key Words: Brugada-type ECG; Ion channel; Ischemia; Right ventricular outflow tract

Patients with Brugada syndrome (BrS) have unique electrocardiographic (ECG) changes of ST-segment elevation in the right precordial leads, V1–V3, and are at high risk for sudden cardiac death due to the development of ventricular fibrillation (VF). The unique ECG features of BrS (i.e., ST-segment elevation and ST-T wave morphology in leads V1–V3) are defined as type 1 (coved type), type 2, and type 3 (saddle-back type) according to the consensus report. The 3 types of ECG are regarded as Brugada-type ECG (Br-ECG), and type 1 is considered an important diagnostic sign for BrS. Br-ECG, however, is not a specific feature of BrS but is often observed in various physiological and pathological conditions including myocardial ischemia. With regard to the mechanism of ST-segment elevation in the right precordial leads and subsequent development of ventricular tachyarrhythmias in BrS, there are 2 proposed theories that are still controversial: one involves the transmural heterogeneity of ventricular repolarization and subsequent development of phase 2 re-entry (the repolarization theory), and the other involves the development of abnormality leading to conduction disturbance and arrhythmogenesis (the depolarization theory). Both theories assume that the site of origin of ECG changes and the focus of ventricular arrhythmia is the right ventricular outflow tract (RVOT).

An abnormal delayed potential was recorded from the epicardium of the RVOT in patients with BrS through the electrode inserted into the conus branch of the right coronary artery, and VT/VF was seen in patients without any obstructive lesion but arrhythmic events were not observed in RVOT ischemia in the case of pre-existing coronary occlusion or stenosis of the conus or RV branch, suggesting the effects of precondition.

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reports,15–18 no detailed studies have been carried out on the association of ventricular tachyarrhythmia with the appearance of Br-ECG in the presence of acute ischemia of the RVOT in humans.

The aim of the present study was therefore to investigate the features of Br-ECG due to acute myocardial ischemia of the RVOT and the relevance to the development of VF.

### Methods

#### Subjects

The subjects consisted of 13 consecutive patients (10 men; mean age, 69 years) who underwent coronary angiography/percutaneous coronary intervention for acute ischemia of the RVOT at Yokohama Minami Kyosai Hospital between March 2006 and March 2016. In all the subjects the area of the RVOT was confirmed to be perfused through the conus and/or RV branch of the RCA. Patients were divided into 2 groups according to the presence of change from normal ECG to Br-ECG during acute ischemia of the RVOT: patients with Br-ECG were defined as group B, and those without it, as group N. Patients in group B were further divided into 2 subgroups according to the development of VF following appearance of Br-ECG: patients with VF were classified into subgroup B-VF, and those without it, into subgroup B-NVF. Br-ECG were classified as type 1 (coved type ST-elevation), type 2, or type 3 (saddle-back type ST-elevation) according to the consensus report.5 Patients who had either complete occlusion of the conus and/or RV branch or a pre-existing Br-ECG at baseline before development of acute ischemia of the RVOT on coronary angiography/coronary intervention were excluded. The study protocol was approved by the ethics committee of Yokohama Minami Kyosai Hospital, and written informed consent was obtained from all participants before the study.

#### Angiography

Coronary angiography was performed using the Judkins technique. Among the 13 patients with acute ischemia of the RVOT, 7 underwent coronary intervention of segment 1 and/or 2 of the RCA over the conus or RV branch, which showed transient subtotal or total occlusion after balloon- or stenting. Three patients had vasospastic angina due to spasm of the conus or RV branch induced by acetylcholine (ACh) provocation test. In these patients, after confirming that there were no significant stenotic lesions in both the RCA and left coronary arteries (LCA), a bipolar electrode catheter was inserted into the RV apex through the right femoral vein and was connected to a temporary pacemaker. The pacing rate was set at 50 beats/min. Increasing doses of ACh were injected into the LCA (20, 50 and 100 μg) and RCA (20, 50 and 70 μg) until ACh-induced coronary vasospasm was detected angiographically or until the maximum dose was given. Coronary vasospasm was defined as total or subtotal occlusion of a single or multiple coronary arteries with delayed filling of the distal segments, associated with chest pain and/or isch-
emic ST-T changes on ECG. In 2 patients, a coronary catheter (4 Fr) was accidentally inserted into the conus branch, leading to wedge angiography, which produced ischemia of the RVOT despite rapid release within 5–8 s from the branch. One patient developed acute ischemia of the RVOT induced by short-term catheter insertion (<8 s) into the RV branch, leading to wedge angiography, which diverged from the proximal segment 1 of the RCA without conus branch.

Parameters
Degree of ST-segment elevation and morphological changes in ST-T wave were evaluated on 12-lead ECG recorded at a paper speed of 25 mm/s for 2 consecutive cardiac cycles during acute ischemic event of the RVOT. A positive morphological change in ST-T wave was defined as a shift from a normal ST segment to either type 1, type 2, or type 3 Br-ECG in any lead of V1–V3. The maximum amplitude of ST-segment elevation at the J point in lead V2, maximum QT interval in 12-lead ECG and T-wave peak to T-wave end interval (Tₚ₋ₑ interval) in lead V1–V4 were measured both at baseline and during the ischemia of the RVOT. The QT interval was defined as extending from the beginning of the QRS complex to where T waves descend onto the isoelectric baseline. The time from normal ECG to the first appearance of ST elevation followed by Br-ECG was calculated.

Statistical Analysis
Data are presented as mean±SD. Two-tailed Welch’s t-test was used to compare non-parametrical variables between groups. Fisher’s exact test was used to evaluate differences in categorical variables between groups. P<0.05 was considered significant.

### Results
Among 13 patients, 9 had positive morphological ST-T wave change (appearance of Br-ECG) during acute ischemia of the RVOT (group B), and the remaining 4 had no ECG change, designated as group N. **Table 1** lists subject clinical characteristics at baseline and angiographic findings. Br-ECG was predominantly observed in male group B patients compared with group N (100% vs. 25%, P<0.01). In addition, Tₚ₋ₑ interval at baseline and during ischemia was longer in group B than in group N (89.4 ms and 95.5 ms vs. 64.5 ms and 78.0 ms, P=0.02, respectively). There were no differences in other clinical parameters or coronary angiographic findings between the 2 groups. Acute ischemia of the RVOT was caused by transient subtotal or total occlusion of the conus or RV branch due to either coronary intervention, accidental catheter insertion, or coronary vasospasm. The cause of acute ischemia was not significantly different between the 2 groups. Ventricular tachycardia (VT)/VF events following the development of Br-ECG were observed in 4 group B patients, but in none in group N.

The clinical and ECG characteristics of the group B patients are listed in **Table 2**. Type 1 and type 2 Br-ECG were observed in 8 and in 2 patients (1 patient had both type 1 and type 2), respectively (**Figure 1**). Four of 9 patients in group B developed VT/VF initiated by a short-coupled premature ventricular contraction, with the QRS morphology arising from the RVOT causing R on T phenomenon (subgroup B-VF: **Figure 2**). **Figure 3** shows a case of type 1 to type 2 Br-ECG with direct catheter insertion into the conus branch followed by an appearance of VF provoked by a short-coupled premature contraction (patient 1). Another case of VF during occlusion of the conus and RV branches by ACh-induced vasospasm is presented in **Figure 4** (patient 2). This patient had J wave

### Table 2. Group B Clinical and Electrocardiographic Characteristics

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Age (years)/Sex</th>
<th>Situation at the time of ECG change</th>
<th>Type of Br-ECG</th>
<th>VT/VF</th>
<th>Maximum voltage of the J point (mV)†</th>
<th>Time from normal to Br-ECG (s)</th>
<th>Organic lesion‡</th>
<th>Coronary spasm</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>80/M</td>
<td>Direct catheter insertion into the CB</td>
<td>Type 2→Type 1</td>
<td>VF</td>
<td>1.09</td>
<td>2</td>
<td>RCA (3)</td>
<td>–</td>
</tr>
<tr>
<td>2</td>
<td>41/M</td>
<td>Occlusion of the CB and RV branches after ACh</td>
<td>Type 1</td>
<td>VF</td>
<td>3.15</td>
<td>48</td>
<td>–</td>
<td>RCA (1–4)</td>
</tr>
<tr>
<td>3</td>
<td>68/M</td>
<td>Direct catheter insertion into the CB</td>
<td>Type 1</td>
<td>PVT</td>
<td>1.86</td>
<td>140</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>4</td>
<td>68/M</td>
<td>Direct catheter insertion into the RV branch</td>
<td>Type 1</td>
<td>VF</td>
<td>1.14</td>
<td>31</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>5</td>
<td>73/M</td>
<td>Occlusion of the CB with intervention</td>
<td>Type 1</td>
<td>–</td>
<td>1.64</td>
<td>634</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>6</td>
<td>73/M</td>
<td>Occlusion of the CB with intervention</td>
<td>Type 1</td>
<td>–</td>
<td>0.92</td>
<td>55</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>7</td>
<td>80/M</td>
<td>Occlusion of the RV branch with intervention</td>
<td>Type 1</td>
<td>–</td>
<td>1.47</td>
<td>166</td>
<td>RCA (1,2)</td>
<td>–</td>
</tr>
<tr>
<td>8</td>
<td>61/M</td>
<td>Occlusion of the CB after ACh</td>
<td>Type 1</td>
<td>–</td>
<td>1.23</td>
<td>212</td>
<td>RCA (CB)</td>
<td>–</td>
</tr>
<tr>
<td>9</td>
<td>61/M</td>
<td>Occlusion of the CB with intervention</td>
<td>Type 2</td>
<td>–</td>
<td>0.63</td>
<td>74</td>
<td>RCA (1), LAD (7, 8), LCX (11)</td>
<td>–</td>
</tr>
</tbody>
</table>

† J point in lead V2. ‡(n), segments of coronary arteries as defined by the American Heart Association Committee Report. CB, conus branch; ECG, electrocardiogram; PVT, polymorphic ventricular tachycardia; VF, ventricular fibrillation; VT, ventricular tachycardia. Other abbreviations as in Table 1.
immediately preceding the appearance of type 1 Br-ECG. The remaining 5 patients did not develop VT/VF and were classified into subgroup B-NVF. Figure 5 shows a B-NVF patient who did not develop VT/VF despite having remarkable coved-type ST elevation (type 1) together with macroscopic T-wave alternans (patient 5). This patient had pre-existing severe stenosis of segment 1–2 of the RCA, and type 1 Br-ECG developed after the conus branch occlusion induced by catheter intervention in segment 1 and 2.
There were no significant differences in clinical characteristics between the B-VF and B-NVF subgroups. Table 3 lists ECG parameters, coronary lesions involving RVOT and causes of ischemic events in the 2 subgroups. The maximum voltage of the J-point elevation and QT interval at baseline were not different between the 2 subgroups. Time to appearance of Br-ECG after occlusion of the conus/RV branch of RCA was not different between the B-VF and B-NVF subgroups. The proportion of patients with organic stenosis in segment 1 and/or 2 involving the RVOT before the procedure was lower in the B-VF than in the B-NVF subgroup (0% vs. 80%, P=0.03). Acute ischemia of the RVOT was mainly caused by coronary intervention of segment 1–2 in the B-NVF subgroup, and by direct catheter insertion into the conus or RV branch in the B-VF subgroup.

**Discussion**

In the present study, patients with angiographically proven acute ischemia of the RVOT frequently had Br-ECG. Br-ECG developed predominantly in male patients. Among patients with Br-ECG, VT/VF was frequently observed in those without pre-existing organic change in the conus or RV branches.
RV branch of the RCA within a short time after ECG change, after occlusion. This suggests that acute regional ischemia of the RVOT without preconditioning may predispose to appearance of Br-ECG, leading to the development of VT/VF, especially in male patients.

Mechanism of Br-ECG and Development of Ventricular Arrhythmia

In experimental studies, global ischemia of the RVOT can produce a heterogeneity of repolarization between the epicardium and the endocardium, leading to ST elevation. This produces a heterogeneity of repolarization between the epicardial and endocardial cells. In this study, Br-ECG due to myocardial ischemia of the RVOT were classified into 2 groups according to initiation of VT/VF. The group without VF consisted of patients with organic stenosis lesions at segment 1–2 of the RCA or conus branch. This may be due to the effects of ischemic preconditioning. Yamaki et al described a case of 90% stenosis of segment 1 of the RCA with coved-type ECG when a coronary balloon was dilated over a conus branch and flow to the site was obstructed. Despite ECG change, no VT/VF was observed. Eichhofer and Cruzen described a case of effort angina in which coronary angiography showed severe stenosis of segment 1–2 of the RCA. After stenting, a conus branch was occluded and the RVOT ischemia was seen mainly in male patients. Ito seems to play an important role in the observed ECG changes. Meanwhile, Tp-e interval is a known marker for dispersion of ventricular repolarization. The prominent higher Tp-e intervals both at baseline and during ischemia in group B could support this repolarization theory.

According to the depolarization theory, conduction delay in the RVOT plays a pivotal role in the pathogenesis of BrS, triggering unique ECG changes and development of ventricular tachyarrhythmia. This theory was derived from the various clinical findings: for example, ultrastructural changes were present in the RV of patients with BrS, as seen in explanted heart or biopsy specimens, and local conduction abnormalities of the RVOT were confirmed on signal-averaged ECG, vectorcardiograms, and body surface maps. Cardiac myocytes of the RVOT in a normal heart can be arrhythmogenic and the embryonic outflow tract consists of slow conducting tissue. Recently, Nademanee et al demonstrated in patients with BrS that fractionated electrograms were recorded at the epicardial side of the RVOT and that catheter ablation of these electrograms eliminated type 1 ECG and VF. These results may provide strong support for the depolarization theory.

Myocardial ischemia of the RVOT could aggravate conduction abnormalities due to decreased Ina and ICaL, together with activation of outward IK-ATP (as already noted, the conditions that could trigger Br-ECG and initiation of VT/VF). Although there was no male predominance of myocardial ischemia of the RVOT, intrinsic sex differences in ion channel distribution, including Ina, might explain the male predominance of ECG changes.

Pathogenesis of VT/VF and Ischemic Preconditioning

Patients who developed Br-ECG due to myocardial ischemia of the RVOT were classified into 2 groups according to initiation of VT/VF. The group without VF consisted of patients with organic stenosis lesions at segment 1–2 of the RCA or conus branch. This may be due to the effects of ischemic preconditioning. Yamaki et al described a case of 90% stenosis of segment 1 of the RCA with coved-type ECG when a coronary balloon was dilated over a conus branch and flow to the site was obstructed. Despite ECG change, no VT/VF was observed. Eichhofer and Cruzen described a case of effort angina in which coronary angiography showed severe stenosis of segment 1–2 of the RCA. After stenting, a conus branch was occluded and ST-segment elevation in V1–V3 leads, similar to the coved-type (type 1) ECG, was noted. ECG change disappeared after 15 min without development of VT/VF. In the present patients, although patient 5 had remarkable coved-type ST
elevation together macroscopic T-wave alternans suggesting the presence of increased inhomogeneity of repolarization, no VT/VF was observed. This could be explained by the fact that this patient had ischemic preconditioning caused by coronary intervention due to pre-existing severe stenosis of segment 1–2 of the RCA. Yan et al reported that a previous episode of ischemia (ischemic preconditioning) reduced the Ito-mediated epicardial phase 1 magnitude and J-wave size after subsequent myocardial ischemia in canine models. Attenuation of the epicardial phase 1 magnitude was associated with a reduction in phase 2 re-entry and the following R-on-T phenomenon of ventricular premature beats. Also in humans, anti-arrhythmic effects of ischemic preconditioning were confirmed on repeated balloon occlusions of coronary arteries. The relatively massive ischemia induced by major branch stenosis of coronary arteries was analyzed in these studies. The influence of ischemic preconditioning on the relationship between fatal ventricular arrhythmia and Br-EKG, however, especially in the setting of local ischemia of the RVOT, is unknown. In this study, the cardioprotective effect of ischemic preconditioning of the RVOT was reflected in the difference in VT/VF induction between the B-VF and B-NVF subgroups.

In canine models, acute ischemia at the RVOT produced complete loss of the Ito-mediated epicardial action potential dome in the ischemic area. The change did not occur in perfused areas; therefore, it caused a significant difference in epicardial repolarization across an area of ischemic border. The heterogeneous loss of the action potential dome across the border could result in a repolarization gradient, causing appearance of phase 2 re-entry and subsequent VT/VF initiation. The border zone may also facilitate augmented conduction abnormalities and re-entrant activity.

Clinical Implications
Acute ischemia of the RVOT produces Br-EKG, and a small but significant number of patients with BrS have complications of vasospastic angina. VT/VF due to acute ischemia of the RVOT with appearance of Br-EKG was seen in patients with coronary spasm or direct catheter insertion into the conus branch and/or RV branch without organic stenosis or occlusion, and similar coronary conditions apply to patients with BrS. Careful attention is needed for male patients requiring coronary spasm provocation test and catheter manipulation for the coronary arteries perfusing the RVOT.

Study Limitations
The present study has some limitations. First, the number of patients who met the inclusion criteria was small, and we could not assess the hypothesis using advanced statistical methods. Second, not all patients underwent examinations for BrS, including pharmacological provocation test and electrophysiological examinations. Therefore, we could not completely exclude patients with BrS. Third, all 4 B-VF patients underwent radioisotope examination before coronary angiography and no ischemia was detected. In contrast, although 3 of 5 B-NVF patients had chest pain with ST-segment depression before cardiac catheter examinations, we could not identify the presence of ischemia in the remaining 2 B-NVF patients.

Conclusion
Acute myocardial ischemia involving the RVOT has a tendency to produce Br-EKG and subsequent VF. This phenomenon occurs predominantly in male patients. Acute ischemia of the RVOT without previous organic stenosis or occlusion (without ischemic preconditioning) is thought to predispose toward the development of VT/VF.

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None.

Disclosures
The authors declare no conflict of interest.

References
VF and Brugada-Type ECG in RVOT Ischemia


