Brugada Syndrome Behind Complete Right Bundle Branch Block

Running title: Aizawa et al.; RBBB in BS patients

Yoshiyasu Aizawa, MD; Seiji Takatsuki, MD; Motoaki Sano, MD; Takehiro Kimura, MD; Nobuhiro Nishiyama, MD; Kotaro Fukumoto, MD; Yoko Tanimoto, MD; Kojiro Tanimoto, MD; Mitsushige Murata, MD; Takashi Komatsu, MD; Hideo Mitamura, MD; Satoshi Ogawa, MD; Toshikazu Funazaki, MD; Masahito Sato, MD; Yoshifusa Aizawa, MD; Keiichi Fukuda, MD

1Dept of Cardiology, Keio University School of Medicine, Tokyo, Japan; 2Dept of Internal Medicine and Memorial Heart Center, Iwate Medical University, Iwate, Japan; 3Tachikawa Hospital, Tokyo, Japan; 4International University of Health and Welfare, Mita Hospital, Tokyo, Japan; 5Saiseikai Kawaguchi General Hospital, Saitama, Japan; 6Division of Research and Development, Tachikawa Medical Center, Niigata, Japan

Address for Correspondence:
Yoshiyasu Aizawa, MD, PhD
Department of Cardiology
Keio University School of Medicine
35 Shinanomachi, Shinjuku-ku
Tokyo 160-8582, Japan
Tel: +81-3-5363-3928
Fax: +81-3-3353-1265
E-mail: yoshiya_aizawa@umin.ac.jp

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Abstract:

**Background**—The characteristic electrocardiogram of BS can be masked by right CRBBB and exposed by resolution of the block or pharmacological or pacing maneuvers.

**Methods and Results**—The study consisted of eleven patients who had BS and CRBBB. BS was diagnosed before the development of CRBBB (n=7), on the resolution of CRBBB, or from new characteristic ST changes that could be due to BS (n=4). Structural heart diseases were excluded, and coronary spasm was excluded based on a provocation test at catheterization. In seven patients, BS was diagnosed before the development of CRBBB. In one patient, BS was diagnosed when CRBBB resolved spontaneously. The precipitating cause for the resolution of CRBBB was, however, not apparent. On repeated ECGs, new additional upward-convex ST elevation was found in V2 and/or V3 in three patients. In two patients, new ST elevation was induced by IC drugs. The QRS duration was more prolonged in the patients with BS and CRBBB, compared to the age- and sex-matched controls: 170±13 ms versus 145±15 ms in V1, and 144±19 ms versus 128±7 ms in V5 (both P<0.0001). The amplitude of R in V1 was larger in the BS patients than in the controls (P=0.0323), but that of R’ was similar (P=0.0560).

**Conclusions**—BS can coexist behind CRBBB, and CRBBB can completely mask BS. BS might be demonstrated by relief of CRBBB or by spontaneous or drug-induced ST elevation. The prevalence, mechanism and clinical significance of a combination of CRBBB and BS are yet to be determined.

**Key words:** bundle-branch block, Brugada syndrome, sodium channels, pacing
Introduction

Ventricular fibrillation (VF) can occur in patients without structural heart diseases, and when it does, it is called idiopathic ventricular fibrillation (IVF). Among primary electrical diseases, BS is characterized by unique ECG patterns of J/ST/T waves. This ECG pattern has been shown to be associated with an increased risk of sudden cardiac death, compared with control subjects, and an ECG diagnosis of BS is very important for risk stratification.

Recently, we observed a case in which the characteristic ECG phenotype of BS was unmasked by relief of CRBBB: when CRBBB resolved spontaneously, the characteristic ECG pattern of BS was found to be underlying. A similar case was reported by another worker. This study attempts to discuss cases with BS that were complicated by CRBBB, and evidence for the presence of BS in CRBBB patients is presented.

Methods

Patients

The study consisted of 11 patients who had CRBBB with the diagnosis of BS. Structural heart diseases were excluded by ECG, by transthoracic echocardiography, and by cardiac catheterization. Coronary spasm was excluded as the cause of VF by provocation tests, using acetylcholine or ergonovine maleate at catheterization.

Definitions of CRBBB and BS

CRBBB was defined as a late R (R’) presenting in V1 or V2, with a slurred and wide S in leads I and V5/V6 and with prolonged duration of QRS ≥120 ms. In the presence of CRBBB on the baseline ECG, we divided the patients into two groups. One group consisted of the patients in whom ECG revealed BS and in whom CRBBB occurred subsequently during the follow-up.
(n=7). The other group consisted of the patients who had CRBBB on the baseline ECG, but BS was diagnosed in the following situations (n=4).

1) Resolution of CRBBB resulted in normal ventricular conduction, in which the characteristic ECG pattern for BS could be seen. The resolution of CRBBB might occur spontaneously (n=1)\(^7\), or it might be induced by the pacing technique (n=2), i.e., Chialle’s intervention.\(^13\)

2) New J/ST changes appeared which could not be explained by CRBBB but could have been due to coved-type ST elevation. The new ECG changes might appear spontaneously on repeated ECG recordings (n=3), or they might be induced during the administration of IC drugs (n=2). Mechanistically, spontaneous or drug-induced exaggeration of J waves of BS had to be involved.

**Provocation tests**

After obtaining written and informed consent, cardiac catheterization was performed to exclude structural heart diseases and coronary artery disease. After the exclusion of significant stenosis, acetylcholine was injected into the coronary artery to exclude coronary spasm as the cause of VF in 5 patients with prior VF: in incremental doses of 50 and 100 mg (in 10 mL of 0.9% saline) over 20 sec into the left and the right coronary artery. If acetylcholine did not induce coronary spasms, 50 mg of intracoronary ergonovine maleate was injected into the right and left coronary arteries over a period of 5 min. The end point was the development of total or subtotal occlusion or the completion of the drug infusion.\(^14\)

Provocation for the characteristic ECG pattern of BS was performed as follows in patients suspected to have the syndrome but lacked type 1 ECG documentation: pilsicainide 1 mg/kg/10 min i.v. The end point was the development of type 1 pattern for BS or the completion
of the drug infusion.\textsuperscript{15} Four of 7 patients prior to the development of CRBBB underwent this provocation test. In 2 of 4 patients with CRBBB but without diagnosis of BS who underwent the drug test it was possible to observe additional widening and bizarre elevation of the ST segment which was considered to signify the presence of BS.

As performed by Chiale et al.,\textsuperscript{13} pacing was attempted at the right ventricular apex to normalize the QRS complexes, and the ECG was analyzed for the characteristic pattern of BS in V1, V2 and V3 in 2 patients during EP study.

CRBBB in the controls

We obtained 200 ECG recordings showing CRBBB in apparently healthy subjects between 20 and 69 years of age. Of these, 55 age- and sex-matched subjects were chosen and compared with the 11 BS patients. All of the subjects underwent annual health examinations and showed normal results upon physical and laboratory examinations, except for CRBBB. Cardiac diseases were denied, and none had symptoms or signs suggestive of tachyarrhythmia or heart failure. Sudden cardiac death was ruled out in all of the family members.

Data analysis

ECGs were recorded repeatedly during hospitalization and during the follow up which included those recorded at higher intercostal spaces. The QRS and ST-T morphologies in V1 and V2 and other ECG parameters were determined in the patients. Then, the cases with specific evidence for BS were presented as mentioned above. Finally, the ECG parameters of CRBBB were compared between the BS patients and the control subjects with CRBBB. The QRS duration was measured from the beginning of the QRS complex to the J-point in V1 or V5.\textsuperscript{11,12} From the QT interval, QTc was determined in the standard manner.

Statistical analysis
The numerical values are presented as the means ± SDs. For comparisons, the differences between groups were analyzed by the Mann-Whitney-Wilcoxon test for continuous variables. Statistical analyses were performed with SPSS software (Statistical Package for the Social Sciences), version 12.0 (SPSS Inc., Chicago, IL). A two-sided P<0.05 was considered statistically significant.

**IRB approval and informed consent**

The study was approved by the Institutional review committee of Keio University School of Medicine. The patients were given written informed consent prior to invasive studies.

**Results**

**CRBBB in BS**

Based on the inclusion criteria, the ECGs of the 11 patients met the criteria for CRBBB: wide QRS duration (>120 ms) and slurred, wide S waves in the left leads: I, aVL, V5, and V6. The clinical characteristics are summarized in **Table 1**.

**CRBBB developing in BS**

In seven of eleven patients, the baseline ECG revealed the characteristic ECG pattern for BS: three spontaneously and four by an IC drug, while CRBBB developed during the follow-up for 2.8 ± 2.5 years ranging 0.2 to 7 years (**Figure 1**, case 5).

**Resolution of CRBBB**

In one patient (case 8), BS was diagnosed when CRBBB resolved spontaneously (**Figure 2A**). On another occasion on a different day, the patient showed a type 2 (saddle-back type) ECG of BS on resolution of CRBBB on 12-lead Holter monitoring (**Figure 2B**). There was a slight difference in the J/ST level between the two recordings (**Figure 2, A and B**): the J point level
was higher when the ST segment showed the coved type, compared to when it showed the saddle back-type elevation (Figure 2). The precipitating cause for the resolution of CRBBB was not apparent.

In two patients (cases 4 and 8), we attempted ventricular pacing to normalize the QRS complexes from the right ventricular apex, which disclosed an coved type elevation in V1 and V2 (Figure 3).

**New ST elevation**

On repeated ECGs, four patients showed new and additional ST elevations in V2 and/or V3 which was considered to be characteristic for BS (Figure 4): spontaneously in 2, during the infusion of IC drugs in 1 and in both occasions in 1 patient (Figure 5, case 11).

**CRBBB in control versus BS patients**

Table 2 shows the comparison of ECG variables between the BS patients with CRBBB and the control subjects. By definition, the QRS duration was prolonged >120 ms in both, but it was wider in the BS patients compared to the control CRBBB subjects: 170±13 versus 145±15 ms in V1 and 144±19 versus 128±7 ms in V5 (P<0.0001 for both). The QT interval was prolonged in the BS patients, but QTc was not. The R’ in V1 was larger in the BS patients than in the control subjects but non-significantly.

**Discussion**

**Major findings of the present study**

The present study showed that some BS patients might be complicated by CRBBB, which completely masks BS. The combination of BS and CRBBB is evident when CRBBB develops during the follow-up of BS patients. In addition, we provided other evidence to prove the
presence of BS in CRBBB patients: BS was disclosed upon the resolution of CRBBB, or new J/ST changes appeared, which can be considered typical for BS. Both can occur spontaneously or can be induced artificially by pacing or drug administration. These findings suggest that CRBBB is not necessarily benign, but unmasking is important to exclude potentially high-risk BS patients.

**Clinical significance of CRBBB**

CRBBB has generally been considered to be benign,\textsuperscript{16-21} but a recent cohort study made it clear that RBBB is associated with both increased cardiovascular risk and all-cause mortality.\textsuperscript{22} In addition, we reported that CRBBB might be observed among IVF patients and that the prevalence of CRBBB was higher in IVF patients than expected in the general population.\textsuperscript{23} BS and coronary spams were excluded, and CRBBB was the only sole ECG phenotype in such patients. Furthermore, CRBBB was shown to be able to conceal the ECG phenotype of BS.\textsuperscript{7,13} From these reports, it can be said that CRBBB does not necessarily indicate a benign ECG finding, but exclusion of the coexistence of CRBBB with BS or IVF is essential.

**Proof of coexisting BS with CRBBB**

Coexisting BS and CRBBB can be proved in some situations. First, when CRBBB develops in BS patients, it is certain that the patients have both BS and CRBBB. In such a situation, CRBBB would completely mask the ECG phenotype of BS (Figure 1). Rolf et al. reported a patient with BS with a resting ECG intermittently displaying a saddle-type and coved-type ECG pattern, which was masked when CRBBB occurred.\textsuperscript{9} A similar case of a BS patient was reported by Nam in 2012.\textsuperscript{24}

On some occasions, we might be able to unmask BS in patients revealing CRBBB. One method would be to prove the coved-type ECG pattern in the normal QRS complex by relieving
CRBBB. CRBBB might be relieved spontaneously, and we would be able to diagnose BS in a normalized QRS, as reported earlier. In this patient, a saddle back-type ECG was observed during 12-lead Holter recording on another occasion, (Figure 2). There was a slight but significant difference in the ST/T segment, depending on the ECG patterns: coved- versus saddle back-type ST elevation (Figure 2A and 2B). These different patterns of ST segments on the two occasions indicate that BS is masked by CRBBB, but the background ECG pattern of BS can affect CRBBB. The mechanism of this resolution was, however, not apparent.

Pacing from the right ventricle normalized the QRS complexes, and this normalization could be another promising intervention to resolve CRBBB. In the present study, this procedure was attempted in two patients on the occasion of implantable cardioverter-defibrillator (ICD) implantation (Figure 3).

New ST elevation
New and coved-type elevation of the ST segment on the ECG of patients with CRBBB might appear in the right leads, which could be explained by BS (Figure 4). J/ST/T in BS is known to show remarkable fluctuation from extreme elevation of the ST segment to normal, and such ECG changes might appear spontaneously or might be induced by the drugs that are used for the provocation of typical ECG patterns for BS: ajmaline or pilsicainide. Cases in which BS was unmasked with these drugs in patients showing CRBBB were reported earlier. Unmasking of BS in CRBBB patients would be due to exaggerated J waves in BS.

In summary, it is certain that BS can be masked by CRBBB, and unmasking of BS in CRBBB patients is very important in diagnosing the potential at-risk patients, such as those with BS.
Study limitations

This was a small case-control study. Although we could point out differences of ECG parameters of RBBB between those with and without BS including QRS duration, this alone would not be sufficient enough to discriminate the "benign" from "malignant" RBBB pattern. However, the interpretation of ECG findings was reasonable and straightforward. When patients with CRBBB had VF, systematically using Chiale's maneuver and/or drug testing with sodium blocking agent would be important. In approximately 25% of patients with BS, genetic abnormalities in cardiac sodium channels might be observed, and it is possible that a genetic abnormality of the sodium channel might be involved in developing CRBBB in BS patients. In the original report on BS, three of 8 patients showed prolonged H-V intervals. However, genetic screening was not performed in the present study. A systematic approach to disclose BS and risk stratification of CRBBB should be attempted.

Conclusions

BS can be masked by CRBBB. To diagnose BS in patients associated with CRBBB, relief of CRBBB, demonstration of typical ST elevation on repeated ECG recordings, pharmacological test or pacing from the right ventricle can be useful. The prevalence, mechanism and clinical significance of the combination of CRBBB and BS are yet to be determined.

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Conflict of Interest Disclosures: None.
References:


Table 1. Clinical Characteristics of IVF patients with complete RBBB

<table>
<thead>
<tr>
<th>Case</th>
<th>Age</th>
<th>Sex</th>
<th>VF</th>
<th>Time of VF</th>
<th>FH</th>
<th>VF at EPS</th>
<th>ICD</th>
<th>ECG changes</th>
<th>Pils/Ach test</th>
<th>VF Rec.</th>
<th>Drugs</th>
<th>Outcome</th>
<th>FU period (year)</th>
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<td>1</td>
<td>46</td>
<td>M</td>
<td>+</td>
<td>Morning</td>
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<td>+</td>
<td>+</td>
<td>New RBBB</td>
<td>Pils/Ach</td>
<td>+</td>
<td>ISP/Bep</td>
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<td>Sy+</td>
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<td>-</td>
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<td>Nd</td>
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<tr>
<td>7</td>
<td>45</td>
<td>M</td>
<td>-</td>
<td>Night</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>Spont BS</td>
<td>Pils/Nd</td>
<td>-</td>
<td>-</td>
<td>Alive</td>
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<tr>
<td>8</td>
<td>69</td>
<td>M</td>
<td>+</td>
<td>Night</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>CRBBB resolved, Spont BS</td>
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<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>Spont BS</td>
<td>Pils/Nd</td>
<td>-</td>
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<td>+</td>
<td>Night</td>
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<td>+</td>
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<td>M</td>
<td>+</td>
<td>Day time</td>
<td>-</td>
<td>+</td>
<td>+</td>
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<td>Pils/Ach</td>
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<td>-</td>
<td>Alive</td>
<td>2.0</td>
</tr>
</tbody>
</table>

Ach: acetylcholine; EPS: Electrophysiologic study; FH: Family history of sudden death; FU period: Follow-up period; ICD: Implantable cardioverter-defibrillator; M: Male; MSVT: monomorphic sustained ventricular tachycardia; Nd: not performed; Sy: syncope; Pils: pilsicainide; Rec: recurrence; VF: Ventricular fibrillation.

Table 2. Comparisons of ECG parameters between the BS patients and control subjects with CRBBB

<table>
<thead>
<tr>
<th>Case</th>
<th>BS with CRBBB</th>
<th>Control CRBBB</th>
<th>P value</th>
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<td>Number</td>
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<td>55</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>55±11</td>
<td>55±10</td>
<td>0.9831</td>
</tr>
<tr>
<td>RR (ms)</td>
<td>897±95</td>
<td>1001±151</td>
<td>0.0314</td>
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<td>PR (ms)</td>
<td>166±16</td>
<td>163±21</td>
<td>0.6838</td>
</tr>
<tr>
<td>QRS duration, V1 (ms)</td>
<td>170±13</td>
<td>145±15</td>
<td>0.0001</td>
</tr>
<tr>
<td>QRS duration, V5</td>
<td>144±19</td>
<td>128±7</td>
<td>0.0001</td>
</tr>
<tr>
<td>QT (ms)</td>
<td>394±11</td>
<td>418±25</td>
<td>0.0032</td>
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<tr>
<td>QTc (ms)</td>
<td>418±22</td>
<td>419±19</td>
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<tr>
<td>r, V1 (mm)</td>
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<td>R', V1 (mm)</td>
<td>12.8±3.5</td>
<td>10.6±3.3</td>
<td>0.0560</td>
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</table>
Figure Legends:

**Figure 1.** The patient was case 5, who showed variable ECG in the right leads (A and B). During the follow-up of 2 years, CRBBB developed without any precipitating cause. The ECG showed a tall R’ in V1, and the QRS duration was wide with slurred wide S on the left.

**Figure 2.** The patient was case 8 in Table 1. He experienced cardiac arrest out-of-hospital and was rescued by emergency personnel. During cardiac catheterization, CRBBB was found to resolve in a single beat, which disclosed coved-type ST elevation in V1 and V2 (A). Resolution of CRBBB occurred twice without apparent cause with similar findings. After ICD implantation, he was monitored by 12-lead Holter, which showed spontaneous resolution of CRBBB occurring twice per day (B). This time, only ST elevation was found in V1 and V2. The different level of the J point suggests that the QRS morphology was affected by the underlying ECG patterns between A and B (arrows).

**Figure 3.** The atrio-ventricular sequential pacing was attempted to normalize the QRS complexes in two patients (Cases 4 and 8). The CRBBB pattern in the baseline (A) was normalized by right ventricular pacing (B). The QRS became narrow with left axis deviation, and leads V1 and V2 showed coved type ST elevation. (B).

**Figure 4.** This is the same patient as in Figure 2. His ECG showed CRBBB on most recordings (A). However, elevation of the ST segment was occasionally observed without apparent cause (B).
Figure 5. The patient was case 11 in Table 1. The baseline ECG was diagnosed as CRBBB. He had out-of-hospital VF and was rescued (A). After admission, a IC-class drug, pilsicainide, was given to exclude BS, but the drug induced coved-type ST elevation in V1, B2 and V3, and he was diagnosed with BS behind CRBBB (B).
Figure 3
Figure 4
Figure 5

A  control

B  After pilsicainide
Brugada Syndrome Behind Complete Right Bundle Branch Block
Yoshiyasu Aizawa, Seiji Takatsuki, Motoaki Sano, Takehiro Kimura, Nobuhiro Nishiyama, Kotaro Fukumoto, Yoko Tanimoto, Kojiro Tanimoto, Mitsushige Murata, Takashi Komatsu, Hideo Mitamura, Satoshi Ogawa, Toshikazu Funazaki, Masahito Sato, Yoshifusa Aizawa and Keiichi Fukuda

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