Brugada Syndrome Behind Complete Right Bundle-Branch Block

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Background—The characteristic ECG of Brugada syndrome (BS) can be masked by complete right bundle-branch block (CRBBB) and exposed by resolution of the block or pharmacological or pacing maneuvers.

Methods and Results—The study consisted of 11 patients who had BS and CRBBB. BS was diagnosed before the development of CRBBB, on the resolution of CRBBB, or from new characteristic ST-segment changes that could be attributable to BS. Structural heart diseases were excluded, and coronary spasm was excluded on the basis of a provocation test at catheterization. In 7 patients, BS was diagnosed before the development of CRBBB. BS was diagnosed when CRBBB resolved spontaneously (n=1) or by right ventricular pacing (n=3). The precipitating cause for the spontaneous resolution of CRBBB, however, was not apparent. On repeated ECGs, new additional upward-convex ST-segment elevation was found in V₅ or V₆ in 3 patients. In 2 patients, new ST-segment elevation was induced by class Ic drugs. The QRS duration was more prolonged in patients with BS and CRBBB compared with age- and sex-matched controls: 170±13 versus 145±15 milliseconds in V₁ and 144±19 versus 128±7 milliseconds in V₅ (both P<0.0001). The amplitude of R in V₁ was larger in the BS patients than in the control subjects (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-segment elevation. The prevalence, mechanism, and clinical significance of a combination of CRBBB and BS are yet to be determined. (Circulation. 2013;128:1048-1054.)

Key Words: Brugada syndrome ■ bundle-branch block ■ cardiac pacing, artificial ■ sodium channels

Ventricular fibrillation (VF) can occur in patients without structural heart diseases; when it does, it is called idiopathic VF. Among primary electric diseases, Brugada syndrome (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.

Clinical Perspective on p 1054

Recently, we observed a case in which the characteristic ECG phenotype of BS was unmasked by relief of complete right bundle-branch block (CRBBB); when CRBBB resolved spontaneously, the characteristic ECG pattern of BS was found to be underlying. A similar case was reported by others. The goal of this study is to discuss patients with BS that were complicated by CRBBB and to present evidence for the presence of BS in CRBBB patients.

Methods

The study consisted of 11 patients who had CRBBB with the diagnosis of BS. Structural heart diseases were excluded by ECG, transthoracic echocardiography, and 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’') wave presenting in V₁ or V₂, with a slurred, wide S in leads I and V₅/V₆ and with prolonged duration of QRS ≥120 milliseconds. If CRBBB was seen on the baseline ECG, we divided the patients into 2 groups. One group consisted of the patients in whom ECG revealed BS and CRBBB occurred subsequently during the follow-up (n=7). The other group consisted of the patients who had CRBBB on the baseline ECG but in whom BS was diagnosed in the following situations (n=4). First, resolution of CRBBB resulted in normal ventricular conduction, in which the characteristic ECG pattern for BS could be seen. The resolution of CRBBB, on the resolution of CRBBB, or from new characteristic ST-segment changes that could be attributable to BS. Structural heart diseases were excluded, and coronary spasm was excluded on the basis of a provocation test at catheterization.

 DOI: 10.1161/CIRCULATIONAHA.113.003472

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Circulation is available at http://circ.ahajournals.org
CRBBB occurred spontaneously (n=1) or it might be induced by the pacing technique (n=3), that is, the Chiale intervention. Second, new J/ST changes appeared that could not be explained by CRBBB but could have been attributable to coved type ST-segment elevation. The new ECG changes appeared spontaneously on repeated ECG recordings (n=3) or were induced during the administration of class Ic drugs (n=2). Mechanistically, spontaneous or drug-induced exaggeration of J waves of BS had to be involved.

Provocation Tests
After the patients provided written 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 seconds into the left and right coronary arteries. If acetylcholine did not induce coronary spasms, 50 mg intracoronary ergonovine maleate was injected into the left and right coronary arteries over a period of 5 minutes. The end point was the development of total or subtotal occlusion or the completion of the drug infusion.

Provocation for the characteristic ECG pattern of BS was performed in patients suspected to have the syndrome but lacking type 1 ECG documentation with pilsicainide 1 mg/kg for 10 minutes intravenously. The end point was the development of type 1 pattern for BS or the completion of the drug infusion. Four of 7 patients before the development of CRBBB underwent this provocation test. In 2 of 4 patients with CRBBB but without the 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., 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, V5, and V6. In 2 patients during the electrophysiological study.

CRBBB in the Control Subjects
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 on 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 family members.

Data Analysis
ECGs were recorded repeatedly during hospitalization and during follow-up, which included those recorded at higher intercostal spaces. The QRS and ST-T morphologies in V1 and V5 and other ECG parameters were determined in the patients. Then, the patients 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. The QT interval, QTc was determined in the standard manner.

Statistical Analysis
The numeric values are presented as mean±SD. For comparisons, the differences between groups were analyzed by the Mann-Whitney-Wilcoxon test for continuous variables. Statistical analyses were performed with SPSS software, version 12.0 (SPSS Inc, Chicago, IL). A 2-sided value of P<0.05 was considered statistically significant.

Institutional Review Board Approval and Informed Consent
The study was approved by the institutional review committee of Keio University School of Medicine. The patients provided written informed consent before the invasive studies.

Results
CRBBB in BS
On the basis of the inclusion criteria, the ECGs of the 11 patients met the criteria for CRBBB: wide QRS duration (>120 milliseconds) 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 7 of 11 patients, the baseline ECG revealed the characteristic ECG pattern for BS, 2 spontaneously and 3 by a class Ic drug.
whereas CRBBB developed during the follow-up of 2.8±2.5 years, ranging from 0.2 to 7 years (patient 5, Figure 1).

Resolution of CRBBB
In 1 patient (patient 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 levels between the 2 recordings (Figure 2A and 2B); the J-point level was higher when the ST segment showed the coved type compared with the saddle-back type of elevation (Figure 2). The precipitating cause for the resolution of CRBBB was not apparent.

In 3 patients (patients 4, 8, and 11), we attempted ventricular pacing to normalize the QRS complexes from the right ventricular apex, which disclosed a coved type elevation in V1 and V2 (Figure 3).

New ST-Segment Elevation
On repeated ECGs, 4 patients showed new and additional ST-segment elevations in V2 or V3 that were considered to be characteristic for BS (Figure 4): spontaneously in 2 patients, during the infusion of a class Ic drug in 1 patient, and both spontaneously and during infusion of a class Ic drug in 1 patient (patient 11, Figure 5).

Figure 1. Patient 5 showed variable ECG in the right leads (A and B). During the 2-year follow-up, complete right bundle-branch block developed without any precipitating cause (C). The ECG showed a tall R' in V1, and the QRS duration was wide with a slurred, wide S on the left lateral leads (C).

Figure 2. Patient 8 experienced out-of-hospital cardiac arrest and was rescued by emergency personnel. During cardiac catheterization, complete right bundle-branch block (CRBBB) was found to resolve in a single beat, which disclosed coved type ST-segment elevation in V1 and V2 (A). Resolution of CRBBB occurred twice without apparent cause with similar findings. After implantation of a cardioverter-defibrillator, he was monitored by 12-lead Holter, which showed spontaneous resolution of CRBBB twice a day (B). This time, only ST-segment 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).
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 milliseconds in both, but it was wider in the BS patients compared with the control CRBBB subjects: 170±13 versus 145±15 milliseconds in V1 and 144±19 versus 128±7 milliseconds 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 nonsignificantly.

**Discussion**

**Major Findings**

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 on 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, but a recent cohort study made it clear that RBBB is associated with both increased cardiovascular risk and all-cause mortality. In addition, we reported that CRBBB might be observed among idiopathic VF patients and that the prevalence of CRBBB was higher in idiopathic VF patients than expected in the general population. BS and coronary spams were excluded, and CRBBB was the sole ECG phenotype in such patients. Furthermore, CRBBB was shown to be able to conceal the ECG phenotype of BS. 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 idiopathic VF is essential.

**Proof of Coexisting BS With CRBBB**

Coexisting BS and CRBBB can be proven 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-back type and coved-type ECG pattern, which was masked when CRBBB occurred. A similar case of a BS patient was reported by Nam in 2012.

On some occasions, we might be able to unmask BS in patients with 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-segment elevation (Figure 2A and 2B). These different patterns of ST segments on the 2 occasions indicate that BS is masked by CRBBB but the background ECG pattern of BS can affect CRBBB. The mechanism of this resolution, however, was 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 3 patients on the occasion of electrophysiology study or implantation of a cardioverter-defibrillator (Figure 3).

**New ST-Segment 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 used to provoke typical ECG patterns for BS, that is, ajmaline\textsuperscript{25} or pilsicainide.\textsuperscript{15,26} Cases in which BS was unmasked with these drugs in patients showing CRBBB were reported earlier.\textsuperscript{13,26} Febrile illness was shown to unmask BS in a patient with CRBBB.\textsuperscript{26} Unmasking of BS in CRBBB patients would be attributable to exaggerated J waves in BS.\textsuperscript{26}

Figure 4. Patient 8 (see also Figure 2). His ECG showed complete right bundle-branch block on most recordings (A). However, elevation of the ST segment was occasionally observed without apparent cause (B).

Figure 5. Patient 11. The baseline ECG was diagnosed as complete right bundle-branch block (CRBBB). He had out-of-hospital ventricular fibrillation and was rescued (A). After admission, a class I\textsubscript{c} drug, pilsicainide, was given to exclude Brugada syndrome (BS), but the drug induced coved-type ST-segment elevation in V\textsubscript{1}, V\textsubscript{2}, and V\textsubscript{3}, and the patient was diagnosed with BS behind CRBBB (B).

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

Study Limitations
This was a small case-control study. Although we could point out differences in ECG parameters of RBBB between
Table 2. Comparisons of ECG Parameters Between the BS Patients and Control Subjects With CRBBB

<table>
<thead>
<tr>
<th></th>
<th>BS With CRBBB</th>
<th>Control CRBBB</th>
<th>P Value</th>
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</thead>
<tbody>
<tr>
<td>n</td>
<td>11</td>
<td>55</td>
<td></td>
</tr>
<tr>
<td>Age, y (yr)</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>
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<tr>
<td>QRS duration, V1</td>
<td>170±13</td>
<td>145±15</td>
<td>&lt;0.0001</td>
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<tr>
<td>V1, mm</td>
<td>1.62±1.34</td>
<td>22.85±1.76</td>
<td>0.0323</td>
</tr>
<tr>
<td>RR, ms</td>
<td>144±19</td>
<td>128±7</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>QT, ms</td>
<td>394±22</td>
<td>418±25</td>
<td>0.0032</td>
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<td>Qtc, ms</td>
<td>418±22</td>
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<tr>
<td>r, V1, mm</td>
<td>1.62±1.34</td>
<td>22.85±1.76</td>
<td>0.0323</td>
</tr>
<tr>
<td>R', V1, mm</td>
<td>12.0±3.5</td>
<td>10.6±3.3</td>
<td>0.0560</td>
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</tbody>
</table>

BS indicates Brugada syndrome; and CRBBB, complete right bundle-branch block.

those with and those without BS, including QRS duration, this alone would not be sufficient 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 the Chiale maneuver or drug testing with a sodium-blocking agent would be important. In 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 the development of CRBBB in BS patients. In the original report on BS, 3 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-segment elevation on repeated ECG recordings, pharmacological tests, 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.

Acknowledgments

We thank Vincent Ventimiglia for his linguistic advice.

Source of Funding

This work was supported by MEXT KAKENHI grant 23790873 (Yoshiyasu Aizawa).

Disclosures

None.

References


**CLINICAL PERSPECTIVE**

Brugada syndrome (BS) and complete right bundle-branch block (CRBBB) can coexist. CRBBB can completely mask BS, but simultaneous diagnosis has never been attempted. This study represents the first series describing this phenomenon. In 11 patients who had BS and CRBBB, BS was diagnosed before the development of CRBBB, on the resolution of CRBBB, or from new characteristic ST-segment changes that could be attributable to BS. The QRS duration was more prolonged and the amplitude of R in V1 was larger in the patients with BS and CRBBB compared with age- and sex-matched control subjects. In BS patients with CRBBB, relief of CRBBB, repeated ECG recordings, or pharmacological tests can be useful to demonstrate typical ST-segment elevation. The prevalence, mechanism, and clinical significance of the combination of CRBBB and BS need to be determined.
Brugada Syndrome Behind Complete Right Bundle-Branch Block
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_Circulation_. 2013;128:1048-1054; originally published online July 31, 2013;
doi: 10.1161/CIRCULATIONAHA.113.003472
_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2013 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/128/10/1048

An erratum has been published regarding this article. Please see the attached page for:
/content/129/16/e465.full.pdf
In the article by Aizawa et al, “Brugada Syndrome Behind Complete Right Bundle-Branch Block,” which appeared in the September 3, 2013 issue of the journal (Circulation. 2013;128:1048–1054), several errors occurred:

1. In the abstract, the sentence beginning, “The amplitude of R in V1 was larger…” should have read, “The amplitude of R in V1 was smaller…”

2. On page 1051, the sentence beginning, “The R´ in V1 was larger in the BS patients…” should have read, “The R´ in V1 was smaller in the BS patients…”

3. In the clinical perspective on page 1054, “smaller” should replace “larger” in the third sentence, to read, “The QRS duration was more prolonged and the amplitude of R in V1 was smaller in the patients with BS and CRBBB compared with age- and sex-matched control subjects.”

The current online version of the article has been corrected. The authors regret the error.