Clinical Significance of the Dispersion of the Activation–Recovery Interval and Recovery Time as Markers for Ventricular Fibrillation Susceptibility in Patients With Brugada Syndrome

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Brugada syndrome (BS) is associated with sudden cardiac death and the markers for ventricular fibrillation (VF) remain unclear, so the activation–recovery interval (ARI) dispersion and recovery time (RT) dispersion were investigated as possible markers in 20 subjects with BS (BS group) and 22 healthy individuals (H group). The 20 BS subjects were divided into 8 cases with documented VF (BS-VF group), 3 of which had recurrences, and 12 without (BS-N group). The corrected dispersion measurements from the standard 12-lead ECG of the QT interval (QTcd), ARI (ARId) and RT (RTcd) were compared among the groups. There were significant differences noted between the BS-VF and BS-N groups for the ARId and the RTcd, but not for the QTcd. Further, there were critical differences, 150 ms1/2, observed for the ARId and RTcd, and these were associated with a prolongation of the maximum ARI or RT, shortening of the minimum ARI or RT, and prolongation only of the maximum QT for the QTcd. Susceptibility to VF may be predicted by the ARId or RTcd in BS. (Circ J 2002; 66: 549–552)

Key Words: Activation–recovery interval dispersion; Brugada syndrome; QT interval dispersion; Recovery time dispersion; Ventricular fibrillation

B rugada syndrome (BS) is a sudden cardiac death syndrome with a specific electrocardiographic (ECG) morphology that includes right bundle branch block and ST segment elevation in the right precordial leads.1,2 Asymptomatic patients with such an ECG morphology are often being detected through routine clinical examination,3 but there are no markers to predict the individual’s susceptibility to ventricular fibrillation (VF). When recording the activation–recovery interval (ARI) and recovery time (RT), the unipolar leads are usually used and Nonokawa et al demonstrated that ARI values in the I, II and III leads of the standard 12-lead ECG strongly correlated with those of the unipolar leads over the left lateral, left lower, and right lower chest4 We investigated the clinical significance of the computer-analyzed QT interval dispersion, ARI dispersion and RT dispersion from the standard 12-lead ECG, as potential markers of a susceptibility to VF in patients with BS.

Methods

Subjects
The subjects consisted of 20 patients with a BS-like ECG morphology (BS group) and 22 healthy individuals (H group). The BS group were observed for a mean of 3.7 years from when the data were first obtained and their ECGs transiently exhibited both the coved type and saddleback type ST segment elevation of more than 0.1 mV in the right precordial leads (V1, V2 and V3). The group was divided into 2 based on the presence or absence of documented VF events. Eight patients with documented VF comprised the BS-VF group (8 males; mean age, 43±11 years, range: 29–67 years), and of these, 3 had recurrent episodes of VF episodes recurred. Two patients, who had rejected an implantable cardioverter defibrillator (ICD), died suddenly and the third survived as a result of an ICD shock during the follow-up period. The remaining 12 patients without VF comprised the BS-N group (10 males, 2 females; mean age, 59±12 years, range: 33–78 years). Sinus rhythm was maintained in all subjects when the data were obtained. Obvious heart disease was not documented by chest X-ray, echocardiography or exercise testing in any of the subjects.

Measurement of QTcd, ARId and RTcd

We recorded 10s of the standard 12-lead ECG on to floppy disk after undergoing an A/D conversion at a 500 Hz sampling frequency. The beat to beat RR interval, QT interval, ARI, and RT were analyzed using QT analyzing software (Fukuda Denshi, Tokyo Japan). The QT interval was defined as the interval between the QRS onset and the T wave offset, the ARI was defined as the interval between the time of minimum dV/dt in the QRS segment and the time
of maximum dV/dt in the T wave, and the RT was defined as the interval between the QRS onset and the time of maximum dV/dt in the T wave (Fig 1). The QT, ARI and RT were measured automatically by the computer from each of the leads of the 12-lead ECG. From the determination of the maximum dV/dt of the T wave, the endpoint of the T wave was confirmed. If it was incorrect because of low voltage or deformity of the T wave, it was manually corrected using the method of Haws et al. For the QT interval, the difference between the maximum and minimum values, corrected for the heart rate (Bazett formula), were measured from the 12-lead ECG (QTcd). The ARI and RT were also measured and corrected in the same manner (ARIcd, RTcd, respectively).

Statistical Analysis
Measurements were represented as the mean value ± standard deviation (SD), compared using the Kruskal-Wallis method and determined positive for p<0.05.

Results

Comparison of Heart Rate
The heart rate when each measurement was performed was 64±8 beats/min in the H group, 66±10 beats/min in the BS-N group, and 64±14 beats/min in the BS-VF group. There was not a statistical difference among the 3 groups.

Comparison of QRS Duration
The duration of QRS was 95±10 ms, 110±11 ms and 121±25 ms for the H group, BS-N group and BS-VF group, respectively. The QRS duration was significantly greater in the BS-VF group than in the H group, but there was no difference with the BS-N group when compared with either the H group or BS-VF group.

Comparison of QTcd
The QTcd values for the H group, BS-N group and BS-

Table 1  Distribution of Maximum and Minimum Values Obtained From the Standard 12-Lead ECG

<table>
<thead>
<tr>
<th>Lead</th>
<th>QT</th>
<th>ARI</th>
<th>RT</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Max</td>
<td>Min</td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>II</td>
<td>2</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>III</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>aVR</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>aVL</td>
<td>4</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>aVF</td>
<td>2</td>
<td>2</td>
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<tr>
<td>V1</td>
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<td>V2</td>
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<td>V5</td>
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<td>2</td>
<td>2</td>
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<tr>
<td>V6</td>
<td>2</td>
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</tr>
</tbody>
</table>

QT, QT interval; ARI, activation–recovery interval; RT, recovery time.
VF susceptibility in patients with Brugada syndrome was observed in III, aVL, and V1 leads in 4, 5, and 3 cases, respectively. In the BS-N group, the maximum ARIs were 100±29 ms$^{1/2}$, 107±36 ms$^{1/2}$, and 183±40 ms$^{1/2}$, respectively (Table 1). The maximum QT interval in the BS-VF group was significantly greater than that in the H group, but there was no difference with the BS-N group when compared with either the H group or BS-VF group (Fig 2). The maximum and minimum values of the QT interval in the H group were 417±31 ms and 364±27 ms, respectively, 419±34 ms and 363±34 ms, respectively, in the BS-N group and 452±49 ms and 376±58 ms, respectively, in the BS-VF group. The maximum QT interval in the BS-VF group was significantly greater in comparison with the other 2 groups, but the minimum QT interval did not differ between the 3 groups. The greater QTcd in the BS-VF group indicated that it was caused by the greater QT interval. In BS-VF group, the maximum QTs were observed in II, V1, V2, V4, and V5 leads in 1, 1, 3, 2, and 1 cases, respectively, and the minimum QTs were observed in I, aVx, and aV1 leads in 2, 1, and 5 cases, respectively. In the BS-N group, the maximum QTs were observed in III, V2, V3, V4, and V5 leads in 1, 1, 1, 3, and 5 cases, respectively, and the minimum QTs were observed in I, III, aV1, and V1 leads in 3, 1, 4, and 4 cases, respectively (Table 1).

Comparison of ARicd

The ARicd values for the H, BS-N, and BS-VF groups were 100±29 ms$^{1/2}$, 104±36 ms$^{1/2}$, and 183±40 ms$^{1/2}$, respectively. The ARicd in the BS-VF group was significantly greater than in the other 2 groups (Fig 3). The maximum and minimum values of the AR in the H group were 286±38 ms and 188±23 ms, respectively, 284±49 ms and 186±21 ms, respectively, in the BS-N group and 323±41 ms and 140±58 ms, respectively, in the BS-VF group. In the BS-VF group, the maximum ARI was significantly greater and minimum ARI significantly smaller in comparison with the other 2 groups. The greater ARicd in the BS-VF group indicated that it was caused by a greater maximum ARI and smaller minimum ARI. Seven patients (87.5%) in the BS-VF group had an ARicd value greater than 150 ms$^{1/2}$, but this was not observed in the other 2 groups. In BS-VF group, the maximum ARs were observed in III and V1 leads in 2 and 6 cases, respectively, and the minimum ARs were observed in aVx, V2, V3, and V4 leads in 1, 1, 3, and 3 cases, respectively. In the BS-N group, the maximum ARs were observed in III, aV1, and V1 leads in 4, 5, and 3 cases, respectively, and the minimum ARs were observed in I, V1, V2, and V3 leads in 1, 5, 3, and 3 cases, respectively (Table 1).

Comparison of RTcd

The RTcd in the H group, BS-N group, and BS-VF group were 96±27 ms$^{1/2}$, 107±29 ms$^{1/2}$, and 173±41 ms$^{1/2}$, respectively. The RTcd in the BS-VF group was significantly greater than in the other 2 groups (Fig 4). The maximum and minimum values of the RT in the H group were 331±35 ms and 237±23 ms, respectively, 332±43 ms and 236±23 ms, respectively, in the BS-N group and 367±46 ms and 198±28 ms, respectively, in the BS-VF group. In the BS-VF group, the maximum RT was significantly greater and minimum RT significantly smaller in comparison with the other 2 groups. The greater RTcd in the BS-VF group indicated that it was caused by a greater maximum RT and smaller minimum RT. Similar to the ARicd, patients with documented VF or who survive sudden death with a VT event during the 15-month follow-up period had an RTcd value greater than 150 ms$^{1/2}$, but this was not observed in the other 2 groups. In BS-VF group, the maximum RTs were observed in III and V1 leads in 2 and 6 cases, respectively, and the minimum RTs were observed in I, III, V1, V2, V3, and V4 leads in 1, 1, 1, 2, and 2 cases, respectively. In BS-N group, the maximum RTs were observed in III, aVx, aV1, and V1 leads in 4, 1, 4, and 3 cases, respectively, and the minimum RTs were observed in I, aV1, V1, V2, V3, and V5 leads in 1, 5, 3, 1, and 1 cases, respectively (Table 1).

Discussion

We have reported that the BS-like ECG morphology without symptoms such as VF and syncope existed in 0.04% of 23,000 healthy subjects examined and 33% of those were symptomatic patients. Further, in a multicenter study in Japan, none of the 34 BS-like ECG patients had any events during the 15-month follow-up period. An adequate treatment method, other than ICD, has been determined at present, so it is important to distinguish those with BS and a high risk of VF. The usual procedure is to induce the ventricular arrhythmia during an electrophysiological study (EPS) but there is a lack of guidelines for treating asymptomatic patients. In general, those who are asymptomatic are observed without treatment, those with syncope undergo an EPS and if VF is inducible, an ICD is implanted, and those with documented VF or who survive sudden death have an ICD. The significance of VF inducibility during the EPS is unclear and needs to be determined and whether it should be undertaken with asymptomatic patients is controversial. Although Brugada et al recommend ICD for all patients with a BS-like ECG morphology, generally it is...
not possible to treat all asymptomatic patients this way.

We reported a transient increase in the QTc of the standard 12-lead ECG for 2–5 days immediately after the VF event, which then decreased in conjunction with a change in the ECG morphology from the coved type to saddleback type; however, there was no difference between these 2 types of ECG morphology in the asymptomatic group. The electrophysiological mechanism of the ST elevation in BS is understood to be a transmural dispersion in the right ventricle and different markers of repolarization have been discussed. In the present comparison of the BS-VF and BS-N groups, the AR1c and RT1c displayed a critical difference, of 150 ms, that was not clear for the QTc. Furthermore, shortening of the minimum ARI or RT was associated with an increase in the dispersion of the AR1c or RTc, but not the QTc. The AR1c and RT1c resulted from an automatic measurement of the differential calculated ECG morphology, and each measurement from the body surface mapping was associated with that from the electrograms of the epicardial mapping. Because the action potential from the epicardial side characteristically changes, by shortening and prolonging, and further, because that change is inhomogeneously distributed in BS, the AR1c and RT1c may strongly indicate that change. The critical dispersion of the AR1c and RT1c, of 150 ms, was determined from observations of a small number of patients with BS. Further investigation of a larger number of patients and observation of patients with BS-N is necessary.

Conclusion

The clinical significance of the AR1c and RT1c as markers for VF susceptibility in patients with BS in a small patient group and a critical difference consisting of a shortening of the AR1c or RT1c of 150 ms, was observed between the symptomatic and asymptomatic patients.

References