Autonomic Imbalance as a Property of Symptomatic Brugada Syndrome

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The autonomic properties in 27 patients with the electrocardiographic morphology of Brugada syndrome were investigated using 24-h Holter monitoring: 10 patients had a history of ventricular fibrillation (VF; Br-VF group) and 17 did not (Br-N group); there were 26 healthy subjects enrolled in this study. All subjects underwent normal Holter data monitoring and power spectral analysis. Few extrasystoles were observed in either group, and the mean heart rate (HR), maximum HR, and total heart beats over 24 h were obtained. All of these measurements were significantly lower in the Br-VF group than in the Br-N and healthy subject groups. The RR interval variability was analyzed over 512 beats every 10 min. The high-frequency component (0.15–0.40 Hz; HF), low-frequency component (0.04–0.15 Hz; LF) and the LF/HF ratio were analyzed over 24 h. The HF was significantly higher and LF/HF ratio lower in the Br-VF group than in the healthy subjects. The HF was also significantly higher than in the Br-N group. During the night (00.00–05.00 h), the HF was significantly higher in the Br-VF group, and the LH/HF lower. During the day (12.00–17.00 h), the HF was significantly higher in the Br-VF group, but there was no difference in the LF/HF. These results indicate that high vagal tone and low sympathetic tone are specific properties of symptomatic Brugada syndrome. (Circ J 2003; 67: 511–514)

Key Words: Autonomic imbalance; Brugada syndrome; Ventricular fibrillation

Brugada syndrome is a cardiac sudden death syndrome that occurs in middle-aged healthy males. It is characterized by a unique electrocardiographic (ECG) morphology of complete or incomplete right bundle branch block and ST segment elevation in the right precordial leads! The level of ST segment elevation and the overall morphology vary from day to day.2–4 Although this alteration is known to be related to autonomic stimulation,5,6 the baseline autonomic properties in patients with this syndrome remain unclear. In the study reported here, we used Holter recordings to measure the autonomic tone in patients with Brugada syndrome.

Methods

Subjects

The subjects were 27 male patients with Brugada syndrome-like ECG morphology and 26 healthy males. The patients were divided into 2 groups: those with demonstrated ventricular fibrillation (VF; Br-VF group; n=10) and those without VF episodes or syncope (Br-N group; n=17). None of the subjects showed obvious structural heart disease on chest X-ray or echocardiography or treadmill exercise test. Further, coronary angiography and ventriculography undertaken by the Br-VF group also revealed normal hearts in all members of the group. Patients with diabetes mellitus, long QT syndrome, or electrolyte abnormalities were excluded from the study, as were patients taking β-blockers, Ca antagonists, angiotensin-converting enzyme inhibitors or class I antiarrhythmic drugs. The age of the subjects in the Br-N group was significantly higher (Br-VF group: 42±16 years; Br-N group: 56±13 years; healthy subjects: 44±16 years), but there was no difference between the other 2 groups (Scheffe multi comparison). The Brugada syndrome-like ECG morphology was defined as incomplete or complete right bundle branch block with ST segment elevation (>0.1 mV) in the right precordial leads (V1, V2 and/or V3 lead) on the standard 12-lead ECG. A typical coved type ST segment elevation was found in all the patients in the Br-VF group, and in 2 patients in the Br-N group during 1–8 years of follow up (3.6±2.2 year).

RR Interval Analysis

Each subject underwent 24-h Holter monitoring (SM-50, Fukuda Denshi Co Ltd) during their usual daily life. In the Br-VF group, it was performed 3–29 (mean, 9.9) days after a VF episode or syncope. All the ECG recordings were analyzed for morphology, any extrasystole mistakes were amended and the R wave trigger was corrected. Spectral analysis was performed over 512 beats every 10 min (SCM-6000, Fukuda Denshi Co Ltd). The high-frequency component (HF: 0.15–0.40 Hz), low-frequency component (LF: 0.04–0.15 Hz) and LF/HF ratio were analyzed.

Statistical Analysis

Measurements are presented as the mean value± standard deviation. Statistical analysis was performed using a Scheffe analysis.
Results

Comparison of the Holter Recordings (Table 1)

A small number of ventricular extrasystoles and supraventricular extrasystoles were observed in each group, but there was no difference in this number between the groups. The mean heart rate (HR), maximum HR and total heart beats over 24 h were significantly lower (p<0.05) in the Br-VF group than in the other 2 groups.

Comparison of the Spectral Analysis

Typical examples from the spectral analysis are shown in Fig 1. The distribution over 24 h clearly showed a difference between the Br-VF and Br-N groups. In the Br-VF group, there was a dense distribution of measurements in the low LF/HF area and in the high HF area over 24 h. During the night (00.00–05.00 h), the difference became less clear. During the day (12.00–17.00 h), there was a clear difference in the distribution, with the measurements being distributed only in the area with a low LF/HF ratio in the Br-VF group and in the area with a low HF in the Br-N group.

Fig 2. Comparisons of the mean HF and mean LF/HF ratio between the 3 groups over 24 h. The HF significantly increased in the Br-VF group, and the LF/HF ratio significantly decreased compared with the healthy subjects, but there was no difference observed between that for the Br-N group and the other 2 groups.

multiple comparison and was defined as significant for p<0.05.

Table 1  Data From the Holter Recordings

<table>
<thead>
<tr>
<th></th>
<th>Br-VF group (n=10)</th>
<th>Br-N group (n=17)</th>
<th>Healthy subjects (n=26)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ventricular extrasystoles (beats/day)</td>
<td>196.55±</td>
<td>418.89±</td>
<td>982.8±</td>
</tr>
<tr>
<td>Supraventricular extrasystoles (beats/day)</td>
<td>73±9</td>
<td>34±46</td>
<td>7±8</td>
</tr>
<tr>
<td>Mean heart rate (beats/min)</td>
<td>67±9*</td>
<td>73±8</td>
<td>79±10</td>
</tr>
<tr>
<td>Maximum heart rate (beats/min)</td>
<td>109±17*</td>
<td>124±16</td>
<td>134±17</td>
</tr>
<tr>
<td>Minimum heart rate (beats/min)</td>
<td>49±6</td>
<td>50±6</td>
<td>52±5</td>
</tr>
<tr>
<td>Total heart beats (/day)</td>
<td>92,036±13,652*</td>
<td>102,205±7,829</td>
<td>109,112±13,910</td>
</tr>
</tbody>
</table>

*p<0.05.
Autonomic Imbalance in Brugada Syndrome

Fig 3. Comparisons of the mean HF and mean LF/HF ratio between the 3 groups during the night (00.00–5.00h). The HF significantly increased in the Br-VF group compared to the other 2 groups, and the LF/HF ratio significantly decreased as compared to the healthy subjects; however, the Br-N group showed no difference in the LF/HF ratio from those of the other 2 groups. During the night, the HF significantly increased and the LF/HF ratio significantly decreased in the Br-VF group in comparison with the other 2 groups, and during the day, the HF significantly increased in the Br-VF group, but there was no difference in the LF/HF ratio between the 3 groups in that time period.

Discussion

It is known that ST segment elevation varies according to the influence of the autonomic stimulation but it is unclear whether or not this autonomic influence affects the occurrence of VF. We compared the baseline autonomic properties in patients with Brugada syndrome between those of patients with and without a history of VF. As an estimation of the autonomic properties, the normal RR interval variability measured from the Holter ECG was used and our results were as follows.

(1) The mean HR, maximum HR, and total heart beats over a 24-h recording were lower in the Br-VF group than in the Br-N group or the healthy subjects.

(2) The HF over 24h, during the night and day, was higher in the Br-VF group than in the Br-N group or the healthy subjects.

(3) The LF/HF ratio in the Br-VF group over 24h was lower than that in the healthy subjects, but there was no difference between the ratios observed in the Br-VF and Br-N groups, or between those in the Br-N group and healthy subjects. However, the lowest HF/LH ratio occurred during the night.

These results suggest that the baseline autonomic properties in the Br-VF patients are increased vagal tone and decreased sympathetic tone. Because that autonomic imbalance was significant in the Br-VF group, but not in the other groups, it might be associated with the occurrence of VF.

Nomura et al used metaiodobenzylguanidine (MIBG) to demonstrate a decrease in the sympathetic tone in patients with Brugada syndrome who had a history of VF. Matsuo et al reported that VF occurred more frequently during the night than during the day, and was most likely between midnight to early morning, which they suggested was caused by increased vagal tone and decreased sympathetic tone.

We compared the autonomic tone evaluated 2–3 days after a VF attack with that evaluated 3 weeks after the attack in patients with Brugada syndrome and found that the increase in vagal tone and decrease in the sympathetic tone were significant 2–3 days after the VF attack, which suggested that a transient autonomic imbalance is associated with the occurrence of VF. Kasanuki et al also reported that a sudden increase in vagal tone was associated with the occurrence of VF. However, although these findings imply that increased vagal stimulation and decreased sympathetic stimulation are associated with the occurrence of VF in patients with Brugada syndrome, the mechanism still remains unclear.

The ECG morphology of Brugada syndrome is believed to be caused by either an accentuation of the notch in the early phase of the action potential or loss of the action potential dome in the epicardium, but not in the endocardium, and the mechanism of the VF is believed to be phase 2 reentry caused by dispersion of the action potential. The dispersion of the action potential is caused by an outward shift in the balance of the membrane current at the end of phase 1. Acetylcholine facilitates such a shift by suppressing the Ca current and furthermore, vagal stimulation exaggerates the ST segment elevation, but the sympathetic influence reduces it.

Though it remains unclear whether or not the degree of ST segment elevation is related to the occurrence of VF, it is possible that the basic reentrant structure is aggravated by an increase in the vagal tone. In the present study, a baseline autonomic imbalance was shown to exist only in the patients in the Br-VF group. The typical coved type ST segment elevation was found in all the patients in the Br-VF group, but was observed in only 2 patients in the Br-N group. Vagal increase may facilitate the ECG morphology change. Therefore, this autonomic imbalance may be a useful marker of the occurrence of VF in patients with the ECG morphology of Brugada syndrome. However, because there was an overlap in the data from each group, a critical borderline was not obtained in the present study.

Conclusion

The combination of vagal increase and sympathetic
decrease was observed in patients with a Brugada syndrome like ECG with a history of VF. This autonomic imbalance may predict those patients with Brugada syndrome who are at high risk.

References