Circadian Variation of Autonomic Nervous Activity in Patients With Multivessel Coronary Spasm

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The present study investigated whether the circadian rhythm of sympathovagal activity is related to the severity of coronary spasm or multivessel coronary spasm. Heart rate variability was examined in 22 consecutive patients with vasospastic angina provoked by intracoronary injection of acetylcholine, who had either multivessel spasm (Group M, n=11) or single vessel spasm (Group S, n=11), in 20 subjects without coronary artery disease (Group C) and 20 patients with effort angina who had organic coronary artery stenosis (Group E). The frequency domain indices were analyzed, including low frequency (LF: 0.04–0.15 Hz) and high frequency (HF: 0.15–0.4 Hz), the latter being an index of efferent parasympathetic activity, and the ratio (L/H) as an index of sympathovagal balance. The circadian variation of the parameters was analyzed by its pattern and was quantified by the difference of the mean values between daytime and nighttime. Although the HF power increased during nighttime in Groups C and S, this increase was attenuated in Groups E and M. The circadian variation of the L/H ratio (ie, a drop during nighttime) was smaller in the S and M groups than in Groups C and E. Accordingly, in Group M, the circadian variation of both sympathetic and parasympathetic nervous activity was attenuated, but in Group S, the variation of sympathetic nervous activity, but not parasympathetic nervous activity, was decreased. These data suggest that relatively enhanced sympathetic nervous activity at night may be involved in the mechanism underlying multivessel coronary spasm. (Jpn Circ J 2001; 65: 593–598)

Key Words: Circadian rhythm; Heart rate variability; Multivessel coronary spasm

Coronary spasm frequently occurs at rest or in the early morning and a number of disorders or dysregulation have been implicated in the pathogenesis, including endothelial dysfunction, which is characterized by the impaired nitric oxide release. Another important factor may be altered autonomic nervous activity particularly acute changes of activity. However, because stimulation of both the sympathetic and parasympathetic nervous system can provoke coronary artery spasm, the precise mechanisms by which spasm is triggered remain to be elucidated.

Several cardiovascular diseases have a circadian variation as observed in variant angina (VA), in which there is an increase of anginal attacks in the early morning. A circadian variation of basal coronary tone or autonomic nervous activity in VA has also been reported by Yasue et al, who showed that the coronary artery's response to intracoronary nitroglycerin during coronary angiography was more sensitive in the morning than in the afternoon. Miwa et al analyzed heart rate variability (HRV) in patients with VA and found enhanced sympathetic nervous activity during the night.

The prognosis of VA is generally believed to be good but not when multivessel spasm is involved, because sudden death may occur as a result of the severe and extensive myocardial ischemia associated with the arrhythmias. Although autonomic nervous activity is implicated, it is unclear whether multivessel spasm is associated with an abnormal circadian rhythm of autonomic nervous activity. Non-invasive techniques, such as HRV and iodine-123 metaiodobenzylguanidine scintigraphy (123I-MIBG) have been used to investigate the role of autonomic nervous system in VA, so we analyzed the HRV in patients with coronary multivessel spasm to elucidate the relation between multivessel coronary spasm and the circadian rhythm of autonomic nervous activity.

Methods

Study Patients

Twenty-two consecutive patients with suspected vasospastic angina were admitted to Jichi Medical School Hospital between March 1994 and June 1997. All of them had chest pain, which occurred at rest in 9, on effort in 7 and both in 6 patients. Transient ST-segment elevation was found in 15, ST-segment depression in 4 and negative T wave in the remaining 3 patients during spontaneous attacks, treadmill exercise or hyperventilation tests. None of the patients had angiographically significant organic coronary stenosis (<25%) and all showed coronary spasm on angiography, associated with ischemic ST-segment changes, after intracoronary injection of acetylcholine (ACh). We defined multivessel coronary artery spasm as the spasm of 2 or 3 of the 3 major coronary arteries (right, left anterior descend-
Coronary Angiography

Coronary angiography was performed after discontinuation of anti-anginal drugs, including calcium antagonists and nitrates, for more than 2 days. If significant stenosis (>75%) was not detected by coronary angiography, inducible angina without rest angina who had organic coronary stenosis (>75%) diagnosed by coronary angiography (Group E) were enrolled. Group C subjects had been referred to hospital because of hypertension, hyperlipidemia or palpitation, were examined by chest X-ray, electrocardiography, echocardiography and 24-h Holter electrocardiography and finally diagnosed as not having obvious ischemic heart disease. In Group E, 9 patients had 1-vessel stenosis, 6 had 2-vessel stenosis and 5 had 3-vessel stenosis. The control groups were age- and sex-matched with the vasospastic angina groups. Any subject with diabetes mellitus, myocardial infarction, cardiomyopathy, valvular heart disease, sinus node disorders or frequent extrasystoles (>1,000 beats/day) or who was taking β-blocking drugs was excluded. All subjects in this study had normal left ventricular performance.

Twenty-four-Hour Holter ECG and Analysis of HRV

The 24-h Holter recording was performed on 2 channels (leads CC5 and CM5, Marquette series 8500). The system digitizes the data from the tapes and applies algorithms for QRS labeling and editing, enabling automated calculation of both spectral and time domain measures of HRV. Fast Fourier transformation was performed to determine the frequency components. Recordings with more than 155 noise or ectopic beats were excluded from the analysis. Spectral measurements were computed for each hour, during which a spectral plot is the average of 30 spectra digitizes the data from the tapes and applies algorithms for QRS labeling and editing, enabling automated calculation of both spectral and time domain measures of HRV. Fast Fourier transformation was performed to determine the frequency components. Recordings with more than 155 noise or ectopic beats were excluded from the analysis. Spectral measurements were computed for each hour, during which a spectral plot is the average of 30 spectra computed over 2-min periods. Power spectra were quantified with the area (power) at 2 frequency bandwidths: 0.04–0.15 Hz (low-frequency [LF] power) and 0.15–0.40 Hz (high-frequency [HF] power). HF power, which is related to respiration, primarily reflects efferent parasympathetic activity at the cardiac level.20,21 The LF/HF (L/H) ratio, an index of sympathovagal balance, was also calculated.22 In order to quantitate circadian variation, averages of HF power and the L/H ratio were calculated separately during daytime (from 10.00 h to 22.00 h) and nighttime (from 22.00 h to 10.00 h). There were 2 different definitions of circadian variation: one was the difference of every 1 h value among the 24 h in each group, and the other was the difference between the daytime and nighttime values. Time-domain analysis included average RR interval (NN), standard deviation of the RR intervals over a 24-h period (SDNN), the percentage of RR intervals with more than 50 ms variation (pNN50), and root-mean square of difference of successive normal R-R intervals (rMSSD).23 Anti-anginal medications were permitted during 24-h Holter recording; so anginal attacks were almost suppressed and only 2 attacks were observed during the recording.

Statistical Analysis

Data are expressed as mean±standard error. Spectral and time-domain measurements of HRV and age were compared between the groups by one-way factorial ANOVA, followed by the Fisher protected least significant difference multiple comparisons test. First, to evaluate whether there was a circadian fluctuation in each group, the circadian variation of HF power and the L/H ratio was analyzed by one-way repeated-measures ANOVA and second, to compare the circadian variation between the groups, the daytime–nighttime difference was analyzed using one-way factorial ANOVA. The incidence of hypertension, hyperlipidemia and smoking and the number of subjects taking calcium antagonists were compared by chi-square test. As shown in the Results, several variables in patient characteristics were different among the groups in which case, multivariate analysis for the difference of HF power or L/H ratio between daytime and nighttime was performed in relation to those variables. Statistical analyses were performed with Statview-J 4.5 statistical software (Abacus Concepts, Inc, Berkeley, CA, USA) on a Macintosh computer. Statistical significance was defined as p<0.05.

Results

Clinical Characteristics of the Study Population (Table 1)

Age, gender, and the number of patients taking calcium antagonists were similar among the groups, but the incidences of hypertension, hyperlipidemia and smoking were significantly different. In the vasospastic angina groups (Groups S and M), more than 80% were men and smokers and either of these variables was not significantly different between the 2 groups.

Comparison of Time-Domain and 24-Hour Frequency Domain Analysis (Table 2)

Mean NN was significantly higher in Groups S and M than in Group C, which might result from the frequent use of diltiazem in Group S (4 patients) and Group M (4 patients), in contrast to nil use in Group C. SDNN, which approximately corresponds to total power in the frequency domain variable, was significantly lower in Group E than in the other groups. With respect to 24-h frequency domain analysis, neither HF power nor the L/H ratio differed among the groups in the present study except that the HF power was significantly lower in Group E than in Group C. Either of these variables was not significantly different between Groups S and M.

Comparison of Frequency Domain Analysis Between Day and Night

Circadian changes in HF power and the L/H ratio for every hour interval were measured and plotted (Fig 1). Whereas HF power increased during nighttime in Groups C and S, this increase seemed to be attenuated in Group E. Moreover, Group M showed only a trivial circadian fluctu-
Table 1  Patient Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Group C (n=20)</th>
<th>Group E (n=20)</th>
<th>Group S (n=11)</th>
<th>Group M (n=11)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>58.2±2.9</td>
<td>61.8±2.5</td>
<td>59.4±1.7</td>
<td>59.4±2.4</td>
<td>NS</td>
</tr>
<tr>
<td>Men</td>
<td>14 (70%)</td>
<td>15 (75%)</td>
<td>9 (82%)</td>
<td>10 (91%)</td>
<td>NS</td>
</tr>
<tr>
<td>Hypertension</td>
<td>8 (40%)</td>
<td>15 (75%)</td>
<td>4 (36%)</td>
<td>5 (45%)</td>
<td>0.02</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>1 (5%)</td>
<td>9 (45%)</td>
<td>0 (0%)</td>
<td>2 (18%)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Smoking</td>
<td>3 (15%)</td>
<td>12 (60%)</td>
<td>9 (82%)</td>
<td>9 (82%)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Taking calcium antagonists</td>
<td>7 (35%)</td>
<td>15 (75%)</td>
<td>7 (64%)</td>
<td>7 (64%)</td>
<td>NS</td>
</tr>
</tbody>
</table>

Group C, control subjects; Group E, patients with effort angina; Group S, patients with single-vessel spasm; Group M, patients with multi-vessel spasm; NS, not significant.

Table 2  Time-Domain Analysis and 24-Hour Frequency Domain Analysis

<table>
<thead>
<tr>
<th></th>
<th>Group C (n=20)</th>
<th>Group E (n=20)</th>
<th>Group S (n=11)</th>
<th>Group M (n=11)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean NN (ms)</td>
<td>849±25</td>
<td>906±28</td>
<td>979±24*</td>
<td>962±28*</td>
</tr>
<tr>
<td>SDNN (ms)</td>
<td>156±9</td>
<td>115±7*</td>
<td>150±123</td>
<td>145±114</td>
</tr>
<tr>
<td>rMSDD (%)</td>
<td>26.9±2.6</td>
<td>21.8±2.0</td>
<td>28.3±1.9</td>
<td>24.4±1.5</td>
</tr>
<tr>
<td>pNN50 (%)</td>
<td>6.1±1.6</td>
<td>4.5±1.4</td>
<td>8.1±2.7</td>
<td>5.0±1.4</td>
</tr>
<tr>
<td>Ln(HF) (ms²)</td>
<td>4.6±0.2</td>
<td>4.1±0.2*</td>
<td>4.6±0.3</td>
<td>4.4±0.1</td>
</tr>
<tr>
<td>L/H ratio</td>
<td>1.26±0.03</td>
<td>1.28±0.03</td>
<td>1.31±0.05</td>
<td>1.26±0.05</td>
</tr>
</tbody>
</table>

NN, RR interval; SDNN, standard deviation of the RR intervals over a 24-h period; rMSDD, root-mean square of difference of successive normal RR intervals; pNN50, the percentage of RR intervals with >50 ms variation; HF, high-frequency power; L/H ratio, low-frequency power/HF ratio. Values are expressed as mean±1SE. *,**p<0.01, 0.05 vs Group C. †p<0.05 vs Group E.

Fig 1. Circadian variations of HF power (A) and L/H ratio (B) were plotted every hour in each group. Data are expressed as mean±SE. P values for circadian variation analyzed by ANOVA are indicated. NS, not significant. Group C, control subjects; Group E, patients with effort angina; Group S, patients with single vessel spasm; Group M, patients with multivessel spasm.
lation in HF power (Fig 1A). In contrast, the L/H ratio decreased during nighttime in Groups C and E, whereas this drop seemed to be less prominent in Group S and was abolished in Group M (Fig 1B). Table 3 shows separately the 12-h HF power and L/H ratio during daytime and nighttime. HF power during nighttime was significantly decreased in Group E compared with Groups C and S. Either of these variables was not significantly different between Group S and Group M. To analyze these circadian variations quantitatively, the daytime–nighttime difference of the average HF power and L/H ratio was calculated. As shown in Fig 2A, the daytime–nighttime difference of HF power was smaller in Groups M and E than in Group C, but not in Group S, and was significantly smaller in Group M than in Group S. On the other hand, the daytime–nighttime difference of the L/H ratio was significantly smaller in Groups S and M than in Group C (Fig 2B). All patients in Groups E, S, and M were inpatients, but 17 control subjects were outpatients. The daytime–nighttime differences in HF power and L/H ratio were, respectively, –0.65±0.31 and 0.14±0.05 in 3 inpatients vs –0.87±0.10 and 0.16±0.03 in the 17 outpatients.

To examine which factors influence the circadian variation of HF power and L/H ratio, multivariate analysis was done (Table 4). In the analysis, which included 4 variables, only ‘multivessel spasm’ was an independent factor for a decreased difference of HF power and L/H ratio between daytime and nighttime. Other variables (ie, incidence of hypertension, hyperlipidemia, and smoking) that were significantly different between the groups were not significantly related to the daytime–nighttime difference of HF power and the L/H ratio.

## Discussion

Multivessel coronary spasm, which can cause sudden cardiac death, probably by lethal arrhythmia, is more frequently observed (76%) than single-vessel coronary spasm when spasm is induced by intracoronary ACh in patients with VA. Therefore, multivessel coronary spasm has clinical importance as a type of ischemic heart disease. However, which factor is related to the severity of coronary spasm remains unknown: endothelial dysfunction, impaired autonomic nervous activity or others? In the present study, we demonstrated that circadian fluctuation of both the parasympathetic and sympathovagal balance was decreased or blunted in patients with multivessel spasm when they were free of anginal attacks. In contrast, only the circadian fluctuation of sympathovagal balance was decreased in patients with single-vessel spasm.

Modulation of the autonomic nervous system is thought to be one of the mechanisms of VA. Yoshi et al reported that both LF and HF power were increased during the minutes preceding ST-segment elevation, which indicates a

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**Table 3 Twelve-Hour Frequency Domain Analysis During Daytime and Nighttime**

<table>
<thead>
<tr>
<th>Group</th>
<th>(n=20)</th>
<th>(n=20)</th>
<th>(n=11)</th>
<th>(n=11)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daytime</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ln(HF) (ms²)</td>
<td>4.1±0.2</td>
<td>3.9±0.2</td>
<td>4.3±0.2</td>
<td>4.4±0.1</td>
</tr>
<tr>
<td>L/H ratio</td>
<td>1.37±0.03</td>
<td>1.33±0.04</td>
<td>1.34±0.05</td>
<td>1.26±0.05</td>
</tr>
<tr>
<td>Nighttime</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ln(HF) (ms²)</td>
<td>4.9±0.2*</td>
<td>4.3±0.2</td>
<td>4.9±0.3*</td>
<td>4.5±0.1</td>
</tr>
<tr>
<td>L/H ratio</td>
<td>1.21±0.03</td>
<td>1.23±0.03</td>
<td>1.28±0.05</td>
<td>1.25±0.05</td>
</tr>
</tbody>
</table>

Daytime, 10.00 h–22.00 h; Nighttime, 22.00 h–10.00 h; HF, high-frequency power; L/H ratio, low-frequency power/HF ratio. Values are expressed as mean±1SE. *p<0.05 vs Group E.

**Fig 2.** Difference in HF power (A) and L/H ratio (B) between daytime and nighttime. Averages of HF power and L/H ratio were calculated separately during daytime (from 10.00 h to 22.00 h) and nighttime (from 22.00 h to 10.00 h), and the difference between the daytime and nighttime values was plotted. *p<0.05, **p<0.01.

**Table 4 Multivariate Analysis for the Daytime-Nighttime Difference of HF Power and L/H Ratio**

<table>
<thead>
<tr>
<th>Independent variable</th>
<th>HF power</th>
<th>L/H ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Standardized coefficient</td>
<td>p value</td>
</tr>
<tr>
<td>No. of diseased vessels</td>
<td>–0.722</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0.186</td>
<td>0.17</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>0.078</td>
<td>0.54</td>
</tr>
<tr>
<td>Smoking</td>
<td>–0.069</td>
<td>0.62</td>
</tr>
</tbody>
</table>

No. of diseased vessels was calculated as 0 vessel = 0, 1 vessel = 1, and multivessel = 2. Sex was calculated as men = 1 and women = 0. R² of HF power and L/H ratio are 0.32 and 0.33, respectively.
spontaneous anginal attack. However, similar changes were observed in control subjects, and they concluded that this phenomenon was not strictly associated with coronary spasm. In contrast, others have reported that relatively enhanced sympathetic nervous activity was observed before or during ST-segment elevation; that is, LF power or the L/H ratio was increased, whereas HF power was decreased or unchanged before or during the attacks. Only 2 studies have used HRV to evaluate autonomic nervous activity during the time free of anginal attacks in patients with VA. Miwa et al, showed, for the first time, that a blunted circadian rhythm of the spectral components (HF power and L/H ratio) was found in patients with VA; and our present results are consistent with that. Moreover, in the present study, the circadian fluctuation of HF power was decreased in patients with multivessel spasm, but not in those with single-vessel spasm. In contrast, the circadian fluctuation of the L/H ratio was disturbed in patients with single-vessel spasm and was abolished in those with multivessel spasm. Thus, decreased parasympathetic nervous activity during nighttime was associated with the severity of coronary spasm. Tsuichiya et al showed that patients with multivessel coronary spasm had a lower HF component and higher L/H ratio in terms of average 24-h values than either patients with noncardiac chest pain or those with single-vessel coronary spasm. In contrast, our results in 12- and 24-h frequency domain analyses showed no significant difference in HF power and L/H ratio among control subjects, patients with single-vessel spasm, and patients with multivessel spasm. The discrepancy may be attributable to the different disease activity related to anti-anginal drug use; anginal attacks occurred frequently in the study by Tsuichiya et al but only 2 attacks occurred in the present investigation. In the study by Miwa et al, anginal attacks were completely suppressed during Holter recording by calcium antagonists, which lower the LF component or elevate the HF component in patients with VA. In our study, however, calcium antagonists, which were used to avoid the influence of spontaneous anginal attacks, affected the results to a lesser degree, because the frequency of medication was almost similar among the groups.

Organic coronary stenosis may also influence HRV. Hayano et al showed that under controlled respiration during angiography, the HF component (0.25 Hz) decreased with increasing severity of coronary stenosis. In the present study, 12-h HF power during nighttime and 24-h HF power were both significantly decreased in patients with organic coronary stenosis compared with control subjects. Moreover, the daytime–nighttime difference of HF power was smaller in patients with organic coronary stenosis than in the control patients, but that of the L/H ratio was not. This pattern is different from that of vasospastic angina. The circadian fluctuation of the L/H ratio was disturbed in patients with single-vessel and multivessel spasm, and that of the HF power was decreased only in patients with multivessel spasm. Therefore, it is unlikely that the modulation of HRV in patients with multivessel coronary spasm resulted from long-term myocardial ischemia. In addition, these changes could not result from short-term myocardial ischemia, because anginal attacks were almost suppressed during Holter recording.

Study Limitations

First, although there was no difference in age, sex, and the number of patients taking calcium antagonists among the groups, several coronary risk factors, including hypertension, hyperlipidemia and smoking, were significantly different. It has been reported that smoking reduced the HF component in a younger population (<30 years old)7. Therefore, we used multivariate analysis to examine whether these factors could affect the daytime–nighttime difference of frequency domain analysis, but none of the factors, except multivessel spasm, was significantly related to the results. Moreover, there was no difference in these factors between the patients with single-vessel spasm and those with multivessel spasm. Thus, we consider that these factors had minimal effect on the difference in HRV measurements between the patients with single-vessel spasm and those with multivessel spasm.

Second, the control subjects did not undergo coronary angiography and patients with organic coronary stenosis did not undergo the induction of coronary artery spasm by ACh. Consequently, some of them might have had coronary stenosis and/or coronary spasm, although the increase of HF power and the reduction of L/H ratio in the nighttime in control subjects were consistent with the previous report by Furlan et al.

Third, 17 of the control subjects were outpatients and their Holter recordings were not done in hospital, so the circadian variation of autonomic nervous activity could have been affected by exogenous factors such as physical activity and the sleep state. With regard to the difference of HRV between inpatients and outpatients, our data do not contradict our assumption that control subjects had greater daytime–nighttime differences in HF power and the L/H ratio than patients with vasospastic angina.

Finally, the study population was so small that a further study with a large population is needed to confirm our findings.

Conclusion

In summary, sympathetic nervous activity, or the sympathovagal balance determined by the frequency domain analysis of HRV, was enhanced in the nighttime in patients with multivessel spasm, which differs from patients with organic stenosis. Although the precise causal relationship has yet to be elucidated, an impaired circadian rhythm of autonomic nervous activity may be responsible for coronary spasm, especially multivessel spasm.

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References


