Role of Circadian Rhythmicity in the Heart Rate Variability Preceding Non-Sustained Ventricular Tachycardia

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The difference in sympathovagal activity preceding non-sustained ventricular tachycardia (NSVT) was examined between patients with and without a circadian rhythm. Thirty-three patients’ Holter monitoring data (41 NSVT episodes) were analyzed regarding the frequency domain measures (low-frequency component [LF: 0.04–0.15 Hz], high-frequency component [HF: 0.15–0.4 Hz], and the ratio of LF to HF [LF/HF]) for each 15-min average from 120 min before each episode of NSVT. The presence of a circadian rhythm was accepted when the rhythm adaptation was significant by cosinor analysis and the acrophase was located at night (22:00–06:00 h) in HF (HF-positive group, n=17), and during the daytime (10:00–20:00 h) in LF/HF (LF/HF-positive group, n=12). The negative groups were identified by the absence of a circadian rhythm (HF-negative group, n=16; LF/HF-negative group, n=21). The serial changes in the HF power before NSVT were significantly different between the HF-positive and -negative groups (p<0.05). The HF increased from 75–60 min before NSVT in the HF-positive group, whereas the HF decreased from 60–45 min in the HF-negative group. The serial changes in the LF/HF ratio were not significantly different between the HF/HF-positive and -negative groups. Thus, the circadian rhythmicity of vagal activity seems to have an important role in the genesis of NSVT. (Jpn Circ J 1998; 62: 887–892)

Key Words: Autonomic nervous system; Circadian rhythm; Heart rate variability; Non-sustained ventricular tachycardia
than 6 beats and terminating spontaneously within 30s. The number of beats and the heart rate in each episode of NSVT were analyzed in relation to HRV. The criteria of NSVT adopted in the present analysis was thus; more than 3 consecutive ventricular premature beats or frequent ectopic beats did not appear during the 120 min preceding NSVT. To compare the distribution of NSVT occurrence, the 24-h day was divided into 4 periods: 00.00–06.00h, 06.00–12.00h, 12.00–18.00h and 18.00–00.00h.

### Analysis of Heart Rate Variability

Both the time domain and frequency domain analyses of HRV were performed with Marquette HRV software.

For the time domain analysis, 3 indices (SDANN, rMSSD, and SDNN) were analyzed. SDANN is the standard deviation for the 5-min mean R–R intervals, rMSSD is the root-mean square for the difference of successive R–Rs, and SDNN is the standard deviation for the mean of all R–R intervals between normal beats. All 3 indices have been suggested to reflect parasympathetic nerve activity.

Spectral plots for the frequency domain analysis were computed in 2-min segments using a 256-point fast-Fourier transformation algorithm. A Hanning window function was applied to minimize spectral leakage between segments without diminishing the frequency resolution. Ectopic beats were replaced by virtual normal beats according to the preceding RR interval. Power spectra from sequential intervals were averaged for each hour, over the entire 24 h and for each 15-min average from 120 min to immediately before the NSVT quantitated by measuring the area in the low-frequency region (LF: 0.04–0.15 Hz), and the high-frequency region (HF: 0.15–0.4 Hz). The data are expressed as the square root of the values. HF was used as an index of vagal tone, and the ratio of low- to high-frequency power (LF/HF) was used as an estimate of sympathetic activity.

### Circadian Rhythmicity

The hourly HF and LF/HF values were analyzed using the single cosinor analysis to evaluate the circadian rhythmicity. With this procedure, it is possible to determine whether or not there is a significant (p<0.05) rhythm within a 24-h period (ie, a circadian rhythm) and to evaluate the rhythm characteristics with 95% confidence limits. The method uses the equation: Y = M + A cos (t - ϕ) to evaluate the rhythmicity of HF and LF/HF. In this equation, M is the midline estimating statistic of rhythm (MESOR), the rhythm-adjusted average; A is amplitude, the difference between the maximum value measured at acrophase and the MESOR in the cosine curve; ϕ is the acrophase, which is the time between the reference time (midnight) and the time with the highest value for the cosine curve function, and ϕ is ϕ/12.

### Study Groups

The study subjects were divided into 2 groups according to the presence or absence of circadian rhythm.

The presence of a circadian rhythm in HF was accepted when the rhythm analysis was significant by cosine fitting and the acrophase was located at night (between 22.00 h and 06.00h) (HF-positive group: 10 males, 7 females; mean age 66.4±2.5 years). The HF-negative group was identified by the absence of a circadian rhythm (4 males, 12 females; mean age 61.9±3.1 years). The presence of a circadian rhythm in LF/HF was accepted when the rhythm adaptation was significant by cosinor analysis and the acrophase was located during the daytime (between 10.00 h and 20.00h) (LF/HF-positive group: 8 males, 4 females; mean age 62.3±3.6 years). The LF/HF-negative group was identified by the absence of a circadian rhythm (14 males, 7 females; mean age 65.2±2.4 years). The power of LF seemed to reflect the sympathetic drive; however, its circadian rhythm was inversely related to the circadian variation of sympathetic activity, because the LF power was high at night, and the sympathetic activity was highest during the daytime. Therefore, the circadian rhythmicity of LF was not evaluated in the present study.

### Table 1 Characteristics of the Study Patients With Non-Sustained Ventricular Tachycardia

<table>
<thead>
<tr>
<th>Underlying disease</th>
<th>No. of patients</th>
<th>No. of beats</th>
<th>Heart rate (beats/min)</th>
<th>HF LF/HF</th>
</tr>
</thead>
<tbody>
<tr>
<td>IHD (n=10)</td>
<td>5</td>
<td>5</td>
<td>16.6±2.6</td>
<td>145.4±8.8</td>
</tr>
<tr>
<td>Cardiomyopathy (n=11)</td>
<td>7</td>
<td>4</td>
<td>16.0±1.2</td>
<td>164.9±7.7</td>
</tr>
<tr>
<td>VHD (n=4)</td>
<td>2</td>
<td>2</td>
<td>16.6±2.6</td>
<td>19.6±1.2</td>
</tr>
</tbody>
</table>

Data are mean±SEM. HF, high-frequency component; LF/HF, ratio of low- to high-frequency component; Positive, positive circadian rhythm; Negative, negative circadian rhythm; VPC, ventricular premature contraction; NSVT, non-sustained ventricular tachycardia; VT, ventricular tachycardia; IHD, ischemic heart disease; VHD, valvular heart disease. *p<0.05 vs positive circadian rhythm.

### Table 2 The Significance of Circadian Rhythmicity

<table>
<thead>
<tr>
<th>HF</th>
<th>Positive</th>
<th>Negative</th>
</tr>
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<tbody>
<tr>
<td>LF/HF</td>
<td>10 (30.3%)</td>
<td>7 (21.2%)</td>
</tr>
</tbody>
</table>

Positive, positive circadian rhythm; Negative, negative circadian rhythm. χ²=7.64, p<0.01.
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significantly different between the HF-positive and -negative groups (4.3±0.8 vs 1.2±0.3 ms, p<0.001; HF, 0.37±0.06 vs 0.22±0.03, p<0.01; LF/HF). The acrophase in HF was significantly different between the HF-positive and -negative groups (80.3±24.7 vs 184.0±24.2 degrees, p<0.01).

Ventricular Premature Contraction and Characteristics of NSVT

The number of ventricular premature beats was not significantly different between the positive and negative groups (HF and LF/HF). The number of beats of NSVT was significantly more in the LF/HF-positive group than in the LF/HF-negative group (28.7±10.4 vs 11.3±1.2 beats, p<0.05). The heart rate during NSVT tended to be lower in the HF-positive group than in the HF-negative group but did not reach statistical significance (145.4±8.8 vs 164.9±7.7 beats/min, p<0.1). There were no significant differences in the number of beats of NSVT between the HF-positive and -negative groups, or in the heart rate during NSVT between the LF/HF-positive and -negative groups (Table 1). The distribution of the NSVT occurrences during 24 h was not significantly different between the positive and negative groups for both HF and LF/HF (Fig 1).

Heart Rate Variability (Table 4)

All 3 time domain indices were significantly higher in the HF-positive group compared with the HF-negative group (SDANN, 125.4±11.8 vs 90.6±5.2 ms; rMSSD, 28.9±2.7 vs 20.9±2.1 ms; SDNN, 139.0±12.5 vs 102.9±6.0 ms; p<0.05, respectively), whereas none of these indices were significantly different between the LF/HF-positive and -negative groups. As for the frequency domain indices, the 24-h average of the HF was significantly higher in the HF-positive group than that in the HF-negative group (10.1±1.0 vs 7.9±1.0 ms, p<0.01). The LF/HF ratio was not significantly different between the LF/HF-positive and -negative groups.

HRV Change Preceding NSVT

When the data of both the positive and negative groups were analyzed together, the power of HF did not show statistical Analysis

All values are expressed as mean±SEM. The time course of HRV before NSVT was analyzed by a repeated-measures analysis of variance (ANOVA) followed by paired or unpaired t test where appropriate. Binomially distributed variables such as the time of NSVT occurrence were analyzed by Chi-square test. Other measurements were analyzed by unpaired t test. Significant differences in cosine curves were determined by F test based on differences in the residual sum of squares. A p value less than 0.05 was considered significant.

Results

The characteristics of the patients are shown in Table 1. Seventeen of the 33 patients (49%) in the HF analysis and 12 patients (34%) in the LF/HF analysis showed a positive circadian rhythm. The age, gender distribution and incidence of each underlying disease were not significantly different between the positive and negative HF and LF/HF circadian rhythm groups. The contingency table of circadian rhythmicity of each HRV parameters is shown in Table 2. Ten of all the patients (30.3%) showed a positive circadian rhythm, and 14 patients (42.4%) showed a negative circadian rhythm in both HF and LF/HF. Two patients showed a positive circadian rhythm only in the HF/HF, which was significantly smaller number than in the other cell (Chi²=7.6, p<0.01).

Circadian Rhythmcity (Table 3)

The MESOR values for HF were significantly higher in the HF-positive group than that in the HF-negative group (10.9±1.0 vs 8.3±1.0 ms, p<0.05). The amplitudes for both HF and LF/HF were significantly higher in the positive groups than in the respective negative circadian rhythm groups (4.3±0.8 vs 1.2±0.3 ms, p<0.001; HF, 0.37±0.06 vs 0.22±0.03, p<0.01; LF/HF). The acrophase in HF was significantly different between the HF-positive and -negative groups (80.3±24.7 vs 184.0±24.2 degrees, p<0.01).

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HRV Change Preceding NSVT

When the data of both the positive and negative groups were analyzed together, the power of HF did not show
significant serial change before NSVT. In contrast, the LF/HF ratio increased from 90–75 min before NSVT and the LF/HF ratio was significantly lower at 75–60 min than at 75–105 min (1.47±0.11 vs 1.64±0.12, p<0.05), as illustrated in Fig 2.

Although the power of HF was not significantly different between the 2 HF groups in the period between 120 and 90 min, the subsequent serial change in the HF before NSVT in the HF-positive group was significantly different from that in the HF-negative group (p<0.05) (Fig 3, left panel). Namely, the power of HF increased from 75–60 min in the HF-positive group and stayed at the high level, whereas it decreased from 75–60 min before NSVT in the HF-negative group staying at a similar low level till NSVT, as illustrated in Fig 3. Thus in the HF-positive group, the power of HF was significantly higher at 15–0 min than at 75–60, 90–75 and 120–105 min before NSVT (12.4±1.3 vs 12.0±2.1, 11.0±1.4, and 11.5±1.3 ms, p<0.05, respectively), and at 45–30 and 30–15 min than at 90–75 min before NSVT (12.6±1.6 and 12.5±1.5 vs 11.0±1.4 ms, p<0.05, respectively). In the HF-negative group, the power was significantly lower at 45–30 min than at 90–75 and

Fig 1. The distribution of the time of occurrence of non-sustained ventricular tachycardia (NSVT). The timing of the NSVT occurrences in each period was not significantly different between the positive and negative groups for both HF and LF/HF. (Open bars) positive circadian group; (Closed bars) negative circadian group. HF, high frequency (0.15–0.4 Hz); LF, low frequency (0.04–0.15 Hz); LF/HF, low frequency/high frequency.

Fig 2. Serial changes in heart rate variability (HRV) preceding non-sustained ventricular tachycardia (NSVT). The power of HF was not significantly changed before NSVT. The LF/HF ratio increased from 90–75 min before NSVT, *p<0.05. (LF, HF as in Fig1.)

Fig 3. Serial changes in heart rate variability (HRV) preceding non-sustained ventricular tachycardia (NSVT) analyzed separately in the positive and negative circadian rhythms. The HF power increased gradually from 75–60 min in the HF-positive circadian rhythm group, whereas the HF power decreased from 60–45 min in the negative circadian rhythm group. The LF/HF ratio increased from 90–75 min before NSVT in both the positive and negative groups. (Open circles) positive circadian groups; (Closed circles) negative circadian groups. *p<0.05. (LF, HF as in Fig1.)
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75–60 min (9.5±1.1 vs 10.7±1.3 and 10.9±1.3 ms, p<0.05, respectively).

In contrast, the change in the LF/HF ratio before NSVT was not significantly different between the 2 LF/HF groups (Fig 3, right panel). The LF/HF increased from 90–75 min before NSVT in both LF/HF groups. In the LF/HF-positive group, the LF/HF ratio was significantly lower at 105–90 min than at 75–60 and 45–30 min before NSVT (1.48±0.20 vs 1.61±0.21 and 1.68±0.20, p<0.05, respectively). In the LF/HF-negative group, the LF/HF ratio was significantly lower at 120–105 and 105–90 min than at 90–75 min before NSVT (1.42±0.12 and 1.42±0.12 vs 1.64±0.14, p<0.05, respectively).

Discussion

The major findings of the present study are as follows. First, the LF/HF ratio preceding NSVT increased in both the LF/HF-positive and -negative groups, while the power of HF preceding NSVT was significantly different between the HF-positive and -negative groups. The HF power in the HF-positive group increased with a concomitant elevation of the LF/HF ratio, whereas the HF power in the HF-negative group decreased before NSVT. Second, all 3 time domain indices were significantly higher in the HF-positive group than in the HF-negative group, whereas the same indices were not significantly different between the LF/HF circadian groups. The time domain indices reflect the vagal activity, and therefore vagal function may be impaired in the HF-negative group compared with the HF-positive group. Third, the heart rate during NSVT was not significantly different between either pair of positive/negative groups, although the number of beats of NSVT was significantly more in the LF/HF-positive group than in the LF/HF-negative group, and the heart rate during NSVT tended to be slower in the HF-positive group than in the HF-negative group. It seems that NSVT occurring in a patient with a positive circadian rhythm of LF/HF would be more critical, whereas NSVT may be less critical in a patient without such a rhythm.

The results of a frequency domain analysis of HRV can be interpreted as an indirect non-invasive manifestation of autonomic nervous activity; the HF power provides a marker of efferent vagal input to the heart, and the LF/HF ratio is a marker of sympathetic nervous tone. The 24-h cycle of HRV (which is defined as a circadian rhythm) may be an important factor because high sympathetic activity that persists throughout a 24-h period may accelerate $\alpha$-receptor down-regulation and promote a reduction of catecholamine stores in the heart. Thus, the patients with reduced circadian rhythmicity of HRV may have impaired autonomic nervous function such as diabetic neuropathy prior myocardial infarction or congestive heart failure. Previous studies demonstrated that patients with NSVT also have reduced circadian variation of HRV, however, we noted that some patients with NSVT have a preserved circadian rhythm. In the present study, the amplitude of both HF and LF/HF was significantly higher in the positive circadian groups than in the negative circadian groups, and the acrophase was shifted to the daytime in the HF-negative group and to the nighttime in the LF/HF-negative group. This indicated that the circadian rhythm of HRV is blunted in the negative circadian groups.

Autonomic nervous function plays an important role in the occurrence of NSVT, elevation of sympathetic nervous activity, and/or suppression of parasympathetic nervous activity. Sympathetic hyperactivity promotes the occurrence of ventricular tachyarrhythmias whereas vagal stimulation may suppress the induction of ventricular tachyarrhythmias by prolonging the effective refractory period and increasing the threshold for ventricular fibrillation. Regarding the HRV, the power of LF and HF tended to increase and the LF/HF ratio significantly increased before NSVT in patients with coronary artery disease or idiopathic ventricular tachycardia. Those studies indicated that the genesis of NSVT may be dominated by sympathetic activity, although they did not mention the role of parasympathetic nervous activity. In fact, in the present study, the HF power was not significantly changed before NSVT when the data of the HF-positive and -negative groups were analyzed together.

In the present study, we found that vagal function may have an important role in the genesis and maintenance of NSVT as does sympathetic activity. In patients with a preserved circadian rhythm of the HF power, in whom vagal function is thought to be preserved, vagal activity may play a role in the suppression of NSVT. In patients with an impaired circadian rhythm of HF, in whom vagal function may be impaired, vagal activity may no longer have a beneficial effect on the genesis and maintenance of NSVT.

Conclusions

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References