Age-Adjusted Heart Rate Variability as an Index of the Severity and Prognosis of Heart Failure

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The age-adjusted, heart rate variability (HRV) was evaluated as a parameter for the severity of heart failure and its prognosis. HRV was obtained by 24-h Holter monitoring in patients with left ventricular dysfunction (LVD). New York Heart Association (NYHA) functional classification, echocardiography, radioisotope ventriculography, and blood examination were performed, and compared between patients and normal subjects. The evaluation was repeated during the follow-up period. Finally, using the lower limit of HRV, patients were divided into either normal or abnormal group for each low-frequency power (LF) and high-frequency power (HF) (age-adjusted HRV). Other parameters of heart failure and prognosis were compared between these 2 groups. HRV tended to be lower in patients with LVD. HF decreased at the early stage of heart failure, but did not decrease progressively. LF decreased progressively. HRV change paralleled the change of NYHA. The abnormal HRV group showed a poor prognosis for cardiac death, but not for sudden cardiac death. In patients with LVD, HRV was decreased compared with the normal subjects. Change in HRV correlated with the change in NYHA classification. Age-adjusted HRV correlated with cardiac-death prognosis, but not for sudden cardiac death. (Jpn Circ J 2000; 64: 32–38)

Key Words: Congestive heart failure; Heart rate variability; Left ventricular dysfunction; Prognosis; Sudden cardiac death

In congestive heart failure, activation of several neurohumoral systems, such as the sympathetic nervous system\(^1\) renin-angiotensin system\(^2\) and the arginine-vasopressin system\(^3\) occurs. To counterbalance the resulting vasconstrictive effects, vasodilatory substances, such as atrial natriuretic peptide (ANP) and prostaglandins, are increased. The level of catecholamines, mostly norepinephrine, increases and its level has been reported to be correlated with the severity of heart failure, as measured by hemodynamic parameters\(^4\) and even with the prognosis of heart failure.\(^5\) These findings suggest a close relation between autonomic nervous tone and heart failure, but noninvasive evaluation of the activity of the autonomic nervous system has been previously difficult. The clinical use of heart rate variability (HRV), however, has permitted the noninvasive evaluation of autonomic nervous tone and heart failure.

HRV derived from 24-h Holter ECG ambulatory monitoring is one of the noninvasive means of assessing the activity of the autonomic nervous system. There are important differences between the type of recording used, as reported by Malik et al\(^6\): short-term recording under strictly controlled conditions and long-term recording during normal daily activities. Holter monitoring has the advantages of allowing the patients to participate in daily activities, and of providing a high predictive value over short-term recording.\(^7\) Frequency-domain analysis of HRV is known to represent the activity of the sympathetic and parasympathetic nervous system separately; that is, low frequency power (LF) represents the activity of both the sympathetic and the parasympathetic nervous systems, and high frequency power (HF) represents the activity of the parasympathetic nervous system alone. The ratio of LF to HF (LF/HF) is used for the evaluation of sympathetic nervous tone. Many studies have shown decreased HRV in patients with congestive heart failure\(^8\) but it remains unclear as to whether it can also be used as an index of the severity of heart failure and its prognosis. The purpose of the present study was to determine the usefulness of the age-corrected HRV as an index of the severity of heart failure and its prognosis. The HRV is known to decrease according to age, which sets a limitation on comparison of HRV between different age groups. Also, the HRV change in each patient could be due to aging not to the severity of heart failure. The lower limit of HRV for each age group has been proposed elsewhere.\(^9\)

Methods

Subjects
From January 1990 to January 1993, 90 patients were selected for the study. The inclusion criteria were (1) good compliance with medication, (2) stable medication for heart failure for more than 2 months, (3) sinus rhythm with less than 15% noise or ectopic beats, and (4) left ventricular dysfunction (LVD) as defined by left ventricular ejection fraction less than 40% on radioisotope ventriculography. Informed consent was obtained, which was approved by the Review Board at Keio University Hospital. In total, 51 patients with old myocardial infarction (mean age, 63.3±10.0 years, M/F = 38/13) and 39 with idiopathic dilated

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cardiomyopathy (mean age, 54.8±14.7 years, M/F=29/10) were studied. Eighty-four patients were taking medication for LVD, 37 were taking β-blockers, 27 were taking angiotensin-converting enzyme inhibitors, and 44 were on digitalis. The patients were evaluated while taking their medication. From our previous study, HRV decreases until the fifth decade of life (40-49 years) and does not change thereafter. From the 90 subjects, 52 subjects above the age of 50 were selected for comparison (mean age, 61.5±12.2 years, M/F=32/20).

Heart Rate Variability
All subjects underwent 24-h Holter monitoring, recorded with a Marquette 8500 and analyzed with a Marquette 8000/T, using HRV software V.001 to yield the HRV. An RR interval signal was generated by taking a 2-min segment of data, and sampling it to fill a 512-point array. Premature extrasystoles were identified and corrected by linear interpolation with the previous and following beats. Each interval that was to be excluded due to extrasystoles or artifacts was replaced by holding the previous coupling interval level throughout the time interval to the next valid coupling interval. The power spectrum was calculated as the squared magnitude of the fast Fourier transform for each segment. The frequency domain measures of HRV were expressed as the power of spectrum for HF, LF, and all frequency, total power (TP; 0.01–1.0Hz). Frequency-domain HRV was analyzed each hour and the LF/HF ratio was calculated. 24-h average HRV and circadian changes of HF and LF/HF were analyzed and compared with the normal control.

Severity of Heart Failure
Three different parameters were used to assess the severity of heart failure. To determine the subjective parameters, the New York Heart Association (NYHA) functional classification was determined for each patient by interviews. Hemodynamic parameters were assessed by transthoracic echocardiography in which the left ventricular end-diastolic diameter (LVEDD), left ventricular end-systolic diameter (LVESEd), and left atrial diameter (LAD) were measured. The left ventricular ejection fraction (LVEF) was measured by using radioisotope ventriculography. Finally, neurohumoral parameters were determined by measuring ANP, norepinephrine, plasma renin activity (PRA), and aldosterone levels after 30 min supine resting. These studies were performed within 5 days of Holter monitoring.

Table 1 Patients Characteristics
<table>
<thead>
<tr>
<th>NYHA functional classification</th>
<th>I</th>
<th>II</th>
<th>III</th>
<th>IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. cases</td>
<td>30</td>
<td>39</td>
<td>19</td>
<td>2</td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>58±12.8</td>
<td>58±12.3</td>
<td>62±14.3</td>
<td>57±17.7</td>
</tr>
<tr>
<td>LVEDD (cm)</td>
<td>5.5±0.9</td>
<td>6.2±1.1</td>
<td>6.5±1.4*</td>
<td>7±1.6</td>
</tr>
<tr>
<td>LVESEd (cm)</td>
<td>4.2±1.0</td>
<td>5±1.2*</td>
<td>5.3±1.5*</td>
<td>7.1±1.9</td>
</tr>
<tr>
<td>LAD (cm)</td>
<td>3.7±0.7</td>
<td>4.0±0.6</td>
<td>4.1±0.8</td>
<td>5.2±0.1</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>39±6.10</td>
<td>29±14.1</td>
<td>26±14.7*</td>
<td>32±14.1</td>
</tr>
<tr>
<td>ANP (pg/ml)</td>
<td>56±24.2</td>
<td>84±292.0</td>
<td>92±741.1</td>
<td>355±283.3</td>
</tr>
<tr>
<td>NE (ng/ml)</td>
<td>0.34±0.19</td>
<td>0.36±0.22</td>
<td>0.42±0.23</td>
<td>0.41±0.06</td>
</tr>
<tr>
<td>PRA (ng ml⁻¹ h⁻¹)</td>
<td>5.2±10.8</td>
<td>5±16.3</td>
<td>5.3±17.0</td>
<td>17±10.5</td>
</tr>
<tr>
<td>Aldosterone (pg/ml)</td>
<td>76±35.0</td>
<td>106±277.2</td>
<td>93±64.3</td>
<td>95±54.9</td>
</tr>
</tbody>
</table>

*p<0.05 vs NYHA I, LVEDD, end-diastolic diameter of left ventricle; LVESEd, end-systolic diameter of left ventricle; LAD, left atrial diameter; LVEF, left ventricular ejection fraction; ANP, atrial natriuretic peptide; NE, norepinephrine; PRA, plasma renin activity.

Table 2 Comparison Between Normal Controls and Patients With Left Ventricular Dysfunction
<table>
<thead>
<tr>
<th>HF (ln (m/s²))</th>
<th>LF (ln (m/s²))</th>
<th>mean NN (ms)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>4.9±0.92</td>
<td>5.98±0.74</td>
</tr>
<tr>
<td>Patients with LVD</td>
<td>3.9±1.03*</td>
<td>4.56±1.29*</td>
</tr>
</tbody>
</table>

*p<0.05 vs Normal. LF, low-frequency power; HF, high-frequency power; LF/HF, ratio of LF over HF; LVD, left ventricular dysfunction.

Age-Adjustment
Because age has a strong influence on HRV, the lower limit of HRV for a certain age has been determined. Subjects aged 16–68 were used and the moving average minus twice the standard deviation of HRV was calculated. These values were plotted against age, and the polynomial curve fitting showed significant correlations, which were considered to be the lower limit of HRV. Each frequency-domain analysis of HRV was determined to be normal or abnormal depending upon the subjects ages and the lower limit of HRV. If the obtained HRV is above the lower limit of the normal range of HRV, it is considered normal and if it is below the lower limit, it is abnormal. Other parameters of heart failure were compared between these normal and abnormal groups of LF or HF.

Follow-up
During the average follow-up period of 1388±507 days, the following were evaluated several times: HRV, NYHA functional classification, hemodynamic parameters, and neurohumoral parameters. The change of HRV was compared with the clinical course: stable, worsening, or recovering. The patients were followed until 31 December 1997. The first HRV analysis (long-term prognosis) and the last HRV analysis (mid-term prognosis) obtained during this follow-up period were used for the evaluation of prognosis. The prognosis for total cardiac death and sudden cardiac death was evaluated between the normal and abnormal groups for LF and HF.

Statistical Analysis
Data were expressed as mean±standard deviation. Variables were compared statistically among more than 2 groups using Scheffe and Bonferroni/Dunn. Kaplan-Meier cumulative survival curves were constructed and compared using the Mantel-Haenszel log rank test. Differences with a p value of <0.05 were regarded as statistically significant.
Fig 1. The circadian changes of frequency-domain heart rate variability (HRV) in (A) normal controls and (B) patients with left ventricular dysfunction. In both groups, HF increases during the nighttime, and decreases during the daytime. LF/HF increases during the daytime, and decreases during the night. However, these circadian changes are significantly diminished in patients with left ventricular dysfunction. HF, high frequency power; LF, low frequency power; LF/HF, calculated by subtracting HF from LF.

### Table 3 Comparison of Heart Rate Variability Among the Different NYHA Classes

<table>
<thead>
<tr>
<th></th>
<th>Normal</th>
<th>Patients with LVD (NYHA functional classification)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>I</td>
</tr>
<tr>
<td>LF (ln ms¹)</td>
<td>5.98±0.74</td>
<td>5.24±0.99*</td>
</tr>
<tr>
<td>HF (ln ms¹)</td>
<td>4.98±0.92</td>
<td>4.49±0.91*</td>
</tr>
<tr>
<td>LF/HF</td>
<td>3.21±2.20</td>
<td>2.68±1.32</td>
</tr>
</tbody>
</table>

*P<0.05 vs Normal, **P<0.05 vs NYHA I, ***P<0.05 vs NYHA II. LF, low-frequency power; HF, high-frequency power; LF/HF, ratio of LF over HF; LVD, left ventricular dysfunction.

### Table 4 Ratio of Abnormal Heart Rate Variability

<table>
<thead>
<tr>
<th></th>
<th>NYHA functional classification</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>I</td>
</tr>
<tr>
<td>Abnormal LF (%)</td>
<td>6.7</td>
</tr>
<tr>
<td>Abnormal HF (%)</td>
<td>10.0</td>
</tr>
</tbody>
</table>

LF, low-frequency power (0.04–0.15 Hz); HF, high-frequency power (0.15–0.40 Hz).

### Results

The distribution of the patients under each medication did not differ among the NYHA classes (Table 1). The LVEDd and LVESe of NYHA class III were larger and LVESe was smaller than those of class I, but none of these parameters showed correlation with the severity of NYHA classification.

Frequency-domain analyses of HRV were compared between the normal controls and patients with LVD (Table 2). HF and LF were significantly lower in patients. However, the NN interval did not show a significant difference between these groups, suggesting that the mean heart rates were similar. The frequency-domain analysis and LF/HF for each hour were obtained and compared between patients and normal subjects (Fig 1). The change in HRV was depressed in the patients, but had a normal tendency: increased HF during nighttime, and increased LF/HF during daytime. Parameters were compared between patients and normal controls (patients vs normal controls). The circadian change of LF/HF (maximum–minimum LF/HF) in the patients was significantly depressed compared with the normal subjects (0.57±0.69 vs 1.84±4.49, p<0.05). Also, the circadian change of HF (maximum–minimum HF) in the patients was significantly less than in the normal subjects (0.57±0.93 vs 0.81±0.93 ln (ms²), p<0.05).

HRV was compared among the different NYHA classifications (Table 3). LF decreased progressively depending on the NYHA classification. In contrast, HF was lower in the patients, but did not progressively decrease beyond NYHA class II. LF/HF did not show a significant difference among the NYHA classes.

### Age-Adjusted HRV

Using the lower limit of frequency-domain analysis of HRV⁰ the HRV in each patient was determined to be normal or abnormal. The percent of abnormal HRV in each NYHA class is shown in Table 4. The ratio of abnormal LF and HF increased progressively with functional class. However, only 40% of the patients had abnormal HRV, even in NYHA class III. Between the normal and abnormal HRV groups, other parameters for the severity of heart failure were compared.

Hemodynamic parameters were compared between the

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normal and abnormal LF groups (normal vs abnormal group). LVEDd (5.9±1.6 vs 6.5±0.9 cm, p=0.08), LVESe (3.9±0.7 vs 4.2±0.9 cm, p=0.07), and LAD (4.8±1.4 vs 5.5±1.1 cm, p=0.08) tended to be larger and LVEF smaller (34.3±5.1 vs 25.9±13.9%, p=0.07) in the abnormal LF group, but did not reach statistical significance. In the abnormal HF group, LVEDd (6.0±1.2 vs 6.0±1.3 cm, p=0.24), LVESe (3.9±0.7 vs 3.9±0.8 cm, p=0.19), and LAD (4.9±1.4 vs 5.0±1.4 cm, p=0.13) did not show significant difference, but LVEF (34.5±15.2 vs 25.8±13.4%, p=0.03) was significantly smaller. As for the neurohumoral parameters, in the abnormal LF group, ANP (67.3±77.9 vs 128.6±90.4 pg/ml, p=0.01) and PRA (4.3±5.6 vs 12.0±15.4 ng ml⁻¹ h⁻¹, p=0.007) showed a significant increase compared with the normal group. Aldosterone (84.1±62.1 vs 122.4±78.4 pg/ml, p=0.06) tended to increase, but norepinephrine (0.35±0.22 vs 0.42±0.17 ng/ml, p=0.27) did not show any difference. In the abnormal HF group, ANP (57.5±56.2 vs 146.0±111.0 pg/ml, p=0.0002), norepinephrine (0.33±0.21 vs 0.46±0.18 ng/ml, p=0.03) and PRA
**Table 5** Clinical Characteristics of Patients Suffering Cardiac Death

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (years), sex</th>
<th>Disease</th>
<th>LVEF (%)</th>
<th>NYHA class</th>
<th>Cause of death</th>
<th>HF, LF (days to death)</th>
</tr>
</thead>
<tbody>
<tr>
<td>H.A.</td>
<td>61, M</td>
<td>OMI</td>
<td>24</td>
<td>2</td>
<td>SCD</td>
<td>nl, nl (152) → nl, nl (41)</td>
</tr>
<tr>
<td>S.I.</td>
<td>66, F</td>
<td>OMI</td>
<td>30</td>
<td>3</td>
<td>CHF</td>
<td>nl, nl (887) → nl, nl (37)</td>
</tr>
<tr>
<td>F.I.</td>
<td>78, M</td>
<td>OMI</td>
<td>9</td>
<td>3</td>
<td>SCD</td>
<td>nl, nl (433) → nl, nl (283)</td>
</tr>
<tr>
<td>H.I.</td>
<td>67, M</td>
<td>OMI</td>
<td>13</td>
<td>3</td>
<td>CHF</td>
<td>nl, ab (113) → ab, ab (67)</td>
</tr>
<tr>
<td>M.K.</td>
<td>59, M</td>
<td>OMI</td>
<td>35</td>
<td>3</td>
<td>SCD</td>
<td>nl, nl (151) → ab, nl (67)</td>
</tr>
<tr>
<td>Y.K.</td>
<td>61, M</td>
<td>DCM</td>
<td>27</td>
<td>2</td>
<td>SCD</td>
<td>nl, nl (871) → nl, nl (457)</td>
</tr>
<tr>
<td>H.M.</td>
<td>66, M</td>
<td>OMI</td>
<td>40</td>
<td>3</td>
<td>CHF</td>
<td>nl, nl (1164) → nl, nl (576) → nl, nl (54)</td>
</tr>
<tr>
<td>T.S.</td>
<td>79, M</td>
<td>DCM</td>
<td>19</td>
<td>3</td>
<td>CHF</td>
<td>nl, nl (1026) → nl, nl (218)</td>
</tr>
<tr>
<td>K.T.</td>
<td>43, M</td>
<td>DCM</td>
<td>13</td>
<td>3</td>
<td>CHF</td>
<td>nl, nl (335) → nl, nl (218)</td>
</tr>
<tr>
<td>T.T.</td>
<td>66, M</td>
<td>DCM</td>
<td>22</td>
<td>2</td>
<td>CHF</td>
<td>ab, nl (62) → ab, nl (42)</td>
</tr>
<tr>
<td>T.M.</td>
<td>47, M</td>
<td>DCM</td>
<td>24</td>
<td>2</td>
<td>aborted SCD</td>
<td>nl, ab (1110) → nl, nl (116)</td>
</tr>
<tr>
<td>S.M.</td>
<td>78, M</td>
<td>OMI</td>
<td>32</td>
<td>3</td>
<td>SCD</td>
<td>nl, nl (450) → nl, nl (39)</td>
</tr>
<tr>
<td>S.M.</td>
<td>47, M</td>
<td>DCM</td>
<td>20</td>
<td>4</td>
<td>CHF</td>
<td>nl, ab (343) → ab, ab (83)</td>
</tr>
<tr>
<td>K.M.</td>
<td>74, M</td>
<td>DCM</td>
<td>24</td>
<td>3</td>
<td>SCD</td>
<td>ab, ab (478) → nl, ab (62)</td>
</tr>
<tr>
<td>T.Y.</td>
<td>75, F</td>
<td>OMI</td>
<td>40</td>
<td>2</td>
<td>CHF</td>
<td>nl, nl (1134) → nl, nl (459)</td>
</tr>
</tbody>
</table>

OMI, old myocardial infarction; DCM, dilated cardiomyopathy; CHF, congestive heart failure; SCD, sudden cardiac death; nl, normal; ab, abnormal; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; HF, high-frequency power; LF, low-frequency power.

**Fig 4.** Survival curves of patients with left ventricular dysfunction in the mid-term follow-up. Survival curves for (A) normal LF vs abnormal LF groups, and (B) normal HF vs abnormal HF groups are shown. In both the abnormal LF and HF groups, the survival rates, free from cardiac death, are significantly lower compared with the normal groups. HF, high frequency power; LF, low frequency power.

4.1±5.6 vs 11.2±14.3 ng ml⁻¹ h⁻¹, p=0.01) showed a significant increase, but aldosterone (85.0±63.4 vs 115.1±75.2 pg/ml, p=0.13) did not show any difference.

**Follow-up**

Eighty patients underwent more than 2 sessions of these evaluations. In these patients, the 2 sessions of examination were compared, depending on their symptomatic change: 'stable' if the NYHA classification had not changed, 'worsening' if the NYHA classification became worse, and 'recovering' if the NYHA classification improved. In the stable group, the 2 sessions of HRV showed significant reproducibility (Fig 2): LF, 4.75±1.34 → 4.77±1.30 ln (ms²); HF, 4.07±1.04 → 4.01±1.05 ln (ms²) (NS). In the recovering group (NYHA 2±0.7 → 1.3±0.5), LF (3.27±1.29 → 4.04±0.79 ln (ms²), p<0.01) and HF (2.92±0.84 → 4.04±0.79 ln (ms²), p<0.01) increased significantly. In the worsening group (NYHA 1±0.6 → 2.7±0.8), LF (4.55±1.21 → 4.02±1.36 ln (ms²), p=0.09) and HF (3.94±1.08 → 3.37±1.18 ln (ms²), p=0.09) tended to decrease. In the worsening or recovering group, these changes of HRV were significantly larger than the stable group (p<0.05). HF and LF changes in each patient during the follow-up period are shown in Figs 3A and B, respectively.

The period between the last HRV study and the end-of-study date (mid-term) was 916±552 days, and the period between the first HRV study and the end-of-study date (long-term) was 1388±507 days. During the follow-up period, 7 patients died of cardiac sudden death (one was resuscitated by a bystander and made a full recovery), 8 patients died from pump failure, and 4 died from noncardiac deaths (Table 5). In the abnormal LF group, cardiac death was significantly higher in the long-term (33 vs 13%, p<0.05) and mid-term (33 vs 14%, p<0.05, Fig 4A) periods compared with the normal LF group. However, in the abnormal HF group, cardiac death was higher in the mid.
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term (29 vs 13%, p<0.05, Fig4B), but did not show any difference in the long-term (20 vs 16%, NS). LF reflected both the long- and mid-term prognosis, but HF reflected only the mid-term prognosis. Neither of the HRV predicted cardiac sudden death.

Discussion

The present study is unique in showing that the age-adjusted HRV is a useful parameter for measuring the severity of heart failure and its prognosis. In the abnormal LF group, the hemodynamic parameters tended to worsen, neurohumoral parameters increased and the long- and mid-term prognoses were significantly poor compared with the normal group. In the abnormal HF group, the LVEF was lower and the neurohumoral parameters were increased. The mid-term prognosis was worse compared with the normal HF group. However, neither abnormal HF nor abnormal LF predicted sudden cardiac death. In addition to the age-adjusted HRV, HRV and its circadian change was decreased in patients with LVDD. LF showed a progressive decrease depending on the NYHA classification, but HF decreased to NYHA class II and did not decrease thereafter. In each patient, the changes in NYHA class and HRV were parallel.

Previous reports suggested that the withdrawal of parasympathetic activity and the concomitant increase of sympathetic activity lead to decreased HRV.

13-15 LF is the indicator of both parasympathetic and sympathetic activity, and has been reported to reflect baroreceptor activity, and the renin-angiotensin system. The decrease in LF can be explained by impaired baroreceptor function.

16,17 Although the sympathetic nervous system is activated in congestive heart failure, most studies report a decreased LF/HF, with only a few reporting an increase in LF/HF. This suggests increased activity of the sympathetic nervous system.

However, the decreased value of LF/HF can be explained by the downregulation of β-receptors or the reduction of myocardial catecholamines secondary to long-standing increased sympathetic nervous tone. The decreased circadian change of HRV has been reported previously,

9,19,20 and may be explained by decreased parasympathetic nervous activity and activated sympathetic nervous activity in heart failure; however, decreased daily activity may also play a role.

Severity of Heart Failure and HRV

There have been some reports on the relation between the severity of heart failure and HRV. Saul et al studied patients with heart failure of NYHA classes III and IV and compared them with the normal control subjects. They found that the HRV was decreased at all frequencies, but only LF correlated with the other parameters, such as cardiac index and pulmonary capillary wedge pressure. Kugel et al compared the frequency-domain analysis of HRV with other parameters, such as LVEF, thermodilution cardiac output, pulmonary capillary wedge pressure, NYHA functional classification, age, norepinephrine level, and muscle sympathetic nervous activity.

14 LF and HF correlated well with muscle sympathetic activity and plasma norepinephrine, and they concluded that the decrease in frequency- and time-domain measurements of HRV was not an indicator of the severity of disease, but rather a marker of sympathoexcitation. However, their report did not show the distribution of NYHA classification and the number of cases was relatively small. In our study, HRV and left ventricular function, NYHA functional classification, and neurohumoral factors were closely related. In addition, the HRV paralleled the change of NYHA class in each patient. From these observations, it is assumed that HRV is an overall parameter for heart failure.

A different pattern of decrease between LF and HF was noticed in the present study. It has been reported previously that HF reflects pure parasympathetic nervous function, whereas LF reflects sympathovagal balance, renin-angiotensin activity, and baroreceptor function. From our observations, it can be assumed that at the early stage of heart failure, parasympathetic nervous activity decreases and sympathetic nervous activity increases. At more advanced stages, progressive sympathetic activation and other forms of compensation, such as renin-angiotensin activation, occurs.

Prognosis and HRV

Several studies have shown that decreased HRV after myocardial infarction is correlated with poor outcome,

21-23 including sudden cardiac death, and pump failure. In the short-term recording of HRV, decreased HRV was observed just before the onset of ventricular fibrillation.

24 These studies have led us to question whether decreased HRV is an indicator of sudden cardiac death. To answer this, a longitudinal study of HRV with regard to the prognosis combined with the severity of heart failure is inevitable.

Kleiger et al reported that patients with SDNN <50ms had a 5.3-times higher risk for mortality than patients with SDNN >100 ms.

19 Taking LVEF and arrhythmia into consideration, SDNN was an independent risk factor. They suggested that increased sympathetic and decreased parasympathetic activity lowers the threshold of ventricular fibrillation. However, the all-cause death was the end-point instead of sudden cardiac death, and they did not include the exercise tolerance parameter in their study. This makes it difficult to conclude that decreased HRV is an index of sudden cardiac death. Some recent studies have shown that HRV can predict the occurrence of cardiac death or sudden cardiac death. Jiang et al reported that SDNN and SDANN predicted an increased risk of death or a life-threatening event.

25 They compared the HRV and other conventional parameters, such as ejection fraction, cardiothoracic ratio and total ventricular premature complexes, but they did not show any difference between groups with or without the events. Szabo et al also evaluated the prognostic value of HRV in ischemic and nonischemic cardiomyopathy patients, and found that only pNN50 and SDNN had an independent prognostic value for an increased mortality.

26 However, LVEF remained the most powerful variable in the risk assessment of these patients. In addition to these time-domain analyses, LF was found to predict survival independently of NYHA class, EF, and ventricular tachycardia on Holter monitoring.

27 It could be assumed that the autonomic nervous imbalance that leads to sudden cardiac death is an abrupt and shorter change, not the baseline change that contributes to pump-failure death. These changes may be difficult to predict from the HRV obtained before death.

Our study was unique in using the age-corrected HRV, which has good correlation with the total cardiac death, but not with sudden cardiac death. Interestingly, abnormal HF predicted only the mid-term prognosis, not the long-term

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prognosis. In contrast, abnormal LF predicted both mid- and long-term prognoses. Thus, it can be assumed that the efficacy of HF in predicting the prognosis was lower than that of LF.

**Conclusion**

HRV, especially LF, is an excellent index for the severity of heart failure, and correlates well with symptomatic changes. The age-adjusted HRV is an excellent prognostic factor for total cardiac death, but not for sudden cardiac death.

**References**


