Decreased Magnitude of Heart Rate Spectral Components in Coronary Artery Disease
Its Relation to Angiographic Severity

Junichiro Hayano, MD, Yusaku Sakakibara, MD, Masami Yamada, MD,
Nobuyuki Ohte, MD, Takao Fujinami, MD, Kiyoko Yokoyama, PhD,
Yosaku Watanabe, PhD, and Kazuyuki Takata, PhD

We analyzed the spectral components of RR interval variability under controlled respiration (15 breaths/min) in 56 patients (age range, 35–73 years) referred for coronary angiography; 14 patients had multivessel disease (group M), 21 had one-vessel disease (group S), and 21 had nonsignificant disease or normal coronary artery (group N). There were 43 healthy controls (age range, 36–71 years) (group C). The patients had no clinical evidence of heart failure, hypertension, diabetes mellitus, or acute stage of infarction and had taken no medication for 3 days. The autoregressive power spectral density of RR interval variability contains two major components, respiratory sinus arrhythmia (RSA) (0.25 Hz) and Mayer wave–like sinus arrhythmia (MWSA) (0.04–0.15 Hz), which have magnitudes that are quantitative markers of cardiac vagal activity and sympathetic activity with vagal modulation, respectively. We represented the magnitudes by the coefficient of component variance (CCV), which provided the amplitude relative to the mean RR interval. The age- and sex-adjusted mean of CCV_{RSA} significantly decreased with advancing angiographic severity (1.64±0.09%, 1.66±0.12%, 1.22±0.13%, and 0.81±0.16% for groups C, N, S, and M, respectively) (p=0.0001). The CCV_{RSA} was unrelated to left ventricular function, previous myocardial infarction, or stenosis of any specific artery including the sinoatrial and atrioventricular node arteries. The CCV_{MWSA} decreased only in group M (p=0.0462). These results indicate that coronary artery disease is associated with vagal dominant impairment in autonomic cardiac function and that reduction in the vagal cardiac function correlates with the angiographic severity. (Circulation 1990;81:1217–1224)

Although many recent studies have demonstrated that reduced vagal cardiac function in patients with coronary artery disease (CAD) is a significant predictor of sudden coronary death and postinfarction mortality, the mechanism for the reduction in the vagal cardiac function in CAD is unknown. Earlier studies have reported that the vagal cardiac function is commonly impaired in CAD; however, few of them have revealed any relation between impairment in the vagal cardiac function and various features of CAD, which include left ventricular function, angiographic severity, and location of diseased coronary arteries. In these studies, the vagal cardiac function has been assessed by heart rate responses to tilting, the Valsalva maneuver, facial water immersion, or deep breathing. These conventional methods inflict a temporary imbalance on the cardiovascular system, and the data can be considerably affected by many hemodynamic control factors other than the vagal cardiac function.

The purpose of this study was to investigate the relation between the autonomic cardiac function and the clinical and angiographic features of CAD. We evaluated the autonomic cardiac function by power spectral analysis of heart rate variability. Heart rate power spectral density in humans contains two major components, reflecting respiratory sinus arrhythmia (RSA) and a 0.04–0.15-Hz fluctuation in the cardiovascular system (Mayer wave–like sinus arrhythmia [MWSA]). The magnitudes of these two components, respectively, provide quantitative and specific indices of vagal cardiac function and sympathetic cardiac function with vagal modulation.
Methods

Subjects

We studied 56 patients (44 men and 12 women) referred for coronary angiography. They fulfilled the criteria of age being at least 35 years old and having no valvular heart disease, hypertension, heart failure (New York Heart Association [NYHA] classes II–IV), conduction block including bundle branch block, frequent ectopic beats, atrial fibrillation, diabetes mellitus, or uremia. The mean age was 52 years (range, 35–73 years).

Twenty-five patients (45%) had a history of myocardial infarction, but none of them was in the acute stage of infarction. Their electrocardiographic findings included abnormal Q wave in 21 patients (38%), ST-T abnormality in 27 patients (48%), and left ventricular hypertrophy in two patients (4%). Their medication included calcium antagonists in 18 patients (32%), nitrates in 19 patients (34%), diuretics in four patients (7%), β-blocker in one patient (2%), and digitals in one patient (2%). All medication, however, was discontinued at least 3 days before the study.

We also studied a control group (group C) of 43 healthy subjects (32 men and 11 women). They were healthy volunteers whose medical status was certified by a full medical checkup including history taking, physical examination, exercise electrocardiography, echocardiography, and supine and standing blood pressures. Their mean age was 48 years (range, 36–71 years). They took no medication during the preceding week.

Autonomic Function Test

The autonomic nervous function test was performed on the day before the coronary angiography in an air-conditioned room (23–24°C) between 2:30 PM and 3:30 PM at least 2 hours after a meal. All subjects were instructed to avoid cigarettes and beverages containing caffeine after 9:00 PM the day preceding the test. All subjects were carefully instructed about the test, and all gave their informed consent.

After a 30-minute rest in the sitting position, each subject was placed on a bed and had electrocardiographic electrodes (CM5, lead) and a respiration sensor (nose-tip thermistor) connected to a polygraph system and to an FM tape recorder (MR-30, TEAC, Japan). After a 10-minute stabilization period, the electrocardiogram (ECG) and respirations were recorded for 5 minutes in the supine position. During the test, the subjects quietly breathed synchronously with a 15/min (0.25 Hz) metronome signal to obtain stationary RSA without a frequency change or phase drift. The synchronization between the metronome signal and the respiration was monitored on the polygraph screen. When the synchronization was found to be poor, the tests were conducted again after repeated instruction.

Spectral Analysis

Off-line analysis was performed on a microcomputer (NEC PC-9801 VX). The ECG and the respiration recordings were played back from the FM tape and digitized at 1,000 samples/sec per channel by analog-to-digital converter (ADX-98E, Canopus Electronics, Kobe, Japan). All RR intervals were measured with the fast peak detection algorithm at an accuracy of 1 msec. All electrocardiographic recordings were reviewed on the computer display by two of the authors (J.H. and Y.S.), and a time series of 200–300 consecutive RR intervals comprising only normal sinus rhythms and in a stationary state was selected for the final analysis.

We used an autoregressive model13–16,18–22 to estimate the power spectral densities of the RR interval variability. The principle of this method has been previously reported13,14,16,19 and its advantages over spectral analysis by fast Fourier transform have been reported in an earlier study.15 The autoregressive coefficients, which are necessary to define the power spectral density estimate, were calculated using the Marple algorithm.21 The model order was chosen as the one that minimized Akaike’s final prediction error figure of merit.20 Moreover, the individual power and center frequencies of each spectral component were computed by spectral component analysis.22 The components with powers of more than 5% of the total power were considered to be significant. Those at 0.04–0.15 Hz were defined to be MWSA and those at the respiration frequency (0.25 Hz) to be RSA (Figure 1).

In considering the RR interval fluctuations caused by each single component relative to the mean RR interval, we represented the magnitude of each component by the parameter we termed the coefficient of component variance (CCV),16 as in the following equation: CCV(%) = 100 · (power of component A)²/(mean RR interval). We also calculated the RR interval variance and the MWSA/RSA ratio, which has been reported by Pagani et al18 to be an index of sympathovagal balance.

![Figure 1. Graphs showing example of autoregressive power spectral analysis of RR interval variability of normal subject. Left panel: Power spectra of individual spectral components. Right panel: Autospectrum, power spectral density. Ordinates are power spectral density (PSD), and abscissas are frequency expressed both in cycles per beat (c/b) and in equivalent Hz (Hz eq.) calculated from mean RR interval. Inset of panels: CCV, coefficient of component variance; F, center frequency; HR, heart rate; MWSA, Mayer wave–like sinus arrhythmia; P, power; RSA, respiratory sinus arrhythmia.](image-url)
| Table 1. Basic Characteristics and Hemodynamic Parameters of Subjects |
|--------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| **Patient data**         | **Group C**     | **Group N**     | **Group S**     | **Group M**     | **p**           |
| **n**                    | 43              | 21              | 21              | 14              | ...             |
| **Age (yr)**             | 48.2±8.8        | 53.2±9.1        | 54.1±8.0        | 58.9±8.1*       | 0.0001          |
| **Sex (M/F)**            | 32/11           | 14/7            | 18/3            | 12/2            | NS              |
| **History of myocardial infarction (0/+)** | 43/0            | 17/4            | 9/12            | 5/9             | 0.0001          |
| **Supine position**      |                 |                 |                 |                 |                 |
| **Heart rate (beats/min)** | 66.5±9.8       | 67.9±11.3       | 69.1±7.4        | 75.8±8.2†       | 0.023           |
| **Systolic BP (mm Hg)**  | 120±14          | 128±16          | 119±14          | 120±17          | NS              |
| **Diastolic BP (mm Hg)** | 76±9            | 80±7            | 73±9            | 75±8            | NS              |
| **Standing position**    |                 |                 |                 |                 |                 |
| **Heart rate (beats/min)** | 78.1±12.1      | 77.8±12.0       | 79.8±8.2        | 86.5±11.1       | NS              |
| **Systolic BP (mm Hg)**  | 117±21          | 116±21          | 105±11          | 113±16          | NS              |
| **Diastolic BP (mm Hg)** | 82±9            | 81±9            | 77±9            | 77±13           | NS              |
| **LVEDP (mm Hg)**        | ...             | 12.5±4.0        | 11.2±4.2        | 12.7±5.5        | NS              |
| **LVEF (%)**             | 63±11           | 58±10           | 53±12‡          |                  | 0.034           |

Data are given as mean±SD. p value based on F statistic for quantitative data and on χ² statistic for categorical data. BP, blood pressure; LVEDP, left ventricular end-diastolic pressure; LVEF, left ventricular ejection fraction; NS, not significant (p>0.05).

*p<0.01, †p<0.05 vs. group C; ‡p<0.05 vs. group N.

Assessment of Angiographic Severity of Coronary Artery Disease

Left-side cardiac catheterization, including selective coronary arteriography by the Judkins technique and left ventricular cineangiography, was performed. The angiograms were interpreted by a panel of cardiologists who were unaware of the autonomic function test. The coronary arteries and branches were divided into 15 segments according to the Ad Hoc Committee on Grading of Coronary Arterial Disease of the American Heart Association, and only the luminal narrowing in the following segments was used in the final assessment: segments 1–3 for the right coronary artery, segments 6 and 7 for the left anterior descending branch, segments 11 and 12 for the circumflex branch, and segment 5 for the left main coronary artery. According to the angiographic severity, the patients were divided into three groups as follows: group N, no disease or narrowing less than 50%; group S, 50% or greater luminal narrowing of a single major coronary artery; group M, 50% or greater narrowing of multiple coronary arteries or the left main coronary artery. Additionally, the presence of significant stenosis (50% or more luminal narrowing) proximal to the origins of or within the sinoatrial node artery and the atrioventricular node artery was also evaluated.

The left ventricular end-diastolic pressure (LVEDP) was measured during the catheterization, and the left ventricular ejection fraction (LVEF) was calculated from the left ventricular cineangiograms using the area-length method.23

Statistical Analysis

The differences in mean values between the groups, except for the heart rate spectral variables, were assessed by one-way analysis of variance followed by the Bonferroni modification of the t test, and the differences in distributions were evaluated by the χ² test with the Yates' correction. Comparisons of the spectral variables among groups were adjusted for the effects of age and sex and assessed by analysis of covariance for general linear models (least-square means method) by means of the STATISTICAL ANALYSIS SYSTEMS (SAS Institute Inc., Cary, North Carolina). The effects of LVEDP and LVEF on the CCVRSA were assessed by partial correlation coefficients (age partialed out). The relations between the CCVRSA and age were assessed by linear regression analysis (least-squares method). A p value less than 0.05 was considered significant.

Results

Cardiac Catheterization

Table 1 shows the population and hemodynamic data of the control group (group C) and the three patient groups divided by the angiographic severity of CAD. Twenty-one patients (38%) had no significant CAD (11 normal coronary and 10 nonsignificant CAD) (group N), 21 (38%) had one-vessel disease (five right coronary artery, 10 left anterior descending, and six circumflex branch disease) (group S), and 14 (24%) had multivessel disease (eight two-vessel, three three-vessel, and three left main coronary artery disease) (group M).

In 33 patients (59%), the sinoatrial node artery was found to originate from the circumflex branch and, in the remaining 23 (41%), from the right coronary artery. The significant stenosis proximal to the origin of or within the artery was found in four patients all belonging to group M. In all patients, the atrioventricular node artery was found to originate from the right
coronary artery. Significant stenosis proximal to the origin of or within the artery was found in 17 patients (seven in group S and 10 in group M).

Effects of Angiographic Severity on Heart Rate Power Spectrum

The RR interval functions and their power spectral densities of representative male patients who are about the same age and have various angiographic severities of CAD are shown in Figure 2. The magnitude of heart rate variability, particularly that of the respiratory component, decreases with advancing angiographic severity. This is demonstrated more clearly by the reduction in area of the RSA peak (at 0.25 Hz equivalent) in the power spectral density.

The CCV\textsubscript{RSA} showed a significant negative correlation with age in both control and patient groups (r=−0.30, −0.48, −0.37, and −0.82 for groups C, N, S, and M, respectively) (Figure 3). Additionally, the mean age and the gender distribution differed significantly among the four groups (Table 1). Thus, we assessed the effects of angiographic severity on heart rate spectral variables after adjusting for the effect of age and sex by analysis of covariance. The mean RR interval, the CCV\textsubscript{RSA}, and the MWSA-to-RSA ratio were affected by age (p=0.0012, 0.0001, and 0.0281, respectively), and the CCV\textsubscript{RSA} and the MWSA-to-RSA ratio were affected by sex (p=0.0290 and 0.0192, respectively). After adjusting for the effect of these covariates, the CCV\textsubscript{RSA} in the patient groups decreased in the order of group N first, then group S, and then group M (p=0.0001), with the value of group N being no different from that of group C (Table 2). On the other hand, the CCV\textsubscript{MWSA} was smaller only in group M, as opposed to that in groups N and C (p=0.0462). The RR interval, RR variance, and MWSA-to-RSA ratio did not differ significantly between these groups.

Additionally, the right panel of Figure 3 shows the distribution of CCV\textsubscript{RSA} in groups N, S, and M by age, with the lower 95% prediction limit for the age relation of the normal controls (group C). Eight
patients in group M (57%), three patients in group S (14%), and only one patient in group N (5%) had a CCVRSA below the prediction limit.

**Effect of Clinical and Angiographic Features on CCVRSA**

The CCVRSA was unaffected by the presence of previous myocardial infarction. After adjusting for the effect of age and sex, we found no significant difference in the CCVRSA between the patients with previous myocardial infarction and those without in any group (Table 3).

The CCVRSA was also unrelated to the stenosis of any specific coronary artery. Dividing the patients in group S by the location of their diseased vessels, we found no significant difference in CCVRSA with regard to the location. Also, the CCVRSA was unaffected by the presence of significant stenosis proximal to the origin of or within the sinoatrial node artery or the ativoventricular node artery.

The subjects in this study had no electrocardiographic abnormalities other than the Q waves and ST-T changes, except that only two patients in group N presented findings of left ventricular hypertrophy.

The age- and sex-adjusted CCVRSA in these two patients were 1.71% and 1.94%.

Additionally, we discontinued all medication for at least 3 days before the study. Although β-blockers and digitalis, which had been administered in two patients in group M, might have certain effects on autonomic cardiac regulation even after 3 days of abstinence, their age- and sex-adjusted CCVRSA values, 0.94% and 0.63%, did not deviate from the distribution of the value for the other patients in group M.

**Effect of Left Ventricular Function**

The CCVRSA was also unaffected by the LVEDP or LVEF (Table 4). When age was partialed out, the partial correlation coefficient of the CCVRSA with these variables was not significant in any group.

**Discussion**

This study demonstrated the relation between the spectral components of heart rate variability and the clinical and angiographic features of CAD. We found that the CCVRSA is reduced in CAD and that the reduction correlates with the angiographic severity but not with the other CAD features, including the presence of previous myocardial infarction, location of diseased coronary arteries, and indices of left ventricular function. The magnitude of the RSA component has been thought to provide a quantitative and specific index of vagal cardiac function.17–19,24 Vagotomy or intravenous atropine eliminate the RSA component,17–19,25 and basic pharmacological and invasive studies have shown a linear relation of the RSA amplitude with vagal cardiac control.26–29 Additionally, we have previously reported that the CCVRSA gives a good estimation of the pharmacologically measured vagal cardiac control with good reproducibility.16,18 Thus, our observation of changes in the CCVRSA in CAD indicates that CAD is associated with a reduction in the vagal cardiac function correlative to the angiographic severity. We also found in this study that the CCVMWSA decreased only in multivessel disease, and that the MWSA-to-RSA ratio is unrelated to the angiographic severity. Although the MWSA component is also eliminated by intravenous atropine, this component in the standing position also contains β-adrenergic-receptor-mediated activity.16–19 The magnitude of the MWSA

<table>
<thead>
<tr>
<th>Variables</th>
<th>Group C</th>
<th>Group N</th>
<th>Group S</th>
<th>Group M</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>RR interval (msec)</td>
<td>916±25</td>
<td>911±33</td>
<td>852±36</td>
<td>814±45</td>
<td>NS</td>
</tr>
<tr>
<td>RR variance (msec)</td>
<td>858±91</td>
<td>861±125</td>
<td>704±135</td>
<td>470±169</td>
<td>NS</td>
</tr>
<tr>
<td>CCVMWSA (%)</td>
<td>1.16±0.08</td>
<td>1.18±0.12</td>
<td>0.98±0.12</td>
<td>0.68±0.16*†</td>
<td>0.0462</td>
</tr>
<tr>
<td>CCVRSA (%)</td>
<td>1.64±0.09</td>
<td>1.66±0.12</td>
<td>1.22±0.13**</td>
<td>0.81±0.16**§</td>
<td>0.0001</td>
</tr>
<tr>
<td>MWSA-to-RSA ratio</td>
<td>0.72±0.07</td>
<td>0.80±0.10</td>
<td>0.91±0.10</td>
<td>0.86±0.14</td>
<td>NS</td>
</tr>
</tbody>
</table>

Data are given as least-squares mean±SEM adjusted for the effects of age and sex. p value based on F statistics for the effect of angiographic severity.

CCV, coefficient of component variance; MWSA, Mayer wave-like sinus arrhythmia; RSA, respiratory sinus arrhythmia; NS, not significant (p>0.05). *p<0.01 vs. group C; †p<0.05, ‡p<0.01 vs. group N; §p<0.05 vs. group S.
component shows an increase while standing, and the increase is blocked by intravenous propranolol.\textsuperscript{16-19,30} Additionally, Pagani et al\textsuperscript{19} reported that the MWSA-to-RSA ratio provides an index of sympathovagal interaction. Thus, our observation of reduced CCV\textsubscript{MWSA} is also attributable to reduced vagal cardiac function in CAD, although the result showing that the MWSA-to-RSA ratio did not change in CAD suggests that sympathetic cardiac function is not reduced in CAD.

In this study, breathing was controlled during the measurement of heart rate variability, and age was factored into the comparison of the spectral component magnitude. In a previous study,\textsuperscript{16} we reported that the CCV\textsubscript{RSA} in normal subjects correlates negatively with respiration frequency when the subjects quietly breathe to various frequencies (6–20/min) of metronome signals. Also, the respiration frequency must be kept above at least 0.15 Hz (9/min) to separate the RSA component from the MWSA component in the power spectrum.\textsuperscript{30} On the other hand, Shannon et al\textsuperscript{30} and ourselves\textsuperscript{16} have demonstrated that the magnitudes of the MWSA and RSA components in normal subjects markedly decline with advancing age up to 30 years. And we have also reported that the CCV\textsubscript{RSA} and CCV\textsubscript{MWSA} continue to decline slowly but significantly thereafter.\textsuperscript{16}

Our observation of reduced CCV\textsubscript{RSA} in CAD supports the findings of earlier studies\textsuperscript{5-7} indicating reduced vagal cardiac function in CAD. Ryan et al\textsuperscript{5} have reported that patients 3 months after myocardial infarction show less slowing of heart rate during facial water (0° C) immersion than age-matched controls. Tristani et al\textsuperscript{6} have reported a diminished change in heart rate during the Valsalva maneuver in coronary patients without heart failure. Bennett et al\textsuperscript{7} have demonstrated less variation in the RR intervals during deep breathing, less bradycardia during the Valsalva maneuver, and a smaller rise in heart rate during lower body negative pressure in postinfarction patients than in age-matched controls. None of these studies, however, has revealed any relation between the reduced vagal cardiac function and the angiographic findings.

Airaksinen et al\textsuperscript{8} have evaluated vagal cardiac function in patients with CAD by measuring the range of heart rate variability during deep breathing and have analyzed its relation to clinical and angiographic findings. Consistent with this study, they found that CAD is associated with impairment in vagal cardiac function independently of the NYHA class, medication, location of diseased coronary arteries, previous transmural myocardial infarction, and indices of left ventricular function. Inconsistent with this study, however, they failed to find any relation between the impairment in vagal cardiac

\textbf{TABLE 3. Effects of Clinical and Angiographic Features on CCV\textsubscript{RSA}}

<table>
<thead>
<tr>
<th>Clinical and angiographic features</th>
<th>Group N</th>
<th>Group S</th>
<th>Group M</th>
</tr>
</thead>
<tbody>
<tr>
<td>History of myocardial infarction</td>
<td>Absent</td>
<td>1.65±0.16 (17)</td>
<td>1.03±0.14 (9)</td>
</tr>
<tr>
<td></td>
<td>Present</td>
<td>1.97±0.35 (4)</td>
<td>1.27±0.14 (12)</td>
</tr>
<tr>
<td></td>
<td>p</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Location of diseased vessel</td>
<td>RCA</td>
<td>...</td>
<td>1.04±0.26 (5)</td>
</tr>
<tr>
<td></td>
<td>LAD</td>
<td>...</td>
<td>1.07±0.17 (10)</td>
</tr>
<tr>
<td></td>
<td>LCx</td>
<td>...</td>
<td>0.93±0.24 (6)</td>
</tr>
<tr>
<td></td>
<td>p</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Stenosis of SA node artery*</td>
<td>Absent</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td></td>
<td>Present</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td></td>
<td>p</td>
<td>...</td>
<td>NS</td>
</tr>
<tr>
<td>Stenosis of AV node artery*</td>
<td>Absent</td>
<td>...</td>
<td>0.97±0.15 (14)</td>
</tr>
<tr>
<td></td>
<td>Present</td>
<td>1.18±0.18 (7)</td>
<td>0.49±0.05 (10)</td>
</tr>
<tr>
<td></td>
<td>p</td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>

Data are given as least-squares mean±SEM (n) adjusted for the effects of age and sex. p value is based on F statistic.

CCV, coefficient of component variance; RSA, respiratory sinus arrhythmia; NS, not significant (p > 0.05); RCA, right coronary artery; LAD, left anterior descending branch; LCx, left circumflex branch; SA, sinoatrial, AV, atrioventricular.

*Stenosis proximal to or within the artery.

\textbf{TABLE 4. Partial Correlations of CCV\textsubscript{RSA} With Indices of Left Ventricular Function}

<table>
<thead>
<tr>
<th>Functions</th>
<th>Group N</th>
<th>Group S</th>
<th>Group M</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>21</td>
<td>21</td>
<td>14</td>
<td>56</td>
</tr>
<tr>
<td>LVEDP</td>
<td>-0.31 NS</td>
<td>0.25 NS</td>
<td>0.15 NS</td>
<td>-0.09 NS</td>
</tr>
<tr>
<td>LVEF</td>
<td>-0.10 NS</td>
<td>-0.26 NS</td>
<td>-0.12 NS</td>
<td>0.10 NS</td>
</tr>
</tbody>
</table>

Data are given as partial correlation coefficients (age partialed).

LVEDP, left ventricular end-diastolic pressure; LVEF, left ventricular ejection fraction; NS, not significant.
function and the angiographic severity assessed by the number of narrowed coronary arteries. We think that the following three points contribute to this discrepancy: First, their subjects are thought to be inappropriate for evaluating the effects of the severity of the vascular lesions because the distribution of the sample was strongly inclined toward those with multivessel disease (80% of patients). Second, the deep breathing method they used in the assessment of vagal cardiac function can inflict a temporary imbalance in the cardiovascular system, and measured heart rate variability can be considerably affected by factors other than vagal cardiac function. Third, their method is unable to eliminate the effects of sympathetic activity on heart rate variability.16

Recently, La Rovere et al31 have measured baroreceptor reflex control of heart rate in 78 men, 4 weeks after a first myocardial infarction. They found that the baroreceptor reflex slope relating change of heart rate to change of systolic blood pressure is significantly lower in patients with three-vessel disease than in those with one-vessel disease. Although the afferent mechanism is different between the arterial baroreceptor reflex and the RSA, the results of La Rovere et al31 are consistent with ours, indicating a correlation of the reduced vagal function with the angiographic severity in patients with CAD.

Many mechanisms can contribute to reduced vagal cardiac function in patients with CAD, and they include 1) reaction of the autonomic cardiovascular control against decreased cardiac function, 2) altered autonomic function as a result of long-term restriction of physical activity, 3) effects of cardiovascular medication on the autonomic nervous function, 4) impairment of the sinoatrial nodal function because of ischemia of the sinoatrial node, and 5) ischemic damage of the intrinsic cardiac nerves and cardiac receptors.32 These mechanisms, however, are unlikely to explain the results of the present study for the following respective reasons: 1) although vagal cardiac function decreases in congestive heart failure,33 we excluded those patients with heart failure belonging to NYHA class II or above, and the CCV$_{RSA}$ was unrelated to LVEDP or LVEF; 2) none of the subjects needed any restriction of his or her usual daily activities; 3) we discontinued all medication at least 3 days before the study, and the CCV$_{RSA}$ also appeared to be unaffected by drugs that can have longer effects, such as β-blockers and digitalis; 4) the CCV$_{RSA}$ was unaffected by the presence of stenosis proximal to the origin of or within the sinoatrial node artery; and 5) the CCV$_{RSA}$ was also unaffected by the presence of any previous myocardial infarction, which is expected to cause extensive damage to the intrinsic cardiac nerves and cardiac receptors.34,35

One possible mechanism that can explain the results of the present study is that reduced vagal cardiac function has an effect on the progression of coronary arteriosclerosis. Kaplan et al36 have shown that cynomolgus macaque monkeys fed an atherogenic diet for 22 months develop coronary atherosclerosis to a different extent depending on their resting heart rate. Monkeys with a habitual high resting heart rate developed lesions in the coronary arteries twofold as extensive as in monkeys with a low resting heart rate. This relation existed independently of serum lipids and blood pressure. Additionally, Perski et al37 have reported a significant association between the minimum and average heart rate recorded during 24-hour continuous monitoring and the severity of coronary atherosclerosis in young male postinfarction patients. This relation seemed to be independent of other established risk factors such as smoking history, systolic and diastolic pressures, and serum lipoproteins. The results of the present study cannot be explained by the relation between the vagal cardiac function and the heart rate because the CCV$_{RSA}$, the index of vagal cardiac function we used in this study, is a value adjusted for the effect of the mean RR interval in its definition. Thus, reduced vagal cardiac function can also be related to the progression of coronary atherosclerosis. To test this hypothesis, further studies including precise analyses of the interrelation among well-established coronary risk factors and vagal cardiac function should be conducted.

Finally, the results of this study can explain a part of the mechanism involved in increased mortality in CAD patients with decreased vagal function. Many recent studies1-4 have shown that patients with reduced vagal cardiac function assessed by heart rate variability have increased susceptibility to sudden coronary death,1,2 increased subsequent mortality after acute myocardial infarction,3 or increased late mortality after coronary angiography.4 Our data suggest that the patients with greater reduction in the vagal cardiac function might have more severe lesions in the coronary arteries.

This study indicates that CAD is associated with vagal dominant impairment in autonomic cardiac function and that the reduction in the vagal cardiac function correlates with the angiographic severity independently of previous myocardial infarction, location of diseased coronary arteries, and left ventricular function. Assessment of autonomic cardiac function by spectral analysis of heart rate variability can provide useful information for the basic pathophysiological understanding and clinical management of CAD.

Acknowledgments

We thank Takeshi Hashimoto, MD, Satoshi Takeuchi, MD, and Junko Ikeda, MD, for their technical assistance, and Robert W. J. Phillips, BA, MA, for his support in the preparation of this manuscript.

References

ambulatory electrocardiographic monitoring. Am J Cardiol 1987;60:86–89

KEY WORDS: nervous system, parasympathetic, angiography, power spectral analysis, arrhythmias
Decreased magnitude of heart rate spectral components in coronary artery disease. Its relation to angiographic severity.
J Hayano, Y Sakakibara, M Yamada, N Ohte, T Fujinami, K Yokoyama, Y Watanabe and K Takata

Circulation. 1990;81:1217-1224
doi: 10.1161/01.CIR.81.4.1217

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1990 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/81/4/1217