Severity in Myocardial Dysfunction Contributed to Long-term Fluctuation of Heart Rate, Rather than Short-Term Fluctuations

Osamu Minamihaba, M.D., Michiyasu Yamaki, M.D., Hitonobu Tomoike, M.D., and Isao Kubota, M.D.

From the First Department of Internal Medicine (O.M., H.T., I.K.) and Division of Medical Informatics (M.Y.), Yamagata University School of Medicine

Background: It is known that heart rate shows complex behavior, long-term fluctuation of heart rate, and short-term fluctuations in heart failure. Analyzing these properties and examining the relationship to the disease, severity may increase the understanding of the background of heart rate variability (HRV).

Methods: In 61 patients (mean age 65 ± 9 years, 32 ischemic heart disease, 29 cardiomyopathy), with myocardial dysfunction, 24-hour ambulatory electrocardiography was performed. After the construction of the time series of R-R intervals, 15 HRV parameters were measured, including mean heart rate, standard deviation of N-N intervals (SDNN), ratio of low frequency/high frequency power (LF/HF), HRV triangular index (TI), and ratio of length/width at the 90% level of all scattered points.

Results: By using the multiple regression analysis, we tested which HRV parameter (HR, SDNN, LF/HF, TI, or length/width) independently correlated with left ventricular ejection fraction (EF) or left ventricular diastolic dimension (EDD). The results demonstrated that TI and SDNN independently correlated with EF (multiple $R = 0.59$). Moreover, TI and SDNN independently correlated with EDD (multiple $R = 0.45$).

Conclusion: TI and SDNN were indicators of the disease severity in myocardial dysfunction, while LF/HF, indicators of autonomic tone, did not have such an ability. It was of interest that the disease severity contributed to long-term fluctuations (TI, SDNN) of heart rate, rather than short-term fluctuations (LF/HF).

A.N.E. 2003;8(2):132-138

ischemic heart disease; cardiomyopathy; ambulatory monitoring

Attention was widely focused on heart rate variability (HRV), since it was reported that HRV was a strong and independent predictor of mortality in myocardial infarction,¹⁻⁷ mainly by the use of frequency-domain analysis;⁸ these studies indicated that HRV was reduced in the high frequency component (>0.04 Hz), and this suggested the decrease in vagal activity.^{9,10} However, its relation to disease severity is poorly understood. It is important to examine the linkage of HRV to disease severity, because it increases the understanding of the significance and the mechanism of the alteration of HRV. Recently, new analytical methods were developed,¹¹⁻¹⁵ including geometric measure, as well as time-domain or frequency-domain analysis. These parameters have enhanced the recognition of

HRV alternation and the assessment of disturbed regulatory mechanism on heart rate. The purpose of the present study was to examine the relationship between new and traditional HRV parameters and the disease severity in patients with myocardial dysfunction.

METHODS

Patient Population

Sixty-one patients (18 women and 43 men, mean age 65 ± 9 years, 32 with chronic stable myocardial infarction and 29 with dilated cardiomyopathy; DCM) were studied. The diagnosis of myocardial infarction was established by

typical chest pain and serum-enzyme changes. The site of myocardial infarction by ECG was anterior in 9 patients, inferior in 15, lateral in 6, and non-Q infarction in 2. The diagnosis of DCM was established by the recommendation from WHO and the National Heart, Lung and Blood Institute.¹⁶ Patients with pulmonary disease, autonomic neuropathy, atrial arrhythmia, sinus node dysfunction, atrioventricular block or implanted pacemaker were excluded from the analysis of HRV. All patients analyzed for HRV were in sinus rhythm and on stable medication for control of myocardial ischemia or CHF symptoms. In this study, patients with hypertension, diabetes mellitus, or treatment with β -blockers were not excluded. In the myocardial dysfunction group, two-dimensional echocardiography was performed by an independent experienced operator. EF was measured according to the area-length technique. EDD was measured at the papillary muscle level using M-mode echocardiography.

All subjects provided informed consent, and the protocol was approved by the Committee on Clinical Investigation of the Yamagata University School of Medicine.

24-Hour Ambulatory ECG Recordings

The 24-hour ambulatory ECG recordings were performed on subjects, who performed ordinary activities and were under routine medication, using a Fukuda SM-50 two-channel recorder (Fukuda Denshi Co., Tokyo, Japan) or a Marquette 8500 recorder (Marquette Electronics Inc., Milwaukee, WI). The recorded data were analyzed using DMW-9000H (Fukuda Denshi Co., Tokyo, Japan). Subjects with <22 hours or normal sinus beats (<97% of total beats) were excluded. The frequency histogram of all R-R intervals was displayed and electrocardiographic strips of the intervals in both tails of the R-R distribution were visually checked. Premature beats and artifacts were carefully eliminated, both automatically and manually. Then the ECG data were digitalized with a sampling frequency of 125 Hz and transferred to a personal computer for the calculation of HRV parameters.

Time-Domain HRV Measures

From the entire 24-hour recording, we measured mean HR and three conventional time-domain measures: the standard deviation of all N-N inter-

vals (SDNN), the square root of the mean of the sum of the squares of differences between adjacent N-N intervals (rMSSD), and the percentage of differences between adjacent N-N intervals >50 ms (%NN50).

Frequency-Domain HRV Measures

Power spectral analysis of HRV was performed on the sequence of N-N intervals of the entire 24-hour segment. The data were processed by the maximum entropy method by the use of CHIRAM software (Suwa Trust, Tokyo, Japan). R-R interval data containing irregular beats were analyzed using the component method. The resulting power spectrum was separated into an ultra-low frequency (ULF, ≤ 0.003 Hz), a very low frequency (VLF, 0.003–0.04 Hz), a low frequency (LF, 0.04–0.15 Hz), a high frequency (HF, 0.15–0.40 Hz), and then the LF power/HF power ratio was calculated. The slope of the 24-hour spectrum was also assessed on a log-log scale by linearly fitting the spectral values.¹⁷ The slope of the linear interpolation of the spectrum in a log-log scale (α , ≤ 0.04 Hz) was measured as one of the frequency-domain measures.

Geometric HRV Measures

We used two approaches for geometric measures. One was the Poincaré plot, which was constructed by plotting each R-R interval (RR_{n+1} ; vertical axis) against the preceding R-R interval (RR_n ; horizontal axis). The Poincaré plot length and width were measured in the middle of the plot and each of them including 90% of all scattered points in longer or shorter line (90% length, 90% width) and the 90% length/90% width ratio was calculated.

The other was the triangular interpolation of frequency distribution of the N-N interval duration.^{6,18} The frequency distribution of the duration of N-N intervals was constructed. A triangle, approximating the curve of the histogram, was shaped by using the minimum square difference method. The baseline width of the distribution measured as a base of that triangle, defined as the triangular interpolation of N-N intervals (TINN), and HRV triangular index (TI), the integral of the density distribution of N-N intervals divided by the modal N-N interval frequency, were used as measurements.

In both the methods, measurements were calculated from the entire 24-hour segment because of the inappropriateness of constructing the geometric pattern with shorter segments of the recordings.¹⁹

Statistical Analysis

Quantitative data are reported as mean $\pm$ standard deviation. Log transformation was performed on four frequency-domain HRV measures: ULF, VLF, LF, and HF. Transformed data were used for statistical analysis. Group differences for categorical data were tested by the analysis of variance followed by Bonferroni's post hoc test. The relationships between the EF, LVEDD, and HRV variables were estimated by Pearson's correlation coefficients. Those between NYHA functional class and HRV variables were studied with Spearman's rank correlation. A P value <0.05 was considered statistically significant. In addition, multiple regression analysis was also performed to examine the relationship between HRV variables and EF or LVEDD. When performing stepwise multiple regression analysis, the entry criterion used was 4.0 for the F value. The statistical analysis was performed using the software package StatView 5.0, SAS Institute Inc., Cary, NC.

RESULTS

NYHA Functional Class and Hemodynamic Measurements

We compared the HRV parameters between patients with NYHA 1 or 2 ($n = 53$) and NYHA 3 or 4 ($n = 8$). The result showed that NYHA 3, 4 had lower TINN, lower TI, lower lnLF, and lnHF, compared to the control group (Table 1).

Next, we dichotomized patients into two groups; normal EF group ($n = 22$; 63 ± 9) and reduced EF group ($n = 27$; $33 \pm 9\%$) by using a cutoff value of 50% of EF. When comparing the two groups (Table 2), TINN and TI in reduced EF (412 ± 174 ms; 48.7 ± 21.5) were significantly lower than those in normal EF (541 ± 174 ms, $P < 0.05$; 66.1 ± 22.1 , $P < 0.05$, respectively). However, frequency-domain measurements did not differ between the two groups.

Patients were also divided into two groups according to LVEDD with a cutoff value of 55 mm. Table 3 shows the comparison of HRV parameters between patients with LVEDD ≤ 55 mm ($n = 22$; 46 ± 5 mm) and LVEDD >55 mm ($n = 27$; 65 ± 9 mm). TI in the group with dilated LVEDD (49.6 ± 20.2) were statistically lower than those in normal LVEDD (65.0 ± 24.4 , $P < 0.05$). None of the time and frequency-domain measures differentiated between the two groups.

Table 1. Measures of HRV Parameters in Patients Classified with NYHA Functional Class (NYHA)

	NYHA 1 or 2 ($n = 53$)	NYHA 3 or 4 ($n = 8$)
Gender (Male/Female)	38/15	5/3
Age (y)	64.2 ± 12.8	65.6 ± 8.65
Time-domain measures		
HR (bpm)	70.1 ± 12.9	75.4 ± 17.5
SDNN (ms)	122 ± 46.0	82.7 ± 32.8
RMSSD (ms)	30.8 ± 21.4	16.2 ± 7.24
%NN50 (%)	8.43 ± 11.5	$1.61 \pm .63$
Geometric measures		
TINN (ms)	516 ± 186	308 ± 138^a
TI	62.4 ± 23.7	36.1 ± 17.5^b
90% length (ms)	553 ± 202	389 ± 150
90% width (ms)	70.7 ± 60.6	32.5 ± 17.3
Length/width	10.2 ± 5.0	13.9 ± 5.1
Frequency-domain measures		
lnULF (ms^2)	7.95 ± 0.72	7.33 ± 1.08
lnVLF (ms^2)	6.98 ± 0.92	6.19 ± 0.95
lnLF (ms^2)	5.25 ± 1.04	3.78 ± 1.27
lnHF (ms^2)	4.54 ± 1.15	3.30 ± 1.32^a
LF/HF	2.47 ± 1.48	1.76 ± 0.72^a
α	-1.25 ± 0.22	-1.28 ± 0.23

HR indicates average heart rate of 24 hours; SDNN, standard deviation of all N-N intervals; rMSSD, the square root of the mean of the sum of the squares of differences between adjacent N-N intervals; %NN50, the percentage of differences between adjacent N-N intervals >50 ms; TINN, triangular interpolation of the histogram of N-N interval durations; TI, heart rate variability triangular index; 90% length, Poincare plot length (longer line) including 90% of all scattered points; 90% width, Lorentz plot width (shorter line) including 90% of all scattered points; length/width, 90% length divided by 90% width; ULF, ultra-low frequency power (≤ 0.003 Hz); VLF, very low frequency power (0.003–0.04 Hz); LF, low frequency power (0.04–0.15 Hz); HF, high frequency power (0.15–0.4 Hz); LF/HF, ratio LF power/HF power; α , slope of the linear interpolation of the spectrum in log-log scale (≤ 0.04 Hz). Values are mean $\pm$ SD. ^a $P < 0.01$ in comparison between NYHA 1–2 and NYHA 3–4 groups, ^b $P < 0.05$.

Regression Analysis

Simple correlations between HRV parameters and NYHA, EF, or LVEDD were examined. As shown in Table 4, the NYHA class significantly correlated with TINN, TI, LF or LF/HF. TINN and TI were weakly correlated with EF. The RMSSD, %NN50, and VLF showed weak correlations with LVEDD. By using the multiple regression analysis, we tested which HRV parameter (HR, SDNN, TI, length/width or LF/HF) was independently correlated with EF or LVEDD. What is evident from Tables 5 and 6, is that TI and SDNN are independently correlated with EF (multiple $R = 0.59$) or LVEDD (multiple $R = 0.45$).

Table 2. Measures of HRV Parameters in Patients Classified with Left Ventricular Ejection Fraction (EF)

	EF $\geq$ 50% (n = 22)	EF < 50% (n = 27)
Gender (Male/Female)	16/6	18/9
Age	66.8 $\pm$ 11.5	60.7 $\pm$ 13.1
Time-domain measures		
HR (bpm)	67.6 $\pm$ 7.73	75.8 $\pm$ 16.9
SDNN (ms)	121 $\pm$ 36.9	106 $\pm$ 49.8
rMSSD (ms)	27.8 $\pm$ 14.8	27.4 $\pm$ 18.3
%NN50 (%)	6.36 $\pm$ 8.13	7.85 $\pm$ 11.5
Geometric measures		
TINN (ms)	541 $\pm$ 174	412 $\pm$ 174 ^a
TI	66.1 $\pm$ 22.1	48.7 $\pm$ 21.5 ^a
90% length (ms)	553 $\pm$ 164	486 $\pm$ 223
90% width (ms)	62.5 $\pm$ 43.8	61.0 $\pm$ 46.5
Length/width	10.7 $\pm$ 3.98	10.9 $\pm$ 6.44
Frequency-domain measures		
lnULF (ms ²)	8.11 $\pm$ 0.56	7.63 $\pm$ 0.99
lnVLF (ms ²)	7.16 $\pm$ 0.72	6.69 $\pm$ 1.20
lnLF (ms ²)	5.54 $\pm$ 1.01	4.81 $\pm$ 1.34
lnHF (ms ²)	4.63 $\pm$ 1.13	4.09 $\pm$ 1.40
LF/HF	2.75 $\pm$ 1.43	2.43 $\pm$ 1.52
α	-1.24 $\pm$ 0.21	-1.24 $\pm$ 0.24

Abbreviations same as Table 1. ^aP < 0.05.**Table 4.** Correlation Coefficients Between HRV Variables and NYHA Functional Class, EF or LVEDD

	NYHA	EF	LVEDD
Time-domain measures			
HR	0.07	-0.19	-0.13
SDNN	-0.39 ^a	0.14	0.22
rMSSD	-0.36 ^a	0.07	0.30 ^b
%NN50	-0.35	-0.03	0.34 ^b
Geometric measures			
TINN	-0.41 ^a	0.30 ^b	-0.07
TI	-0.41 ^a	0.33 ^b	-0.14
90% length	-0.25	0.06	0.21
90% width	-0.19	-0.09	0.29
Length/width	0.20	-0.03	-0.18
Frequency-domain measures			
lnULF	-0.23	0.19	-0.03
lnVLF	-0.29	0.13	0.10
lnLF	-0.44 ^a	0.18	0.10
lnHF	-0.30	0.08	0.19
LF/HF	-0.08	0.09	-0.03
α	-0.06	-0.03	-0.03

NYHA indicates New York Heart Association functional class; EF, left ventricular ejection fraction; LVEDD, left ventricular end diastolic dimension. ^aP < 0.01, ^bP < 0.05.**Table 3.** Measures of HRV Parameters in Patients Classified with Left Ventricular End Diastolic Dimension (LVEDD)

	LVEDD < 55 mm (n = 22)	LVEDD $\geq$ 55 mm (n = 27)
Gender (Male/Female)	14/8	20/7
Age (years)	65.5 $\pm$ 10.1	61.7 $\pm$ 14.4
Time-domain measures		
HR (bpm)	70.4 $\pm$ 10.1	73.6 $\pm$ 16.6
SDNN (ms)	117 $\pm$ 40.6	109 $\pm$ 48.3
rMSSD (ms)	24.4 $\pm$ 11.4	30.1 $\pm$ 19.7
%NN50 (%)	5.28 $\pm$ 7.46	8.73 $\pm$ 11.7
Geometric measures		
TINN (ms)	530 $\pm$ 193	421 $\pm$ 164
TI	65.0 $\pm$ 24.4	49.6 $\pm$ 20.2 ^a
90% length (ms)	536 $\pm$ 180	499 $\pm$ 216
90% width (ms)	52.5 $\pm$ 26.1	69.1 $\pm$ 55.1
Length/width	11.6 $\pm$ 4.38	10.2 $\pm$ 6.16
Frequency-domain measures		
lnULF (ms ²)	7.95 $\pm$ 0.57	7.64 $\pm$ 0.99
lnVLF (ms ²)	6.88 $\pm$ 0.86	6.80 $\pm$ 1.12
lnLF (ms ²)	5.08 $\pm$ 1.16	4.97 $\pm$ 1.28
lnHF (ms ²)	4.17 $\pm$ 1.07	4.28 $\pm$ 1.35
LF/HF	2.83 $\pm$ 1.36	2.36 $\pm$ 1.55
α	-1.28 $\pm$ 0.20	-1.22 $\pm$ 0.25

Abbreviations same as Table 1. ^aP < 0.05.

Table 5. Multiple Regression Analysis of the Relationship Between Left Ventricular Ejection Fraction and HRV Parameters

Independent Variables	Standardized Regression Coefficient	Standard Error	Regression Coefficient	P
HR	-0.181	0.224	-0.222	NS
SDNN	-0.525	0.091	-0.190	<0.05
TI	0.656	0.165	0.481	<0.01
Length/width	-0.046	0.494	-0.146	NS
LF/HF	0.230	1.761	2.708	NS

HR indicates heart rate; SDNN, standard deviation of all N-N intervals; TI, heart rate variability triangular index. LF/HF, low frequency power divided by high frequency power. R for entire model = 0.59.

DISCUSSION

The results of the present study indicated that SDNN and TI were independent markers reflecting the severity of myocardial dysfunction. The HF and LF components in the frequency-domain analysis are common tools for evaluating autonomic imbalance. However, its relation with the degree of myocardial dysfunction was relatively weak. The SDNN and TI reflect the long-term fluctuation of the heart rate (minutes or hours per cycle), and the HF and LF reflect short-term fluctuation (3 or 10 sec per cycle). It was of interest that disease severity contributed to the long-term fluctuation of heart rate, rather than short-term fluctuation.

Myocardial Dysfunction and HRV

In myocardial dysfunction, a reduced HRV has been repeatedly reported, mostly by the use of frequency-domain analysis. Saul et al.²⁰ measured the spectral power of HRV and compared 25 patients with chronic CHF and 21 normal volunteers. The results showed that the spectral power over

0.04 Hz (high frequency component, HF) was reduced in CHF patients. Van de Borne et al.²¹ also reported the reduced LF power in 21 patients with chronic heart failure, compared to the normal subjects. Lombardi et al.²² also showed that patients with reduced ejection fraction were characterized by a diminished R-R variance, especially reduced LF component power.

However, reported correlation between disease severity and HF or LF, seems to be low. Kienzle et al.²³ examined the relationship between the HRV measurement and the disease severity of CHF. Their results indicated that the HRV parameters derived from frequency-domain analysis did not correlate with left ventricular ejection fraction, left ventricular end-diastolic pressure, or NYHA functional class. Only a weak correlation was observed between cardiac output and HF and LF components ($r = 0.42, 0.49$). The results of the present study on LF and HF components were concordant with their findings.

Sudden cardiac death is another important concern in managing myocardial dysfunction. HRV is

Table 6. Multiple Regression Analysis of the Relationship Between Left Ventricular End-diastolic Dimension and HRV Parameters

Independent Variables	Standardized Regression Coefficient	Standard Error	Regression Coefficient	P
HR	0.138	0.158	0.129	NS
SDNN	0.954	0.068	0.284	<0.001
TI	-0.812	0.111	-0.462	<0.001
Length/width	-0.224	0.331	-0.517	NS
LF/HF	-0.175	1.204	-1.478	NS

HR indicates heart rate; SDNN, standard deviation of all N-N intervals; TI, heart rate variability triangular index; LF/HF, low frequency power divided by high frequency power. R for entire model = 0.45.

also useful for stratifying the risk of sudden cardiac death. Martin²⁴ retrospectively reported that five sudden-death patients had low SDNN. Algra et al.²⁵ measured the frequency power of HRV in a larger population (193 sudden death), and concluded that 0.05–0.5 Hz power or 0.02–0.05 Hz power separated the risk of sudden cardiac death. SDNN or 0.02–0.05 Hz power, i.e. the long-term fluctuation on heart rate could be an important indicator of the risk stratification of sudden cardiac death, as well as short-term fluctuation.

Background of HRV Parameters

We used various parameters of HRV in the present study. The simplest variable is the SDNN. SDNN reflects the long-term fluctuation of heart rate, when it is calculated from 24-hour data.¹⁹ The mechanism of long-term fluctuation is still unknown. A candidate oscillator is the central nervous system or the hormonal factor. Further investigation will be needed for clarifying the control mechanism of long-term fluctuation in myocardial dysfunction. Additionally, two parameters were studied in time-domain analysis; (1) rMSSD, the square root of the mean differences between successive beats, and (2) NN50, the proportion derived by dividing NN50 by the total number of N-N intervals. These were indices of short-term variation.¹⁹

The frequency-domain parameters were extensively examined in relation to the autonomic tone,^{10,26,27} by use of the spectral fast-Fourier transform or the autoregression analysis. Studies on vagal stimulation, muscarinic receptor blockade, and vagotoni indicated that HF components reflect the vagal activity.^{2,9,10,28,29} Moreover, studies on sympathetic modulation indicated that the LF component reflects a sympathetic tone.^{2,10} The ULF or VLF components are the frequency-domain parameters reflecting the longer-term variation of heart rate. However, in the present study, we could not find the disease-related alternation in those components.

The geometrical method has been recently employed for HRV analysis. In the present study, we analyzed the (1) histogram of R-R intervals and (2) the Poincaré plot (a diagram in which each the R-R interval is plotted as a function of the previous R-R interval). The HRV index derived from the R-R histogram has been attracting attention, because Cripps et al.³⁰ reported that the risk of sudden cardiac death or the development of sustained

ventricular arrhythmias is seven times greater in patients with an HRV index <25 than in those with an index ≥ 25 . The present study suggested that this parameter also was the best parameter for indicating the disease severity.

Clinical Implication

Our results demonstrated that the combined use of TI and SDNN was the most powerful indicator for estimating the disease severity in patients with myocardial dysfunction. Since both parameters are simple measures, they have no methodological problem seen in spectral analysis such as length of data, window, or algorithms (FFT or autoregressive method). This strengthens its merit for clinical use.

In conclusion, TI and SDNN were good indicators of myocardial dysfunction, while the HF or LF component, indicators of autonomic tone, showed only a limited and weak correlation. Since the HF and LF components account for only approximately 5% of total power, the remaining 95% of HRV power should contain important clinical information.

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