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Reduced Heart Rate Variability and Mortality Risk in an Elderly Cohort

The Framingham Heart Study

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Background The prognostic implications of alterations in heart rate variability have not been studied in a large community-based population.

Methods and Results The first 2 hours of ambulatory ECG recordings obtained on original subjects of the Framingham Heart Study attending the 18th biennial examination were reprocessed to assess heart rate variability. Subjects with transient or persistent nonsinus rhythm, premature beats >10% of total beats, <1 hour of recording time, processed time <50% of recorded time, and those taking antiarrhythmic medications were excluded. The associations between heart rate variability measures and all-cause mortality during 4 years of follow-up were assessed. There were 736 eligible subjects with a mean age (\pm SD) of 72 ± 6 years. The following five frequency domain measures and three time domain measures were obtained: very-low-frequency power (0.01 to 0.04 Hz), low-frequency power (0.04 to 0.15 Hz), high-frequency power (0.15 to 0.40 Hz), total power (0.01 to 0.40 Hz), the ratio of low-frequency to high-frequency power, the standard deviation of total normal RR intervals, the percentage of differences between adjacent normal RR intervals that are >50 milliseconds, and the square root of the mean of the squared

differences between adjacent normal RR intervals. During follow-up, 74 subjects died. In separate proportional hazards regression analyses that adjusted for relevant risk factors, very-low-frequency power ($P<.0001$), low-frequency power ($P<.0001$), high-frequency power ($P=.0014$), total power ($P<.0001$), and the standard deviation of total normal RR intervals ($P=.0019$) were significantly associated with all-cause mortality. When all eight heart rate variability measures were assessed in a stepwise analysis that included other risk factors, low-frequency power entered the model first ($P<.0001$); thereafter, none of the other measures of heart rate variability significantly contributed to the prediction of all-cause mortality. A 1 SD decrement in low-frequency power (natural log transformed) was associated with 1.70 times greater hazard for all-cause mortality (95% confidence interval of 1.37 to 2.09).

Conclusions The estimation of heart rate variability by ambulatory monitoring offers prognostic information beyond that provided by the evaluation of traditional risk factors. (*Circulation*. 1994;90:878-883.)

Key Words • electrocardiography • epidemiology • heart rate • mortality

Heart rate variability is used to assess cardiac autonomic function.¹ It is influenced by various physiological factors including age,² postural changes,³ and time of day.⁴ Pathological conditions such as congestive heart failure,⁵ diabetic neuropathy,^{6,7} and coronary heart disease⁸ also are associated with alterations in heart rate variability. Although reduced heart rate variability predicts outcome in postinfarction patients,⁹⁻¹¹ its prognostic role has not been studied in a large community-based population.

Framingham Heart Study participants undergoing a routine biennial examination were assessed with 2-hour ambulatory ECG recordings to evaluate the prognostic implications of heart rate variability in this closely monitored community-based, elderly population.

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Methods

Study Sample

In 1948, a sample of 5209 residents of Framingham, Mass, was selected to undergo biennial examinations in a prospective study. Selection criteria and study design have been reported.¹²⁻¹⁴ In the 18th examination cycle (1983 to 1985), 1028 ambulatory ECG recordings of approximately 2 hours' duration were obtained during routine clinic examinations of 1825 surviving study subjects.

Processing of Ambulatory Recordings

The first 2 hours of ambulatory recordings were reprocessed for heart rate variability using a Cardiodata/Mortara Mk5 Holter analysis system. Beat-by-beat RR interval data were obtained from the beat stream file. For intervals of ectopy or artifact less than or equal to two RR intervals, a linearly interpolated beat was substituted.¹⁵ Five frequency domain and three time domain measures were obtained; they are listed and defined in Table 1.

Frequency Domain Analysis

Frequency domain analysis was performed by calculating the power density spectrum using the fast Fourier transform method on 100-second blocks of data resampled at 1.28 samples per second and subjected to a Hamming window.¹⁵ If there was a run of arrhythmia or artifact longer than one beat in length, the 100-second block was terminated, the partial block was discarded, and a new block was started at the end of the unusable period. The resulting 100-second

TABLE 1. Definitions for Time and Frequency Domain Measures of Heart Rate Variability

Variable	Unit	Definition
Time domain variables		
SDNN	ms	Standard deviation of normal RR intervals
pNN50	%	Percentage of differences between adjacent normal RR intervals that are >50 ms
r-MSSD	ms	Square root of the mean of the squared differences between adjacent normal RR intervals
Frequency domain variables		
Total power	ms ²	Energy in the power spectrum between 0.01 and 0.40 Hz (based on a 100-second sampling method)
High-frequency power	ms ²	Energy in the power spectrum between 0.15 and 0.40 Hz
Low-frequency power	ms ²	Energy in the power spectrum between 0.04 and 0.15 Hz
Very-low-frequency power	ms ²	Energy in the power spectrum between 0.01 and 0.04 Hz (based on a 100-second sampling method)
Low-frequency/high-frequency	None	Ratio of low-frequency to high-frequency power

SDNN indicates standard deviation of normal RR intervals; pNN50, percentage of differences between adjacent normal RR intervals >50 milliseconds; and r-MSSD, square root of the mean of squared differences between adjacent normal RR intervals.

All heart rate variability measures were based on 2-hour recordings.

power spectra were corrected for attenuation resulting from the sampling and the Hamming window and averaged. The frequency range of the power spectra was 0.01 to 0.64 Hz. This 100-second method was intended to avoid any assumption about sinus node activity in consecutive arrhythmias in which sinus node activity was unknown. When longer time blocks are used, larger amounts of data are discarded because of consecutive premature beats or artifact. On the other hand, when shorter time blocks are used, the minimum frequency at which the power spectrum that can be measured is greater than 0.01 Hz. The mean duration of processed time for analyses was 94.2 minutes, corresponding to 56.5 100-second blocks.

Time Domain Analysis

The standard deviation of normal RR intervals (SDNN), percentage of differences between adjacent normal RR intervals exceeding 50 milliseconds (pNN50), and the square root of the mean of the squared differences between adjacent normal RR intervals (r-MSSD) were calculated from all normal RR intervals included in the first 2 hours of each recording.

Premature Complexes

Normal QRS complexes and arrhythmias were diagnosed under constant visual monitoring. Complex or frequent ventricular arrhythmia was defined as 30 or more premature ventricular depolarizations per hour, multiform, repetitive, or R-on-T premature beats. A prior Framingham Heart Study report described the prognostic significance of complex or frequent ventricular arrhythmia.¹⁶ Supraventricular premature beats were stratified into three groups as follows: less than 120 per hour, 120 to 240 per hour, and more than 240 per hour.

For a tape to be eligible for this study, we required that it have 60 or more minutes of analyzable data,^{10,11} at least 50% time processed, and premature beats less than 10% of total beats.¹⁷

Clinical Covariates

Risk factors possibly predisposing to coronary heart disease¹² were recorded at each examination. Variables that might be

associated with autonomic function also were considered, including coffee and alcohol consumption, cigarette smoking, and use of cardioactive medications. Alcohol consumption (ounces per week) was calculated using the following formula: ounces of ethanol = 0.57 × (1 measure of liquor) + 0.44 × (12 ounces of beer) + 0.40 × (3 to 4 ounces of wine).¹⁸

With subjects seated, systolic and diastolic blood pressures were measured twice by the examining physician using a mercury column sphygmomanometer positioned near eye level. Diabetes was defined on the basis of a nonfasting blood glucose level ≥200 mg/dL (≥11.10 mmol/L) or the use of insulin or an oral hypoglycemic agent. Mean heart rate was calculated from the ambulatory monitoring recording used for the analysis of heart rate variability.

At each follow-up examination since 1948, interim events (myocardial infarction and congestive heart failure) have been assessed with the help of medical history, physical examination, and 12-lead ECG. In addition, medical records were obtained for participants who did not attend an examination, and these were evaluated for evidence of interim events. All suspected interim events were reviewed by a committee of three physicians who evaluate pertinent medical records, hospitalization records, and pathology reports. The definitions of myocardial infarction and congestive heart failure have been described.¹⁹

Outcome Events

All deaths were evaluated by a committee of three physicians who determined probable cause after review of hospital records, autopsy findings, death certificates, and interviews with family members. The end point of this study was all-cause mortality. The follow-up was 4 years.

Statistical Methods

Measures of heart rate variability were transformed by natural logarithm because their distributions were skewed. Their correlations were assessed with Pearson's correlation coefficients. Before the principal mortality analyses, clinical risk factors related to mortality were determined, using a stepwise multivariable proportional hazards regression mod-

TABLE 2. Evaluable Cases

Study sample		5209
Dead before 18th examination		2493
Did not attend 18th examination		891
Attended 18th examination		1825
No ambulatory ECG data		797
Rhythm or artifact exclusions		278
Other than sinus rhythm	(n=43)	
Atrial fibrillation	25	
Pacemaker implantation	5	
Wandering pacemaker	7	
AV dissociation	3	
Ectopic sinus rhythm	3	
Frequent VPBs	(n=12)	
Frequent SVPBs	(n=33)	
Excessive artifact	(n=160)	
Combined reasons*	(n=30)	
Antiarrhythmic medication use		14
Eligible subjects		736

AV indicates atrioventricular; VPBs, ventricular premature beats; and SVPBs, supraventricular premature beats. Frequent VPBs or SVPBs are premature beats more than 10% of total beats.

*Excluded because of combination of VPBs, SVPBs, and artifact.

el,^{20,21} from the following variables: age, sex, history of myocardial infarction or congestive heart failure, systolic and diastolic blood pressures, diuretic use, β -blocker use, diabetes, cigarette smoking, alcohol consumption, the presence of complex or frequent ventricular arrhythmia, and the presence of supraventricular premature beats.

Separate analyses were performed for each measure of heart rate variability to assess its relation to mortality; all analyses adjusted for clinical risk factors. Finally, the joint associations between measures of heart rate variability and mortality were evaluated with a stepwise multivariable proportional hazards analysis. Hazard ratios and 95% confidence intervals were computed for each variable. The statistical significance level was set at .05 for each significance test (two-sided) without adjustment for number of tests. For descriptive purposes, Kaplan-Meier survival plots were computed for tertiles of low-frequency power.

Results

Of the 5209 original Framingham Heart Study subjects, 1825 attended the 18th examination and 1028 had an ambulatory ECG. A total of 292 subjects were excluded for reasons listed in Table 2. Excessive artifact was the major reason (n=160) for exclusion. Clinical characteristics of the 736 eligible subjects are presented in Table 3. The mean age of subjects was 72 years (range, 63 to 93); there were 297 (40%) men. A history of myocardial infarction was present in 68 subjects (9%) and a history of congestive heart failure in 13 subjects (2%). The clinical characteristics of eligible subjects were remarkably similar to those of examined subjects who did not have ambulatory monitoring (n=796) and also to subjects excluded for rhythm, artifact, or medication use (n=292) except that eligible subjects were about 2 years younger and had about two beats per minute lower heart rate (on 12-lead ECG) than the other groups.

TABLE 3. Clinical Characteristics of 736 Eligible Subjects

Age, y		72±6
Men, %		40
History of myocardial infarction, %		9
History of congestive heart failure, %		2
Systolic blood pressure, mm Hg		142±21
Diastolic blood pressure, mm Hg		76±10
Mean heart rate, beats per minute		74±12
Diabetes mellitus, %		12
Medication use		
β -Blockers, %		17
Calcium antagonists, %		2
Digitalis, %		3
Diuretics, %		34
Smokers, %		15
Coffee		
None, %		29
1-2 cups/d, %		47
≥3 cups/d, %		24
Alcohol		
None, %		44
1-2 oz/wk, %		22
≥3 oz/wk, %		35
Time recording started (median, range)		13:00, 8:30-14:30
Processed time, min		94±20
VPBs		
≤30/h, %		88
>30/h, %		12
SVPBs		
<120/h, %		88
120-240/h, %		10
≥240/h, %		2

VPBs indicates ventricular premature beats; SVPBs, supraventricular premature beats.

Values are mean±1 SD or percentages unless stated otherwise.

Correlations Between Measures of Heart Rate Variability

Correlation coefficients relating measures of heart rate variability (after natural logarithmic transformation) are presented in Table 4. Two groups of very highly correlated variables were observed. First, the average correlation was $r=.91$ among high-frequency power, pNN50, and r-MSSD. Second, a mean correlation of $r=.87$ was found among total power, very-low-frequency power, low-frequency power, and SDNN. In contrast, the correlations between variables in different groups were much lower ($r=.20$ to $.60$). Finally, the ratio of low-frequency to high-frequency power belonged in neither group, although it was correlated better with the first group (mean $r=-.46$) than with the second (mean $r=.25$).

TABLE 4. Pearson Correlations Among Measures of Heart Rate Variability

	ln VLF*	ln LF	ln HF	ln TP*	ln LF/HF	ln SDNN†	ln pNN50	ln r-MSSD	ln Mean Heart Rate
Mean value	6.79	5.66	4.79	7.20	0.87	4.17	3.26	3.21	4.29
SD	0.76	0.82	0.85	0.73	0.57	0.33	1.32	0.44	0.16
ln VLF*		0.85	0.61	0.96	0.32	0.86	0.47	0.48	-0.55
ln LF			0.77	0.94	0.30	0.75	0.57	0.60	-0.39
ln HF				0.76	-0.38	0.63	0.87	0.93	-0.39
ln TP*					0.22	0.86	0.59	0.62	-0.54
ln LF/HF						0.15	-0.48	-0.52	0.02
ln SDNN†							0.53	0.54	-0.51
ln pNN50								0.94	-0.39
ln r-MSSD									-0.43

VLF indicates very-low-frequency power; LF, low-frequency power; HF, high-frequency power; TP, total power; LF/HF, ratio of low-frequency to high-frequency power; SDNN, standard deviation of normal RR intervals; pNN50, percentage of differences between normal RR intervals >50 milliseconds; and r-MSSD, square root of the mean of squared differences between adjacent normal RR intervals.

All correlations achieved statistical significance at $P < .0001$ except between ln LF/HF and in mean heart rate ($P = .64$).

Mean heart rate was calculated from all heartbeats included in frequency domain analyses.

*Based on a 100-second sampling method.

†Based on 2-hour recording.

Heart Rate Variability and Mortality

Among the 736 eligible subjects, the mean follow-up time was 3.9 years, during which there were 74 deaths. The two most common causes of death were cancer ($n=21$) and coronary heart disease ($n=18$); there were 9 deaths due to other cardiovascular conditions (including stroke), 16 deaths from other causes, and 10 deaths from unknown cause. Four-year survival in the study sample (90%) was comparable to that observed in subjects who attended the clinic examination but did not receive a monitor (89%) and those who were excluded from eligibility due to artifact, arrhythmia, or medication use (88%). As expected, survival in subjects who did not attend the index examination was slightly lower (84%); this group included homebound subjects and those in hospitals and nursing homes.

Age, sex, history of myocardial infarction or congestive heart failure, diuretic use, and presence of complex or frequent ventricular premature beats were each associated with mortality in preliminary analyses; therefore, they were included as covariates in the stepwise multivariable analyses of outcome. Table 5 lists hazard ratios for all-cause mortality per 1 SD decrement of heart rate variability measures (all natural log transformed). All five frequency domain measures were significantly associated with all-cause mortality in unadjusted analyses; except for the ratio of low-frequency to high-frequency power, all remained significant after adjustments for other risk factors. On the other hand, SDNN was the only time domain variable that was a significant predictor of all-cause mortality after adjusting for other risk factors. Low-frequency power had the most significant hazard ratio among heart rate variability measures, with hazard ratios (per 1 SD decrement) of 1.70 to 1.87. A 1 SD decrement in natural log-transformed low-frequency power was associated with an increase of 70% in the hazard for all-cause mortality, adjusting for age, sex,

and clinical risk factors (95% confidence interval for increase, 37% to 109%; $P < .0001$). All eight heart rate variability measures were used in stepwise multivariable hazards models that incorporated age, sex, and clinical risk factors. Low-frequency power ($P < .0001$) was the first and only heart rate variability measure to enter the model with a significance level of $P < .15$. Even after forcing SDNN into the models, low-frequency power entered next ($P = .0001$), rendering SDNN no longer statistically significant. Kaplan-Meier survival plots (Figure) reveal a direct relation between tertiles of low-frequency power and survival.

Additional Analyses

The mortality hazard ratio for low-frequency power was nearly identical in diabetics and nondiabetics, and it was essentially unchanged after we accounted for selected interaction terms (age and sex with complex or frequent ventricular premature beats and age with diuretic use).

Since mean heart rate was the strongest clinical determinant of heart rate variability, it was included in additional analyses of mortality. Inclusion of mean heart rate in the multivariable model had little or no impact on the results of the age, sex, and risk factor adjusted analyses.

Discussion

In postinfarction patients, reduced heart rate variability has been reported to predict risk for subsequent mortality; this has been documented both for 24-hour and 2- to 15-minute recordings.^{9-11,22} Our results, based on 2-hour monitoring, demonstrate that reduced heart rate variability also predicts mortality in a population-based sample of elderly subjects.

High-frequency power is a marker of vagal influence on heart rate.^{1,3,23} Although low-frequency power has been reported to be a marker of cardiac sympathetic tone,²⁴ it is also suspected to reflect parasympathetic modulation.²⁵ In postinfarction patients, it is speculated

TABLE 5. Proportional Hazards Regression Analysis of the Impact of Heart Rate Variability Measures on All-Cause Mortality

	Hazard Ratio*	95% Confidence Interval	P
Unadjusted association with all-cause mortality			
ln SDNN†	1.48	(1.22, 1.81)	.0001
ln pNN50	1.08	(0.86, 1.35)	.5310
ln r-MSSD	1.08	(0.85, 1.36)	.5278
ln VLF‡	1.62	(1.40, 1.87)	.0001
ln LF	1.87	(1.55, 2.26)	.0001
ln HF	1.42	(1.13, 1.80)	.0030
ln TP‡	1.73	(1.44, 2.09)	.0001
ln LF/HF	1.62	(1.33, 1.97)	.0001
Age- and sex-adjusted association with all-cause mortality			
ln SDNN†	1.44	(1.18, 1.76)	.0004
ln pNN50	1.16	(0.93, 1.45)	.1791
ln r-MSSD	1.20	(0.96, 1.49)	.1081
ln VLF‡	1.57	(1.34, 1.84)	.0001
ln LF	1.75	(1.43, 2.13)	.0001
ln HF	1.43	(1.14, 1.78)	.0018
ln TP‡	1.65	(1.36, 2.01)	.0001
ln LF/HF	1.32	(1.07, 1.63)	.0084
Age, sex, and clinical risk factors§ adjusted for association with all-cause mortality			
ln SDNN†	1.38	(1.13, 1.70)	.0019
ln pNN50	1.19	(0.95, 1.49)	.1228
ln r-MSSD	1.23	(0.99, 1.54)	.0610
ln VLF‡	1.51	(1.27, 1.79)	.0001
ln LF	1.70	(1.37, 2.09)	.0001
ln HF	1.43	(1.15, 1.79)	.0014
ln TP‡	1.60	(1.30, 1.96)	.0001
ln LF/HF	1.23	(0.99, 1.53)	.0637

Abbreviations are as in Table 4.

Based on 74 deaths among 736 subjects. Mean values and standard deviations of each heart rate variability measure are in Table 4.

*Hazard ratio of instantaneous death rates comparing subjects who differ by a 1 SD decrement for the variable in question.

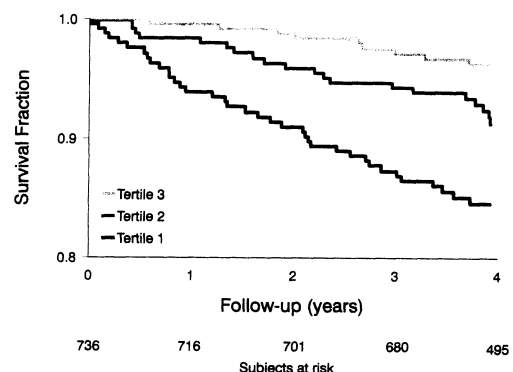
†Based on 2-hour recording.

‡Based on a 100-second sampling method.

§Clinical risk factors included age, sex, history of myocardial infarction or congestive heart failure, presence of complex or frequent ventricular premature beats, and diuretic use.

that reduced heart rate variability is a reflection of increased sympathetic activity, which is a predisposing factor for myocardial ischemia and fatal arrhythmias.^{9,26}

The biological mechanism explaining the association of heart rate variability with mortality is unknown. If parasympathetic predominance is protective against myocardial ischemia and fatal arrhythmias, one would expect high-frequency power to figure more prominently as a predictor of mortality. In this elderly population, low-frequency power had the largest hazard ratio of all eight heart rate variability measures. Hayano et al^{8,27} suggested a causal role for autonomic imbalance in the pathogenesis of coronary arteriosclerosis because patients with coronary heart disease have been reported to have lower heart rate variability than normal subjects. Although altered heart rate variability may con-



Kaplan-Meier survival curves according to tertiles of low-frequency power. Tertile values for low-frequency power are <218.9, 219.92 to 415.51, and >415.8 milliseconds squared.

tribute to mortality in a causal manner, the higher mortality observed in our subjects with reduced heart rate variability also may be due to subclinical coronary artery disease. Alternatively, reduced heart rate variability might simply identify subjects in poor health before death—it may be a marker of risk rather than an etiologic factor.

Limitations

In the present study, the number of outcomes was too small and the follow-up period was too short to study individual causes of death. Nevertheless, this is the first cohort study to identify an association between heart rate variability and mortality in a population-based sample. Another limitation of this study is that the lower limit of the frequency domain analyses was 0.01 Hz; as such, we were unable to evaluate signals below this limit. Additionally, the time domain analyses were based on 2 hours of data; the values obtained from short-term recordings will differ from those based on longer periods of observation. This was an elderly sample of survivors of a carefully characterized study population; additional population-based studies are needed to determine if these findings are generalizable to younger age groups and those with different clinical characteristics.

Clinical Implications

Whether reduced heart rate variability plays a causal role or is merely a marker of risk, heart rate variability measures may identify individuals at increased risk for mortality. Until these findings are confirmed by other population-based studies, we do not advocate the routine use of heart rate variability assessment for risk stratification. Modification of heart rate variability using medications^{25,28} or physical exercise²⁹ has been reported, but the benefits of modification of heart rate variability are not known. We conclude that the estimation of heart rate variability by ambulatory ECG monitoring offers prognostic information beyond that provided by the evaluation of traditional risk factors.

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