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Association Between Reduced Heart Rate Variability and Cognitive Impairment in Older Disabled Women in the Community: Women's Health and Aging Study I

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Abstract

OBJECTIVES—To examine the independent association between heart rate variability (HRV), a marker of cardiac autonomic function, and cognitive impairment.

DESIGN—Cross-sectional analysis of baseline data from Women's Health and Aging Study I.

SETTING—Urban community in Baltimore, Maryland.

PARTICIPANTS—A subset of 311 physically disabled, community-dwelling women aged 65 and older whose HRV data were obtained.

MEASUREMENTS—Reduced HRV was defined as the lowest quartile of each of several HRV measures exploring time and frequency domains and compared with the remaining three quartiles. Cognitive impairment was defined as a Mini-Mental State Examination score less than 24. Multiple logistic regression was used to model the independent relationship between reduced HRV and prevalent cognitive impairment.

RESULTS—The age-, education-, and race-adjusted prevalence of cognitive impairment was higher in those with reduced HRV than in those with nonreduced HRV. After adjusting for relevant demographic and clinical characteristics, participants with reduced HRV were significantly more likely than those with nonreduced HRV to have cognitive impairment; these findings were consistent across different HRV indices. In particular, reduced high-frequency power, indicative of decreased parasympathetic activity, was associated with 6.7 times greater odds of cognitive impairment (95% confidence interval = 2.27–20.0).

CONCLUSION—Cardiac autonomic dysfunction, particularly decreased parasympathetic activity, was independently associated with cognitive impairment in older disabled women in the community. This finding may improve understanding of the pathophysiological basis of cognitive impairment.

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The potential role of HRV as a cause or consequence of cognitive impairment needs to be elucidated in future studies.

Keywords

heart rate variability; cognition; autonomic nervous system

Cognitive impairment is a major public health problem in the elderly population because of its significant effect on individuals, families, the healthcare system, and society. It is estimated that Alzheimer's disease affects 4 million people in the United States and that the prevalence of this pathologic condition doubles every 5 years beyond age 65.¹ Cognitive impairment that is not severe enough to be diagnosed as dementia is probably more prevalent than all types of dementia combined, and it is often associated with some degree of functional impairment.² Known risk factors for cognitive impairment, Alzheimer's disease, vascular dementia include a genetic predisposition, family history, depression, dysregulation in the hypothalamus-pituitary-adrenal axis system, high blood pressure, high cholesterol, smoking, poor lung function, glucose dysregulation, atherosclerosis, and inflammation.³

Heart rate variability (HRV), beat-to-beat alterations in sinus rhythm, is a marker of cardiovascular autonomic function.⁴ Reduced HRV is a strong independent predictor of cardiovascular events and cardiovascular mortality and all-cause mortality in high-risk^{5,6} as well as community-dwelling populations.^{7,8} Reduced HRV has also been linked to a number of risk factors for cognitive impairment, including hypertension,⁹ diabetes mellitus,¹⁰ depression,¹¹ and subclinical inflammation,¹² although the direct relationship between HRV and cognitive impairment has not been investigated. Understanding the nature of the relationship between reduced HRV and cognitive impairment might provide insight into pathophysiological mechanisms that contribute to the development of cognitive impairment in the elderly population and new clues for the development of novel preventive strategies.

The overall objective of this study was to test the hypothesis that reduced HRV is associated with prevalent cognitive impairment in disabled, community-dwelling older women, independent of traditional risk factors for cognitive impairment.

METHODS

Study Population

Data for this study came from the baseline evaluations that were conducted between 1992 and 1995 in the Women's Health and Aging Study (WHAS) I.¹³ WHAS I is a prospective, observational study designed to investigate the epidemiology of progression of physical disability in a cohort of 1,002 women aged 65 and older who represented the one third most-disabled women living in the community. Subjects were considered eligible if they had self-reported difficulties in two or more physical domains of disability and had a Mini-Mental State Examination (MMSE) score of 18 or higher. Details of study design, population recruitment and characteristics, and procedures have been described elsewhere.¹⁴ The institutional review board of the Johns Hopkins Medical Institutions approved the research protocols. Informed consent was obtained from all participants. HRV data were obtained in a subset of 389 participants. Although this subset of participants was not truly randomly selected, it can be considered to be a random sample, because the selection process was not related to HRV, cognitive function, or any of the important confounders. There was no major difference in baseline characteristics between those who had HRV measurements and those who were included in the total cohort (data not shown). Two subjects who were not identified as white or black and 76 who had inadequate or missing HRV data were excluded, and 311 participants were ultimately included in the analysis. Between November 1992 and February 1995, trained,

certified research assistants conducted standardized face-to-face interviews and physical examinations at participants' homes.

Measurement and Analysis of HRV

Two hours of ambulatory continuous electrocardiographic recording were obtained at rest using a Holter recorder. The Holter recordings were digitized and processed for HRV analysis using standard commercial software (SpaceLabs FT3000a, Redmond, WA). Peaks of QRS complexes were identified using a computer algorithm and confirmed by an investigator (LAF). Periods during which beat identification was poor were excluded from the analysis.

Time and frequency domain indices were analyzed. Time domain indices were the standard deviation of normal RR intervals (SDNN (ms)), the standard deviation of the average normal RR intervals over a 5-minute period (SDANN (ms)), the square root of the mean squared differences of successive normal RR intervals (RMSSD (ms)), and the number of interval differences of successive normal RR intervals greater than 50 ms (NN50 (counts)). Using the Fourier analysis, the following frequency domain was calculated for 2-minute epochs, and the epochs were integrated over the 2-hour recording: very low frequency power (VLF, <0.04 Hz, ms^2), low frequency power (LF, 0.04–0.15 Hz, ms^2), and high frequency power (HF, 0.15–0.40 Hz, ms^2). The SDNN assesses overall HRV, the SDANN estimates long-term variation in heart rate, and the RMSSD and NN50 reflect short-term variation and thus are highly correlated with the HF power.⁴ The VLF power is thought to reflect, in part, the influence of the renin-angiotensin-aldosterone system.⁴ The HF power is mainly modulated by parasympathetic activity, and the LF power is modulated by sympathetic and parasympathetic activities.⁴

The analyses were initially performed using HRV as a continuous variable and divided into quartiles, but a nonlinear relationship was observed that only the lowest quartiles of each HRV index were associated with cognitive impairment. This was also consistent with previous studies^{5,8,10,15,16} that demonstrated a nonlinear association between HRV and the risk of clinical outcomes. Therefore, subjects were dichotomized for each HRV index into reduced HRV (i.e., the lowest quartile: <32 ms for SDNN, <32.5 ms for SDANN, <22 ms for RMSSD, <63 counts for NN50, <448.5 ms^2 for VLF, <177.5 ms^2 for LF, and <97.5 ms^2 for HF) and nonreduced HRV (i.e., the remaining three quartiles).

SDNN, SDANN, and RMSSD were available for 308 of the subset of 311 participants included in this analysis, and NN50, VLF, LF, and HF were available in 300.

Measurement of Cognitive Function and Other Covariates

The primary outcome was cognitive impairment assessed according to baseline MMSE score. Because it was shown that an MMSE score of less than 24 of 30 provides reasonable sensitivity and specificity for moderate to severe cognitive impairment,¹⁷ study subjects were categorized into two groups according to baseline MMSE score: those with or without cognitive impairment (MMSE score <24 and ≥ 24 , respectively).

The following covariates were also assessed: age, race, years of education, smoking status, current drinking, beta-blocker use, body mass index (BMI), presence of depressive symptoms Score >5 on the short version of the Geriatric Depression Scale (GDS),¹⁸ regular exercise more than 6 months per year, and low physical activity. Systolic and diastolic blood pressures were calculated as the average of three measurements. Left ventricular hypertrophy according to the Minnesota code¹⁹ and resting heart rate were obtained from a 12-lead electrocardiographic recording. Serum total cholesterol and serum interleukin (IL)-6 were also measured. Diagnosis of hypertension was self-reported. A panel of physicians adjudicated diagnoses of myocardial

infarction, angina pectoris, congestive heart failure, stroke, diabetes mellitus, peripheral artery disease, and pulmonary disease (asthma, chronic obstructive lung disease, and restrictive lung disease) according to standardized algorithms.¹³

Statistical Analysis

Baseline characteristics were compared between those with and without prevalent cognitive impairment using the Fischer exact test for categorical variables and two-sample *t* test and Wilcoxon rank sum test for continuous variables. Age, education, and race-adjusted prevalence of cognitive impairment of subjects with reduced HRV were compared with those with nonreduced HRV for each index.

Multiple logistic regression was used to estimate the odds ratio (OR) and 95% confidence interval (CI) of cognitive impairment as a function of reduced HRV. To assess the association between HRV and cognitive impairment that demographic and clinical factors do not explain, multivariate-adjusted ORs were calculated for each HRV index. Because the objective of this study was to estimate the strength of association between HRV and cognitive impairment and not to derive a prediction model for cognitive impairment, the covariates in the multiple logistic regression models were determined a priori based on current knowledge. The model included age, race (white or black), education (≤ 8 years, 9–11 years, ≥ 12 years), smoking (never, former, or current), current drinking (yes or no), regular exercise (yes or no), low physical activity (yes or no), beta-blocker use (yes or no), BMI (< 25 kg/m², 25–29 kg/m², ≥ 30 kg/m²), left ventricular hypertrophy (yes or no), short GDS score greater than 5 (yes or no), heart rate (beats per minute), systolic and diastolic blood pressure (mmHg), serum total cholesterol (< 200 mg/dL, 200–239 mg/dL, ≥ 240 mg/dL), serum IL-6 (< 1.48 pg/mL, 1.48–2.29 pg/mL, 2.30–3.57 pg/mL, ≥ 3.58 pg/mL), and history of cardiovascular disease (yes or no) and pulmonary disease (yes or no). Serum IL-6 level was included in quartiles because of its nonlinear relationship with cognitive impairment in exploratory analysis. A composite, dichotomous variable was created for angina pectoris, myocardial infarction, congestive heart failure, hypertension, stroke, diabetes mellitus, and peripheral artery disease. Indicator variables were generated for missing data in BMI, exercise, low physical activity, serum total cholesterol, and serum IL-6. There was no evidence of collinearity between variables according to variance inflation factors. Potential interactions between age and each HRV index were explored in multivariate-adjusted models.

Statistical significance was indicated as $P < .05$. All statistical analyses were performed using Stata version 8.2 (StataCorp, College Station, TX).

RESULTS

The distribution of selected demographic and clinical characteristics of study participants according to cognitive function is presented in Table 1. Cognitive impairment, defined as an MMSE score less than 24, was found in 52 of 311 participants (17%) and was positively associated with older age, black race, lower education, low physical activity, lower BMI, presence of depressive symptoms, history of peripheral artery disease, and lower VLF power ($P < .05$ for all). In addition, participants with cognitive impairment were less likely to be current drinkers and on beta-blockers and more likely to have left ventricular hypertrophy, faster resting heart rate, higher blood pressure, lower cholesterol, and lower HRV than those free of cognitive impairment, although these associations were not statistically significant.

The prevalence of cognitive impairment after adjusting for age, education, and race was consistently higher in those with reduced HRV than in the rest of the study participants (Figure 1). The difference was statistically significant for RMSSD ($P = .004$), VLF ($P = .04$), LF (P

= .04), and HF ($P < .001$), but not significant for SDNN ($P = .06$), SDANN ($P = .11$), and NN50 ($P = .07$).

The unadjusted and adjusted ORs and 95% CIs of cognitive impairment comparing reduced HRV compared with nonreduced HRV are displayed in Table 2. Overall, participants with reduced HRV were more likely to have cognitive impairment than those with nonreduced HRV, independent of relevant demographic and clinical characteristics, including subclinical inflammation measure according to serum IL-6. The association was statistically significant for HF (OR = 6.74, 95% CI = 2.27–20.0), RMSSD (OR = 3.37, 95% CI = 1.26–9.03), and NN50 (OR = 3.29, 95% CI = 1.14–9.49). The associations between cognitive impairment and the rest of HRV indices, although in the expected direction, were not statistically significant. There was no evidence of interactions between each HRV index and age in multivariate-adjusted models.

DISCUSSION

This study showed that reduced RMSSD, NN50, and HF power were associated with prevalent cognitive impairment according to MMSE scored in disabled community-dwelling older women, after adjusting for relevant demographic and clinical characteristics, including subclinical inflammation according to serum IL-6. This suggests that decreased parasympathetic control of heart rate is associated with cognitive impairment. Although only RMSSD, NN50, and HF power reached statistical significance, the data also showed consistent associations between reduced HRV and cognitive impairment across all the HRV indices.

However, the strength of association varied between HRV indices, which suggests that one HRV measure may be a better indicator of cognitive impairment than others. RMSSD, NN50, and HF power, indicators of short-term variations in heart rate mediated by parasympathetic activity,⁴ were more closely associated with cognitive impairment than SDANN, an indicator of long-term variations in heart rate mediated by sympathetic and parasympathetic activities. This finding is consistent with decreased parasympathetic activity observed in patients with Alzheimer's disease.²⁰ SDNN, an overall measure of HRV, may not be as sensitive as HF power for measuring parasympathetic activity.

The results were consistent with those from the previous studies that examined the association between HRV and other clinical outcomes. Several prospective studies reported that reduced HRV was associated with incident coronary heart diseases,^{8,16} diabetes mellitus,¹⁰ and hypertension.¹⁵ After adjusting for demographic variables and clinical characteristics, it was found that the lowest quartile of each HRV index was associated with greater odds of cognitive impairment than the remaining three quartiles.

In this analysis, race was a strong confounder of the association between reduced HRV and cognitive impairment. Despite many favorable characteristics such as higher education, higher participation in exercise, lower BMI, and lower prevalence of hypertension, diabetes mellitus, and peripheral artery disease, whites were more likely to have reduced HRV than blacks. This suggests reduced parasympathetic tone in whites compared to blacks, which was also shown by previous studies.^{21,22} However, the prevalence of cognitive impairment was higher among blacks, even after adjusting for potential confounders and risk factors. The odds ratios of cognitive impairment associated with reduced HRV were similar between whites and blacks in stratified analyses (data not shown).

Potential Mechanisms

Biological mechanisms can be used to explain the independent association between reduced HRV and cognitive impairment found in this study. HRV and blood pressure variability (BPV)

in response to challenge are inversely correlated.^{23,24} Physiologically, blood pressure is kept constant within a certain range to maintain adequate perfusion to vital organs, including the brain. When blood pressure increases, baroreceptors in the aorta and carotid artery sense the increase in blood pressure, and the vasomotor center in the medulla increases parasympathetic tone, which results in a decrease in heart rate and contractility. When blood pressure decreases, the vasomotor center decreases parasympathetic tone and increases sympathetic tone, increasing heart rate and contractility in the heart and resistance in blood vessels. As such, the baroreflex mechanism has an important role in maintaining perfusion through modulation of the heart rate and contractility via the cardiac autonomic nervous system.^{24,25} Therefore, individuals with cardiac autonomic dysfunction, indicated by reduced HRV, are more prone to increased BPV. Studies also have shown that an increase in short-term BPV is associated with cognitive dysfunction^{26,27} and hypertensive brain damage, such as silent cerebral white matter lesions²⁸ and lacunar infarction.²⁹ Finally, it has been shown that cerebral white matter lesions are related to a generalized reduction in cerebral perfusion pressure.³⁰ These findings suggest that chronic intermittent reductions in cerebral blood flow secondary to increased blood pressure fluctuation may contribute to development of cognitive impairment. Furthermore, it has been reported that reduced HRV is associated with increased risk of type 2 diabetes mellitus¹⁰ and that increased daytime BPV predicts early carotid atherosclerosis progression;³¹ both of these are known risk factors for cognitive dysfunction. However, this biological mechanism could not be validated in the current study because measurements of BPV or intermediate outcomes related to cognitive impairment, such as brain imaging, which can show decreased perfusion or subtle ischemic changes, were not available.

Another possible explanation is that reduced HRV is a consequence of autonomic dysfunction that may occur with central nervous system changes in dementia. It has been reported that patients with Alzheimer's disease have decreased parasympathetic tone, which can cause reduced HRV.²⁰

Limitations

There are several limitations to this study. Because it was a cross-sectional study, it was impossible to investigate whether reduced HRV preceded the development of cognitive impairment or how HRV changed over time and affected cognitive function in individuals. This issue will be more clearly elucidated in a prospective study. Three hundred eleven subjects whose HRV data were measured were used. As previously mentioned, even though the selection process was not related to HRV, cognitive function, or any of the important confounders, it was not completely random, and a possibility of selection bias cannot be excluded with certainty. The number of study participants included in the study was small, which limited statistical power in detecting the difference in prevalence of cognitive impairment between HRV categories. Some of the HRV quartiles did not have enough cases, resulting in imprecise estimates. In the analysis, multiple hypothesis testing was not corrected for, which could increase the probability of falsely declaring a risk factor to be an etiological factor. Addressing this issue appropriately is challenging. Bonferroni correction is overly conservative for correlated tests, which would be the case for this study. Furthermore, given the observational nature of this study, there is the possibility that unmeasured and residual confounders may have accounted at least partly for the observed association. Even though information on the presence of diseases was collected, information on disease severity was not measured. Genetic factors and endocrine dysregulation, both of which could potentially mediate the association between HRV and cognitive impairment, were not considered. In addition, because of the circadian nature of HRV,⁴ measuring HRV at different times of the day probably has introduced important noise into the analysis.

The original WHAS I cohort included women with co-morbidities and moderate to severe disabilities who are the one-third most-disabled women living in the community.¹³ Thus, generalization of the findings to relatively healthy older adults is limited. In addition, individuals with an MMSE score less than 18 were excluded from the study.¹³ Therefore, it is possible that those with the worst physical or cognitive function, who were more likely to have reduced HRV, were underrepresented in the original cohort, resulting in underestimation of the strength of association between reduced HRV and cognitive impairment.

Implications of this Study

This study showed that reduced RMSSD, NN50, and HF power, indicative of decreased parasympathetic cardiac autonomic regulation, were significantly associated with cognitive impairment, adjusting for possible confounders and cardiovascular risk factors, in a population of disabled women living in the community. It was suggested that cardiac autonomic dysfunction could be one of several potential mechanisms leading to cognitive impairment, but whether HRV is a factor in the causal pathway needs to be further investigated. Larger population-based prospective studies are warranted to confirm the findings as well as to further investigate the nature of the relationship between cardiac autonomic dysfunction and cognitive impairment.

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Figure 1.

Age-, education-, and race-adjusted prevalence of cognitive impairment by heart rate variability index. *Reduced heart rate variability (HRV) was defined as the first quartile (25th percentile) of each HRV index, whereas nonreduced HRV was defined as the remaining upper three quartiles. †Statistically significant ($P < .05$). SDNN = standard deviation of normal RR intervals; SDANN = standard deviation of the average normal RR intervals over a 5-minute period; RMSSD = square root of the mean squared differences of successive normal RR intervals; NN50 = number of interval differences of successive normal RR intervals greater than 50 ms; VLF = very low frequency power; LF = low frequency power; HF = high frequency power.

Table 1
Demographic and Clinical Characteristics of Study Subjects by Mini-Mental State Examination (MMSE) Score

Characteristics *	MMSE Score		P-value
	<24 (n = 52)	≥24 (n = 259)	
Age, n (%)			.007
65–74	14 (26.9)	118 (45.6)	
75–84	15 (28.8)	80 (3.9)	
≥85	23 (44.2)	61 (23.5)	
Race, n (%)			<.001
White	22 (42.3)	191 (73.8)	
Black	30 (57.7)	68 (26.2)	
Education, years, n (%)			<.001
0–8	38 (74.5)	101 (39.0)	
9–11	5 (9.8)	58 (22.4)	
≥12	8 (15.7)	100 (38.6)	
Smoking status, n (%)			.63
Never	30 (57.7)	129 (49.8)	
Former	17 (32.7)	98 (37.8)	
Current	5 (9.6)	32 (12.4)	
Current drinking, n (%)	3 (5.8)	42 (16.2)	.05
Exercise, n (%)	6 (13.3)	25 (1.3)	.60
Low physical activity, n (%)	32 (65.3)	113 (45.9)	.02
Beta-blocker, n (%)	8 (15.4)	58 (22.4)	.35
Body mass index (kg/m ²) n (%)			.04
Normal (<25)	18 (42.9)	63 (26.3)	
Overweight (25–30)	15 (35.7)	84 (35.0)	
Obese (≥30)	9 (21.4)	93 (38.7)	
Left ventricular hypertrophy, n (%)	18 (34.6)	64 (25.3)	.17
Resting heart rate, mean ± SD	74.4 ± 11.8	71.9 ± 11.4	.17
SBP, mmHg, mean ± SD	142.7 ± 21.2	139.3 ± 22.2	.30
DBP mmHg, mean ± SD	66.4 ± 1.9	65.4 ± 16.3	.59
Total cholesterol, mg/dL, n (%)			.15
<200	12 (36.4)	60 (29.0)	
200–239	15 (45.4)	74 (35.7)	
≥240	6 (18.2)	73 (35.3)	
Interleukin-6, pg/mL, median (25 th percentile, 75 th percentile) [†]	2.40 (1.63, 3.09)	2.30 (1.47, 3.59)	.92
Short Geriatric Depression Scale score>5, n (%)	17 (32.7)	50 (19.3)	.04
Disease prevalence, n (%)			
Angina	11 (21.2)	79 (3.5)	.24
Myocardial infarction	11 (21.2)	33 (12.7)	.13
Congestive heart failure	9 (17.3)	66 (25.5)	.29
Hypertension	34 (66.7)	146 (56.4)	.21
Stroke	7 (13.5)	33 (12.7)	.82
Diabetes mellitus	11 (21.2)	56 (21.6)	1.00
Peripheral artery disease	25 (48.1)	64 (24.7)	.001
Pulmonary disease	17 (32.7)	117 (45.2)	.13
Heart rate variability, median (25 th percentile, 75 th percentile) [†]			
SDNN, ms	40.5 (28, 65)	44 (32, 60)	.67
SDANN, ms	39 (30, 53.5)	44.5 (34, 57)	.09
RMSSD, ms	33 (19.5, 69.5)	32 (23, 56)	.97
NN50, counts	131 (47, 864)	222 (67, 731)	.60
VLF, ms ²	647 (376, 982)	761 (470, 1385)	.04
LF, ms ²	276 (156, 991)	358 (186, 688)	.51
HF, ms ²	233 (74, 815)	201 (109, 530)	.82

* Missing observations are 1 for education, 22 for exercise, 16 for low physical activity, 29 for body mass index (BMI), 6 for left ventricular hypertrophy, 1 for systolic blood pressure (SBP) and diastolic blood pressure (DBP), 71 for total cholesterol, 79 for interleukin-6, 1 for hypertension, 3 for standard deviation of normal RR intervals (SDNN), standard deviation of the average normal RR intervals over a 5-minute period (SDANN), and square root of the mean squared differences of successive normal RR intervals (RMSSD), and 11 for number of interval differences of successive normal RR intervals >50 ms (NN50), very low frequency (VLF), low frequency (LF), and high frequency (HF).

[†] Summarized as median [25th percentile, 75th percentile], because of skewed distribution.

SD = standard deviation.

Unadjusted and Adjusted Odds Ratios and 95% Confidence Intervals of Cognitive Impairment Comparing Reduced Versus Nonreduced Heart Rate Variability (HRV) of Various HRV Indices

Table 2

HRV Index	Unadjusted		Adjusted for Age, Education, and Race		Multivariate Adjusted*	
	Odds Ratio (95% Confidence Interval)		P-value			
Standard deviation of normal RR intervals	1.82 (0.95–3.49)	.07	2.01 (0.96–4.21)	.06	1.75 (0.66–4.61)	.26
Standard deviation of the average normal RR intervals over a 5-minute period	1.59 (0.83–3.03)	.16	1.82 (0.87–3.82)	.11	1.54 (0.57–4.19)	.40
Square root of the mean squared differences of successive normal RR intervals	1.73 (0.90–3.33)	.10	3.12 (1.45–6.72)	.004	3.37 (1.26–9.03)	.02
Number of interval differences of successive normal RR intervals >50 ms	1.23 (0.62–2.44)	.55	2.05 (0.94–4.48)	.07	3.29 (1.14–9.49)	.03
Very low frequency	1.77 (0.92–3.41)	.09	2.17 (1.02–4.62)	.04	2.17 (0.79–5.92)	.13
Low frequency	1.98 (1.03–3.79)	.04	2.21 (1.05–4.64)	.04	2.59 (0.96–6.97)	.06
High frequency	2.46 (1.29–4.68)	.006	5.44 (2.41–12.2)	<.001	6.74 (2.27–20.0)	.001

Note: Reduced HRV was defined as the first quartile (25th percentile) of each HRV index; non-reduced HRV was defined as the remaining upper three quartiles.

* The model included age, race, education, smoking, current drinking, exercise, low physical activity, beta-blocker use, body mass index, left ventricular hypertrophy, short Geriatric Depression Scale score>5, heart rate, systolic and diastolic blood pressure, total cholesterol, interleukin-6, and history of cardiovascular disease and pulmonary disease.