Novel predictor of prognosis from exercise stress testing: Heart rate variability response to the exercise treadmill test

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Background Although the prognostic power of heart rate variability (HRV) at rest has been demonstrated, the prognostic potential of exercise-induced HRV has not been investigated. We aimed to evaluate the prognostic power of exercise-induced HRV during and after standard exercise testing.

Methods Time- and frequency-domain HRV analysis was performed on R-R interval data taken from 1335 subjects (95% male, mean age 58 years) during the first and last 2 minutes of exercise treadmill testing and the first 2 minutes of recovery. Cox survival analysis was performed for the 53 cardiovascular and 133 all-cause mortality end points that accrued during the 5.0-year mean follow-up.

Results After adjusting for potential confounders, greater root mean square successive difference in R-R interval during peak exercise and recovery, greater high-frequency (HF) power and percentage of HF power, lower percentage of low-frequency power, and lower ratio of low frequency to HF during recovery were significantly associated with increased risks for all-cause and cardiovascular death. Of all time-domain variables considered, the log of the root mean square successive difference during recovery was the strongest predictor of cardiovascular mortality (adjusted hazard ratio 5.0, 95% CI 1.5-17.0 for the top quintile compared with the lowest quintile). Log HF power during recovery was the strongest predictor of cardiovascular mortality in the frequency domain (adjusted hazard ratio 5.9, 95% CI 1.3-25.8 for the top quintile compared with the lowest quintile).

Conclusions Exercise-induced HRV variables during and after clinical exercise testing strongly predict both cardiovascular and all-cause mortality independent of clinical factors and exercise responses in our study population. (Am Heart J 2007;153:281-8.)

The heart rate response to exercise and heart rate recovery from exercise reflect autonomic control of heart rate and have been shown to predict cardiovascular prognosis.[1-6] The postulated pathophysiologic basis of these observations is that autonomic imbalance can increase the risk for experiencing cardiovascular events.[7-9] Heart rate variability (HRV), or differences in beat-to-beat interval (R-R interval) among successive heart rate cycles, is also thought to reflect cardiovascular responses to autonomic activity. Heart rate variability has been related to respirations, baroreflexes, and thermal regulation.[10,11] These factors are reflected in spectral analysis studies of HRV, which have identified 3 major components of the HRV spectrum: a high-frequency (HF) peak (HF >0.1 Hz) corresponding to respiratory sinus arrhythmia under ordinary circumstances, a low-frequency (LF) peak (LF 0.04-0.09 Hz) that is thought to be related to arterial pressure control, and a very low-frequency (VLF) component (VLF <0.04 Hz) that is thought to be an expression of peripheral vasomotor regulation.[10,11]

Low time- and frequency-domain HRV have been shown to be associated with increased mortality in the Framingham cohort[12] and in survivors of acute myocardial infarction,[13,14] increased incidence of new cardiac events,[15] and increased incidence of cardiovascular morbidity and mortality in subjects without coronary disease.[16] The frequency of the prevalent LF oscillation has also been shown to predict outcome in patients with previous myocardial infarctions.[17] All of these studies evaluated HRV at rest. To date, however, no studies

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This study was supported in part by a grant from the Stanford Medical Scholars research program.

Submitted June 5, 2006; accepted November 1, 2006.

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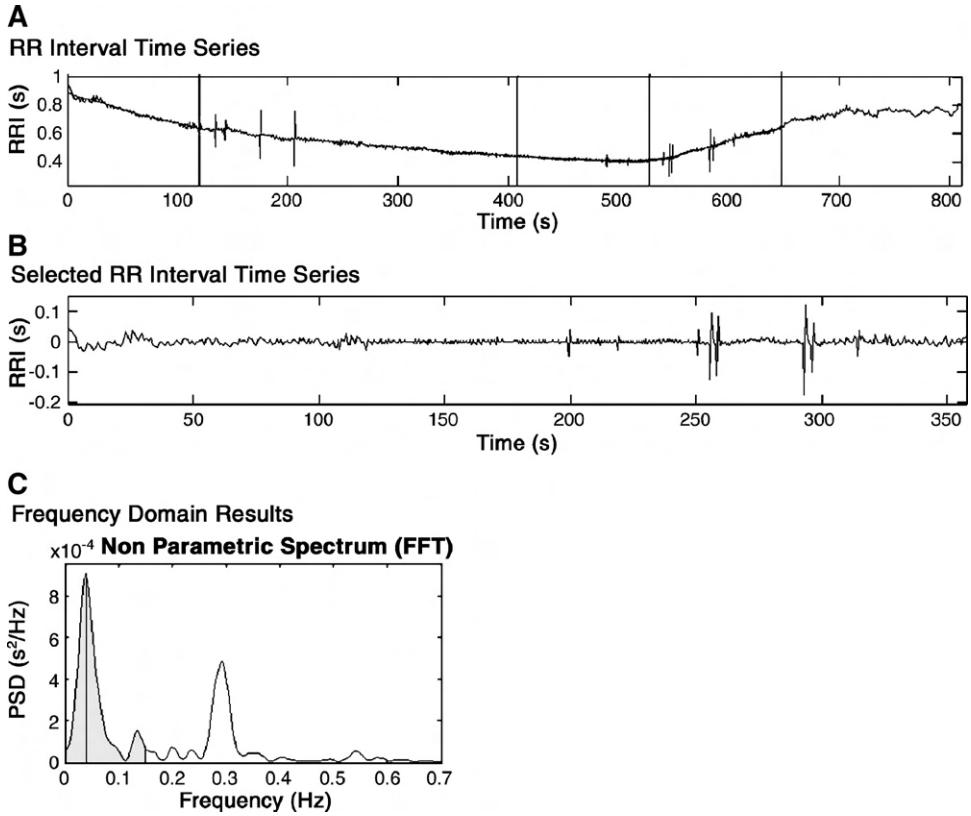
0002-8703/$ - see front matter

doi:10.1016/j.ahj.2006.11.001

Figure 1



Detrending and frequency-domain transformation of R-R interval variability. **A**, Raw R-R interval tachogram for an exercise test. **B**, Detrended R-R time series from the first and last 2 minutes of exercise and the first 2 minutes of recovery. **C**, R-R interval spectral power for the first 2 minutes of exercise generated by fast Fourier transform.

have been performed to investigate the prognostic potential of exercise-induced HRV (EI-HRV). We aimed to investigate the prognostic potential of EI-HRV by retrospective analysis of EI-HRV data and outcomes for 1335 patients who underwent a standard clinical exercise test.

Methods

Study population

A total of 1651 subjects referred for routine clinical exercise tests from 1997 to 2004 at Palo Alto Veterans' Affairs Health Care System (Palo Alto, CA) were evaluated. No imaging was performed in conjunction with these tests. The mean follow-up period was 5.0 $\pm$ 2.0 years. The study was approved by the Stanford University Institutional Review Board, and each patient gave informed written consent.

Because frequent ectopy can affect spectral-analysis variables of HRV, we excluded subjects with greater than 10% premature ventricular complexes (n = 132), atrial fibrillation (n = 27), supraventricular tachycardia (n = 20), paced rhythms (n = 5), or excessive recording noise (n = 65). Subjects with insufficient recordings (<4 minutes of exercise or 2 minutes of recovery, n = 67) were also excluded, leaving 1335 (95% male, mean age 57.7 $\pm$ 12.4 years) subjects for inclusion in the study. Of the subjects who were excluded, 45 (14%) died of all causes, and 17 (38%) of these deaths were due to cardiovascular causes. Excluded subjects had significantly more coronary disease than subjects included in the study (23% vs 17%, $P < .05$); their baseline characteristics were otherwise similar.

Exercise stress testing

Subjects were exercise tested using a ramp protocol. A pretest survey form was used to customize the protocol so that the predicted peak exercise capacity would be achieved within 10 minutes of exercise.[18] Subjects were encouraged to assume a supine position for recovery immediately after peak exertion. Exercise capacity was estimated in metabolic equivalents from treadmill speed and grade. Twelve-lead electrocardiogram data were recorded at 500 Hz and analyzed by a Schiller Holter system. After physician review and editing, all correctly

Table I. Baseline characteristics of study population

Characteristic	All subjects (N = 1335) Mean ± SD	Survivors (n = 1202) Mean ± SD	All deaths (n = 133) Mean ± SD	Cardiovascular deaths (n = 53) Mean ± SD
Age (y)	57.7 ± 12.4	57.0 ± 12.1	64.4 ± 13.1*	68.4 ± 12.0†
Female, no./total (%)	71/1335 (5)	64/1201 (5)	7/133 (5)	3/53 (6)
Resting heart rate	78 ± 15	78 ± 15	78 ± 16	75 ± 17
Resting systolic blood pressure (mm Hg)	131 ± 19	130 ± 19	134 ± 18*	135 ± 18
Smoking				
Ever, no./total (%)	769/1335 (58)	673/1202 (56)	96/133 (72)*	34/53 (64)
Currently, no./total (%)	278/1335 (21)	241/1202 (20)	37/133 (28)*	10/53 (19)
Diabetes, no./total (%)	192/1335 (14)	173/1202 (14)	19/133 (14)	4/53 (8)
Congestive heart failure, no./total (%)	75/1335 (6)	55/1202 (5)	20/133 (15)*	13/53 (25)†
Chronic obstructive pulmonary disease, no./total (%)	66/1335 (5)	59/1202 (5)	7/133 (5)	3/53 (6)
Prior coronary disease,‡ no./total (%)	231/1335 (17)	190/1202 (16)	41/133 (31)*	21/53 (40)†
β-Blocker use, no./total (%)	290/1335 (22)	259/1202 (22)	31/133 (23)	18/53 (34)†
Digoxin use, no./total (%)	46/1335 (3)	32/1202 (3)	14/133 (11)*	9/53 (17)†

*$P < .05$ when compared to survivors.
†$P < .05$ when compared to survivors and subjects who died of noncardiovascular causes.
‡Prior coronary disease defined as prior angioplasty, bypass surgery, myocardial infarction, or Q waves.

Table II. Exercise test variables

Variable	All subjects (N = 1335) Mean ± SD	Survivors (n = 1202) Mean ± SD	All deaths (n = 133) Mean ± SD	Cardiovascular deaths (n = 53) Mean ± SD
Heart rate increase (beat/min)*	72 ± 25	73 ± 25	59 ± 23†	56 ± 22‡
Heart rate recovery at 2 min (beat/min)§	47 ± 21	47 ± 21	41 ± 19†	40 ± 19‡
Duke treadmill score	7.4 ± 5.2	8.0 ± 4.8	4.5 ± 5.7†	2.7 ± 6.2‡
Premature ventricular complexes during exercise‖	0 (0-2)	0 (0-2)	1 (0-7)†	2 (0-9)‡
Premature ventricular complexes at 5-min recovery‖	0 (0-2)	0 (0-2)	1 (0-7)‡	2 (0-8)‡

*Defined as peak heart rate minus rest heart rate.
†$P < .05$ when compared to survivors.
‡$P < .05$ when compared to survivors and subjects who died of noncardiovascular causes.
§Defined as peak heart rate minus heart rate at 2 minutes of recovery.
‖Values are reported as median (interquartile range).

identified R-R intervals were included in subsequent analysis to preserve the temporal nature of the interval series.

Heart rate variability analysis

We resolved R-R interval data during the first and last 2 minutes of exercise and the first 2 minutes of recovery into HF (0.15-0.6 Hz), LF (0.04-0.15 Hz), and VLF (<0.04 Hz) components by nonparametric fast Fourier transform. Version 1.1 of the HRV Analysis Software (Biosignal Analysis and Medical Imaging Group, University of Kuopio, Kuopio, Finland) was used for all transformations. The baseline trend in heart rate introduced by the exercise test was removed using the "smoothness priors" method.[19] Detrended time series were cubically interpolated and resampled at 4 Hz, and the fast Fourier transform was windowed with 256-sample-width Hanning windows with 50% overlap (Figure 1). Spectral powers of the VLF, LF, and HF bands were expressed in absolute units and as a percentage of total (VLF + LF + HF) power. The ratios of low frequency to high frequency and the root mean square successive difference (rMSSD) in R-R interval were also calculated for the detrended R-R interval series for all exercise periods.

Outcomes

The outcomes evaluated in this study were all-cause and cardiovascular mortality. Cardiovascular mortality was defined as death of subjects with a history of cardiovascular disease and no identifiable noncardiovascular cause in either the Veterans Affairs Health Care System electronic medical record or the California Health Department Service database. Cause of death was determined by study personnel blinded to exercise test results (J.V.F., G.E, V.F.F.).

Statistical methods

One-way analysis of variance was used to characterize changes in EI-HRV variables during different exercise periods. Baseline characteristics and exercise test variables were compared according to outcome by 2-tailed t tests (for normally distributed continuous variables), Mann-Whitney U tests (for nonnormally distributed continuous variables), or χ^2 tests (for categorical variables).

Univariable and multivariable Cox proportional hazards analyses were used to evaluate the prognostic power of EI-HRV variables. Each EI-HRV variable that was a significant predictor of mortality was evaluated in a separate multivariable model. The multivariable model included all exercise test variables that significantly predicted cardiovascular mortality (Duke treadmill score [defined as described[20]], heart rate increase with exercise, and heart rate recovery at 2 minutes) and a clinical risk factor score that was derived using principle components analysis. Briefly, the principle component of clinical variables that differed significantly between survivors and nonsurvivors (age, history of congestive heart failure, β-blocker use, digoxin use, and prior coronary disease, which was defined as prior angioplasty, bypass surgery, myocardial infarction, or Q waves) was used to calculate a clinical risk factor score for each subject. The associations between covariates were evaluated by correlation matrix. No correlation coefficients were greater in magnitude than 0.6, and EI-HRV variables that were subsequently used in survival analysis did not strongly correlate with any clinical or exercise test variable ($r = -0.26$ to 0.33). The proportional hazards assumption was evaluated for each variable by the scaled Schoenfeld residual.

Separate multivariable Cox survival analyses including exercise test responses and clinical risk factors were used to assess the additional prognostic value of EI-HRV variables. The predictive power of each model was ranked by Akaike information criteria on the χ^2 scale, and discriminative accuracy was evaluated by the right-censored concordance index derived from the D_{xy} rank correlation and calculated using 200 bootstrap samples.[21]

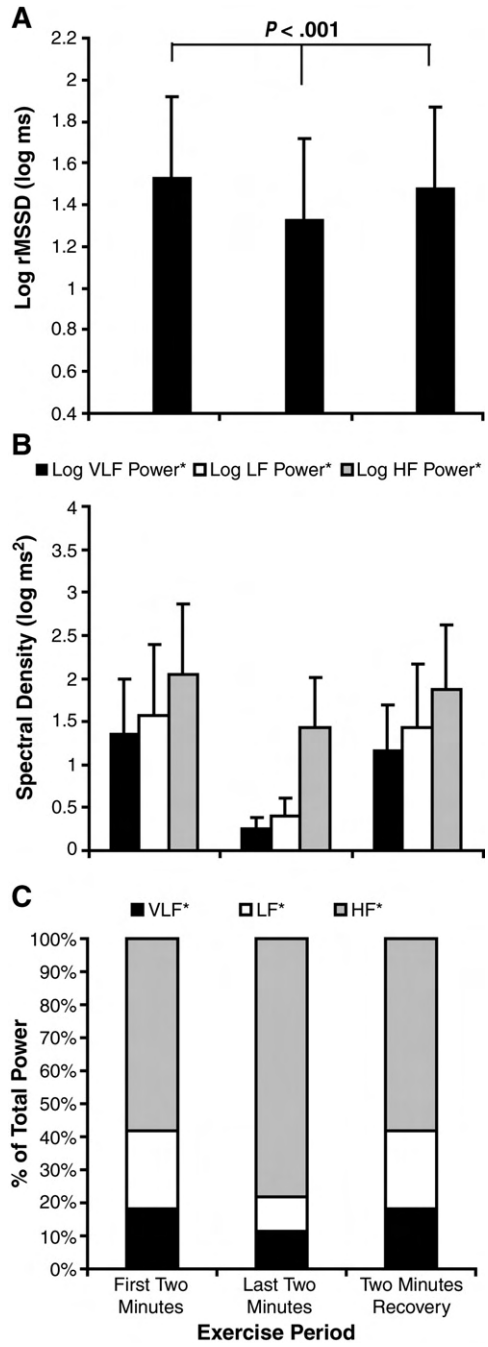
Variables that were nonnormally distributed (rMSSD, absolute HF, LF, and VLF power) were log-transformed before statistical analysis or, where more appropriate, are reported as median with interquartile range (number of premature ventricular complexes during exercise and recovery). Statistical analyses were performed using NCSS (NCSS, Kelseyville, UT) and the "Design" and "Hmisc" libraries in S-Plus version 7.0 (Insightful, Seattle, WA). A 2-sided P value of <.05 was considered statistically significant.

Results

Baseline characteristics and exercise test variables

Baseline characteristics are described in Table I. There were 133 (10%) deaths by the end of the follow-up period, and 53 (40%) of these deaths were due to cardiovascular causes. Survivors and subjects who died of noncardiovascular causes were significantly younger, had less prior coronary disease, less congestive heart failure, and less digoxin or β-blocker use than subjects who died of cardiovascular causes ($P < .05$).

Figure 2



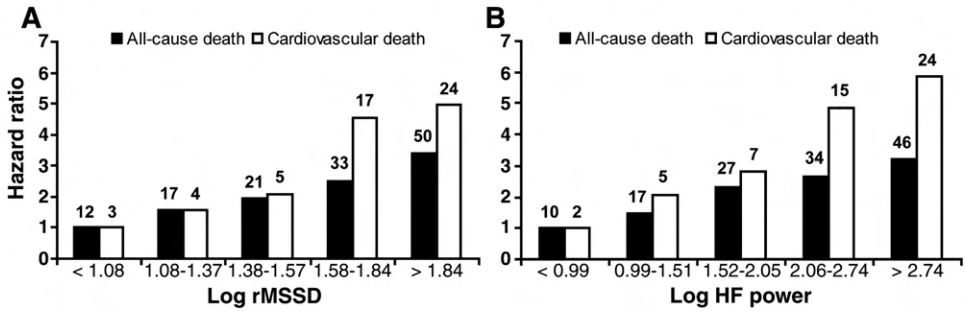
Time- and frequency-domain EI-HRV variables during exercise and recovery in all subjects. **A**, rMSSD; **B**, power spectral density of VLF, LF, and HF bands; and **C**, percentage of total power distributed to VLF, LF, and HF bands. Asterisk indicates $P < .05$ by analysis of variance among different exercise periods.

Table III. Association between EI-HRV and all-cause and cardiovascular mortality according to Cox regression analysis

		All-cause mortality			Cardiovascular mortality		
Variable	**Analysis**	**Hazard ratio* (95% CI)**	***P***	**Discriminative accuracy (C index)**	**Hazard ratio* (95% CI)**	***P***	**Discriminative accuracy (C index)**
Log rMSSD during peak exercise	Univariable	1.6 (1.4-1.8)	<.001	0.60	2.0 (1.6-2.6)	<.001	0.68
	Multivariable	1.4 (1.2-1.7)	<.001	0.56	1.7 (1.3-2.2)	<.001	0.61
Log rMSSD during recovery	Univariable	1.6 (1.4-1.8)	<.001	0.62	2.3 (1.8-3.1)	<.001	0.71
	Multivariable	1.5 (1.2-1.8)	<.001	0.56	1.8 (1.3-2.5)	<.001	0.62
LF power during recovery	Univariable	1.3 (1.1-1.5)	.001	0.54	1.5 (1.2-1.8)	.001	0.58
	Multivariable	1.3 (1.1-1.5)	.002	0.53	1.4 (1.1-1.7)	.01	0.55
Peak LF frequency during recovery	Univariable	1.3 (1.1-1.5)	.001	0.54	1.6 (1.3-2.0)	<.001	0.61
	Multivariable	1.1 (0.9-1.3)	NS	–	1.3 (1.0-1.7)	NS	–
LF% during recovery	Univariable	0.7 (0.6-0.8)	<.001	0.55	0.5 (0.4-0.8)	<.001	0.60
	Multivariable	0.7 (0.6-0.8)	.001	0.54	0.6 (0.4-0.8)	.003	0.58
Log HF power during recovery	Univariable	1.6 (1.4-1.9)	<.001	0.61	2.2 (1.7-2.8)	<.001	0.72
	Multivariable	1.4 (1.2-1.7)	<.001	0.56	1.8 (1.3-2.4)	<.001	0.62
HF% during recovery	Univariable	1.6 (1.3-1.9)	<.001	0.58	2.1 (1.5-2.9)	<.001	0.63
	Multivariable	1.5 (1.2-1.7)	<.001	0.56	1.8 (1.3-2.5)	.001	0.59
LF/HF ratio during recovery	Univariable	0.6 (0.4-0.8)	.001	0.54	0.3 (0.2-0.7)	.003	0.57
	Multivariable	0.6 (0.4-0.8)	.003	0.53	0.4 (0.2-0.8)	.01	0.56

Each parameter was evaluated in a separate multivariable model. The multivariable model included Duke treadmill score, heart rate increase, heart rate recovery at 2 minutes, and a clinical risk factor score (principle component of age, history of congestive heart failure, prior coronary disease, digoxin use, and β-blocker use). *C index*, Concordance index; *NS*, not significant.
*Hazard ratios shown are for an increase of 1 SD in each parameter.

Figure 3



Association between quintiles of EI-HRV variables and cardiovascular death according to multivariable Cox survival analysis. Log rMSSD during recovery (**A**) and log HF power during recovery (**B**). Numbers above each bar indicate the number of subjects. Each variable was evaluated in the same multivariable model as in Table III. The reference group in each case is the bottom quintile of each variable.

Exercise test variables for all groups are described in Table II. Survivors and subjects who died of non-cardiovascular causes achieved significantly greater Duke treadmill scores, had a greater heart rate increase with exercise, a greater drop in heart rate at 2 minutes of recovery, and fewer premature ventricular complexes during exercise or recovery than subjects who died of cardiovascular causes ($P < .05$).

Heart rate variability response to exercise in all subjects

The HRV response to exercise in all subjects is described in Figure 2. We observed a decrease in log rMSSD and in the spectral power of all 3 bands as exercise intensity increased (Figure 2, *A* and *B*). This was countered by an increase in log rMSSD and in spectral power during recovery ($P < .001$ among different exercise periods) (Figure 2, *A* and *B*). The fraction of power distributed to the HF band (HF%) increased in the last 2 minutes of exercise testing, whereas the fraction of power distributed to both VLF (VLF%) and LF (LF%) bands decreased relative to the first 2 minutes of exercise testing. There was an increase in VLF% and LF% during recovery relative to peak exercise, whereas HF% was lower during recovery than during peak exercise ($P < .001$ among different exercise periods) (Figure 2, *C*).

Table IV. Predictive power and discriminative accuracy for cardiovascular death of exercise test responses, clinical variables, and EI-HRV variables according to Cox regression analysis

Model variables	Predictive power (AIC)	Discriminative accuracy (C index)
Duke treadmill score	23.2	0.71
Duke treadmill score, age, history of congestive heart failure, prior coronary disease	58.2	0.78
Duke treadmill score, heart rate recovery, heart rate increase, age, history of congestive heart failure, prior coronary disease	58.1	0.77
Duke treadmill score, heart rate recovery, heart rate increase, age, history of congestive heart failure, prior coronary disease, log rMSSD during recovery	68.6	0.80
Duke treadmill score, heart rate recovery, heart rate increase, age, history of congestive heart failure, prior coronary disease, log HF power during recovery	69.1	0.81

AIC, Akaike information criterion (χ^2 scale).

β-Blocker use was associated with significantly higher log rMSSD, log HF power, and log LF power during peak exercise and higher log rMSSD, log HF power, and log LF power during recovery ($P < .05$).

Exercise-induced HRV variables and prognosis

Results of univariable and multivariable Cox survival analysis of EI-HRV variables are shown in Table III. After adjusting for confounders, greater log rMSSD during peak exercise and recovery were significantly associated with increased risks for all-cause and cardiovascular mortality ($P < .001$). Similarly, greater log HF power and HF% during recovery were significantly associated with increased all-cause and cardiovascular mortality ($P < .01$). Shorter period peak LF components, higher log LF power, and lower LF% and LF/HF ratios during recovery were significant predictors of increased all-cause mortality ($P < .01$); the peak LF frequency, LF%, and LF/HF ratio also predicted cardiovascular death ($P < .05$). These results were essentially unchanged by the substitution of all clinical variables that differed between survivors and subjects who died of cardiovascular causes (age, history of congestive heart failure, β-blocker use, digoxin use, and prior coronary disease) for the clinical risk factor score. Similarly, the inclusion of premature ventricular complex counts in the multivariable model did not affect these results.

Log rMSSD during recovery had the most accurate association with cardiovascular mortality of all time-domain EI-HRV variables, whereas log HF power during recovery was the most accurate frequency-domain predictor of cardiovascular death (Table III). The adjusted hazard ratio for all-cause and cardiovascular mortality increased progressively with each quintile of log rMSSD and log HF power during recovery, yielding a hazard ratio for cardiovascular death of 5.0 (95% CI 1.5-17.0) and 5.9 (95% CI 1.3-25.8) for the top quintiles of log rMSSD and log HF power, respectively (Figure 3). Both variables augmented the predictive power and discriminative accuracy of other exercise test variables and clinical risk factors in Cox survival analysis for cardiovascular death (Table IV). In the subpopulation without any premature ventricular complexes during recovery (n = 611), log rMSSD and log HF power during recovery had greater discriminative accuracy (concordance index 0.75 and 0.74 for log rMSSD and log HF power, respectively) than in the population as a whole.

Discussion

Time-domain EI-HRV variables and prognosis

In a novel investigation of the prognostic potential of EI-HRV, we found that greater short-term EI-HRV during peak exercise and recovery were associated with increased risks for all-cause and cardiovascular mortality after adjusting for potential confounders. These results contrast to results of resting HRV studies, which show that higher variability in beat-to-beat interval is associated with better prognosis.[12-16] At rest, higher R-R interval variability is thought to reflect a "healthy" cardiovascular response to autonomic control.[15] As has been previously observed,[21-23] our results suggest that exercise elicits a different pattern of autonomic and nonautonomic modulation of beat-to-beat intervals that is not easily accounted for by current explanations for resting HRV.

Frequency-domain EI-HRV variables and prognosis

After adjusting for potential confounders, we found that increased log HF power and HF%, shorter period peak LF components, lower LF%, and lower LF/HF ratios during recovery from clinical exercise testing were significantly associated with increased risks for all-cause and cardiovascular mortality. These results are surprising in that higher HF power at rest, which is thought to reflect parasympathetic modulation of heart rate, has been shown to be predictive of better prognosis.[12,17] Faster heart rate recovery from exercise testing, which is also postulated to partially reflect vagal tone, has been shown to be associated with better prognosis.[4-6] We found that faster heart rate recovery predicted better prognosis, as did lower HF HRV during recovery. These results add further support to previous studies[22-24] that illustrate the shortcomings of extending interpretations

of spectral parameters of HRV at rest to the setting of dynamic exercise.

Heart rate variability response to exercise in all subjects

In a large unselected cohort, we confirmed results[22,23] that R-R interval variability, as well as the spectral densities of all 3 bands, decreased as exercise intensity increased. We also confirmed observations by others[22,23] that HF%, which is thought to reflect relative parasympathetic influence on the sinoatrial node while at rest, significantly increased with increased exercise intensity. Furthermore, we found that HF% is lower in the first 2 minutes of recovery than in the last 2 minutes of dynamic exercise testing. As was previously concluded,[22-24] an extension of the resting paradigm for HF HRV is unsatisfactory to describe these changes in the HRV spectrum in response to exercise.

Implications for interpretation of HRV data during and after exercise

The pathophysiologic basis for our findings is uncertain. However, our data confirm previous observations[22-24] that current explanations for the physiologic genesis of time- and frequency-domain parameters of HRV at rest do not necessarily explain the HRV response to dynamic exercise testing. Interpretations of spectral analysis parameters of EI-HRV may be complicated by tonic autonomic activity during and after exercise and the nonstationary nature of the R-R interval time series. There are, however, possible alternative interpretations for these results. Others have postulated that nonneuronal mechanisms dominate the HRV spectrum at increasing workloads[23,24]; this may also be the case during recovery from dynamic exercise. Atrial stretch, direct mechanical oscillations related to increased respirations, and metaboreflexes have been proposed as possible nonneuronal determinants of HRV during and after exercise.[24,25] Differences in cardiovascular responses to these nonneuronal stimuli between survivors and nonsurvivors may have contributed to our findings.

Furthermore, at rest, very high HF and short-term HRV are thought to be related to sinus arrhythmia of nonrespiratory origin and have been associated with worse outcomes.[26] Accentuated sympathovagal antagonism at the sinoatrial node has been shown to contribute to nonrespiratory sinus arrhythmia.[27] During recovery from exercise testing, vagal activity antagonizes residual exercise-induced adrenergic activity, and these mechanisms likely contribute to HF and short-term HRV. Recently, time-domain measures of HRV over various short time intervals during recovery from exercise were shown to directly correlate with parasympathetic effect.[28] The authors also note greater HRV in subjects with coronary artery disease, who presumably had an ischemic response to exercise.[28] A high degree of heart rate pattern randomness induced by sympathovagal antagonism in the setting of ischemia might explain our observation of an association between greater HF and short-term HRV and increased cardiovascular mortality. Investigation into these and other nonlinear aspects of EI-HRV is warranted.

Lastly, although we excluded subjects whose recordings were dominated by ectopic beats, we analyzed all R-R intervals in the remaining subjects to simulate online exercise-testing analysis and to avoid uncertainty introduced by editing of ectopic beats.[29] Therefore, ectopy may have contributed to our findings. However, neither excluding subjects with premature ventricular complexes nor adjusting for premature ventricular complex counts in the multivariable Cox survival model significantly altered our results. In fact, the discriminative accuracy of both variables was improved upon exclusion of subjects with ectopy. More investigation into the relationships between exercise-induced ectopy, EI-HRV, and prognosis is warranted.

Study limitations

One of the main limitations of the study was the lack of resting electrocardiogram recordings for these subjects. This precluded comparison of EI-HRV markers with known resting HRV variables and prevented us from determining if the prognostic power of EI-HRV is independent of resting HRV measurements.

As this was a hypothesis-generating retrospective study, it was designed primarily to evaluate associations between EI-HRV and outcome. Prospective studies are needed to determine causative associations, elucidate the physiologic basis of our findings, and assess issues of measurement reproducibility. Furthermore, our study population was composed of predominantly male older subjects, and the results may not be generalizable to other populations.

These findings represent the results of preliminary EI-HRV analysis using newly developed methodology. In an attempt to address the nonstationary nature of the signal, we detrended the R-R interval series before time- and frequency-domain analysis. In doing so, R-R interval dynamics with the same periodicity as the heart-rate decay curve may be lost. It is possible that different analytical windows and alternative detrending, filtering, and frequency domain transformation methods may provide more prognostic information. More investigation into the methodological aspects of EI-HRV analysis is warranted.

Current methodological limitations forced us to exclude patients with frequent ectopy during the exercise period. These subjects had a higher overall cardiovascular mortality rate during follow-up than subjects included in the survival analysis (5.3% vs 4.0%), and frequent ectopy during exercise has been associated

with worse prognosis.[30] More satisfactory methods for dealing with ectopic beats during spectral analysis are needed to allow investigation of prognostic implications of EI-HRV in patients with ectopy.

Conclusions

This novel analysis of EI-HRV data and outcome yields a simple, noninvasive method for predicting the risk of cardiovascular mortality that augments existing exercise-testing criteria. With prospective confirmation of these findings and additional refinement, this analytical methodology could be easily integrated into computer-based diagnostic exercise-testing systems that are currently available.

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