Autonomic Markers as Predictors of Nonfatal Acute Coronary Events after Myocardial Infarction

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Background: Autonomic markers, such as heart rate variability (HRV), heart rate turbulence (HRT), and baroreflex sensitivity (BRS) provide information on the risk of all-cause mortality after an acute myocardial infarction (AMI), but their value in predicting nonfatal cardiac events is not well known.

Methods: A consecutive series of 675 patients with an AMI were followed up to 30 months. At baseline, the patients underwent a 24-hour Holter recording, and assessment of BRS using phenylephrine test. Several parameters of HRV and HRT were determined.

Results: After the follow-up, 98 patients (15%) had a nonfatal acute coronary event. Among the studied variables, the short-term scaling exponent alpha1 ($P = 0.002$), power-law slope beta ($P = 0.008$), low-frequency component of HRV power spectrum ($P < 0.001$), turbulence slope ($P < 0.001$), and BRS ($P < 0.001$) had the strongest association with the occurrence of nonfatal acute coronary events in univariate comparisons. After adjustment with relevant clinical variables (such as age, gender, ejection fraction, functional class, medication, diabetes) in the Cox proportional hazards model, alpha1 and beta remained as statistically significant predictors of nonfatal acute coronary events (HR = 2.0 [1.2–3.2, 95% CIs, $P = 0.006$] for alpha1 ≤ 1.025), (HR = 1.9 [1.2–3.1, $P = 0.008$] for beta ≤ -1.507).

Conclusion: Several autonomic markers provide information on the risk of recurrent nonfatal coronary events after an AMI. Altered fractal heart rate behavior seems to be the strongest independent predictor of such events.

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heart rate; heart rate variability; heart rate turbulence; baroreflex sensitivity; myocardial infarction

Several autonomic markers, such as heart rate variability (HRV), heart rate turbulence (HRT), and baroreflex sensitivity (BRS), predict mortality in postinfarction patients.[1–3] However, data about their value in predicting nonfatal cardiac events after an acute myocardial infarction (AMI) are limited.[4] Unlike sudden cardiac deaths,[5,6] recurrent coronary events in general postinfarction populations are not rare in the current treatment era. It would be important to recognize the patients who are at the highest risk for recurrent acute coronary events. These patients could be selected for most advanced invasive and drug treatment strategies including sustained effective antithrombotic, aggressive lipid lowering, and long-acting angiotensin converting enzyme-inhibiting therapies. Therefore, this study was aimed to assess the value of autonomic markers (HRV, HRT, and BRS) in predicting the risk of recurrent acute coronary events during a follow-up of a consecutive series of patients with an AMI.

METHODS

Study Population

A single-center, prospective follow-up study, the Multiple Risk Factor Analysis Trial (MRFAT),[7,8] included a consecutive series of patients with AMI during the first 7 days after the initial event. The details of the study have been published previously.[7,8] The diagnosis of AMI was confirmed according to modern guidelines.[8] The patients were excluded, if they were older than 75 years, had unstable angina at recruitment, dementia, alcoholism, drug abuse,

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nonsinus rhythm, or were unable to give an informed consent. If a patient underwent coronary bypass operation before discharge or died during the hospital stay, he/she was not included in the analysis. The Ethical Committee of the University of Oulu approved the study protocol, and all patients were required to give an informed consent. A special emphasis was put on optimizing cardiac medication, particularly beta-blocker therapy, by the time of discharge. The study initially included 700 patients with AMI.

Left Ventricular Function

Left ventricular systolic function was measured with two-dimensional echocardiography from 2 to 7 days after AMI using methodology that has been described in detail previously.[8]

Electrocardiographic Recordings

The patients had a 24-hour ECG recording between days 5 and 14 after AMI using an Oxford Medilog system (Oxford Medilog 4500, Oxford Medical Ltd., Oxford, United Kingdom).

Analyses of Autonomic Markers

The standard deviation of all NN intervals (SDNN) measured from the 24-hour recording, and low-frequency (LF) and high-frequency (HF) components of the HRV power spectrum using standard techniques,[9] were determined as conventional measurements of HRV. The detrended fluctuation analysis was used to calculate the short-term scaling exponent α_1. In this technique, the variability of integrated and detrended time series is measured in observation windows of different sizes and shown as a function of the size of the observation window on a log-log scale. The short-term scaling exponent α_1 describes the short-term (<11 beats) fractal-like scaling properties of the RR interval time series. The details of the method have been published previously.[10–12] For estimating the long-term fractal heart rate behavior, the power-law slope β was determined. A plot of spectral power and frequency on a log-log scale shows linear portion between 10^{-4} and 10^{-2} Hz. The slope of this relationship describes long-term scaling characteristics of HRV in the region of the ultralow- and very-low-frequency bands. The details of the method are described elsewhere.[13,14] HRV was analyzed from 89% of the follow-up patients.

Turbulence slope (TS) was analyzed as a measure of HRT. TS was calculated as the highest slope of the regression line over any of the five successive sinus beat RR intervals during first 15 sinus beat RR intervals after a ventricular premature depolarization. The analysis was done from the averaged RR intervals following the ventricular premature depolarizations. The details of the method have been published previously.[2,15] HRT could be analyzed from 83% of the follow-up patients.

BRS was measured as the rate-pressure response to intravenous phenylephrine using the methodology described in detail elsewhere.[16] The analysis was done between the days 5 and 21 after the AMI for 69% of the follow-up patients.

Follow-Up and End Points

For the occurrence of nonfatal acute coronary events, the patients were followed up to 30 months after the AMI. A nonfatal acute coronary event was defined as a recurrent acute myocardial infarction or unstable angina pectoris, which did not result in death. A recurrent myocardial infarction was confirmed according to same guidelines that were used for the initial event.[8] The first recurrent nonfatal acute coronary event during the follow-up period was considered as a primary endpoint of this analysis. Total mortality was also analyzed during the follow-up period for comparing the predictive power of the autonomic markers between nonfatal acute coronary events and all-cause mortality as endpoints.

Statistical Analysis

The SPSS statistical software (version 11.5, SPSS Inc., Chicago, IL, USA) was used in the analysis of the data. Statistical significances of differences in continuous clinical variables and autonomic markers between patients with and without recurrent acute coronary events during the follow-up were assessed using the standard *t*-test. The chi-square test was used for studying the statistical significances of the differences in categorical variables between the patients with and without the primary endpoint. The receiver operator characteristics (ROC) curve analysis was used to evaluate the accuracy of the autonomic markers in predicting recurrent coronary events, and to determine optimal cut points of these markers at the sensitivity range from 25% to 50%. The Kaplan-Meier curves were computed

to show cumulative proportional probabilities of recurrent nonfatal acute coronary events and all-cause mortality in patients with and without unfavorable values of autonomic risk markers. The log rank test was used to assess the statistical significance of the differences between the curves. The multivariate Cox regression analysis was used to adjust the autonomic risk markers to age and gender and other risk variables. The correlations between the autonomic risk markers were estimated by analyzing the Pearson correlation coefficients. A P value < 0.05 was considered to be statistically significant.

RESULTS

Of the 700 patients, 675 were discharged alive. After these 675 patients were followed up to 30 months, 98 (15%) patients had experienced a nonfatal acute coronary event (20 ± 12 months follow-up on average), and 68 (10%) had died (28 ± 6 months follow-up on average). The clinical characteristics of the patients with and without a recurrent coronary event during the follow-up are shown in Table 1. The patients who had an acute coronary event during follow-up, were significantly older, more often of female sex, had significantly worse functional class, and more frequently having diabetes than patients without such an event. Patients with a recurrent coronary event were statistically significantly more frequently on warfarin, digitalis, and calcium-blocker therapy compared with the patients without a recurrent coronary event.

Autonomic Markers as Predictors of Recurrent Acute Coronary Events

The values of LF, the power-law slope β, the short-term scaling exponent α_1, TS, and BRS were statistically significantly lower in patients with a recurrent acute coronary event compared to the patients without such an event during the follow-up (Table 2). All these autonomic markers, except LF, also showed significant association with the occurrence of recurrent coronary events in a univariate Cox regression analysis (Table 3). After adjustment with relevant clinical variables, such as age, gender, ejection fraction, functional class, diabetes, and medication, in the Cox proportional hazards model, the short-term scaling exponent α_1 and the

Table 1. Clinical Characteristics of the Study Patients with and without a Recurrent Acute Coronary Event during the Follow-Up

	Without Recurrent Coronary Event (n = 577)	With Recurrent Coronary Event (n = 98)	P
Age (years)	61 ± 10	66 ± 9	<0.001
Male/female	439/138 (76%/24%)	64/34 (65%/35%)	0.02
Ejection fraction (%)	45 ± 9	44 ± 9	0.10
NYHA class, I/II/III	411/107/59 (71%/19%/10%)	55/21/22 (56%/21%/23%)	<0.01
History			
Diabetes	123 (21%)	36 (37%)	<0.01
Previous AMI	118 (20%)	28 (29%)	0.07
Hypertension	280 (49%)	53 (54%)	0.32
Smoking	385 (67%)	71 (72%)	0.26
Type of AMI, Q/non-Q/Int	291/245/41 (50%/43%/7%)	41/50/7 (42%/51%/7%)	0.42
Location of AMI, Ant/Inf/Int	257/249/71 (45%/43%/12%)	50/33/15 (51%/34%/15%)	0.08
Medication			
β-blockers	559 (97%)	92 (94%)	0.06
Statins	200 (35%)	36 (37%)	0.72
Aspirin	483 (84%)	75 (77%)	0.06
Warfarin	60 (10%)	17 (17%)	0.04
ACE/ATII-inhibitors	217 (38%)	46 (47%)	0.09
Diuretic drugs	138 (24%)	32 (33%)	0.07
Digitalis	31 (5%)	12 (12%)	<0.05
Ca-blockers	37 (6%)	16 (16%)	<0.01
Amiodarone	9 (2%)	3 (3%)	0.30

The values are means ± SD or the number of the patients. ACE = angiotensin-converting enzyme; AMI = acute myocardial infarction; ATII = angiotensin II; Ca = calcium; NYHA = New York Heart Association; Q/non-Q/Int = Q-wave/non-Q-wave/Indeterminate.

Table 2. Autonomic Markers in Study Patients

	Without Recurrent Coronary Event (n = 577)	With Recurrent Coronary Event (n = 98)	P
Heart rate (Holter-based)	57.8 ± 10.4	57.3 ± 11.9	0.65
HRV			
SDNN (ms)	97 ± 32	91 ± 35	0.14
HF (ms^2)	258 ± 541	193 ± 212	0.053
LF (ms^2)	474 ± 627	305 ± 332	<0.001
Power-law slope β	−1.30 ± 0.19	−1.38 ± 0.24	0.008
Short-term scaling exponent α_1	1.23 ± 0.23	1.12 ± 0.33	0.002
HRT			
Turbulence slope (ms/NN)	5.65 ± 6.09	3.81 ± 3.91	<0.001
BRS			
Rate-pressure response (ms/mmHg)	9.38 ± 8.45	6.20 ± 5.27	<0.001

The values are means ± SD. BRS = baroreflex sensitivity; HF = high-frequency component of heart rate variability (HRV) power spectrum; HRT = heart rate turbulence; LF = low-frequency component of HRV power spectrum; NN = normal-to-normal RR interval; SDNN = the standard deviation of all NN intervals. Look in the Methods section for details.

power-law slope β remained as statistically significant predictors of nonfatal acute coronary events (Table 3).

Accuracy of Autonomic Markers in Predicting Nonfatal Coronary Events

When optimal cutpoints were defined from the ROC curves at the sensitivity level from 25% to 50% for the Kaplan-Meier curve analysis, α_1, β, TS, and BRS, all had a statistically significant power in discriminating the patients with and without recurrent coronary events during the follow-up (Figs. 1–2). The fractal measure of HRV, the short-term scaling exponent α_1 in particular, performed the best in separating the patients with and without acute coronary events at this sensitivity level. In the ROC curve analysis, all the four above-mentioned autonomic markers had a similar overall accuracy in predicting recurrent acute coronary events (Figs. 3–4). However, the fractal measures of HRV, the short-term scaling exponent α_1 in particular, performed somewhat better at high specificity, and TS and BRS at high sensitivity levels. The overall accuracy of the fractal measures of HRV and TS in predicting all-cause mortality was somewhat better than in predicting recurrent coronary events (Figs. 3–4). However, at the optimal cutpoint for coronary events in the sensitivity range from 25% to 50%, the predictive accuracy of the short-term scaling exponent for acute coronary events and all-cause mortality was similar (Figs. 1 and 2).

Associations between the Autonomic Markers

The correlations between the fractal measures of HRV, LF, TS, and BRS are shown in Table 4. All these autonomic markers had a significant, but relatively weak correlation with each other. The short-term scaling exponent α_1 and the power-law slope β had somewhat closer relationship to each other,

Table 3. Autonomic Markers as Univariate and Multivariate Predictors of Recurrent Coronary Events

	Univariate Analysis			Multivariate Analysis		
Autonomic Markers	**HR**	**95% CI**	**P**	**HR**	**95% CI**	**P**
LF ≤ 139 ms^2	1.38	(0.88–2.14)	0.16	0.88	(0.55–1.42)	0.60
Power-law slope $\beta \leq -1.507$	2.45	(1.54–3.89)	<0.001	1.92	(1.19–3.12)	0.008
Short-term scaling exponent $\alpha_1 \leq 1.025$	3.04	(1.96–4.73)	<0.001	1.98	(1.21–3.22)	0.006
Turbulence slope ≤ 1.3 ms/NN	1.67	(1.05–2.66)	0.03	1.24	(0.77–2.00)	0.39
BRS ≤ 2.63 ms/mmHg	2.21	(1.25–3.90)	0.007	1.34	(0.72–2.50)	0.35

HR = Hazards ratios obtained from the Cox regression. CI = confidence intervals. Other abbreviations are same as in Table 2.

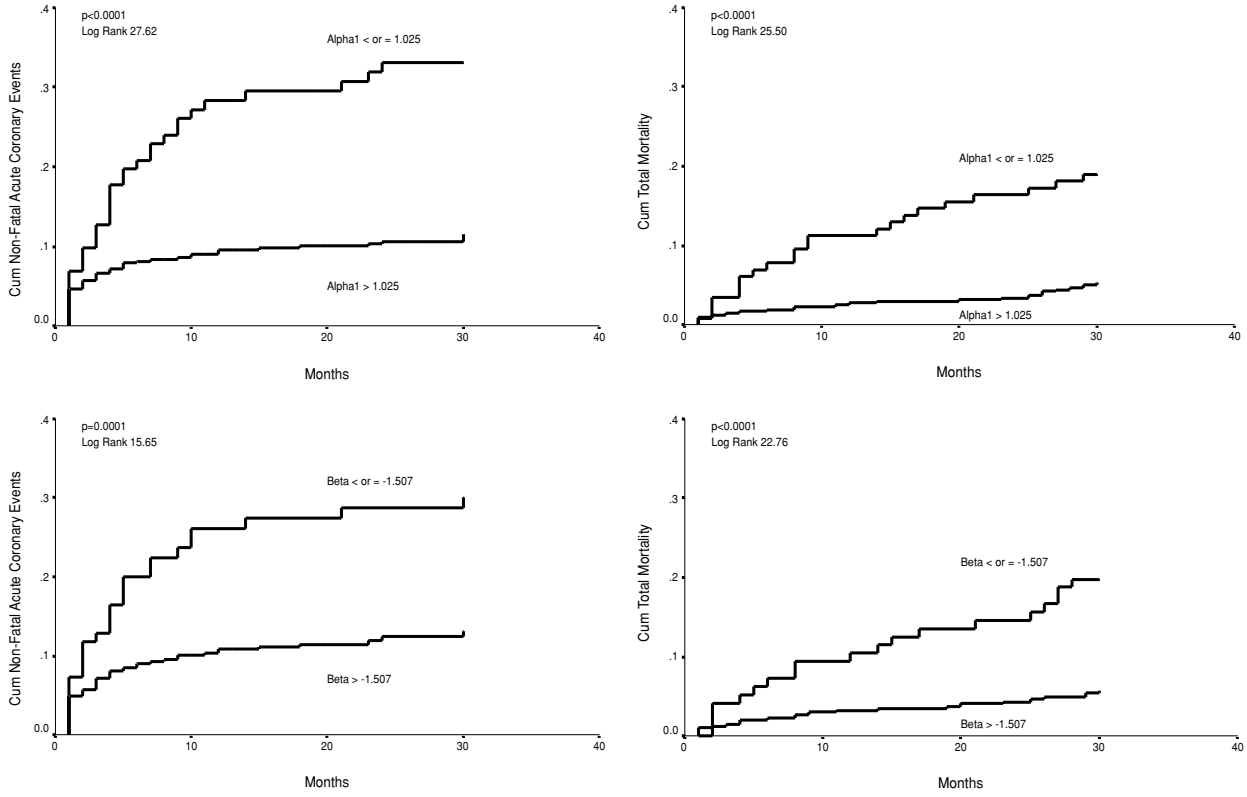

Figure 1. Cumulative proportional probability of nonfatal acute coronary events for patients with the short-term scaling exponent alpha1 $\leq$ or $>$ 1.025 (upper left chart), for patients with the power-law slope beta $\leq$ or $>$ -1.507 (lower left chart). Cumulative proportional probability of all-cause mortality for patients with the short-term scaling exponent alpha1 $\leq$ or $>$ 1.025 (upper right chart), for patients with the power-law slope beta $\leq$ or $>$ -1.507 (lower right chart).

and LF, TS, and BRS to each other than to the other autonomic markers.

DISCUSSION

This analysis shows that several autonomic markers, including the short-term and long-term fractal measures of HRV, HRT, and BRS, predicted the occurrence of nonfatal recurrent acute coronary events during the follow-up of consecutive series of survivors with AMI of whom the vast majority was on beta-blocking medication. The short-term scaling exponent α_1, and the power-law slope β, retained their predicting power after adjusting with relevant clinical variables suggesting that the altered fractal heart rate behavior yields important independent information about the risk of nonfatal acute coronary events in postinfarction patients.

Heart Rate Variability and Cardiac Events

Several studies have shown that impaired HRV predicts mortality in postinfarction patients.[17–19] However, the value of HRV parameters in predicting nonfatal cardiac events is not well known. Tsuji et al. evaluated the impact of reduced HRV on risk for cardiac events in a community-based population free of clinically apparent coronary artery disease or congestive heart failure.[4] They used conventional measures of HRV and found that decreased HRV was significantly associated with the risk for a cardiac event, which was defined as angina pectoris, myocardial infarction, coronary heart disease death, or congestive heart failure. Their findings can be partly explained by the notion that decreased HRV may reflect subclinical cardiac disease. Our follow-up study included patients with AMI. Therefore our findings cannot be attributed to the detection of occult coronary artery disease by

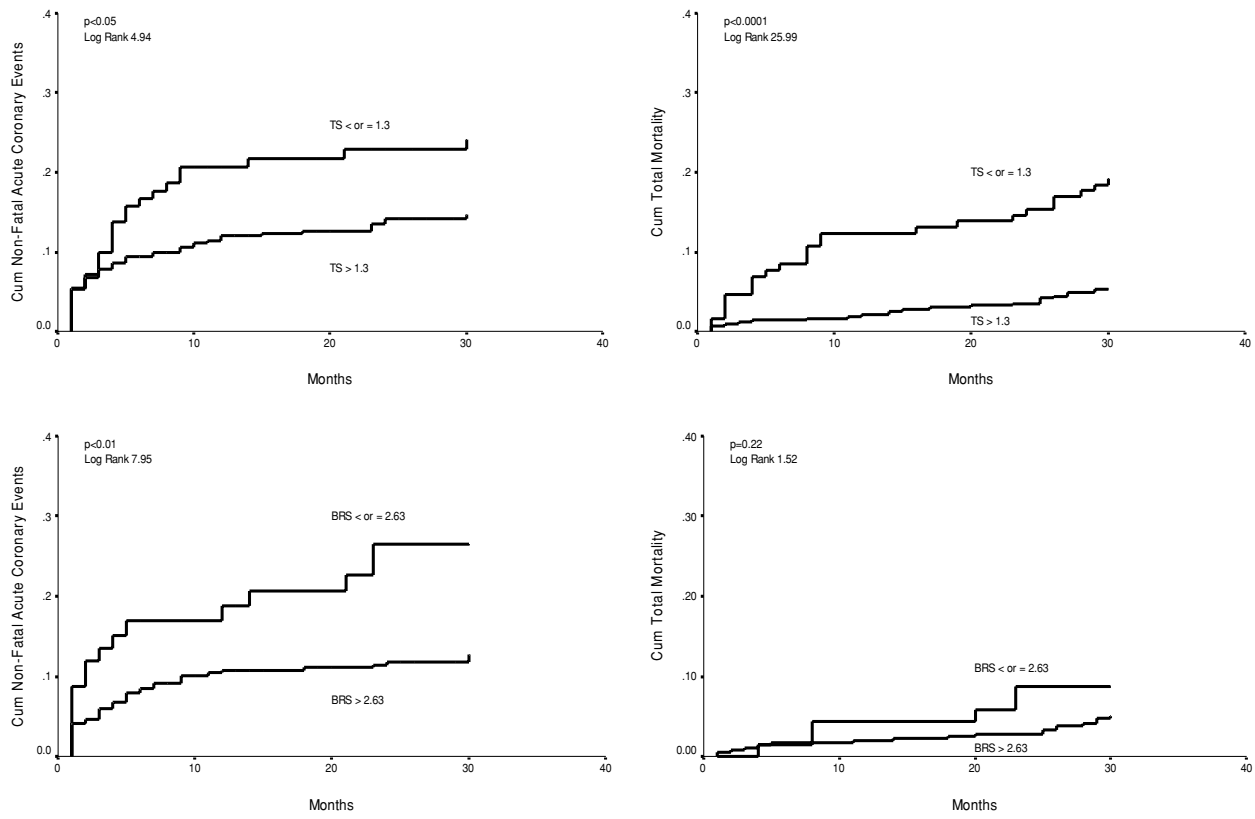

Figure 2. Cumulative proportional probability of nonfatal acute coronary events for patients with the turbulence slope (TS) ≤ or > 1.3 ms/NN (upper left chart), for patients with the baroreflex sensitivity (BRS) ≤ or > 2.63 ms/mmHg (lower left chart). Cumulative proportional probability of all-cause mortality for patients with the turbulence slope (TS) ≤ or > 1.3 ms/NN (upper right chart), for patients with the BRS ≤ or > 2.63 ms/mmHg (lower right chart).

reduced HRV. However, the analysis of HRV can give an insight into the progression of focal coronary atherosclerosis,[20] a phenomenon that may be a mechanistic link between the association of impaired HRV and increased occurrence of recurrent coronary events in the present patients with AMI.

Among the studied autonomic markers, only the short-term scaling exponent α_1 and the power-law slope β, remained statistically significant predictors of nonfatal acute coronary events after adjusting with clinical variables. This finding supports the concept that altered fractal heart rate behavior may reveal more delicate pathophysiological disturbances in relation to the risk for recurrent coronary events than can be detected by conventional measures of HRV, HRT, or BRS. Recent experiments in healthy subjects show that sympathetic activation in the presence of enhanced vagal outflow results in decreased short-term fractal organization of heart rate dynamics represented by lower values of the short-term scaling exponent α_1.[21] This observation supports the view that short-term fractal heart rate behavior is determined by sympathovagal interaction also in pathological conditions, such as myocardial infarction. The short-term scaling exponent has a relatively good correlation with the LF/HF ratio in controlled recording conditions, but the association is weak in ambulatory 24-hour recording conditions.[22] In patients with extensive myocardial infarction, LF is usually reduced and HF relatively preserved or only slightly decreased resulting also in a decreased short-term scaling exponent.[23] In this study, the patients who experienced a nonfatal coronary event during the follow up had significantly lower LF compared to the patients without such an event. This may indicate more extensive myocardial infarction/more advanced coronary heart disease in patients who had a recurrent coronary event.

The mechanism why autonomic markers predict mortality after AMI has not been clear. Most often, altered autonomic regulation has been

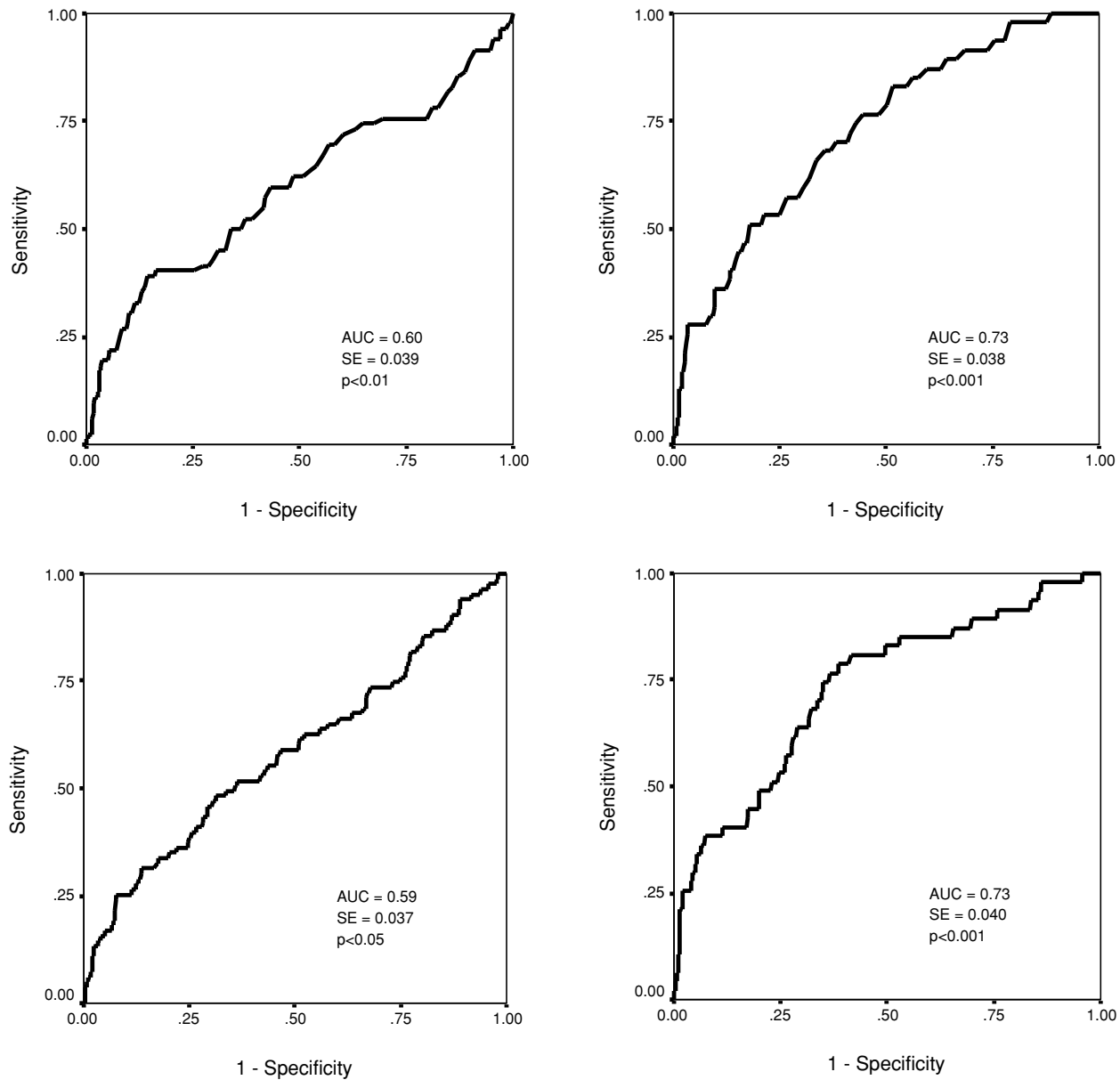

Figure 3. Receiver operator characteristics (ROC) curve for the short-term scaling exponent α_1 in predicting nonfatal acute coronary events (upper left chart) and all-cause mortality (upper right chart). The ROC curve for the power-law slope β in predicting nonfatal acute coronary events (lower left chart) and all-cause mortality (lower right chart). AUC = area under the curve; SE = standard error.

considered to be associated with vulnerability to fatal arrhythmias.[1] This study provides further insight into the possible mechanistic link. It seems plausible to speculate that altered autonomic regulation increases the risk of acute complications of atherosclerotic plaques, leading either to a nonfatal coronary event, sudden death, or even to progressive heart failure.

Heart Rate Turbulence and Baroreflex Sensitivity as Predictors of Cardiac Events

HRT is considered to be a measure of the autonomic response to perturbations of blood pressure after single ventricular premature depolarization and to be significantly associated with BRS.[2,15,24]

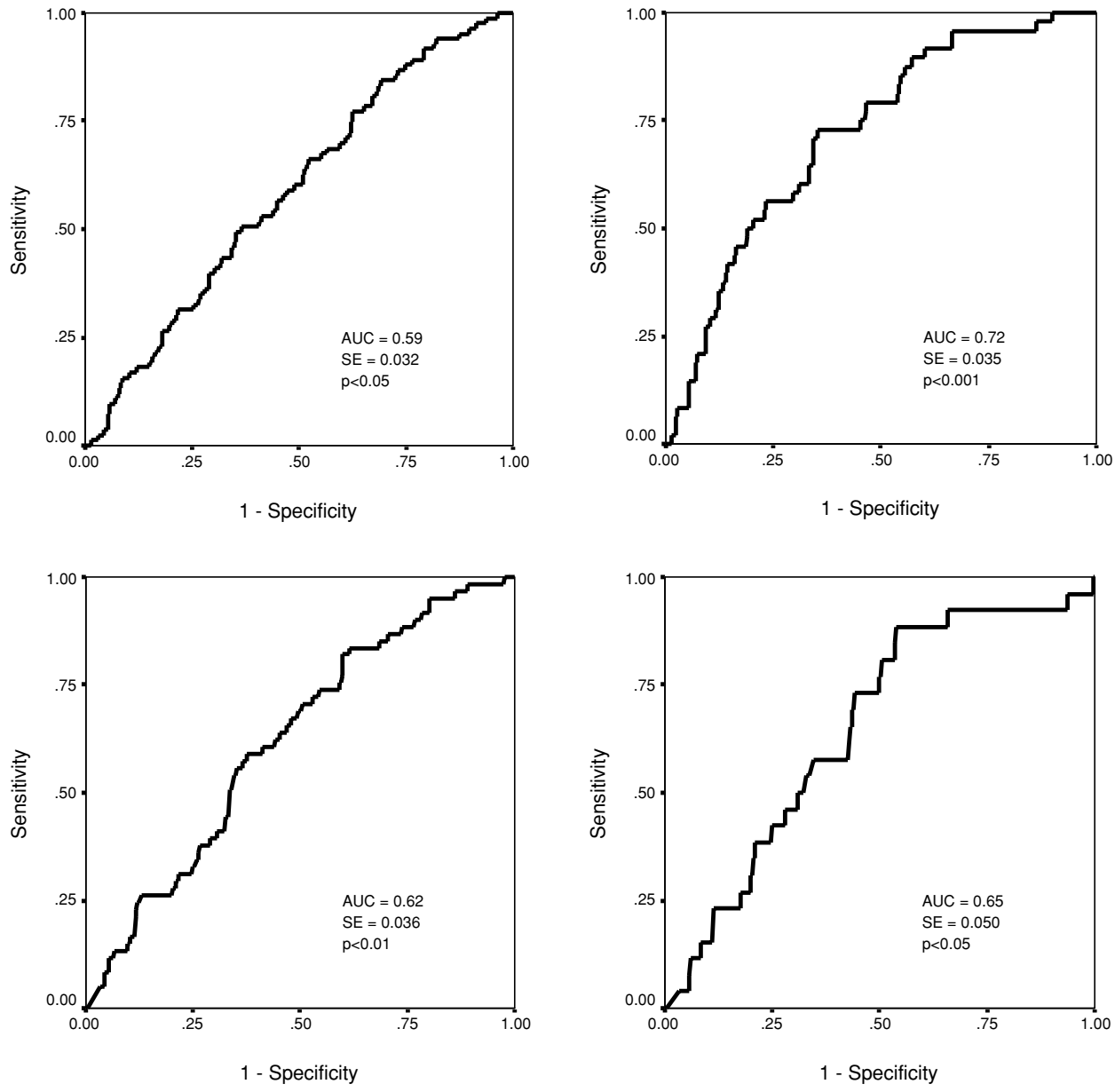

Figure 4. Receiver operator characteristics (ROC) curve for the turbulence slope in predicting nonfatal acute coronary events (upper left chart) and all-cause mortality (upper right chart). The ROC curve for the baroreflex sensitivity in predicting nonfatal acute coronary events (lower left chart) and all-cause mortality (lower right chart). AUC = area under the curve; SE = standard error.

In our study, there was a significant, but relatively weak correlation between HRT and BRS. Both HRT and BRS are known to predict mortality after AMI.[2,3,6,15,25] However, data on their value in predicting nonfatal coronary events are very limited. In this study, both HRT and BRS were significant predictors of recurrent acute coronary events in patients with AMI. HRT and BRS had a similar overall accuracy in predicting coronary events compared to the fractal HRV measures. However, the fractal measures of HRV, the short-term scaling exponent in particular, performed better at high specificity levels, especially when the cut-point was optimized. In addition, HRT and BRS did not remain as significant predictors of coronary events after adjusting with clinical variables. All the four

Table 4. Associations of the Autonomic Markers with Each Other in the Study Population

	LF	β	α_1	TS	BRS
LF		0.27†	0.11*	0.38†	0.44†
β	0.27†		0.36†	0.30†	0.24†
α_1	0.11*	0.36†		0.23†	0.17†
TS	0.38†	0.30†	0.23†		0.34†
BRS	0.44†	0.24†	0.17†	0.34†	

The values are Pearson's correlation coefficients. α_1 = the short-term scaling exponent, β = the power-law slope; BRS = baroreflex sensitivity; LF = the low-frequency component of heart rate variability power spectrum; TS = turbulence slope. * = $P < 0.05$, † = $P < 0.001$.

above-mentioned autonomic markers, except BRS, had somewhat better accuracy in predicting all-cause mortality than in predicting coronary events. However, at the cutpoint optimized for coronary events, the predicting power of the short-term scaling exponent was similar for nonfatal acute coronary events and all-cause mortality.

Potential Clinical Implications and Study Limitations

High-risk postinfarction patients with severely depressed left ventricular function benefit from a prophylactic implantable cardioverter-defibrillator therapy.[26] Although the vast majority of sudden cardiac deaths occurs in patients with relatively well-preserved left ventricular function, it is difficult to identify these patients in advance as the annual incidence of sudden cardiac death is under 1% in general AMI populations during the modern treatment era.[5,6] As shown in this study, nonfatal acute recurrent coronary events are much more common in patients with AMI. Identifying the patients at highest risk of recurrent coronary events for optimal treatments, would prevent some of these patients to shift toward more higher-risk categories with need for device therapies. If the present findings can be confirmed in other follow-up studies, the autonomic markers, the short-term fractal heart rate behavior in particular, could serve as markers for the risk of recurrent acute coronary events in patient with AMI.

Autonomic markers may have different value in predicting cardiac events in patients with and without preserved left ventricular function.[6] Due to limited number of patients with depressed left ventricular function, we were not able to do subgroup analyses in the present AMI population. Somewhat smaller proportion of patients had BRS testing, which may cause a potential bias in terms of predictive accuracy of this parameter in this analysis.

CONCLUSION

Several autonomic markers predict nonfatal recurrent acute coronary events after AMI. Breakdown of heart rate fractal organization seems to be the most powerful independent predictor of such events.

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