Fractal Analysis of Heart Rate Dynamics as a Predictor of Mortality in Patients With Depressed Left Ventricular Function After Acute Myocardial Infarction

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A number of new methods have been recently developed to quantify complex heart rate (HR) dynamics based on nonlinear and fractal analysis, but their value in risk stratification has not been evaluated. This study was designed to determine whether selected new dynamic analysis methods of HR variability predict mortality in patients with depressed left ventricular (LV) function after acute myocardial infarction (AMI). Traditional time- and frequency-domain HR variability indexes along with short-term fractal-like correlation properties of RR intervals (exponent α) and power-law scaling (exponent β) were studied in 159 patients with depressed LV function (ejection fraction <35%) after an AMI. By the end of 4-year follow-up, 72 patients (45%) had died and 87 (55%) were still alive. Short-term scaling exponent α (1.07 ± 0.26 vs 0.90 ± 0.26, p <0.001) and power-law slope β (−1.35 ± 0.23 vs −1.44 ± 0.25, p <0.05) differed between survivors and those who died, but none of the traditional HR variability measures differed between these groups. Among all analyzed variables, reduced scaling exponent α (<0.85) was the best univariable predictor of mortality (relative risk 3.17, 95% confidence interval 1.96 to 5.15, p <0.0001), with positive and negative predictive accuracies of 65% and 86%, respectively. In the multivariable Cox proportional hazards analysis, mortality was independently predicted by the reduced exponent α (p <0.001) after adjustment for several clinical variables and LV function. A short-term fractal-like scaling exponent was the most powerful HR variability index in predicting mortality in patients with depressed LV function. Reduction in fractal correlation properties implies more random short-term HR dynamics in patients with increased risk of death after AMI.   ©1999 by Excerpta Medica, Inc.

(Am J Cardiol 1999;83:836–839)

Conventional time- and frequency-domain measurements of heart rate (HR) variability provide prognostic information on patients after acute myocardial infarction (AMI),[1–4] but the utility of various HR variability measurements has not been well defined in patients with depressed left ventricular (LV) function. A number of new methods based on nonlinear dynamics and fractal analysis ("chaos theory") have been recently developed to quantify HR dynamics.[5,6] Preliminary studies have suggested their utility in providing information on prognosis in patients with heart failure[7] and in assessing vulnerability to life-threatening arrhythmias.[8] The present study was designed to assess the utility of selected dynamic analysis methods of HR variability in predicting mortality in a population of patients with AMI and depressed LV function. In particular, we sought to determine whether these new measurements of HR behavior (based on fractal scaling) add prognostic information to conventional indexes in predicting death during long-term follow-up.

METHODS

Patients: Patients for this study were selected from the TRAndolapril Cardiac Evaluation (TRACE) population, including patients with AMI and LV wall motion index <1.2 (ejection fraction <35%).[9,10] This substudy comprised 193 patients in whom 24-hour ambulatory electrocardiographic recordings were performed in 1 of the participating centers of this multicenter trial. Twenty-four-hour Holter recordings were performed 3 to 7 days after AMI. The TRACE study was a double-blind, placebo-controlled study in which patients were randomized to oral trandolapril or placebo. Details of enrollment and baseline variable measurements have been described previously.[9,10] All patients in this substudy were drawn from the placebo group. Of the 193 eligible patients, results on 159 are reported. Thirty-four patients were excluded because of signal artifacts (n = 12), unsuccessful data collection (n = 13), or frequent arrhythmias (n = 9).

TABLE I Baseline Clinical and Heart Rate Variables of the Subjects Who Died by the End of the 4-Year Follow-up and Those Who Had Remained Alive

Clinical data (n = 159):	Alive (n = 87)	Dead (n = 72)	p Value
Age (yrs)	61 ± 11	69 ± 8	<0.001
Men/women	72/15	50/22	<0.05
NYHA Functional class II–IV (%)	59 (68%)	30 (42%)	<0.01
Prior AMI	18 (21%)	27 (38%)	<0.05
Angina pectoris	30 (34%)	39 (54%)	<0.05
Thrombolytic therapy	52 (60%)	33 (46%)	NS
Diuretic treatment	44 (51%)	62 (86%)	<0.001
β blocker treatment	28 (32%)	9 (13%)	<0.01
Ambulatory ECG data			
Average RR interval (ms)	755 ± 146	743 ± 148	NS
SDNN (ms)	86 ± 28	91 ± 10	NS
ULF power (ms^2)	5,911 ± 5,115	6,160 ± 7,968	NS
VLF power (ms^2)	565 ± 491	650 ± 1,210	NS
LF power (ms^2)	308 ± 467	263 ± 488	NS
HF power (ms^2)	221 ± 366	268 ± 488	NS
β	−1.35 ± 0.23	−1.44 ± 0.25	<0.05
α	1.07 ± 0.25	0.90 ± 0.26	<0.001
VPCs/hour	26 ± 62	71 ± 140	<0.05

EGG = electrocardiographic; HF = high frequency; LF = low frequency; SDNN = standard deviation of all RR intervals; ULF = ultra-low frequency; VLF = very low frequency; VPCs = ventricular premature complexes; α = short-term fractal-like scaling exponent from detrended fluctuation analysis; β = power-law scaling exponent of long-term heart rate variability.
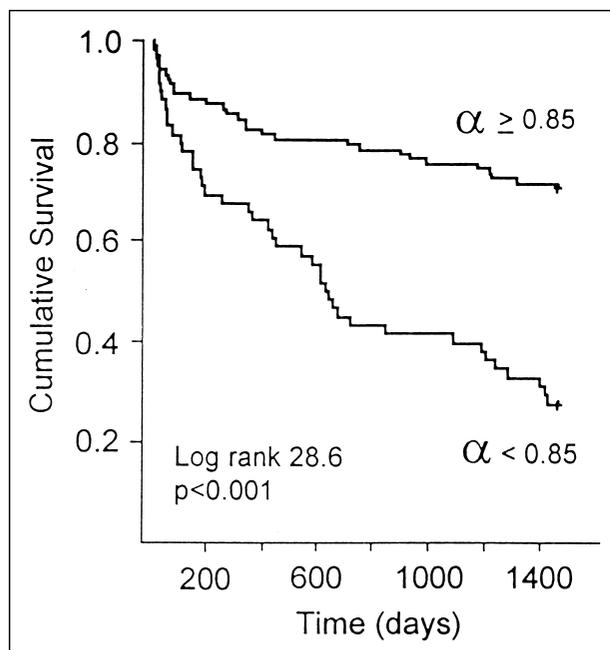

FIGURE 1. Kaplan-Meier survival curves for the subjects with the short-term fractal-like scaling exponent (α) <0.85 or ≥0.85. The estimated cumulative survival rate over a 4-year period was 70% in those with an exponent ≥0.85 and 28% in those with an exponent <0.85.

Ambulatory electrocardiographic recordings and analysis of heart rate variability: All the subjects were monitored for 24 hours with a Holter recorder. After transfer of the electrocardiographic data to microcomputer, the RR interval series were edited both manually and automatically.[11,12] Premature beats and artifacts were deleted with previously described methods.[11,12] Only recordings with qualified beats for at least a 20-hour period and with >85% of qualified sinus beats were included in the analysis of HR dynamics.

The SD of all normal-to-normal RR intervals (SDNN) and geometric HR variability index were computed as standard time-domain measurements from the entire recording period according to Task Force Recommendations.[13] Spectral power was quantified by fast-Fourier transform analysis in 4 frequency bands: <0.0033 Hz (ultra low frequency) 0.0033 to 0.04 Hz (very low frequency), 0.04 to 0.15 Hz (low frequency) and 0.15 to 0.40 Hz (high frequency).[12] Ultra- and very low-frequency spectral components were computed over the entire recording interval.[13] Low- and high-frequency components were computed from the segments of 512 RR intervals and the average values of the entire recording interval were calculated for these components.[13]

Power law (1/f) scaling of RR interval variability was calculated over the frequency range 10^{-4} to 10^{-2} Hz. A robust line-fitting algorithm of log (power) on log (frequency) was applied to the power spectrum between 10^{-4} to 10^{-2} Hz and the slope (exponent β) of this line was calculated. The details of this method have been described previously.[6,12]

Detrended fluctuation analysis technique was also used to quantify fractal scaling properties of RR interval data.[4–7] In this method the root-mean-square fluctuation of integrated and detrended time series is measured at each observation window and plotted against the size of the observation window on a log–log scale. The fractal-like signal (1/f signal spectrum) results in an exponent value 1 (α = 1.0). The white Gaussian noise (random signal) results in a value of 0.5 (α = 0.5) and the Brownian noise signal (1/f^2 signal spectrum) in an exponent value of 1.5. The details of this analysis method have been described previously.[5,7,8] In this study, HR correlations were defined only for short-term (<11 beats, α) RR interval data, based on our previous findings on a short-term scaling exponent as a predictor of life-threatening arrhythmias.[8]

Statistical analysis: Univariable comparisons of baseline characteristics were performed with the chi-square test for categorical variables and with the 2-sample t test for continuous variables. Relative risk and 95% confidence intervals were calculated for each univariable predictor of all-cause mortality. A p value of <0.05 was considered significant. Cox proportional hazards regression analyses were used to assess the association between different risk predictors and mortality. To find the best cutoff points for various variables, the dichotomization cutoff points that maximized the hazards ratio obtained from the Cox regres-

TABLE II Univariable Predictors of Mortality and Their Relative Risks and Multivariable Predictors of Mortality in Proportional Hazards Regression Analysis

Predictors of	Univariable Predictors of Mortality			Multivariable Mortality		
	Relative Risk	95% CI	p Value*	Relative Risk	95% CI	p Value†
Clinical variables						
Age >70 yrs	2.16	(1.47–3.20)	<0.0001	1.29	(1.01–1.66)	<0.05
Men	0.83	(0.70–1.00)	<0.05	1.08	(0.81–1.45)	NS
History of angina pectoris	1.57	(1.10–2.25)	<0.05	1.46	(1.14–1.87)	<0.01
NYHA class II–IV	1.81	(1.26–2.60)	<0.01	1.19	(0.91–1.56)	NS
Diuretic	1.70	(1.36–2.14)	<0.0001	1.71	(1.21–2.42)	<0.001
β blocker	0.39	(0.22–0.77)	<0.01	0.72	(0.49–1.06)	NS
Wall motion index <1.0	2.16	(1.47–3.20)	<0.0001	1.43	(1.10–1.85)	<0.01
Prior AMI	2.16	(1.47–3.20)	<0.0001	1.03	(0.72–1.34)	NS
Ambulatory ECG data						
α <0.85	3.17	(1.96–5.15)	<0.0001	1.55	(1.19–2.02)	<0.001
β <−1.5	1.83	(1.19–2.82)	<0.01	1.13	(0.87–1.48)	NS
VPCs/h >10	2.43	(1.45–4.07)	<0.001	1.05	(0.79–1.38)	NS

*p Values determined in chi-square analysis; †p values determined in multivariate Cox regression analysis.
CI = confidence intervals; ECG = electrocardiographic; NYHA = New York Heart Association classificaiton; VPCs = ventricular premature complexes; α = short-term fractal-like scaling exponent of detrended fluctuation analysis; β = power-law scaling exponent of long-term HR variability

sion model were sought, with mortality as the end point.

RESULTS

By the end of 4-year follow-up, 72 subjects (45%) had died and 87 (55%) were still alive. Among the clinical variables, angina pectoris, cardiac medication, functional class, sex, and LV systolic function differed significantly between the patients who had died and those who survived (Table I). For HR variability measures, the scaling exponents α and β differed significantly between the survivors and nonsurvivors, but no differences were observed in conventional measures of HR variability (Table I).

The best cutoff point for predicting mortality was <0.85 for the exponent α (56 subjects, 35%). Among all univariable factors, reduced α was the most powerful predictor of mortality (relative risk 3.17; 95% confidence interval, 1.96 to 5.15; p <0.001; positive predictive accuracy 65% and negative predictive accuracy 86%, Figure 1, Table II). When all univariable predictors of mortality were included in multivariable Cox proportional hazards analysis, mortality was predicted independently by the use of diuretic medication, the value of short-term fractal exponent α, angina pectoris, LV ejection fraction, and age (Table II).

DISCUSSION

The main finding of this study is that a short-term fractal scaling exponent was the most powerful measure of HR dynamics in predicting mortality among patients with AMI and depressed LV function. This index provided prognostic information independent of the clinical variables and the degree of LV dysfunction.

Twenty-four hour spectral and nonspectral measurements of HR variability have been found to be indicators of long-term prognosis after AMI in several studies.[1–4] There are salient differences between the present population and previous study populations that may explain the divergent results regarding the prognostic value of traditional 24-hour HR variability. Previous studies have included post-MI patients mostly with relatively well-preserved LV function[1–4] and only small numbers of patients with severely depressed LV function. Therefore, the mortality rate has been lower in previous studies compared with the present one in which a longer follow-up was also available. The mechanism of death in post-MI patients with impaired and preserved LV function may also be different, perhaps explaining the divergent results. Results of this study do not allow conclusions regarding the lack of prognostic value of traditional measurements of HR variability because of a relatively small patient population, but does give preliminary information on the usefulness of fractal analysis methods in risk stratification of patients with depressed LV function, suggesting that their prognostic performance should be studied in similar larger populations.

Analysis methods derived from nonlinear system theory, have suggested prominent new approaches for quantifying complex fluctuations. Normal HR time series have been shown to be fractal-like because they display self-similar (scale-invariant) fluctuations over a wide range of time scales.[5,6,14] In this study, the exponent α was chosen to measure short-term correlation properties of RR interval data, and power-law scaling exponent β to quantify the correlation properties over very- and ultra-low frequency bands.[5,6,8] These measurements differ from traditional HR variability measurements because they are not related to the magnitude of variability, but rather to the distribution of spectral characteristics and correlation features of HR behavior. Neither of these HR variability measurements correlate strongly with traditional measurements of HR variability.[6,8]

It has been suggested that fractal properties may be an organizing principle for physiologic structure and

function.[14] Changes in the organization pattern of this kind may result in a less adaptable system favoring vulnerability to various pathologic states.[14] This hypothesis has been supported by recent studies that have shown that altered power-law scaling of RR intervals are associated with an increased risk of mortality in post-MI patients and in elderly subjects.[6,11] Also, a breakdown of fractal scaling was associated with an increased risk of mortality in a cross-sectional study including a small number of heart failure patients and controls.[7]

The present results show that a fractal scaling exponent of HR dynamics gives prognostic information beyond that obtained by conventional HR variability analysis methods in a population of patients with AMI and depressed LV function. Further studies in larger populations will be needed to further define the clinical utility of new fractal measurements of HR variability for risk stratification of high risk post-MI patients.

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