Fractal Correlation Properties of R-R Interval Dynamics and Mortality in Patients With Depressed Left Ventricular Function After an Acute Myocardial Infarction

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Background—Preliminary data suggest that the analysis of R-R interval variability by fractal analysis methods may provide clinically useful information on patients with heart failure. The purpose of this study was to compare the prognostic power of new fractal and traditional measures of R-R interval variability as predictors of death after acute myocardial infarction.

Methods and Results—Time and frequency domain heart rate (HR) variability measures, along with short- and long-term correlation (fractal) properties of R-R intervals (exponents α_1 and α_2) and power-law scaling of the power spectra (exponent β), were assessed from 24-hour Holter recordings in 446 survivors of acute myocardial infarction with a depressed left ventricular function (ejection fraction $\leq 35\%$). During a mean$\pm$SD follow-up period of 685 ± 360 days, 114 patients died (25.6%), with 75 deaths classified as arrhythmic (17.0%) and 28 as nonarrhythmic (6.3%) cardiac deaths. Several traditional and fractal measures of R-R interval variability were significant univariate predictors of all-cause mortality. Reduced short-term scaling exponent α_1 was the most powerful R-R interval variability measure as a predictor of all-cause mortality ($\alpha_1 < 0.75$, relative risk 3.0, 95% confidence interval 2.5 to 4.2, $P<0.001$). It remained an independent predictor of death ($P<0.001$) after adjustment for other postinfarction risk markers, such as age, ejection fraction, NYHA class, and medication. Reduced α_1 predicted both arrhythmic death ($P<0.001$) and nonarrhythmic cardiac death ($P<0.001$).

Conclusions—Analysis of the fractal characteristics of short-term R-R interval dynamics yields more powerful prognostic information than the traditional measures of HR variability among patients with depressed left ventricular function after an acute myocardial infarction. (***Circulation***. 2000;101:47-53.)

Key Words: mortality ∎ heart rate ∎ infarction

A nalysis of time and frequency domain measures of heart rate (HR) variability from 24-hour ambulatory ECG recordings provides prognostic information on patients after an acute myocardial infarction.[1–4] A number of new methods based on nonlinear system theory ("chaos theory and fractals") have been recently developed to quantify the complex HR dynamics and to complement the conventional measures of HR variability.[5–12] New fractal analysis methods have already provided clinically useful information on patients with impaired left ventricular function,[13–15] but their prognostic power has not been proved in large-scale studies.

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In the present investigation, we assessed the use of various fractal analysis methods of HR variability to predict death in a population of patients with acute myocardial infarction (MI)

and depressed left ventricular function. The prediction of death was evaluated in survivors of acute MI included in the Danish Investigations of Arrhythmia and Mortality on Dofetilide (DIAMOND-MI) trial. We also sought to determine whether these new fractal measures of R-R interval dynamics predict specifically either arrhythmic or nonarrhythmic cardiac death.

Methods

Population

A substudy of the DIAMOND MI trial was conducted in 37 Danish coronary care units that included patients with an acute MI and a left ventricular wall motion index of ≤ 1.2 (equal to an ejection fraction of ≤ 0.35). A detailed study design has been previously described.[16] A substudy of the DIAMOND trial was designed to assess the prognostic power of various measures of HR variability in predicting death in this population. In this subset of patients, a 24-hour Holter

TABLE 1. Baseline Characteristics of Patients Who Died and Those Who Remained Alive by the End of the Follow-Up

	Alive (n=332)	Dead (n=114)	P*
Clinical data			
Age, y	65±11	70±9	<0.001
BP, mm Hg	119±17/72±11	115±19/71±10	NS
Sex, M/F	256/76	84/30	NS
NYHA class			
I–II	248 (75%)	61 (54%)	
III–IV	84 (25%)	53 (46%)	<0.001
Thrombolytic therapy			
Yes	202 (61%)	47 (41%)	
No	130 (39%)	67 (59%)	<0.001
ACE inhibitor			
Yes	163 (49%)	47 (41%)	
No	169 (51%)	67 (59%)	NS
β-Blocker			
Yes	148 (45%)	41 (39%)	
No	184 (55%)	73 (61%)	NS
Wall motion index	1.07±0.15	0.98±0.21	<0.001
Holter data			
VPDs			
No./h	18±58	35±82	
Log (No.)/h×10	2.2±10.0	7.4±10.2	<0.001
NSVT, n (%)			
Yes	31 (9)	20 (18)	
No	301 (91)	94 (82)	<0.05

NSVT indicates nonsustained ventricular tachycardia; VPD, ventricular premature depolarization.

*Calculated with 2-sample *t* test for continuous data and with χ^2 test for other variables.

recording was obtained in 645 patients 5 to 10 days after MI. The patients were followed for a mean of 685±360 days after randomization, and the Events Committee of the DIAMOND trial classified the deaths according to the CAST criteria,[17] except that resuscitated cardiac arrest was not counted as death.

Ambulatory ECG Recordings

All of the subjects were monitored for 24 hours with an ambulatory 2-channel ECG recorder (Tracker, Reynolds, UK) with an R-R interval sampling frequency of 128 Hz. The data were sampled digitally and transferred to a microcomputer for the analysis of HR variability. The HR variability analysis techniques have been described elsewhere.[5,13,14,18,19] The methods are briefly described here.

Nonspectral and Spectral Analyses of HR Variability

After the transfer of the ECG data to a microcomputer, the R-R interval series were edited both manually and automatically.[14,19] Only recordings with at least 20 hours of data and with >85% of qualified sinus beats were included in the analysis of HR variability. The nonspectral and spectral measures of HR variability were analyzed according to the methods recommended by the task force.[20] The SD of all normal-to-normal R-R intervals (SDNN) and the geometric HR variability index were computed as standard time domain measures from the entire recording period. Spectral power was quantified through fast Fourier transform analysis in 4 frequency bands: <0.0033 Hz (ultralow frequency), 0.0033 to 0.04 Hz (very

low frequency [VLF]), 0.04 to 0.15 Hz (low frequency), and 0.15 to 0.40 Hz (high frequency).[20] Ultralow-frequency and VLF spectral components were computed over the entire recording interval.[20] Low- and high-frequency components were computed from the segments of 512 R-R intervals, and the average values of the entire recording interval were calculated for these components.[20]

Poincaré Plot Analysis

The Poincaré plot is a graph in which each R-R interval is plotted as a function of the previous R-R interval. The quantitative 2-dimensional analysis of these plots has been described in detail previously.[18] Briefly, scattergrams of successive R-R intervals were plotted for the entire 24-hour period, and the SD of instantaneous R-R interval variability and the SD of continuous variability (SD2) were then analyzed

Power-Law Scaling Analysis

The power-law relation of R-R interval variability was calculated from the frequency range of 10^{-4} to 10^{-2} Hz. The point power spectrum was logarithmically smoothed in the frequency domain, and the power was integrated into bins spaced 0.0167 log (Hz) apart. A robust line-fitting algorithm of log (power) versus log (frequency) was then applied to the power spectrum between 10^{-4} to 10^{-2} Hz, and the slope of this line was calculated, yielding the scaling exponent (β). The details of this method have been described previously.[19,21]

Detrended Fluctuation Analysis

The detrended fluctuation analysis technique was used to quantify the fractal scaling properties of short- and intermediate-term R-R interval time series. The root-mean-square fluctuation of integrated and detrended time series is measured at different observation windows and plotted against the size of the observation window on a log-log scale. The details of this method have been described elsewhere.[5,13,15] The HR correlations were defined separately for short-term (<11 beats, α_1) and longer-term (>11 beats, α_2) R-R interval data (scaling exponents).[5,14] Both 32 α_1 and α_2 were analyzed from segments of 8000 R-R intervals and averaged to obtain mean values for the entire recording period. Scaling exponents were calculated both for real R-R interval data after editing only for artifacts and for the same preedited data that were used in traditional analyses.

Statistical Analysis

The measures of R-R interval variability and clinical data were used as the explanatory variables in univariate comparisons. Univariate comparisons were performed with the χ^2 test for categorical variables and the 2-tail 2-sample *t* test for continuous variables. The Pearson correlation coefficient was used to estimate the correlations between different variables. The frequency domain measures of HR variability were transformed to natural logarithms, because their distributions were skewed. A value of $P<0.05$ was considered to indicate statistical significance.

x proportional hazards regression analyses were used to assess the association between different risk predictors and mortality by using the SPSS for Windows version 7.5. The continuous R-R interval variability measures were dichotomized. To find the best cut points for various variables, the dichotomization cut points that maximized the hazards ratio obtained from the Cox regression model were sought, with all-cause mortality as the end point. The dichotomization procedure was performed within the 10th to 70th percentiles in 5th-percentile steps for each variable. Kaplan-Meier estimates of the distribution of the times from the baseline to death were computed, and log-rank analysis was performed to compare the survival curves. Each measure was first tested univariately and then retested after adjustment for other post-MI risk factors in the Cox regression model. The sensitivity, specificity, and predictive accuracy values of R-R interval variability measures for all-cause mortality were also analyzed.

TABLE 2. Baseline R-R Interval Variability of Patients Who Died and Those Who Remained Alive by the End of Follow-Up in Total Study Group and in Patients Randomized to Receive Placebo or Dofetilide

	Alive	Dead	P
Nonspectral analysis			
Mean R-R interval, ms	817±149	763±119	<0.01
Placebo group*	800±136	753±98	<0.05
Dofetilide group†	836±150	773±139	<0.01
SDNN, ms	87±33	74±28	<0.001
Placebo group	84±33	74±24	<0.05
Dofetilide group	89±32	75±33	<0.01
HRVI	23±9	19±8	<0.001
Placebo group	23±9	19±7	<0.01
Dofetilide group	24±9	20±8	<0.01
SD1, ms	20±10	20±11	NS
Placebo group	20±12	19±9	NS
Dofetilide group	20±11	22±12	NS
SD2, ms	78±35	65±29	<0.001
Placebo group	77±37	64±26	<0.01
Dofetilide group	79±33	67±31	<0.05
Spectral analysis			
ULF power			
ms^2	4828±3893	3894±3244	
ln	8.2±0.8	7.9±1.0	<0.001
Placebo group	8.2±0.8	8.0±0.8	<0.07
Dofetilide group	8.2±0.8	7.8±1.1	<0.01
VLF power			
ms^2	703±983	477±584	
ln	6.1±1.0	5.6±1.1	<0.001
Placebo group	6.1±0.9	5.7±0.9	<0.01
Dofetilide group	6.1±1.0	5.6±1.2	<0.01
LF power			
ms^2	432±503	362±961	
ln	5.6±1.0	5.1±1.0	<0.001
Placebo group	5.6±1.0	5.1±0.9	<0.01
Dofetilide group	5.6±1.0	5.1±1.2	<0.01
HF power			
ms^2	264±425	230±304	
ln	5.0±1.0	4.9±1.1	NS
Placebo group	4.9±1.0	4.8±0.9	NS
Dofetilide group	5.0±1.0	4.9±1.2	NS
LF/HF ratio	2.22±1.85	1.65±1.51	<0.001
Placebo group	2.43±2.3	1.67±1.1	<0.01
Dofetilide group	2.07±1.2	1.63±1.8	<0.05
Fractal analysis			
α_1	0.83±0.20	0.67±0.19	<0.001
Placebo group	0.83±0.21	0.64±0.20	<0.001
Dofetilide group	0.83±0.19	0.69±0.18	<0.001
α_1 (edited)	1.04±0.22	0.90±0.21	<0.001
Placebo group	1.05±0.22	0.91±0.21	<0.001
Dofetilide group	1.04±0.21	0.88±0.22	<0.001

TABLE 2. Continued

	Alive	Dead	P
α_2	0.90±0.14	0.83±0.18	<0.001
Placebo group	0.90±0.14	0.84±0.19	<0.01
Dofetilide group	0.90±0.14	0.82±0.17	<0.01
α_2 (edited)	1.08±0.11	1.05±0.15	<0.01
Placebo group	1.09±0.11	1.07±0.11	NS
Dofetilide group	1.07±0.14	1.02±0.16	<0.01
β	−1.35±0.19	−1.43±0.22	<0.01
Placebo group	−1.33±0.19	−1.41±0.21	<0.05
Dofetilide group	−1.37±0.20	−1.44±0.24	<0.05

α_1 and α_2 indicate scaling exponents analyzed by detrended fluctuation analysis from short and intermediate time windows, respectively; β, slope of power-law regression line of HR variability between frequencies 10^{-2} and 10^{-4}; edited, analysis of fractal measures of R-R interval variability after editing of the premature beats; HRVI, heart rate variability index; ln, logarithmic transformation of power spectral measures; LF, low-frequency power; SD1, instantaneous R-R interval variability analyzed with Poincare plots; SD2, continuous R-R interval variability analyzed with Poincare plots; and ULF, ultralow-frequency power.

*Placebo group indicates patients randomized to receive placebo treatment (n=216).

†Dofetilide group indicates patients randomized to receive dofetilide treatment (n=217).

Results

Results are reported on 446 patients who fulfilled the criteria for meaningful R-R interval variability analysis. Patients were excluded because the ECG data could not be analyzed due to signal artifacts (n= 55), long or frequent episodes of atrial tachyarrhythmias (n= 45), or unsuccessful signal collection (n= 49) or due to frequent premature beats on the ECG recordings (<85% qualified sinus beats) (n=50).

Univariate Predictors of Death

During the follow-up period of 685±360 days, 114 (25.6%) patients died. Seventy-five deaths (17.0%) were classified as arrhythmic, and 28 (6.3%) were classified as nonarrhythmic cardiac deaths. The baseline characteristics of the patients who survived and those who died during the follow-up period are shown in Table 1. The results of R-R interval variability analyses for the total study group and separately for the patients randomized to receive placebo (n=216) or dofetilide (n=217) are shown in Table 2. The mean R-R interval, SDNN, HR variability index, and SD2 differed significantly between the survivors and nonsurvivors. All power spectral components, except the HF component, also differed between the groups. The fractal analysis indices obtained through the detrended fluctuation method and the power-law scaling method were also different between survivors and nonsurvivors (Table 2). The differences in the measures of HR variability between the survivors and those who died were the same as those between the patients randomized to receive either placebo or dofetilide.

Table 3 shows the sensitivity, specificity, and predictive accuracy values of various measures of R-R interval variability as predictors of all-cause mortality. Among the R-R interval variability measures, the reduced short-term scaling

TABLE 3. Sensitivity, Specificity, and Predictive Accuracy of R-R Interval Variability Indices in Prediction of All-Cause Mortality Rates

	Sensitivity, %	Specificity, %	Positive Predictive Accuracy, %	Negative Predictive Accuracy, %	Overall Accuracy, %
α_1 <0.75 (n=168)	62	73	46	84	65
α_1 (edited) <0.85 (n=117)	48	80	43	81	62
β <−1.5 (n=112)	36	77	38	76	57
Mean R-R interval <750 ms (n=147)	44	63	30	76	53
SDNN <65 ms (n=131)	39	75	34	78	56
HRVI <16 (n=108)	35	79	37	78	57
ULF (ln) <8.1 (n=210)	36	55	29	78	53
VLF (ln) <5.75 (n=168)	54	67	38	79	58
LF (ln) <5.5 (n=228)	58	60	36	79	58
LF/HF ratio <1.6 (n=205)	58	59	35	79	56

For abbreviations, see legend to Table 2.

exponent α_1 had the best overall accuracy (Table 3). Scaling exponent α_1 analyzed from the real R-R interval data performed slightly better than that analyzed from the data edited for premature beats as a predictor of death. Figure 1 shows examples of Kaplan-Meier survival curves and mortality rates. Among the R-R interval variability measures, the reduced short-term scaling exponent (<0.75) was the dichotomized variable that most powerfully predicted the differences in survival curves.

Multivariate Predictors of Death

Table 4 shows the univariate and multivariate relative risks adjusted for other risk variables for dichotomized R-R interval variability measures as predictors of all-cause, arrhythmic, and nonarrhythmic cardiac death. The short-term scaling exponent was also the most powerful independent predictor

Figure 1. Kaplan-Meier survival curves of patients with a scaling exponent α_1 ≥0.75 and <0.75, respectively (top left); patients with SDNN of ≥65 and <65 ms, respectively (top right); patients with natural logarithm of very-low-frequency spectral component (ln VLF) of ≥5.75 and <5.75, respectively (bottom left); and scaling exponent β of ≥−1.5 and <−1.5 (bottom right).

of all-cause mortality after adjustment for other variables. It independently predicted arrhythmic death, which was not predicted by the other measures of HR variability after adjustment for clinical risk factors.

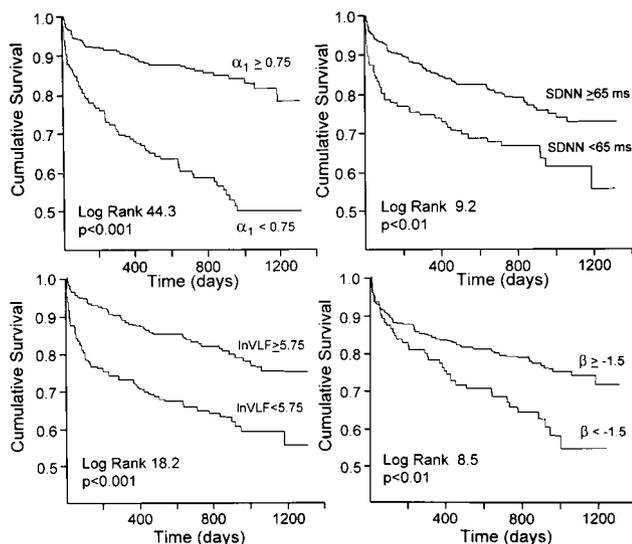## Characteristics of R-R Interval Data With Reduced Short-Term Scaling Exponent

The characteristics of R-R interval dynamics with a low α_1 value were evaluated by printing out the R-R interval tachograms, portions of ECG recordings, power spectra, and Poincaré plots for all cases with an α_1 value of <0.75. Figure 2 shows the typical R-R interval data obtained from the patients with a low α_1 value.

Discussion

The main finding of this study was that a short-term fractal-like scaling exponent of R-R interval time series is a better predictor of death than the traditional measures of HR variability among patients with acute MI and depressed left ventricular function. These data confirm and generalize the preliminary observations, which have suggested the clinical applicability of fractal analysis methods in the risk stratification of patients with left ventricular dysfunction.[13–15] A measure of R-R interval dynamics, which reflects the correlation properties (or randomness) of short-term HR behavior, provided prognostic information on all-cause, arrhythmic and nonarrhythmic cardiac deaths independent of the clinical variables and the degree of left ventricular dysfunction.

Nonspectral and Spectral Analyses of R-R Interval Variability and Death

The independent prognostic power of the traditional indices of HR variability was generally not as strong as that reported in prior studies,[1–4] and none of the time or frequency domain measures provided independent prognostic information on the risk of arrhythmic death. A recent study of patients with heart failure also showed that analysis of SDNN from 24-hour ECG recordings does not provide independent information on the risk of sudden death.[22] The previous studies have mostly included post-MI patients with relatively well

TABLE 4. Prediction of All-Cause, Arrhythmic, and Nonarrhythmic Cardiac Mortality by R-R Interval Variability Measures Before and After Adjustment for Other Risk Predictors With Cox Regression Analysis

	Unadjusted Relative Risk	Significance (*P*)	Adjusted Relative Risk	Significance (*P*)
All-cause deaths (n=114)				
α_1 <0.75	3.0 (1.6–4.2)	<0.001	2.0 (1.4–2.7)	<0.001
α_1 (edited) <0.85	2.8 (1.5–4.0)	<0.011	1.8 (1.3–2.5)	<0.01
β <−1.5	1.8 (1.2–2.6)	<0.01	1.3 (0.8–1.9)	NS
SDNN <65	1.8 (1.2–2.6)	<0.01	1.3 (0.9–2.0)	NS
SD2 <55	2.2 (1.5–3.2)	<0.001	1.6 (1.1–2.5)	<0.05
HRVI <16	2.0 (1.3–2.9)	<0.001	1.5 (1.0–2.3)	<0.05
VLF (ln) <5.75	2.2 (1.5–3.2)	<0.001	1.6 (1.1–2.4)	<0.05
LF (ln) <5.5	2.2 (1.5–3.2)	<0.001	1.7 (1.1–2.6)	<0.05
LF/HF ratio <1.6	2.1 (1.4–3.0)	<0.001	1.5 (1.0–2.3)	<0.05
Arrhythmic deaths (n=75)				
α_1 <0.75	2.5 (2.2–3.9)	<0.001	1.4 (1.1–1.7)	<0.05
α_2 <0.85	1.6 (1.0–2.6)	<0.05	1.1 (0.7–1.6)	NS
β <−1.5	1.6 (0.9–2.6)	NS	1.3 (0.8–2.2)	NS
SDNN <65	2.0 (1.2–3.2)	<0.01	1.4 (0.9–2.8)	NS
SD2 <55	1.9 (1.2–3.1)	<0.05	1.4 (0.8–2.4)	NS
HRVI <16	1.9 (1.1–3.1)	<0.05	1.4 (0.8–2.5)	NS
VLF (ln) <5.75	2.1 (1.3–3.4)	<0.01	1.6 (0.9–2.6)	NS
LF (ln) <5.5	1.8 (1.1–2.9)	<0.05	1.3 (0.8–2.2)	NS
LF/HF ratio <1.6	1.9 (1.2–3.0)	<0.01	1.4 (0.8–2.3)	NS
Nonarrhythmic cardiac deaths (n=38)				
α_1 <0.75	4.1 (2.8–6.9)	<0.001	2.6 (1.6–4.2)	<0.01
α_2 <0.85	1.6 (0.9–3.8)	NS	1.0 (0.5–2.0)	NS
β <−1.5	2.5 (1.2–5.3)	<0.05	1.5 (0.7–3.3)	NS
SDNN <65	2.1 (1.0–4.4)	<0.05	1.5 (0.7–3.3)	NS
SD2 <55	3.1 (1.5–6.4)	<0.01	2.5 (1.1–6.0)	<0.05
HRVI <16	2.5 (1.2–5.3)	<0.05	1.9 (0.8–4.2)	NS
VLF (ln) <5.75	3.5 (1.6–7.5)	<0.001	2.5 (1.1–5.8)	<0.05
LF (ln) <5.5	4.0 (1.6–9.8)	<0.001	3.3 (1.3–9.3)	<0.05
LF/HF <1.6	4.0 (1.7–9.5)	<0.001	2.3 (1.0–5.7)	<0.05

The 95% CIs are given in parentheses. Adjustments were made for age, NYHA class, wall motion index, medication, ventricular arrhythmias on 24-hour ECG recordings, and randomization to dofetilide or placebo.

For abbreviations, see legend to Table 2.

preserved left ventricular function[1–4] or patients with heart failure due to various causes.[22] The mechanisms of death may be different in post-MI patients with preserved and impaired left ventricular function. In the former category, death after acute MI is commonly related to a reinfarction or recurrent acute ischemic events, whereas in the latter category, a primary arrhythmic event and progressive heart failure are the most probable mechanisms of death.[23]

Fractal Analysis of R-R Interval Dynamics and Death

Analysis methods derived from nonlinear dynamics, based on chaos theory and fractal mathematics, have opened a new approach for the study and understanding of the characteristics of dynamic phenomena.[24] HR time series in healthy subjects are fractal-like, because they display self-similar

(scale-invariant) fluctuations over a wide range of time scales.[9,25] In the detrended fluctuation analysis method used here, the fractal-like correlation properties of R-R interval dynamics are quantified in short and intermediate time scales (ie, from seconds to minutes) over a 24-hour period.[5,13,14] This analysis method differs from the traditional measures of HR variability, because it does not measure the magnitude of variability but rather the distribution of spectral characteristics at various frequencies and other features in HR behavior that cannot be detected through methods based on moment statistics.

The short-term fractal scaling exponent α_1 proved to be the most powerful predictor of death compared with the other HR variability measures, and it clearly added to the prognostic value of both nonspectral and spectral measures in the present population. Of note, short-term scaling exponent analyzed
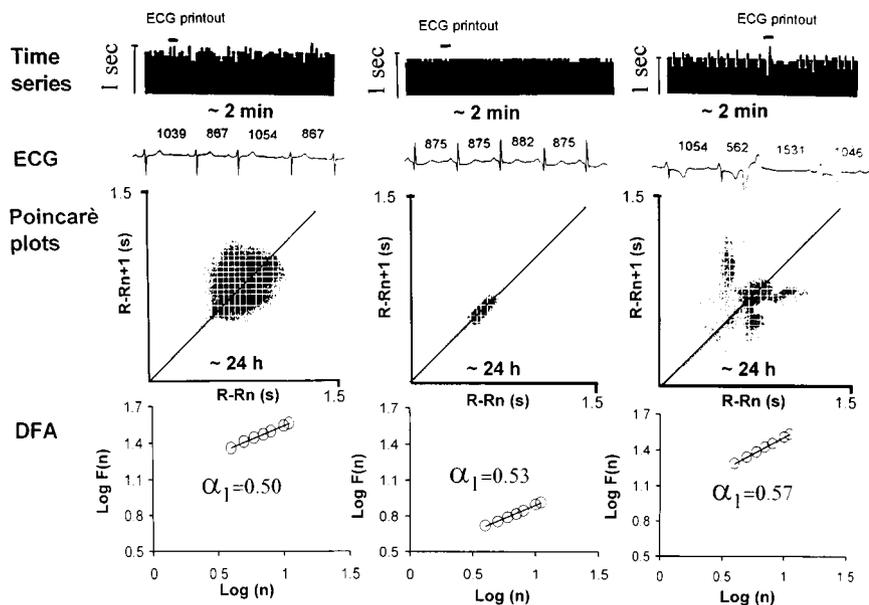
Figure 2. Three examples of typical R-R interval tachograms (2-minute periods), portions of ECG (4 seconds), Poincaré plots (analyzed over 24 hours), and α_1 scaling exponents (24-hour period average, analyzed from segments of 8000 consecutive beats) of 3 patients with a low α_1 value. Left, An example describes R-R interval dynamics with large abrupt (often alternating) changes in R-R intervals without changes in p-wave morphology (sinus beats without evidence of ectopic atrial beats) resulting in a ball-shaped Poincaré plot and a low short-term scaling exponent. Middle, An example of almost fixed R-R interval dynamics with a low overall variability and a torpedo-shaped Poincaré plot. Right, An example of frequent premature ventricular beats resulting in a complex Poincaré plot and a reduced short-term scaling exponent value. DFA indicates detrended fluctuation analysis.

from the real R-R interval data without exclusion of the premature beats performed even better as a predictor than that analyzed after editing for premature beats. A reduction in the short-term scaling exponent reflects a loss of the short-term correlation properties of R-R intervals. From a dynamic point of view, this observation supports the previous speculations on the meaning and significance of fractal-like R-R interval behavior for the maintenance of normal cardiovascular function.[24]

A specific abnormality in cardiovascular neural regulation may explain an increase in the randomness of HR behavior and its association with a risk of dying. Sympathoexcitation is one of the potential mechanisms responsible for this abnormality. Recent observations have shown that norepinephrine infusion may cause similar alterations in HR behavior[26] as that observed here in association with a reduced short-term scaling exponent. Complex R-R interval dynamics have also been shown to be associated with high levels of norepinephrine in patients with heart failure.[27] Traditional analysis methods are able to reveal reduction in overall variability but not the other abnormalities of HR behavior caused by sympathoexcitation.

Study Limitations

The purpose of the present study was to examine the prognostic value of various HR variability measures of 24-hour recordings during normal "free-running" conditions, with recognition of the potential confounding effects of nonstationarities due to irregularities in breathing patterns, physical activity, and other factors. Because standardized conditions were not used, in this study we were not able to compare the prognostic power of fractal and spectral measures of HR variability analyzed in strictly controlled conditions. Uncontrolled conditions may underestimate the predictive power of spectral measures of HR variability, which are highly sensitive to irregularities in breathing patterns and other nonstationarities.

Conclusions

The results show that the analysis of short-term fractal correlation properties of HR dynamics has significant prognostic value independent of the clinical risk factors and that it significantly adds to the prognostic value of traditional HR variability analysis. Short-term scaling exponent can be easily analyzed from ambulatory ECG recordings without time-consuming preprocessing and editing of the real R-R interval data, which may have practical implications for risk stratification. Prospective studies in other post-MI populations may be necessary to confirm these findings, and experimental studies are necessary to confirm the mechanisms behind the increase in the randomness of short-term R-R interval dynamics.

Acknowledgments

References

1. Kleiger RE, Miller JP, Bigger JT, Moss AJ, the Multicenter Post-Infarction Research Group. Decreased heart rate variability and its association with increased mortality after myocardial infarction. *Am J Cardiol*. 1987;59:256–262.
2. Bigger JT Jr, Fliess GL, Steinmann RC, Rolnitzky LM, Kleiger RE, Rottman JN. Frequency domain measures of heart period variability and mortality after myocardial infarction. *Circulation*. 1992;85:164–171.
3. Zuanetti G, Neilson JM, Latini R, Santoro E, Maggioni AP, Ewing DJ. Prognostic significance of heart rate variability in post-myocardial infarction patients in the fibrinolytic era: the GISSI-2 results. *Circulation*. 1996;94:432–436.
4. La Rovere MT, Bigger JT, Marcus FI, Mortara A, Schwartz PJ, for the ATRAMI. Baroreflex sensitivity and heart-rate variability in prediction of total cardiac mortality after myocardial infarction. *Lancet*. 1998;351:478–484.
5. Peng CK, Havlin S, Stanley HE, Goldberger AL. Quantification of scaling exponents and crossover phenomena in nonstationary heartbeat time series. *Chaos*. 1995;5:82–87.

6. Pincus SM, Goldberger AL. Physiologic time-series analysis: what does regularity quantify? *Am J Physiol*. 1994;226:H1643–H1656.

7. Skinner JE, Carpeggiani C, Landisman CE, Fulton KW. Correlation dimension of heartbeat intervals is reduced in conscious pigs by myocardial ischemia. *Circ Res*. 1991;68:966–976.

8. Skinner JE, Pratt CM, Vybiral T. A reduction in the correlation dimension of heartbeat intervals precedes imminent ventricular fibrillation in human subjects. *Am Heart J*. 1993;125:731–743.

9. Yamamoto Y, Hughson RL. Coarse-graining spectral analysis: new method for studying heart rate variability. *J Appl Physiol*. 1991;71:1143–1150.

10. Saul JP, Albrecht P, Berger RD, Cohen RJ. Analysis of long-term heart rate variability: methods, 1/f scaling and implications. In: *Computers in Cardiology*. Silver Spring, Md: IEEE Computer Society Press; 1987;419–422.

11. Grassberger P, Procaccia I. Measuring the strangeness of strange attractors. *Physica D*. 1983;9:189–208.

12. Glenny RW, Robertson HT, Yamashiro S, Bassingthwaighte JB. Applications of fractal analysis to physiology. *J Appl Physiol*. 1991;70:2351–2367.

13. Ho KKL, Moody GB, Peng CK, Mietus JE, Larson MG, Levy D, Goldberger AL. Predicting survival in heart failure cases and controls using fully automated methods for deriving nonlinear and conventional indices of heart rate dynamics. *Circulation*. 1997;96:842–848.

14. Mäkikallio TH, Høber S, Køber L, Torp-Pedersen C, Peng C-K, Goldberger AL, Huikuri HV, for the Trace Investigators. Fractal analysis of heart rate dynamics as a predictor of mortality in patients with depressed left ventricular function after acute myocardial infarction. *Am J Cardiol*. 1999;83:836–839.

15. Lombardi F, Sandrone G, Mortara A, Torzillo D, La Rovere MT. Signorini MG, Gerutti S, Malliani A. Linear and nonlinear dynamics of heart rate variability after acute myocardial infarction with normal and reduced left ventricular ejection fraction. *Am J Cardiol*. 1996;77:1283–1288.

16. The DIAMOND Study Group. Dofetilide in patients with left ventricular dysfunction and either heart failure or acute myocardial infarction: rationale, design, and patient characteristics of the DIAMOND study. *Clin Cardiol*. 1997;20:704–710.

17. Greene HL, Richardson DW, Barker AH, Roden DM, Capone RJ, Echt DS, Friedman LM, Gillespie MJ, Hallstrom AP, Verter J, and the CAPS Investigators. Classification of deaths after myocardial infarction as arrhythmic and nonarrhythmic (the Cardiac Arrhythmia Pilot Study). *Am J Cardiol*. 1989;63:1–6.

18. Huikuri HV, Seppänen T, Koistinen MJ, Airaksinen KEJ, Ikäheimo MJ, Castellanos A, Myerburg RJ. Abnormalities in beat-to-beat dynamics of heart rate before the spontaneous onset of life-threatening ventricular tachyarrhythmias in patients with prior myocardial infarction. *Circulation*. 1996;93:1836–1844.

19. Huikuri HV, Mäkikallio TH, Airaksinen KEJ, Seppänen T, Puukka P, Räihä IJ, Sourander LB. Power-law relationship of heart rate variability as a predictor of mortality in the elderly. *Circulation*. 1998;97:2031–2020.

20. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. Heart rate variability: standards of measurement, physiological interpretation, and clinical use. *Circulation*. 1996;93:1043–1065.

21. Bigger JT Jr, Steinman RC, Rolnitzky LM, Fleiss JL, Albrecht P, Cohen RJ. Power law behavior of RR-interval variability in healthy middle-aged persons, patients with recent acute myocardial infarction, and patients with heart transplants. *Circulation*. 1996;93:2142–2151.

22. Nolan J, Batin PD, Andrews R, Lindsay SJ, Brooksby P, Mullen M, Baig W, Flapan AD, Cowley A, Prescott RJ, Neilson JMM, Fox KAA. Prospective study of heart rate variability and mortality in chronic heart failure: results of the United Kingdom Heart Failure Evaluation and Assessment of Risk Trial (UK-Heart). *Circulation*. 1998;98:1510–1516.

23. Mehta D, Curwin J, Gomes JA, Fuster V. Sudden death in coronary artery disease: acute ischemia versus myocardial substrate. *Circulation*. 1997;96:3215–3223.

24. Goldberger AL. Non-linear dynamics for clinicians: chaos theory, fractals, and complexity at the bedside. *Lancet*. 1996;347:1312–1314.

25. Iyengar N, Peng C-K, Morin R, Goldberger AL, Lipitz LA. Age-related alterations in the fractal scaling of cardiac interbeat interval dynamics. *Am J Physiol*. 1996;271:R1078–R1084.

26. Tulppo MP, Mäkikallio TH, Seppänen T, Airaksinen KEJ, Huikuri HV. Heart rate dynamics during accentuated sympathovagal interaction. *Am J Physiol*. 1998;274:H810–H816.

27. Woo MA, Stevenson WG, Moser DK, Middlekauff HR. Complex heart rate variability and serum norepinephrine levels in patients with advanced heart failure. *J Am Coll Cardiol*. 1994;23:565–569.