Heart Rate Dynamics in Patients With Stable Angina Pectoris and Utility of Fractal and Complexity Measures

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Dynamic analysis techniques may uncover abnormalities in heart rate (HR) behavior that are not easily detectable with conventional statistical measures. However, the applicability of these new methods for detecting possible abnormalities in HR behavior in various cardiovascular disorders is not well established. Conventional measures of HR variability were compared with short-term (≤11 beats, α_1) and long-term (>11 beats, α_2) fractal correlation properties and with approximate entropy of RR interval data in 38 patients with stable angina pectoris without previous myocardial infarction or cardiac medication at the time of the study and 38 age-matched healthy controls. The short- and long-term fractal scaling exponents (α_1, α_2) were significantly higher in the coronary patients than in the healthy controls (1.34 ± 0.15 vs 1.11 ± 0.12 [p <0.001] and 1.10 ± 0.08 vs 1.04 ± 0.06 [p <0.01], respectively), and they also had lower approximate entropy (p <0.05), standard deviation of all RR intervals (p <0.01), and high-frequency spectral component of HR variability (p <0.05). The short-term fractal scaling exponent performed better than other heart rate variability parameters in differentiating patients with coronary artery disease from healthy subjects, but it was not related to the clinical or angiographic severity of coronary artery disease or any single nonspectral or spectral measure of HR variability in this retrospective study. Patients with stable angina pectoris have altered fractal properties and reduced complexity in their RR interval dynamics relative to age-matched healthy subjects. Dynamic analysis may complement traditional analyses in detecting altered HR behavior in patients with stable angina pectoris. ©1998 by Excerpta Medica, Inc.

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Heart rate (HR) variability is widely used in assessing neuroautonomic control of the heartbeat.[1–3] However, traditional statistical measures provide limited information about HR behavior because nonlinear mechanisms may also be involved in the genesis of HR dynamics.[4] A number of new methods have recently been developed to quantify complex HR dynamics.[5–12] They may uncover abnormalities in the time-series data that are not apparent using conventional statistics.[8–13] This retrospective study tested the hypothesis that fractal and complexity measures of HR behavior are altered in patients with stable angina pectoris.

METHODS

Subjects: Thirty-eight consecutive patients with stable angina pectoris and without previous myocardial infarction who had been referred for angiographic examination because of a history of chest pain and electrocardiographic evidence of ischemic ST-segment depression (>0.1 mV) during an exercise test were included in the series. Characteristics of patients with coronary artery disease are listed in Table I. No cardiac medication was allowed during the 24-hour Holter recordings, and β-blocking therapy had been withdrawn at least 8 days before and calcium antagonists at least 2 days before. Patients with diabetes mellitus, anginal chest pain, or ischemic ST-segment depression during the recording were excluded.

The control group comprised 38 randomly selected age-matched (mean age 58 ± 5 years) and sex-matched (29 men, 9 women) healthy subjects. All patients underwent a complete physical examination and their medical history revealed no cardiovascular disease or use of medication. Similarly, all controls had normal arterial blood pressure, a 12-lead electrocardiogram, echocardiographic data (M-mode, 2-dimensional, and Doppler echocardiography), and fasting blood glucose. Subjects with evidence of ischemic ST-segment depression (>0.1 mV) during the exercise test or 24-hour recording were not included.

Left-sided cardiac catheterization was performed by Judkins' technique on all coronary patients within 2 months of the electrocardiographic recordings. Coronary artery stenoses with >50% diameter luminal narrowing of the main branches were considered significant. The patients were grouped into 1-, 2- and 3-vessel disease according to these criteria. An exercise electrocardiogram on all subjects was obtained using a symptom-limited bicycle test, increasing the workload by 15 W/min.[14] A horizontal or downsloping ST depression of >0.1 mV occurring 0.08 second after the J point was considered to be of ischemic

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TABLE I Characteristics of Patients

	Patients With CAD (n = 38)
Age (yr)	55 ± 9
Men/women	29/9
NYHA class 1–2	23 (61%)
NYHA class 3	15 (39%)
Number of major coronary arteries narrowed >50% in diameter	
1	17 (45%)
2	6 (16%)
3	15 (39%)
LV ejection fraction (%)	71 ± 7

Values are expressed as mean ± SD or number (%).
LV = left ventricular; NYHA = New York Heart Association classification.

origin. The criterion for an ischemic episode during the 24-hour recording was ≥1 mm of horizontal or downsloping ST-segment depression lasting ≥1 minute.

Analysis of heart rate variability: The electrocardiographic data were sampled digitally and transferred to a microcomputer for analysis. The RR interval series was passed through a filter that eliminates premature beats and noise. All questionable portions of RR interval data were printed out on a 2-channel electrocardiogram at a paper speed of 25 min/s to confirm the sinus origin of the RR interval data. After this, all questionable portions containing artifacts or ectopic beats were excluded manually, and only segments with >90% qualified beats were included in the final analysis. The details of this technique have been described previously.[13,15]

An autoregressive model was used to estimate the power spectrum densities of HR variability.[15,16] Linear trends were abolished from the RR interval data segments of 512 samples to make the data more stationary. The power spectra were quantified by measuring the area in 2 frequency bands: 0.04 to 0.15 Hz (low frequency) and 0.15 to 0.40 Hz (high frequency). The ratio of these frequency components was also calculated. The mean length and standard deviation of all RR intervals were computed as time domain measures.

Approximate entropy is a measure that quantifies the regularity of time series. The details of the method have been described by Pincus and Huang[6] and Pincus and Goldberger,[9] and recently by us.[13] Data for the analyses of approximate entropy from the 24-hour measurements were divided into segments of 4,000 RR intervals and averages calculated for these. Two input variables, m and r, must be fixed in order to calculate approximate entropy, and m = 2 and r = 20% of the standard deviation of the data sets were chosen as suitable values on the basis of previous findings of good statistical validity.[6,9] Approximate entropy values were also calculated with various r values (from 0.1 to 0.3) for all subjects.

The detrended fluctuation analysis technique is a modified root-mean-square analysis of a random walk that has been validated for physiologic time series and quantifies the presence or absence of fractal correlation properties.[5,10,17–19] The root-mean-square fluctuation of integrated and detrended time series is measured in each observation window and plotted against the size of the window on a log-log scale. In this study, HR correlations were defined separately for short-term (≤11 beats, α_1) and long-term (>11 beats, α_2) fluctuations in the RR interval data (short- and long-term scaling exponents) based on the previous finding of a ''crossover point'' on the log-log plot.[5,19] The details of this method have been described previously.[5,10,17,18] The effect of the number of excluded beats, i.e., ventricular premature beats, on detrended fluctuation analysis was studied by increasing progressively the number of deleted beats from the same data set. The short-term scaling exponent did not change significantly if <15% of the beats were randomly excluded. In the final analysis only segments containing >90% pure sinus beats were included. The number of ventricular premature beats or qualified RR intervals did not differ significantly between groups.

Statistical analysis: Results are expressed as mean ± SD. The Mann-Whitney U test was used to compare data between groups, and the Spearman correlation coefficient to calculate the correlation between the dynamic measures and conventional indexes of heart rate variability. A p value <0.05 was considered significant. Stepwise multiple regression analysis was performed to find the strongest independent predictor to differentiate the coronary artery disease group from healthy controls.

RESULTS

Clinical characteristics of the coronary patients are listed in Table I. They had significantly higher values for the short-term scaling exponent than the healthy controls ($p < 0.001$, Figures 1 and 2 and Table II), and also a higher long-term scaling exponent ($p < 0.01$), whereas approximate entropy was lower (with $r = 0.2$ [$p < 0.05$] and with $r = 0.1$ [$p < 0.01$]). There was no significant difference in the mean RR interval between groups, but the standard deviation of all the RR intervals was lower in the coronary artery disease group ($p < 0.01$), as was high-frequency spectral power ($p < 0.05$). In the stepwise multiple regression analysis, the short-term fractal scaling exponent was the strongest independent predictor in differentiating stable coronary patients from healthy controls in this study.

As expected, all the time and spectral measures of HR variability demonstrated highly significant correlations with each other (from $r = 0.65$ [$p < 0.001$] to $r = 0.81$ [$p < 0.001$]). The short-term scaling exponent and approximate entropy were not related to any single measure of HR variability, but correlated significantly with the ratio of low- to high-frequency spectral components ($r = 0.76$ [$p < 0.001$] and $r = -0.35$ [$p < 0.01$], respectively). When the groups were matched ($n = 32$ for both) with respect to the ratio between the low- to high-frequency spectral components (3.5 ± 1.6 vs 3.2 ± 1.1, p = NS), the short-term scaling exponent value was still higher in the coronary patient group (1.31 ± 0.15 vs 1.10 ±

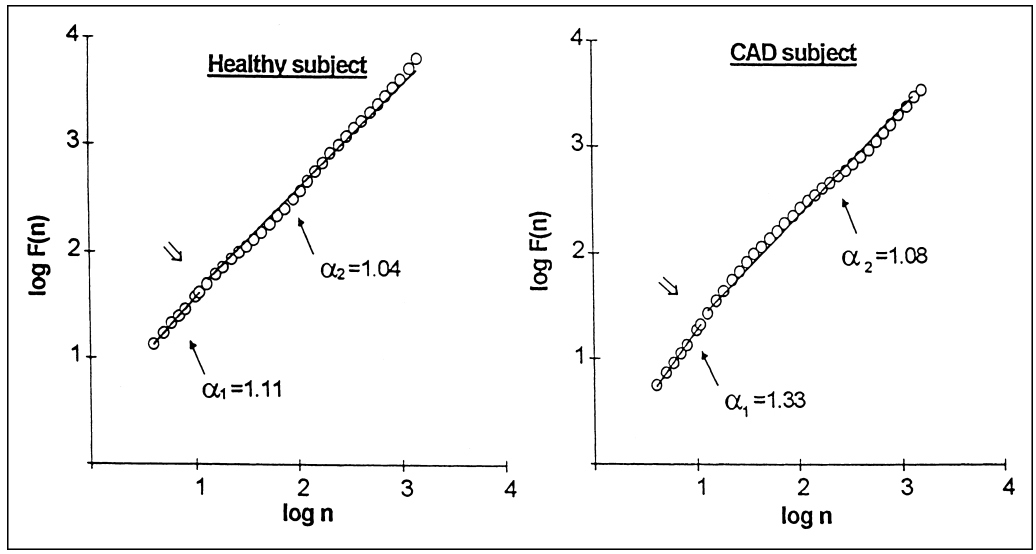

FIGURE 1. Examples of detrended fluctuation analysis data for a healthy subject and a patient with stable angina pectoris. The healthy subject typically shows a short-term scaling exponent (α_1) value ~1.0, indicating physiologic fractal behavior of heartbeat dynamics. In contrast, the patient with stable angina pectoris shows a long-term scaling exponent (α_1) ~1.3, indicating an alteration in fractal correlation properties. Note the "crossover" behavior in the 2 scaling exponents *(arrows)*, best seen in the data from the patient.

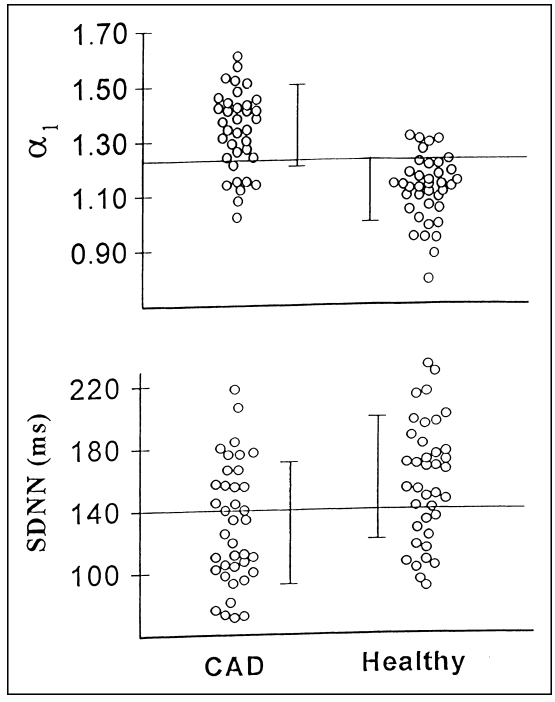

FIGURE 2. Individual values of the short-term scaling exponent (α_1) and standard deviation of all RR intervals (SDNN) of healthy subjects and patients with stable angina pectoris.

0.12, p <0.001). Also, when the groups were matched (n = 32 for both) with respect to the standard deviation of all the RR intervals, the patients had higher short-term scaling exponent values (1.34 ± 0.14 vs 1.11 ± 0.13, p <0.001) and lower approximate entropy values (0.92 ± 0.18 vs 1.04 ± 0.14, p <0.01). When approximate entropy was computed with different r values the coronary patient group had significantly smaller approximate entropy values than controls when r was between 0.1 and 0.25, but the groups did not differ from each other when the r value 0.3 was used. No significant association was observed between the short-term scaling exponent of HR behavior and the following clinical variables: age (r = −0.2, p = NS), sex (1.22 ± 0.18 in men vs 1.20 ± 0.15 in women, p = NS), angiographic severity of coronary artery disease (1.31 ± 0.13 in patients with 1-vessel disease vs 1.31 ± 0.17 in patients with 3-vessel disease, p = NS), functional class (1.32 ± 0.15 in class 2 vs 1.38 ± 0.16 in class 3, p = NS), or left ventricular ejection fraction (r = 0.1, p = NS).

DISCUSSION

The main findings of this study are compared with healthy controls. Patients with stable angina pectoris had altered correlation properties in their RR interval dynamics (i.e., loss of normal fractal characteristics and enhanced regularity in HR tracings as estimated by dynamic measures of HR behavior). Furthermore, the short-term fractal scaling exponent performed better than other measures in detecting abnormalities in HR behavior in this group of patients. Previous studies have shown that healthy heartbeat dynamics have a fractal-like temporal structure, with self-similar fluctuations over a wide range of time scales.[20,21] This feature corresponds to a fractal scaling exponent value of ~1 in detrended fluctuation analysis.[5] The present study shows that this normal fractal property of RR interval dynamics is altered in patients with stable angina pectoris. The steeper slopes of correlation properties of the RR interval time series indicate a *reduction* in fractal correlation.[5,10] Of interest, similar changes in the short-term scaling exponent have been previously described in healthy elderly subjects compared with healthy young subjects.[10]

TABLE II 24-Hour Heart Rate Variability Data

	Patients With Coronary Artery Disease (n = 38)	Healthy Controls (n = 38)
Mean RR interval (ms)	858 ± 119	889 ± 122
SDNN (ms)	131 ± 39†	157 ± 37
HF power (ms^2)	236 ± 294*	364 ± 357
LF power (ms^2)	682 ± 539	911 ± 746
LF/HF ratio	4.0 ± 2.3	3.1 ± 1.7
α_1	1.34 ± 0.15‡	1.11 ± 0.12
α_2	1.10 ± 0.08†	1.04 ± 0.06
ApEn	0.93 ± 0.17*	1.02 ± 0.15

*p <0.05; †p <0.01; ‡p <0.001, significance of differences between patients with uncomplicated coronary artery disease and healthy controls.

Values are expressed as mean ± SD.

ApEn = approximate entropy; HF = high-frequency power component of heart rate variability; LF = low-frequency power component of heart rate variability; Mean RR = average of lengths of RR intervals; SDNN = standard deviation of all RR intervals.

The background for altered short-term fractal scaling properties is speculative. This finding may be partly related to changes in the spectral characteristics of HR behavior. In patients with stable angina pectoris, a significant reduction in the high-frequency spectral band indicates a dominant role for the low-frequency control mechanisms. The loss of high-frequency fluctuations may correspond to more regular (less complex) short-term signal behavior associated with a higher short-term scaling exponent and a lower approximate entropy value. The ratio of the low- to high-frequency components did correlate with the short-term fractal scaling exponent of heartbeat behavior in this study. However, fractal correlation properties appear to probe features of the data that are not simply related to spectral ratios. Indeed, when the groups were matched with respect to the ratio between the low- to high-frequency spectral components, the short-term scaling exponent value was still significantly higher in coronary patients than in healthy subjects, confirming that dynamic analysis of heartbeat behavior gives complementary and independent information that cannot be detected by traditional spectral analysis techniques.[18]

Approximate entropy is a recently introduced statistic for quantifying the predictability or regularity of time series data. It measures the logarithmic likelihood that runs of patterns that are close to each other will remain close in the next incremental comparison. A greater likelihood of consistent patterns (high regularity) producing smaller approximate entropy values corresponds to less randomness in time series. Analysis of the data of this study revealed that patients with stable angina pectoris had lower approximate entropy than healthy subjects, consistent with a reduced complexity of RR interval dynamics. Reduction of complexity was observed with all recommended r values,[6] but not with the r value 0.3, which results in a loss of detailed system information. Reduced complexity in HR dynamics has been previously found in sick neonates and in patients with postoperative complications after cardiac surgery.[11,12] In contrast, higher values for approximate entropy have been observed in patients with a previous myocardial infarction compared with healthy controls.[13] High complexity values in postinfarction patients correlate with different spectral characteristics in HR variability, i.e., reduction in low-frequency component and low- to high-frequency ratio in patients with a prior myocardial infarction,[13,22] in contrast to increased low- to high-frequency ratio in patients with stable angina pectoris.[23,24] The basis of these differences remains to be determined.

Fractal correlation properties and approximate entropy in this study with relatively small group sizes were not related to the clinical or angiographic severity of coronary artery disease, suggesting that the loss of fractal correlation properties and the reduction in heartbeat complexity are not simply a consequence of end-organ damage caused by ischemic heart disease, but may reflect altered neuroautonomic interaction that may predispose to the development of ischemic heart disease. Further studies in larger populations are needed to confirm the utility of these new dynamic measures of HR variability in the diagnosis and prognosis of coronary artery disease, as well as to elucidate the mechanisms of alterations in fractal scaling exponents and complexity measures.

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