The «Chaos Theory» and Nonlinear Dynamics in Heart Rate Variability Analysis: Does it Work in Short-Time Series in Patients with Coronary Heart Disease?

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Background: Dynamic analysis techniques may quantify abnormalities in heart rate variability (HRV) based on nonlinear and fractal analysis («chaos theory»). The article emphasizes clinical and prognostic significance of dynamic changes in short-time series applied on patients with coronary heart disease (CHD) during the exercise electrocardiograph (ECG) test.

Methods: The subjects were included in the series after complete cardiovascular diagnostic data. Series of R-R and ST-T intervals were obtained from exercise ECG data after sampling digitally. The «range rescaled analysis» method determined the fractal dimension of the intervals. To quantify fractal long-range correlation's properties of heart rate variability, the detrended fluctuation analysis technique was used. Approximate entropy (ApEn) was applied to quantify the regularity and complexity of time series, as well as unpredictability of fluctuations in time series.

Results: It was found that the short-term fractal scaling exponent (α_1) is significantly lower in patients with CHD (0.93 ± 0.07 vs 1.09 ± 0.04 ; $P < 0.001$). The patients with CHD had higher fractal dimension in each exercise test program separately, as well as in exercise program at all. ApEn was significant lower in CHD group in both RR and ST-T ECG intervals ($P < 0.001$).

Conclusions: The nonlinear dynamic methods could have clinical and prognostic applicability also in short-time ECG series. Dynamic analysis based on «chaos theory» during the exercise ECG test point out the multifractal time series in CHD patients who loss normal fractal characteristics and regularity in HRV. Nonlinear analysis technique may complement traditional ECG analysis.

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«chaos theory»; nonlinear dynamics; heart rate variability;
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Heart rate variability (HRV) reflects the modulation of cardiac function by autonomic and other physiological systems, and its measurements from electrocardiograph (ECG) recordings may be the useful method for both clinical and scientific purposes.

No physiological variables will give a time series that is stationary or periodic. However, the beat-to-beat fluctuation in heart rate partly reflects the interplay between various perturbations of cardiovascular function and the response of the cardiovascular regulatory systems to these perturbations and initially raised behavior.¹ Thus, by studying HRV,

we have an opportunity to study the cardiac dynamic behavior influenced by a variety of endogenous and exogenous factors. Continuous changes in sympathetic and parasympathetic neural impulses exhibit changes in heart rate and cause oscillation around the mean heart rate. The increasing evidence to suggest that the heart is not a periodic oscillator under normal physiologic conditions and the commonly used moment statistics of HRV may not be able to detect subtle, but important changes in heart rate time series.²

Heart rate variability has been analyzed conventionally with linear statistical measures (time

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and frequency domain methods), which measure the overall magnitude of RR intervals fluctuations around its mean value.³ However, it provides limited information about HRV, mostly because nonlinear mechanisms seem to be also involved in the genesis of heart rate dynamics. Therefore, several new analysis method of heart rate behavior, motivated by nonlinear dynamics and «chaos theory», has been developed to quantify the dynamics of heart rate fluctuations.⁴ They may uncover abnormalities in the time series data, which were not apparent using conventional linear methods. A few studies have shown that decreased fluctuation of RR intervals implicates an increased risk for arrhythmic events, an increased mortality rate in patients with a previous myocardial infarction, and increased risk for sudden death.^{5,6}

The recent nonlinear studies mostly analyzed data from long-time series of RR intervals based on ambulatory 24-hours ECG recording. However, that series, during the daily life are not so controlled and comparable between the subjects, because of different activity in the same time. The long-time series results are based on whole RR interval data analysis, so series sometimes, are not suitable for subtle dynamic changes analysis.⁷

This study was designed to test the hypothesis that some dynamical analysis methods can reveal subtle abnormalities in heart rate behavior not only in long-time series from 24-hours ECG, but also in short-time heartbeat series (approximately 15 minutes and approximately 2000 RR or ST-T intervals) during the controlled, comparable regimens between the subjects as exercise ECG test is. In addition, the study was performed for the first time not to analyze only dynamic changes in RR intervals, but also the possible subtle HRV changes in ST-T intervals.⁷

PATIENTS AND METHODS

Patients

Two hundred consecutive patients with stable coronary heart disease (CHD) without previous myocardial infarction were included in the series (100 males), based on history of chest pain and non-invasive diagnostic measurements (ECG at rest, Doppler echocardiography, 24-hours continuous ECG, exercise ECG test, and laboratory coronary risk factors data). Coronary heart disease was confirmed by angiographic results.

No cardiac medication was allowed on day of testing, and β -blocking therapy had been withdrawn at least 7 days before and calcium antagonists at least 2 days before. Patients with silent ischemia during the 24-hour ECG recording and diabetes mellitus were excluded.

The control group consisted of 100 randomly selected age-matched (mean age 57 ± 6 years), and sex-matched (50 male) healthy subjects. All controls after a complete noninvasive examination and their medical history revealed no cardiovascular disease or use of medication. They had normal ECG at rest, echocardiography data (M-mode, two dimensional, and Doppler echocardiography), 24-hours ECG recording, normal arterial blood pressure, and fasting blood glucose.

An exercise ECG on all subjects for HRV analysis was obtained using a symptom or ECG changes limited test. A horizontal or down sloping ST-T segment depression of ≥ 0.1 mV occurring 0.08 second after the J point was considered to be of ischemic origin.

METHODS

Series of R-R intervals were obtained from high resolution ECG during the exercise ECG test on sampling frequency 1000 Hz, and the recording time scale was approximately 15 minutes and about 2000 beats. The ECG data were digitized by the Wave Book 512 (Iotech., Cleveland, Ohio, USA), and transferred to a computer for analysis.⁸

The RR interval series was passed through a filter that eliminates noise, artifacts, and premature beats. All RR interval series was first edited automatically, after which careful manual editing was performed by visual inspection of the each RR interval. After this, all questionable portions were excluded manually, and only segments with >90 % pure sinus beats were included in final analysis. The ST-T interval series was edited manually after signal passed (moving average) filter with own developed ST-T segment analyzing software.⁷

The mean length of all RR and ST-T intervals and standard deviation (SD) of intervals were computed as time domain measures. Three different nonlinear and fractal methods were applied: fractal dimension (FD), detrended fluctuation analysis (DFA), and approximate entropy (ApEn).

The FD was calculated over the Hurst exponent (H) by the formula: $FD = 2 - H$. The Hurst

exponent of the RR and ST-T interval series was determined by the (range rescaled analysis):

$$(R/S) : \{R(n)/S(n) \sim n^H\},$$

where H is the Hurst exponent. Hurst exponent $= \log(R/S)/\log(n)$, where n is the length of the time box.⁹ Hurst exponent of 0.5 represents signal with the characteristics of ordinary random walk or Brownian motion. Values for $H < 0.5$, reflect negative correlation between the increments or antipersistent time series, and for $H > 0.5$, positive correlation between the increments or persistent natural series.^{10,11} Fractal dimension for the first time was determined separately for each program of exercise test, which could show the possible multifractal time series.

DFA is a modified root mean square analysis of a random walk used to quantify fractal long-range correlation properties of the HRV.¹² It quantifies the presence or absence of fractal long-range correlation properties. Root mean square fluctuation of integrated and detrended time series is calculated by formula:

$$F(n) = \sqrt{1/N \sum_{k=1}^n [y(k) - y_n(k)]^2}.$$

This calculation was repeated over all time scales (box size) to characterize the relationship between $F(n)$, the average fluctuation, as a function of box size. Typically, $F(n)$ will increase with box size n . A linear relationship on a log-log plot indicates the presence of power law (fractal) scaling.^{13,14}

In this study, HRV was characterized by a scaling exponent α , the slope of the linear relating $\log F(n)$ to $\log(n)$, separately for short-term (≤ 11 beats per box, α_1), and long-term (≥ 11 beats per box, α_2) fluctuations in the RR and ST-T series data. ApEn was used to measure the complexity of time series data. It also quantified the regularity or predictability of data. ApEn measured the logarithmic likelihood runs of patterns that are close to each other and will remain close in next incremental comparison.¹⁵ Two input variables, m and r , have to be fixed to compute ApEn. The values, $m = 2$ and $r = 20\%$ of the SD of the data sets have been recommended for time series.^{16,17}

Statistical Analysis

The data were analyzed using the commercially available SPSS software (SPSS for Windows, ver-

sion 11.0, SPSS Inc. Chicago, IL, USA). Results are expressed as mean $\pm$ SD. A P value < 0.05 was considered significant. Student's t -test for normally distributed variables and nonparametric Mann-Whitney U test for continuous values were used to compare data between groups. Receiver operating characteristic (ROC) analysis was used to plot the sensitivity versus one-specificity for the 18 logistic regression models (plus basic model).^{18,19}

RESULTS

The baseline characteristics from noninvasive cardiovascular data of healthy controls and patients with CHD are listed in Table 1. There was a significant difference between the CHD patients and healthy controls in maximum ST-T segment depression during the exercise ECG test as well as in metabolic oxygen consumption.

The heart rate variables during the exercise ECG test were presented in Table 2. There were no differences observed in conventional linear time domain measures of HRV (average RR and ST-T intervals and SDNN).

The FD was significantly higher in patients with CHD, but only in RR interval series. During the program I and program II exercise ECG test, the most significant difference occurs between the values of FD for the two populations.

The results of exercise test data set show existence of crossover phenomena between short-time scales by the DFA method. Healthy subjects typically show physiologic fractal behavior of heartbeat dynamics, whereas the patients with CHD show an alteration in fractal correlation properties. A significant difference was found between patients with CHD and healthy controls in short-time scales of DFA (α_1), both in RR and ST-T intervals, but not in long-time DFA series (α_2).

ApEn was significantly lower in patients with CHD, both in RR and ST-T intervals data.

The results of nonparametric Mann-Whitney U test were practically the same compared to Student's t -test results, except for FD value in program II exercise ECG test for ST-T interval analysis. Those results could be possible and can be presented as (box and whisker) graphs.

ROC analysis unveiled 19 models of logistic regression with predictive values of linear and nonlinear variables. First, the basic logistic regression model was applied based on noninvasive cardiovascular data (whole variance/ $R^2_s = 0.273$; ROC

Table 1. The Baseline Characteristics of Noninvasive Cardiovascular Data

Variables	Healthy (100)		CHD Patients (200)		t-test	P
	$\bar{x}$	SD	$\bar{x}$	SD		
Age	57.13	5.88	59.37	8.58	1.176 ^a	NS
ECG at rest (freq.)	69.07	10.29	69.23	12.31	0.057 ^b	NS
Exercise ECG ST-T depression (mm)	0.26	0.15	1.82	0.65	12.871 ^a	***
Exercise MET (O ₂ L/min)	8.81	1.67	7.40	1.01	3.976 ^a	***
ECHO EF (%)	64.10	4.76	61.60	5.03	1.978 ^b	NS
E/A (m/s)	1.03	0.20	0.79	0.19	4.793 ^b	***
LVendD (mm)	52.13	2.49	56.47	3.39	5.644 ^b	***
24-hours ECG (freq.)	74.70	8.49	71.30	9.45	1.466 ^b	NS
24-hours ECG ST-T depression (mm)	0.23	0.16	1.68	0.63	12.159 ^a	***

Values are expressed as mean $\pm$ SD.

^aVariance (SD²) statistical significant difference; ^bvariance equal.

P < 0.05; **P < 0.01; ***P < 0.001, significance level for differences between CHD patients and healthy controls, NS, no significance.

ECG = Electrocardiography; LV = left ventricular; E/A = wave diastolic echocardiography function; MET = metabolic oxygen consumption; ECHO EF = echocardiography ejection fraction.

Table 2. Linear and Nonlinear Heart Rate Variables Data From Exercise ECG Test

Variables	Healthy (100)		CHD Patients (200)		t-test	P
	$\bar{x}$	SD	$\bar{x}$	SD		
Mean RR interval (ms)	621.60	50.17	601.50	67.42	1.310 ^b	NS
SD RR (ms)	119.83	23.82	122.23	28.20	0.356 ^b	NS
Mean ST-T interval (ms)	200.93	13.37	198.77	13.97	0.614 ^b	NS
SD ST-T (ms)	23.60	4.77	24.13	5.70	0.393 ^b	NS
RR FD pre-trigger	1.34	0.04	1.31	0.02	4.403 ^a	*
RR FD Program I	1.26	0.05	1.36	0.03	10.023 ^a	***
RR FD Program II	1.18	0.05	1.41	0.03	21.311 ^a	***
RR FD Relaxation	1.27	0.05	1.37	0.02	9.368 ^a	***
RR FD at all	1.26	0.04	1.36	0.02	12.071 ^a	***
ST-T FD pretrigger	1.38	0.04	1.36	0.04	1.307 ^b	NS
ST-T FD Program I	1.40	0.06	1.42	0.04	0.960 ^a	NS
ST-T FD Program II	1.44	0.06	1.46	0.04	1.541 ^b	NS
ST-T FD Relaxation	1.37	0.03	1.41	0.04	3.766 ^a	***
ST-T FD at all	1.40	0.03	1.41	0.03	1.543 ^b	NS
RR interval α_1	1.09	0.04	0.93	0.07	10.775 ^a	***
RR interval α_2	1.35	0.04	1.35	0.04	0.911 ^b	NS
ST-T interval α_1	1.12	0.04	0.82	0.11	13.869 ^a	***
ST-T interval α_2	1.39	0.05	1.41	0.05	1.309 ^b	NS
RR interval ApEn	1.08	0.13	0.91	0.13	4.876 ^b	***
ST-T interval ApEn	1.07	0.11	0.94	0.13	4.165 ^b	***

Values are expressed as mean $\pm$ SD.

^aVariance (SD²) statistical significant difference; ^bvariance equal.

P < 0.05; **P < 0.01; ***P < 0.001, significance level for differences between CHD patients and healthy controls, NS, no significance.

FD = Fractal dimension; α_1 and α_2 = detrended fluctuation analysis in short and long-time series; ApEn = approximate entropy.

Table 3. Results of Logistic Regression Models

Variables	χ^2 test	ROC Area	P
Mean RR interval	2.9	0.752	0.231
Mean ST-T interval	0.3	0.757	0.852
FD RR interval pre-trigger	15.1	0.989	0.0001
FD RR interval relaxation	51.8	0.998	0.00001
FD ST-T interval pre-trigger	2.0	0.758	0.16
FD ST-T interval relaxation	12.7	0.836	0.00036
RR intervals α_1	53.8	0.987	0.00001
RR interval α_2	0.5	0.785	0.46
ST-T interval α_2	2.9	0.761	0.009
RR interval ApEn	10.9	0.834	0.00095
ST-T interval ApEn	10.4	0.850	0.00125

FD = fractal dimension; α_1 and α_2 = detrended fluctuation analysis in short and long-time series; ApEn = approximate entropy.

area = 0.752). This data was not significant, but cause of possible correlation with linear and non-linear data, it were included in other 18 models. The most interesting ROC analyzed model results are presented in Table 3. Models with absolutely separated CHD patients from healthy subjects because of high significant have not been presented. One of most interesting model (ApEn in RR interval series) was presented graphically in Figure 1.

Figure 1. ROC analysis of sensitivity and one - specificity for the dependence of CHD due to ApEn values in RR interval analysis (area = 0.834, P = 0.00095).

DISCUSSION

Nonlinear methods are based on the «chaos theory» and fractals. Chaos describes natural system in a different way, because it can account for nature's randomness and no periodicity. The «chaos theory» could help in better understanding heart rate dynamics taking that the healthy heartbeat is slightly irregular and in some way chaotic. Non-linear fractal methods may give new insights into HRV in the context of physiological changes.²⁰

Traditional linear statistical measures provide limited information about HRV, because nonlinear mechanisms are also involved in the genesis of heart rate dynamics. A number of new methods have recently been developed to quantify complex HRV.^{21,22}

The main goal of this study was to investigate the clinical and prognostic significance of nonlinear methods in HRV in short-time series under controlled physical activity during the exercise ECG test. In addition, this study tested the hypothesis that subtle dynamic changes of HRV could be already seen in ST-T segment in patients with stable CHD.

The patients with stable coronary artery disease showed no persistent time series, altered correlation properties in their RR and ST-T interval dynamics, i.e., loss of normal fractal characteristics, and enhanced regularity and complexity in heart rate tracings.

Dynamic analysis of HRV in this study gave independent information that could not be detected by traditional linear time-domain analysis technique. Healthy subjects have a distinct circadian rhythm

of HRV, but this rhythm seems to be blunted in stable CHD patients. Fractal correlation properties and FD may reflect altered neuroanatomic interaction that may predispose to the development of CHD.

The time series of RR intervals during the exercise ECG test mostly had a time duration of approximately 15–18 minutes (about 2000 heartbeats). But, in paper only 4 regimens are statistically presented (15 minutes at all; so call pretrigger program –3 minutes at rest before test is starting, program I and II, each 3 minutes, and the relaxation program which was restricted to 6 minutes). Except in a few cases, CHD patients were not able to complete higher exercise programs (III or IV of standard Bruce protocol) for medical reasons. Statistical analysis, to be relevant was based only on programs, which all subjects were passed.

The results of FD showed a clear separation between CHD patients and healthy control subjects, not only in whole time series, but also in program I and II, and during the relaxation exercise ECG test. The long-time (memory effect) quantified by the value of the FD is found to decrease in CHD patients and the oscillations around linear trend lines are more. The FD calculated over the scaling Hurst exponent represents the global behavior of nonlinear trends with oscillations around included. This type of behavior suggests the presence of multiple timescale processes related to multifractality of the time series during the exercise test programs.²³

The results of R/S method analysis are supported by the DFA results. The short-term fractal-scaling exponent was very sensitive about the fractal organization of heartbeat behavior. Some previous studies has shown that healthy heartbeat dynamics have a fractal-like temporal structure, with self-similar fluctuations over a wide range of time scales.⁴ This study implicated that this normal fractal property of RR interval dynamics is altered in patients with coronary artery disease. This finding is partly related to changes in the spectral characteristics of heart rate behavior.²⁴ In patients with uncomplicated coronary artery disease, a significant reduction in the high frequency spectral band indicates a dominant role of the low frequency band.²⁵

The loss of high frequency fluctuations corresponds to more regular (less complex) short-term signal behavior associated with a higher short-term scaling exponent as well as a lower ApEn value. The findings in this study did correlate with the short-term fractal-scaling exponent of heartbeat behavior.

It confirms that dynamic analysis of heartbeat behavior gives complementary and independent information that cannot be obtained by traditional spectral analysis techniques.²⁶

The changes in heart rate behavior variables in this study were more sensitive than clinical and ECG changes, suggesting that the loss of fractal correlation properties and the reduction in heartbeat complexity are not simply caused by ischemic heart disease, but probably by altered sympathovagal interaction. The concept of sympathoexcitation is supported by observations of more complex Poincaré plots of successive RR intervals in heart failure patients with high norepinephrine levels.²⁶ Similar changes have also been observed upon intravenous infusion of physiological doses of norepinephrine in young healthy adults.²⁷ Random, uncorrelated beat-to-beat RR interval behavior may also reset the repolarization dynamics of the myocardium and thereby increase vulnerability to arrhythmogenesis.²⁸

ApEn was performed to quantify the regularity or predictability the time series data during exercise test. It has been applied to classify complex systems that include both deterministic chaotic and stochastic processes with 2 other nonlinear methods, because ApEn measure cannot certify chaos alone. ApEn was significantly lower in patients with CHD, both in RR and ST-T intervals during the test. Reduced complexity of heart rate dynamics has been found in sick neonates and in patients with post-operative complications after cardiac surgery.²⁹ A lower sympathetic tone may also explain the reduction in the very high frequency spectral component and the change in beat-to-beat complexity and, consequently, the decrease in ApEn. The moderate correlation of fractal correlation properties and ApEn suggests that dynamic fractal behavior and the complexity of RR interval dynamics are related to neuroautonomic interactions. The abnormalities in the autonomic modulation of heart rate could be observed in various cardiovascular and cerebrovascular disorders. Altered cardiovascular neural regulation may be a sign of an underlying subclinical vascular disease. The prognostic role of altered short-term heart rate behavior is that it may reflect impairment in the adaptive systems during acute perturbations, such as myocardial ischemic events.

In conclusions, this study shows that fractal correlation properties of RR intervals are altered in patients with stable CHD. The subtle nonlinear changes have been partly seen also in ST-T

intervals, and dynamic analysis during the exercise ECG test separately suggested the presence of multifractal time series.³⁰ Further studies in larger population will be needed to define the clinical utility of new fractal measurements of HRV in short-time series for risk stratification in patients with CHD, and other cardiovascular disorders. We could make a conclusion that dynamic analysis of HRV may be also applied (inside) RR intervals and in different daily activities so closed to real life.

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