

Non-Linear Analysis of Heart Rate Variability in Patients with Coronary Heart Disease

G Krstacic, A Krstacic, M Martinis, E Vargovic, A Knezevic, A Smalcelj,
M Jembrek-Gostovic, D Gamberger, T Smuc

Institute for Cardiovascular Disease and Rehabilitation, University Clinic "Vuk Vrhovac", "Rudjer Bosković" Institute, CDV info, Clinical Hospital Center "Rebro", Zagreb, Croatia

Abstract

The article emphasizes clinical and prognostic significance of non-linear measures of the heart rate variability, applied on the group of patients with coronary heart disease (CHD) and age-matched healthy control group. Three different methods were applied: Hurst exponent (H), Detrended Fluctuation Analysis (DFA) and approximate entropy (ApEn). Hurst exponent of the R-R series was determined by the range rescaled analysis technique. DFA was used to quantify fractal long-range-correlation properties of heart rate variability. Approximate entropy measures the unpredictability of fluctuations in a time series. 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 lower Hurst exponent in each program of exercise test separately, as well as approximate entropy than healthy control group ($P < 0.001$).

1. Introduction

Heart rate variability (HRV) reflects the modulation of cardiac function by autonomic and other physiological systems, and its measurements from electrocardiography (ECG) recordings during an exercise ECG test may be the useful method for both clinical and scientific purposes [1,2].

Traditional linear statistical measures (time and frequency domain) provide limited information about HRV, mostly because non-linear mechanisms seem to be also involved in the genesis of HR dynamics [3]. A number of new methods have been recently developed to quantify complex heart rate dynamics. They may uncover abnormalities in the time series data, which are not apparent using conventional linear statistic methods [4].

This study tested the hypothesis that fractal and complex measurements of HRV are altered in patients with CHD.

2. Methods

2.1. Patient groups

Fifty patients with CHD were included in the series, based on history of chest pain and non-invasive diagnostic measurements (ECG at rest, echocardiography, 24-hours ECG, exercise ECG test and laboratory coronary risk factors data), with ECG evidence of ischemic ST-segment depression (≥ 0.1 mV) during an exercise test.

They were 59 ± 8 years old, 26 male. 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 40 randomly selected age-matched (mean age 57 ± 6 years), and sex-matched (20 male) healthy subjects. All controls after a complete non-invasive examination and their medical history revealed no cardiovascular disease or use of medication. They had normal ECG at rest, echocardiography data (M-mode, 2-D dimensional and Doppler echocardiography), 24-hours ECG recording, normal arterial blood pressure and fasting blood glucose.

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

2.2. Analysis of HRV

Series of R-R intervals were obtained from high resolution ECG during the exercise ECG test (sampling frequency 1000 Hz), and the recording time scale was approximately about 1800 beats. The ECG data were digitised by the WaveBook 512 (Iotech. Cal. USA), and transferred to a computer for analysis.

The R-R interval series was passed through a filter that eliminates noise, artefacts and premature beats. All R-R interval series was first edited automatically, after which careful manual editing was performed by visual inspection of the each R-R interval. After this, all questionable portions were excluded manually, and only segments with > 90% sinus beats were included in final analysis[4].

The Hurst exponent of the R-R interval series was determined by the «range rescaled analysis» (R/S): $\{R(n) / S(n) \sim n^H\}$, where H is the Hurst exponent (H). Hurst exponent (H) = $\log(R / S) / \log(n)$ where n is the length of the time box.

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 anti persistent time series, and for $H > 0.5$, positive correlation between the increments or persistent natural series.

Hurst exponent was determined separately for each program of exercise test including 180 seconds baseline ECG before the exercise (so called “prê trigger”) and six minutes of relaxation after the exercise test.

Detrended fluctuation analysis, which is a modified root-mean-square analysis of a random walk, was used to quantify fractal long-range correlation properties of the HRV was used. DFA 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.

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, α_1), and long term (≥ 11 beats, α_2) fluctuations in the R-R series data [5].

Results are expressed as mean \pm standard deviation (SD). A p value < 0.05 was considered significant. The Mann-Whitney test was used to compare data between groups.

3. Results

The baseline clinical and heart rate variables of healthy controls and patients with coronary heart disease are listed in Table 1. There were no differences observed in conventional statistical linear measures of HRV (average RR intervals and SDNN). The Hurst exponent was significantly lower in patients with CHD, as well as approximate entropy. Figure 1 depicts

distribution of values of the Hurst exponent during the stages of exercise testing, for the CHD patients and control group. During the Program 1 and Program 2 stages, the most significant difference occurs between the values of Hurst exponent for the two populations. The results of exercise test data set show existence of crossover phenomena between short time scales by the DFA method. A significant difference was found between patients with CHD and healthy controls in short time scales. (Table 2). Healthy subjects typically show physiologic fractal behaviour of heartbeat dynamics, while the patients with CHD show an alteration in fractal correlation properties. There were no differences for the long-term series Approximate entropy was significantly lower in patients with CHD.

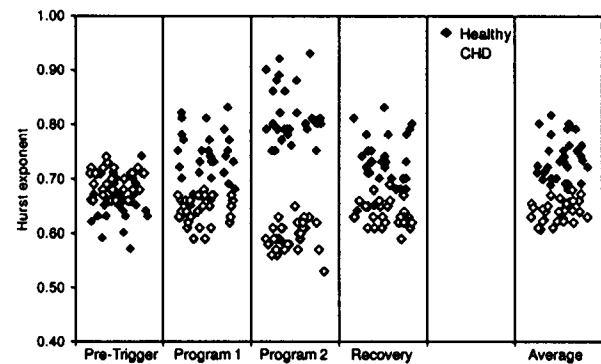


Fig 1. Distribution of Hurst exponent for the CHD patients and healthy control group, during different stages of the exercise testing.

4. Conclusions

The main goal was to investigate the clinical and prognostic significance of non-linear methods and to correlate the results of dynamic examinations between patients with CHD and healthy control group.

Results of this study give preliminary information on the usefulness of fractal analysis methods in risk stratification of patients with CHD.

The present study shows that normal fractal properties of R-R interval dynamics is altered in patients with CHD, as estimated by R/S and DFA methods. Dynamic analysis of HRV gives independent information that cannot be detected by traditional linear analysis technique. Healthy subjects have a distinct circadian rhythm of HRV, but this rhythm seems to be blunted in coronary heart disease (CHD) patients [4]. Fractal correlation properties and fractal dimension in this study may reflect altered neuroanatomic interaction that may predispose to the development of CHD. Further studies in larger population will be needed to further define the clinical utility of new fractal measurements of HRV for risk stratification in patients with CHD, but we could make a conclusion that

Table 1. Clinical variables of the subjects in the study.

Clinical data (n=90)	Healthy controls (n=40)	Patients with CHD (n=50)
Age (yrs)	57 ± 6	59 ± 8
Men / Women	20/20	26/24
ECG at rest (freq)	75	78
VPCs /hour	3 ± 0.5	4 ± 1.5
LV ejection fraction	64 ± 5.0	62 ± 4.9
E/A wave (m/s)	1.0 ± 0.2	0.8 ± 0.2
MET	8.8 ± 0.6	7.4 ± 1.0
ERG ST	0.3 ± 0.1	1.8 ± 0.6

ECG= electrocardiography; VPCs= ventricular premature contractions; LV= left ventricular; E/A wave= diastolic echocardiography function, MET= metabolic oxygen consumption, ERG ST= maximum ST depression during exercise test

Table 2. The heart rate variables of subjects in the study (linear and non-linear data (\bar{x} -mean value, SD-standard deviation and results of the t-test).

Variables	Healthy subjects		CHD		Significance
	\bar{x}	SD	\bar{x}	SD	
R-R	621,60	50,17	601,50	67,42	NS
SD R-R	119,83	23,82	122,23	28,20	NS
R-R H-Pre-trigger	0,66	0,04	0,69	0,03	*
R-R H-Program 1	0,74	0,05	0,64	0,03	***
R-R H-Program 2	0,82	0,05	0,60	0,03	***
R-R H-Relaxation	0,73	0,05	0,63	0,02	***
H R-R	0,74	0,04	0,64	0,02	***
R-R α_1	1,09	0,04	0,93	0,07	***
R-R α_2	1,35	0,04	1,35	0,04	NS
R-R ApEn	1,08	0,13	0,91	0,13	***

(* P value < 0.05; ** P value < 0.01, *** P value < 0.001; NS – Non significant)

R-R= RR intervals, SD R-R= standard deviation of all RR intervals, H Pretrigger= Hurst exponent in “pre-trigger”, H Program 1= Hurst exponent in first program of exercise test, H Relaxation= Hurst exponent in relaxation after exercise test, H R-R= mean value of Hurst exponent during the exercise text, α = fractal-like scaling exponent from detrended fluctuation analysis, ApEn= approximate entropy

dynamic analysis of HRV may enhance detection of coronary heart disease.

References

- [1] Huikuri HV. Heart rate variability in coronary artery disease. *Journal of Internal Medicine* 1995; 237: 349-57.
- [2] Tulppo MP, Makikallio TH, Seppanen T, Laukkanen RT, Huikuri HV. Vagal modulation of heart rate during exercise: effects of age and physical fitness. *Am J. Physiology* 1998; 274:424-29.
- [3] Goldberger AL. Non-linear dynamics for clinicians: chaos theory, fractals, and complexity at the bedside. *Lancet* 1996;347: 1312 –14.
- [4] Makikallio TM, Ristimae T, Airaksinen AE, Peng CK, Goldberger AL, Huikuri HV. Heart rate dynamics in patients with stable angina and utility of fractal and

complexity measures. *Am. Journal of Cardiology* 1998; 81:27-31.

- [5] Krstacic G, Martinis M, Vargovic E, Knezevic A, Krstacic A, Smalcelj A, Jembrek-Gostovic M. Non-Linear Dynamics in Patients with Stable Angina Pectoris. *Computers in Cardiology IEEE* 2001;28:45-48.
- [6] Krstacic G, Martinis M, Vargovic E, Krstacic A, Smalcelj A, Jembrek-Gostovic M. Non-Linear Dynamics in Heart Rate Variability. *Acta Clinica Croatica* 2001:40-49.

Address for correspondence:

Goran Krstacic
 Institute for Cardiovascular Disease and Rehabilitation
 Draskoviceva 13, 10 000, Zagreb, Croatia
 E-mail: goran.krstacic@zg.hinet.hr