Dynamic Non-Linear Changes in Heart Rate Variability in Patients with Coronary Heart Disease and Arterial HypertensionTreated by Amlodipine Besylate

G Krstacic[1], A Krstacic[2], M Martinis[3], E Vargovic[4], A Knezevic[3], M Jembrek-Gostovic[1], A Smalcelj[5], D Milicic[5], M Bergovec[6], M Gostovic[1]

Institute for Cardiovascular Disease and Rehabilitation[1], University Hospital of Traumatology[2], Institute "Rudjer Boskovic"[3], CDV info[4], University Hospital Centre «Rebro»[5], University Hospital «Dubrava»[6], Zagreb, Croatia

Abstract

The article emphasizes clinical and prognostic significance of non-linear measures of the heart rate variability (HRV). It was applied on the group of patients with stable coronary heart disease (CHD) and arterial hypertension (AH) before and after 6 months treatment by amlodipine besylate (5 mg daily). Two different methods were applied: Hurst exponent (H) and Detrended Fluctuation Analysis (DFA). 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. It was found that the short-term fractal scaling exponent (α_1) is significantly lower in patients with CHD, as well as Hurst exponent. But, after 6 months treatment with calcium channel blocker amlodipine besylate the results of HRV are normalize.

Keywords: non-linear dynamics, "chaos theory", heart rate variability, stable coronary heart disease, amlodipine besylate.

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 and arterial hypertension and could be better after treating by calcium channel blocker.

2. Methods

2.1. Patient groups

Fifty patients with stable coronary heart disease (CHD) without previous myocardial infarction and with arterial hypertension (≥ 150/90 mmHg) were included in the series, based on history of chest pain and non-invasive diagnostic measurements with ECG evidence of ischemic ST–segment depression (≥ 0.1mV) during an exercise ECG treadmill test and 24-hours dynamic ECG.

The HRV measurement was provided before and after 6 months treating by calcium channel blocker amlodipine besylate (5 mg daily).

They were 57 ± 6 years old, 25 male. Patients with silent ischemia during the 24–hour ECG recording and diabetes mellitus were excluded.

The control group consisted of 50 randomly selected age–matched (mean age 55 ± 7 years), and sex–matched (26 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 [6].

2.2. Analysis of heart rate variability

Series of R-R intervals were obtained from high resolution ECG during the exercise ECG test (sampling frequency about 1000 Hz), and the recording time scale was approximately about 1500 beats. The ECG data were digitised by the WaveBook 512, 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 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 > 85% sinus beats were included in final analysis[7].

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.

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. 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:

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

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 [6,7].

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

2.3. Amlodipine besylate

Amlodipine besylate (NORVASC*, Pfizer) is a type of medicine called a long-acting calcium channel blocker (CCB). Norvasc is used to treat high blood pressure and angina pectoris. Angina is often a pain or pressure in chest that keeps coming back when part of heart does not get enough blood. Norvasc works to relax the blood vessels. This means that blood pressure can be lower, and angina pain can be reduced or controlled.

3. Results

The baseline clinical and heart rate variables of healthy controls and patients with coronary heart disease and arterial hypertension are listed in Table 1. There were no differences observed in conventional statistical linear measures of HRV (average R-R intervals and SDRR). The Hurst exponent was significantly lower in patients with stable CHD and arterial hypertension before any medical treatment. 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

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

Clinical data (N=100)	**Healthy controls (N=50)**	**Patients with CHD (N=50)**
Age (yrs)	55 ± 7	57 ± 6
Men / Women	26/24	25/25
ECG at rest (freq)	80	88
VPCs /hour	3 ± 0.5	7 ± 1.5
LV ejection fraction	63 ± 5.2	59 ± 3.8
E/A wave (m/s)	1.1 ± 0.2	0.7 ± 0.2
MET	8.3 ± 0.6	7.2 ± 1.0
ERG ST (mm)	0.4 ± 0.1	1.6 ± 0.6

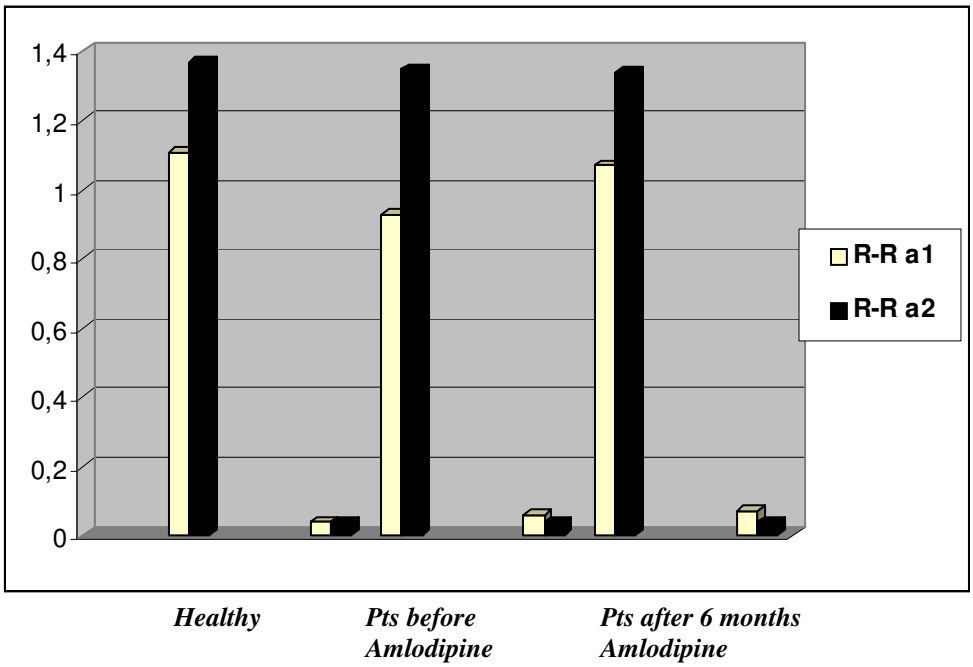
ECG= electrocardiography; VPCs= ventricular premature contractions; LV= left ventricular; E/A wave= diastolic echocardiography function, MET= metabolic oxygen consumption, ERG ST= maximum ST depression during exercise test

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).

	HEALTHY		***Pts before AMLODIPINE***		***Pts after 6 months AMLODIPINE***		
Variables	**X**	**SD**	**X**	**SD**	**X**	**SD**	**Signif.**
R-R	**620,63**	**50,17**	**605,52**	**67,42**	**607,34**	**67,42**	**NS**
SD R-R	**119,83**	**23,82**	**122,23**	**28,2**	**122,23**	**28,2**	**NS**
H R-R	**0,76**	**0,04**	**0,62**	**0,02**	**0,73**	**0,02**	*******
R-R α_1	**1,11**	**0,04**	**0,93**	**0,06**	**1,07**	**0,07**	*******
R-R α_2	**1,37**	**0,04**	**1,35**	**0,04**	**1,34**	**0,04**	**NS**

(* 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 R-R - mean value of Hurst exponent during the exercise text, α= fractal-like scaling exponent from detrended fluctuation analysis, (α_1 - short time series, α_2 – long term series)

Figure 1. The variations of detrended fluctuation analysis (DFA) during the exercise test before and after 6 months of taking the amlodipine besylate



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 are 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 [6,7]. Fractal correlation properties and fractal dimension in this study may reflect altered neuroanatomic interaction that may predispose to the development of CHD.

This study showed a benefit of using the calcium channel blockers in treatment of stable angina pectoris and arterial hypertension in relation to heart rate variability, possible because of calcium ions which play a fundamental role in the activation of cells.

An influx of calcium ions into the cell trough specific ion channels is required for myocardial contraction, and for determining peripheral vascular smooth muscle. The amlodipine besylate exert vasodilatator effects on the coronary vessels, as well as depressant effects on cardiac contractility, heart rate, and conduction [8]. All those effects may be important in mediating their antianginal effects. The intrinsic negative inotropic properties may be offset by a baroreceptor-mediated reflex augmentation of beta-adrenergic tone consequent to vasodilatation and a decrease in blood pressure.

Further studies in larger popopulation will be needed to further define the clinical utility of new fractal measurements of HRV for risk stratification in patients with CHD. We could make a conclusion that dynamic analysis of HRV during and after the treatment with some medicine may enhance detection of cardiovascular heart disease as well as the benefit of using some cardiovascular drugs in relation to changes of heart rate variability.

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Address for correspondence:
Goran Krstacic MD, Ph.D.
Institute for Cardiovascular Disease and Rehabilitation, Draskoviceva 13
10 000 Zagreb, Croatia
E-mail: goran.krstacic@zg.htnet.hr