

# The Chaos Theory and Non-linear Dynamics in Heart Rate Variability in Patients with Heart Failure

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## Abstract

*This study evaluate and quantify the non-linear dynamic changes of heart rate variability based on "chaos theory" and fractal mathematics in 250 patients with heart failure during 12 months. Some different non-linear methods were applied: Fractal dimension (FD), detrended fluctuation analysis (DFA) and Approximate entropy (ApEn). Fractal correlation properties and fractal dimension in this study may reflect altered neuroanatomic interaction that may predispose to the development of severe HF. It was found that the short-term fractal scaling exponent ( $\alpha_1$ ) is significantly lower in patients with HF. The patients with HF had also lower approximate entropy and higher fractal dimension with positive impact of modern HE therapy.*

## 1. Introduction

Heart rate variability (HIV) reflects the modulation of cardiac function by autonomic and other physiological systems, and its measurements from 24-hours electrocardiograph recording 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 HIV, 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 HIV are altered in patients with HF, and how significant is an impact of modern standard therapy.

## 2. Methods

The group of 250 patients with HF were included in the series, based on history and standard non-invasive diagnostic measurements (ECG, echocardiography, 24-hours ECG, exercise ECG test (partly) and laboratory data).

They were  $\geq 65$  years old, echocardiography EF LV  $< 40\%$ , NYHA class II-III and LVIDd  $> 2.9$  cm/m<sup>2</sup>. They all received standard therapy for heart failure (diuretics, digoxin,  $\beta$ -blockers, spironolactone, nitrate and ACE-i or ARB's).

The control group consisted of 100 randomly selected age-matched and sex-matched 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, 24-hours ECG recording, normal arterial blood pressure and fasting blood glucose.

Series of R-R intervals were obtained from high resolution ECG during the 24-hours ECG (sampling frequency 1000 Hz), and the recording time scale was approximately about 100 000 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, artifacts 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  $> 90\%$  sinus beats were included in final analysis [5].

The fractal dimension (FD) was estimated from the Hurst exponent of the R-R series. The Hurst exponent of the R-R interval series was determined by the «range rescaled analysis» (R/S).

Detrended fluctuation analysis (DFA), 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:

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

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  $\alpha$ , the slope of the linear relating  $\log F(n)$  to  $\log(n)$ , separately for short term ( $\leq 11$  beats,  $\alpha_1$ ), and long term ( $\geq 11$  beats,  $\alpha_2$ ) fluctuations in the R-R series data [6,7].

Approximate entropy (ApEn) is a measure and parameter that quantifies the regularity or predictability of time, and the creation of information in a time series. A low value of the entropy indicates that the time series is deterministic, and a high value indicates randomness.

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 HF are listed in Table 1. There were no differences observed in conventional statistical linear measures of HRV. The fractal dimension was significantly higher in patients with HF. The results show existence of crossover phenomena between short time scales estimated by the DFA method. A significant difference was found between patients with HF and healthy controls in short time scales (Table 2). The results show that patients with HF had loss normal fractal characteristics and enhanced regularity in HRV, while patients with modern therapy for HF after 12 months show benefit in HRV.

### 4. Discussion and conclusions

The main goal of study was to investigate the clinical and prognostic significance of non-linear methods and to correlate the results of dynamic examinations between patients with HF and healthy control group. Results of this study give preliminary information on the usefulness

of fractal analysis methods in risk stratification of patients with HF.

The present study shows that normal fractal properties of R-R interval dynamics are altered in patients with HF, 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 HF patients [6, 7]. Fractal correlation properties and fractal dimension in this study may reflect altered neuroanatomic interaction that may predispose to the development of HF.

In conclusion, the measurement of fractal scaling exponent in short-time series, fractal dimension and approximate entropy could give complimentary information on abnormal HR behaviour in patients with HF, and positive impact of modern standard treatment of HF patients. [9]

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 HF and some other cardiovascular diseases.

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

<b>Clinical data (N=400)</b>	<b>Healthy controls (N=100)</b>	<b>Patients with HF (N=250)</b>
<i>Age (yrs)</i>	61 ± 7	66 ± 6
<i>Men / Women</i>	50/50	200/50
<i>ECG at rest (freq)</i>	72	62
<i>VPCs /hour</i>	3 ± 0.5	30 ± 10
<i>LV ejection fraction</i>	65 ± 5.2	37 ± 3.8
<i>E/A wave (m/s)</i>	1.1 ± 0.2	06 ± 0.2
<i>LVIDd cm/m<sup>2</sup></i>	2,2 ± 0.6	3,2 ± 0,5

ECG= electrocardiography; VPCs= ventricular premature contractions; LV= left ventricular; E/A wave= diastolic echocardiography function.

Table 2. Heart rate variables (linear and non-linear data)

<i>Variables</i>	<i>HEALTHY Pts</i>		<i>HF Pts</i>		<i>HF Pts after 12 months</i>		<i>P</i>
	<i>X</i>	<i>SD</i>	<i>X</i>	<i>SD</i>	<i>X</i>	<i>SD</i>	
<i>R-R</i>	<b>641,25</b>	<b>49,17</b>	<b>620,50</b>	<b>57,42</b>	<b>617,24</b>	<b>43,42</b>	<b>NS</b>
<i>SD R-R</i>	<b>121,67</b>	<b>25,82</b>	<b>126,20</b>	<b>27,11</b>	<b>124,22</b>	<b>23,26</b>	<b>NS</b>
<i>FD R-R</i>	<b>1,20</b>	<b>0,04</b>	<b>1,57</b>	<b>0,02</b>	<b>1,36</b>	<b>0,02</b>	<b>***</b>
<i>R-R α<sub>1</sub></i>	<b>1,12</b>	<b>0,03</b>	<b>0,90</b>	<b>0,07</b>	<b>1,07</b>	<b>0,076</b>	<b>***</b>
<i>R-R α<sub>2</sub></i>	<b>1,35</b>	<b>0,03</b>	<b>1,39</b>	<b>0,05</b>	<b>1,33</b>	<b>0,02</b>	<b>NS</b>
<i>ApEn</i>	<b>1,06</b>	<b>0,02</b>	<b>0,88</b>	<b>0,04</b>	<b>1,01</b>	<b>0,04</b>	<b>***</b>

(\*\*\* P value < 0.001; NS – Non significant); R-R= RR intervals, SD R-R= standard deviation of all RR intervals, FD R-R - fractal dimension, α= fractal-like scaling exponent from DFA (α<sub>1</sub> - short time series, α<sub>2</sub> – long term series); ApEn – approximative entropy

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