FRACTAL DIMENSION AND POWER-LAW BEHAVIOR REPRODUCIBILITY AND CORRELATION IN CHRONIC HEART FAILURE PATIENTS

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ABSTRACT

Nonlinear analysis of HRV, particularly the fractal dimension and 1/f beta parameters, has been recognized to provide valuable information in the prognostic classification of cardiac patients. The reproducibility of these methods, however, is not known. In this study we addressed these issues in a population of chronic heart failure (CHF) patients. We analyzed 3 ECG Holter recordings from 22 clinically stable CHF patients by 1/f log scaling of power spectrum and the fractal dimension of the HRV curve, assessing the reproducibility of each index. Our results show that Fractal dimension parameter exhibits similar reproducibility and a higher reliability than both 1/f and spectral parameters. Moreover, we found that fractal dimension index is quite correlated with 1/f slope and describe possibly complementary aspects of heart rate dynamics.

1 INTRODUCTION

The analysis of heart rate variability (HRV) is a well-recognized tool in the investigation of the autonomic control of the heart [1]. Moreover, definitive evidence has recently been provided on the independent prognostic value of HRV with respect to well-established risk stratifiers such as depressed left ventricular function and frequent ventricular arrhythmias [2].

Although most studies on HRV have been performed using time- and frequency-domain linear methods, it has been suggested that nonlinear analysis of HRV might provide valuable information for the physiological interpretation of heart rate fluctuations and for the risk assessment of cardiac patients [1]. Among the numerous non-linear parameters related to the fractal behaviour of the HRV signal, two classes have gained wide interest in the last years: that based on the 1/f-like relationship, starting from the spectral power [3-7], and that based on Fractal features. The latter has traditionally been approached following the chaos-theory field and it aims to model the attractor extracted from HRV sequences [8] or to estimate the fractal dimension (FD) calculated from the beta exponent [9].

However, the fractal dimension can be also extracted directly from the HRV sequence by means of many methods [10-12] thus measuring the characteristic signal variability. In this work we used this approach, utilizing the fractal dimension estimated by means of the Higuchi method. In this way a better estimation of this parameter was obtained because the errors due to the indirect estimation of DF from the beta exponent are eliminated

This study was conceived to appraise the reliability and reproducibility of 1/f and FD parameters and assess their mutual relationship. These two aspects are of great importance in making decisions about their inclusion in clinical trials and experimental studies.

2 METHODS

2.1 Studied population

We studied 22 patients (62 ± 9 years old, male) with clinically stable CHF (Weber C class), in sinus rhythm. All patients selected showed a left ventricular ejection fraction at rest <40% evaluated by a radionuclide angiography.

All patients were under stable therapy since at least 3 months with ACE-inhibitors and furosemide; 11 patients took digoxin and 18 nitrates. No patients were under beta-blockers or calcium-antagonist therapy. In order to assess short- and long-time reproducibility, all patients underwent three 24-hour ECG Holter recordings spaced 2±1 days between first and second recording (short-time) and 96±26 days between first and third recording (long-time).

2.2 Holter analysis

For all CHF and normal subjects, twenty-four-hour ambulatory ECGs were recorded with a portable three-channel tape recorder and processed with Marquette 8000 T system.

All recordings were performed while the patients were allowed to standing or sitting next to their beds. Other activities were not allowed. In order to be considered eligible for the study, each recording had to have at least 12 hours of analyzable RR intervals. Moreover, this period had to include at least half of the nighttime (from 00:00 AM trough to 5:00 AM) and half of the daytime (from 7:30 AM trough to 11:30 PM) [13].

Each beat was labeled as normal or aberrant according to recognition by the algorithm for tape analysis and after an investigator's verification.

2.3 1/f analysis

This technique derives from the underlying power-law behavior exhibited by long-time HRV time series. Studies have shown [3-7] that the spectral density function of HRV decreases approximately as the reciprocal of frequency, and it can be easily described in a log-log scale by the intercept and slope of the regression line over approximately two decades of frequency (10^{-4},10^{-2} Hz) (Fig. 1).

It has been shown that the slope and intercept of 1/f log-scaling of Fourier spectra are substantially influenced by the autonomic input to the heart and that the combination of both indexes was an excellent predictor of death after myocardial infarction [4].

According to these works, for each patient, the RR time series was automatically corrected for ectopic beats and resampled at 2 Hz by cubic spline interpolation.

Data were then FFT transformed and the resulting 24-hour power spectrum was obtained. Linear regression analysis between log(power) and log(frequency) was performed on the portion of the power spectrum between 10^{-4} and 10^{-2} Hz, and the slope and the intercept at 10^{-4} Hz were computed.

2.4 Fractal dimension analysis

The Higuchi's algorithm [11] is based on the measure of the mean length of the curve L(k) by using a segment of k samples as a unit of measure. From a given time series X(1), X(2), ... X(N), the algorithm constructs k new time series; each of them, Xm^k, is defined as

Xm^k: X(m), X(m+k), X(m+2∗k), .. , X(m+int((N-m)/k)*k)

where m=1,2,...,k and k are integers indicating the initial time and the interval time, respectively.

Then the length, $L_m(k)$, of each curve Xm^k is calculated as

$$L_m(k) = \{ (\sum_{i=1,F} |X(m+i*k)-X(m+(i-1)*k)|) * (N-1)/(F*k) \}/k \quad (1)$$

where F=int((N-m)/k, N is the total number of samples and the term (N-1)/(F∗k) is a normalization factor. Thus $L_m(k)$ represents the normalized sum of the segment lengths which join pairs of points distant k samples, starting from the m-th sample, X(m), with m=1, 2, ... k.

Finally, the length of the curve for the time interval k, L(k), is calculated as the mean of the k values L_m (k) for m=1, 2, ..., k. If the L(k) value is proportional to k^{-D}, the curve is fractal-like with the dimension D. Then, if L(k) is plotted against k, for k ranging from 1 to kmax, on a double logarithmic scale, the data should fall on a straight line with a slope equal to -D. Thus, by means of a least-square linear best-fitting procedure applied to the series of pairs (k, L(k)), obtained by increasing the k value in (1), the angular coefficient of the linear regression of the graph ln(L(k)) vs. ln(1/k), which constitutes the D estimation, is evaluated.

Studies have demonstrated that the complexity measured by a fractal dimension is reduced in some pathologies [9, 14].

Only tracts of at least 250 consecutive QRS complexes normally classified were considered in the analysis excluding RR intervals immediately preceding or following not normal beats.

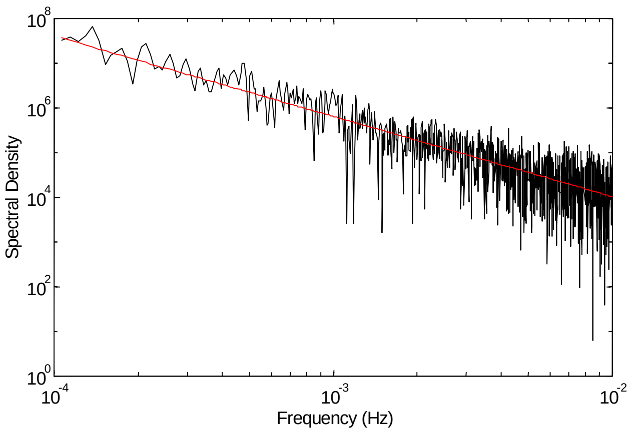

Figure 1: Power law behavior and 1/f log scaling regression

2.5 Spectral analysis

To compare the reproducibility values of the previous non-linear techniques with those of the traditional linear techniques, we performed also spectral analysis by custom software [15] on 5 minutes RR sequences extracted from 24-hours holter recordings.

Sequences containing artifacts or large transients or containing over 5% of ectopies were discarded, while the few ectopic beats eventually present in accepted sequences were automatically corrected by an interpolating algorithm.

Power spectral density was estimated by the Blackman-Tukey method in all accepted segments after linear trend removal. The total power (TP) and the power in the low frequency band (0.04-0.15 Hz) and high frequency band

(0.15-0.45 Hz) were then computed by numerical integration. The latter two powers were finally transformed into normalized units dividing them by their sum.

Being complementary measurements, only the total power and the normalized high frequency power (HFnu) were considered in the study.

2.6 Statistical analysis

Shapiro-Wilk statistic was used to test the normality of the distribution of all variables applying the appropriate transformation in case of violation.

To assess the clinical stability of the patients during the study period, the variables describing the hemodynamic status, neurohormonal activation and exercise performance were analyzed by a repeated measures ANOVA.

Short- and long-term reproducibility of HRV indexes were first assessed testing for systematic changes by a paired t-test. To quantify the reproducibility, we used the standard error of measurement (SEM) [16] after normalization by the mean of observed values.

The SEM, which was computed as the root mean square error of the 1-way random effects ANOVA on short-term and long-term paired measurements, has the following two uses.

First, if a single measurement is taken on a given subject, an approximate 95% confidence interval for the patient's underlying steady-state value can be obtained as $X \pm 1.96 \cdot$ SEM, where X is the observed measurement.

Second, if one observes a change in a patient's index after a period of treatment, then to be 95% confident that a real change has occurred the absolute difference between the 2 measurements has to be at least 2.8 times the SEM [16].

From the same 1-way analysis of variance the intraclass correlation coefficient (ICC) was derived. This statistic is the fraction of the total observed variability of a given measurement that is due to the variance of the patients' steady state values, and is an index of reliability of measurements [16]. An ICC below 0.4 is commonly considered to represent poor reliability, whereas above 0.75 is considered to represent excellent reliability. Fair or good is in between [16].

All hypothesis tests (two-tailed) were performed at the 0.05 significance level.

3 RESULTS

As shown in Tab. 1, patients maintained relatively clinical stable conditions during the study period, with just a small variation in their VO_{2max} during exercise tests while the Left Ventricle Ejection Fraction (% LVEF) and the Norepinephrine values show not significant differences among the studies.

Considering the short-time reproducibility, it can be seen (Table 2) that for fractal dimension and 1/f intercept the SEM remains within the 3.4% of the mean, while it is about four times bigger for the 1/f slope and ranges between 4% and 9% for spectral parameters.

In the long-time analysis, the SEM of fractal dimension as well as of the power law and of the frequency-domain parameters were substantially similar to those of short-time.

Table 1. Assessment of the clinical stability of the patients during the study period by ANOVA test.

	Study 1	**Study 2**	**Study 3**	**p**
LVEF (%)	28.8±6.6		29.2±5.7	0.38
Norepinephrine	387±169	397±165	409±175	0.17
VO_{2max}	12.09±2.2	12.36±1.7	12.9±1.81	0.038*

The ICC values, in the short-time situation, show that FD and spectral parameters present an excellent reliability while the 1/f indexes have only a poor grade.

In the long-time situation, ICC remains similar to that of the short-time case for FD and power spectral parameters while it sensibly changes, with opposite sign, for the 1/f slope and intercept parameters (Table 2).

Table 2. Mean value and SD of all parameters, short- and long-time normalized SEM and ICC in CHF patients.

	Mean	SD	SEM % Short -time	SEM % long-time	ICC Short -time	ICC Long -time	P Short -time	P Long -time
FD	1.74	0.14	3.39	3.85	0.78	0.77	0.92	0.55
Slope	-1.55	0.30	14.29	11.39	0.38	0.72	0.28	0.79
Int	7.29	0.27	2.59	3.53	0.40	0.12	0.36	0.97
TP	2067	2168	4.13	3.99	0.90	0.91	0.79	0.98
HFnu	0.4	0.1	9.09	10.33	0.78	0.72	0.63	0.99

Table 3. Mean values of the correlation coefficients between 1/f and FD parameters.

		FD
Slope	r	-0.75
Intercept	r	0.23

Mean values among the three studies of the correlation coefficients between 1/f parameters and Fractal dimension are shown in Tab. 3. FD parameter was not correlated with 1/f intercept while it is correlated with the slope.

4 DISCUSSION

The p-values in Table 2 show that, both for short and long-time situations, for all the parameters the differences among the three studies are not significant. Moreover, the ICC values (Table 2) indicate that the FD and the spectral parameters are reliable for short and long-time analyses while the 1/f intercept was not and the 1/f slope shows a good reliability only for long-time evaluation.

The SEM% results show that Fractal dimension parameter as well as the 1/f intercept had a good short-time reproducibility, with a SEM under 3.4% of the mean of observed values. Comparatively, the reproducibility of spectral parameters and 1/f slope, is much worse.

In the long-time evaluation, the reproducibility of FD parameter as well as of spectral parameters and of 1/f indexes does not show substantial changes.

In summary, FD index appears to be more reliable than 1/f indexes and with a reproducibility level comparable to that of the total power and the 1/f intercept. Hence, it seems more suitable to be used in clinical applications than the 1/f indexes and slightly better than the spectral parameters.

The correlation between FD and 1/f slope parameter confirms a link between the two indexes though the evaluation of FD from the 1/f slope does not appear a reliable procedure, particularly in the short-time analysis when 1/f slope shows a low ICC and a large SEM%.

It is thus likely that the FD describes different and, possibly, complementary aspects of HRV with respect to 1/f indexes.

In conclusion, our study suggests that fractal dimension parameters obtained from morphologic quantification of HR Variability, directly in the time series sequence, can give additional information with respect to 1/f and power spectral parameters and hence it could be considered for future risk assessment studies of chronic heart failure patients. Furthermore, care must be taken in using certain parameters, especially the 1/f slope parameter, due to their poor reproducibility.

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