Reproducibility of Non Linear Analysis parameters in Chronic Heart Failure patients

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Abstract: Nonlinear analysis of HRV, particularly the 1/f method and Poincarè plots, has been recognized to provide valuable information in the prognostic stratification of cardiac patients. The reproducibility of these methods, however, is not known, nor the relationship between them. 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 Poincarè plot analysis and 1/f log scaling of power spectrum, assessing the reproducibility of each index and comparing it with that of classical spectral indexes. We also compared the mean value of each parameter with that of a matched sample of normal subjects. Our results show that Poincarè plot indexes exhibit a higher reproducibility than all other HRV indexes, whereas 1/f slope parameters are the less reproducible. Moreover, we found that Poincarè indexes are poorly correlated with 1/f indexes and describe possibly complementary aspects of heart rate dynamics.

Keywords: Poincarè plots, Heart Rate Variability, Heart Failure

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 [2,3,4]. 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 patients with cardiac and non cardiac diseases [1,5-15]. Two non linear methods, in particular, have gained wide interest in the last years: the 1/f method and Poincarè plots[16,17]. The latter has traditionally been based on visual classification of 2-dimensional (2D) plots. To overcome the inherent limitations of subjective judgement, we have recently proposed a new method for the automatic measurement of a set of parameters describing major features of the plots [18,19].
This study was conceived to appraise the reproducibility of 1/f and Poincaré plots 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 Study 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-term reproducibility, all patients underwent three 24-hour ECG Holter recordings spaced 2±1 days between first and second recording (short-term) and 96±26 days between first and third recording (long-term). To the purpose of evaluating the clinical meaning of obtained reproducibility values, we also considered 22 Holter recordings from age-matched normal subjects.

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) [20]. 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-term HRV time series. Studies have shown [4] 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).

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

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 [21]. 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 Poincaré plots analysis

This technique is based on the analysis of the maps constructed by plotting each RR interval against the preceding one. Usually these plots were just visually classified regarding the pattern’s difference with a normal comet-shaped pattern.
Studies have demonstrated that abnormal Poincaré bi-dimensional plots, visually inspected and classified, are better predictors of mortality in heart failure patients than conventional indexes [23].

One major limitation of the Poincaré method is the subjective evaluation of the plots. To overcome this problem, the automatic quantification of morphological characteristics of 2D and 3D plots have been recently proposed by our group [18,19] extracting measures of the extension and dispersion of the ellipsoidal cloud of points like length (L), wideness (W) and area (A) of the 2D plot and the number of peaks (Np) and the length of the three radii of the semi-ellipse of inertia _x, _y, _z of the 3D plot (Fig. 2).

Only normal classified QRS complexes were considered in the analysis excluding RR intervals preceding or following not-normal beats and plotting only time-closed RR couples.

![Figure 2: Poincaré plot 2D and 3D analysis](image)

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 [24] 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 normalized high frequency power (HFnu) was considered in the study.

3. Statistical analysis

Kolmogorov-Smirnov (KS) test was used to assess the normality of the distribution of all variables.

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 was quantified using the standard error of measurement (SEM) after normalization by the mean of observed values. The SEM 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±1.96·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 [25].

Unpaired t-test was used to compare the means of all parameters between CHF patients and normal subjects.

The association between the two sets of nonlinear parameters was assessed by the Pearson correlation coefficient or, in case of violation of normality, the Spearman coefficient.

The relationship between nonlinear indexes and neurohormonal activation parameters was investigated by a multivariate linear regression analysis.

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

4. Results

As shown in Tab. 1, patients maintained relatively clinical stable conditions during the study period,
with just a small variation in their VO$_{2\text{max}}$ during exercise tests.

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

<table>
<thead>
<tr>
<th></th>
<th>Study 1</th>
<th>Study 2</th>
<th>Study 3</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVEF (%)</td>
<td>28.8±6.6</td>
<td>29.2±5.7</td>
<td>0.38</td>
<td></td>
</tr>
<tr>
<td>NE</td>
<td>387±169</td>
<td>397±165</td>
<td>0.17</td>
<td></td>
</tr>
<tr>
<td>VO$_{2\text{max}}$</td>
<td>12.09±2.2</td>
<td>12.36±1.7</td>
<td>12.9±1.81</td>
<td>0.038*</td>
</tr>
</tbody>
</table>

NE: norepinephrine

Considering the short-term reproducibility, it can be seen that for Poincarè plot parameters and 1/f intercept the SEM remains within the 2.5% of the mean, while it is more than five times bigger for the 1/f slope and ranges between 4% and 9% for spectral parameters.

In the long-term, the SEM of all Poincarè plot increased with respect to short-term, ranging between 3% and 11% of the mean, while the SEMs of the power law and of the frequency-domain parameters were substantially similar.

The unpaired t-test showed a highly significant difference between the two study populations for all parameters, except for W and $\rho_x$ (Tab. 2).

Table 2. Mean value and SD of all parameters, short- (SEMS) and long-term (SEML) normalized SEM in CHF patients. Mean values, SD and % difference with respect to CHF patients are also reported for a matched sample of normal subjects.

<table>
<thead>
<tr>
<th></th>
<th>CHF</th>
<th>CHF</th>
<th>NORMALS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean±SD</td>
<td>SEMS</td>
<td>SEML</td>
</tr>
<tr>
<td>L</td>
<td>649±164</td>
<td>0.87</td>
<td>3.12</td>
</tr>
<tr>
<td>W</td>
<td>226±114</td>
<td>2.04</td>
<td>10.70</td>
</tr>
<tr>
<td>A</td>
<td>11228±5513</td>
<td>2.07</td>
<td>6.55</td>
</tr>
<tr>
<td>$\rho_x$</td>
<td>46±13</td>
<td>2.56</td>
<td>7.25</td>
</tr>
<tr>
<td>$\rho_y$</td>
<td>113±24</td>
<td>2.05</td>
<td>5.36</td>
</tr>
<tr>
<td>Slope</td>
<td>106±31</td>
<td>2.11</td>
<td>6.45</td>
</tr>
<tr>
<td>Int</td>
<td>7.29±0.30</td>
<td>14.29</td>
<td>11.39</td>
</tr>
<tr>
<td>TP</td>
<td>2067±2168</td>
<td>4.13</td>
<td>3.99</td>
</tr>
<tr>
<td>HFnu</td>
<td>0.4±0.1</td>
<td>9.09</td>
<td>10.33</td>
</tr>
</tbody>
</table>

Correlation coefficients between all nonlinear parameters are shown in Tab. 3. With the exception of the three radii of the semi-ellipse of inertia, Poincarè plot parameters were not correlated with 1/f parameters. Moreover, even when the p-values were significant, the strength of the correlation was rather weak.

Table 3: Correlation between Power-Law regression parameters and Poincarè 2D and 3D indexes.

<table>
<thead>
<tr>
<th></th>
<th>2D parameters</th>
<th>3D parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>L</td>
<td>W</td>
</tr>
<tr>
<td>r</td>
<td>-0.05</td>
<td>-0.04</td>
</tr>
<tr>
<td>p</td>
<td>0.24</td>
<td>0.06</td>
</tr>
</tbody>
</table>

In multivariate regression analysis, using all nonlinear indexes as potential explicative variables and norepinephrine level as the dependent variable, only $\rho_x$ and $\rho_y$ resulted independently associated to neurohumoral activation, with a model $R^2 = 0.72$ and $p < 0.001$ for both variables.

5. Discussion

Our results show that Poincarè plot indexes have a good short-term reproducibility, with a SEM under 3% of the mean of observed values. Comparatively, the reproducibility of spectral parameters and 1/f indexes, especially the slope, is much worse.

In the long-term evaluation, the reproducibility of Poincarè plot indexes decreases, with a normalized SEM about 3-times that observed in short-term. Conversely, the reproducibility of spectral parameters and of 1/f indexes does not show substantial changes.

In order to get a rough idea on the impact of the measured reproducibilities on clinical practice, we can multiply the normalized SEM by 2.8, obtaining an estimate of the percentage change needed for a given parameter to be 95% confident that a real change has occurred.

This value can then be compared with the average percentage difference between normal and pathological subjects, as this difference describes the potential range of variation of each parameter in case of improvement of the disease.

Doing this, we can observe that for all Poincarè indexes, but W and $\rho_x$, the 95% threshold is much
less than the range of variation of the parameter, whereas for the 1/f and spectral indexes it is comparable or even greater than the range. Hence, Poincarè indexes appear to be definitely more suitable to be used in clinical applications than the other non-linear and linear indexes.

Regarding the correlation between the two set of nonlinear parameters, only the size of the three radii of the semi-ellipse of inertia showed a significant albeit poor correlation with the slope and intercept of 1/f plots. Hence, only the 3D indexes of Poincarè maps seem to carry information about the dynamics of HRV which is related to power-law characteristics. It is thus likely that the other indexes of Poincarè plots describe different and, possibly, complementary aspects of HRV with respect to 1/f indexes. This is not totally unexpected as power-law regression parameters reflect the distribution of HRV power due to long-term variability, while the beat-to-beat approach of Poincarè plot parameters can detect patterns related both to short- and long-term variability.

An interesting further finding of the study revealed by multivariate regression analysis is that only 3D Poincarè parameters are independently associated with plasma norepinephrine level, indicating that they "contain" the information of 1/f indexes and better explain norepinephrine variability.

In conclusion, our study suggests that parameters obtained from morphologic automatic quantification of Poincarè plots can give additional information with respect to 1/f parameters and hence both sets of parameters should be considered for future risk assessment studies of chronic heart failure patients. Furthermore, care must be taken in using certain parameters, specially the 1/f slope parameter, due to their poor reproducibility.

References


