Usefulness of 7-day Holter Monitoring for Heart Rate Variability Nonlinear Dynamics Evaluation

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Abstract

Although a number of studies have addressed the clinical usefulness of Heart Rate Variability (HRV) as a marker of the autonomic activity, there are few studies about the short-term day-to-day reproducibility of HRV nonlinear indices. A database of 31 7-Day Holters (7DH) from Chronic Heart Failure patients was used to analyze the reliability of nonlinear dynamics and to evaluate the usefulness of 7DH recordings against the 24-hour recordings. On the one hand, scaling exponents $\alpha 1$ and $\alpha 2$ from Detrended Fluctuations Analysis, and Sample Entropy, were compared at two randomly selected days; day and night periods were also analyzed separately. On the other hand, the values obtained for each single day were compared to the ones for the 7DH. Intraclass Correlation Coefficients showed strong correlation for the indices between two random days, specially in the night period, hence suggesting that this could be the more suitable period to perform the calculations in terms of reliability. Significant differences were found for every single day of the week compared to the 7DH for $\alpha 2$. Therefore, 7DH can improve the understanding of long-term fractal correlation properties given by nonlinear indices.

1. Introduction

Heart Rate Variability (HRV) is a relevant marker of the Autonomic Nervous System (ANS) control on the heart. This marker has been proposed for risk stratification of lethal arrhythmias after acute myocardial infarction, as well as for prognosis of sudden cardiac death events [1, 2]. A wide number of HRV indices have been proposed in the literature. Many studies suggest that nonlinear methods are better suited to extract relevant information from HRV signal in terms of complexity. Nonlinear indices rely on the idea that fluctuations in the RR intervals may reveal characteristics from complex dynamic systems. Under this assumption, healthy states will correspond to more complex patterns than pathological states [2–4].

There are few studies about the clinical information provided by HRV nonlinear indices in recordings longer than 24-hour. Furthermore, the stability of temporal and spectral indices of HRV has been addressed in the literature [5]. Also nonlinear indices have been paid some attention [6] in this setting, however, their reliability in long term recordings has been shortly assessed.

In this work, the reproducibility of three nonlinear HRV indices is analyzed, namely, the scaling exponents $\alpha 1$ and $\alpha 2$ from the Detrended Fluctuation Analysis (DFA), and the sample Entropy (SampEn). Additionally, the usefulness of 7-Day Holter (7DH) recordings versus the usual 1-Day Holter (1DH) for HRV nonlinear dynamics evaluation is adressed.

The structure of the paper is as follows. First, the 7DH recordings in Congestive Heart Failure (CHF) patients and the HRV nonlinear indices are presented. Next, the data analysis is described, and following, the results are presented. Finally, conclusions are summarized.

2. Dataset

The database consisted of 31 7DH from patients with stable CHF. All patients had left ventricular ejection fraction $\leq$ 50% and were clinically stable. The 3-channel electrocardiographic recordings with $x - y - z$ orthogonal leads were obtained using a commercially available device (Lifecard CF^{TM}, Del Mar Reynolds, Issaquah, Washington). The raw electrocardiographic data, stored in a proprietary format, were exported to the International Society for Holter and Noninvasive Electrocardiology Standard (ISHNE), by using custom-made software and in accordance with the specifications provided by the manufacturer. The data were processed by using standard Holter analysis software (ELA Medical^{TM}, Sorin Group, Paris, France). A visual check of the QRS complex classification and every arrhythmic event was performed by a trained cardiologist, and manual corrections were made when needed.

The recordings were preprocessed to exclude artifacts and ectopic beats. Furthermore, RR intervals lower than 200 ms and greater than 2000 ms were excluded, as well as those which differed more than 20% from the previous and the subsequent RR intervals [1]. All the recordings had at least 85% of sinus beats. The nonlinear indices were computed on the NN interval series.

3. HRV nonlinear indices

The DFA is a well-established method for assessing and quantifying short-term and long-term correlations in time series with non-stationarity [7]. This algorithm determines the scaling behavior of a time series based on the computation of a scaling exponent, α. Given N data points of a time series, the DFA procedure consists of four steps. First, the time series is integrated as follows

$$y(k) = \sum_{i=1}^{k}(x(i) - \tilde{x})$$

where $x(i)$ is the i-th NN interval and $\tilde{x}$ is the average NN interval. Next, the integrated time series $y(k)$ is divided into N_s non-overlapping segments of equal length s. Following, a least squares linear regression is fitted to each segment. Coordinate y of the fitted line is denoted by $y_s(n)$, and it represents the linear trend for each given segment. Finally, the root-mean square fluctuation, $F(s)$, of the detrended integrated series is quantified by

$$F(s) = \sqrt{\frac{1}{N}\sum_{k=1}^{N}(y(k) - y_s(k))^2}$$

This computation is repeated over all scales, i.e., segment lengths, yielding a relationship between $F(s)$ and segment length s. If the data $x(n)$ is self-similar, the fluctuation function $F(s)$ increases by following a power-law

$$F(s) = s^{\alpha}$$

Index α quantifies the correlation properties of a time series. For instance, a value $\alpha = 1.5$ indicates that the successive increments in the RR-interval time series are uncorrelated, corresponding to the Brownian motion [8]. Values $1 < \alpha < 1.5$ indicates anti-persistent behavior, i.e., the successive increments in the time series are negatively correlated. In contrast, $1.5 < \alpha < 2$ indicates persistent long-term correlations, i.e., the successive increments are positively correlated. Scaling exponent α is estimated as the slope of the regression in the log-log plot of $F(s)$ vs s.

HRV signals have been found to show, at least, bi-scaling (bi-fractal) behavior. Therefore, two scaling exponents are needed in order to characterize the fractal correlations properties of the HRV signal, one for short-term (between 3 and 16 beats), denoted by $\alpha 1$, and the other for long-term ($N > 16$ beats), denoted by $\alpha 2$ [9].

Entropy-based methods provide a quantification of the irregularity of a temporal series. Among them, SampEn [10], which is a modification of the Approximate Entropy [4], holds some properties which are appropriate for the study of physiological signals. The SampEn is the negative natural logarithm of the conditional probability that two sequences which are similar for m points remain similar for $m + 1$ points. Thus, a lower value of SampEn indicates more self-similarity in the time series. In order to compute the $SampEn$, the specification of two parameters is previously required, namely, the embedded dimension m, that is, the length of the vectors to be compared, and a noise filter threshold r.

The procedure for *SampEn* calculation given N data points is as follows

- $B_i^m(r)$ is defined as $(N-m-1)^{-1}$ times the number of template vectors $\mathbf{x}_m(j)$ similar to $\mathbf{x}_m(i)$ (within r) where $j = 1...N - m$ with $j \neq i$.
- The average of $B_i^m(r)$ for all i is calculated as

$$B^m(r) = \frac{1}{N-m}\sum_{i=1}^{N-m} B_i^m(r)$$

- Similarly $A_i^m(r)$ is defined as $(N - m - 1)^{-1}$ times the number of template vectors $\mathbf{x}_{m+1}(j)$ similar to $\mathbf{x}_{m+1}(i)$ (within r) where $j = 1...N - m$ with $j \neq i$.
- The average of $A_i^m(r)$ for all i is calculated as

$$A^m(r) = \frac{1}{N-m}\sum_{i=1}^{N-m} A_i^m(r)$$

- *SampEn(m,r)* and its statistic *SampEn(m,r,N)* are defined as follows

$$SampEn(m,r) = \lim_{N\to\infty}\{-\ln[A^m(r)/B^m(r)]\}$$

$$SampEn(m,r,N) = -\ln[A^m(r)/B^m(r)]$$

SampEn is robust to noise and outliers, hence it has been widely applied to characterize the HRV signal [10].

4. Data analysis

DFA indices were computed for each 7HD recording, for every single day (24-hours), and also for the day (8:00-24:00) and night periods (24:00-8:00). SampEn was computed hourly and then the mean value was obtained for each 7HD recording, for each day, and for the night and day periods.

The indices distributions were checked to detect possible outliers (values over 3 standard deviations away from the mean). Lilliefors test was used to test the normality of

Table 1. *HRV indices for two randomly selected days and its difference (mean ± standard deviation), p-value for the paired t-test, ICC and its 95% confidence interval, and Pearson correlation coefficient (r). For transformed variables, results are expressed in original units and in log units. Paired $t-test$ was calculated after the transformations.*

Index	Day 1	Day 2	Difference (2-1)	p	ICC	r
24 Hours						
$SampEn$	0.58±0.34	0.63±0.36	-0.05±0.18	0.16	0.75, [0.55,0.87]	0.77
$\alpha1$	1.25±0.14	1.23±0.19	0.01±0.11			
$ln((1-\alpha1)+0.5)$	-1.60±0.79	-1.60±0.80	0.01±0.62	0.95	0.72,[0.49,0.85]	0.69
$\alpha2$	1.07±0.10	1.05±0.10	0.02±0.05	0.06	0.86,[0.74,0.93]	0.88
Day						
$SampEn$	0.52±0.22	0.56±0.25	-0.05±0.18	0.16	0.72,[0.50,0.86]	0.74
$\alpha1$	1.26±0.13	1.23±0.18	0.02±0.13	0.33	0.66,[0.40,0.82]	0.69
$\alpha2$	1.12±0.10	1.10±0.09	0.02±0.06	0.07	0.77,[0.57,0.88]	0.79
Night						
$SampEn$	0.73±0.34	0.76±0.36	-0.04±0.23			
$ln(SampEn)$	-0.43±0.50	-0.39±0.51	-0.05±0.30	0.40	0.83,[0.68,0.91]	0.83
$\alpha1$	1.23±0.18	1.23±0.23	-0.01±0.11	0.83	0.85,[0.72,0.93]	0.88
$\alpha2$	0.96±0.13	0.95±0.12	0.02±0.07	0.17	0.82,[0.66,0.91]	0.83

the distribution of all variables, and the appropriate transformation was applied when normality was not fulfilled.

In order to assess the reliability of the indices, two days were randomly selected from the 7HD, maintaining the same days for all the patients and for all the time periods. The indices were computed for the two days, and the reproducibility was assessed by means of paired t-tests (significance level set to 0.05).

In addition, the Intraclass Correlation Coefficients (ICC) and its 95% confidence interval for single measures were obtained from the 1-way ANOVA to estimate the correlation between two different measurements on a patient. The SPSS statistical package was used for this purpose. The ICC is a reliability index of the measurements, given by the ratio of the variance of interest over the sum of the variance of interest plus error [11], this is, the proportion of the total observed variance of a measurement that is associated with differences among the measured patients. The ICC ranges from 0 to 1, hence, the lower the random error relative to variability among subjects, the closer the ICC will be to 1. Pearson correlation coefficients were also computed for comparison.

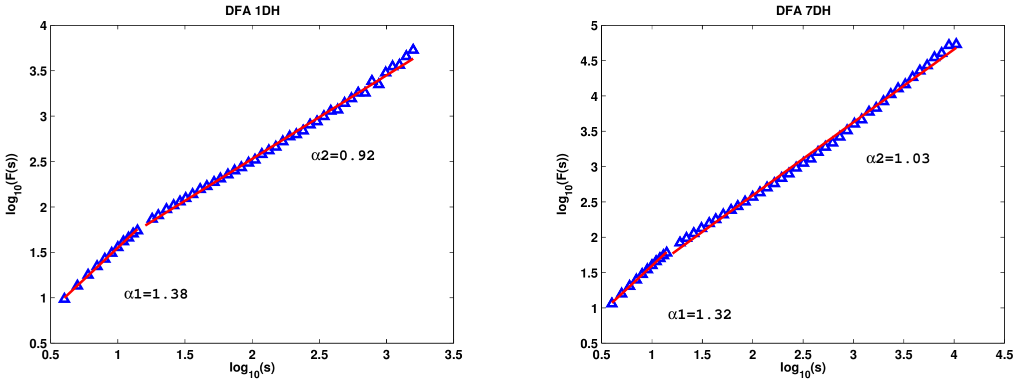
Finally, aiming to evaluate the usefulness of 7DH recordings versus the usual 1DH recordings, the indices computed for each day were compared to the indices computed for the complete 7HD recordings, and compared by means of paired t-tests (significance level set to 0.05).

5. Results

One patient was discarded from the analysis since it was found to be paced. The distributions of all indices fulfilled the normality assumption except for $SampEn$ nighttime values from Monday and Wednesday, α_1 24-hour values from Sunday, and α_1 daytime values from Saturday. $SampEn$ values were right skewed, and they were transformed by using the natural logarithm ($ln(SampEn)$). Index α_1 values were left skewed, and they were transformed by first reflecting the distribution, and then adding a constant before applying the natural logarithm ($ln(1-\alpha_1+c)$). Results from transformed variables are given in original and in logarithmic units. The statistical tests were applied after the transformations.

Regarding the reproducibility and reliability of the computed HRV nonlinear indices, Table 1 shows the mean and the standard deviation and the difference of the indices from two randomly selected days, which turned out to be Wednesday (day 1) and Sunday (day 2). The values are shown for 24-hours, for the day time, and the for night time. The p-$values$ for the paired t-$test$ between each pair of sets and the ICC with its 95% confidence intervals are shown, as well as the Pearson correlation coefficient (r). All the p-$values$ indicated that there was no significant difference between the values obtained from the two different days for any of the indices. The ICC values showed good reliability for the three indices for all time periods, α_1 day time values showed the lowest ICC (0.66), while α_2 24-hour values showed the largest ICC (0.86). The reliability of the indices was considerably stronger during the night time period than during the daytime period for the three indices. For $SampEn$ and α_1, it was also stronger during night time than during 24-hours, but not for α_2. The Pearson correlations were slightly higher than the ICC in most cases, but the trends were exactly the same as for the ICC. They presented higher correlation during the night time period than during the day time period for the three indices, and also higher than during 24-hours for $SampEn$ and α_1.

Regarding the usefulness of 7DH recordings against the 1DH recordings, the paired t-$tests$ between each single day and the 7DH recording were not significant for any of the days for $SampEn$ index. For α_1 index, it was not significant for all the days except for Tuesday, however it



(a) (b)

Figure 1. *Example of DFA indices computed for a 1DH (a), and computed for a 7DH (b).*

was largely significant for all days for α_2 index, with a highest $p\text{-}value$ of 0.017. The significant differences on this index are consistent, since the 7DH recordings allow the use of larger scales to compute α_2. Fig 1 shows an example of α_1 and α_2 indices computed for a 1DH (Fig 1 (a)) and for a 7DH (Fig 1 (b)).

6. Conclusions

It can be summarized that significant differences have not been found between the values of the HRV nonlinear indices at two random days. The indices show good reliability, specially in the night period, therefore these could be the more appropriate period to perform the calculations when working with nonlinear HRV indices.

Furthermore, 7DH could yield to an improvement of the understanding of long-term fractal correlation properties given by α_2.

Acknowledgements

This work has been partially supported by Research Projects from Medtronic Ibrica, and from Spanish Government (TEC2010-19263, TEC2009-12098, and URJC-CM-2010-CET-4882).

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