Reproducibility of the Heart Rate Variability Regularity Index in Chronic Heart Failure Patients

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Abstract

Among non linear analysis of HRV, information domain analysis has recently gained wide interest, allowing to evaluate regularity, defined as the degree of recurrence of a pattern in a signal.

The reproducibility of this method, however, is not known and in this study we addressed this issue in the population of chronic heart failure (CHF) patients.

We analyzed three 24-hour ECG Holter recordings in 25 clinically stable CHF patients by a regularity index, based on the evaluation of the conditional entropy.

We studied the mean values over 24 hours and, separately, during the nighttime and daytime periods to assess the regularity index reproducibility by the standard error of within-patient variability.

Results suggest the need of an appropriate signal detrending to fulfill stationarity criteria and to obtain a better reproducible regularity indexes in long-term recordings.

1. Introduction

Measurements of heart rate variability has emerged as a valuable and noninvasive tool for studying the cardio-respiratory control system in various pathological conditions [1].

Moreover, definitive evidence has recently been provided on the independent prognostic value of heart rate variability with respect to well-established risk stratifiers [2].

In chronic heart failure (CHF), with a complex abnormality of the autonomic control to the heart [3], HRV analysis is commonly used in the definition of prognosis of these patients [4,5].

Although most studies on heart rate variability have been performed using time- and frequency-domain linear methods, it has been suggested that nonlinear analysis of heart rate variability may provide more valuable information for the physiological interpretation of heart rate fluctuations and for the risk assessment of cardiac patient [1].

Among nonlinear techniques, information domain analysis of cardiovascular variability has recently gained wide interest, allowing to evaluate regularity, defined as the degree of recurrence of a pattern in a signal [6].

Aim of the paper is the study of the reproducibility of heart rate variability regularity index in patients with chronic heart failure.

This study should help to understand the range of applicability of this index in clinical settings and to compare its reliability with the reproducibility of the other linear [7,8] and nonlinear [9,11] heart rate variability indexes.

2. Study population

We studied 25 CHF patients (62±9 years old, male, NYHA functional class II and III) in sinus rhythm.

All patients selected showed a left ventricular ejection fraction <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 patient was 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 scheduled as follows: after a control recording (analysis #1), the Holter recording was repeated after 2±1 days (analysis #2), and after 96±26 days (analysis #3).

3. Holter analysis

All subjects underwent a 24-hour Holter ECG recording by a portable three-channel tape recorder, processed by a Marquette 8000 T system (the sample frequency was 128 Hz).

All recordings were performed while the patients were allowed to standing or sitting next to their beds. Other activities were not allowed.

We studied all 24 hour recordings and, separately, nighttime and daytime periods. We defined as nighttime the period from 0 to 5 AM and daytime from 8 to 12 AM, considering the remaining hours as transitional times in which the sleeping/waking status was likely to be variable.

In order to be considered eligible for the study, each recording had to have at least 12 hours of analyzable RR intervals, including at least half of the nighttime and half of the daytime period [7].

Each beat was labeled according to an automatic Holter analysis and classification was verified by an expert cardiologist. Sequences containing artifacts or large transients or containing > 5% of ectopies were automatically discarded. Few ectopic beats present in accepted sequences were automatically corrected by an interpolating algorithm.

4. Regularity analysis

A regularity index previously defined and validated [6,12] was utilized. This index is based on the calculation of the conditional entropy (CE) quantifying the amount of information carried by the most recent sample of a pattern of length L as a function of L. CE(L) was estimated as the difference between the Shannon entropy over patterns of length L and that over patterns of length L-1. A correction term was utilized to prevent the artificial decrease of the CE due to the shortness of the data set. The corrected CE (CCE) was flat when the series did not exhibit any recurrence, it went to zero when the series was fully repetitive and it showed a minimum when repetitive patterns are embedded in noise.

After the normalization by the Shannon entropy of the series, the minimum of the normalized CCE (NCCE) was taken as an index of regularity. It ranged from 0 to 1 (i.e. the minimal and maximal degree of recurrence respectively). The index was calculated over segments of 300 cardiac beats (after linear detrending), 70% overlapped, and the values were averaged over each period considered (day, night and 24 hour).

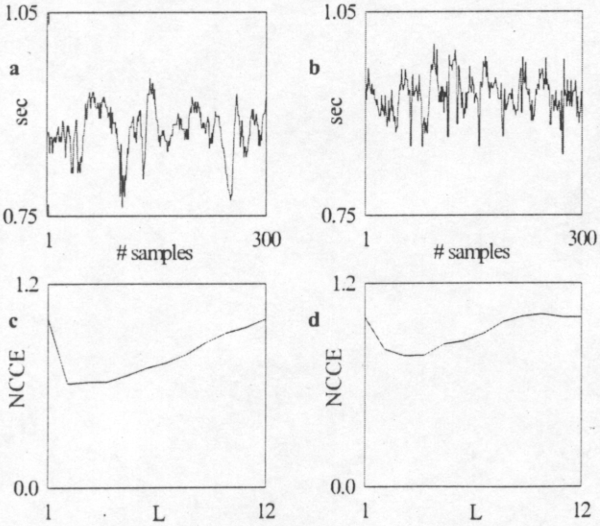

Figure 1. Examples of RR interval series at daytime (a) and nighttime (b) respectively and their relevant NCCE functions (c and d respectively). The regularity index is 0.39 at daytime and 0.23 at nighttime.

An example of regularity analysis is shown in Fig.1. The presence of more regular pattern during the day (Fig.1a) than during the night (Fig.1b) produces a deeper minimum in Fig.1c than in Fig.1d.

5. Statistical analysis

The Kolmogorov-Smirnov 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 (Tab 1).

The reproducibility of the heart rate variability regularity index was quantified in each period (day, night and 24 hour) using the standard error of measurement (SEM).

The SEM (Tab.3) was calculated as the square root of the sum (over the entire sample) of the squared differences between regularity indexes derived from different analyses (#1 vs #2, #2 vs #3, #1 vs #3) divided by the degrees of freedom.

An overall SEM (Tab 4) value was calculated as the square root of the sum of the squared differences between regularity indexes derived from different analyses and the overall mean regularity indexes for each patient divided by the degrees of freedom. The overall SEM was also normalized by the mean of all the observed values for each period over the entire sample (SEM%).

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 $X \pm 1.96 \cdot SEM$, where X is the observed measurement.

Second, if one observes a change in a patient's index after a period of treatment, then the absolute difference between the 2 measurements has to be at least 2.8 times the SEM to be 95% confident that a real change has occurred [13]. All hypothesis tests (two-tailed) were performed at the 0.05 significance level. All data are expressed as mean±SD.

6. Results

As shown in Tab. 1, patients maintained relatively clinical stable conditions during the study period in terms of LVEF and levels of norepinephrine (NOR), with just a small variation in their $VO2_{max}$, which is not clinically meaningful.

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

	#1	#2	#3	p
LVEF (%)	28.8±6.6	-	29.2±5.7	0,38
NOR	387±169	397±165	409±175	0,17
VO_{2max}	12.09±2.2	12.36±1.7	12.9±1.81	0,038*

In order to respect the recordings selection criteria described in Sect.3 [7], the final analysis has been performed over 21 subjects. Four subjects had to be discarded because of a lack of sufficient data record length during the study periods. The following Tab. 2 shows the mean regularity index and standard deviation values over the three study periods in the CHF population.

Table 2. Regularity index, mean and standard deviation (sd) values, during the three study periods in the CHF population.

	Day	**Night**	**24h**
mean	0.404	0.376	0.389
sd.	0.055	0.062	0.060

When we separately calculated the SEM values between each couple of analysis (#1 vs #2, #2 vs #3 and 1 vs #3), we found the smallest SEM values between #2 and #3 analyses (ranged from 0.045 to 0.069, Tab.3).

Table 3. SEM values between each couple of analysis

	#1 vs #2	**#2 vs #3**	**#1 vs #3**
Day	0.096	0.069	0.070
Night	0.078	0.046	0.064
24h	0.094	0.045	0.089

Finally, the SEM values, calculated considering the entire three recording sets, fell down around 0.03, during the day and over the total 24h, and around 0.04, during the night.

Table 4. SEM and SEM% values over the entire set of data

	Day	**Night**	**24h**
SEM	0.036	0.041	0.031
SEM %	8.881	10.888	8.005

The SEM normalized by the mean of all the observed values (SEM%) ranged from 8% (during the 24h) to 11% (during the night) and it was around 9% during the day (Tab.4).

7. Discussion

To have an idea on the impact of the measured reproducibility on clinical practice, we can compare the mean regularity index difference between Normals and CHF subjects with 2.8*SEM value.

In a previous study [14], considering 24 hour Holter recordings, we found a mean difference between Normal and CHF subjects ranging around 0,05. In the light of our results, unfortunately this value is smaller that 2.8*SEM, thus rendering critical to distinguish healthy subjects from CHF.

Conversely the difference in the regularity index mean value raises up to 0.15 if we consider short-term registrations under well-defined, rigorously tested, laboratory conditions [12], thus permitting a clear separation between the two populations.

This low discriminating power of the regularity index in Holter recordings might be due to non-stationarity and trends increasing regularity, which strongly affect heart rate variability in long-term recordings.

Two examples on typical non-stationaries observed in Holter recordings are showed in Fig.2. In both traces a sudden decrease in the RR interval and the rapid return to the original mean value create a V-pattern. As a result the NCCEs (Fig.2c,d) exhibit a minimum deeper with respect to the minimum found when more stationary sequences are analyzed (see Fig.1). The presence of this non-stationaries increase the variability of the regularity index, thus affecting its reproducibility.

This consideration suggests the need of an appropriate signal detrending, more complex than a simple subtraction of a straight line (e.g. a suitable high-pass filter), to fulfill stationarity criteria and to obtain better reproducible regularity indexes in long-term recordings.

In addition to improve preprocessing techniques, it seems to be mandatory to modify the algorithm, thus

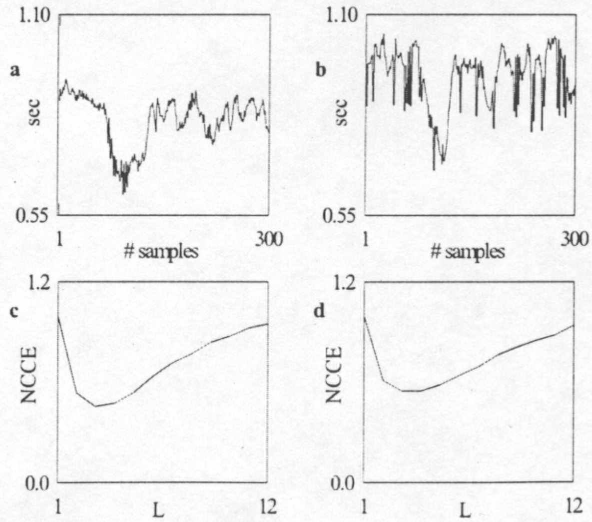

Figure 2. Examples of RR interval series at daytime (a) and nighttime (b) respectively with typical non-stationarities and their relevant NCCE functions (c and d respectively). A sudden decrease of the RR interval and its return to the average value can be noticed both in a and b. In (a) the return to the average value is characterized by the initiation of a slow rhythm. The regularity indexes are 0.54 at daytime and 0.45 at nighttime largely above the mean values at daytime and nighttime.

rendering it more flexible in the presence of non-stationarities.

Although it has been shown [14] that CHF patients lose the circadianity of the regularity index, the higher overall SEM values during the night in Tab. 4 might be explained by a wider spread of the data due to the coexistence of reduced regularity index values as a result of an increased nighttime vagal activity and large regularity index values related to the presence of non stationarities like that shown in Fig.2b. It is worth noting that SEM values calculated over the entire three sets of data exhibit a significant decrease as a result of the increase of the degrees of freedom of the statistical analysis.

8. Conclusions

This study demonstrates that care must be taken with the application of the regularity index over long-term recordings. The low reproducibility of the results is the effect of the presence in HRV Holter recordings of several non-stationarity periods. Therefore, it seems to be important to improve the NCCE evaluation in long-term recordings by including features capable of dealing with non-stationarities.

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