Rhythmometric Analysis of Heart Rate Variability Indices During Long Term Monitoring

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Abstract

Long-term monitoring of ECG signals is receiving much attention, still being an open issue how to deal with this massive source of information. In particular, Heart Rate Variability (HRV) indices have been widely used to characterize the state of the autonomous regulation of the heart from 24-hour Holter monitoring, but there is few knowledge on the long-term evolution of HRV indices. A data set of 7-day Holter recordings in 12 Congestive Heart Failure (CHF) patients was assembled. For its analysis, an automatic rhythmometric procedure was designed, allowing to characterize the ultradian and the infradian components, with possible inclusion of near-periodic fluctuations. A bootstrap hypothesis test allows us to systematically adjust the model architecture for each patient. The temporal evolution of relevant time-domain (AVNN, SDNN, NN50), frequency-domain (LF, HF, HFn, LF/HF), and nonlinear (α_1, SampEn) HRV indices, was analyzed. Larger relative deviations from the daily average pattern were more clearly observed in nonlinear indices and in NN50. Infradian subharmonic was mostly present in NN50, AVNN, α_1, and SampEn. Long-term monitoring of HRV conveys new relevant rhythmometric information that can be analyzed with the proposed automatic procedure.

1. Introduction

Benefits of long-term monitoring are receiving much attention for clinical applications such as the detection of recurrences after ablation for atrial fibrillation (AF) [1]. Also, 7-day ambulatory ECG monitoring, following acute stroke or transient ischemic attack, has identified patients with AF which were not detected with 24-hour recordings [2]. Therefore, the clinical usefulness and meaning of a number of well-known clinical indices is likely to be analyzed in the long-term monitoring setting.

Heart Rate Variability (HRV) is a relevant marker of the autonomic nervous system control on the heart, and it has been widely studied, mostly in 24-hour ECG recordings. However, there are few studies about the HRV markers in long-term monitoring. Furthermore, circadian HRV has been well characterized in healthy and pathological subjects [3], and ultradian (components at frequencies larger than that corresponding to 24 hours period) rhythms have also been paid some attention [4], but infradian cycles of HRV have not been yet analyzed with detail.

In order to analyze the long-term variations of HRV indices in time-scales larger than 24-hour, we assemble a data base of Congestive Heart Failure (CHF) patients 7-day Holter. To analyze such amount of information we propose an automatic rhythmometric analysis procedure for characterizing both the ultradian and the infradian components, also accounting for possible narrow-band fluctuations, which uses a bootstrap hypothesis test to select the model architecture (number and nature of components).

The structure of the paper is as follows. The 7-day Holter recordings in CHF patients are described, and the used HRV indices are briefly presented. Next, the proposed rhythmometric analysis method is introduced, and then it is used to study the rhythmometric parameters of the patient data base, both in the time and in the frequency domain. Finally, conclusions are summarized.

2. Data set and HRV indices

A data base of 7-day Holter recordings, from patients with CHF, were assembled in the Arrhythmia Unit of Hospital Universitario Virgen de la Arrixaca (Spain). RR-interval series were used to perform the rhythmometric analysis. All data were filtered 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 [5]. A population of 21 recordings was initially considered. In order to obtain reliable estimations, those recordings with less than 80% of sinus beats were ruled out. HRV markers were computed at 15-

min intervals for each subject, by requiring each 15-min segment to have more than 80% of sinus beats to compute the markers. Finally, only those recordings with more than 80% of usable segments were accepted into the data base, hence obtaining a final population of 12 patients.

A wide number of HRV indices have been proposed in the literature, which can be roughly divided into three families, namely, time-domain, spectral, and nonlinear methods. Time-domain methods used were mean of NN intervals (AVNN), standard deviation of NN intervals (SDNN), and the number of pairs of adjacent NN intervals differing by more than 50 ms (NN50). Frequency-domain methods used were power in low and high frequency ranges (LF and HF), these two markers in normalized units (LFn and HFn), and the ratio between LF and HF (LF/HF). Finally, non linear methods used were scaling exponent α_1 from Detrended Fluctuations Analysis (DFA), that assess the short term fractal correlation properties (between 3 and 16 beats), and sample entropy (SampEn), that quantifies the irregularity of a temporal series.

3. Rhythmometric model selection

Several works (see [6] and references therein) have studied the circadian variation of a biological parameter using a physiological time series given by N pairs of values $\{t_i, y_i\}_{i=1}^{N}$, by fitting a set of cosine curves:

$$y_i = M + A_0 cos(2\pi f_0 t_i + \phi_0) + e_i \qquad (1)$$

for $i = 1, ..., N$, where M is the rhythm-adjusted mean or mesor, A_0 is the fitted cosine amplitude, f_0 is the fundamental frequency (set by the analyst on the basis of empirical physiological information and usually considered as 24 hours), ϕ_0 is the acrophase (lag from a defined reference timepoint to the crest time in the cosine curve fitted to the data), and e_i is the residual (difference between the model estimation and the real data). The N values of random variable y correspond to the HRV markers to be analyzed. Regarding the fitting regression method, we considered Least Squares (LS) for simplicity and because it provides the best estimation (unbiased and minimum variance) when both normality and homoscedasticity of the residuals are fulfilled, then being equivalent to the maximum likelihood criterion.

To analyze long-term recordings, in this paper we extend the model in (1) to be able to model both ultradian and infradian rhythms, i.e., frequencies higher and lower, respectively, than frequency corresponding to 24 hours period. On the one hand, to take into account infradian rhythms, we consider one sub-harmonic term of frequency $f_1 = f_0/2$, given by

$$I = A_1 cos(2\pi f_1 t + \phi_1) \qquad (2)$$

For ultradian rhythms, we consider up to five harmonic components u_k, with $k = 2, \cdots, 6$, whose frequencies correspond to $f_k = k f_0$, hence comprising a band between 4 and 24 hours,

$$U = \sum_{k=2}^{6} u_k = \sum_{k=2}^{6} A_k cos(2\pi k f_0 t + \phi_k) \qquad (3)$$

To take into account near-periodic or narrow band fluctuations, we also consider two additional terms for every harmonic and subharmonic. These terms, denoted as F^- and F^+, correspond to cosine functions which deviate from the main frequency $\pm\Delta f = \pm f_s/N$, where f_s is the sampling frequency. This way,

$$F_k^- = A_k^- cos(2\pi(f_k - \Delta f)t + \phi_k^-) \qquad (4)$$
$$F_k^+ = A_k^+ cos(2\pi(f_k + \Delta f)t + \phi_k^+) \qquad (5)$$

for $k = 0, 1, \cdots, 6$. Taking into account the above components, the proposed model is an extension of cosinor model in (1), given by

$$\begin{aligned} y &= M + A_0 cos(2\pi f_0 t + \phi_0) + F_0^- + F_0^+ \\ &+ I + F_1^- + F_1^+ + U + \sum_{k=2}^{6} \left(F_k^- + F_k^+\right) \qquad (6) \end{aligned}$$

In order to automatically select the spectral components of interest in (6), and avoiding subjectivity in the model choice, we propose an automatic method to select the spectral components of interest in each signal. In brief, we start with the simplest model, corresponding to $\{A_k = 0\}_{k=1}^{6}$ and $\{A_k^- = A_k^+ = 0\}_{k=0}^{6}$ (equivalent to (1)), and progressively include one new term according to its statistical significance.

To determine if the addition of a new term is statistically relevant, a paired bootstrap hypothesis test is made, which considers the mean power of the residuals corresponding to the previous model *vs.* the new model. If the test provides significant improvement with new model, a second bootstrap hypothesis test compares the new model with an auxiliary model. The latter has the same number of components, but just considering harmonics of f_0; i.e., it considers neither sub-harmonics nor fluctuations, but it has the same number of freedom degrees. If the second test favors the auxiliary model, then the previous model is selected as the best fitting; otherwise, the same process is repeated by considering one additional spectral component. This procedure allows us to automatically find the best fitting model with the minimum number of spectral components.

4. Simulations and results

The proposed rhythmometric method was tested by using synthetic sinusoidal signals, including a different number of harmonics, subharmonics, and fluctuations. White

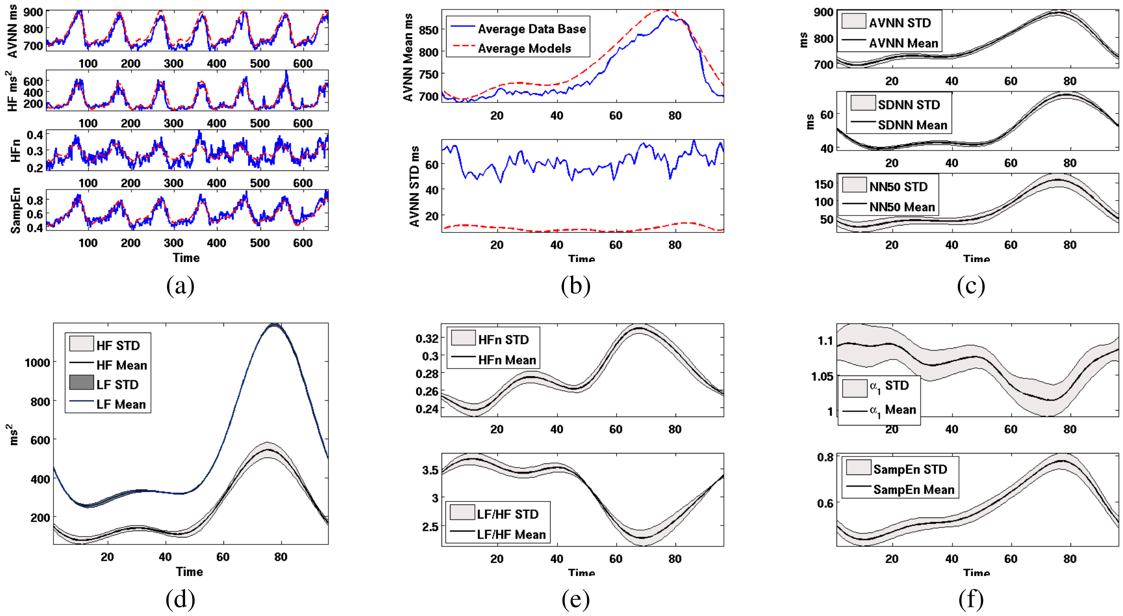

Figure 1. *Rhythmometric analysis of long term monitoring in HRV parameters. (a) Examples of populational HRV indices during 7 days. (b) Populational daily-averaged AVNN and its daily-averaged standard deviation. (c) Time-domain results. (d) Frequency domain results (LF and HF). (e) Frequency domain results (HF normalized and ratio). (f) Nonlinear parameters. Time units indicate sampling periods (15 min), time origin at 9AM.*

gaussian noise was added (SNR of 20, 10, and 5 dB). The percentage of right choices achieved by our method was calculated for each group of signals and for each SNR. When using signals with harmonic and subharmonic components only, the method chose the correct models for all the tested SNR values. Fluctuations were almost always correctly detected on harmonic components, but it failed in some cases on subharmonic components for noisy signals, due to the fact that the spectral component of subharmonic $f_0/2$ is very close to spectral component f_0. The method was also tested in square waves, constructed by adding a number of coefficients of the Fourier Series, yielding sinusoidal components with decreasing amplitudes. Again, signals with harmonics, subharmonic, and fluctuations on harmonic components, were almost always correctly detected, with few errors found for SNR = 5 dB. Some errors were also found when detecting fluctuations on subharmonics, always lower than 22%.

The rhythmometric procedure was used to analyze some of the most relevant HRV markers in the long-term monitoring data base, including temporal (AVNN, SDNN, NN50), spectral (LF, HF, LFn, HFn, LF/HF), and nonlinear (α_1, SampEn) indices. All of them were obtained in time windows of 15 min, yielding a local estimation of their fluctuations. Figure 1(a) depicts the time evolution of the populational mean for several HRV indices during 7 days, showing that they can change significantly from one day to another. In order to characterize their time stability, rhythmometric models were adjusted (dashed red line). Due to the consideration of different kinds of components, the models were able to account for individual and intrinsic day-to-day changes. The populational average daily profile, together with its standard deviation, were obtained for each index in each patient (Fig. 1(b) for AVNN). The daily standard deviation averaged for all the patients can be considered to account for inter-patient daily variations.

Daily averages and standard deviations (shaded bands) for HRV markers can be observed in Fig. 1(c-f). The higher the bands, the higher the populational average inter-day variation. In temporal parameters (Fig. 1(c)) the bands were significantly larger for NN50 than for AVNN and SDNN, due to these two parameters having lower number of harmonics and of fluctuations included in the model (see Table 1). Also note the significantly similar profile of these three time-domain parameters.

Frequency parameters are shown in Fig. 1(d). Their populational average has a highly similar profile, whereas the band is larger for HF parameter, indicating it exhibits larger populational daily variations. With respect to normalized frequency parameters (Fig. 1, HFn (and LFn, which can be trivially obtained from it) shows not only an average profile highly similar to the inverse of LF/HF, but also their standard deviation bands are similar, indicating their equivalence in terms of information content.

Non linear parameters (Fig. 1(f)) have markedly larger standard deviation bands, indicating a high number of

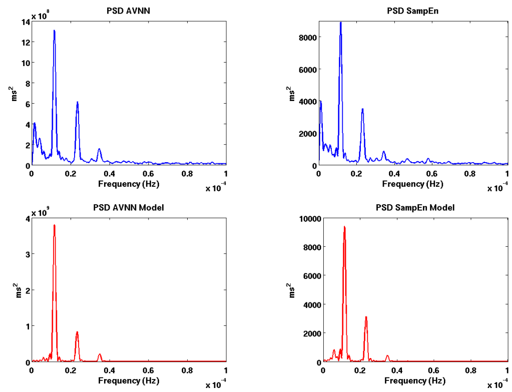

Figure 2. *Spectral averages (top) and averaged models (bottom), AVNN (left) and SampEn (right).*

spectral components, specially in the case of α_1 exponent. Also, it is relevant to note that the time profile of the populational average of α_1 is markedly different from the other HRV indices, which is in coherence with the fact of this parameter being often an independent marker of the autonomous system state.

Table 1 shows the model parameters given for all the HRV indices. Percentage of power (relative to the mesor level) explained by the model was larger in AVNN, NN50, HF, and Sampen, which indicates that these parameters are better fitted by a rhythmometric model than the others. Near-periodic fluctuations were mostly present in NN50, HF, α_1, and Sampen, whereas subharmonics were mostly present in NN50, AVNN, α_1, and Sampen. Although these two elements (subharmonics and fluctuations) are not always considered in conventional rhythmometric analysis, this shows that they can have a relevant explanatory capacity in the model for some HRV indices, and hence they should be taken into account. Figure 2 details the spectral profiles of two indices and their fitted models. Whereas the rhythmometric models keep some infradian power, the

Table 1. *Results for the models: number of harmonics (N_h, mean $\pm$ standard deviation), percentage of patients with subharmonics (% I) and with fluctuations (% F) in their models, and percentage of power explained by the model (% Pw, m $\pm$std).*

Index	N_h	% I	% F	% Pw
AVNN	2.2 ± 0.8	33	16.7	53.7 ± 21.4
SDNN	2.2 ± 0.7	8.3	8.3	26.8 ± 17.3
NN50	2.7 ± 1.0	41.7	58.3	39.0 ± 18.5
HF	2.1 ± 0.9	8.3	25	36.4 ± 16.7
LF	2.2 ± 0.4	0	8.3	24.0 ± 18.9
HFn	2.6 ± 1.1	16.7	8.3	23.1 ± 15
LF/HF	2.1 ± 0.6	0	8.3	17.5 ± 10.7
$\alpha 1$	2.6 ± 1.0	25	25	15.3 ± 6.5
SampEn	2.4 ± 0.9	25	25	33.4 ± 17.6

studied infradian component $f_0/2$ is not enough and further infradian components should be taken into account in future studies.

5. Conclusions

Long-term monitoring of HRV can be readily addressed with the automatic rhythmometric procedure. As shown in CHF patient data base, daily variations in HRV indices can be explained by narrow band fluctuations in the ultradian components, by infradian components, or both. Further development and analysis will be devoted to assess the infradian HRV content.

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