Heart Rate Variability Characterized by Refined Multiscale Entropy Applied to Cardiac Death in Ischemic Cardiomyopathy Patients

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Abstract

In this work, Refined Multiscale Entropy (RMSE) was applied to characterize risk of cardiac death in ischemic cardiomyopathy patients, analyzing heart rate variability (HRV) by means of RR series during daytime and nighttime. RMSE approach measures an entropy rate in different time scales of a series, giving a multiscale characterization of complexity of that series. RMSE showed statistically significant differences (p<0.05) during daytime and nighttime only in middle time scales (τ=4-15 and τ=3-16, respectively). For these scales, RMSE was higher in low risk (SV) than in high risk (CM) group of cardiac death, indicating a reduction of the entropy-based complexity in CM when it was compared with SV. No statistical differences between risk groups were presented at time scale τ=1 (unfiltered original RR series). It can be concluded that the dynamics in middle time scales should be considered to better describe the HRV of patients with cardiac death.

1. Introduction

The dynamics involved in the beat-to-beat variability of the heart occur over a large set of temporal scales, being influenced by several regulatory mechanisms. These mechanisms operate in different time scales ranging from few seconds as the autonomic nervous system, respiratory system and vasomotor control, until time scales of the order of minutes or hours as chemoreflex control, thermoregulation and hormonal regulation [1]. As a result, a single time scale is not enough to completely describe the heart rate variability (HRV), and scaling techniques are required to characterize its behavior.

Techniques as mutual information function [2], detrended fluctuation analysis [3] and multiscale entropy (MSE) [4] have been applied to study HRV at multiscale level. Concretely, MSE evaluates an entropy rate over different time scales of a time series, obtaining information of the time series complexity on each one of the time scales. Refined Multiscale Entropy (RMSE) [5] was proposed as a refinement of MSE, since it offers a way to solve two shortcomings that produce the MSE dependence on variance and on the shape of the power spectrum of the considered series.

In this work, RMSE was applied to characterize risk of cardiac death in ischemic dilated cardiomyopathy (IDC) patients, analyzing HRV by means of RR series of 24h holter-ECG during daytime and nighttime. The end-point was age-matched patients that suffered CM after a follow-up of three years. In order to differentiate low and high risk of cardiac death, a statistical analysis was applied on each entropy measure that was obtained with RMSE.

2. Methods

2.1. Analyzed database

Patients from MUSIC (MUerte Subita en Insuficiencia Cardiaca, Sudden Death in Heart Failure) study were analyzed in the present work. A total of 222 patients (aged 63.2±0.56 years, 86.9% male) with ischemic dilated cardiomyopathy (IDC) were enrolled in the present study. Patients were followed for three years. The inclusion criteria were: sinus rhythm, symptomatic chronic heart failure with New York Heart Association functional class (*NYHA*) II or III, and ischemic etiology of heart failure. Age-matched IDC patients were studied considering cardiac mortality as end-point. The analysis considers 30 patients that suffered cardiac mortality (CM) due to sudden cardiac death, progressive heart failure or myocardial infarction, as a high risk group and 192 survivors (SV) as a low risk group. The MUSIC study was approved by the Ethical Committee of the institution and all subjects gave their written informed consent before participation.

The RR series, intervals between consecutive heart beats, were obtained from 24h ECG-Holter recordings with a sampling frequency of 200 Hz (Spiderview recorders, ELA Medical, Sorin Group, Paris). An adaptive filter [6] was applied to the RR series in order to replace ectopic beats and artifacts by interpolated RR intervals. Indeed, the level of interpolated beats related to the total number of RR intervals was less than 1.5%. Therefore, a possible alteration of the results due to the filter procedure can be discarded. The HRV was analyzed during the daytime and nighttime by means of RR series of length 10,000 beats for both periods.

Ad-hoc simulations, including Gaussian white noise (GWN) and autoregressive (AR) processes, were also considered. GWN simulates a fully unpredictable process and a second order AR process driven by GWN simulates a partially predictable process. The second order AR process (AR025) was shaped to have a power spectrum peak with central frequency at 0.25 cycles/sample and pole modulus ρ=0.98.

2.2. Methodology

MSE [4] is based on three steps: i) progressive elimination of the fast time scales; ii) coarse graining procedure necessary to assess entropy rate; iii) calculation of the entropy rate. The first two steps, indicating the refinements that RMSE include to eliminate two shortcomings of MSE, are described in the following.

i) Elimination of the fast time scales [4]: given a time series $x=\{x(i),\ i=1,\ldots,N\}$, this is divided into nonoverlapping frames of length τ, where τ is the scale factor and takes integer values equal or greater than 1. Samples inside each frame are averaged as:

$$x^{\tau}(j)=\frac{1}{\tau}\sum_{i=(j-1)\tau+1}^{j\tau}x(i) \qquad 1\le j\le\frac{N}{\tau} \tag{1}$$

producing a new time series $x^{\tau}=\{x^{\tau}(j),\ j=1,\ldots,N/\tau\}$ with length given by N/τ. At $\tau=1$, x^1 is the original time series. The same result can be obtained filtering the original time series x by applying a finite-impulse response (FIR) filter (2) and downsampling the filtered time series with the factor τ [7].

$$x^{\tau}(j)=\frac{1}{\tau}\sum_{k=0}^{\tau-1}x(j-k) \qquad 1\le j\le N \tag{2}$$

This FIR filter is a low-pass filter with a very poor frequency response: it is characterized by a very slow roll-off of the main lobe, large transition band and important side lobes in the stopband. Due to the side lobes, the maximal frequency in the filtered signal obtained after applying (2) is never below f_c=0.5/τ, where f_c is the normalized filter's cutoff frequency. As a result, this filter does not completely eliminate fast temporal scales above f_c, and thus, the subsequent downsampling procedure produces aliasing generating spurious oscillations in the frequency range from 0 to f_c. This shortcoming has been eliminated in RMSE [5] by replacing the FIR filter with a low-pass Butterworth filter, which has a squared magnitude of its frequency response given by

$$\left|H(e^{j2\pi f})\right|^2=\frac{1}{1+\left(f/f_c\right)^{2n}} \tag{3}$$

where n and f_c indicate the filter order and the cutoff frequency, respectively. In the present study n=6 and f_c=0.5/τ, so that f_c corresponds with normalized Nyquist frequency when τ=1. The series was processed in both the forward and backward directions to perform zero-phase filtering. The original time series x is filtered with (3) and subsequently downsampled by the scale factor τ, thus obtaining the time series x^{τ}. The magnitude of the frequency response of this filter is flat in the passband, sidelobes in the stopband are not present, and the roll-off is fast. Therefore, this Butterworth filter ensures a more accurate elimination of the components with frequency above f_c with respect to the FIR filter, thus reducing aliasing when the filtered series are downsampled.

ii) Coarse graining procedure: in MSE, patterns of length L are similar if they are closer than a parameter r in the L-dimensional phase space, according to a given definition of distance, which is defined as the maximum absolute difference between their components. In MSE, the parameter r is set as a percentage of the standard deviation (SD) of the original time series and it remains constant for all scale factors, i.e. r=SD[x]%. Since the procedure for the elimination of the fast temporal scales acts as a low-pass filter, filtered series are characterized by a lower SD as a function of the scale factor τ and, accordingly, the cloud of points in the L-dimensional phase space occupies a smaller region, i.e. the patterns become closer. Therefore, given a constant parameter r, more patterns will be considered indistinguishable while increasing τ, thus artificially decreasing entropy rate and increasing regularity with the scale factor. This shortcoming has been eliminated in RMSE by continuously updating the parameter r as a percentage of the SD of the filtered series, i.e. r^{τ}=SD[x^{τ}]% [7].

iii) Sample entropy [8], $SE(\tau)$, was used as entropy rate in RMSE. It was calculated with r^{τ}=0.15*SD[x^{τ}] and m=L=2, where SD[x^{τ}] is the standard deviation of x^{τ} and m is the number of samples in a pattern.

2.3. Statistical analysis

Mann-Whitney U test was applied to compare the risk groups of cardiac death during the same period (daytime or nighttime). Wilcoxon signed-rank test was used to assess the significance of the differences between sample entropy indexes derived during daytime or nighttime inside the same risk group (SV or CM). A p-value<0.05 was considered as significant.

3. Results and discussion

Figure 1a shows the mean values of the variance as a function of the scale factor τ, in the case of the application of the FIR filter, obtained from the analysis of the simulated series GWN and AR025. Independently of the type of filter utilized to eliminate fast temporal scales, the variance of GWN and AR025 processes decreased while increasing the scale factor: the fastest decrement was associated to AR025 process that contains most of its energy in the high frequency band. It is worth noting that the coarse of variance relevant to AR025 process exhibited ripples when calculated using the FIR filter. The original MSE (Fig.1b) decreased independently of the type of simulation but the decrease was monotonic in the case of GWN, while it exhibited ripples in the case of AR025 process. The course of MSE_{CGR} (Fig.1c), which corresponds to MSE including the refinement in the coarse graining procedure, was completely different from that of MSE. In fact, MSE_{CGR} was flat in the case of GWN and rapidly increased and, then, oscillated in the case of AR025. The course of RMSE (Fig.1d) was similar to that of MSE_{CGR} except for the AR025 process: indeed, in this case RMSE reached a plateau without oscillating. These results suggest that the MSE course reduction in large time scales, which was observed in all the simulated series, is mainly due by the reduction in SD caused by filtering the fast time scales. AR025 process, which was designed with a relevant frequency component coinciding with the cutoff frequency of the low-pass filter in time scale τ=2, has allowed to show if the FIR and Butterworth low-pass filters can efficiently rejects high frequencies and avoid the aliasing. These results show that FIR filter cannot prevent aliasing, especially in presence of processes with dominant peaks in the HF band, as in AR025. The merger of the considered time scales with the faster ones, only partially rejected by the FIR filter, produces the ripples in the course of variance and sample entropy.

Figure 2 shows the course of RMSE calculated over the RR series in IDC patients classified in low (SV) and high (CM) risk of cardiac death. Risk groups are compared during daytime (Fig. 2a) and nighttime (Fig. 2b), while circadian variations are compared in SV group (Fig. 2c) and in CM group (Fig. 2d). During both daytime and nighttime all the curves exhibited a minimum at short time scale followed by an exponential increment with τ. Risk groups showed significant differences over a large interval of scales both during daytime (Fig. 2a at τ=4-15) and during nighttime (Fig. 2b at τ=3-16), being the entropy-based complexity smaller in CM than in SV group. These results indicate a reduction of the HRV complexity in patients with a high degree of disease. In contrast, there are not significant differences in the shortest and largest time scales when the risk groups were compared. During the daytime, the largest statistical differentiation was obtained at the time scale τ=7 with a p-value=0.0109 (SV: SE=1.293±0.025 and CM: SE= 1.115±0.068). During the nighttime, the largest statistical differentiation was obtained at the time scale τ=8 with a p-value=0.0022 (SV: SE=1.427±0.025 and CM: SE= 1.216±0.072).

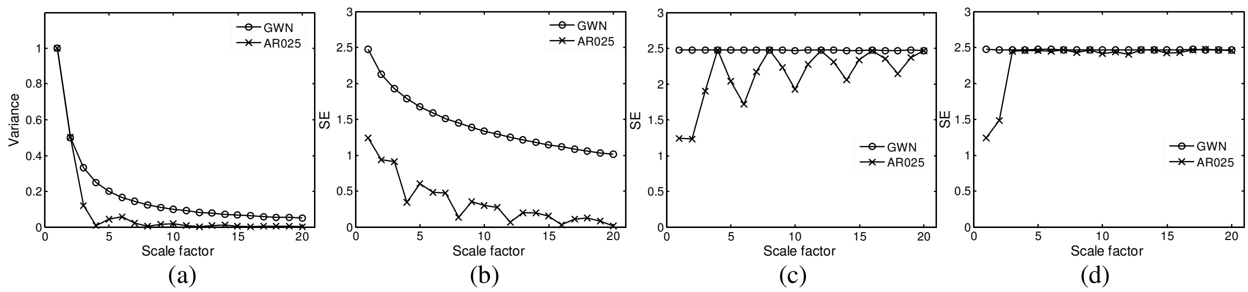

Figure 1. Mean values of the variance (a), MSE (b), MSE_{CGR} (c) and RMSE (d) as a function of the scale factor in 50 realizations of simulated series: GWN and AR025. In (a) variance is calculated after the application of the FIR filter.

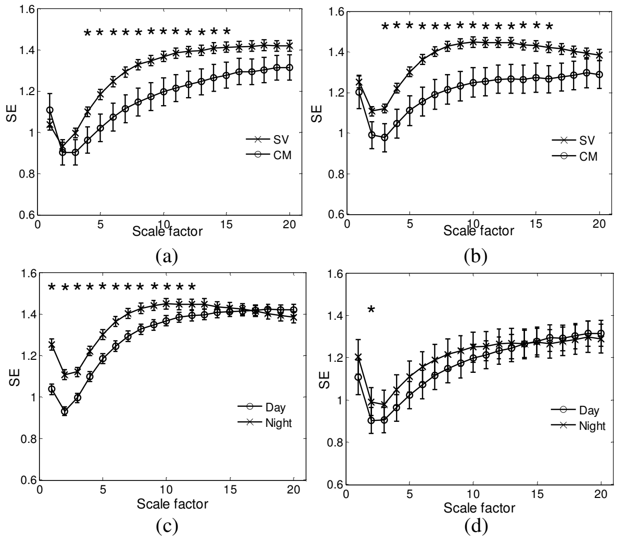

Figure 2. Mean values (± standard error) of RMSE as a function of the scale factor derived from the RR series in IDC patients classified in low (SV) and high (CM) risk of cardiac death. SV and CM are compared during daytime (a) and during nighttime (b). Daytime and nighttime are compared in SV (c) and CM (d) groups. Significant statistical differences with $p<0.05$ are marked with ⋆.

Comparing daytime and nighttime, SV group showed significant differences in short and middle time scales (Fig. 2c at τ=1-12) while CM group can only differentiate at τ=2 (Fig. 2d), being the entropy-based complexity significantly larger during nighttime than daytime. These results suggest that complexity in SV group presents circadian variations more evident than in CM group. Must be noted that differences between daytime and nighttime are more evident in short scales, where the respiratory-related oscillations are present.

4. Conclusions

The ad-hoc simulations (GWN and AR025) have allowed highlight two shortcomings in MSE, for which: MSE measures not only the variations of complexity as a function of the scale factor τ but also the variations in the power of the signal; MSE is biased by the inclusion of spurious components due to an effect of aliasing. Additionally, the ad-hoc simulations have shown how the two refinements that were included in RMSE can solve the two shortcomings identified in MSE.

The application of RMSE, in order to characterize the HRV complexity in IDC patients, has allowed statistical significant differences are found between the high and low risk groups of cardiac death. These differences were in middle and middle-large time scales, while for the time scale τ=1, which is equivalent to the original signal, there were not significant differences between risk groups, reinforcing the importance for a multiscale analysis in order to better characterize the HRV in IDC patients.

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