Analysis of time statistics of extreme variations of heart beat fluctuations

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Abstract

We analyzed heart beat fluctuations in terms of return times of extreme values of the RR increments. We considered 24 hours Holter ECG signals of 90 healthy individuals and 90 unhealthy ones suffering of congestive heart failure (chf). The increment time series ΔRR corresponding to sleep and daily activity were studied separately. In both cases, our results pointed out strong differences in the median return times of the positive high thresholds between healthy and unhealthy people.

Introduction

In recent years it has become clear that many physiological signals contain much more information than that catched by conventional statistical tools [1,2]. In particular, the detection in heart beats time series of several features typical of complex systems, like long-term correlations [3-6], multifractality [4], non-Gaussianity [7,8], etc., stimulated the use of advanced statistical methods, as detrended fluctuation analysis [3], multifractal detrended fluctuation analysis [6], wavelet transform [9], diffusion entropy [10,11] and the development of models of the intrinsic dynamics of the heart regulatory systems [1,12,13]. Recently, some authors [14-17] highlighted the effectiveness of extreme value analysis in the study of several complex systems of different nature. Therefore we performed this kind of analysis on time series of heart beat increments [18]. In the following, we shortly present the procedure that we adopted in this study and some of its results. Further details and results can be found in Ref. [18].

Materials and methods

The time series analyzed consisted of three groups of 24 hours Holter ECG signals [18]:

- **rlvs group**: The rlvs group consisted of 90 patients hospitalized in the 1st Department of Cardiology of Medical University in Gdansk, Poland (9 women, 81 men, the average age was 57$\pm$10) all suffering of reduced left ventricular systolic function, as recognized by echocardiogram in terms of low left ventricular ejection fraction (LVEF$\leq$40, mean LVEF=30.2 $\pm$ 6.7) [9]. The additional criteria which excluded subjects from the rlvs group were: the myocardial infarction or coronary revascularization in the last

six months, persistent atrial fibrillation, sinus-node disease, diabetes mellitus, kidney failure with creatine level greater than 2 in the last six months.

- **nsr_gda group:** One of the two control groups was made of 39 healthy individuals (4 women, 35 men, the average age is 54±7) without past history of cardiovascular disease, with both echocardiogram and electrocardiogram in normal range [9].
- **nsr2db group:** Another control group was provided by the Physionet database [19-23] and it included beat annotation files for 54 long-term ECG recordings of subjects with normal sinus rhythm (30 men, aged 28.5 to 76, and 24 women, aged 58 to 73).

The rlvs and nsr_gda groups were digitized by using Delmar Avionics recorder (Digitorder) and then analyzed and annotated by means of a Delmar Accuplus 363 system (fully interactive method) by an experienced physician to extract the interbeat RR records [9]. Only the intervals between normal beats (NN) were considered while intervals associated with non-normal beats were eliminated. The minimum number of qualified sinus beats required for the signal to enter into the study was 85% [9]. A moving window average filter was applied to eliminate outliers due to the missed beat detection. No interpolation was done for the eliminated intervals. Further details concerning the treatment of the RR data can be found in Refs. [9,18]. The third group of signals were digitized at 128 samples per second and the beat annotations were obtained by automated analysis with manual review and correction. The same filtering procedure was applied also to this group of signals. For other details see Refs. [19-23].

Two continuous subsets were extracted manually from each RR signal: one corresponding to daily activity and the other to sleep [9,18]. We grouped together the 39 nsr_gda time series and 51 time series chosen among the nsr2db group, obtaining 90 control group signals, from now denoted as ``healthy'' while the rlvs signals are denoted as ``unhealthy''.

We denoted as r_i the i-th interval RR (expressed in milliseconds) with $i \in [1, N]$ ($N \approx 2\times10^4$ for the sub-series considered here). As usual in the literature, the increment Δr_i was defined as: $\Delta r_i \equiv r_{i+1} - r_i$ with $i \in [1, N-1]$. Then we considered:

$$x_i = \frac{\Delta r_i - m}{\sigma} \qquad (1)$$

where m and σ are respectively the average and the standard deviation of the Δr_i series. Therefore, the normalized series x_i had zero mean and unit standard deviation. We looked for extreme events in the Δr_i series defined in terms of a threshold q expressed in units of σ.

The time t_j associated with the occurring of j-th extreme event was defined by the following condition:

$$t_j^q \; is \; event \; if \begin{cases} x_j > q \quad for \; q > 0 \\ x_j < q \quad for \; q < 0 \end{cases} \qquad (2)$$

The return time τ^q_j of the threshold q was defined as the time interval between two consecutive overcoming of the threshold [15-18], i.e. as:

$$\tau_j^q \propto t_{j+1}^q - t_j^q \qquad (3)$$

For each series we computed the mean return time $\langle\tau\rangle^q_k$ as mean of the τ^q_j over the n^q_k events occurring for the k-th individual, and the median return time M^q_k, defined as the median of the distribution of τ^q_j [18]. The results of our analysis are reported in the next section.

Results and Discussion

Figure 1 displays the median return times to the threshold q=2.5 of the x_i for all the 90 healthy individuals, M^q_k with k=1,...90. The median return times in this figure were obtained from the time series corresponding to daily activity. Figure 2 shows the same quantities, M^q_k with k=1,...90, calculated for the unhealthy patients (again daily activity). The differences between the median return times of the two sets of data are evident, at a qualitative level, even by eyes. The value 2.5 of the threshold q for these figures was selected because it provided a good compromise between enough statistics and significative difference between healthy and unhealthy individuals expected for high thresholds.

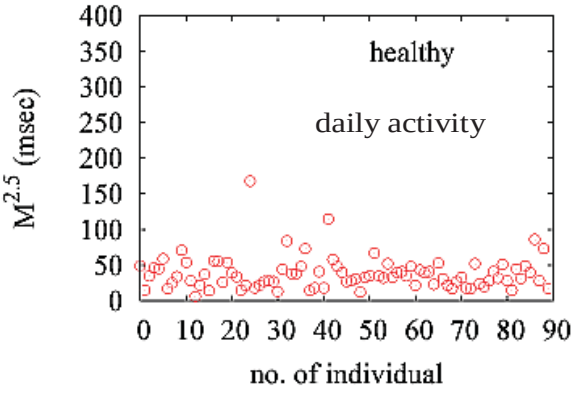

Figure 1. Median return times of the threshold q=2.5 (in σ units) during daily activity for 90 healthy people (nsr_gda and nsr2db groups).

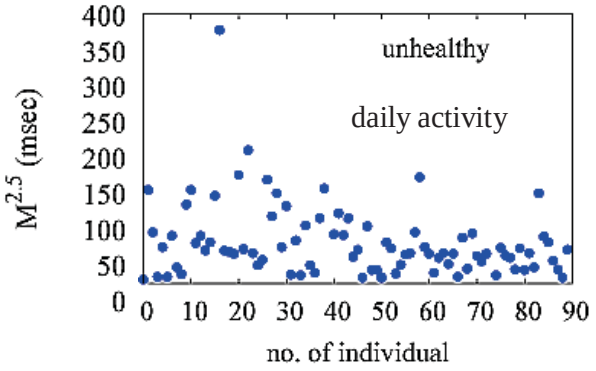

Figure 2. Median return times of the threshold q=2.5 (in σ units) during daily activity for 90 unhealthy people (rlvs group).

A similar behavior was found by comparing the median return times to the threshold q=2.5 of the x_i coming from the sleeping state time series, calculated for all the 90 healthy individuals, Fig.3, and the 90 unhealthy ones, Fig. 4.

Moreover, for each individual k series, separately for daily activity and sleep and for healthy and unhealthy people, we performed a systematic extreme value analysis, calculating the mean $<\tau>^q_k$ and the median return times M^q_k for several threshold values, $q>0$ and $q<0$.

By making use of the Mann-Whitney non-parametric test, we performed, for each threshold q, the comparison between the two sets of data, M^q_k with k=1,...90, for healthy and unhealthy individuals. The same procedure was also applied to compare the sets of data, $<\tau>^q_k$ with k=1,...90, for healthy and unhealthy individuals as a function of q. Before commenting the results of this analysis, it must be noted that for our sample sizes the results of the Mann-Whitney test can be interpreted in terms of the so called Z statistics. This implies that values $Z>Z_c$=1.96 allow to discard the null hypothesis that two sets of data (two distributions) are the same at the significance level of 5%.

We found that for positive and quite large values of q, typically q>2.5, the statistics of healthy and unhealthy individuals is significantly different, as proved by values of the Z-score greater than Z_c. Instead, no statistically significant difference between healthy and unhealthy time series was found for the return times of the x_i to negative thresholds. All the details of these calculations can be found in Ref. [18], including the Z-score values and the values of $<M^q>$ and σ_q, respectively average and standard deviation over the 90 patients of M^q_k for each of the two groups (healthy/unhealthy) and for several positive and negative q values.

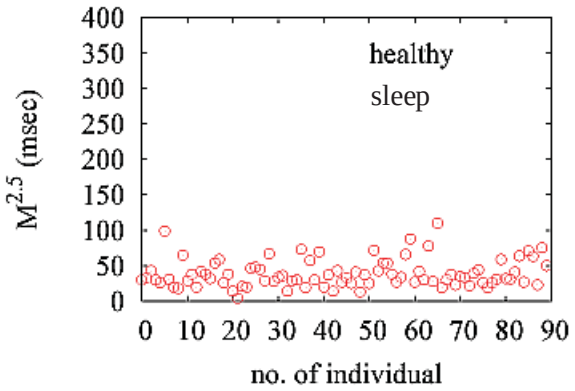

Figure 3. Median return times of the threshold q=2.5 (in σ units) during sleep for 90 healthy people (nsr_gda and nsr2db groups).

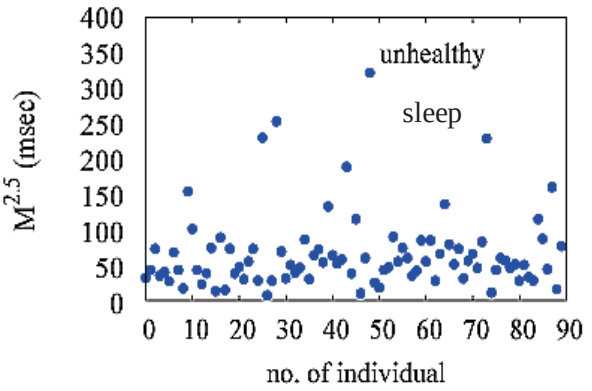

Figure 4. Median return times of the threshold q=2.5 (in σ units) during sleep for 90 unhealthy people (rlvs group).

This result can be explained by saying that healthy individuals have more often than the unhealthy the tendency to suddenly slow their heartbeat rate (thus more frequently obtaining larger positive increments of the RR intervals). This behavior is not so trivial because an intuitive reasoning should lead to a tendency of unhealthy people to avoid sudden increase of heartbeat rate but, as stated before, we didn't observe significant differences for *q<0*.

Finally, we checked the stability of our results with respect to the sampling rate. To this purpose, we added a white Gaussian noise to the RR intervals and we took the Gaussian width equal to half of the sampling time [18]. We found that our results are quite robust, at least for sampling rate greater than or equal to 128 that is the lowest used for the data of this paper.

Conclusions

We performed an extreme value analysis of the RR intervals times series extracted from 24-h Holter ECG signals of 90 healthy people (nsr_gda and nsr2db groups [9]) and 90 unhealthy people suffering of congestive heart failure (rlvs group [9]). We studied separately sub-series corresponding to daily activity and sleep. We focused on the return times of threshold values of the normalized RR increments, x_i [18]. Despite the simplicity of the technique used, our analysis pointed out some interesting features [18]. In particular, we found significant differences in the median return times M_k^q of a high positive thresholds between healthy and unhealthy individuals. We underline that, to our knowledge, our study is the first in the literature of the heart beat fluctuations in terms of extreme value analysis. In any case these features need further investigations to be fully understood also from a physiological point of view and eventually correlated with the disease evolution and mortality risks.

Acknowledgements

The authors are deeply indebted to Prof. D. Makowiec (University of Gdañsk) which kindly provided the time series analyzed in this work. The authors also thank Dr. L. Urso (Clinica ``Petrucciani'', Lecce) for helpful and stimulating discussions.

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