Long-term Correlations and Complexity Analysis of the Heart Rate Variability Signal during Sleep

Comparing Normal and Pathologic Subjects

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Entropy, detrended fluctuation analysis, 1/f slope, symbolic dynamics

Summary

Background: Physiological sleep is characterized by different cyclic phenomena, such as REM, nonREM phases and the Cyclic Alternating Pattern (CAP), that are associated to characteristic patterns in the heart rate variability (HRV) signal. Disruption of such rhythms due to sleep disorders, for example insomnia or apnea syndrome, alters the normal sleep patterns and the dynamics of the HRV recorded during the night.

Objectives: In this paper we analyze long-term and complexity dynamics of the HRV signal recorded during sleep in different groups of subjects. The aim is to investigate whether the calculated indices are able to capture the different characteristics and to discriminate among the groups of subjects, classified according sleep disorders or cardiovascular pathologies.

Methods: Parameters, able to detect the fractal-like behavior of a signal and to measure the regularity and complexity of a time series, are calculated on the HRV signal acquired during the night. Different groups of subjects were analyzed: healthy subjects with high sleep efficiency, healthy subjects with low sleep efficiency, subjects affected by insomnia, heart failure patients, subjects affected by obstructive sleep apnea.

Results: The evaluated parameters show significant differences in the groups of subjects considered in this work. In particular heart failure patients have significant lower entropy and complexity values, whereas apnea patients show an increased irregularity when compared with normal subjects with high sleep efficiency.

Conclusions: This work proposes indices that can be used as global descriptors of the dynamics of the whole night and can discriminate among different groups of subjects.

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1. Introduction

In the last decades many works have demonstrated that the heart rate variability (HRV) signal contains important and relevant information about the autonomic nervous system (ANS) which controls the heart frequency itself. Many different parameters in the time and in the frequency domain as well as indices that quantify non-linearity and complexity have been proposed in order to describe and quantify the status of the autonomic nervous system in relation to many different pathologies [1]. Time and frequency domain analyses on short periods (200–300 heartbeats, corresponding to time windows ranging between 3 and 5 minutes) provide well accepted indices related to the activation of the two different branches of the autonomic nervous system: the sympathetic and the parasympathetic subsystems. However, new approaches have been proposed in order to shorten the analysis window till a single beat duration on one side [2] or to assess long-term dynamics on the other one [3].

In the study of sleep, different patterns of the HRV signal, explored in the frequency domain on a very short time basis, have been demonstrated to be related to sleep macrostructure (transitions between rapid eye movement, REM, and nonREM sleep) and microstructure (cyclic alternating pattern, CAP sleep), to the presence of apneas and of arousals. Moreover, sleep classification has been successfully performed by considering as input parameter indices assessed from HRV signal [4–6].

However, sleep disturbances have also a great impact on the long-term dynamics of sleep, such as the REM-nonREM cycles, the rhythmic sequences of apneas, the presence of prolonged periods of wake, etc. Thus the investigation of long-term correlations in the heart rate during sleep may add new hints and knowledge about these sleep disturbances.

In literature many different parameters are proposed for the quantification of long-term correlations in the HRV signal, and many different groups of subjects have been investigated. Since Bigger et al. [7] proved the clinical relevance of the slope of the RR signal power spectrum in a group of 715 subjects after an acute myocardial infarction, the concept of power spectrum slope and long-term correlation became popular.

Costa et al. analyzed the Multiscale Entropy (MSE) in patients with heart failure in two scenarios: day- and nighttime [8]. They observed that the long-term HRV behavior during sleep and during day is similar, but with an entropy higher for the sleep time. Furthermore, they also showed that in the large scales of the MSE, the long-term HRV behavior is comparable for both young and elderly healthy subjects.

For subjects with congestive heart failure only a shift of the entropy values was obtained but not a significant change in the trend of the MSE curves. Thus, differences between the day versus night dynamics of subjects with a severe cardiac pathology are less marked than for healthy subjects. The author suggested moreover that a loss of differentiation in the complexity of sleep/wake dynamics may be a useful new index of reduced adaptive capacity.

The detrended fluctuation analysis (DFA) was also proposed as method for the classification of sleep stages, in the work of Bunde et al. [9]. By using DFA up to fourth order they found that long-range correlations reminiscent to the wake phase are present only in the REM phase.

In the present work we analyzed the HRV recorded during sleep period in different groups of subjects classified according to their sleep characteristics or their cardiovascular pathologies. Different indices were measured for each signal. The objective of this paper is to investigate whether the proposed indices are able to capture the different characteristics and to discriminate among the groups of subjects, classified according sleep disorders or cardiovascular pathologies.

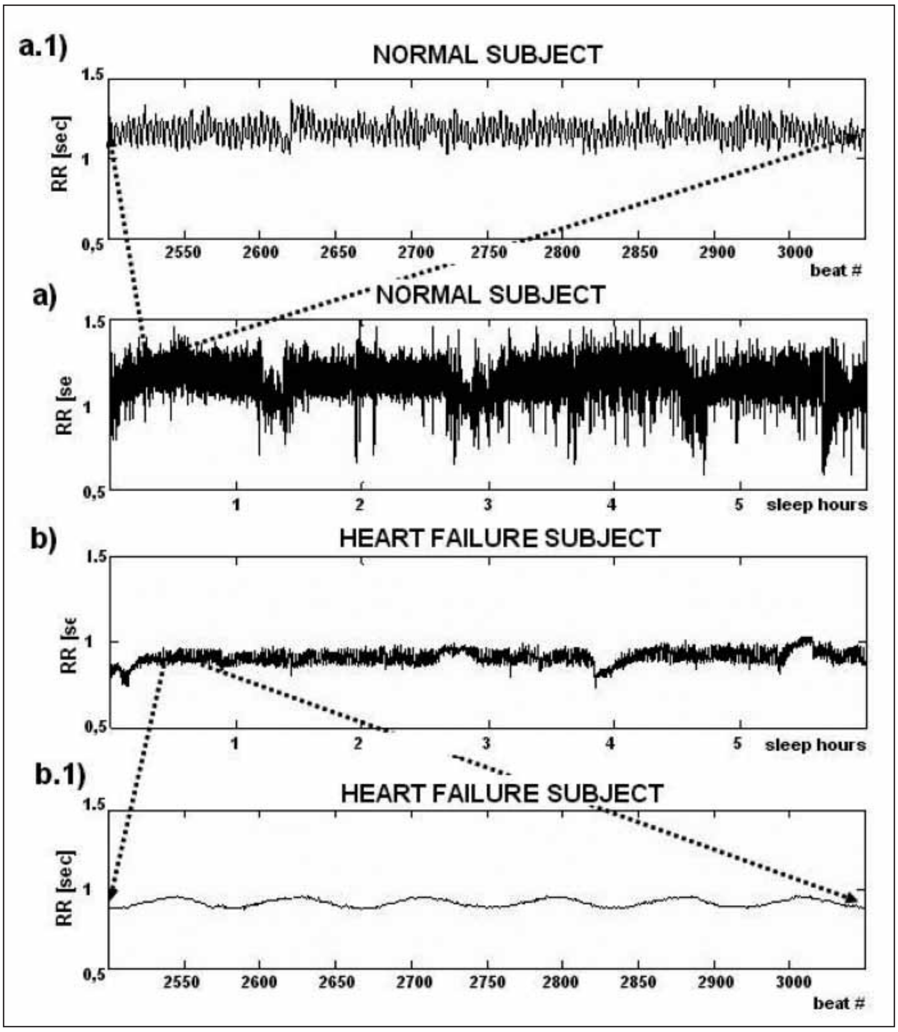

Fig. 1 HRV signal during sleep recorded from a) normal subject with high sleep efficiency and b) a heart failure patient; the short-term dynamics are shown in plots a.1) and b.1).

2. Methods

An example of the HRV signals recorded during six hours of sleep is illustrated in ►Figure 1. The HRV signals refer to a) a normal subject with high sleep efficiency (time of sleep/time in bed) and b) from a heart failure patient. Panel a.1) and b.1) show respectively the short-term dynamics (500 beats) of the same time sequences. It is possible to note that the two series are characterized by different patterns both on the long and on the short term. In order to properly describe the long-term correlation and dynamics different parameters have been implemented as described in the following.

2.1 Parameters

2.1.1 Sample Entropy (SampEn)

SampEn(2,0.2) measures, with a tolerance r, the regularity of patterns comparing them to a given pattern of length m (m and r are fixed values: m is the detail level at which the signal is analyzed and r is a threshold, which filters out irregularities) [10, 11]. The adopted parameters in the present application are $m = 2$ and $r = 0.2$.

2.1.2 Multiscale Entropy (MSE)

MSE was proposed in order to capture HRV fluctuations at different degrees of resolution, i.e. in a multiscale manner [12]. The first step to compute MSE is the construction of the coarse-grained time series. Given a time series of N points $\{x_i\}$, the coarse-grained time series $\{y^{(\tau)}\}$, determined by the factor τ, are constructed as follows:

$$y_j^{(\tau)} = \frac{1}{\tau}\sum_{i=(j-1)\tau+1}^{j\tau} x_i, \text{ for } 1 \le j \le \frac{N}{\tau}$$

For each of these new time series, an entropy measure is calculated and the obtained value is plotted as a function of the coarse-graining scale factor. In this work the proposed indices were the average of the MSE values estimated over the time scale from 1 to 5 (MSE_1) and from 10 to 20 (MSE_2).

2.1.3 Lempel-Ziv Complexity (LZC)

The measure of complexity introduced by Lempel and Ziv assesses the so-called algorithmic complexity, which is defined according to information theory as the minimum quantity of information needed to define a binary string. In case of random strings, the algorithmic complexity is the length of the string itself. In fact any compression effort will produce an information loss. The LZC quantifies the rate of new patterns arising with the temporal evolution of the signal. In order to estimate the LZC for a biological signal, it is necessary to transform the time series into symbolic sequences. The algorithm to assess LZC and the coding procedure is fully described in [13]. In this work we adopted both the binary LZC(2) and the ternary LZC(3) coding procedure.

2.1.4 Detrended Fluctuation Analysis (DFA)

The DFA can be simply defined as a modified root mean square analysis of a random walk [14]. Briefly, the time series to be analyzed is firstly integrated. Next, the integrated time series is divided into boxes of equal length, n. In each box of length n, a least squares line which fits the data (representing the trend in that box) is estimated. Next, the integrated time series is detrended by subtracting the local trend in each box. The root-mean-square fluctuation $F(n)$ of this integrated and detrended time series is calculated. This computation is repeated over all time scales (box sizes) to characterize the relationship between $F(n)$, the average fluctuation, and the box size n. A linear relationship on a log-log plot indicates the presence of power law (fractal) scaling. Under such conditions, the fluctuations can be characterized by a scaling exponent ν, the slope of the line relating log $F(n)$ to log n. In this work two scaling exponents are proposed: one represents an estimation of the *short-term* fluctuations ($a1$ ($n = 4–16$)) and one of the *long-term* fluctuations ($a2$) ($n = 16–64$).

Table 1 Groups of analyzed subjects

# of subjects	Classification	Age (range) years	Source
17	Normal subjects, high sleep efficiency [a]	40–50	Sleep Center h. S. Raffaele Milano, Italy
8	Normal subjects, low sleep efficiency	40–50	Sleep Center h. S. Raffaele Milano, Italy
11	Insomnia subjects	35–50	Sleep Center h. S. Raffaele Milano, Italy
43	Obstructive apnea patients [a]	27–63	www.physionet.org
15	Heart failure patients	22–71	www.physionet.org

2.1.5 1/f Slope

The slope of the power-low regression line of HRV fitted to the power spectrum for $f < 0.01$ Hz [7]. This index is strongly correlated to the DFA indices when a scaling law is present, but it does not permit to separately analyze the short- and long-term components, as for the DFA.

2.2 Analysis Protocol

►Table 1 describes the five groups of patients analyzed in the present work. Subjects coming from the Sleep Center of the S. Raffaele Hospital underwent a polysomnographic evaluation, as well as the apnea patients downloaded from the Physionet database, while signals of heart failure patients come from Holter recordings (www.physionet.org). The sampling frequency of the ECGs recorded at the S. Raffaele Hospital was 128 Hz, while the signals from Physionet were sampled at 100 Hz. The ECG was extracted from the polysomnography and Holter data; R peaks were detected from ECG using a derivative built and tested algorithm and parabolic interpolation was added in order to overcome the limitation due to a low sampling rate [2]. The RR time intervals were expressed as a function of the beat number and parameters described in the previous section were calculated for each RR series obtained during the whole sleep time without discarding any events (i.e. arousals, apenas, or other) in order to capture any possible long-term dynamics contained in the signals. An ANOVA statistics was then applied in order to put into evidence the capabilities of the different parameters in discriminating the different groups of subjects. Comparisons between groups were performed through post-hoc analysis with all-pairs Bonferroni test.

3. Results

►Table 2 shows the mean values, and the related standard deviations, of the proposed indices for each group of analyzed subjects. Although the statistics were evaluated for each possible group pair, results are commented only comparing each group with normal subjects with high sleep efficiency (HSE). The † symbol in the table represents a difference statistically significant ($p < 0.05$).

The normal subjects with low sleep efficiency do not differ from subjects with high sleep efficiency. Patients affected by obstructive apnea syndrome are characterized by a decrease of an overall regularity (SampEn(0,0.2)), and an increase of irregularity for high scale factor (MSE_2). The LZC(3) reported for this group the highest complexity values, close to 1, which could be correlated to a loss of regulation and to a drift towards random fluctuations.

The patients affected by insomnia seem to be similar to healthy subjects, except for a decrease of an overall regularity.

The heart failure patients showed similar results as for the 24 h Holter recordings which were already reported in literature: a decrease of overall regularity and at dif-

Table 2 Values (avg ± std) of the indices considered in this work from different type of healthy and unhealthy subjects

	Healthy		Unhealthy		
	HSE	LSE	Insomnia	Apnea	Heart failure
SampEn(2,0.2)	1.20 ± 0.07	1.19 ± 0.09	0.91 ± 0.12†	0.97 ± 0.04†	0.90 ± 0.10†
MSE$_1$	0.88 ± 0.19	0.82 ± 0.14	0.75 ± 0.17	0.96 ± 0.28	0.65 ± 0.16†
MSE$_2$	0.98 ± 0.25	1.02 ± 0.17	0.92 ± 0.19	1.47 ± 0.28†	0.95 ± 0.42
LZC(2)	0.92 ± 0.06	0.92 ± 0.03	0.92 ± 0.04	0.93 ± 0.04	0.87 ± 0.10†
LZC(3)	0.79 ± 0.05	0.80 ± 0.03	0.78 ± 0.07	0.90 ± 0.04†	0.80 ± 0.09
DFA a$_1$	1.18 ± 0.22	1.20 ± 0.19	1.31 ± 0.12	1.44 ± 0.27†	0.92 ± 0.23†
DFA a$_2$	1.03 ± 0.09	1.05 ± 0.08	1.01 ± 0.08	0.85 ± 0.09†	1.05 ± 0.10
1/f slope	0.71 ± 0.19	0.58 ± 0.32	0.95 ± 0.23	0.86 ± 0.49	1.34 ± 0.50†

HSE = high sleep efficiency (higher than 85%), LSE = low sleep efficiency (lower than 85%), † = a significant difference with respect to HSE group (p-value <0.05)

ferent time scales, a reduction of the complexity and a higher fractal scaling slope (1/f slope).

4. Discussion and Conclusion

This work aimed at finding global parameters able to summarize sleep characteristics, related to a whole night, in a single index. The proposed parameters have demonstrated their ability in achieving such result. Further, some interesting observations can be derived from the obtained values. First of all, groups of normal subjects with high and low sleep efficiency do not show any significant difference. Insomnia subjects, that are normal unless for the sleep quality, differ from the control group only for SampEn(2,0.2). This means that the long-term correlation and complexity of the HRV during sleep is not related to the sleep quality, but rather seems to be an overall characteristic of the underlying controlling system. The decreased SampEn(2,0.2) in insomnia patients puts into evidence an increased regularity, but not completely confirmed by other parameters.

The increase of complexity in apnea patients can be related both to the apneas that are superimposed to the physiological rhythms and to a rhythm disruption caused by apneas that do not allow the sleep to follow its regular cycles: in fact, due to the arousals caused by apneas, often the subjects are unable to reach deep sleep.

Results obtained from heart failure patients confirm what was already reported in literature for 24 h Holter recordings [3].

The use of these parameters could be useful in the identification of sleep disorders such as apnea and insomnia. They can also find application in the stratification of the cardiovascular pathologies as well as in the evaluation of progressive health deterioration. In particular, this approach seems very interesting in the congestive heart failure patients, because recent results have demonstrated that the sleep events are prognostic of sudden death [15]. It is worth noting that the HRV during sleep could provide parameters more robust than the ones provided by 24 h recordings, because the signals are less affected by external disturbances (position, activity, etc.) and then better reflect the underlying regulating mechanisms.

A critical point in the present work could be the different ages of the considered groups. In fact heart failure patients' age ranges between 22 and 75 years, while normal subjects and apnea patients are between 35 and 60. Many papers report a decreased heart rate variability in elderly people, but they are usually referred to short-term evaluations and to time or frequency domain analysis (linear indices), while no clear results are reported for long-term dynamics and non-linear indices. In [16] an increased approximate entropy was reported during night in elderly subjects, while other parameters are different only when evaluated on the 24 h, and may reflect also differences in the activity and in the lifestyle. In the work of Costa et al. [8], moreover, the MSE was not different at large scale factors between young and elderly healthy people, in the sleep period.

A more detailed study on larger groups is needed for clarifying this point, however we demonstrated the usefulness of the presented indices for the identification of sleep disturbances and the characterization of sleep in cardiovascular pathologies.

We should also observe that some of the analyzed data come from sleep centers and polysomnographic recordings, while other data come from home monitoring through Holter recordings. However, the analysis was limited to the sleep time, and this ensures that data are comparable, as they are not affected by external environment, physical activity or other disturbing effects.

It is worth remarking that during sleep HRV can be obtained non-obtrusively (i.e. through sensorized bed sheets, or smart beds) and without interfering with the subject's daily life. Finally, these indices are simple and have low computational cost, then they could be easily implemented in DSP devices for home monitoring and automatic classification and can provide complementary information to the standard clinical polysomnography.

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