Nocturnal evolution of heart rate variability indices in sleep apnea

María J. Lado a,*, Arturo J. Méndez a, Leandro Rodríguez-Liñares a, Abraham Otero b, Xosé Á. Vila a

a Department of Computer Science, ESEI, University of Vigo, Campus As Lagoas s/n, 32004 Ourense, Spain
b Department of Information and Communications Systems Engineering, University San Pablo CEU, 28668 Madrid, Spain

Article history:
Received 23 January 2012
Accepted 23 September 2012

Keywords:
Electrocardiogram (ECG)
Obstructive sleep apnea (OSA)
Apnea hypopnea index (AHI)
Heart rate variability (HRV)
Spectral analysis

1. Introduction

One of the most common sleep disorders is Obstructive Sleep Apnea (OSA), with a prevalence around 4% in men and 2% in women [1]. OSA causes snoring, decreased sleep quality and daytime sleepiness. Several studies have also demonstrated its relationship with the development of hypertension, heart failure, sudden death and other cardiovascular diseases [2].

An apnea episode is defined as a cessation of respiratory airflow during at least 10 s. When this cessation is partial instead of total, it is called hypoapnea. An estimate of the severity of the patient’s condition is calculated by dividing the number of apneas occurred by the number of hours of sleep; the greater this ratio is, the more severe the patient’s disorder is. In a similar way, a hypoapnea index can be calculated by dividing the number of hypopneas by the number of hours of sleep. The apnea/hypopnea index (AHI) is the most accepted index used to quantify the severity of an OSA patient. It is calculated as the average number of apneas and hypoapneas per hour of sleep [3]. The AHI combines apneas and hypoapneas, and gives an overall assessment of the severity of the patient’s condition.

The gold standard for the diagnosis of sleep apnea is polysomnography; but this is an expensive and uncomfortable procedure, because it requires admitting the patient to a hospital sleep unit, and implies the connection of multiple sensors (EEG and ECG electrodes, plethysmograph, pulse oximeter, etc) to the subject [4].

In an attempt to characterize or diagnose this sleep disorder without polysomnography, many techniques that try to correlate apnea with other physiological manifestations of OSA have been proposed. Some authors tried to diagnose apnea from oxygen saturation drops [5,6], others analyzed snoring with specialized microphones [7] and many others studied alterations in the patient’s electrocardiograms [8,9]. Furthermore, several devices for ambulatory diagnosis of sleep apnea have been proposed [6,10,11].

In 2000, the Computers in Cardiology conference proposed a competition for identifying OSA patients using only the ECG [12]. In many occasions, results yielded 100% correct classification rate [13], although the representativeness of the database used in these papers (Apnea-ECG database [14]) is questionable [15].

The best results in terms of classification accuracy were achieved with an algorithm that performs spectral analysis of heart rate variability (HRV) [13]. In 1981, Akselrod [16] demonstrated experimentally the relationship between HRV and the autonomic nervous control system. Since then, its clinical usefulness in various pathologies such as myocardial infarction, hypertension, heart failure, transplantation, etc., has been studied [17,18]. The typical HRV spectrum of a healthy person at rest is mainly composed of two components: a low frequency band (LF), from 0.04 to 0.15 Hz; and a high frequency band (HF) with range from 0.15 to 0.4 Hz. The HF band is correlated with the parasympathetic system, while the LF band is correlated with both the sympathetic and parasympathetic systems. Many studies use the LF/HF ratio as an index of “imbalance” of the autonomic nervous control system [8,9,19]. Other authors have also analyzed the power in the 0.003–0.04 Hz band (called VLF or very low frequency) and in the 0–0.003-Hz band (called ULF or ultra low frequency) [20].

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Among all the studies analyzing the correlation between these spectral indices and apneic events we will comment about three of them. Gula et al. [8] used a database containing 25 patients and concluded that LF and HF bands are higher in patients with severe apnea and normal ones, versus patients with mild apnea. The experiment by Jianling et al. [21] was performed on 95 patients, and showed that all variability indices (VLF, LF, HF, LF/HF and total HRV spectral power) are greater in patients with apnea. Finally, the work by Park et al. [22], with 59 OSA patients, agrees with Gula et al. [8], detecting a significant increase in VLF, LF, HF/HF and total power in patients with severe apnea, compared to those with mild apnea. No significant differences were observed in the HF band. As we have shown in a previous paper [15], comparing experimental results in this area is difficult, since studies are often performed using a low number of patients, and they usually differ in aspects such as analysis methodology, apnea definition or limits of spectral bands.

All these papers have the same goal: the analysis of nocturnal sleep apnea by studying the HRV during the whole ECG recording, and comparing the results with those obtained for healthy subjects. However, until this moment, no studies have been carried out comparing intervals of the recordings with repeated apnea episodes and intervals without them, regardless the patient suffering from OSA or not. This could be valuable information to analyze if changes in HRV indices are caused by a chronic imbalance in the patient’s autonomic system (therefore, the HRV indices of intervals without apneas should present different characteristics in OSA patients and in control patients), or by a temporary imbalance that only occurs during apneic events system (therefore, the HRV indices of intervals without apneas should be similar in OSA patients and in control patients). Moreover, the evolution of the HRV indices during the night has not been studied.

In this paper, we have analyzed the HRV power spectrum of 46 polysomnographic recordings. The goals of the present paper are threefold: (1) to verify if the conclusions of the previous studies that analyze the HRV indices of full-night ECG recordings are reproducible in our database; (2) to analyze the behavior of these indices in short periods of time; and (3) to study the evolution of these indices throughout the night. To achieve these goals, we have compared the HRV spectral components in intervals where patients have experienced apneas and in intervals corresponding with normal breathing. We have also studied the trend evolution of the HRV spectral components throughout the night, in severe and mild OSA patients and in control ones.

2. Methods

2.1. Patients

The database used in this paper consists of 46 polysomnographic recordings obtained from 46 patients who participated in a study at the Sleep Unit of the University Complex of Santiago de Compostela (CHUS). Recordings were performed with the commercial polysomnograph SOMNOscreenIM, built by SOMNOmedics GMBH, and which provides a one lead ECG sampled at 256 Hz.

Forty-one patients were males and five were females. Their average age was 57.0 ± 11.8 (mean ± std) years, with a minimum age of 27 and maximum of 78. The mean weight was 89.2 ± 13.8 kg, with an average body mass index (BMI) of 32.0 ± 4.5 kg/m².

After the polysomnographic test, 20 patients were diagnosed with severe OSA (AHI > 15) and 16 did not suffer from OSA (AHI < 5). The 10 remaining patients were diagnosed as suffering from mild OSA (5 < AHI < 15). The AHI of the whole set of patients ranged from 0.3 to 97.7.

2.2. Algorithm implementation

Apneas and hypoapneas were identified over the patient’s polysomnographic recordings by means of an algorithm previously developed for this purpose [23]. The algorithm uses the fuzzy set theory to represent the morphological characteristics of pathological events such as apneas, hypoapneas and desaturations. These morphological criteria can be configured by an expert. When identifying apneas and hypoapneas, the algorithm presents a false positive rate of 2.6% and 6.0%, respectively, with a corresponding false negative rate of 0.9% and 3.4% [23].

After applying this algorithm, all apneic and hypoapneic episodes were detected and counted for all the polysomnographic recordings, in order to calculate their AHI. Each recording was classified as belonging to a NORMAL subject (AHI < 5), a MILD OSA patient (5 < AHI < 15), or a SEVERE OSA patient (AHI > 15).

One of the objectives of this work was to analyze HRV indices during apneic events and during normal breathing, regardless of patient diagnosis. Each apnea episode can last from 10 s to more than 1 min. However, the resolution in frequencies required for obtaining reliable spectral HRV indices does not allow the analysis of these indices in each individual apnea episode due to their short span. Thus, we have decided to segment each recording in 5-min intervals, and to analyze the HRV indices in each interval. Each interval was also classified depending on the number of apnea/hypoapnea events that it contained and the duration of these events. In this way, each segment was labeled with one of the following labels: NORMAL, APNEIC or BORDERLINE, according to the following rule:

\[
T = 100\times(T_{\text{apnea}} + 0.5\times T_{\text{hypoapnea}})/300
\]

IF \((T > 20)\) then APNEIC
ELSE IF \((T < 10)\) then NORMAL
ELSE BORDERLINE

where \(T_{\text{apnea}}\) is the total time in which the patient was in apnea during the 5-min interval, and \(T_{\text{hypoapnea}}\) is the total time in which the patient was in hypoapnea during the 5-min interval. Considering only apnea episodes, this rule labels an interval as APNEIC if apneic episodes occupy more than 20% of the time, as NORMAL if they last less than 10%, and BORDERLINE in other case. The factor 0.5 for hypoapnea episodes is because apneas have stronger disrupting effects in the patient’s sleep architecture than hypoapneas. Fig. 1 shows an example of this classification.

Beat detection was performed with an algorithm developed by the authors [24], which is a modified version of the algorithm by Hamilton and Tompkins. [25]. The beat detection system is equipped with a graphical interface that shows detected beats as visual marks, drawn over the electrocardiogram. This graphical interface allows the user to delete incorrectly detected beats or to add missing ones. The whole database used in this study was revised by the authors using this tool; thus, all errors in the automatic beat detection were manually corrected.

Afterwards, ASCII files containing sequences of beats were created. These files were processed with our heart rate variability analysis tool, called RHVR [26]. This tool is a software package for R, the popular statistical computing environment. Among many other features, RHVR includes HRV analysis both in time and frequency domains, as well as nonlinearity indices. Briefly, the typical RHVR spectral analysis is a 4-step process that involves:

1. Heart rate signal calculation: the instantaneous heart rate can be defined as the inverse of the time separation between two
consecutive heart beats. The beats separation was obtained from each ASCII file containing the beat positions.

(2) Artefacts suppression: if incorrect outputs were produced in the previous step, an algorithm for reducing these artefacts was applied [27]. As a result, the filtered non-equispaced heart rate signal was obtained.

(3) Interpolation: in order to calculate the power spectrum of the heart rate signals, an equispaced heart rate signal needs to be obtained. To perform this task, a cubic spline interpolation was applied, with an interpolation frequency of 4 Hz. After this step, we have obtained a new heart rate signal, adequate for performing the spectral analysis.

(4) Power spectral analysis: since we are interested in analyzing the temporal evolution of HRV parameters, a Short-Time Fourier Transform (STFT) was applied using 1-min windows shifted 2 s. From this time-frequency map, power in the LF (0.05–0.15 Hz) and HF (0.15–0.4 Hz) bands was obtained. A second analysis was performed using 5-min windows shifted 10 s for obtaining the power in the VLF (0.003–0.05 Hz) band.

Fig. 2 shows the temporal evolution of the spectral indices for a patient of our database. The behavior of the spectral parameters corresponding to the HRV (total power), LF, HF, VLF, ULF and the LF/HF ratio are shown. All these indices were analyzed and studied, as presented in the following section. However, this paper presents no results regarding the LF/HF ratio and the ULF power, because no interesting nor significant results were derived from the analysis of these indices.

2.3. Study and statistical analysis

To comply with the main objectives of this work, three different analyses were performed: (1) global analysis; (2) five-minute interval analysis; and (3) nocturnal ECG evolution:

(1) Global analysis: to evaluate possible differences in HRV for patients suffering from severe apnea, mild apnea patients and normal subjects, the HRV spectral components during the full recording were obtained and analyzed for each polysomnogram. Average values and standard deviations of the components were also calculated among those patients who belonged to the same category: NORMAL (16 patients), MILD (10 patients) and SEVERE (20 patients).

(2) Five-minute interval analysis: each polysomnographic recording was divided into 5-min intervals, labeled as explained in Section 2.2. The spectral components were obtained for each interval, instead of for the full recording. Comparisons for the different groups of labeled intervals among the three groups of patients were performed. Table 1 shows the number of APNEIC, BORDER-LINE and NORMAL 5-min intervals belonging to the recordings of patients diagnosed as MILD and SEVERE OSA, and NORMAL.

(3) Nocturnal ECG evolution: nocturnal evolution of the spectral parameters was analyzed using 1-min windows shifted 2 s. Mean values of each of the HRV components were obtained for each patient group.

To validate the results obtained from each of the previous analyses, a statistical study was conducted to verify if significant differences were present among the different groups of patients and episodes. For this study, a t-test was applied, since data were proven to be normally distributed. From this analysis, the 95% confidence intervals (95% CIs) and p-values were calculated. A general statistical condition for two independent sets to be significantly different with respect to a given variable is that the variable does not assume a zero value within the corresponding 95% confidence interval [28]. This constraint was considered for the calculation of statistical differences for the three types of episodes or ECG recordings.

3. Results

3.1. Global analysis

Fig. 3 shows the results of the global analysis, obtained for each group of patients. Power in VLF, HF and LF bands was analyzed, as well as the total power (HRV).
It can be seen that all HRV spectral indices were greater for healthy subjects than for OSA patients. Furthermore, if only SEVERE and MILD apnea patients are considered, the spectral values are greater for the first group of patients.

To better assess these results, statistical analysis was performed. Significant differences were found for all the parameters and patients groups, being the \( p \)-value in all cases less than 0.001. This proves that, using these parameters, it is possible to discriminate between OSA and normal patients.

3.2. Five-minute interval analysis

To perform the analysis, the 5-min intervals were classified as stated before, and the spectral indices were obtained for each interval type and patient type: NORMAL, BORDERLINE and APNEIC intervals, belonging to healthy subjects, and patients suffering from both severe and mild OSA; i.e., there are a total of nine different types of intervals. The mean values of the indices for each type of interval are shown in Fig. 4.

If we analyze the LF plot in Fig. 4, it can be observed that this value is greater for NORMAL subjects than for SEVERE and MILD apnea patients, regardless the interval type. This last patient group reaches lower values in all the three groups of episodes (NORMAL, BORDERLINE and APNEIC). It must also be remarked that both MILD and SEVERE apnea patients obtain similar values for the LF index in both BORDERLINE and APNEIC episodes, while, if only NORMAL episodes are considered, SEVERE apnea patients give a LF value greater than the corresponding to MILD apnea patients.

A similar behavior can be found in the HF index: NORMAL subjects present greater values for this parameter. MILD apnea patients presented in all the interval types clearly lower HF values than the other patient groups. The total power and VLF behave in a similar way as HF.

<table>
<thead>
<tr>
<th>INTERVALS</th>
<th>PATIENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>NORMAL</td>
<td>MILD APNEA</td>
</tr>
<tr>
<td>NORMAL</td>
<td>1110</td>
</tr>
<tr>
<td>APNEIC</td>
<td>84</td>
</tr>
<tr>
<td>TOTAL</td>
<td>1629</td>
</tr>
</tbody>
</table>

Table 1 Distribution of NORMAL, BORDERLINE and APNEIC 5-min intervals for the three groups of individuals: NORMAL subjects, and MILD and SEVERE OSA patients.

If we analyze the LF plot in Fig. 4, it can be observed that this value is greater for NORMAL subjects than for SEVERE and MILD apnea patients, regardless the interval type. This last patient group reaches lower values in all the three groups of episodes (NORMAL, BORDERLINE and APNEIC). It must also be remarked that both MILD and SEVERE apnea patients obtain similar values for the LF index in both BORDERLINE and APNEIC episodes, while, if only NORMAL episodes are considered, SEVERE apnea patients give a LF value greater than the corresponding to MILD apnea patients.

A similar behavior can be found in the HF index: NORMAL subjects present greater values for this parameter. MILD apnea patients presented in all the interval types clearly lower HF values than the other patient groups. The total power and VLF behave in a similar way as HF.
Statistical analysis to corroborate if significant differences were present was performed for all the spectral parameters among the different groups of patients and types of 5-min intervals. Results yielded significant differences ($p$-values < 0.001) for all the spectral components, with the sole exception of the LF component in patients suffering mild OSA in the BORDERLINE and APNEIC intervals. In all the other cases there are significant differences in the HRV indices, indicating that healthy subjects and patients suffering from OSA do not behave in the same way, neither during normal breathing nor during apnea.

3.3. **Nocturnal ECG evolution**

A study of the evolution of the spectral parameters during the night was conducted. Results are shown in Fig. 5. OSA patients show reduced values that remain nearly constant along the night. Nevertheless, normal patients show higher values at the beginning of the sleep period, and converge to values similar to those of the OSA patients toward the end of the night. LF values do not have a specific tendency along the night for any group.

4. **Discussion**

The findings of this study include a decrease in all HRV indices in patients with both severe and mild apnea, compared to normal subjects. In the literature, analyzing the relationship between HRV indices and OSA, we found papers from Gula et al. [8] and Park et al. [22] to be the most consistent with our results. We do not propose clinical interpretation of these findings, but other references discuss this topic [9,21].

A more detailed analysis, performed using 5-min segments, corroborates the findings of record-by-record analysis. Indices decrease in subjects with severe apnea compared to normal ones, but they do decrease even more in case of mild apnea patients in the three interval types. This suggests that these indices could be used not only for diagnosing or assessing the severity of OSA patients, but also to establish the moments of the night where these episodes occur, or what percentage of sleep time is affected by this disorder.

Fig. 4 shows that in severe OSA patients the LF and HF indices, as well as the total HRV power, take lower values in intervals labeled as APNEA than in those labeled as NORMAL. Although more subtle, this behavior in LF and HF is also present in patients with mild OSA. These decreases are statistically significant. This behavior (decrease of the HRV indices) is consistent with an increased cardiovascular risk during the 5-min intervals with apnea episodes in patients with severe or mild OSA. The increased cardiovascular risk may be related to the negative pressures on the rib cage during apneas.

Surprisingly, control patients behave in an opposite way: the LF and HF indices take (statistically significant) lower values in intervals labeled as NORMAL than in those labeled as APNEA. This could be explained by the activation of compensatory mechanisms during the episodes of hypoxia caused by the apneas. These mechanisms pretend to compensate the decrease in the upper airways section with a higher activity of the pharyngeal muscle [29].

The compensatory mechanisms may be damaged in OSA patients due to the frequent intervals of hypoxia, thus explaining different behaviors in patients with OSA and in control patients. This hypothesis would be consistent with the fact that even in the intervals without apnea, OSA patients have a reduced HRV variability. However, more research is needed to confirm this hypothesis.

Finally, we have analyzed the evolution of these indices overnight looking for patterns. The results confirm the previous conclusions, especially in HF, VLF and HRV indices. In all these
cases, OSA patients showed constant low values throughout the night. However, normal subjects typically begin the night with high indices values that decrease through the night to reach values that are typical of OSA patients at the end of the sleep time. If low values of HRV indices can be interpreted as cardiovascular risk, these results corroborate other researchers' findings, that have shown that cardiovascular events are more likely during the last hours of the night [30,31]. This tendency is generally not present in OSA patients, who have a high cardiovascular risk throughout the night.

In conclusion, this study seems to be coherent with other author's observations on the relationship among HRV spectral components and OSA. Furthermore, we have compared these indices in 5-min intervals labeled as NORMAL, BORDERLINE and APNEIC, according to the proportion of the interval where the patient suffered apnea episodes. We have found statistically significant differences in the HRV spectral components among the three patient groups in all the types of intervals. This shows that even during normal breathing OSA patients present HRV alterations. Finally, we have also analyzed the evolution of these indices during the night, observing different patterns depending on the condition of the patient: apnea patients present a HRV evolution compatible with having higher cardiovascular risk throughout the night, while normal patient evolution is compatible with having a lower risk at the beginning of the night that increases towards the end. Future works will address the issue of validating these results with a greater number of patients. Specially interesting will be to analyze whether mortality rates due to cardiovascular factors in OSA patients is concentrated at the end of the night, similarly to the situation of the general population.

5. Summary

Heart rate variability (HRV) is a non-invasive measurement of the autonomic nervous system with proven clinical value in diagnosing multiple diseases. There are many studies that have addressed the relationship between HRV and obstructive sleep apnea (OSA). Most of these studies are based on comparing OSA patients with normal ones, or comparing patients with distinct levels of OSA, with the goal of discriminating among them. Moreover, these papers are usually focused at analyzing the HRV behavior in a full-night ECG recording. This paper presents the results of a double analysis of spectral parameters in 46 patients admitted to a hospital sleep unit. First, we have obtained the HRV spectral indices for all patients and we have analyzed the differences among OSA and normal patients along the whole night. This study yielded statistically significant differences among patients suffering from severe versus mild apnea, and versus healthy subjects, corroborating the result s obtained by other researchers. Afterwards, the HRV indices were calculated in every 5-min interval of the patient's recordings in order to look for significant differences between intervals in which apneas had occurred and intervals in which no apneas had occurred. Results show that HRV indices in both apneic intervals and in normal breathing are statistically different for OSA patients and for healthy subjects. Finally, we analyzed the nocturnal evolution of these indices. OSA patients present approximately constant low values throughout the night, while control patients present higher values that decrease towards the end of the nocturnal rest. These findings are in agreement with the hypothesis that cardiovascular risk remains nearly constant along the night for OSA recordings, while for normal subjects the risk increases, becoming higher at the end of the night.

Conflict of interest statement

None

Acknowledgments

This work has been partially supported by the Spanish MEC and the European FEDER under Grant TIN2009-14372-C03-03.

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