Respiratory Sinus Arrhythmia in apnea patients with apnea associated comorbidities

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Abstract

The strength of the Respiratory Sinus Arrhythmia (RSA) in patients with Obstructive Sleep Apnea (OSA) might help to understand the correlation between apnea and Cardiovascular Diseases (CVD). For estimating the RSA, Heart Rate Variability (HRV) analyses can be used. The High Frequency (HF, 0.15 Hz - 0.4 Hz) band of the power spectrum of the tachogram is recognized to contain the information related to breathing. However, this assumption might produce wrong RSA estimates, since the respiratory rate can occur outside the HF band. In this work, the strength of the RSA in OSA patients with apnea associated comorbidities was estimated using respiratory and electrocardiogram (ECG) signals. For this, the shared frequency content between respiration and HRV was characterized with methods that calculate respiratory frequency bands different to the HF. These methods were applied in a dataset of OSA patients and apnea-associated comorbidities. Even though there were no significant differences between groups, patients with more severe apnea and comorbidities presented an apparently higher RSA level. This observation might illustrate the function of the RSA as a compensation mechanism to reduce the workload exerted by the heart and to compensate for an abnormal blood pressure.

1. Introduction

Obstructive Sleep Apnea (OSA) is a disorder in which patients present airflow cessations during the night. This syndrome is estimated to affect between 9-38% of the adults in Europe and North America [1]. In the long term, the OSA syndrome is associated with the development of Cardiovascular Diseases (CVD). For this reason, explaining the correlation between OSA and cardiac comorbidities is an active research topic. One of the main mechanisms affected in OSA patients is the breathing, which is widely accepted to modulate the Heart Rate (HR) activity through a phenomena called the Respiratory Sinus Arrhythmia (RSA). Hence, the estimation of the strength of this modulation might serve to evaluate OSA patients and their cardiovascular status.

The RSA is observed as an increased HR during inspiration and a decreased HR during expiration. Despite of being known since 1733, the physiological role of the RSA remains under debate. The most widely accepted hypothesis suggests that the RSA matches perfusion and ventilation, improving the efficiency of the pulmonary circulation and gas exchange. Nevertheless, this hypothesis still needs to be proven [2]. One recent study suggests that the RSA is a mechanism to reduce the workload exerted by the heart [3] and a second study gives evidence of the function of RSA on the regulation of the blood pressure (BP) [4].

Currently, it is widely accepted that the respiratory information can be found in the High Frequency (HF, 0.15 Hz - 0.4 Hz) band of the Power Spectral Density (PSD) of the Heart Rate Variability (HRV) [5]. However, the respiratory rate might occur at frequencies different to this range. As a result, the quantification of the RSA using the total power in the HF band might produce wrong estimates of this modulation [6]. Therefore, this work aims to investigate the RSA in patients with different OSA levels and apnea associated comorbidities using frequency bands other than the HF. For this, the -3 dB Bandwidth (BW) and the Occupied 95% Bandwidth (OBW) of the respiratory signals were used to define the frequency components produced by the respiratory modulation on the HRV. The RSA was estimated based on two different HR represen-

tations [10]. These methods were applied in two datasets of patients with different severities of apnea and apnea-associated comorbidities. The results were compared with the standard normalized HF power (HFn). [5].

2. Materials

Two datasets with electrocardiogram (ECG) and thoracic Respiratory Inductive Plethysmography (RIP) signals were used. The first dataset consists of 110 Polysomnography (PSG) recordings of patients with different severities of OSA and associated comorbidities. The ECG and RIP were acquired with a sampling frequency of 500 Hz. The apneas and sleep stages were annotated by sleep specialists according to the AASM 2012 scoring rules [7]. The OSA severity was assessed with the Apnea Hypopnea Index (AHI), i.e. average number of apneic events per hour of sleep. 100 patients were matched for age, gender and Body Mass Index (BMI). In this subgroup, there were 50 OSA patients (AHI>15) without comorbidities and 50 OSA patients (AHI>15) with comorbidities (hyperlipidemia: 49, hypertension: 40, diabetes: 5, myocardial infarction: 4, stroke: 2). 33 of the 50 patients with comorbidities were taking beta-blockers at the moment of the recordings. The remaining 10 subjects (AHI<15) did not present comorbidities. This dataset will be referred to as the UZ Leuven dataset.

The second dataset contains signals from the Sleep Heart Health Study (SHHS) [8]. In total, 5793 PSG recordings were available. 100 recordings from volunteers with an AHI lower than 5 and without complaints related to apnea were selected (50 with cardiac problems and 50 healthy subjects). The sleep stages, arousals, oxygen desaturations and respiratory events were manually annotated by sleep specialists. To match the AASM 2012 rules, the AHI was computed taking into account all apneas and hypopneas with arousals or oxygen desaturations of at least 3%. The ECG was sampled at 125 Hz and the RIP at 10 Hz. These recordings will be referred to as the SHHS dataset. The demographics of both datasets are summarized in Table 1.

Table 1. Demographics of the used datasets

Dataset	N	Age Years	BMI Kg/m^2	AHI Events/h	Sex
UZ Leuven	110	47.3±10.6 (38-55 , 26-68)	29.3±4.6 (25.9-32.8 , 20.7-44.7)	37.8±23.8 (21.4-53.25 , 1.8-111.4)	M: 82 W: 28
SHHS	100	50.4±7.8 (44-55 , 39-66)	29.3±4.4 (25.7-32.3 , 21.2-46.8)	2.9±1.3 (1.86-4.01 , 0-4.9)	M:78 W: 22

The age, BMI and AHI are given as the mean values ± the standard deviation. Below are the ranges given as (25th percentile - 75th percentile, minimums - maximums)

3. Methods

3.1. Preprocessing and segment extraction

The signals in the SHHS dataset were first up-sampled to 500 Hz with a cubic spline interpolation. Moreover, the respiratory signals in both datasets were bandpass filtered (0.05 Hz - 1 Hz) twice in forward and reverse directions to remove the baseline and high frequency artifacts with a zero phase distortion. Afterwards, the R-peaks in the ECG signals of both datasets were detected with the version of the Pan-Tompkins algorithm proposed in [9]. Next, the detected peaks were visually corrected for miss-detections and ectopic beats. Subsequently, these R-peaks were used to generate two hearth rhythm representations: a signal d_{RR} obtained after applying a cubic spline interpolation to the RR intervals series, and a Heart Rate (HR) signal d_{HR} generated with the Integral Pulse Frequency Modulation (IPFM) model as described in [10]. Both representations were computed with a sampling frequency of 4 Hz. Finally, the RIP signals were also re-sampled to 4 Hz. The segmentation described in the next paragraph was initially proposed in [11], where the same dataset was used but the signals were analyzed with a different approach.

After preprocessing, epochs of 5 minutes with 50% overlap were extracted. From these, only non-Rapid Eye Movement (NREM) segments without apneas were selected. 1 minute after the annotated offset was used as the beginning of the segments in order to eliminate possible biases generated by the recovery period after an apneic event [12]. Finally, segments contaminated with artifacts or containing very irregular respirations were visually identified and removed from the analysis. As a result, a different number of segments was available for each patient and patients with less than 5 usable segments were discarded (8 patients from UZ Leuven and 22 patients from SHHS).

3.2. RSA quantification

Firstly, the PSDs of the RIP, d_{RR} and d_{HR} signals were computed using the Welch's method with a hamming window of 40 s with 20 s overlap. Afterwards, the RSA was quantified as follows:

1. The PSD of the respiration was characterized by:
   1.1. The frequency limits of the bandwidth at -3dB (BW)
   1.2. The frequency limits of the occupied bandwidth where the signal has 95% of the power (OBW)
2. Afterwards, the influence of the respiration on the heart rate (i.e. RSA) was quantified as:
   2.1. The power contained in the PSD of the HR representations in the frequency bands obtained in step 1. This power was normalized with the total power in the band between 0.04 Hz and 1 Hz. This calculation was repeated separately for the d_{RR} and d_{HR} signals
   2.2. The mean Magnitude Squared Coherence (MSC) in the same frequencies obtained in step 1. The MSC was computed as described in [13]. This calculation was done

only using d_{RR} signal

3.3. Comparison of the methods

To compare the methods, different approaches were used. First, the relationships between age and the RSA estimates were evaluated with a linear regression. The R^2, R^2_{adj} and correlation coefficients (ρ) were computed on each case. In addition, the significance of the calculated ρ was evaluated. These regressions were used for selection, assuming the hypothesis that the RSA is linearly degraded in elderly populations [14], and that good methods should better represent this relationship. Second, the capability of the RSA estimates to discriminate the patients according to their conditions was assessed. For this, the boxplots of the different groups were observed and significant differences were analyzed using the Kruskall-Wallis test with a 95% confidence interval.

4. Results and Discussion

Table 2 shows the computed R^2, R^2_{adj}, ρ and p-values for the regressions between age and the RSA estimates. The p-values indicate that the ρ in this dataset are significant for all the RSA estimates. However, the ρ values are below 0.6 in all cases, indicating that the correlation is moderate negative in the best case (d_{HR}-BW). Nevertheless, these values are only used to compare the methods and select the one that produces the best correlation. All the values in the table indicate that the d_{HR}-BW combination better represents the degradation of RSA with age. Here, it is important to highlight that, during the visual removal of the contaminated segments, also only regular respirations with a narrow band were preserved. These bands are better captured with the BW method. It is also observed that the HT signal obtained with the IPFM model produces slightly better regressions. This improvement, however, is lower than it might be expected after previous studies [15]. A reason for this result might be the lack of abundant ectopic beats in the signals and the visual corrections to the R-peaks that were done during preprocessing. The benefit of the IPFM model would be more visible without this step and in patients with more ectopic beats. It is also possible that the measured respiratory rates are low. The differences would be more significant with higher respiratory rates, since the low pass effect is more notable in the of the d_{RR} representation than in the d_{HR} representation [17].

Figure 1 shows the boxplots for different groups of patients and for the RSA estimates. Only the methods with R^2 higher than 0.1 for the regression with age are displayed. Despite of the fact that the differences between groups are not significant (p>0.05), an apparently increased RSA estimate is shown in the boxplots for unhealthier populations. This result might have been due to confounding variables. Therefore, the influence of the medication intake on the RSA estimates in the group of patients with comorbidities in the UZ Leuven dataset was checked. There were no significant differences between the RSA estimates related to medication for the d_{RR}-BW and HFn methods (p>0.05). However, there were significant differences between the two groups with the d_{RR}-BW estimate (p<0.05). In all cases, an apparently higher RSA estimate was observed in the patients without medication. In addition, significant differences in the distribution of the age of the subjects in the different groups were not found (p>0.1). Finally, it was seen that the group of patients with AHI<15 and without comorbidities have a significantly lower BMI compared to the other groups (p<0.005). It was also observed that, despite of the fact that the differences were not significant, patients with higher AHI have an apparently higher BMI in the UZ Leuven dataset. The different tests also support the observation of an increased RSA in unhealthier conditions.

Table 2. Regression statistics between the different RSA estimates and Age

Method	R^2	R^2_{adj}	ρ	p-value
d_{HR}-BW	0.256	0.251	-0.506	2.65×10^{-12}
d_{RR}-BW	0.240	0.235	-0.490	2.44×10^{-12}
MSC-BW	0.097	0.092	-0.312	4.40×10^{-5}
d_{HR}-OBW	0.084	0.078	-0.290	1.52×10^{-4}
d_{RR}-OBW	0.074	0.068	-0.271	3.73×10^{-4}
MSC-OBW	0.072	0.067	-0.270	4.01×10^{-4}
HFn	0.119	0.113	-0.345	5.81×10^{-6}

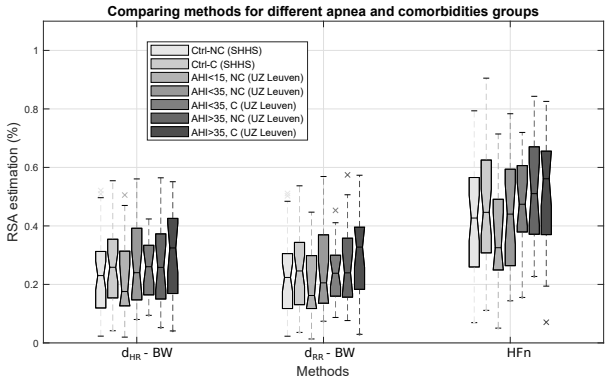

Figure 1. Boxplots of the RSA estimates for different apnea and comorbidity groups (C stands for patients with Comorbidities and NC for patients with No Comorbidities)

The finding of an increased RSA in unhealthier subjects contrasts to previous studies suggesting that it should be higher in healthier populations [16]. This result might be an evidence to support the hypothesis that the RSA serves as a mechanism to reduce the workload in the heart [3]. In

other words, the heart in unhealthier subjects needs to work harder to maintain the body function, and the RSA serves as a mechanism to compensate for this additional effort. The group of patients in the unhealthier groups might be reflecting an over-compensation. This interpretation could agree with the modeling presented in [3]. Another possible explanation for the results might be the role of RSA for stabilizing the blood flow and Blood Pressure (BP) [4]. It is possible that in subjects with hypertension (40 of the patients with comorbidities), the RSA is over activated in order to compensate for an abnormal BP. Finally, the control groups taken from the SHHS dataset displayed median RSA estimates similar to some of the unhealthy groups in the UZ Leuven Dataset. A possible explanation for this result might be the fact that, in the SHHS dataset, the subjects were volunteers. On the other hand, the UZ Leuven contains signals from patients who had symptoms that brought them to the hospital, so they cannot be completely considered as normal.

5. Conclusions and Future Work

An apparently increased RSA estimate in patients with OSA problems and apnea-associated comorbidities was observed in the UZ Leuven dataset. This might be the result of an over-compensation mechanism to reduce the workload of the heart in patients with cardiac problems [3] and to compensate for abnormal variations in BP [4].
The results also suggest that using the -3dB BW of the respiration is better to characterize the degradation of the RSA with age when a regular respiratory rate occurs.
Additional analyses including BP signals or deriving the BP from the available signals are needed. Also, it is necessary to investigate the results obtained for the SHHS dataset, since the RSA estimates here do not match the observations in the UZ Leuven dataset. Finally, more methods to quantify the RSA will be explored.

Acknowledgements

Agentschap Innoveren & Ondernemen (VLAIO): STW 150466 OSA+. European Research Council. The research leading to these results has received funding from the European Research Council under the European Unions Seventh Framework Programme (FP7/2007-2013) / ERC Advanced Grant: BIOTENSORS (no 339804)/ TARGID - Development of a novel diagnostic medical device to assess gastric motility ♯: C32-16-00364/ imec funds 2017. Carolina Varon is a postdoctoral fellow of the Research Foundation-Flanders (FWO). This paper reflects only the author's views and the Union is not liable for any use that may be made of the contained information.

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