Investigating Phase Coherence between Respiratory Sinus Arrhythmia and Respiration in Depressed Patients with Obstructive Sleep Apnea across the Sleep Stages

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Abstract

The aim of this study is to investigate if the phase coherence of respiratory sinus arrhythmia (RSA) and respiration exists in obstructive sleep apnea (OSA) patients with and without major depression disorder (MDD), and if it exists, how does it differ across the sleep stages. Overnight electrocardiograms (ECG) and thoracic movements using thoracic pneumography were recorded from control subjects (38); OSA subjects with major depression (40) and OSA subjects without major depression (40). The interbeat intervals (RRI) and respiratory movement were extracted from 5-minute segments of ECG signals with a single apneic event during rapid eye movement (REM) and non-rapid eye movement (NREM) sleep. Both RRI and respiration were resampled at 10 Hz and band passed filtered (0.10–0.4 Hz). Hilbert transform was used to extract instantaneous phases of the RSA and respiration. Subsequently, time dependent phase coherence (λ) between RSA and respiration was obtained. Heart rate variables (HRV) were also calculated. During REM and NREM sleep, higher λ and lower low frequency (LF) were found in the OSAMDD+ group compared to the OSAMDD- group ($p<0.05$). Our findings suggest that depression has lowered the sympathetic activites when it is accompanied with OSA, allowing for stronger synchronization between RSA and respiration.

1. Introduction

Obstructive sleep apnea (OSA) is defined as frequent episodes of blockages of the upper airway during sleep. It is especially characterized by sleep decreases (hypopnea) or pauses (apnea) in breathing. The existence and severity of OSA are measured by an apnea hypopnea index (AHI), which is the number of hypopnea and apnea events per hour of sleep [1].

OSA is often associated with a wide range of comorbidities. Some of the most common comorbid conditions include cardiovascular, respiratory, endocrine, metabolic, and psychiatric symptoms. Many studies have shown a significant association between OSA and depressive symptomatology. More specifically, the prevalence of depression in OSA patients has been reported to be from 5 to 63 precent [2].

The association between depression and sleep problems remains elusive. It is not clear whether depression may cause sleep problems, or sleep problems may cause or contribute to depressive disorders. The most frequently occurring symptoms of OSA and depression are sleep disturbance and fatigue. Both issues can disguise each other because of their similarities. The comorbidity of OSA and depression also might suggest that both illnesses may share a neurobiological pathway. The serotoninergic system which has a central role in regulating mood and circadian rhythm also has a role in controlling the upper-airway dilatator motor neurons [1].

Several studies reported that depressed subjects presented a decrease in heart rate variability (HRV) when compared with healthy subjects [3,4]. Furthermore, OSA patients have a higher number of sympathetic activities than healthy individuals as well as their HRV is substantially being changed due to surges in heart rate associated with repetitive cycles of apnea-hypopnea [5].

One of the most important components of HRV is Respiratory Sinus Arrhythmia (RSA). RSA is related to the high frequency component (HF) of HRV and has been associated with parasympathetic activity [6]. RSA also can enhance pulmonary gas exchange to maintain high gas consumption efficiency [7]. RSA is common in the young and reduces with age. Additionally, RSA magnitude is increased by exercises [8].

Recently cardiorespiratory phase synchronization has gained more attention [9,10]. Multiple studies have also investigated cardiorespiratory synchronization in OSA patients. Their analysis in sleep stages for OSA patients reflected a significantly higher cardiorespiratory synchronization in non-rapid eye movement (NREM) sleep compared to rapid eye movement (REM) sleep in OSA patients. This reduction of phase coupling in REM sleep could be due to long-term associated noises from higher brain regions [5,11]. Investigators have also studied the phase coherence between hemodynamic variable RAS and the respiratory system during induced mental stress. They showed how mental stress could affect the phase lag variations between RSA and respiratory. The study found that the degree of phase coherence was positively correlated with RSA amplitude and HF power, suggesting that the degree of phase coherence may be associated with vagal activity as well. Additionally, they found that respiratory frequency decreased as phase coherence

increased, but the mechanism was not clear [6]. However, no study has ever investigated the phase coherence of RSA and respiration in depressed patients with OSA during nocturnal sleep.

Thus, it remains to be answered if the phase coherence of RSA and respiration exists in OSA patients with and without major depression disorder (MDD), and if it exists, how does it differ across the sleep stages? This study will investigate if the phase coherence of RSA and respiration can be used as trait marker for distinguishing between depressed and non-depressed OSA patients

2. Method

2.1. Participants and data collection

Overnight polysomnography was performed on 92 subjects at the American Center for Psychiatry and Neurology (ACPN) in Abu Dhabi, among which 40 had only OSA (OSAMDD-), and 40 had OSA with major depression (OSAMDD+), and 6 healthy subjects (CONT). Additionally, 32 controls without OSA or major depression are taken from the Stanford Technology Analytics and Genomics in Sleep (STAGES) dataset [12]. The level of clinical depression was assessed by a consultant psychiatrist (VL) using the Patient Health Questionnaire-9 (PHQ-9). The PHQ-9 is a 9-item self-reported questionnaire measuring the severity of depressive symptoms. For each item, the respondent chooses one or more response options rated from 0 (absence of symptom) to 3 (nearly every day). Total scores range from 0 to 27 and represent the sum of the highest level endorsed on each item. The PHQ-9 scores 5, 10, 15, and 20 representing mild, moderate, moderately severe, and severe depression, respectively [13]. In this study, subjects with a positive score of 10 and above for PHQ-9 were categorized as having major depression.

ECG and piezoelectric belt based thoracic movement signals were used in this study and were recorded for ACPN data at a sampling rate of 100 Hz and 10 Hz, respectively, and for STAGES data at a sampling rate of 200 Hz and 50 Hz, respectively.

2.2. Data Analysis

For the analysis, intervals of 5 min from ECG and thoracic movement signals with an individual apneic event have been selected from REM sleep and NREM sleep stages (stage 1 and 2). On average, 3 intervals were selected from each sleep stage for each subject. Apneas in the intervals were scored as follows: An obstructive apnea is characterized by 10 seconds blockage of the oronasal airflow despite continuous chest and abdominal movements. An obstructive hypopnea is characterized by 10 seconds of partial blockage of the upper airway, causing a 50% decrease of the airflow [1].

Both RRI and respiration were resampled at 10 Hz and high-pass-filtered at 0.1 Hz, and then, low-pass filtered at 0.4 Hz. Zero-phase digital filtering was performed in which the data was filtered in forward and reverse directions to avoid phase distortion. Hilbert transform was used to calculate instantaneous phases of the the RSA [ΦRSA (tk)] and respiration [Φ RESP(tk)]. Then, time dependent phase coherence (λ) between RSA and respiration was obtained through the following equation:

$$\lambda(\mathrm{t_k}) = \left| \frac{1}{N} \sum_{j=k-\frac{N}{2}}^{k+\frac{N}{2}} \mathrm{e}^{-[\Phi \mathrm{RSA}\,(\mathrm{t_k}) - \Phi\,\mathrm{RESP}(\mathrm{t_k})] mod\ \pi 2} \right|^2$$

where N denotes the number of data samples. The λ value is always ≤ 1. The amplitude of RSA (A_{RSA}) was calculated from the average instantaneous amplitude of oscillatory signal of RRI ($v(t)$). The Respiratory Frequency (f_R) was calculated by dividing the $\Phi_{\mathrm{RESP}}(t)$ derivative by 2π as a function of time [7].

2.3. HRV

Spectral analysis using Welch's method was performed on linearly resampled (4 Hz) time series [15]. The 256-point fast Fourier transform was repeatedly computed with fifty precent overlap between adjacent segments. Then, the spectral power of each segment was computed and averaged. Hanning window was used for avoiding spectral leakage. After that, spectral powers in the low frequency (LF) band (0.04–0.15 Hz) and high frequency (HF) band (0.15–0.40 Hz) was obtained by integration. Normalized index of HF and LF powers were also computed by HF/(Total Power) and LF/(Total Power), respectively .

2.4. Statistical Analysis

Nonparametric Mann-Whitney U-test was used to check the differences between OSA patients with MDD (OSAMDD+) vs. OSA patients without MDD (OSAMDD-), OSA patients with MDD (OSAMDD+) vs. healthy subjects (CONT), and OSA patients without MDD (OSAMDD-) vs. healthy subjects (CONT) during both REM and NREM sleep. Values of $p < 0.05$ were considered as significant.

3. Results and Discussion

Figure 1 shows an example of a 5-min interval with a single apneic event taken from the polysomnography for a

subject with OSA and MDD in NREM sleep. Figure 2 demonstrates the analysis performed on this 5-min interval and the obtained results including R-R intervals (RRI), Respiratory movement (Resp), Instantaneous phases for breathing and RRI (φ), and phase coupling coefficient (λ).

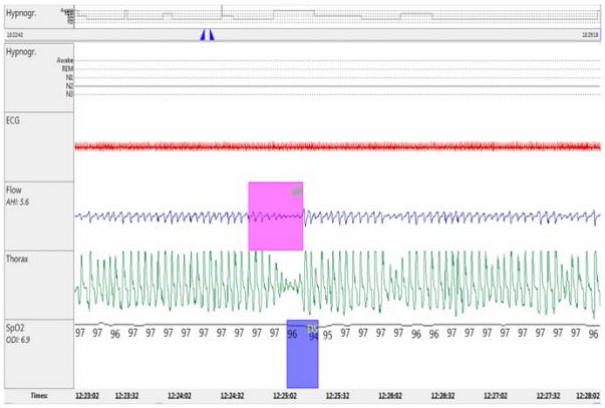

Fig.1. 5 min interval with a single apneic event taken from the polysomnography for a subject with OSA and MDD in NREM sleep.

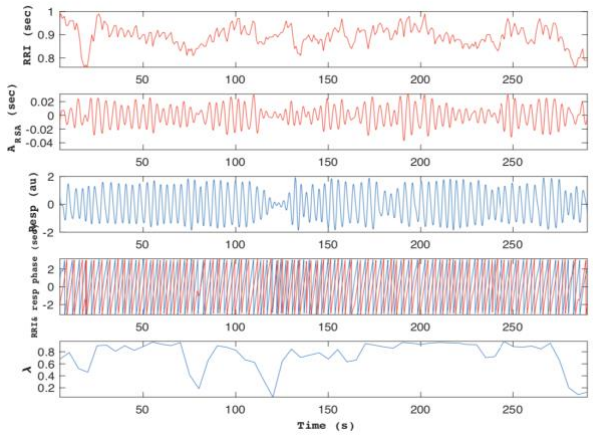

Fig.2. R-R intervals (RRI), Respiratory movement (Resp), Instantaneous phases for breathing and RRI (φ), and phase coupling coefficient (λ) obtained from the analysis preformed on 5-min interval with a single apneic event taken from a subject with OSA and MDD in NREM sleep.

Table 1. Demographics of participants. *p<0.05 and ** p<0.01 for OSAMDD+ vs. OSAMDD-; †p<0.05 and †† p<0.01 for OSAMDD- vs Control; ¥p<0.05 and ¥¥ p<0.01 for OSAMDD+ vs Control.

	OSAMDD+ (40)	OSMDD- (40)	CONT (38)
Gender(M/F)	**(21/19)**	**(27/13)**	**(12/26)**
Age	**43.30±10.71**	**45.05±11.25**	**40.62±14.36**
BMI (kg/m²)	**31.78±5.87**	**33.45±9.78**	**30.32±5.54**
(AHI /hour)	**23.05±14.79**	**22.83±15.21††**	**1.66±1.54¥¥**
NREM (AHI /hour)	**27.79±19.90**	**23.71±17.71††**	**1.79±1.82 ¥¥**
REM (AHI /hour)	**31.31±24.29**	**29.56±22.15††**	**2.08±3.27 ¥¥**

Table 2. Mean±SD of cardiorespiratory and HRV variables. *p<0.05 and ** p<0.01 for OSAMDD+ vs. OSAMDD-; †p<0.05 and †† p<0.01 for OSAMDD- vs Control;¥p<0.05 and ¥¥ p<0.01 for OSAMDD+ vs Control.

	OSAMDD+	OSMDD-	CONT
NREM Sleep			
f_R (breaths/min)	**16.66±2.35**	**17.34±2.97††**	**21.44±3.55¥¥**
A_{RSA}(ms)	**26.6±40.3**	**34.1±39.8†**	**19.1±13.0**
λ	**0.67±0.13 ****	**0.56±0.19 ††**	**0.63±0.12 ¥**
VLF (bpm²)	**4.72±5.12****	**7.75±8.59**	**8.04±10.23¥¥**
LF (bpm²)	**3.54±4.22***	**4.61±4.61**	**5.53±7.20**
HF (bpm²)	**1.56±1.55**	**2.08±3.18**	**2.52±4.51**
LF/HF	**4.14±8.60***	**5.15±6.00**	**4.10±3.85**
nLF	**65.41±18.75***	**70.75±18.96**	**69.76±18.26**
nHF	**34.59±13.59***	**29.25±18.96**	**30.24±18.26**
REM Sleep			
f_R (breaths/min)	**17.15±2.05**	**17.37±2.76 ††**	**22.04±3.07¥¥**
A_{RSA}(ms)	**31.2±45.0**	**26.9±37.4 †**	**18.7±22.8 ¥¥**
λ	**0.57±0.15 ****	**0.50±0.17 ††**	**0.62±0.12¥**
VLF (bpm²)	**11.97±13.75**	**13.81±13.88**	**16.11±18.41**
LF (bpm²)	**3.81±3.79***	**5.08±4.75**	**4.64±5.91**
HF (bpm²)	**1431±1620**	**1695±2834**	**2051±3924**
LF/HF	**4.46±4.82****	**6.70±7.43**	**5.06±4.56**
nLF	**71.85±15.87****	**76.89±16.35**	**75.05±15.17**
nHF	**28.15±15.87****	**23.11±16.35**	**24.95±15.17**

Demographic characteristics and AHI of all subjects are displayed in Table 1. Table 1 also showed no significant difference on age and BMI between the three groups, which can eliminate ageing and weight impacts on the results. In addition, Table 1 showed no significant difference on AHI for both NREM and REM sleep stages between OSA patients with and without major depression, which can eliminate OSA severity impact on the results. It was found that both OSAMDD+ and OSAMDD- groups had significantly lower f_R and higher amplitude of RSA compared to the control group during NREM and REM sleep. This result agrees with the literature in which respiratory frequency f_R, and amplitude of RSA are reciprocal [6,15].

λ was significantly increased in OSMDD+ compared to OSAMDD- during both light NREM and REM sleep. These variations in λ could not be ascribed to variations in RSA nor in f_R, as no significant difference was found between the two groups in theses variables. However, the differences in λ might be due to reduction in the sympathetic cardiac activities in depressed subjects, making the RSA rhythm less erratic, and therefore, phase-locking with respiratory signal more likely. Several investigators have demonstrated that depression decreases the HRV [3,4]. In this study, LF power and the LF-HF ratio have significantly decreased in OSMDD+ compared to OSAMDD- during both NREM and REM sleep, suggesting that sympathetic activity was decreased [16]. Simultaneously, the parasympathetic activity was also increased as nHF was significantly increased in OSMDD+ compared to OSAMDD-. A possible explanation for this is that the sympathetic nerve activity may alter the transduction property of the cardiac vagal efferent nerve. There is evidence that neuromodulators are released in sympathetic nerve terminals that can exert an inhibitory

action on the RRI oscillations [17,18], suggesting that the high levels of sympathetic activity may decrease the magnitude of RSA which in turn can affect the degree of phase coherence (λ) [6]. Given that sympathetic activity can be decreased by depression, an increase in the degree of phase coupling of RSA in OSMDD+ compared to OSMDD- may appear to be an indication of predominance of parasympathetic activity in the depressed OSA group. Perhaps, this is related to the effect of the neuromodulators on parasympathetic effector junctions of the heart. In less sympathetic stimulation, less neuromodulators would be released from sympathetic nerve terminals and thereby, less inhibition would be excreted on the vagal innervation of the heart.

Mixed results were found for λ values in OSMDD+ when compared to the control group. λ was significantly higher during NREM sleep in OSMDD+ compared to controls. Despite OSA patients having higher sympathetic activities than healthy individuals as well as their HRV being changed, primarily with substantial increase in the VLF caused by repetitive cycles of apnea-hypopnea [5], our results showed that sympathetic activity and VLF power were decreased in OSMDD+ compared to controls and this might be due to the impact of depression in reducing the HRV. On the other hand, it was found that λ was significantly lower during REM sleep in OSMDD+ compared to the control group. An explanation for this observation of a lower λ during REM sleep is that sympathetic tone is dominant in REM sleep compared to NREM sleep [11]. Therefore, the decrease in sympathetic activity caused by depression may be negligible. Furthermore, comparison between OSMDD- and control group showed that λ values significantly decreased in OSA patient, which is expected because OSA subjects have been reported to have a higher sympathetic activity compared to healthy subjects [5].

In this study, we conclude that depression could lower the sympathetic activity when accompanied with OSA, allowing for stronger synchronization between RSA and respiration. We also conclude that the phase coherence (λ) could differ between OSA with and without MDD as well as between OSA patients and healthy subjects. Our findings suggest that the phase synchronization index between RSA and respiratory movement could be used as a trait marker for distinguishing between depressed and nondepressed OSA patients.

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