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**Research Article**

# Heart Rate Variability in Obstructive Sleep Apnea.

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**Abstract**

**Introduction:** Obstructive Sleep Apnea (OSA) is characterized by repeated episodes of upper airway obstruction leading to increased airway resistance and respiratory effort, producing oxygen desaturation, hypercapnia and central nervous system arousal. The intermittent hypoxemia and carbon-dioxide retention is responsible for the changes in autonomic and hemodynamic responses to sleep. Heart rate variability (HRV) is a marker of autonomic activity and can be analyzed using time-domain and frequency-domain methods. This study was undertaken to compare the HRV in patients with Obstructive Sleep Apnea Syndrome (OSAS) and normal subjects.

**Methods:** Heart rate variability in 30 controls (Group I) and 30 patients with Obstructive Sleep Apnea Syndrome (Group II) aged 35-45 yrs was studied by using electrocardiographic data obtained during Polysomnography. Low frequency (LF) power, High frequency (HF) power and Low frequency/ High frequency ratio (LF/HF) were analyzed using frequency-domain analysis.

**Results:** There was a significant difference ($p < 0.001$) in LF power and LF/HF ratio of patients with OSAS when compared to the controls, with the values of the OSAS patients being higher, indicating a strong sympathetic activity and a significant difference ($p < 0.001$) in HF power, with the values of the OSAS patients being lower, suggesting parasympathetic blunting.

**Conclusion:** In our study, there was evidence of increased Sympathetic activity and a Parasympathetic attenuation in patients with Obstructive Sleep Apnea. Further studies can evaluate the usefulness of HRV indices for the non-invasive screening of asymptomatic patients suspected to have OSAS.

**Keywords:** Autonomic Activity, Heart Rate Variability, Obstructive Sleep Apnea

## 1. Introduction

Obstructive Sleep Apnea (OSA) is characterized by repeated episodes of upper airway obstruction leading to increased airway resistance and respiratory effort, producing oxygen desaturation, hypercapnia and central nervous system arousal[1]. Airflow is restored, but the intermittent hypoxemia and carbon-dioxide retention experienced by such patients is thought to be responsible for the changes in autonomic and hemodynamic responses to sleep[1,2] .These alterations in autonomic activity are carried over into wakefulness and may cause the cardiovascular diseases associated with OSA including the sympatho-vagal imbalance[1].

Patients with OSA have been proven to have high levels of sympathetic nervous system activity[3]. The chronic

sympathetic activity is thought to be the link between OSA and cardio-vascular disease[4]. In a review of the neural and humoral mechanisms mediating the cardiovascular responses in OSA patients, Phillips and Somers conclude that during sleep, the increased blood pressure and sympathetic nerve traffic are a manifestation of the autonomic and hemodynamic disruption, while during wakefulness, the baroreflex and chemoreflex dysfunction may contribute to the increased blood pressure and sympathetic nervous system activity[5]. Shamsuzzaman *et al*. systematically reviewed studies of OSA from 1966 to 2003 and concluded that there was convincing evidence implicating OSA in the development of hypertension, cardiac ischaemia, congestive heart failure and cardiac arrhythmias[6].

Heart rate variability (HRV) is a quantitative marker of autonomic activity. It can be analyzed using time-domain methods and frequency-domain methods[7]. In the time-domain analysis, variables like standard deviation of NN (normal RR) intervals (SDNN), the square root of the mean squared difference of successive NNs (RMSSD) etc., are studied[7]. Roche *et al* suggest the use of time-domain heart rate variability as an accurate and inexpensive tool for screening patients with suspected Obstructive Sleep Apnea Syndrome (OSAS) as they found that its sensitivity was 90% [8]. Earlier researchers had also suggested using HRV to screen for OSAS even at a time when there was no automation of RR interval calculation[9]. Aljadeff *et al*. found that OSAS altered the beat-to-beat variation in children, especially at a slow heart rate and even suggested using HRV as a screening tool to diagnose OSAS in children[10].

Frequency-domain analysis of HRV involves spectral analysis and is usually done by fast-Fourier transformation in which measurement of LF (low frequency) and HF (high frequency) power components is made in absolute values of power ($ms^2$) or in normalized units (n.u.)[7]. Noda *et al*. found that circadian rhythms of the LF, HF, and LF/HF ratio differed significantly in patients with severe OSAS when compared with those with mild OSAS and control subjects and concluded that sleep-disordered breathing and severe oxygen desaturation might influence HRV not only during sleep but also during the daytime[11]. Gula *et al*. found that there was no significant difference in LF or HF power between patients with severe OSAS, moderate OSAS, controls and OSAS patients using Continuous Positive Airway Pressure (CPAP) [12]. They also found that the LF: HF ratio (which represents sympatho-vagal balance), was higher in patients with moderate OSAS compared to controls and patients with severe OSAS[12]. The LF/HF ratio and mean powers of low frequency (LF), very low frequency (VLF) and total frequency (TF) were found to be higher in patients with severe OSAS when compared to moderate OSAS in a study by Park *et al*., and they concluded that the frequency- domain indices revealed the difference between the groups better than time-domain indices with the LF/HF ratio being the most useful parameter to estimate the Apnea Hypopnea index (AHI) in OSAS patients[13].

Although Kufoy *et al*. did not specifically study frequency-domain measures (i.e. HF, LF, and VLF); they found that HRV improves in the first night of CPAP use in severe OSA patients and suggested that CPAP treatment should not be delayed in such patients[14]. Balachandran *et al* studied HRV in asymptomatic OSA patients and controls and found that daytime time-domain and frequency-domain HRV indices were significantly decreased in asymptomatic OSA subjects demonstrating a decrease in cardiac vagal modulation and suggested that further studies should be done to evaluate these indices for the non-invasive screening of obese asymptomatic OSA patients before they develop overt cardiovascular disease[15]. Narkiewicz *et al*. found that altered cardiovascular variability in patients with OSA is seen even in the absence of other diseases like hypertension and heart failure and that there may be a link between the degree of alteration in cardiovascular variability and the severity of OSA[16]. They suggest that such abnormalities in cardiovascular variability in patients with OSA may be the cause of subsequent development of overt cardiovascular disease [16]. Using the data collected from patients during diagnostic Polysomnograms, Reynolds *et al*. sampled the electrocardiogram from different sleep stages; analyzed it for frequency-domain heart rate variability and concluded that the decrease in HRV during REM sleep in the obese patients with apnea suggested the possibility of an autonomic dysfunction[17]. In view of the above findings of different researchers, the present study was therefore undertaken to compare the heart rate variability (HRV) in patients diagnosed with Obstructive Sleep Apnea Syndrome (OSAS) and normal subjects using electrocardiographic data obtained from Polysomnography and frequency-domain analysis.

## 2. Methods

This study was conducted in the Institute of Physiology & Experimental Medicine, Madras Medical College, Chennai, Tamil Nadu, India. 30 normal controls (Group I) and 30 patients with Obstructive Sleep Apnea Syndrome (Group II) of both sexes in the age group of 35 - 45 years participated in the study. Informed consent was obtained. Controls were age and BMI matched.

The diagnosis of Obstructive Sleep Apnea Syndrome (OSAS) was based on history, clinical examination and overnight Polysomnographic recordings. An apnea-hypopnea index (AHI) of ≥ 10 episodes of apnea or hypopnea per hour of sleep was used to diagnose OSAS. Individuals with co-existing Diabetes Mellitus, systemic hypertension, ischemic heart disease, congestive heart failure , renal disease and neuromuscular disorders; patients with limitation in exercise tolerance and patients with history of intake of drugs affecting the autonomic nervous system were excluded.

Controls and OSAS patients underwent nocturnal Polysomnography with standard methods[18] using RMS software. The sleep stages were monitored using 2 pairs of EEG leads (C4-A1 and O2-A1), 2 pairs of electro-oculographic leads, and chin electro-myographic leads. Air flow was monitored using an oro-nasal thermo-coupler; respiratory efforts by respiratory plethysmography and arterial oxygen saturation by pulse oximetry. The Polysomnography was scored manually according to standard criteria. Apnea was defined as the absence of air flow for >10 seconds in the presence of persistent respiratory efforts while hypopnoea was defined as the association of a reduction of ≥50% of the amplitude of respiratory efforts during ≥10 seconds along with a decrease in arterial oxyhemoglobin saturation of ≥4%. The apnea/hypopnoea index (AHI) was calculated as the number of episodes of apnoea and hypopnoea per hour of sleep and an AHI≥10 was used for diagnosing OSAS. Each episode of apnea was characterized by measuring apnea duration and mean and minimal arterial oxyhemoglobin saturation.

Heart Rate Variability (HRV) was evaluated from the electrocardiographic data. Each QRS complex was identified, and the RR interval was calculated. Only normal to normal beats were considered for analysis. Power spectral analysis of the converted ECG signal was done using fast Fourier transformation. Low frequency (LF) power, High frequency (HF) power and Low frequency/ High frequency ratio (LF/HF) were analyzed using frequency-domain analysis. These variables were chosen as the high frequency band (0.15-0.40 Hz) is influenced by parasympathetic input and the low frequency band (0.04-0.15 Hz) is influenced by sympathetic input (both expressed in normalized units) while the low frequency/high frequency ratio can be used as an estimate of sympathovagal balance. Data thus collected was subjected to statistical analysis using SPSS 17. Values were expressed as Mean ± SD. Unpaired Student t test was used to compare the parameters between the two groups and a 'p' value of < 0.05 was considered as being significant.

## 3. Results

This study was done to compare the Heart Rate Variability in 30 patients with Obstructive Sleep Apnea Syndrome (OSAS) and 30 normal controls using electrocardiographic data obtained from Polysomnography and frequency-domain analysis. There was a significant difference in the LF power (p value < 0.001) of the OSAS patients in Group II when compared to the controls in Group I, with the values of Group II being higher. There was also a significant difference in the HF power (p<0.001) of the OSAS patients in Group II when compared to the controls in Group I with the values of Group II being lower. It was also found that the LF/HF ratio of the OSAS patients in Group II was significantly higher (p<0.001) than that of the controls (Table 1).

**Table 1: Comparision of the Heart Rate Variability (HRV) variables between controls (Group I) and Obstructive Sleep Apnea Syndrome patients (GroupII).**

| S. No. | HRV variable | Group I (Controls) | Group II (OSAS patients) | p value |
|---|---|---|---|---|
| 1. | LF power | 44.66 ± 8.13 | 60.71±9.93 | < 0.001* |
| 2. | HF power | 55.21 ± 8.22 | 19.47±2.37 | < 0.001* |
| 3. | LF/HF | 0.86 ± 0.31 | 3.17±0.67 | < 0.001* |

Results expressed as mean and standard deviation of the Low frequency (LF) power and High frequency (HF) power expressed in normalized units (n.u) and the LF/HF ratio, obtained by frequency-domain analysis of the heart rate variability (HRV) in the two groups, p< 0.05 being considered significant.

## 4. Discussion

Our study revealed that there was a significant difference (p <0.001) in LF power and LF/HF ratio of patients with Obstructive Sleep Apnea Syndrome (OSAS) when compared to the controls, with the values of the OSAS patients being higher, indicating a strong sympathetic activity. This finding is in agreement with the findings of other researchers. Park *et*

*al*. also found that these values were higher in patients with severe OSAS when compared to moderate OSAS and they concluded that the frequency-domain indices of heart rate variability revealed the difference between the groups better[13]. Noda *et al*. found that circadian rhythms of the LF, HF, and LF/HF ratio differed significantly in patients with severe OSAS when compared with those with mild OSAS and controls [11]. They concluded that HRV may be affected even during the daytime[11]. Like us, Reynolds *et al*. also sampled the electrocardiogram from polysomnography; analyzed it for frequency-domain heart rate variability and their findings on the HRV during REM sleep in obese patients with apnea suggested that there was an autonomic dysfunction[17].

In addition, we found that there was a significant difference ($p < 0.001$) in HF power, with the values of the OSAS patients being lower than that of the controls suggesting parasympathetic blunting. Our findings about LF and HF power differ from the findings of Gula *et al*. who found that there was no significant difference in LF or HF power between patients with severe OSAS, moderate OSAS, controls and OSAS patients using Continuous Positive Airway Pressure (CPAP) [12]. There could be many possible reasons for this, like differences in analysis methodology, criteria or limits for spectral bands, in addition to sample size itself. There were 8 patients with severe OHA, 5 with moderate OHA, 7 controls and 5 patients on CPAP in the study by Gula *et al*[12]. However, Gula *et al*. found that the LF/HF ratio was higher among patients with moderate OSAS compared to controls and patients with severe OSAS[12]. The LF/HF ratio represents sympathovagal balance. Although we had not classified our OSAS patients on the basis of their severity, we too did find that the LF/HF ratio was higher in the OSAS patients when compared to the controls. In the study by Gula *et al*., patients with an apnea-hypopnea index (AHI) > 30 were classified as having severe OSA and those with an AHI of 10-30 were considered to have moderate OSA. We had chosen a threshold of AHI $\geq$10 to make the diagnosis of OSA[12].

Our findings regarding the heart rate variability in patients with OSAS need to be considered in the light of findings of other researchers like Balachandran *et al*. who studied heart rate variability (HRV) and even found evidence of decrease in cardiac vagal modulation in asymptomatic OSA subjects using time-domain and frequency-domain HRV indices[15]. They proposed conducting further studies to explore the possibility of using heart rate variability for the non-invasive screening of obese asymptomatic OSA patients before they develop overt cardiovascular disease[15]. Narkiewicz *et al*. even felt that there may be a link between the degree of alteration in cardiovascular variability and the severity of OSA[16]. They also found that the alteration in heart rate variability is seen even in the absence of other diseases like hypertension and heart failure[16]. We had specifically excluded patients suffering from these diseases in our study. Since Kufoy *et al*. found that heart rate variability improves in the first night of use of Continuous Positive Airway pressure (CPAP) in severe Obstructive sleep Apnea (OSA) patients; they suggested that treatment should not be delayed[14]. Accurate screening and prompt treatment are therefore required and from our findings it appears that frequency-domain analysis of Heart Rate Variability has potential for use in screening. Roche *et al*. however suggest the use of time-domain heart rate variability analysis as an accurate, sensitive and inexpensive tool for screening patients with suspected OSAS[8].

Limitations of our study include the sample size; possibility of blunting of HRV due to co-existent undiagnosed diseases like Diabetes Mellitus in spite of strict exclusion criteria being used; the use of Polysomnography itself (which patients could considered uncomfortable) instead of a more simple method to study HRV and the failure to study timed-domain indices (which other researchers had found to be accurate screening tools for OSAS). However our intention was only to get preliminary data about the HRV using frequency-domain analysis in our patients with OSAS using the available resources; further studies can be planned to compare all the HRV variables using both time-domain methods and frequency-domain methods in a larger sample using other devices, and possibly even in asymptomatic obese patients suspected to have OSAS.

## 5. Conclusion

Our study done to compare the heart rate variability using frequency- domain analysis in patients with Obstructive Sleep Apnea Syndrome (OSAS) revealed that there was evidence of increased sympathetic activity and a parasympathetic attenuation in patients with OSAS as evidenced by the higher LF and LF/HF ratios and the lower HF in the OSAS patients. Further studies in larger samples can be planned to evaluate these frequency-domain indices and also the time-domain indices for the non-invasive screening of asymptomatic patients suspected to have OSAS, even before they develop OSAS or cardiovascular disease.

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