

# Impaired Autonomic Balance During Sleep in Obstructive Sleep Apnea: Origin or Result

A Baharav, Z Shinar, Y Dagan, S Akselrod

Tel Aviv University, Sheba Medical Centre, Tel Aviv, Israel

## Abstract

*The ECG may be used as a means to uncover information on the function of organs and systems besides the heart itself. We aimed at the study of the autonomic function in adult patients with Obstructive Sleep Apnea Syndrome (OSAS) and expected their autonomic balance to be shifted towards sympathetic predominance.*

*The study included 12 OSAS patients and 12 subjects with no respiratory disturbance during sleep, as diagnosed by attended, whole night polysomnography (PSG), and scored according to standard criteria. The time-frequency decomposition of beat to beat Heart Rate Variability (HRV), detected from the ECG, served to evaluate autonomic function.*

*The results showed an overall increased sympathetic activity during sleep and sympathetic predominance during SWS in patients, as compared to control subjects. The degree of sympathetic predominance correlated well with the severity of sleep apnea.*

## 1. Introduction

There is increasing evidence that indicates an association between OSAS and cardiovascular morbidity, hypertension included [1-3]. The mechanisms that link between the two frequent disorders, OSAS and hypertension are not understood. Some studies indicate that autonomic mechanisms are involved in the concomitant existence of these disorders [4,5].

Sleep and its structure involve great cyclic changes in autonomic activity and any sleep disturbance is to be expected to cause some degree of autonomic dysfunction.

The evaluation of autonomic function during sleep by means of HRV analysis allows represents a fine non invasive tool of investigation [6-8].

In a previous study we investigated the autonomic function during sleep in children with sleep related breathing disorder [5]. Since the study in children was performed by means of standard steady state spectral analysis of HRV, some information concerning transient events such as apneas might have been lost. Thus in the present study we employed the recently developed time-

frequency wavelet approach [9,10].

The specific aim of the study was to detect and define the autonomic dysfunction in patients with OSAS.

## 2. Methods

The study population included 24 subjects referred to the sleep laboratory for a sleep study with various complaints including one or more of the following: snoring, poor sleep quality, excessive daytime sleepiness, some degree of fatigue. All patients underwent complete whole night polysomnography (PSG) including recordings of 4 EEG leads, 2 eye movement, chin and leg surface EMG, ECG (standard lead II), airflow, respiratory effort (chest and abdomen), O<sub>2</sub> saturation, body position and snoring channel. The data was sampled and stored for off line scoring and analysis.

Sleep stage scoring and respiratory disturbance were performed by an expert in the field, according to standard criteria [11]. Arousals, respiratory events (obstructive apneas and hypopneas), leg movements were carefully registered along with sleep architecture for each subject. The respiratory Disturbance Index (RDI) commonly defined as the density of apneas and hypopneas per hour of sleep served as cutoff point to discriminate between two groups of subjects: (I) A first one included 12 subjects with no diagnosed sleep disorder and  $RDI \leq 5$  and represented the normal control group; (II) A second one with  $RDI > 5$  and no other sleep disorder represented the OSAS group.

The ECG sampled at a 200Hz was later analyzed by an algorithm that included the following steps: (1) Automatic detection of R wave peaks and manual correction of erroneous detections; (2) Equally sampling of RR intervals (RRI) resulting in a RRI series; (3) Time dependent spectral analysis of the obtained RRI series by means of an wavelet transform algorithm [10]. The results of the wavelet transform were integrated for specific frequency ranges to yield three arrays as a function of time along the night: (1) VLF power between 0.005-0.04 Hz; (2) LF power between 0.04-0.15 Hz; (3) HF power between 0.15-0.45 Hz. Analysis of one of the respiratory channels was performed by means of the same wavelet transform to ensure that the HF range was entrained with the respiration rate. We further calculated

some more parameters as a function of time along the night: (1) LF/HF known as the autonomic or sympathovagal balance [ref] Total Power (Tot), normalized values of LF (NLF=LF/(mean HR)) and HF (NHF=HF/(meanHR)), %VLF (VLF as a percentage of Total Power).

An Autonomic Balance Index (ABI) was defined as:

$ABI_{SLEEP STATE} = (\%SLEEP STATE)(LF/HF)_{SLEEP STATE}$   
calculated for each subject for each sleep state and a

general ABI over the night was calculated:

$ABI = ABI_{LS} + ABI_{SWS} + ABI_{REM}$

Statistical analysis was performed as to compare HRV time-dependent parameters within each group as they change with the sleep-wake state and correlate with respiratory disturbance (multiple measures ANOVA) and we compared between the two groups (unpaired, two-tailed t-test).

### 3. Results

Normal subjects were younger ( $27.5 \pm 15.2y$ ) than OSAS patients ( $42.3 \pm 11.2y$ ) and significantly slimmer with BMI  $24.8 \pm 4.6$  versus  $29.5 \pm 3.2$  in subjects diagnosed with sleep apnea. Male sex predominated in the abnormal group (9m/3f and 7m/5f respectively).

The two groups also differed, as expected, in terms of sleep architecture and quality. The specific results are presented in table 1.

Table 1: Sleep characteristics in normal subjects and in OSAS patients

Sleep feature	Normal mean(stdev)	OSAS mean(stdev)
TST (minutes)	390.3(70.8)	389.4(52.4)
%SWS	28.3(7.3)	25.8(7.9)
%LS	42.7(6.5)	47.6(12.9)
%REM	19.5(5.9)	16.7(4.8)
%WTAS	8.3(10.3)	12.0(7.8)
Arousals	78.4(37.9)	168.6(95.4)
Stage shift index	12.7(2.4)	17.7(4.4)
Sleep efficiency	89.4(11.7)	85.3(8.5)
RDI	1.6(1.5)	35.6(21.4)
Mean Sat O <sub>2</sub>	96.9(1.5)	94.4(2.5)

TST - total sleep time, WTAS - wake time after sleep onset,

\* for significant difference  $p < 0.05$

Total power of HRV was higher in OSAS patients at all sleep-wake stages, wakefulness included, as it appears in figure 1.

The total power of HRV decreased during sleep as compared to wakefulness, with a gradual decrease upon the deepening of NREM sleep, and minimal values during SWS in both OSAS patients and normal subjects.

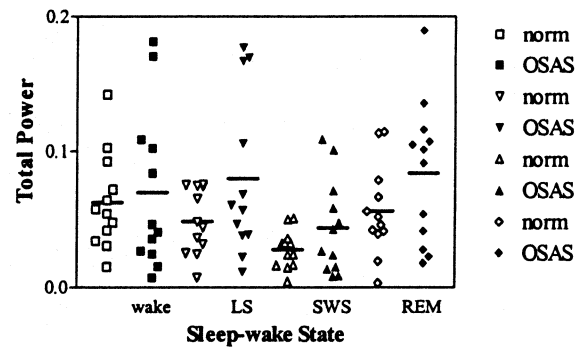


Figure 1: The Total power during various sleep stages in OSAS patients and normal subjects.

The same behavior was detected for the other spectral components: VLF, LF, HF. The normal group displayed significant decrease in Tot, VLF, LF, %VLF and LF/HF with the deepening of NREM sleep with minimal values during SWS (multiple measures ANOVA), see figures 2.

A similar trend was observed in OSAS group. The difference between VLF, LF during Wakefulness, LS and SWS was highly significant ( $p < 0.001$ , two-tailed t-test). The decrease in %VLF (defined as VLF/Tot), was also very significant and reached minimal values during SWS ( $p < 0.001$ ). One has to note that when a patient reaches SWS there are less respiratory events than during LS.

The LF/HF ratio decreased in OSAS patients towards lowest values during SWS, however this behavior was inconsistent and did not reach statistical significance.

As to the differences between the groups during SWS, The Obstructive Apnea group showed significantly higher LF and LF/HF values, see table 2.

Table 2: Spectral variables during SWS in normal subjects and in OSAS patients

Variable		Normals Mean(stdev)	OSAS Mean(stdev)
VLF	ns	0.0108 (0.006)	0.0166 (0.011)
LF	**	0.0072 (0.003)	0.0136 (0.012)
HF	ns	0.0099 (0.007)	0.0139 (0.015)
Tot	ns	0.028 (0.014)	0.044 (0.035)
%VLF	ns	0.028 (0.093)	0.044 (0.093)
LF/HF	**	0.84 (0.27)	1.53 (0.87)

\*\* for  $p < 0.001$ , two-tailed t-test

The Autonomic Balance was significantly higher at all sleep stages in OSAS patients as shown in figure 4.

The Autonomic Balance LF/HF was higher in most OSAS patients during wakefulness also, as it appears in figure 3.

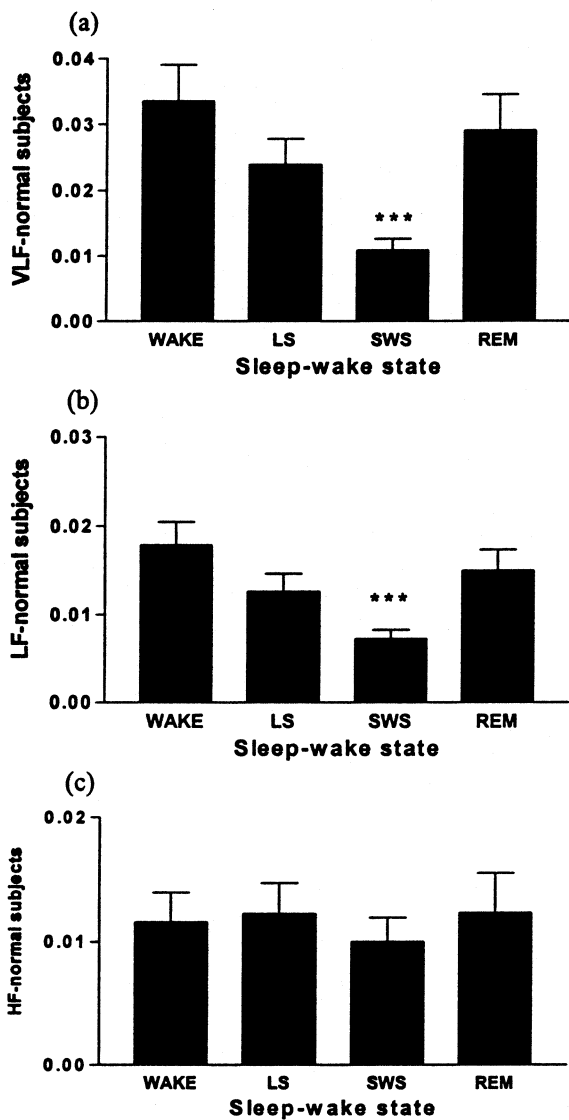


Figure 2: Charts of (a) VLF, (b) LF, (c) HF in normal subjects. \* for  $p < 0.05$ , \*\* for  $p < 0.001$ , \*\*\* for  $p < 0.0001$  two-tailed t test

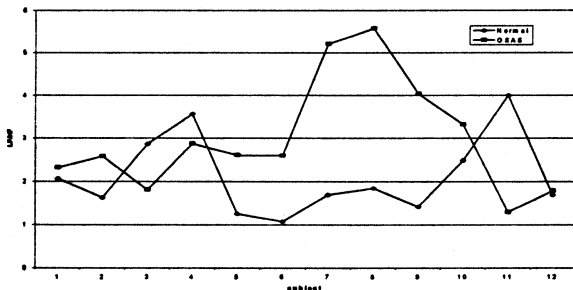


Figure 3: Autonomic Balance during wakefulness in both study groups. The X axis represents individual subjects (12 in each group)

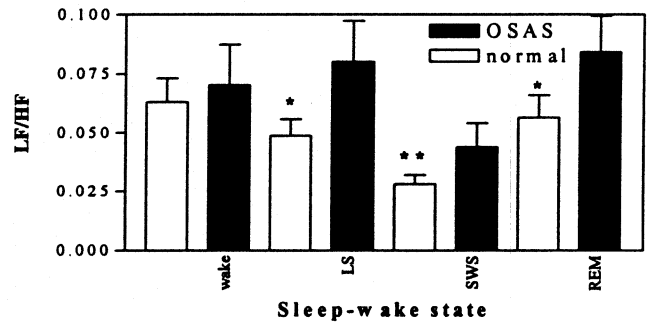


Figure 4: Autonomic Balance during various sleep stages in normal subjects and OSAS patients. \* for  $p < 0.05$ , \*\* for  $p < 0.001$ .

The Autonomic Balance Index, defined in the previous section, was calculated for the whole night sleep, and separately for each sleep stage. It was higher significantly in OSAS group and correlated well with the RDI as presented in figure 4.

No correlation was found between the number of arousals, the density of arousals per hour of sleep and the respiratory or the autonomic balance index.

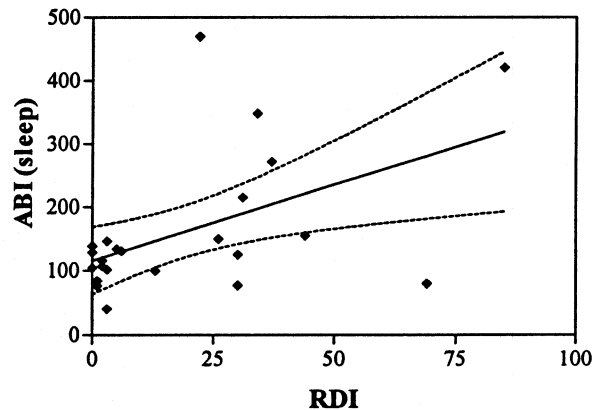


Figure 5: Autonomic Balance Index correlates with the Respiratory Disturbance Index. The Dashed Line represents the 95% confidence interval (Pearson correlation  $r^2 = 0.2559$ ) for all 24 subjects in the study.

#### 4. Discussion

The present study throws some light and brings up additional questions on the issue of autonomic function in patients with OSAS. Some of the findings were expected: sleep apnea is more frequent in males, the propensity to develop the disorder increases with age and patients are overweight when compared with subjects not affected by sleep related breathing disorder.

The autonomic changes during normal sleep were

previously described by HRV methods [5] or by direct measurements of sympathetic activity [4,5]. The present results in the normal group show a decrease in the Total power of HR variability along with a significant decrease of power in the LF range, without an accompanying significant decrease in the HF spectral component with the deepening of NREM sleep. These findings suggest that the autonomic activity, and sympathetic activity decrease in NREM sleep with an obvious parasympathetic predominance during SWS. A surge in sympathetic activity during REM sleep brings the level of activity of the Autonomic Nervous System to levels similar to those during wakefulness.

The same trend was observed in OSA patients, however the levels of sympathetic activity were significantly higher in this group during wakefulness, as well as during the various sleep stages, SWS included. The autonomic balance in these subjects was significantly higher during all sleep stages. Thus patients are more sympathetically driven during sleep, and most of them have also increased sympathetic activity during wakefulness.

The Autonomic Balance Index shows a good correlation with the respiratory disturbance index indicating that the worse the breathing obstruction the higher the Autonomic Balance Index. This autonomic up-regulation does not result from the sleep disruption observed in the OSAS group and measured by the density of detected EEG arousals.

The findings of this study suggest that OSAS patients have increased sympathetic activity during sleep, some of them display the same during wakefulness. Seemingly, this impairment is not the result of the sleep disruption that comes along with the respiratory obstruction. One can think that the increased sympathetic drive represents a factor in the development of the disease, as it does in hypertension.

## References

- [1] Bliwise DL, Bliwise NG, Partinen M, Poursley AM, Dement WC. Sleep Apnea and mortality in an age cohort. *Am J Public Health* 1988; 78:544-547.
- [2] Young T, Peppard P, Palta M, Hla KM, Fin L, Morgan B, Skatrud J. Population based study of sleep-disordered breathing as a risk factor for hypertension. *Arch Intern Med* 1997;157:1746-1752.
- [3] Peppard PE, Young T, Palta M, Skatrud J. Prospective study of association between sleep disordered breathing and hypertension. *N Engl J Med* 2000;342:1378-1384.
- [4] Somers VK, Dyken ME, Mark AL, Aboud FM. Sympathetic neural mechanisms in obstructive sleep apnea. *J Clin Invest.* 1995;96:1897-1904.
- [5] Baharav A, Kotagal S, Pratt J, Rubin BK, Akselrod S. The autonomic control in children with obstructive sleep apnea. *Clinical Autonomic Research* 1999;9:345-351.
- [6] Baharav A, Shinar Z, Sivan Y, Toledo E, Keselbrenner L, Akselrod S. Autonomic Changes Associated With Sleep Onset Investigated by Time Frequency Decomposition of Heart Rate Variability. *Sleep* 1998;21(3 suppl):208.
- [7] Otzenberger H, Gronfier C, Simon C, Charloux A, Ehrhart J, Piquard F, Brandenberger G. Dynamic heart rate variability: a tool for exploring sympathovagal balance continuously during sleep in men. *Am J Physiol.* 1998;275(3 Pt 2):H946-50.
- [8] Baharav A, Kotagal S, Gibbons V, Rubin BK, Pratt G, Karin J, Akselrod S. Fluctuations in autonomic nervous activity during sleep displayed by power spectrum analysis of heart rate variability. *Neurology* 1995;45:1183-7.
- [9] Keselbrenner L, Akselrod S. Selective discrete Fourier transform algorithm –SDA – for time-frequency analysis: Methods and application on simulated and cardiovascular signals. *IEEE Trans. Biomed. Eng.* 1996;43:789-802.
- [10] Toledo E, Gurevich O, Hod H, Eldar M, Akselrod S. The use of a Wavelet Transform for the Analysis of Nonstationary Heart Rate Variability Signal during Thrombolytic Therapy as a Marker of Reperfusion. *Computers in Cardiology* 1998;25:609-612.
- [11] Rechtschaffen A, Kales A, eds. A manual of standardized terminology, techniques and scoring system for sleep staging in human subjects. US government Printing Office, NIH Publication 204, 1968.

Address for correspondence:

Prof. Solange Akselrod  
 Physics Dept.  
 Tel-Aviv University  
 Ramat-Aviv, Tel-Aviv  
 Israel  
 solange@tau.ac.il