



## The Effect of Gender on Hypertension in OSAS Patients

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**Objective:** There are limited data about the effect of gender on the tension and rate pressure product (RPP) in patients with OSAS. The aim of the present study was to explore the effect of gender on hypertension (HT) and RPP in patients with OSAS.

**Methods:** A diagnostic polysomnography was performed in all patients for overnight. OSAS diagnosed patients were included in this study. Sleep stages and respiratory events were manually scored. According to the findings of polysomnography, the effect of gender on tension in patients with OSAS was statistically analyzed.

**Results:** Three hundred forty seven patients consisting of 280 males and 67 females with OSAS were included in the present study. The mean age was  $50 \pm 15$  years in females and  $48 \pm 12$  years in males. The body mass index (BMI) was  $28 \pm 6$  kg/m<sup>2</sup> in females and  $28 \pm 5$  kg/m<sup>2</sup> in males. There was a positive correlation between the apnea/hypopnea index (AHI) with max systolic blood pressure (SBP) and RPP ( $p < 0.01$ ) in the male group, and a positive correlation between AHI with min PTT in the female group ( $p < 0.01$ ); however, there was no correlation between AHI and max SBP in females ( $p > 0.05$ ).

**Conclusion:** The present study confirms previous findings of a relationship between obstructive sleep apnea with SBP. This relationship was evident in males but not identifiable in these females. These data suggest a possible gender difference in susceptibility to hypertension development in OSAS.

**Key Words:** Obstructive Sleep Apnea Syndrome, Hypertension, Gender Effect

### OSAS'lı Hastalarda Cinsiyetin Hipertansiyon Üzerine Etkisi

**Amaç:** Bu çalışmada OSAS'lı hastalarda hipertansiyon ve RPP (rate pressure product) üzerinde cinsiyetin etkilerini araştırmayı amaçladık.

**Metod:** Tüm hastalara bir gece boyunca diagnostik polisomnografi uygulandı. OSAS teşhisi konulan hastalar çalışmaya dahil edildi. Uyku süreçleri ve respiratuar durumlar polisomnografi bulgularına göre skorlandı. OSAS'lı hastalarda cinsiyetin tansiyon üzerindeki etkileri istatistiksel olarak analiz edildi.

**Bulgular:** Çalışmaya 280 erkek ve 67 kadın olmak üzere 347 hasta dahil edildi. Kadınlarda yaş ortalaması  $50 \pm 15$ , erkeklerde  $48 \pm 12$ 'di. Vücut kitle indeksi (The body mass index (BMI)) kadınlarda  $28 \pm 6$  kg/m<sup>2</sup>, erkeklerde  $28 \pm 5$  kg/m<sup>2</sup> olarak bulundu. Burada erkek gruplarında maksimum sistolik kan basıncı ve RPP ile AHI (apnea/hypopnea index) arasında pozitif bir ilişki ( $p < 0.01$ ), kadın gruplarında ise min PTT ile AHI arasında pozitif bir ilişki bulundu ( $p < 0.01$ ); ancak kadınlarda max SBP ile AHI arasında ilişki bulunamadı.

**Sonuç:** Bu çalışma SBP ile obstruktif sleep apne arasındaki ilişkiye ilişkin önceki bulguları doğrulamaktadır. Bu ilişki erkeklerde açık olarak görülürken kadınlarda bulunamamıştır. Bu bilgiler OSAS'lı hastalarda hipertansiyona yatkınlıkta cinsiyet farklılıklarının etkisinin olası olduğunu göstermektedir.

**Anahtar Kelimeler:** Obstruktif Uyku Apnesi, Hipertansiyon, Cinsiyet Etkisi

### Introduction

Obstructive sleep apnea syndrome (OSAS) is a condition characterized by repetitive episodes of cessation of breathing followed by arousals during sleep. This syndrome has been associated with hypertension (HT), stroke, and myocardial ischemia in

epidemiologic and prospective observational studies.<sup>1-5</sup> Although the pathophysiologic mechanisms underlying the association between OSAS and cardiovascular disease are not fully understood, OSAS is characterized by an increase in inspiratory effort during the repetitive episodes of apneas, episodic hypoxemia, recurrent arousals, reflex sympathetic activation, increased arterial stiffness, and consequent marked transient increases in arterial blood pressure.<sup>5-8</sup>

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The prolonged repetitive rises in blood pressure (BP) are likely to induce vascular shear stress, which has been shown to contribute to the formation of atherosclerotic plaques.<sup>9</sup> In patients with HT the prevalence of OSAS has been reported as high as 50%<sup>10</sup> The severity of OSAS is an important factor in the nocturnal elevation in BP, affecting the circadian variation of BP and cardiac arrhythmias.<sup>6,8</sup>

In the present study, the interaction between OSAS and the rate-pressure product (RPP) was determined, the RPP has been reported to be the index which is best correlated with myocardial oxygen consumption.<sup>11</sup> The primary aim of the present study was to explore the effect of gender on HT and RPP in patients with OSAS.

## Methods

### Study sample

In the present study, 347 patients diagnosed with OSAS in Sleep Laboratory of Department of Pulmonary Medicine, Istanbul between February 2000 and 2006, were enrolled. The group of patients with OSAS consisted of 280 males and 67 females. Patients were usually referred by general practitioners, internists, pulmonologists, or ear, nose, and throat surgeons. The patients questioned about the history of HT and those who were under treatment for HT were excluded. The effect of gender on tension and cardiac parameters were analyzed in patients with OSAS. The body mass index (BMI) was calculated as the weight in kilograms divided by the square of the height in meters. In the present study, the product of the heart rate and systolic blood pressure (SBP) were obtained from ambulatory data and RPP was calculated as  $SBP \times \text{heart rate}/100$ . All patients had normal renal function and were not using any cardiovascular drugs.

### Polysomnographic Measurements

For each subject, an overnight sleep study was recorded between 10:30 pm and 6:00 am in a sleep laboratory under the observation of a technician. Recordings were recorded with a 28-channel polysomnograph (SOMNO medics GmbH & Co. KG, Kist, Germany) consisting of a flow sensor for nasal and oral breath flow, a laryngeal microphone, a 3-channel electrocardiograph, stress-sensitive belt for the thorax and the abdomen (1 belt for each), a positional sensor for determination of body movement, and a periodic limb movement of sleep (PLMS). The presence and the stages of sleep were monitored using two pairs of electroencephalographic leads (EEG; C<sub>4</sub>-A<sub>1</sub>, C<sub>3</sub>-A<sub>2</sub>), and two pairs of electrooculographic leads (EOC). Standard methods were used for the recordings.<sup>12,13</sup> Arterial oxygen saturation was continuously recorded by a pulse oximeter for overnight.

The polysomnography (PSG) records were manually scored according to standard criteria.<sup>13</sup> Apnea was defined as the absence of airflow for >10 seconds, despite persistent respiratory efforts. Hypopnea was defined as a  $\geq 50\%$  reduction in the amplitude of respiratory efforts for at least 10 seconds, in addition to a fall in arterial oxyhemoglobin saturation of at least 4%. The apnea/hypopnea index (AHI) was defined as the number of episodes of apnea and hypopnea per hour of sleep. An AHI >5 and the aforementioned criteria were used to designate patients as OSAS or non-OSAS. The severity of OSAS was determined by the AHI and the mean and lowest arterial oxygen saturation (SaO<sub>2</sub>) during sleep. Patients with an AHI <5 were diagnosed as OSAS-negative, patients with an AHI between 5 and 14 were diagnosed as mild OSAS, patients with an AHI between 15 and 29 were diagnosed as moderate OSAS, and patients with an AHI  $\geq 30$  were diagnosed as severe OSAS.

### Definition of Hypertension

The HT study group was composed of patients who had HT on physical examination before the PSG and those who were diagnosed as HT during the PSG evaluation. The BP of patients is higher usually between 6 AM and 6 PM and a BP cutoff value is accepted as 140/90 mmHg in order to determine the normal and abnormal levels. In contrast, the nighttime mean BP is lower and values higher than 125 mmHg is indicative of HT. Since, the present study was carried out overnight, patients with SBP  $\geq 125$  was accepted as hypertensive. Moreover, the average SBP was accepted as continuous variable.<sup>14</sup> PTT was obtained from the ECG and the plethysmographic curve of pulse oximetry of the finger, by using the PSG device for sleep screening. Tension was measured by using the PTT in the nighttime.

### Statistical Analysis

Tests of normality were performed to verify the distribution of study variables. Both the Kolmogorov-Smirnow test and the skewness and kurtosis tests showed that AHI and several covariates were not normally distributed in the study group. Therefore, the Mann-Whitney U test was used to evaluate differences in continuous variables between genders and gender sub-groups. The Chi-square test was performed for grouped variables. Odds ratios (ORs), as measures of relative risk, were estimated using linear regression analysis, and 95% confidence intervals (CIs) were calculated. Differences in the AHI groups were assessed by Chi-square tests for categorical variables; for continuous variables the Kruskal-Wallis rank sum test and Post Hoc Bonferoni and Tamhane tests were used. For analysis of the degree of linear relationship between two quantitative variables, Spearman and Pearson correlation analyses were used; to establish a cause and effect relationship, controlled experiments were

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performed,<sup>15</sup> and this analysis was shown to have a power of 80% with 2-sided significance at 5%. All correlation tests were 2-tailed. Multivariable logistic regression models were performed to control for confounding factors. Multivariate linear regression analysis was performed after logarithmic transformation of the RPP. Interaction of the mean SBP were investigated with analysis of correlation and logistic regression after the stratification of HT. Logistic regression analysis was used to obtain adjusted estimates of the probability of having HT in relation to the BMI, age, and obstructive sleep apnea parameters (AHI categories: 5-14.9, 15-29.9, and >30). Statistical analysis was performed with SPSS 11.5 software (SPSS Inc., Chicago, IL, USA). The significance level was accepted as  $p < 0.05$ .

### Results

Three hundred forty seven patients with OSAS were enrolled in the present study. The mean age was  $50 \pm 15$  years in females and  $48 \pm 12$  years in males. The BMI was  $28 \pm 6$  kg/m<sup>2</sup> in females and  $28 \pm 5$  kg/m<sup>2</sup> in males. The mean AHI was detected  $19 \pm 18$  per/h in males and  $14 \pm 12$  per/h in females. The mean SBP was  $118 \pm 26$  mmHg in males and  $116 \pm 12$  mmHg in females. The minimum pulse transient time (min PTT) was  $262 \pm 11$  ms in males and  $265 \pm 12$  ms in females. The RPP were  $80 \pm 15$  in males and  $79 \pm 12$  in females. The clinical characteristics of the patients with OSAS are summarized in Table 1.

**Table 1.** Characteristics of the study group

	Females (n=67)	Males (n=280)	P value
Age	50±15	48±12	NS
BMI	28±6	28±5	NS
Snoring Time	20±20	24±20	NS
AHI	14±12	19±18	NS
REM	7±8	7±10	NS
Stage 3	12±11	10±9	NS
Min SaO <sub>2</sub>	84±8	82±10	NS
Mean SaO <sub>2</sub>	93±3	93±3	NS
Max HR	118±26	124±32	NS
Mean HR	68±7	67±8	NS
Min PTT	265±12	262±11	NS
Mean SBP	116±12	118±14	NS
RPP	79±12	80±15	NS

BMI: Body Mass Index, kg/m<sup>2</sup>; AHI: Apnea-hypopnea Index per/hr; REM: Rapid Eye Movement; Min SaO<sub>2</sub>: Minimum Oxygen Saturation; Mean SaO<sub>2</sub>: Mean Oxygen Saturation; Max HR: Maximum Heart Rate; Mean HR: Mean Heart Rate; Min PTT: Minimum Pulse Transient Time; Mean SBP: Mean Systolic Blood

Pressure; RPP: Rate Pressure Product; NS: Non-significant

The RPP had a reverse relationship with oxygen saturation based on multivariable linear regression analysis independent from the rapid eye movement (REM), AHI, and age in all patient groups (OR, -1.45; 95% CI, 2,1-0,8;  $p < 0.001$ ). When both groups were examined separately, a relationship between oxygen saturation and RPP was observed in males. There was a significant correlation between AHI with REM, stage 3, mean Spo<sub>2</sub>, RPP, min PTT, mean heart rate (HR), max SBP and BMI in males (Table 2).

**Table 2.** Correlation between AHI with different PSG parameters in both genders

	AHI		
	Female r*, p value	Male r*, p value	Total r*, p value
Age	NS	NS	NS
REM	NS	-0.28, <0.001	-0.25, <0.001
Stage 3	NS	-0.18, <0.01	-0.13, <0.05
Mean SaO <sub>2</sub>	-0.3, <0.05	-0.34, <0.001	-0.3, <0.001
RPP	NS	0.2, <0.01	0.2, <0.001
Min PTT	0.28, <0.05	-0.15, <0.05	-0.18, <0.01
Mean HR	0.27, <0,05	0.21, <0.01	0.2, <0.001
Max SBP	NS	0.21, <0,01	0.1, <0.05
BMI	NS	-0.28, <0.001	0.25, <0.001

\*Spearman correlation coefficient (rho); REM: Rapid Eye Movement; AHI: Apnea-hypopnea Index per/hr; Mean SaO<sub>2</sub>: Mean Oxygen Saturation; RPP: Rate Pressure Product; Min PTT: Minimum Pulse Transient Time; Mean HR: Mean Heart Rate; Mean SBP: Mean Systolic Blood Pressure; BMI: Body Mass Index, kg/m<sup>2</sup>; NS: Non-significant

In contrast, there was no correlation between AHI with age, REM, stage 3, RPP, max SBP and BMI in females. However, a significant correlation was existed between AHI and mean Spo<sub>2</sub>, mean HR, min PTT in females.

There were significant correlations between max SBP and BMI, AHI, age, mean SaO<sub>2</sub>, mean HR, and min PTT in males. These correlations did not exist in females except with min PTT (Table 3).

When we evaluated the mean SaO<sub>2</sub>, a significant correlation was observed between the mean SaO<sub>2</sub> with BMI, AHI, RPP, mean SBP, REM, and min PTT in males. However, a significant correlation only existed with BMI in females (Table 4).

**Table 3.** Correlation between SPB with different PSG parameters in both genders

	Max SBP	
	Female r*, p value	Male r*, p value
<b>BMI</b>	NS	0.2, <0.05
<b>AHI</b>	NS	0.21, <0,01
<b>Age</b>	NS	0.2, <0.01
<b>Mean SaO<sub>2</sub></b>	NS	-0.2, <0.01
<b>Mean HR</b>	NS	0.26, <0.001
<b>REM</b>	NS	NS
<b>Min PTT</b>	-0.6, <0.001	-0.8, <0.001

\*Spearman correlation coefficient (rho); Max SBP: Maximum Systolic Blood Pressure; BMI: Body Mass Index, kg/m<sup>2</sup>; AHI: Apnea-hypopnea Index per/hr; Mean SaO<sub>2</sub>: Mean Oxygen Saturation; Mean HR: Mean Heart Rate; REM: Rapid Eye Movement; Min PTT: Minimum Pulse Transient Time; NS: Non-significant

**Table 4.** Correlation between mean O<sub>2</sub> saturation with different PSG parameters in the group

	Mean SaO <sub>2</sub>	
	Female (n=67) r*, p value	Male (n=280) r*, p value
<b>BMI</b>	-0.36, <0.01	-0.51, <0.001
<b>AHI</b>	NS	-0.33, <0.001
<b>RPP</b>	NS	-0.28, <0.001
<b>Mean SBP</b>	NS	-0.2, <0.01
<b>REM</b>	NS	0.2, <0.05
<b>Min PTT</b>	NS	-0.24, <0.001

\*Spearman correlation coefficient (rho); Mean SaO<sub>2</sub>: Mean Oxygen Saturation; BMI: Body Mass Index, kg/m<sup>2</sup>; AHI: Apnea-hypopnea Index per/hr; RPP: Rate Pressure Product; Mean SBP: Mean Systolic Blood Pressure; REM: Rapid Eye Movement; Min PTT: Minimum Pulse Transient Time; NS: Non-significant

The prevalence of HT in patients with severe OSAS (AHI≥30) was 44.6% in males (OR, 2.3; 95% CI, 1.2-4.3; p < 0.01) and 17% in females (OR, 0.8; 95% CI, 0.1-7.3; P=NS). The prevalence of obesity was 62.5% in males (OR, 4.0; 95% CI, 2.2-7.5; P < 0.001) and 50 % in females (OR, NS).

## Discussion

This study showed that OSA is very common phenomenon in this middle-aged and elderly cases of HT. An independent relationship between OSA and HT was confirmed. However, there was some data suggest that susceptibility to HT development in OSA may be sex dependent. The aim of this present study was to assess the effects of gender on tension and RPP in patients with OSAS.

The relationship between HT and OSAS has been demonstrated in several studies.<sup>16-18</sup> However, there is few studies that has discussed the effects of gender on HT in patients with OSAS.<sup>19-27</sup> In the current study, despite to the significant correlations between SBP with BMI, AHI, age, mean Spo<sub>2</sub>, mean HR, and min PTT in males, these correlations were not observed in females, with the exception of min PTT.

The pathophysiology of the hemodynamic impact of OSAS is complicated and not entirely understood. Several important regulatory mechanisms in cardiovascular homeostasis are considered to be affected by OSAS.<sup>22</sup> The negative intrathoracic pressure resulting from the continuing effort of breathing against the closed upper airway increases with the duration of apnea, thus it directly increases vagal tone.<sup>23,24</sup> Linberg et al.<sup>19</sup> investigated 2,943 patients with OSAS in 6,132 cases suspicious for OSAS and demonstrated that 12% of the patients with HT had snoring, and 7.4% of the patients with HT did not have snoring.<sup>19</sup> HT is a common complication of OSAS, and has been reported in 30%-36% of patients with OSAS.<sup>25,26</sup> Kim et al.<sup>27</sup> reported a higher prevalence of HT in males than females (32.5% vs. 12.5%) and in the younger age group of males the prevalence of HT was also higher. However, as the age increased the prevalence of HT was similar for both genders. Our data were similar to the other studies with a prevalence of HT with severe OSAS (AHI≥30) was 44.6% in males and 17% in females. Although the both group were in similar age, the prevalence of HT was higher in males.

A relationship between SBP and OSAS has been reported in certain studies; HT is one of the most common co-morbidities in OSAS.<sup>17,28</sup> Mohsenin et al.<sup>28</sup> reported a higher risk for HT in males than females. We also established similar results in which the risk of HT was significantly higher in male patients with OSAS having AHI>30 than in females (p<0.01).

There was a significant correlation between AHI with REM, stage 3, mean Spo<sub>2</sub>, RPP, min PTT, mean HR, max SBP, and BMI in males. In contrast to the males, there was no correlation between AHI with REM, stage 3, RPP, max SBP, and BMI in females. However, there was a significant correlation between AHI with mean SaO<sub>2</sub>, mean HR, min PTT in females.

There were correlations between BMI with mean SaO<sub>2</sub> in both genders (p<0.05); however, there were no gender differences in terms of the mean SaO<sub>2</sub>.

It has been reported that left ventricular hypertrophy is more common in patients with OSAS.<sup>29,31</sup> The frequency of left ventricular hypertrophy increases with the severity of OSAS. The greater prevalence of left

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ventricular hypertrophy in apneic patients has been suggested to be related with elevation of post-load during apneic episodes and sympathetic hyperstimulation.<sup>32</sup> However, differences between genders in terms of the cardiac load were not evaluated in these patients. According to our study results, there was a correlation between the RPP with AHI in males in contrast to the females. It can be concluded that cardiac work increased in the male group compared to the female group.

BMI, AHI, age, mean SaO<sub>2</sub>, mean HR, REM and min PTT were significantly correlated with max SBP in male patients with OSAS. It was demonstrated that the prevalence of HT increases with elevated AHI and severity of OSAS. However, the max SBP was only related with the min PTT in females. Mohsenin et al.<sup>28</sup> reported similar results; specifically, they reported that HT increased with age, BMI, and AHI. Although, female patients with OSAS were in similar age in the current study, the relationship with age was not shown in females in terms of HT.

The current study differs from the previous studies in several other important aspects, relationship between min PTT with SBP, and relationship between RPP with AHI in males was shown. There was a correlation between min PTT with max SBP in both genders, however, correlation between RPP with AHI only males group. This was compatible with our results about relationship between SBP with AHI in males.

Our studies had some limitations, the number of the female patients was less than the male patients. Also, the diastolic BP could not be evaluated with our PSG device.

In conclusion, the current study confirms previous findings of a relationship between obstructive sleep apnea and SBP. This relationship was evident in males but not identifiable in these females. These data cause to be thought a possible sex-dependent difference in susceptibility to hypertension development in sleep breathing disorders.

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