

# Implications of continuous positive airway pressure on heart rate variability in patients with obstructive sleep apnea: Does gender matter?

## Obstrüktif uyku apneli hastalarda sürekli pozitif havayolu basıncı tedavisinin kalp hızı değişkenliği üzerine etkisi: Cinsiyetin önemi nedir?

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### ABSTRACT

**Objective:** This study was designed to determine the effectiveness of continuous positive airway pressure (CPAP) treatment on the improvement of heart rate variability (HRV) and whether gender plays a role in HRV in patients with moderate to severe obstructive sleep apnea syndrome (OSAS).

**Methods:** Consecutive patients with recently diagnosed moderate to severe OSAS underwent continuous synchronized electrocardiographic monitoring and were prospectively considered for inclusion in the study. HRV was analyzed before starting CPAP therapy and 1 year thereafter. The effects of CPAP on HRV were evaluated in men and women separately to ascertain whether there are gender differences in the clinical manifestations of OSAS and whether female HRV responses to CPAP are similar to those of men.

**Results:** A total of 18 patients (10 men, median age: 56 years) were included in the study. There were no significant differences in the baseline clinical characteristics of the male and female patients. After 1 year of CPAP treatment, heart rate decreased ( $p<0.05$ ) and time domain parameters increased ( $p<0.05$ ) in both men and women. None of the frequency domain parameters changed in women ( $p>0.05$ ), whereas the high frequency power measured increased ( $p<0.05$ ) and the ratio of low frequency to high frequency decreased ( $p<0.05$ ) in men after 1 year of CPAP treatment. The increase in HRV after 1 year of CPAP therapy was significantly higher in men than in women ( $p<0.05$ ).

**Conclusion:** CPAP therapy reduced enhanced cardiac sympathetic nerve activity in patients with OSAS assessed according to HRV. The beneficial effect of long-term CPAP therapy on HRV was more pronounced in men.

### ÖZET

**Amaç:** Bu çalışmada, orta ve ciddi obstrüktif uyku apne sendromlu (OUAS) hastalarda sürekli pozitif hava yolu basıncı (SPHB) tedavisinin kalp hızı değişkenliğini (KHD) iyileştirmedeki etkinliğini ve bu etkinlikte cinsiyetin rol oynayıp oynamadığını araştırmayı amaçladık.

**Yöntemler:** Orta ve ciddi OUAS tanısı olan ve dışlama kriterleri dışında kalan ardışık hastalar çalışmaya ileriye yönelik olarak dahil edilerek, sürekli senkronize elektrokardiyografik inceleme yapıldı. SPHB tedavisine başlanmadan önce ve tedavi başlangıcından bir yıl sonraki sürede KHD analizi yapıldı. SPHB'nin, KHD üzerine olan etkilerinde cinsiyet farklılığı olup olmadığını incelemek ve SPHB yanıtının kadın ve erkeklerde farklı olup olmadığını analiz etmek için erkek ve kadınlarda ayrı ayrı değerlendirme yapıldı.

**Bulgular:** Çalışmaya 18 hasta (10 erkek, ortanca yaş 56) dahil edildi. Erkek ve kadın hastalar arasında bazal klinik özellikler açısından anlamlı farklılık yoktu. Bir yıllık SPHB tedavisi sonrasında hem erkek hem kadınlarda; ortalama kalp hızının azaldığı ( $p<0.05$ ), zaman temelli KHD parametrelerinin arttığı ( $p<0.05$ ) gözlemlendi. Bir yıllık tedavi sonrası kadınlarda frekans temelli KHD parametrelerinde bir değişiklik görülmezken ( $p>0.05$ ); erkeklerde HF'de yükselme ( $p<0.05$ ), LF/HF oranında düşme ( $p<0.05$ ) saptandı. Ayrıca, bir yıllık SPHB tedavisinden sonra KHD'deki artış, erkeklerde kadınlardan anlamlı olarak daha yüksekti ( $p<0.05$ ).

**Sonuç:** SPHB tedavisi OUAS hastalarında kardiyak sempatik aktiviteyi azaltmakta ve KHD'yi arttırmaktadır. Uzun süreli SPHB tedavisinin bu faydalı etkileri erkeklerde daha belirgin olarak ortaya çıkmaktadır.

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Obstructive sleep apnea syndrome (OSAS) is characterized by the repetitive narrowing or collapse of the upper airway during sleep when complete or partial obstruction of the airway causes apnea or hypopnea.<sup>[1]</sup> Previous studies have demonstrated that OSAS is an independent risk factor for the development of hypertension, coronary artery disease, and arrhythmias.<sup>[2–4]</sup> Patients with OSAS experience arterial oxygen desaturation and chronic intermittent hypoxia-hypercapnia during sleep that elicit sympathetic overactivity and diminished parasympathetic activity to the heart, leading to hypertension and depressed baroreflex sensitivity, which affect the interactions between respiratory and the cardiovascular system.<sup>[5]</sup> Impairment of cardiac autonomic function, i.e., sympathetic hyperactivity and diminished parasympathetic activity, in OSAS patients may cause increased blood pressure and decreased heart rate variability (HRV), resulting in numerous cardiovascular diseases.<sup>[6–8]</sup> Continuous positive airway pressure (CPAP) therapy is the gold standard treatment for patients with OSAS and the current data suggest that structural and functional changes of the left and right ventricles are closely associated with the severity of OSAS and show significant improvement after CPAP treatment.<sup>[9–11]</sup> HRV is the variation in the time interval between consecutive heartbeats, and is the most commonly applied clinical method to evaluate cardiac autonomic function.<sup>[12]</sup> Although previous studies have demonstrated a decreased HRV in patients with OSAS,<sup>[8,13]</sup> the effect of long-term CPAP treatment on HRV has not been thoroughly studied in these patients. Moreover, no gender-specific results have been reported, and it remains unclear whether women's responses to CPAP are similar to those of men.

Therefore, the aim of this study was to analyze the hypothesis that autonomic dysfunction attributed to OSAS can be characterized by 24-hour Holter monitoring and that CPAP treatment has a modulatory effect on this phenomenon in both men and women.

## METHODS

### Study design and patient population

Consecutive female and male CPAP-naïve patients with a diagnosis of OSAS who were referred to the outpatient cardiology clinic for cardiovascular examination from the outpatient clinic of the respiratory sleep disorders unit and did not present any of the

exclusion criteria were included in this prospective study after providing written, informed consent. This study was approved by the Local Ethics Committee (17/01/2013 – 20478486-021).

Patients complaining of excessive daytime somnolence, restless sleep, snoring episodes during sleep, and diagnosed with moderate to severe OSAS with polysomnography were included. Patients with an apnea-

hypopnea index (AHI) score of 15–30 were categorized as having moderate OSAS and those with an AHI score of  $\geq 30$  were categorized as severe OSAS. CPAP treatment was offered to all patients with an AHI of  $\geq 15$  and all of these patients who were willing to use CPAP for at least 1 year were included in the study. The patients were grouped by gender and evaluated separately. Data of demographic, clinical, anthropometric, and HRV parameters measured at the start and end of the study were collected for all of the patients. The HRV time domain and frequency domain parameters of male and female patients at baseline and after 1 year of CPAP treatment were compared.

Fifty-two patients with OSAS (documented in the respiratory sleep disorders unit) were evaluated at baseline within 1 month of beginning CPAP treatment. As this was to be a long-term study, the compliance of patients with CPAP therapy was important. It has been reported that CPAP treatment compliance could be demonstrated in the early weeks and predictable for long-term use.<sup>[14]</sup> Therefore, the patients were re-evaluated 4 weeks after the initiation of CPAP treatment. They were asked to determine their CPAP use as hours per night. Only patients who had more than 5 hours of CPAP use every night were enrolled in the study. At the end of the follow-up period, 18

### Abbreviations:

AHI	Apnea-hypopnea index
BMI	Body mass index
CPAP	Continuous positive airway pressure
HF	High frequency power
HRV	Heart rate variability
LF	Low frequency power
NN	Normal-to-normal
NN50	Number of pairs of adjacent NN intervals differing by more than 50 milliseconds in the entire recording
NuHF	Normalized value of HF bands
NuLF	Normalized value of LF bands
OSAS	Obstructive sleep apnea syndrome
pNN50	NN50 count divided by the total number of all NN intervals
rMSSD	Square root of the mean of the sum of the squares of successive differences between normal heartbeats
RR	Interval between 2 successive R waves of the QRS signal
SDNN	Standard deviation of all intervals between normal R peaks
SDANN	Standard deviation of the 5-minute average of NN intervals

patients with uninterrupted CPAP therapy for at least 5 hours per night during the year were included in the final study.

Diabetes mellitus was defined as a fasting glucose of  $\geq 126$  mg/dL, random glucose of  $\geq 200$  mg/dL, or the use of hypoglycemic medications. The average of 2 seated blood pressure measurements was used. Body mass index was calculated as weight divided by height<sup>2</sup> and expressed as kg/m<sup>2</sup>. Individual risk factors were evaluated and hyperlipidemia was defined according to the 2016 European Society of Cardiology and the European Atherosclerosis Society Guidelines for the Management of Dyslipidaemias.<sup>[15]</sup> Prior history of obstructive coronary heart disease was determined systematically using a combination of self-report (a history of myocardial infarction, coronary revascularization, or angiographic evidence of stenosis in 1 or more coronary arteries of  $>50\%$  of the luminal diameter), electrocardiogram results, review of all available prior medical records, and physician contact. All of the patients underwent a screening with transthoracic echocardiography during their first admission to the outpatient cardiology clinic.

The exclusion criteria were pregnancy, atrial fibrillation and other cardiac arrhythmias, chronic obstructive or restrictive pulmonary disease, obstructive coronary artery disease, severe valvular heart disease, severe kidney or hepatic failure, heart failure with reduced ejection fraction, cardiac pacemaker, history of cerebrovascular disease, psychiatric disorder, cancer, other sleep disorders, patients previously treated with CPAP, thyroid or other endocrine diseases such as diabetes mellitus, and treatment with antiarrhythmic (beta blockers, calcium channel blockers, and other antiarrhythmic drugs), anticholinergic, or antidepressant medications. Patients who indicated during follow-up or at the conclusion of 1 year that they had used the CPAP device for fewer than an average of 5 hours/night, were considered noncompliant with the CPAP treatment and were excluded from the study.

### **Polysomnography and continuous positive airway pressure**

The sleep study was performed using a monitored respiratory polygraph (Smart Sleep System; Medicare Flaga hf, Reykjavik, Iceland). The recordings were read manually, based on the definitions of respiratory events proposed by the American Academy of Sleep

Medicine.<sup>[16]</sup> The average number of apneas and hypopneas per hour was recorded as the AHI. CPAP was indicated in patients with an AHI score of  $\geq 15$  events/hour. CPAP therapy was initiated at an empirical pressure of 8 cmH<sub>2</sub>O for 1 month. Subsequently, when tolerance to treatment was considered appropriate, optimal pressure was applied with auto-CPAP titration (S9 AutoSet; ResMed, San Diego, CA, USA).

### **Heart rate variability analysis**

A standard ambulatory Holter recording system (Century Series 2000/3000 Holter monitoring system, version 1.32; Biomedical Systems, St. Louis, MO, USA) was used to conduct an assessment before starting CPAP treatment, and again after 1 year of treatment. A 3-channel recorder was used to document the electrocardiographic traces. All of the recordings were analyzed after manual adjustment of the RR intervals (RR), the time elapsed between 2 successive R waves of the QRS signal. During the recordings, the patients were asked to continue their daily activities and nightly sleep routine without any special activity. The HRV was evaluated using both time domain and frequency domain analysis. The mean heart rate, mean RR, standard deviation of all normal-to-normal RR intervals (SDNN), standard deviation of the 5-minute average of normal-to-normal intervals (SDANN), the number of pairs of adjacent NN intervals differing by more than 50 milliseconds in the entire recording (NN50) divided by the total number of all NN intervals (pNN50), and the square root of the mean of the sum of the squares of differences between adjacent NN intervals (rMSSD) were measured in the time domain analysis of HRV.

Misclassified drop beats deviating more than 3 SD from the mean normal RR interval of each epoch were identified, and epochs with  $>4\%$  of non-normal RR intervals were excluded from further analysis. A minimum of 50% analyzable data in the 24-hour recording was required for analysis. Frequency-domain criteria were used to calculate the total power, average very-low frequency, average low frequency (LF), average high frequency (HF), and average LF/HF ratio. Normalized values of HF (nuHF) and LF (nuLF) bands were recalculated using the formulas of  $\text{nuLF} = \text{LF}/(\text{HF} + \text{LF})$  and  $\text{nuHF} = \text{HF}/(\text{HF} + \text{LF})$ . The definitions and the clinical implications are summarized in Table 1.

**Table 1. Definitions of heart rate variability parameters**

Variable	Units	Description
Time domain analysis		
RR	ms	Mean RR interval
SDNN	ms	Standard deviation of all NN, the intervals between normal R peaks
SDANN	ms	Standard deviation of the averages of NN intervals in all 5-minute segments of the entire recording
rMSSD	ms	The square root of the mean of the sum of the squares of differences between adjacent NN intervals
NN50 count	ms	Number of pairs of adjacent NN intervals differing by more than 50 ms in the entire recording
pNN50	%	NN50 count divided by the total number of all NN intervals
Frequency domain analysis		
5-minute total power	ms <sup>2</sup>	The variance of NN intervals over the temporal segment
VLF	ms <sup>2</sup>	Power in very-low frequency range ( $\leq 0.04$ Hz)
LF	ms <sup>2</sup>	Power in low frequency range (0.04–0.15 Hz)
HF	ms <sup>2</sup>	Power in high frequency range (0.15–0.40 Hz)
LF/HF		LF/HF ratio
LF norm	n.u.	LF/(total power – VLF) X 100 or LF/(LF+HF) X 100
HF norm	n.u.	HF/(total power – VLF) X 100 or HF/(LF+HF) X 100

## Follow-up

All of the patients included in the study were followed up in the outpatient clinics of cardiology and the respiratory sleep disorders unit at 1, 3, 6, and 12 months to monitor adherence to treatment, review their general status, and to maintain a record of protocol. CPAP treatment was considered adequate when the system counter registered more than 5 hours per night. The use of drugs that could potentially affect HRV or the rate of arrhythmias, such as beta blockers, betamimetics, and antiarrhythmic agents, was discouraged during the trial. Adherence to CPAP therapy during the study was also assessed based on remote monitoring data.

## Statistical analysis

Categorical variables were expressed as counts and percentages, and were analyzed using a chi-square test. The Wilcoxon signed-rank test was used to compare changes in HRV parameters before and after CPAP treatment. Continuous variables are presented as median, first quartile and third quartile, or mean $\pm$ SD, depending on the distribution of the data. The Mann-Whitney U test was performed to assess female and male differences in HRV parameters and

clinical characteristics. All analyses were performed with IBM SPSS Statistics for Windows, Version 21.0 (IBM Corp., Armonk, NY, USA). A 2-sided p value of  $<0.05$  was considered statistically significant.

## RESULTS

The clinical characteristics and physical examination findings of the study population are described in Tables 2 and 3. There were no significant differences in the baseline clinical and demographic characteristics between the male and female patients. Of the 18 patients (10 men, 8 women) who completed the uninterrupted, 1-year CPAP therapy, the median age was 56 years and the median body mass index was 30 kg/m<sup>2</sup>. In all, the body mass index (BMI) of 50% exceeded the criteria for an obesity diagnosis ( $>30$  kg/m<sup>2</sup>). Hypertension was present in 50% of the patients, and 72.2% had dyslipidemia. The median AHI value recorded for the total study population was 26 per hour. Ten patients (55.6%) were smokers and 5 patients (27.8%) consumed alcohol. There were no significant differences in the median heart rate, blood pressure, or BMI values between women and men at baseline and after 1 year of CPAP treatment.

**Table 2. Baseline clinical characteristics of the study population**

	Overall (n=18)	Male (n=10)	Female (n=8)	<i>p</i>
Age (years)	56 (49–64)	58 (51–66)	55 (48–63)	0.392
Smoking	10 (55.6)	6 (60.0)	4 (50.0)	0.068
Alcohol use	5 (27.8)	3 (30.0)	2 (25.0)	0.424
Body mass index (kg/m <sup>2</sup> )	30 (27–34)	30 (27–35)	29 (26–33)	0.674
Heart rate (bpm)	73 (65–84)	72 (63–83)	74 (65–85)	0.467
Obesity	9 (50)	5 (50)	4 (50)	0.992
Hypertension	9 (50.0)	5 (50.0)	4 (50.0)	0.999
Hyperlipidemia	13 (72.2)	7 (70.0)	6 (75.0)	0.485
Valve disease (mild or moderate)	8 (44.4)	4 (40.0)	4 (50.0)	0.098
Apnea hypopnea index (events/h)	26 (22–32)	28 (24–35)	24 (20–31)	0.055

Data are given as median, first quartile and third quartile, or number (percentage).

**Table 3. Physical examination findings of patients with 1 year of uninterrupted CPAP treatment**

	Initial data			1 year later		
	Male	Female	<i>p</i>	Male	Female	<i>p</i>
Heart rate (bpm)	72 (63–83)	74 (65–85)	0.467	62 (55–66)	65 (56–69)	0.315
Body mass index (kg/m <sup>2</sup> )	30 (27–35)	29 (26–33)	0.892	31 (27–36)	30 (27–33)	0.714
Systolic blood pressure (mmHg)	132 (122–143)	128 (123–138)	0.117	130 (119–141)	127 (118–138)	0.103
Diastolic blood pressure (mmHg)	86 (79–95)	83 (78–94)	0.361	84 (75–94)	81 (74–93)	0.295

Data are given as median, first quartile and third quartile. CPAP: Continuous positive airway pressure.

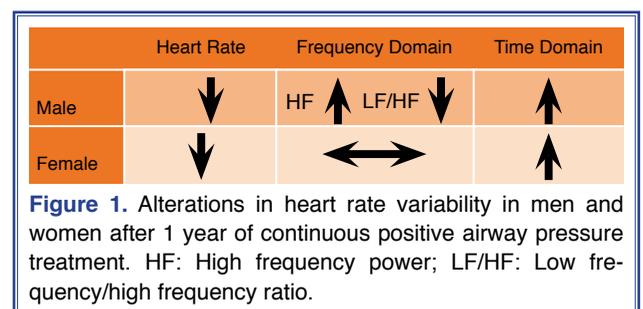
Table 4 provides a comparison of HRV values obtained before and after 1 year of CPAP treatment in men. There was a significant increase in all time domain HRV parameters after long-term CPAP therapy in male patients with moderate to severe OSAS: RR ( $p=0.013$ ), SDNN ( $p=0.015$ ), SDANN ( $p=0.018$ ), rMSSD ( $p=0.001$ ), and pNN50 ( $p=0.002$ ). The mean heart rate significantly decreased after 1 year of treatment ( $p=0.022$ ). According to frequency domain analysis, there was a significant increase in HF ( $p=0.028$ ), and a significant decrease in the LF/HF ratio ( $p=0.041$ ) after 1 year of CPAP therapy.

Table 5 illustrates the comparison of HRV values in women before and after 1 year of CPAP therapy. As in the male patients, there was a significant increase in all time domain HRV parameters after long-term CPAP therapy in the female patients: RR ( $p=0.019$ ), SDNN ( $p=0.016$ ), SDANN ( $p=0.015$ ), rMSSD ( $p=0.003$ ), and pNN50 ( $p=0.001$ ). The mean heart rate was significantly decreased in women after CPAP treatment ( $p=0.025$ ). There were no signif-

icant differences in the frequency domain analysis in women.

In brief, heart rate decreased and time domain parameters increased in both men and in women after 1 year of CPAP treatment. None of the frequency domain parameters changed in women; however, the HF increased and LF/HF rate decreased in men after 1 year of uninterrupted CPAP treatment (Fig. 1).

A comparison of HRV parameters between men and women at baseline and after 1 year of uninterrupted CPAP therapy is provided in Table 6. Although



**Table 4. Comparison of heart rate variability parameters before and after 1 year of continuous positive airway pressure treatment in men**

	Initial data	1 year later	<i>p</i>
	Mean±SD	Mean±SD	
Time domain analysis			
Heart rate (bpm)	72±5	62±6	0.022
Interval between 2 successive R waves of the QRS signal (ms)	812.1±108.3	979.2±110.6	0.013
Standard deviation of all intervals between normal R peaks (ms)	82.1±26.7	119.5±39.2	0.015
Standard deviation of the 5-minute average of NN intervals (ms)	71.2±21.9	107.6±37.3	0.018
Square root of the mean of the sum of the squares of successive differences between normal heartbeats (ms)	38.8±22.4	59.2±23.4	0.001
NN50 count divided by the total number of all NN intervals (%)	9.2±6.6	19.1±10.2	0.002
Frequency domain analysis			
Very-low frequency (ms <sup>2</sup> )	278.1±82	309.9±84.5	0.378
Low frequency (n.u.)	80±15.6	76.2±16.2	0.401
High frequency (n.u.)	24.2±9.6	37.3±13.1	0.028
Low/High frequency	3.2±1.7	2.1±1.3	0.041

SD: Standard deviation.

**Table 5. Comparison of heart rate variability parameters before and after 1 year of continuous positive airway pressure treatment in women**

	Initial data	1 year later	<i>p</i>
	Mean±SD	Mean±SD	
Time domain analysis			
Heart rate (bpm)	74±6	65±4	0.025
Interval between 2 successive R waves of the QRS signal (ms)	775.6±89.7	897.3±97.8	0.019
Standard deviation of all intervals between normal R peaks (ms)	76.8±20.4	91.4±29.2	0.016
Standard deviation of the 5-minute average of NN intervals (ms)	66.5±19.4	88.3±27.1	0.015
Square root of the mean of the sum of the squares of successive differences between normal heartbeats (ms)	34.3±14.7	46.8±20.1	0.003
NN50 count divided by the total number of all NN intervals (%)	8.2±4.1	16.1±9.5	0.001
Frequency domain analysis			
Very-low frequency (ms <sup>2</sup> )	255.7±87.4	288.1±84.8	0.461
Low frequency (n.u.)	78.7±18.6	75.2±13.1	0.792
High frequency (n.u.)	27.9±12.5	32.8±15.1	0.069
Low/High frequency	3.0±1.8	2.6±1.4	0.150

SD: Standard deviation.

there were no significant differences between men and women at baseline, compared with the women, the men had significantly higher time domain parameters (RR, SDNN, SDANN, rMSSD) and had a significantly lower LF/HF rate after 1 year of CPAP treatment.

## DISCUSSION

Our study results have demonstrated that treatment of moderate to severe OSAS using CPAP decreased heart rate and increased HRV at 1 year in men and women.

**Table 6.** Comparison of heart rate variability parameters between men and women at baseline and after 1 year of uninterrupted continuous positive airway pressure therapy

	Initial data			1 year later		
	Men	Women	<i>p</i>	Men	Women	<i>p</i>
Time domain analysis						
RR (ms)	810 (740–830)	770 (710–806)	0.095	970 (856–1010)	890 (788–940)	0.036
SDNN (ms)	80 (69–90)	75 (64–86)	0.117	118 (88–141)	90 (76–112)	0.041
SDANN (ms)	70 (61–83)	66 (59–77)	0.419	107 (81–128)	87 (73–99)	0.031
rMSSD (ms)	36 (29–41)	31 (26–38)	0.603	57 (41–65)	44 (34–55)	0.026
pNN50 (%)	9 (7–12)	8 (6–10)	0.202	19 (12–24)	16 (11–22)	0.121
Frequency domain analysis						
VLF (ms <sup>2</sup> )	274 (205–320)	255 (196–309)	0.261	303 (218–339)	286 (201–327)	0.101
LF (n.u.)	80 (72–91)	77 (71–88)	0.887	75 (70–81)	74 (68–80)	0.902
HF (n.u.)	23 (17–29)	26 (18–31)	0.398	37 (25–40)	32 (22–34)	0.053
LF/HF	3.2 (1.6–3.6)	3 (1.8–3.3)	0.601	2 (1.2–3)	2.5 (1.3–3)	0.043

Data are given as median, first quartile and third quartile. RR: Interval between 2 successive R waves of the QRS signal; SDNN: Standard deviation of all intervals between normal R peaks; SDANN: Standard deviation of the 5-minute average of NN intervals; rMSSD: Square root of the mean of the sum of the squares of successive differences between normal heartbeats; pNN50: NN50 count divided by the total number of all NN intervals; VLF: Very-low frequency; LF: Low frequency; HF: High frequency.

All of the time domain HRV measures significantly increased both in men and women. While none of the frequency domain parameters changed in women, HF increased and LF/HF decreased in men after 1 year of CPAP treatment. Moreover, the increase in HRV was significantly higher in men than in women after CPAP therapy. As HRV is a good indicator of autonomic nervous system activity, it is likely that CPAP treatment is able to reduce cardiac autonomic dysfunction in patients with OSAS. The results of our study suggest that this effect is more pronounced in men.

Although multiple studies have evaluated the effect of CPAP therapy on cardiovascular end points in patients with OSAS,<sup>[17–20]</sup> very few have analyzed the impact of CPAP treatment on HRV.<sup>[21–23]</sup> Palma et al.<sup>[21]</sup> evaluated 30 patients with OSAS (14 with moderate and 16 with severe OSAS) and 20 age- and gender-matched controls in a baseline polysomnographic study after a full night of acute CPAP treatment and after long-term (~2 years) CPAP therapy. The authors found that the OSAS patients exhibited an increased LF, decreased HF, and increased LF/HF ratio during sleep when compared with the controls. They also demonstrated that acute CPAP therapy decreased the LF modulations and the LF/HF ratio, and increased the HF modulations during sleep in patients

with severe OSAS. Moreover, similar to our study, long-term CPAP therapy decreased LF modulations and the LF/HF ratio with increased HF modulations during sleep in patients with moderate and severe OSAS. In another single-center study, Kufoy et al.<sup>[22]</sup> evaluated 39 patients with severe OSAS (AHI >30) to determine how HRV in OSAS patients is affected after acute, very short-term CPAP therapy in a single night of treatment. The authors reported that short-term CPAP treatment improved HRV in patients with severe OSAS. However, in contrast to our study, the changes were similar in men and women in the basal and CPAP night measurements, which suggested that gender does not influence the improvements seen in autonomic nervous system activity from CPAP treatment. This discrepancy may be explained by the fact that Kufoy et al. analyzed acute and very short-term (1 night) effects of CPAP treatment. However, our study results suggest that the beneficial effects of long-term (at least 1 year) of CPAP treatment may be more pronounced in men. Grau et al.<sup>[23]</sup> prospectively studied 26 consecutive patients with recently diagnosed severe OSAS. The incidence of arrhythmia and HRV were analyzed before starting CPAP therapy and 1 year thereafter. This study revealed that CPAP therapy decreased the mean heart rate and only partially improved HRV exclusively during waking hours, as

indicated by an increase in LF and HF parameters. In contrast to our study, none of the time domain parameters improved after CPAP, with the single exception of rMSSD. This may be related to the fact that 23% of the patients were diabetic in the Grau et al. study, since previous studies have shown that type 2 diabetes mellitus was associated with an overall diminished HRV, which can lead to cardiac autonomic neuropathy.<sup>[24]</sup> In a recent meta-analysis, a total of 249 patients with OSAS from 11 prospective studies were analyzed.<sup>[25]</sup> The outcome was defined as the change of spectral HRV parameters of LF, HF, and the LF/HF ratio with CPAP treatment for at least 1 month. As in our study, this analysis showed that CPAP therapy for at least 1 month decreased LF power and the LF/HF ratio, increased HF power, and provided improved cardiac autonomic activity.<sup>[25]</sup> Nicholl et al.<sup>[26]</sup> studied 25 patients with moderate to severe OSAS before CPAP and after 4 weeks of effective CPAP therapy. The primary outcome was an evaluation of the association between CPAP treatment and HRV and arterial stiffness responses to and recovery from an angiotensin II challenge. The results of this study suggested that CPAP therapy was associated with delayed cardiovagal reactivation after a stressor and down-regulation of the arterial renin-angiotensin system in both men and women with OSAS.

The causal link between OSAS and cardiovascular disease has remained controversial for many years, but there is now strong evidence that OSAS is an independent risk factor for cardiovascular disease<sup>[27]</sup> and that CPAP treatment can improve sleep architecture, cardiovascular indices, and other comorbidities, such as metabolic syndrome.<sup>[28–31]</sup> Only a few studies have evaluated the impact of long-term CPAP treatment on the cardiac sympatho-vagal balance. It is reasonable to hypothesize that HRV in patients with OSAS may be different in men and women, as it has been shown that healthy women have a higher vagal tone than men.<sup>[32]</sup> However, OSAS was described as a disease primarily of men, and gender differences in OSAS have not been well studied. The role of gender in the outcome response to CPAP treatment is, therefore, unknown. Our study revealed a significant increase in all time domain parameters in men and women. However, compared with women, HRV values increased more in men after 1 year of uninterrupted CPAP therapy. Moreover, according to the frequency domain parameters, HF increased and the LF/HF ratio decreased

after 1 year of CPAP treatment in men, which may be attributed to the normalized breathing pattern in those patients, since these parameters are strongly dependent on respiration frequency and depth.<sup>[33]</sup>

Our study results suggest that CPAP therapy may be more beneficial in men than in women, as frequency domain parameters (HF, LF/HF) improved only in men and time domain parameters increased more in men compared with women. Previous studies have shown that an increase in HF and a decrease in LF/HF is a marker of cardiac parasympathetic activity;<sup>[5]</sup> thus, long-term CPAP treatment could increase the cardiac vagal predominance of HRV. Further studies are needed to evaluate the influence of long-term CPAP therapy on HRV, preferably in both women and men.

### Study limitations

The major limitation of the present study is the small number of the patients. As a result, designing a larger study with more cases could be more informative. This study was not a randomized analysis of the effect of CPAP on HRV, and therefore may not be generalized to all patients with OSAS.

### Conclusion

Long-term treatment with CPAP in OSAS patients reduced the sympathovagal imbalance and increased parasympathetic modulations to the heart, particularly in men. Long-term CPAP treatment might have the potential to reduce the risk for mortality and morbidity in this population, although more studies are needed to confirm this.

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## REFERENCES

1. Eckert DJ, Malhotra A. Pathophysiology of Adult Obstructive

- Sleep Apnea. *Proc Am Thorac Soc* 2008;5:144–53. [\[CrossRef\]](#)
2. Yaggi HK, Concato J, Kernan WN, Lichtman JH, Brass LM, Mohsenin V. Obstructive sleep apnea as a risk factor for stroke and death. *N Engl J Med* 2005;353:2034–41. [\[CrossRef\]](#)
  3. Sorajja D, Gami AS, Somers VK, Behrenbeck TR, Garcia-Touchard A, Lopez-Jimenez F. Independent association between obstructive sleep apnea and subclinical coronary artery disease. *Chest* 2008;133:927–33. [\[CrossRef\]](#)
  4. Jean-Louis G, Zizi F, Clark LT, Brown CD, McFarlane SI. Obstructive sleep apnea and Cardiovascular Disease: Role of the Metabolic Syndrome and Its Components. *J Clin Sleep Med* 2008;4:261–72.
  5. Guilleminault C, Poyares D, Rosa A, Huang YS. Heart rate variability, sympathetic and vagal balance and EEG arousals in upper airway resistance and mild obstructive sleep apnea syndromes. *Sleep Med* 2005;6:451–7. [\[CrossRef\]](#)
  6. Smith RP, Veale D, Pépin JL, Lévy PA. Obstructive sleep apnoea and the autonomic nervous system. *Sleep Med Rev* 1998;2:69–92. [\[CrossRef\]](#)
  7. Aydin M, Altin R, Ozeren A, Kart L, Bilge M, Unalacak M. Cardiac autonomic activity in obstructive sleep apnea: time-dependent and spectral analysis of heart rate variability using 24-hour Holter electrocardiograms. *Tex Heart Inst J* 2004;31:132–6.
  8. Urbanik D, Gać P, Martynowicz H, Poręba M, Podgórski M, Negrusz-Kawecka M, et al. Obstructive sleep apnea as a predictor of reduced heart rate variability. *Sleep Med* 2018;54:8–15. [\[CrossRef\]](#)
  9. Spicuzza L, Caruso D, Di Maria G. Obstructive sleep apnea syndrome and its management. *Ther Adv Chronic Dis* 2015;6:273–85. [\[CrossRef\]](#)
  10. Romero-Corral A, Somers VK, Pellikka PA, Olson EJ, Bailey KR, Korinek J, et al. Decreased Right and Left Ventricular Myocardial Performance in Obstructive Sleep Apnea. *Chest* 2007;132:1863–70. [\[CrossRef\]](#)
  11. Dursunoglu N, Dursunoglu D, Ozkurt S, Gür S, Ozalp G, Evyapan F. Effects of CPAP on right ventricular myocardial performance index in obstructive sleep apnea patients without hypertension. *Respir Res* 2006;7:22. [\[CrossRef\]](#)
  12. Stein PK, Bosner MS, Kleiger RE, Conger BM. Heart rate variability: a measure of cardiac autonomic tone. *Am Heart J* 1994;127:1376–81. [\[CrossRef\]](#)
  13. Véber O, Lendvai Z, Ronai KZ, Dunai A, Zoller R, Lindner AV, et al. Obstructive sleep apnea and heart rate variability in male patients with metabolic syndrome: cross-sectional study. *Metab Syndr Relat Disord* 2014;12:117–24. [\[CrossRef\]](#)
  14. Weaver TE, Grunstein RR. Adherence to continuous positive airway pressure therapy: the challenge to effective treatment. *Proc Am Thorac Soc* 2008;5:173–8. [\[CrossRef\]](#)
  15. Catapano AL, Graham I, De Backer G, Wiklund O, Chapman MJ, Drexel H, et al; ESC Scientific Document Group. 2016 ESC/EAS Guidelines for the Management of Dyslipidaemias. *Eur Heart J* 2016;37:2999–3058. [\[CrossRef\]](#)
  16. Kapur VK, Auckley DH, Chowdhuri S, Kuhlmann DC, Mehra R, Ramar K, et al. Clinical Practice Guideline for Diagnostic Testing for Adult Obstructive Sleep Apnea: An American Academy of Sleep Medicine Clinical Practice Guideline. *J Clin Sleep Med* 2017;13:479–504. [\[CrossRef\]](#)
  17. McEvoy RD, Antic NA, Heeley E, Luo Y, Ou Q, Zhang X, et al. CPAP for Prevention of Cardiovascular Events in Obstructive Sleep Apnea. *N Engl J Med* 2016;375:919–31.
  18. Chai-Coetzer CL, Luo YM, Antic NA, Zhang XL, Chen BY, He QY, et al. Predictors of long-term adherence to continuous positive airway pressure therapy in patients with obstructive sleep apnea and cardiovascular disease in the SAVE study. *Sleep* 2013;36:1929–37. [\[CrossRef\]](#)
  19. Jennum P, Tønnesen P, Ibsen R, Kjellberg J. Obstructive sleep apnea: effect of comorbidities and positive airway pressure on all-cause mortality. *Sleep Med* 2017;36:62–6. [\[CrossRef\]](#)
  20. Aggarwal S, Nadeem R, Loomba RS, Nida M, Vieira D. The effects of continuous positive airways pressure therapy on cardiovascular end points in patients with sleep-disordered breathing and heart failure: a meta-analysis of randomized controlled trials. *Clin Cardiol* 2014;37:57–65. [\[CrossRef\]](#)
  21. Palma JA, Iriarte J, Fernandez S, Alegre M, Valencia M, Artieda J, et al. Long-term continuous positive airway pressure therapy improves cardiac autonomic tone during sleep in patients with obstructive sleep apnea. *Clin Auton Res* 2015;25:225–32. [\[CrossRef\]](#)
  22. Kufoy E, Palma JA, Lopez J, Alegre M, Urrestarazu E, Artieda J, et al. Changes in the heart rate variability in patients with obstructive sleep apnea and its response to acute CPAP treatment. *PLoS One* 2012;7:e33769. [\[CrossRef\]](#)
  23. Grau N, Bazan V, Kallouchi M, Rodriguez D, Estirado C, Corral MI, et al. Long-term Impact of Continuous Positive Airway Pressure Therapy on Arrhythmia and Heart Rate Variability in Patients With Sleep Apnea. [Article in English, Spanish] *Arch Bronconeumol* 2016;52:17–23. [\[CrossRef\]](#)
  24. Benichou T, Pereira B, Mermillod M, Tauveron I, Pfabigan D, Maqdasy S, et al. Heart rate variability in type 2 diabetes mellitus: A systematic review and meta-analysis. *PLoS One* 2018;13:e0195166. [\[CrossRef\]](#)
  25. Guo W, Lv T, She F, Miao G, Liu Y, He R, et al. The impact of continuous positive airway pressure on heart rate variability in obstructive sleep apnea patients during sleep: A meta-analysis. *Heart Lung* 2018;47:516–24. [\[CrossRef\]](#)
  26. Nicholl DDM, Hanly PJ, Zalucky AA, Mann MC, MacRae JM, Poulin MJ, et al. CPAP Therapy Delays Cardiovascular Reactivation and Decreases Arterial Renin-Angiotensin System Activity in Humans With Obstructive Sleep Apnea. *J Clin Sleep Med* 2018;14:1509–20. [\[CrossRef\]](#)
  27. McNicholas WT, Bonsignore MR; Management Committee of EU COST ACTION B26. Sleep apnoea as an independent risk factor for cardiovascular disease: current evidence, basic mechanisms and research priorities. *Eur Respir J* 2007;29:156–78. [\[CrossRef\]](#)

28. McArdle N, Douglas NJ. Effect of continuous positive airway pressure on sleep architecture in the sleep apnea-hypopnea syndrome: a randomized controlled trial. *Am J Respir Crit Care Med* 2001;164:1459–63. [\[CrossRef\]](#)
29. Gilman MP, Floras JS, Usui K, Kaneko Y, Leung RS, Bradley TD. Continuous positive airway pressure increases heart rate variability in heart failure patients with obstructive sleep apnoea. *Clin Sci (Lond)* 2008;114:243–9. [\[CrossRef\]](#)
30. Peled N, Abinader EG, Pillar G, Sharif D, Lavie P. Nocturnal ischemic events in patients with obstructive sleep apnea syndrome and ischemic heart disease: effects of continuous positive air pressure treatment. *J Am Coll Cardiol* 1999;34:1744–9. [\[CrossRef\]](#)
31. Sharma SK, Agrawal S, Damodaran D, Sreenivas V, Kadhavan T, Lakshmy R, et al. CPAP for the metabolic syndrome in patients with obstructive sleep apnea. *N Engl J Med* 2011;365:2277–86. [\[CrossRef\]](#)
32. Ye L, Pien GW, Weaver TE. Gender differences in the clinical manifestation of obstructive sleep apnea. *Sleep Med* 2009;10:1075–84. [\[CrossRef\]](#)
33. Gaşior JS, Sacha J, Jeleń PJ, Zieliński J, Przybylski J. Heart Rate and Respiratory Rate Influence on Heart Rate Variability Repeatability: Effects of the Correction for the Prevailing Heart Rate. *Front Physiol* 2016;7:356. [\[CrossRef\]](#)

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