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ORIGINAL RESEARCH

The Elevated Central Chemosensitivity in Obstructive Sleep Apnea Patients with Hypertension

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Purpose: Hypertension is a common comorbidity in obstructive sleep apnea (OSA), in which dysfunction of the autonomic nervous system plays an integral part. Chemoreflex is essential for ventilatory control and cardiovascular activity. This study aimed to determine whether central chemosensitivity was increased in OSA patients with hypertension and the potential role of the autonomic nerve activity in this relationship.

Patients and Methods: A total of 77 men with OSA were included in this cross-sectional study. We measured hypercapnic ventilatory response (HCVR) by the rebreathing method under isoxic hyperoxia to test the central ventilatory chemosensitivity since hyperoxia silences the peripheral chemoreceptors' response to CO_2. To elevate the autonomic nerve activity, time-domain, frequency-domain, and non-linear variables of heart rate variability were calculated over 5-min records. Univariate and multivariate linear regression analyses were used to find the determinants of HCVR.

Results: The median HCVR was 2.3 (1.8, 3.3), 2.1 (1.6, 3.0), and 3 (2.2, 3.7) L/min/mmHg in all participants, OSA patients, and OSA patients with hypertension, respectively. Hypertension was significantly associated with elevated HCVR after adjusting for age, central obesity, OSA severity, daytime sleepiness, and diabetes mellitus. Compared with OSA patients, OSA patients with hypertension had higher body mass index, worse nocturnal hypoxia, and lower time-domain variables and frequency-domain variables. After adjusting for age, apnea-hypopnea index, central obesity, and beta-blocker usage, approximate entropy was independently negatively associated with HCVR in OSA patients with hypertension.

Conclusion: This study demonstrated elevated central chemosensitivity in OSA patients with hypertension. Compared with OSA patients, OSA patients with hypertension had attenuated parasympathetic nerve activity. This study preliminarily illustrated that elevated central chemosensitivity might be associated with weak adaptability of the cardiac autonomic nervous system in OSA patients with hypertension.

Keywords: obstructive sleep apnea, central chemosensitivity, hypercapnic ventilatory response, hypertension, autonomic nerve activity

Introduction

Obstructive sleep apnea (OSA) is a common sleep-disordered breathing that involves multiple mechanisms, including increased airway collapsibility, low respiratory arousal threshold, and unstable ventilatory control.[1] Unstable ventilatory control, characterized as high loop gain, contributes to periodic apnea by amplifying the ventilation's magnitude after recovery from airway collapse.[2] Loop gain is an engineering theory utilized to evaluate the negative feedback control system's stableness, which comprises controller gain, plant gain, and the delay between the two. Controller gain mirrors ventilatory chemoreflex in the respiratory system, and smaller lung volume might produce higher plant gain.[3] Hyperactivity of chemoreceptors has been confirmed in patients with OSA, which contributes to unstable ventilatory control and repeated airway obstruction.[4,5]

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Central and peripheral chemoreceptors modulate both ventilatory control and neural circulatory control.[6] In patients with heart failure, activation of central chemoreceptors was shown to be correlated with the augmentation of ventilation and sympathetic drive.[7] Familial dysautonomia, a rare hereditary autonomic neuropathy, shows the synergy between dysfunction of autonomic neurons and reduced ventilatory chemoreflex.[8] In patients with Lewy body dementia, the reduced central chemoreflex was shown to be associated with impaired heart rate variability (HRV).[9] The sympathovagal imbalance relating to apnea events is associated with arrhythmia and cardiovascular diseases for patients with OSA.[10] Moreover, sustained increase of sympathetic nerve activity has been found in patients with OSA during sleep[11] and resting wakefulness.[12] However, in previous studies, conflicting findings were made regarding the alterations of parasympathetic nerve activity in patients with OSA during sleep and daytime.[13] The mechanisms by which OSA leads to elevated sympathetic nerve activity include overactivity of peripheral chemoreceptors and inordinate central sympathetic outflow.[14] The modification of parasympathetic activity in the central chemoreflex has been found in lamb models,[15] while the relationship between central chemoreflex and autonomic nerve activity in patients with OSA has not been reported yet. Considering the complex interaction between central chemoreceptors and cardiovascular neural control,[16,17] the correlation between central chemoreflex and autonomic nerve activity in patients with OSA is worth noting.

Hypertension is a common comorbidity or complication in patients with OSA. In spontaneously hypertensive rats, augmented central ventilatory chemosensitivity increases the ventilation, sympathetic nerve activity, and arterial blood pressure, which still existed when peripheral chemoreceptors were attenuated by hyperoxia.[18] The melanocortin system[19] and orexin neurons[18] might play a remarkable role in the complex interaction between central sympathetic efferents and central chemoreceptor activity. However, the link between hypertension and central chemosensitivity in patients with OSA was ambiguous. Meanwhile, excessive sympathoexcitation[20] and diminished parasympathetic activity[21] play an integral part in the development and progression of hypertension. Thus, we assumed that there might be a significant relationship between autonomic nerve activity and central chemoreflex in OSA patients with hypertension.

Hypercapnic ventilatory response (HCVR) measured by the rebreathing method under isoxic hyperoxia has often been used to test the central ventilatory chemosensitivity since hyperoxia silences the peripheral chemoreceptors' response to CO_2.[22,23] In this study, we intended to confirm the association between hypertension and HCVR in patients with OSA. We also explored the relationship between autonomic nerve activity and HCVR in OSA patients with hypertension.

Materials and Methods

Participants

This cross-sectional study was conducted in the sleep unit of Peking Union Medical College Hospital in Beijing, China. This study included adult men with OSA (age ≥ 18 years). The diagnosis for OSA was based on an apnea-hypopnea index (AHI) equal to or greater than 5/h combined with either associated symptoms (such as sleepiness, snoring, or observed apneas) or related diseases (such as hypertension, diabetes, and cardiovascular diseases). Besides, those with an AHI ≥ 15/h also met the diagnosis criteria, even when they were free of associated symptoms and diseases.[24] Participants were excluded if one of the following criteria was met: (1) also suffering from cardiovascular diseases, such as arrhythmia, coronary disease, or heart failure; (2) impaired pulmonary function, such as percentage of predicted forced expiratory volume in 1 s (FEV1% predicted) < 80%, percentage of predicted forced vital capacity (FVC% predicted) < 80%, or FEV1/FVC ratio < 70%; (3) acute or chronic kidney disease, liver disease, or neuromuscular disease; (4) smoking in the past year; (5) receiving continuous positive airway pressure treatment in the past year; (6) refusal to undergo rebreathing tests; and (7) electrocardiography (ECG) data not appropriate for HRV analysis.

This study was conducted in accordance with the Declaration of Helsinki. The Clinical Research Ethics Committee of Peking Union Medical College Hospital approved the experimental protocol (JS-2627). All patients provided written informed consent.

Polysomnography and Data Collection

Whole-night polysomnography was performed using a standard device (Embla N7000; Natus Medical Incorporated, Broomfield, CO, USA). Sleep state and associated respiratory events were evaluated following the American Academy of

Sleep Medicine manual (Version 2.3).[25] Total sleep time (TST) and percentages of sleep stages [stages 1, 2, 3, and rapid eye movement sleep] were collected. The AHI was calculated as the number of apnea and hypopnea events per hour. An AHI ≥ 15/h was used as the threshold to divide participants into those with mild OSA and moderate-to-severe OSA. Obstructive apnea index (OAI) and central apnea index (CAI) were defined as the sum of obstructive or central apnea events per hour. Oxygen desaturation index (ODI), lowest values of peripheral blood oxygen saturation ($LSpO_2$), and percent of time spent at peripheral blood oxygen saturation beneath 90% (T_{90}) were used to describe the severity of nocturnal hypoxia.

The participants' demographic data were collected, including age, body mass index (BMI), waist circumference (WC), and neck circumference. BMI was calculated as weight (in kg)/height^2 (in m^2). Obesity was defined as BMI ≥ 28 kg/m^2.[26] Central obesity was defined as WC ≥ 90 cm for men.[27] Diabetes mellitus was diagnosed when the patients had a history of diabetes mellitus or had received treatment for this condition. Hypertension was diagnosed when the individuals currently used antihypertensive medications or met the 2020 definition of hypertension of the International Society of Hypertension (systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg at two different times).[28] In this study, the pharmacotherapy for hypertension included calcium channel blocker, beta-blocker, diuretic, and renin-angiotensin system inhibitor. All participants completed the Epworth Sleepiness Scale (ESS) questionnaire and Pittsburgh Sleep Quality Index (PSQI). ESS score ≥ 11 reflects daytime sleepiness,[29] while PSQI > 5 is associated with poor sleep quality.[30]

HRV

Lead II ECG was used to record the R-R intervals with polysomnography equipment during the total time in bed. We aimed to analyze autonomic nerve activity during wakefulness, so we collected 5-min R-R intervals during wakefulness before sleep for each participant. The wakefulness was identified by an electroencephalogram. All subjects were asked to maintain a supine position and relaxed tidal breathing during the ECG acquisition. We used the software Kubios HRV (version 3.4; Kubios Co., Kuopio, Finland) for HRV analysis.[31] We analyzed time-domain, frequency-domain, and non-linear variables in accordance with the guidelines.[32,33] The time-domain variables included the mean heart rate, the standard deviation of R-R intervals (SDNN), square root mean squared differences between successive R-R intervals (RMSSD), and the percentage of adjacent R-R intervals with a difference greater than 50 ms (pNN50). With Welch's periodogram method (300 s window width and 50% overlap window). Fast Fourier transformation was used for frequency-domain analysis. The very low-frequency range (VLF, 0–0.04 Hz), low-frequency range (LF, 0.04–0.15 Hz), high-frequency range (HF, 0.15–0.4 Hz), normalized LF power (LFnu), normalized HF power (HFnu), and LF/HF ratio were measured. In non-linear metrics, approximate entropy (ApEn) and sample entropy (SampEn) were used to quantify the regularity of the R-R series.

HCVR and Spirometry

In the morning, the participants undertook the rebreathing tests in accordance with Duffin's method.[23] They sat at a table, and breathed with a nose peg and a mouthpiece connected to a closed one-way circuit with a 6 L plastic rebreathing bag containing the test gas. The bag initially had a gas mixture of 13% O_2/6% CO_2 /balanced nitrogen, and 100% O_2 was fed into the rebreathing bag to maintain end-expiratory oxygen partial pressure at 150 mmHg during the test. The test lasted 3–5 min or was terminated when end-tidal carbon dioxide partial pressure was higher than 60 mmHg, or minute ventilation exceeded 100 L/min. The volume transducer and gas sampling port of the cardiopulmonary exercise cart (MasterScreen CPX; Jaeger, Hoechberg, Germany) were connected with the mouthpiece and rebreathing bag to collect the data (end-tidal carbon dioxide partial pressure and minute ventilation). Breath-by-breath measurements monitored expired gas concentrations and minute ventilation. HCVR was evaluated by relating end-tidal carbon dioxide partial pressure with minute ventilation during the rebreathing test using linear regression, representing the central chemosensitivity.

After 30 min of rest, the participants underwent spirometry. The cardiopulmonary exercise cart was used to assess the pulmonary function of participants. The data of FEV1% predicted, FVC% predicted, and FEV1/FVC ratio were acquired.

Statistical Analysis

We calculated mean ± standard deviation or median (interquartile range) for continuous variables depending on the data distribution. Categorical variables were presented as the number and percentage. Univariate linear regression analyses were used to find the determinants of HCVR. The relationship between HCVR and hypertension was assessed using multivariate linear regression in three adjusted models [model 1 adjusted for age; model 2 adjusted for age, OSA severity (AHI ≥ 15 /h), and daytime sleepiness (ESS ≥ 11); model 3 adjusted for central obesity (WC ≥ 90 cm), diabetes mellitus, and all variables in model 2]. The comparison between OSA patients and OSA patients with hypertension was conducted by independent Student's *t*-test, Mann–Whitney *U*-test, or Pearson's $\chi 2$ test depending on the data distribution. For statistical analysis, the natural logarithmic transformation of VLF, LF, and HF was used. The factors correlating with HCVR in OSA patients with hypertension were selected by univariate linear regression analyses. Furthermore, we used multiple forward stepwise linear regression analyses (likelihood ratio) to find the determinants of HCVR in OSA patients with hypertension. SPSS version 21.0 (Chicago, IL, USA) was used for data analysis. A two-sided $P < 0.05$ was considered to reflect statistical significance.

Results

Characteristics of Recruited Participants

As shown in Supplementary Figure 1, 135 men took part in this study and 58 men were excluded. Overall, 5 participants showed abnormal pulmonary function (FEV1/FVC < 70%), 40 participants were current smokers, 5 participants did not complete the rebreathing test, and 8 participants had ECG data that were not appropriate for HRV analysis. Thus, 77 men were enrolled in this study. The clinical characteristics of the 77 enrolled men are shown in Table 1. The median age of all participants was 41 years. The median BMI was 27.4 kg/m^2 and 40.3% of patients were obese. The median WC was 97.0 cm and 83.1% of patients were diagnosed with central obesity. The median values of FEV1% predicted, FVC% predicted, and FEV1/FVC ratio were 97.2 (90.0, 104.0) %, 100.5 (91.5, 105.0) %, and 79.6 (77.0, 83.8) %, respectively. The median HCVR was 2.3 (1.8, 3.3) L/min/mmHg. The median AHI was 38.8/h and 72.7% of participants were classified as having moderate-to-severe OSA. The incidences of daytime sleepiness, poor sleep quality, hypertension, and diabetes mellitus were 57.1%, 70.1%, 50.7%, and 13.0%, respectively.

Elevated HCVR in OSA Patients with Hypertension

As shown in Figure 1, age, hypertension, and central obesity were positively associated with HCVR (all *P* values < 0.05). Patients with moderate-to-severe OSA tended to have augmented HCVR compared with patients with mild OSA. The relationships of obesity, poor sleep quality, daytime sleepiness, and diabetes mellitus with HCVR were not significant. In adjusted models, we found that hypertension was significantly associated with elevated HCVR after adjusting for age, central obesity, OSA severity, daytime sleepiness, and diabetes mellitus (Table 2).

Comparison Between OSA Patients and OSA Patients with Hypertension

As shown in Table 3, the mean age did not differ between OSA patients and OSA patients with hypertension. The OSA patients with hypertension had higher BMI, percentage of obesity, and neck circumference. However, the WC and percentage of central obesity did not differ between the two groups. The OSA patients with hypertension had lower values of FEV1% predicted and FVC% predicted. The FEV1/FVC was similar between the two groups. The median HCVR was 3.0 (2.2, 3.7) L/min/mmHg in OSA patients with hypertension and 2.1 (1.6, 3.0) L/min/mmHg in OSA patients. The AHI, OAI, and CAI did not differ significantly between the two groups. The OSA patients with hypertension had worse nocturnal hypoxia (higher ODI and T_{90}, and lower $LSpO_2$). The TST and the percentages of sleep stages did not differ between the two groups. The percentages of daytime sleepiness, poor sleep quality, and diabetes mellitus also did not differ between the two groups.

The mean heart rate was 71.9 ± 9.5 bpm in OSA patients and 74.6 ± 10.0 bpm in OSA patients with hypertension, which were not significantly different (Table 4). Compared with the OSA patients, the OSA patients with hypertension had lower time-domain (RMSSD and SDNN) and frequency-domain variables (ln VLF, ln HF, and HFnu). In addition,

Table 1 Clinical Features of All Participants

Variables	n = 77
Age, years	41.0 (35.0, 50.0)
BMI, kg/m^2	27.4 (25.0, 29.4)
BMI ≥ 28kg/m^2, %	31 (40.3%)
Neck circumference, cm	40.0 (39.0, 42.0)
WC, cm	97.0 (91.0, 104.0)
WC ≥ 90cm, %	64 (83.1%)
FEV1% predicted, %	97.2 (90.0, 104.0)
FVC % predicted, %	100.5 (91.5, 105.0)
FEV1/FVC, %	79.6 (77.0, 83.8)
HCVR, L/min/mmHg	2.3 (1.8, 3.3)
AHI, /h	38.8 (14.5, 59.8)
AHI ≥ 15/h, %	56 (72.7%)
OAI, /h	23.4 (4.7, 47.1)
CAI, /h	0.0 (0.0, 0.3)
ODI, /h	30.3 (11.4, 52.9)
$LSpO_2$, %	83.0 (76.0, 88.0)
T_{90},%	0.6 (0.1, 4.5)
TST, min	411.8 (373.0, 453.5)
Stage 1, %TST	7.3 (4.8, 12.3)
Stage 2, %TST	44.6 (38.6, 66.1)
Stage 3, %TST	24.5 (12.6, 32.4)
Stage REM, %TST	15.9 (11.1, 19.5)
ESS ≥ 11, %	44 (57.1%)
PSQI > 5, %	54 (70.1%)
HTN, %	39 (50.7%)
DM, %	10 (13.0%)

Abbreviations: BMI, body mass index; WC, waist circumference; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; HCVR, hypercapnic ventilatory response; AHI, apnea-hypopnea index; OAI, obstructive apnea index; CAI, central apnea index; ODI, oxygen desaturation index; $LSpO_2$, lowest values of peripheral blood oxygen saturation; T_{90}, percent of time spent at peripheral blood oxygen saturation beneath 90%; TST, total sleep time; REM, rapid eye movement; ESS, Epworth Sleepiness Scale; PSQI, Pittsburgh Sleep Quality Index; HTN, hypertension; DM, diabetes mellitus.

the OSA patients with hypertension had a higher LF/HF ratio than OSA patients. In non-linear metrics of HRV, SampEn and ApEn did not differ between the two groups.

Factors Correlating with HCVR in OSA Patients with Hypertension

The relationships between clinical features, HRV variables, and HCVR in OSA patients with hypertension are shown in Supplementary Table 1. We only found a significantly negative relationship between ApEn and HCVR. Moreover, we found that ApEn was independently associated with HCVR after adjusting for age, AHI, central obesity, and beta-blocker usage (Figure 2).

Discussion

This study first demonstrated that OSA patients with hypertension had elevated central chemosensitivity compared with OSA patients. Moreover, using HRV analysis, we found that augmented central chemosensitivity was associated with reduced adaptability of the autonomic nervous system in OSA patients with hypertension.

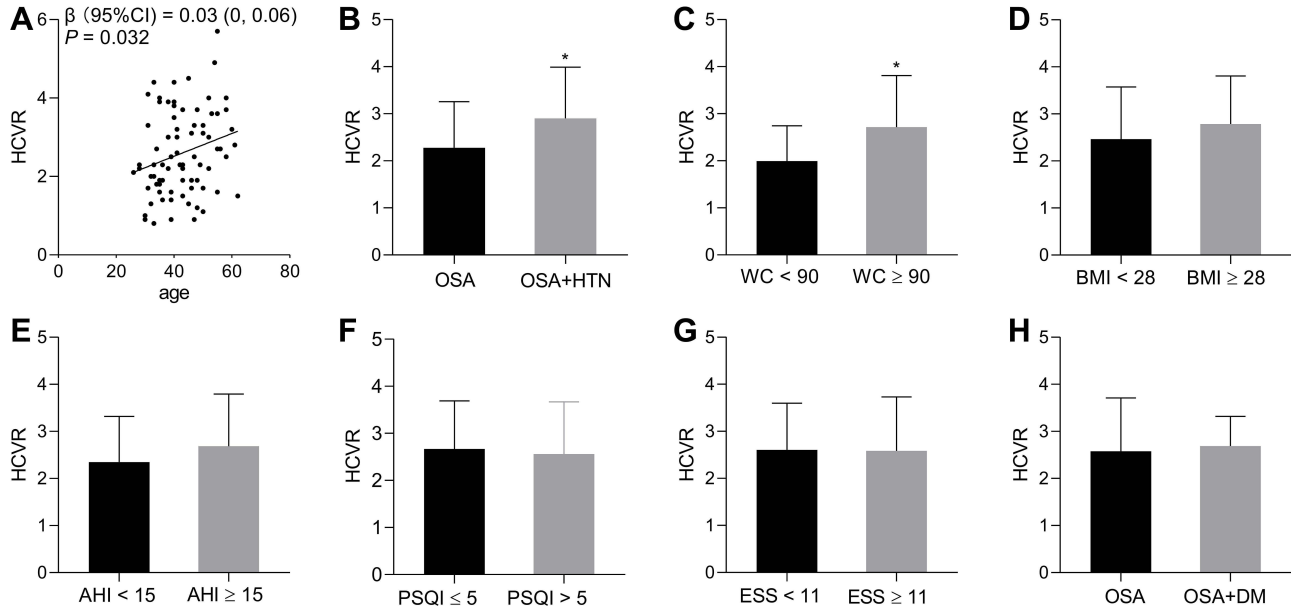

Figure 1 The determinations of HCVR in patients with OSA. (**A**) The relationship between age and HCVR. (**B**) The relationship between hypertension and HCVR. (**C**) The relationship between central obesity and HCVR. (**D**) The relationship between obesity and HCVR. (**E**) The relationship between OSA severity and HCVR. (**F**) The relationship between poor sleep quality and HCVR. (**G**) The relationship between daytime sleepiness and HCVR. (**H**) The relationship between diabetes mellitus and HCVR. *$P < 0.05$.

Abbreviations: HCVR, hypercapnic ventilatory response; OSA, obstructive sleep apnea; HTN, hypertension; WC, waist circumference; AHI, apnea-hypopnea index; BMI, body mass index; PSQI, Pittsburgh Sleep Quality Index; ESS, Epworth Sleepiness Scale; DM, diabetes mellitus.

The retrotrapezoid nucleus is the key nodal point of central ventilatory control.[34] Hypercapnia activates the central chemoreceptors by increasing the central hydrogen ion concentration.[35] Thus, HCVR might be a suitable method to measure the central chemosensitivity and the maintenance of isoxic hyperoxia disrupted the effect of peripheral chemoreceptors at the same time. There is controversy in the literature about the determinants and modified factors of HCVR in patients with OSA. The mechanism of central chemoreflex might differ between males and females. Sin et al[36] found that age and daytime $PaCO_2$ were primary determinants of HCVR in men, and BMI was a significant factor for HCVR in women. Wang et al[37] also found that obstructive sleep apnea/hypopnea index was positively associated with HCVR in asymptomatic patients with OSA. In this study, we explored the determinants of HCVR only in male patients and found a positive relationship between age and HCVR. However, we did not find a significant relationship between AHI and HCVR. The relationships of HCVR with OAI, CAI, severity of nocturnal hypoxia, daytime sleepiness, and poor sleep quality were also not significant in this study. Ge et al[38] found that ventilatory chemosensitivity was increased in obese men. Meanwhile, Earing et al[39] found that BMI mediated the relationship between AHI and HCVR. We also found the increased HCVR in OSA patients with central obesity. Narkiewicz et al[40] found that obesity selectively potentiated central chemosensitivity. Central obesity was also found to be linked to increased morbidity of metabolic diseases and cardiovascular diseases; thus, the relationship between BMI or central obesity

Table 2 The Relationship Between Hypertension and HCVR

Model	β (95% CI)	*P* value
Crude model	0.63 (0.16, 1.10)	0.010
Adjusted Model 1	0.57 (0.10, 1.03)	0.018
Adjusted Model 2	0.50 (0.02, 0.99)	0.043
Adjusted Model 3	0.51 (0.01, 1.01)	0.044

Notes: Model 1, adjusted for age; Model 2, adjusted for age, OSA severity and daytime sleepiness; Model 3, adjusted for central obesity, diabetes mellitus and all variables in Model 2.

Abbreviations: HCVR, hypercapnic ventilatory response; CI, confidence interval.

Table 3 The Comparison of Clinical Features Between OSA Patients and OSA Patients with Hypertension

	OSA (n=38)	OSA+HTN (n=39)	*P* value
Age, years	41.5 ± 8.5	43.9 ± 9.6	0.253
BMI, kg/m^2	26.4 ± 3.0	28.9 ± 4.4	0.005
BMI ≥ 28kg/m^2, %	11 (28.9%)	20 (51.3%)	0.046
Neck circumference, cm	40.0 (37.0, 41.0)	41.0 (39.0, 42.5)	0.026
WC, cm	96.5 ± 9.6	100.6 ± 11.2	0.092
WC ≥ 90cm, %	30 (78.9%)	34 (87.2%)	0.335
FEV1%predicted, %	99.0 ± 9.1	94.3 ± 10.3	0.038
FVC %predicted, %	101.9 ± 8.4	95.8 ± 10.3	0.006
FEV1/FVC, %	79.9 ± 4.0	80.7 ± 4.7	0.450
HCVR, L/min/mmHg	2.1 (1.6, 3.0)	3.0 (2.2, 3.7)	0.009
AHI, /h	27.2 (12.4, 54.7)	43.3 (21.2, 62.7)	0.101
AHI ≥ 15/h, %	24 (63.2%)	32 (82.1%)	0.063
OAI, /h	19.4 (4.3, 45.7)	28.1 (10.1, 56.2)	0.144
CAI, /h	0 (0, 0.3)	0 (0, 0.4)	0.724
ODI, /h	20.8 (8.3, 50.6)	37.7 (14.5, 63.6)	0.026
$LSpO_2$, %	85.5 (79.0, 88.0)	81.0 (73.0, 85.5)	0.019
T_{90},%	0.1 (0, 1.7)	1.8 (0.3, 10.5)	0.005
TST, min	410.9 (373.0, 450.6)	417.4 (367.3, 455.3)	0.866
Stage 1, %TST	7.4 (4.7, 13.0)	7 (5.1, 11.8)	0.988
Stage 2, %TST	44.1 (36.9, 54.5)	58.0 (39.9, 68.2)	0.099
Stage 3, %TST	26.2 ± 13.0	23.2 ± 17.3	0.398
Stage REM, %TST	16.8 ± 6.2	14.2 ± 6.3	0.067
ESS ≥ 11, %	23 (60.5%)	21 (53.8%)	0.554
PSQI > 5, %	26 (68.4%)	28 (71.8%)	0.746
DM, %	2 (5.3%)	8 (20.5%)	0.087

Abbreviations: BMI, body mass index; WC, waist circumference; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; HCVR, hypercapnic ventilatory response; AHI, apnea-hypopnea index; OAI, obstructive apnea index; CAI, central apnea index; ODI, oxygen desaturation index; $LSpO_2$, lowest values of peripheral blood oxygen saturation; T_{90}, percent of time spent at peripheral blood oxygen saturation beneath 90%; TST, total sleep time; REM, rapid eye movement; ESS, Epworth Sleepiness Scale; PSQI, Pittsburgh Sleep Quality Index; HTN, hypertension; DM, diabetes mellitus.

Table 4 The Comparison of HRV Variables Between OSA Patients and OSA Patients with Hypertension

	OSA (n=38)	OSA+HTN (n=39)	*P* value
Mean heart rate, bpm	71.9 ± 9.5	74.6 ± 10.0	0.225
RMSSD, ms	20.4 (14.0, 31.5)	15.3 (10.2, 22.5)	0.018
SDNN, ms	26.4 (21.3, 37.7)	21.3 (14.7, 29.1)	0.014
pNN50, %	1.3 (0, 10.9)	0.3 (0, 2.5)	0.082
ln VLF, ms^2	4.31± 1.3	3.6 ± 1.2	0.019
ln LF, ms^2	5.8 ± 1.0	5.3 ± 1.2	0.071
ln HF, ms^2	5.3 ± 1.3	4.4 ± 1.3	0.004
LFnu	60.5 ± 19.0	68.8 ± 20.0	0.064
HFnu	38.0 (27.4, 51.8)	26.0 (16.5, 45.7)	0.038
LF/HF ratio	1.6 (0.9, 2.6)	2.8 (1.2, 5.1)	0.038
ApEn	1.1 ± 0.1	1.1 ± 0.1	0.803
SampEn	1.6 ± 0.2	1.5 ± 0.2	0.314

Abbreviations: HRV, heart rate variability; OSA, obstructive sleep apnea; HTN, hypertension; SDNN, standard deviation of R-R intervals; RMSSD, square root mean squared differences between successive R-R intervals; pNN50, the percentage of adjacent R-R intervals with a difference greater than 50 ms; VLF, very low-frequency range; LF, low-frequency range; HF, high-frequency range; LFnu, normalized LF power; HFnu, normalized HF power; ApEn, approximate entropy; SampEn, sample entropy.

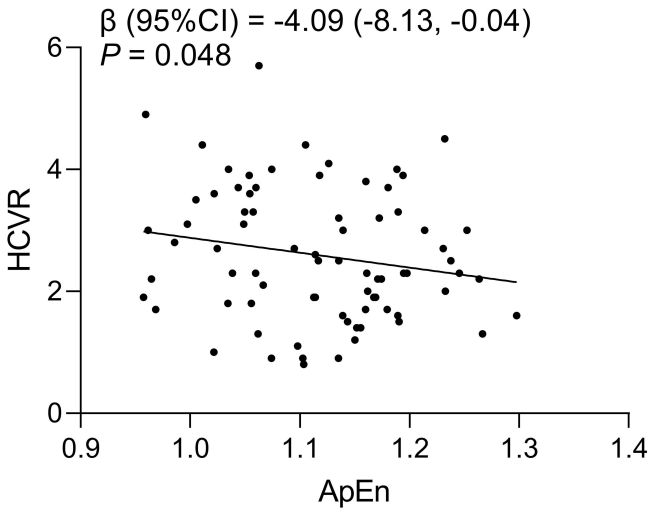

Figure 2 The association between ApEn and HCVR in OSA patients with hypertension.
Abbreviations: ApEn, approximate entropy; HCVR, hypercapnic ventilatory response; OSA, obstructive sleep apnea; CI, confidence interval.

and altered central chemoreflex requires further study. Furthermore, patients with OSA combined with diabetes[41] and metabolic syndrome[42] also had increased HCVR. In this study, we also found the elevated HCVR in OSA patients with hypertension after adjusting for age, central obesity, OSA severity, diabetes mellitus, and daytime sleepiness.

HRV analysis is an applicable approach to measure autonomic nerve activity. In HRV analysis, time-domain variables (RMSSD and pNN50) and frequency-domain variable (HF) are associated with parasympathetic preponderance. In this study, OSA patients with hypertension had lower RMSSD, ln HF, and HFnu values than OSA patients, which indicated decreased parasympathetic activity in the former. LF and LF/HF ratio are often used to reflect the sympathetic activity. LF reflected a mixture of sympathetic activity, parasympathetic activity, and other factors.[43] In this study, there was no significant difference in lnLF or LFnu between the two groups. Moreover, we found a higher LF/HF ratio in OSA patients with hypertension. However, Billman[43] demonstrated that it was inappropriate to interpret increased LF/HF ratio as reflective of sympathetic overactivity. Thus, there was no adequate evidence to support increased sympathetic nerve activity in OSA patients with hypertension in this study. On the other hand, SDNN directly reflects the autonomic nerve activity, and diminished values of SDNN revealed a poor prognosis in patients with cardiovascular disease.[44] In this study, OSA patients with hypertension also showed unadaptable autonomic nerve activity and an intensive risk of cardiovascular events, according to the diminished values of SDNN. Moreover, in this study, OSA patients with hypertension had lower lnVLF. VLF is not a direct marker of sympathetic or parasympathetic activity. Previous studies found that VLF is related to the activity of the renin-angiotensin system.[45] This system plays a vital role in regulating the progression of hypertension.[46]

Coupling between ventilation and sympathetic activity was reported in chronic intermittent hypoxia rats[47] and spontaneously hypertensive rats.[48] This study preliminarily explored the association between central chemosensitivity and autonomic nerve activity in OSA patients with hypertension. In this study, we found a negative relationship between ApEn and HCVR in OSA patients with hypertension. In terms of HRV, entropy is used to interpret the complexity of fluctuations in R-R intervals. Raised entropy indicates greater adaptability of the autonomic nervous system.[49] Moreover, ApEn and SampEn were decreased when the sympathetic nerves were activated,[50] or parasympathetic nerves were depressed.[51] However, we did not find a significant relationship between SampEn and HCVR, which might have been due to the different theoretical ideas behind ApEn and SampEn.[52] Thus, overactivity of the central chemoreceptors might be related to weak adaptability of the cardiac autonomic nervous system.

Strong evidence has demonstrated that elevated peripheral chemosensitivity contributes to excessive activation of the sympathetic nervous system.[53] We described for the first time the relationship among hypertension, autonomic nerve activity, and central chemosensitivity in patients with OSA. Owing to the heterogeneity of OSA and the limited available

therapies for OSA, the pharmacological remedies targeted at ventilatory chemoreflex might reduce the severity of OSA, the morbidity of cardiovascular disease, and mortality. However, several limitations of our study should be noted. First, this was a cross-sectional study, so conclusions on the causality between central chemosensitivity and hypertension could not be drawn. There are also many etiologies and types of hypertension, so more studies are needed to analyze the correlation between HCVR and different causes of hypertension. More studies are also needed to verify the relationship between central chemosensitivity and cardiovascular prognosis in patients with OSA. Second, the mechanism of ventilatory control is convoluted, which might be influenced by ethnicity, sex, and age. However, this study included only Chinese men. Thus, large real-world studies are needed and a simpler method to measure ventilatory chemosensitivity is also required for future research.

Conclusion

Compared with patients with OSA, OSA patients with hypertension had higher central chemosensitivity. OSA patients with hypertension also had attenuated parasympathetic nerve activity compared with OSA patients. Moreover, this study preliminarily illustrated that elevated central chemosensitivity might be associated with weak adaptability of the cardiac autonomic nervous system in OSA patients with hypertension.

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Disclosure

Dr Xiaona Wang reports a patent for a device for measuring ventilatory control based on hypercapnic ventilatory response issued to ZL 2021 2 1127108.9. The authors declare that no financial or other relationships might lead to a conflict of interest in the present article.

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