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Research Paper

The Association between the Phenotype of Excessive Daytime Sleepiness and Blood Pressure in Patients with Obstructive Sleep Apnea-Hypopnea Syndrome

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Abstract

Objective Investigate the clinical features and the blood pressure (BP) pattern of the phenotype of excessive daytime sleepiness (EDS) in OSAHS.

Methods A total of 508 Chinese adults with suspected OSAHS were referred to our sleep laboratory from October 2009 to May 2012. On the same night of polysomnography (PSG), the levels of blood pressure were measured before sleeping (bedtime BP) and immediately after waking up in the next morning (morning BP). EDS was recognized as Epworth Sleepiness Scale (ESS)≥9. Subjects were classified into four groups based on the apnea-hypopnea index (AHI) from PSG as follows: control (simple snoring) group (control, n=104) with AHI<5; mild group (mild, n=89) with AHI≥5 and <15; moderate group (moderate, n=70) with AHI≥15 and<30; and severe group (severe, n=245) with AHI ≥30. The differences and correlations between BP and PSG parameters in EDS and non-EDS group of OSAHS patients were analyzed.

Results In all subjects, ESS was positively correlated with morning diastolic blood pressure (DBP), Mean arterial pressure (MAP) and bedtime DBP (r=0.144, 0.102 and 0.114, respectively, each P value<0.05). In OSAHS patients, ESS was only positively correlated with morning DBP (r=0.137, P<0.05). OSAHS patients with EDS phenotype were younger and were more likely to have the symptom of waking up feeling tired (36.1% vs. 23.2%, p=0.023), who had lower MSaO2, longer SIT90 (the ratio of time of SpO2 below 90% in total sleep time) and higher DBP (bedtime as well as morning). In patients with AHI≥15, ESS was correlated positively with both bedtime and morning DBP after controlling the confounding effects of age, sex, BMI, AHI and nadir nocturnal oxygen saturation(r=0.126,0.143, respectively, both P values<0.05). And in OSAHS patients of EDS phenotype, the bedtime DBP, bedtime MAP, morning DBP, and morning MAP were 3~5 mm Hg higher than that in patients of non-EDS phenotype(P<0.05). In the moderate and severe OSAHS group, patients with EDS phenotype were younger and had a lower mean blood oxygen saturation (MSaO2), longer time of SpO2 below 90% and higher SIT90 than patients with non-EDS phenotype (P<0.05). In hypertensive OSAHS patients, patients with EDS were also younger and had higher micro-arousal index (MiI), as well as higher morning DBP, morning MAP and bedtime DBP than that in non-EDS group (P<0.05).

Conclusions EDS in OSAHS patients is a special phenotype, which was characterized by younger age, higher DBP and more severe hypoxic load. This feature is mainly manifested in moderate and severe OSAHS patients. It is very important to identify the phenotype of EDS in patients with OSAHS, who may meet more benefits from effective treatment of OSAHS by correcting the intermittent nocturnal hypoxia and sleep fragmentation.

Key words: Obstructive sleep apnea hypopnea syndrome (OSAHS); Epworth sleepiness scale (ESS); excessive daytime sleepiness (EDS); Blood pressure (BP); AHI; Chinese adults.

Introduction

Obstructive sleep apnea-hypopnea syndrome (OSAHS) is characterized by repeated episodes of apnea or hypopnea during sleep leading to oxygen desaturation and/or arousal, and is associated with daytime sleeping. OSAHS has been drawing more attention as an important cause of medical morbidity and mortality in recent years. The clinical manifestations of OSAHS appear to be heterogenous. Excessive daytime sleepiness (EDS) is one of well recognized symptoms of OSAHS, increasingly considered a significant public health problem which is not only because of effects on cognitive function and workplace performance, but also because of accumulated evidence that in the presence of OSAHS, EDS is associated with an increased risk of hypertension [1,2], glucose deregulation [3,4], and all-cause mortality [5] in older adults. But not all the patients diagnosed by PSG have EDS. From a retrospective, cross-sectional study, EDS proved to be highly prevalent (87.2%) among OSAHS patients, among whom 52.3% had severe and 34.9% had moderate EDS [6]. Several publications showed EDS in patients with OSAHS has relationship with different patterns of blood pressure. In non-EDS hypertensive patients with OSAHS, after continuous positive airway pressure (CPAP) therapy, there was no significant fall in mean 24-h blood pressure, in contrast to the fall seen in EDS patients with OSAHS [7,8]. Kapur et al. found that the association of OSAHS with hypertension was stronger in individuals who reported daytime sleepiness than in those who did not [1].

Therefore, we hypothesized that OSAHS accompanied by EDS was a special phenotype, which was characterized by certain clinical features, particularly its links with hypertension. Identification of the phenotype that characterizes OSAHS in individual patients could be diagnostically and therapeutically useful, as causative mechanisms, long-term outcomes and treatment response may vary across different OSAHS subtypes. In this context, we studied the clinical characteristics, blood pressure variations and polysomnography (PSG), in order to elucidate clinical features of the phenotype of EDS in the presence of OSAHS and the correlations between the phenotype and BP.

Methods

Patients

A total of 512 consecutive patients with suspected OSAHS underwent full-night PSG from October 2009 to May 2012 were recruited in the study. Four patients were excluded because of incomplete information. Finally, 508 patients (aged 20–83 years, 387 men and 121 women) entered this retrospective study. All study procedures were approved by ethics committee of Peking University First Hospital.

Physical examination and sleep questionnaires

All subjects underwent a detailed clinical interview with a questionnaire pertaining to symptoms of SDB, medical history, sleep habits and other sleep disorders, as well as the Epworth sleepiness scale (ESS)[9,10]. The ESS assesses the general level of daytime sleepiness by having individuals evaluate the likelihood of drowsiness during eight different daytime situations. Scores ≥9 are considered to be excessive daytime sleepiness (EDS), otherwise, to be non-EDS (scores 0–8).The general information was recorded, such as age, sex, body mass index (BMI), abdomen circumference (AC) and neck circumference (NC).

Polysomnography and parameters

Each subject underwent overnight PSG in sleep laboratory. The following parameters were continuously recorded: electroencephalography, electrooculography, electromyography of chin muscles, electrocardiography, and oxygen saturation (pulse oximeter). Respiratory effort was measured by thoracoabdominal strain gauges and oronasal airflow (thermistor signals and pressure cannula).

All procedures were performed by experienced technicians. All computerized sleep data were further manually analyzed by permanent professional staffs. Sleep staging was performed according to the rules of the American Academy of Sleep Medicine [11]. Apnea was defined as a cessation of airflow for at least 10 seconds, and hypopnea was defined as a reduction in the amplitude of respiratory flow signal of at least 50% for a minimum of 10 seconds accompanied by a 4% drop in oxygen saturation. The apnea-hypopnea index (AHI) is the total number of apneas and hypopneas per hour of actual sleep time. The other respiratory variables consisted of the longest time of apnea (TAmax) and the longest time of hypopnea (THmax).The oxygen desaturation index (ODI) was defined as the total number of dips in SpO2 ≥4% per hour of sleep.Time of SpO2 below 90% and its ratio in TST (SIT90), mean blood oxygen saturation (MSaO2) and lowest SpO2 (%) was also calculated. Micro-arousal index (MiI) was defined as the total number of micro-arousal per hour of sleep.

In this study, disease severity was assessed by AHI. The study population was classified into four groups: snoring group (AHI<5), mild sleep apnea

group (AHI ≥ 5 and <15), moderate sleep apnea group (AHI ≥15 and <30), and severe sleep apnea group (AHI ≥ 30) [12].

BP measurements

Each subject had their BP assessed when they were referred to the sleep laboratory. Bedtime BP was taken after a 30-minute rest before sleep.Morning BP was taken immediately after waking up. The average of BPs on three consecutive readings was used for the analysis. Mean arterial pressure (MAP) was defined as (systolic BP−diastolic BP)/3 + diastolic BP in mm Hg. Hypertension was defined as systolic BP (SBP) of at least 140 mm Hg, diastolic BP (DBP) of at least 90 mm Hg, or existing hypertensive history (ever diagnosed by physicians and/or current treatment with antihypertensive medications).

Statistical analysis

The statistical analysis was performed by SPSS 17.0 for windows (SPSS Inc, USA). Anthropometry, PSG parameters and ESS in 508 patients were collected and showed as a descriptive analysis. The descriptive statistics of skewed distribution samples were expressed as median (minimum–maximum), and values of normal distribution were reported as mean ± standard deviation (SD).One way analysis of variance (ANOVA) was used for whole difference and Bonferroni post hoc multiple comparisons were used for differences between groups.The Kruskal-Wallis ranksumtestwas suitable for the data of abnormal distributions. Mann–Whitney test for continuous variables that were not normally distributed. Linear correlation analysis and linear fitting were performed for influential power estimating. To eliminate effects from related confounders, we performed partial correlations between target variables. The chi-square tests were used to analyze the frequencies.

Results

Anthropometric and PSG data

There were 508 subjects (aged 20–83 years, 387 men and 121 women) who were analyzed, with a mean age of (50.0±13.0), BMI of (27.5±4.1) kg/m^2, and ESS of (11.2±5.4). Totally 67.8% (229 in 338) OSAHS patients presented EDS, and 56.1% (285 in 508) patients had hypertension. Bivariate correlations showed ESS was positively correlated with AHI, MiI and ODI, and negatively correlated with lowest SpO2 (r=0.174, 0.161, 0.166 and -0.201, respectively, and each P value<0.001). ESS was higher in severe group than that in mild group. OSAHS patients exhibited higher ESS than simple snoring patients (control).

Different blood pressure pattern in subjects with different severity

All subjects were divided into four groups: simple snoring group (AHI<5, n=104), mild sleep apnea group (AHI ≥ 5 and <15, n=89), moderate sleep apnea group (AHI ≥15 and <30, n=70), and severe sleep apnea group (AHI ≥ 30, n=245). Table 1 summarizes the characteristics of the four groups. It is certain that there were significant differences in the parameters of the oxygen saturation and respiratory events among the four groups. Patients with more severe degree have larger BMI, longer neck and abdominal circumferences as well as more severe EDS. The seven parameters of blood pressure (bedtime SBP, bedtime DBP, bedtime MAP, morning SBP, morning DBP, morning MAP and ΔSBP) were different among the four groups, although slight, but statistically significant. Especially, the severe group has the highest BP and the largest ΔSBP (morning SBP minus bedtime SBP).

Different blood pressure pattern in different phenotype of EDS in all OSAHS patients

There was no statistical difference found in sex, BMI, AHI, ODI, MiI and the symptom of waking up with dry mouth between EDS group and non-EDS group in OSAHS patients. More OSAHS patients with EDS experienced the symptom of waking up feeling tired (36.1% vs. 23.2%, P=0.023). OSAHS patients with EDS phenotype were younger than those with non-EDS phenotype and had lower MSaO2, higher SIT90 and higher DBP (bedtime as well as morning) (Table 2).

Bivariate correlations were performed between ESS and BPs. In all subjects, ESS was positively correlated with bedtime DBP, morning DBP, and MAP (r=0.114, 0.144, and 0.102, respectively, each P value<0.05). In all the OSAHS patients, ESS was only positively correlated with morning DBP (r=0.137, P<0.05). In mild OSAHS patients, ESS was negatively correlated with bedtime SBP (r=-0.326, P=0.004). In OSAHS subjects with AHI≥15, ESS was positively correlated with morning DBP (r=0.172, P <0.05), morning MAP (r=0.130, P <0.05) and bedtime DBP (r= 0.146, P value<0.05). In order to eliminate confounder effects from age, sex, BMI, AHI and lowest SpO2, we performed partial correlations between ESS and BPs, which showed that ESS was positively correlated with bedtime and morning DBP(r=0.126 and 0.143, P <0.05).

To diminish the effects of disease severity on the BPs pattern, we made subgroup analysis in each severity. In patients with AHI≥15, bedtime DBP, bedtime MAP, morning DBP, and morning MAP were 3~5 mm Hg higher in EDS group than that in

non-EDS patients(P<0.05). In the same group, patients with EDS phenotype were younger and had a lower MSaO2 and higher SIT90 than non-EDS patients (P<0.05). (Table 3). Patients with AHI<15 did not present this kind of difference.

Table 1. Characteristics of subjects according to disease severity (n=508).

	Snoring(n=104)	Mild OSAHS (n=89)	Moderate OSAHS (n=70)	Severe OSAHS (n=245)	P-Value
Gender(male/female)	67/37	59/30	51/19	210/35	0.000
Age (years)	47.98±13.60	50.03±11.62	50.64±12.52	50.62±13.32	0.358
NC (cm)	38.25(30.00-48.0)	40.00(30.0-48.00)	40.00(29.00-56.00)[a]	42.00(10.00-57.00)[a□]	0.000
AC (cm)	95.00(15.00-121.00)	96.00(76.00-123.00)	99.00(71.00-134.00)[a]	103.25(17.00-160.0)[a□]	0.000
BMI (kg/m²)	25.10(17.10-33.40)	25.6(19.10-36.70)	27.45(15.60-38.90)[a]	28.40(16.00-43.90)[a□]	0.000
ESS (points)	9(0-24)	9(0-21)	10(2-21)	12(1-24)[a□]	0.002
AHI (everts/h)	1.40(0-4.90)	9.40(5.0-14.9)[a]	22.50(15.50-29.80)[a□]	60.60(30.50-117.40)[a□※]	0.000
Lowest SpO2 (%)	89.0(73.00-96.00)	85.00(65.0-95.0)[a]	80.00(63.00-95.00)[a□]	68.00(62.00-95.00)[a□※]	0.000
MSaO2 (%)	95.00(59.0-98.00)	94.00(65.0-95.0)	94.00(87.00-96.00)	91.00(74.00-97.00)[a□※]	0.000
TAmax (s)	20.30(0-98.70)	38.30(10.30-88.5)	36.85(13.00-123.70)[a□]	63.50(11.80-152.70)[a□※]	0.000
THmax (s)	23.00(0-120.40)	27.60(15.30-76.80)	28.80(15.60-97.30)[a]	36.20(14.80-106.20)[a□※]	0.000
SIT90 (%)	0.09(0-92.45)	0.85(0.97-55.0)[a]	4.58(0.05-66.73)[a□]	24.23(0.45-90.25)[a□※]	0.000
MiI (everts/h)	18.15(0.55-8.00)	22.45(0-51.30)	23.6(0-55.70)[a]	35.70(0-106.70)[a□※]	0.000
ODI (everts/h)	2.20(0-75.9)	8.70(1.60-51.90)[a]	20.90(0.80-33.60)[a□]	53.40(0.90-161.40)[a□※]	0.000
Bedtime SBP (mmHg)	120.71±14.83	124.20±14.26	123.74±13.68	126.49±15.30 [a]	0.014
Morning SBP (mmHg)	122.97±16.39	128.28±14.58	129.12±15.88	133.39±17.81 [a]	0.000
Bedtime DBP (mmHg)	77.00±10.45	80.14±10.292	79.93±10.31	83.39±10.01 [a]	0.000
Morning DBP (mmHg)	81.35±10.23	84.79±11.63	85.01±11.67	88.81±11.10 [a□]	0.000
Bedtime MAP (mmHg)	91.55±10.97	94.82±10.68	94.82±9.99	97.75±10.59 [a]	0.000
Morning MAP (mmHg)	95.22±11.62	99.29±11.02	99.72±11.89	103.67±11.95 [a□]	0.000
ΔSBP (mmHg)	2.51±12.00	4.08±8.58	5.85±10.29	6.89±13.04	0.027
ΔDBP (mmHg)	4.79±8.57	4.66±10.20	5.40±8.46	5.37±9.03	0.901
ΔMAP (mmHg)	4.03±8.81	4.46±8.17	5.60±7.89	5.88±9.19	0.290

[a] P < 0.05 for the comparison with control groups; □P < 0.05 for the comparison with mild group; ※P < 0.05 for the comparison with moderate group; NC: neck circumference. AC: abdomen circumference. BMI: body mass index. AHI: apnea-hypopnea index. ESS Epworth Sleepiness Scale. MSaO2: mean blood oxygen saturation. TAmax: longest time of apnea. THmax: the longest time of hypopnea. SIT90: the ratio of time of SpO2 below 90% in total sleep time ; MiI: micro-arousal index. ODI: oxygen desaturation index. DBP: diastolic blood pressure; MAP: mean arterial pressure; SBP: systolic blood pressure; SDB: sleep disordered breathing; ΔMAP: morning MAP minus bedtime MAP; ΔBP: morning BP minus bedtime BP; ΔSBP: morning SBP minus bedtime SBP; ΔDBP: morning DBP minus bedtime DBP.

Table 2. Demographic, Polysomnographic and BP pattern in OSAHS Patients with different phenotype of EDS.

	EDS (ESS≥9) N=229	non-EDS (ESS<9) N=109	p-Value
Gender(male/female)	184/45	79/30	0.104
Age (years)	48.80±12.70	53.00±12.30	0.002*
NC (cm)	41.00(10.00-56.00)	41.00(29.00-52.00)	0.407
AC (cm)	102.00(17.00-160.00)	99.00(71.00-160.00)	0.189
BMI (kg/m²)	28.00(19.40-43.90)	27.10(15.60-40.10)	0.090
ESS (points)	13(9-24)	6(0-8)	<0.001*
AHI (everts/h)	42.00(5.00-117.40)	32.40(5.00-94.80)	0.072
Lowest SpO2 (%)	74.00(60.00-95.00)	79.00(60.00-95.00)	0.095
MSaO2 (%)	92.00(74.00-98.00)	93.00(62.00-97.00)	0.019*
TAmax (s)	51.50(11.8-132.10)	40.50(10.30-129.60)	0.055
THmax (s)	32.60(14.80-106.20)	30.40(15.60-60.90)	0.243
SIT90 (%)	14.20(0-84.12)	8.66(0-97.55)	0.047*
MiI (everts/h)	30.85(0-106.70)	29.30(0-67.00)	0.170
ODI (everts/h)	38.40(0.9-161.40)	35.10(4.00-99.20)	0.405
Bedtime SBP (mmHg)	125.64±14.96	125.18±12.87	0.784
Bedtime DBP (mmHg)	82.73±10.53	80.07±9.04	0.019*
Morning SBP (mmHg)	131.52±17.12	130.22±14.73	0.505
Morning DBP (mmHg)	88.45±12.30	84.59±9.52	0.002*
Bedtime MAP (mmHg)	97.04±10.94	95.30±8.82	0.124
Morning MAP (mmHg)	102.81±12.61	99.80±9.48	0.018*
Waking up feeling tired	79(36.1%)	23(23.2%)	0.023*
Waking up with dry mouth	143(66.5%)	59(56.7%)	0.069

* P < 0.05. EDS: excessive daytime sleepiness. NC: neck circumference. AC:abdomen circumference. BMI: body mass index. AHI: apnea-hypopnea index. ESS: Epworth Sleepiness Scale. MSaO2: mean blood oxygen saturation. TAmax: longest time of apnea. THmax: the longest time of hypopnea. SIT90: the ratio of time of SpO2 below 90% in total sleep time. MiI: micro-arousal index. ODI: oxygen desaturation index. SBP: systolic blood pressure. DBP: diastolic blood pressure. MAP: mean arterial pressure.

Table 3. Demographic, Polysomnographic and BP Data for EDS Versus non-EDS in Patients with AHI≥15(positive results except AHI presented).

	EDS (ESS≥9) N=183	non-EDS (ESS<9) N=78	P-Value
Age (years)	49.00±12.90	53.00±13.10	0.023*
ESS (points)	14(9-24)	6(1-8)	<0.001*
AHI (everts/h)	51.90(15.50-117.40)	51.75(15.90-94.80)	0.279
MSaO2 (%)	92.00(74.00-96.00)	93.00(74.00-97.00)	0.022*
SIT90 (%)	21.12(0.05-84.12)	15.60(0.15-90.25)	0.025*
Evening DBP (mmHg)	83.25±10.30	79.86±9.55	0.012*
Morning DBP (mmHg)	89.39±11.68	84.51±10.09	0.002*
Evening MAP (mmHg)	97.72±10.62	94.91±9.31	0.047*
Morning MAP (mmHg)	103.85±12.44	99.72±9.89	0.012*

* P < 0.05. EDS: excessive daytime sleepiness. ESS: Epworth Sleepiness Scale. AHI: apnea-hypopnea index. MSaO2: mean blood oxygen saturation. SIT90: the ratio of time of SpO2 below 90% in total sleep time. DBP: diastolic blood pressure. MAP: mean arterial pressure.

Table 4. Demographic,Polysomnographic and BP Data for different phenotypes of EDS in patients with OSAHS and Hypertension(positive results except AHI presented).

	EDS (ESS≥9) N=146	non-EDS (ESS<9) N=60	P-Value
Age (years)	49.20±13.00	54.10±12.30	0.013*
ESS (points)	13.5(9-24)	6(0-8)	<0.001*
AHI (everts/h)	40.08(5.20-117.40)	39.15(5.80-94.80)	0.254
MiI (everts/h)	32.30(0-106.70)	27.80(0-67.00)	0.021*
Bedtime DBP (mmHg)	86.57±10.23	83.10±9.69	0.026*
Morning DBP (mmHg)	94.17±11.01	88.80±9.50	0.001*
Morning MAP (mmHg)	109.23±10.22	105.41±7.75	0.010*

* P < 0.05. EDS: excessive daytime sleepiness. ESS: Epworth Sleepiness Scale. AHI: apnea-hypopnea index.MiI: micro-arousal index. DBP: diastolic blood pressure. MAP: mean arterial pressure.

Different blood pressure pattern in different phenotype of EDS in the patients with OSAHS as well as hypertension

In all the patients suffered from OSAHS and hypertension at the same time, morning DBP, morning MAP and bedtime DBP in EDS group were higher than that in non-EDS group (P<0.05). Similarly, those hypertensive OSAHS patients with EDS were younger and had higher MiI than those without EDS (both P values<0.05). (Table 4).

In patients with hypertension and mild OSAHS, EDS subjects were younger, but had lower AHI, ODI and value of lowest SpO2, each P value<0.05. There was no significant difference of BP valuables between EDS and non-EDS patients.

In patients with hypertension and moderate to severe OSAHS, morning DBP and morning MAP were 5.69 mm Hg and 4.35 mm Hg higher in EDS subjects than that in non-EDS patients, respectively (P<0.05).

Correlation analysis between BPs and PSG parameters

In all subjects, ΔMAP(morning MAP minus bedtime MAP) was positively correlated with AHI, age, BMI and ODI,and negatively correlated with lowest SpO2, r=0.096, 0.107, 0.094, 0.108 and-0.10, respectively, and all P values<0.05. ΔSBP (morning SBP minus bedtime SBP) was positively correlated with AHI(r=0.148, P<0.05), age(r=0.181, P<0.05), BMI(r=0.154, P<0.05),ODI(r=0.163, P<0.05)and SIT90(r=0.137, P<0.05), and negatively correlated with lowest SpO2(r=-0.157, P<0.05) and MSaO2(r= -0.118, P<0.05).

In all OSAHS patients, ΔSBP was positively correlated with age (r=0.178, P <0.05) and BMI (r=0.107, P <0.05), and negatively correlated with lowest SpO2 (r= -0.104, P <0.05).

In patients with OSAHS and hypertension, ΔSBP was positively correlated with age(r=0.252, P<0.05) and AC(r= 0.171, P <0.05).

Subgroup analysis: All subjects were divided into four groups by AHI. In each group, correlation analysis was performed, with ΔBP (morning BP minus bedtime BP) as dependent variables and PSG parameters as independent variables.

1. In simple snoring subjects, ΔBP especially ΔSBP was positively correlated with MiI, r=0.450, P values<0.05. This gives us a hint that, frequent micro-arousals may be an important factor affecting the nocturnal changes of BP, especially the SBP, in non-OSAHS patients.

2. In mild OSAHS patients, ΔSBP was positively correlated with BMI(r=0.281, P <0.05) and negatively correlated with lowest SpO2(r= -0.225, P <0.05). ΔMAP was positively correlated with ODI(r=0.260, P <0.05).

3. In moderate OSAHS patients, linear fitting with ESS and ΔDBP (morning DBP minus bedtime DBP) showed a positive correlation (r^2=0.0095,

ΔDBP=0.565*ESS-0.011, P < 0.05).

4. No significant difference of correlation analysis of ΔBP and PSG parameters was found in severe OSAHS patients.

Discussion

According to the population-based studies, the prevalence of obstructive sleep apnea associated with accompanying daytime sleepiness is approximately 3% -7% of adult men and 2%- 5% of adult women in the general population, and disease prevalence is higher in certain population subsets, such as obese or elderly people [13].Numerous epidemiological data collected in community populations have provided convincing evidences for the independent and definite association between OSA and hypertension [14,15]. The seventh report of the Joint National Committee identified OSA as a secondary cause of hypertension [16]. In severe OSAHS patients without EDS, CPAP failed to reduce the arterial blood pressure [7]. In patients with OSAHS but without EDS, the prescription of CPAP compared with usual care did not result in a statistically significant reduction in the incidence of hypertension or cardiovascular events [17]. EDS was proved to be associated with cardiovascular morbidities and mortalities [18, 19]. Our results showed that OSAHS patients with EDS, who were younger and more likely to have the symptom of waking up feeling tired, had higher DBP and heavier load of nocturnal hypoxia than those without EDS, especially in patients with moderate to severe OSAHS. Therefore, we believe that EDS is not only an important symptom but also a special phenotype in OSAHS with certain clinical characteristics, especially with respect to complications.

In this study, patients with more severe OSAHS showed more severe EDS and had more high bedtime as well as daytime BP. Bivariate correlations demonstrated that ESS was positively correlated with AHI, MiI and ODI in all subjects. Further analysis showed that OSAHS patients with EDS were younger and had lower MSaO2, higher SIT90, and higher DBP than those without EDS. In subset group with moderate to severe OSAHS, ESS was positively correlated with morning and bedtime DBP. Thus we can describe such a special group of OSAHS patients with EDS who present more severe nocturnal oxygen desaturation as well as higher BP, especially DBP. Previous studies showed that OSAHS patients have a higher prevalence of diastolic hypertension than that of systolic hypertension [20, 21], and the DBP increased earlier than SBP in patients with OSAHS [22]. P. Loberes et al found that only the ESS was associated with 24-h DBP, and patients with EDS showed a significantly higher frequency of diastolic non-dipping pattern in contract with those without EDS [23]. Baguet et al. showed that in newly diagnosed OSAHS patients without previous history of hypertension, isolated diastolic hypertension was very common[20].These suggest that the special state of sleep in OSAHS patients might have different effects on SBP and DBP. The mechanisms of pathogenesis of hypertension in patients with OSAHS are very complicated. Mechanism researches showed that intermittent hypoxia that OSAHS patients experience during sleep resulted in increased peripheral chemoreceptor tonic hyperactivity [24] and sympathetic nervous system activity [25], as well as elevated catecholamine levels [26], which eventually led to higher DBP levels [27]. Previous studies in combination with our results indicate that the OSAHS patients with EDS phenotype have higher DBP than non-EDS, which might be partly due to younger age (with good vascular elasticity) and heavy hypoxic load (severe and long-time nocturnal hypoxia).

There are various determining factors of EDS in OSAHS, but the results are not consistent. A cross-sectional study showed that nocturnal hypoxemia biomarker predicts sleepiness in patients with severe obstructive sleep apnea (AHI>50)[28]. Another study found that OSAHS patients with EDS showed more hypoxemia, but there were no significant differences between OSAHS patients with or without EDS [29]. Some studies suggested that nocturnal hypoxemia and increased sympathetic cardiac tone caused by frequent arousal were key factors responsible for EDS in patients with sleep-disordered breathing [30, 31]. Even more, CPAP treatment for patients with moderate and severe OSA as well as coronary heart diseases can significantly reduce DBP and improved the ESS score [32]. So, there may be some common mechanisms associated with nocturnal intermittent hypoxia in OSAHS linking EDS to elevated DBP which might partly provide explanation for higher DBP levels in OSAHS patients with EDS. It is necessary to take further basic and clinical investigation.

To eliminate the confounder effect from disease severity, we carried out subgroup analysis. In patients with AHI≥15, EDS patients were younger and had a lower MSaO2 and longer SIT90 than non-EDS patients. Moreover, in moderate and severe OSAHS (AHI≥15), DBP and MAP (both bedtime and morning) were 3~5 mm Hg higher in patients with EDS than that in patients without EDS. Such results were not found in mild and control group (simple snoring group). In our study, the more severe of EDS, the higher of AHI, MiI, ODI and more sleep fragmentation. This phenomenon is similar to previous studies, OSAHS patients with the phenotype of EDS were

younger and had a more severe symptoms [33, 34].Younger age and obesity were considered as significant risk factors for EDS in OSAHS patients [35].

To eliminate the disturbance of patients with normal blood pressure, we performed analysis in OSAHS patient with hypertension. EDS patients were also younger and had higher MiI, DBP (both bedtime and morning) and morning MAP. Subgroup analysis in moderate to severe OSAHS patients with hypertension showed similar results. The DBP difference between EDS and non-EDS was small (about 3~5 mm Hg) but significant. Meta-analyses of randomized controlled trials have shown that decreasing of BP is associated with a reduction of 30% to 40% in the cardiovascular events [36, 38]. It is of special importance for the patients with OSAHS and hypertension as well as EDS to accept the effective treatment of OSAHS in order to improve the long-term cardiovascular prognosis.

The manifestation of PSG valuables and BP were different according to the phenotype of EDS in different severity of OSAHS. In moderate and severe patients, statistical difference had been found in MSaO2, SIT90 and lowest SpO2 between EDS and non-EDS. In simple snoring patients, changes in BP were associated with frequent micro-arousals. Sleep fragmentation with arousals was considered as a factor independent of sympathetic activation caused by intermittent hypoxia contributing to blood pressure elevation [39]. In mild OSAHS patients, ΔBP had the trend of positive association with BMI, LSaO2 and ODI, suggesting that obesity and nocturnal oxygen desaturation may contribute more to the BP elevation of mild OSAHS group. Therefore, weight loss would have clinical benefits on the hypertension of OSAHS patients. In moderate OSAHS patients, ΔDBP was correlated positively with ESS. Given that blood pressure is regulated by complicated neurohumoral pathway, the mechanism link of EDS and hypertension need further research. Recently, Grimaldi and colleagues reported [40] the nighttime "non-dipping BP profile" for both systolic and diastolic pressure observed in patients with narcolepsy-cataplexy compared to normal controls. Given that hypocretin play a role in respiratory and cardiac control as well as interaction between sleep and cardiovascular system, authors supposed that may be the result not only of the hypocretinergic deficiency *per se* but also of the altered sleep/wake regulation. Because it was reported that OSAHS patients had lower levels of plasma orexin-A [41] and could be improved by CPAP treatment [42], we suppose this might also contribute to the association between EDS and hypertension in our study of OSAHS.

There were some limitations in our study. Firstly, we just evaluated the subjective EDS by ESS but not the objective measurement by multiple sleep latency tests. Secondly, nearly half of subjects in the study were severe OSAHS patients which may lead to selected bias. Thirdly, single overnight PSG were conducted for each subject, which may result in first night effects (FNE). But our previous study showed that only mild FNE was found in two consecutive nights of PSG in adult Chinese snorers with slightly influence on the division of severity and several EEG parameters but will not change the diagnosis of OSAHS [43]. Fourthly, BP measurements of bedtime and morning cannot reveal the dynamic changes of 24h comprehensively, but they were good indicators for accumulated effects of whole night sleep. The ideal method shall be ambulatory blood pressure monitoring (ABPM), however, it may disturb the sleep on the night of PSG. Fifth, we did not consider insomnia into our variables, which may be in association with hypertension. But all the subjects recruited in this study had no history of severe insomnia.

Conclusion

Our study support EDS in OSAHS patients is a special phenotype characterized by younger age, higher DBP and more severe hypoxic load, which might associated with an increased cardiovascular risk. This feature is mainly manifested in moderate and severe OSAHS patients with EDS. It is very important to identify the phenotype of EDS in patients with OSAHS, because it might be this group of patients who can meet more benefits from effective treatment of OSAHS by correcting the intermittent nocturnal hypoxia and sleep fragmentation.

Abbreviations

AC:abdomen circumference; AHI: apnea-hypopnea index; BMI: body mass index;BP: blood pressure; CPAP: continuous positive airway pressure; DBP: diastolic blood pressure; ESS: Epworth Sleepiness Scale; EDS: excessive daytime sleepiness; MAP: mean arterial pressure; MiI: micro-arousal index; MSaO2: mean blood oxygen saturation; NC: neck circumference; ODI: oxygen desaturation index; OSAHS: Obstructive sleep apnea hypopnea syndrome; PSG: polysomnography; SBP: systolic blood pressure; SDB: sleep disordered breathing; SIT90: the ratio of time of SpO2 below 90% in total sleep time ; TAmax: longest time of apnea; THmax: the longest time of hypopnea; ΔMAP: morning MAP minus bedtime MAP; ΔBP: morning BP minus bedtime BP; ΔSBP: morning SBP minus bedtime SBP; ΔDBP: morning DBP minus bedtime DBP.

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Competing Interests

The authors have declared that no competing interest exists.

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