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## ORIGINAL ARTICLE

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### Effects of Obstructive Sleep Apneas on Endothelial Function and Autonomic Modulation in Adult Man<sup>△</sup>

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**Key words:** obstructive sleep apnea; hypertension; endothelial function; autonomic modulation; sympathetic activity

**Objective** To study the effects of obstructive sleep apneas on endothelial function and autonomic modulation.

**Methods** From June 2009 to June 2011, male patients with obstructive sleep apnea hypopnea syndrome (OSAHS) were consecutively enrolled in this study. Patients with an apnea/hypopnea index (AHI) of greater than 15 and without previous treatment for OSAHS were included as Group OSAHS and obese subjects with an AHI of less than 5 were included as non-OAHS controls (Group Control). Electrocardiography and beat-to-beat blood pressure were continuously recorded from the radial artery by applanation tonometry which was synchronized with polysomnography recording. Endothelial function was measured by arterial augmentation index (AAI). Spectral analysis of heart rate variability (HRV) and blood pressure variability (BPV) were computed for cardiac parasympathetic modulation (high frequency power, HF); sympathetic modulation (low frequency power, LF), sympathovagal balance (LF/HF power of R-R variability, LF/HF) and BPV sympathetic modulation (BPV LF) in normalized units [total power of the components/(total power-very LF power)×100].

**Results** Finally, 27 moderate-severe OSAHS patients and 22 non-OAHS obese controls were recruited in the Group OSAHS and Group Control, respectively. In Group OSAHS, the age was  $43.3 \pm 9.3$  year-old, body mass index (BMI) was  $36.8 \pm 8.7$  kg/m<sup>2</sup>; in Group Control, the age was  $42.9 \pm 8.6$  year-old, BMI was  $34.4 \pm 7.9$  kg/m<sup>2</sup>; there were no significant differences in age and BMI between the Group OSAHS and Group Control (all  $P > 0.05$ ). The baseline AAI ( $12.5\% \pm 2.2\%$  vs.  $8.2\% \pm 2.1\%$ ) and BPV LF ( $68.3\% \pm 13.5\%$  vs.  $61.1\% \pm 11.7\%$ ) of the Group OSAHS were significantly higher than those of the Group Control (all  $P < 0.05$ ). And after overnight sleep, systolic BP ( $143.7 \pm 14.2$  vs.  $132.8 \pm 13.3$  mm Hg), diastolic BP ( $87.7 \pm 7.7$  vs.  $78.6 \pm 5.5$  mm Hg), HRV LF ( $69.7\% \pm 14.4\%$  vs.  $64.3\% \pm 12.1\%$ ), HRV LF/HF ( $3.7 \pm 2.0$  vs.  $2.3 \pm 1.3$ ) and BPV LF ( $77.8\% \pm 15.6\%$  vs.  $68.3\% \pm 13.5\%$ ) of the Group OSAHS were significantly increased (all  $P < 0.001$ ), while HRV HF was significantly decreased ( $21.1\% \pm 9.3\%$  vs.  $27.5\% \pm 10.3\%$ ,  $P < 0.05$ ) from baseline.

**Conclusions** The baseline endothelial function and autonomic modulation are impaired in OSAHS patients, which happened prior to hypertension and other cardiovascular complications. And the load effects of overnight obstructive breathing events could induce blood pressure and sympathetic activity increasing in the morning in OSAHS patients without acute aggravation in endothelial dysfunction.

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**O**BSTRUCTIVE sleep apnea hypopnea syndrome (OSAHS) has been linked to long-term cardiovascular morbidity and mortality.<sup>1-4</sup> The prevalence of hypertension in OSAHS patients is 50%-60%, and that of heart failure is 11%-37%, and OSAHS prevalence in stroke patients is 64% or 77% in female and male respectively, but the mechanism is not very clear. Arterial endothelial dysfunction and sympathetic nerve activity increasing are independent risk factors of cardiovascular morbidity and mortality, and also could be the primary causes of cardiovascular morbidity and mortality increasing in OSAHS.

Repetitive obstructive breathing events and recurrent arousals are the basic pathophysiological changes in OSAHS. We have demonstrated that obstructive breathing events could cause temporary arterial endothelial dysfunction in OSAHS patients which happened prior to blood pressure increasing,<sup>5, 6</sup> so we presume that the baseline arterial endothelial function in OSAHS is also dysfunctional, but this was not proved yet. We have also previously demonstrated that acute sleep deprivation could cause sympathetic nerve activity increasing in health subjects,<sup>7, 8</sup> and chronic sleep deprivation due to recurrent arousals is very common in OSAHS patients, so we presume that sympathetic nerve activity also increases in OSAHS patients.

The purposes of our study are to evaluate the independent effects of OSAHS on vascular endothelial function and autonomic modulation: firstly, to assess the difference between OSAHS patients and controls in baseline arterial endothelial function and autonomic modulation; secondly, to evaluate the load effects of overnight obstructive breathing events on vascular endothelial function and autonomic modulation in OSAHS patients.

## PATIENTS AND METHODS

### Patients and protocol

All male adult subjects referred to the sleep lab in Peking Union Medical College Hospital for sleep study from June 2009 to June 2011 were consecutively recruited for this study. Subjects with an apnea/hypopnea index (AHI) of greater than 15 and without previous treatment for OSAHS were included as Group OSAHS and subjects with an AHI of

less than 5 were included as non-OSAHS controls (Group Control). All subjects included were free of hypertension, coronary heart disease, cerebrovascular disease, and diabetes. This study was approved by Peking Union Medical college Hospital ethical committee, and all subjects gave informed consent before participating in the study.

All subjects reported to the sleep laboratory at 20:30, and after undergoing a complete medical history taking and physical examination by the physician investigators, standard nocturnal polysomnography (PSG) and continuous non-invasive beat-to-beat blood pressure from the radial artery were recorded from 21:30 until 7:00 in the following morning. And 15 minutes' artifact free data were recorded in supine awake state before and after the PSG recording respectively.

### Nocturnal PSG

Sleep was recorded using standard polysomnographic measurements including central and occipital referential electroencephalography (EEG; C4/A1, O2/A1, C3/A2, O1/A2), right and left electrooculography (EOG), submental and anterior tibialis electromyography (EMG), electrocardiography (ECG) with precordial surface electrodes, nasal and oral airflow measured by thermistors and nasal pressure transducers, thoracoabdominal respiratory movements with piezo sensor bands, and arterial oxyhemoglobin saturation (SaO<sub>2</sub>) with a finger pulse oximeter (Embla, type XN, USA). Data were collected and stored on an Embla signal recording system with Somnologica Software (Flagstaff, Medical Devices, USA).

An obstructive apnea event was defined as a cessation of upper airway flow in association with continued respiratory effort of at least 10 seconds. An obstructive hypopnea event was defined as a discernible decrease but not cessation in airflow of at least 10 seconds from the section immediately preceding, with continued respiratory effort, and associated with EEG arousal and/or decline in SaO<sub>2</sub> of at least 3% following resumption of airflow to its baseline. EEG arousal was defined as an abrupt and discrete change in EEG frequency, with or without increased electromyogram activity. AHI was defined as the number of apnea plus hypopnea episodes per hour of sleep. OSAHS was defined as the presence of more than 5 obstructive apneas or

hypopneas per hour of sleep. Sleep staging was performed according to standard criteria<sup>9, 10</sup> by a sleep specialist.

### Beat-to-beat blood pressure recording

Continuous beat-to-beat blood pressure was recorded from the radial artery by applanation tonometry using a non-invasive wrist oscillometric device (Model 7000, Colin Medical Instruments Corp., San Antonio, TX, USA). The signal was sampled at 200 Hz/channel with an analog-to-digital converter (DAQ-700, National Instruments, Austin, TX, USA).

### Arterial augmentation index (AAI)

The digitized arterial pressure waveform was analyzed using customized LabView software. An algorithm detects the waveform's inflection point on the upstroke, which signals the onset of the reflected wave and thus divides the arterial pressure wave into an early and late systolic peak.

As a measure of arterial stiffness, AAI, a time domain estimate of the contribution of arterial pressure wave reflection to pulse pressure, was calculated through the superimposition of a series of sequential arterial pulse waveforms, which was averaged. The third derivative of the waveform was then taken, and the inflection point was found as the derived waveform intercepts the X-axis at the systolic shoulder. The AAI was calculated as the ratio of augmented systolic blood pressure (SBP) to pulse pressure and expressed as a percentage (Fig. 1).<sup>11</sup>

### Autonomic modulation

The digitized ECG and arterial pressure waveforms were analyzed using customized LabView software to obtain spectral components of heart rate variability (HRV) and blood pressure variability (BPV). The spectral power of the oscillatory components of R-R variability and BPV were

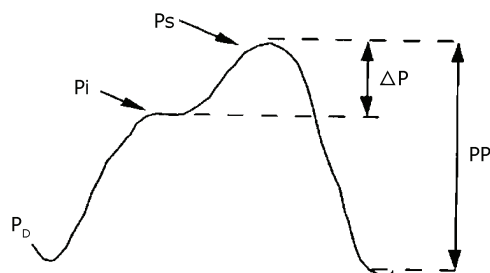


**Figure 1.** Illustration of the AAI.

AAI: arterial augmentation index;  $P_D$ : diastolic pressure;  $P_i$ : inflection pressure;  $P_s$ : systolic pressure; PP: pulse pressure.

AAI is calculated as the ratio of augmented  $P_s$  (from the inflection point to systolic peak) to PP and expressed as a percentage.  $AAI = (P_s - P_i) / (P_s - P_D) \times 100 = \Delta P / PP \times 100$ .

calculated with an interval method for computing Fourier transforms. Power in the low frequency (LF, 0.05 to 0.15 Hz), and high frequency (HF, >0.15 to 0.40 Hz) range was calculated for HRV. HF power of R-R variability (HRV HF) is considered a function of cardiac parasympathetic nervous system activity to the heart. The LF component (HRV LF), while not modulated by a single arm of the autonomic nervous system is considered, normalized for total power, as a representative index of sympathetic activity to the heart. The LF power-HF power ratio of R-R variability (HRV LF/HF) is considered an index of the balance of sympathovagal input to sinoatrial node activity, and has been found to be representative of sympathetic to parasympathetic balance in both physiologic and pathophysiologic conditions. To define sympathetic modulation of BPV, beat-to-beat SBP was analyzed for LF modulation (0.04-0.15 Hz), as this activity appears to be most specific for sympathetic modulation of the microcirculation, without influence of the respiratory system.<sup>7, 8</sup>

### Data analysis

For each subject, 5 minutes of artifact free data before and after the overnight PSG were analyzed respectively. Heart rate, respiratory rate (RR), SBP, diastolic blood pressure (DBP), and mean arterial pressure (MAP) were averaged over the same collection periods. HRV HF, HRV LF, HRV LF/HF, and BPV LF were reduced, averaged, and analyzed over the same collection periods for each condition (before and after the overnight PSG). Spectral components for all analyses were expressed as normalized units and calculated as: absolute power of the components/(total power - very LF power)  $\times 100$ .<sup>12, 13</sup> Ten successive cardiac cycles of each minute over the same 5 minutes period (5 epochs for each conditions) were analyzed for AAI, and the mean value from 5 epochs of 10 successive cardiac cycles during the 5 minutes in each condition (before and after the overnight PSG) was obtained in each subject. For each variable, data collected during each 3-5 minutes period was averaged to a single value for each subject and expressed as mean  $\pm$  SD.

The data in the supine relaxed awakening state before overnight PSG represent the baseline condition of the subjects, while the data just after whole night PSG represent the load effects of overnight sleep.

### Statistical analysis

Student's *t* tests were used to analyze the difference between the parameters before and after overnight sleep in OSAHS patients and non-OSAHS controls respectively. Comparisons among the data before and after sleep be-

tween OSAHS patients and non-OSAHS controls were made by repeated measures analysis of variance (ANOVA). All analyses were done with SPSS 17.0. Statistical significance was considered at the level of  $P=0.05$ .

## RESULTS

### Characteristics of the subjects

Totally, 27 moderate-severe OSAHS patients and 22 non-OSAHS obese controls entered the final data analysis. All the subjects included were male. There was no significant difference in age ( $43.3 \pm 9.3$  vs.  $42.9 \pm 8.6$  years) and body mass index ( $36.8 \pm 8.7$  vs.  $34.4 \pm 7.9$  kg/m<sup>2</sup>) between the Group OSAHS and Group Control (all  $P>0.05$ ), while AHI was significantly higher and nadir SaO<sub>2</sub> was significantly lower in the Group OSAHS compared to the Group Control ( $57.6 \pm 29.4$  vs.  $2.8 \pm 1.3$ ,  $P<0.001$ ;  $80.2\% \pm 8.8\%$  vs.  $93.8\% \pm 3.7\%$ ,  $P<0.001$ , respectively).

### Comparison of baseline endothelial function and autonomic modulation between the Group OSAHS and Group Control

There were no significant differences in baseline heart rate, SBP, DBP, HRV LF, HRV HF and HRV LF/HF between the Group OSAHS and Group Control (all  $P>0.05$ ), while baseline AAI and BPV LF in OSAHS patients were significantly higher than those in controls (all  $P<0.05$ , Table 1).

### Comparison of endothelial function and autonomic modulation before and after overnight sleep in the Group OSAHS

In the Group OSAHS, after overnight sleep, heart rate and AAI had no significant changes, while SBP, DBP, HRV LF, HRV LF/HF and BPV LF increased significantly (all  $P<0.001$ ) and HRV HF decreased significantly ( $P<0.05$ ) from baseline (Table 1).

### Comparison of endothelial function and autonomic modulation before and after overnight sleep in the Group Control

All the cardiovascular parameters in the Group Control showed no significant change from baseline to post sleep (all  $P>0.05$ , Table 1).

## DISCUSSION

This study suggests that: (1) compared to that of obese controls, the baseline endothelial function and autonomic modulation of the moderate-severe OSAHS patients have been impaired in some degree, even without hypertension or other cardiovascular complications; (2) with the load effects of the overnight obstructive breathing events in OSAHS patients, blood pressure in the morning increased significantly and the autonomic modulation would get more dysfunctional, with no acute aggravation in endothelial function impairment.

Previous studies have demonstrated that obesity and many metabolic diseases have endothelial function impairment and autonomic modulation dysfunction, and most OSAHS patients complicate with obesity, diabetes and dyslipidemia, so it is very difficulty to exclude the confounding influence of obesity and other metabolic diseases in many associated studies between OSAHS and cardiovascular diseases. In our study, subjects with metabolic diseases above were all excluded, and the body mass index of the controls also matches with that of OSAHS patients. Further, to exclude the confounding effects of gender, all the subjects included in the study were male. The results of our study demonstrated that even without cardiovascular and metabolic diseases, the baseline endothelial function and autonomic modulation have been impaired in OSAHS patients compared to non-OSAHS obese controls.

**Table 1.** Cardiovascular parameters before and after overnight sleep in both groups<sup>§</sup>

| Group         | Time                  | <i>n</i> | HR (bpm) | SBP (mm Hg)              | DBP (mm Hg)            | AAI (%)               | HRV LF (%)              | HRV HF (%)            | HRV LF/HF             | BPV LF (%)              |
|---------------|-----------------------|----------|----------|--------------------------|------------------------|-----------------------|-------------------------|-----------------------|-----------------------|-------------------------|
| Group Control | Baseline              | 22       | 65.1±7.7 | 131.5±12.2               | 79.7±5.8               | 8.2±2.1               | 62.7±11.5               | 28.5±9.6              | 2.7±1.5               | 61.1±11.7               |
|               | After overnight sleep | 22       | 64.2±8.2 | 127.3±11.3               | 77.6±5.1               | 7.4±1.9               | 61.5±10.8               | 29.1±11.1             | 2.5±1.2               | 60.5±12.4               |
| Group OSAHS   | Baseline              | 27       | 64.7±8.3 | 132.8±13.3               | 78.6±5.5               | 12.5±2.2 <sup>▲</sup> | 64.3±12.1               | 27.5±10.3             | 2.3±1.3               | 68.3±13.5 <sup>▲</sup>  |
|               | After overnight sleep | 27       | 66.3±7.8 | 143.7±14.2 <sup>††</sup> | 87.7±7.7 <sup>††</sup> | 13.2±3.4              | 69.7±14.4 <sup>††</sup> | 21.1±9.3 <sup>*</sup> | 3.7±2.0 <sup>††</sup> | 77.8±15.6 <sup>††</sup> |

§: Plus-minus values are means±SD.

1 mm Hg=0.133 kPa; OSAHS: obstructive sleep apnea hypopnea syndrome; HR: heart rate; SBP: systolic blood pressure; DBP: diastolic blood pressure; AAI: arterial augmentation index; HRV: heart rate variability; LF: low frequency; HF: high frequency; BPV: blood pressure variability.

<sup>▲</sup> $P<0.05$  compared with the baseline data of the Group Control; <sup>\*</sup> $P<0.05$ , <sup>††</sup> $P<0.001$  compared with the baseline data of the Group OSAHS.

Obstructive sleep apnea has been identified as an independent and additive risk factor for the development of systemic hypertension and its complications,<sup>1, 2, 14-17</sup> and associated with the acute increase of blood pressure during obstructive breathing events and sustained increasing of nocturnal and daytime blood pressure.<sup>3, 18-21</sup> Our study confirmed that after the overnight obstructive breathing events, blood pressure in OSAHS patients increased significantly from the baseline before sleep. But the comprehensive mechanisms of blood pressure increasing in the morning in OSAHS patients are still not clear, several mechanisms like neurologic, humoral, and cellular factors including repetitive hypoxia and hypercapnea, changes in chemoreflex, baroreflex, sympathetic activity and changes in humoral cardiovascular control mechanism, endothelial dysfunction and vascular remodeling caused by repetitive hypoxia, and systemic stress reaction caused by recurrent arousals and sleep fragmentation have been postulated,<sup>22-24</sup> but the cause-effect relationship among these factors are not clearly defined. Our study demonstrated that blood pressure increasing in the morning in OSAHS patients was only associated with acute increasing in sympathetic activity, but with no acute impairment in endothelial function, which implicates acute increasing in sympathetic activity caused by the load effects of repetitive hypoxia, chemoreflex, baroreflex, repetitive arousals and sleep fragmentation due to recurrent airway obstructing events during sleep would be the primary factor causing morning blood pressure increasing. It also implicates those changes in autonomic modulation in OSAHS patients could happen earlier than endothelial dysfunction, while daytime hypertension could be the consequence of chronic endothelial function impairment.

Conclusively, our study demonstrated the baseline endothelial function impairment and autonomic modulation dysfunction in OSAHS patients, which happen prior to hypertension and other cardiovascular complications. And also, we demonstrated that load effects of overnight obstructive breathing events could induce blood pressure and sympathetic activity increasing in the morning in OSAHS patients with no acute aggravation in endothelial dysfunction, which suggested that morning blood pressure increasing is more associated with autonomic modulation dysfunction than endothelial function impairment.

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