Original Article

Aortic Pressure Augmentation as a Marker of Cardiovascular Risk in Obstructive Sleep Apnea Syndrome

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Obstructive sleep apnea syndrome (OSAS) is associated with increases in cardiovascular morbidity and mortality. Vascular changes in individuals with OSAS have not been fully elucidated, however. The possible impact of OSAS on the extent of aortic pressure augmentation (AG), an indicator of cardiovascular risk, was investigated. Forty-five consecutive male patients aged 35 to 78 years (56.0±9.6 years) who were referred to the sleep clinic of Nagoya University Hospital for screening and treatment of OSAS and 71 age-matched healthy men were enrolled in the study. AG was derived from the pressure waveform measured at the radial artery by applanation tonometry. The number of apnea and hypopnea episodes per hour (apnea-hypopnea index [AHI]) was determined by standard polysomnography. AG was significantly greater in OSAS patients than in controls (9.0±4.1 *vs.* 6.4±3.4 mmHg, $p<0.001$), and it was significantly reduced in 19 OSAS patients treated with continuous positive airway pressure. AG was also significantly correlated with the AHI ($r=0.562$, $p<0.001$) and age ($r=0.356$, $p=0.016$) but not with the serum concentrations of low and high density lipoprotein-cholesterol, triglyceride, or glycosylated hemoglobin. Stepwise multiple regression analysis revealed that the AHI was the most significant contributing factor to the increased AG in OSAS patients ($\beta=0.109$, $r=0.530$, $p<0.001$). OSAS may thus have an adverse effect on vascular function that can be ameliorated by appropriate treatment. (*Hypertens Res* 2008; 31: 1109–1114)

***Key Words*: obstructive sleep apnea syndrome, cardiovascular disease, vascular, continuous positive airway pressure, augmentation**

Introduction

Obstructive sleep apnea syndrome (OSAS) is characterized by recurrent episodes of sleep apnea that are associated with hypoxia, fluctuations in heart rate and blood pressure, arousal, and consequent fragmented sleep, all of which can result in an activation of the sympathetic nervous system (*1*–*3*). The most common neuropsychiatric manifestation of OSAS is excessive daytime sleepiness that is secondary to the sleep fragmentation and loss of slow-wave sleep, and other major and long-term manifestations of OSAS are apparent in the cardiovascular system (*1*). Epidemiological studies have thus implicated OSAS as a risk factor for the development of cardiovascular and cerebrovascular diseases (*4*–*6*). Moreover, individuals with OSAS manifest increased circulating con-

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centrations of both endothelin-1 and vascular cell adhesion molecule-1 as well as spontaneous platelet activation, all of which are risk factors for cardiovascular morbidity and mortality (*7–9*). It is therefore clinically important to assess possible changes in the morphological and physiological features of the vasculature in OSAS in order to be able to predict and to prevent such cardiovascular complications.

The central aortic pressure wave is composed of a forward-traveling wave generated by left ventricular ejection and a later-arriving reflected wave from the periphery. As aortic and arterial stiffness increase, the transmission velocity of both forward and reflected waves increases, causing the reflected wave to arrive earlier in the central aorta and to augment the central blood pressure in late systole. Augmentation of the central aortic pressure wave is thus a manifestation of wave reflection (*10*, *11*). Central arterial pressure and the degree of its augmentation can be studied noninvasively by sphygmography with the applanation tonometry technique. Pulse wave analysis is simple to perform, rapid, and highly reproducible and provides an indirect assessment of central aortic blood pressure (*12*). Aortic pressure augmentation (AG) predicts adverse outcomes in patients with coronary artery disease (*13*, *14*). Although a possible relation between OSAS and the pathogenesis of atherosclerosis has been suggested (*15*), vascular changes in patients with OSAS have not been fully investigated.

In the present study, we examined the augmentation of central aortic pressure as well as conventional cardiovascular risk factors in individuals with OSAS.

Methods

Subjects

Forty-five consecutive male patients aged 35 to 78 years (56.0±9.6 years) who were referred to the sleep clinic of Nagoya University Hospital for screening and treatment of OSAS were enrolled in the study. They were not receiving regular medication. As controls, we recruited 71 healthy men aged 40 to 75 years (56.2±7.6 years) without OSAS as determined with a home screening test and self-reported questionnaire and who were free from medication and had no history of cardiovascular disease or diabetes mellitus. The control group had normal electrocardiograms, echocardiographic findings, and blood pressure. The questionnaire was used to obtain data on their medical history, current medications, smoking history, daytime sleepiness on the Epworth sleepiness scale, body mass index (BMI), snoring, and history of observed apnea. Brachial blood pressure was measured by sphygmomanometry with the subject in the sitting position after a 5-min rest. The reported blood pressure values were averages of the second and third measurements. Hypertension was defined as either a systolic blood pressure of >140 mmHg or a diastolic blood pressure of >90 mmHg (or both). The study protocol was approved by the Ethics Review Board of Nagoya University School of Medicine (approval No. 238), and written informed consent was obtained from all study participants.

Sleep Study

Standard polysomnography (ALICE 3; Respironics, Murrysville, USA) was performed for all patients with OSAS. The electroencephalogram (C3-A2, C4-A1, O1-A2, O2-A1), electrooculogram, electromyogram, and electrocardiogram were recorded continuously, and respiration was monitored with oronasal thermistors and thoracoabdominal strain gauges. Apnea was defined as a cessation of airflow through the mouth and nose for ≥10 s, and hypopnea was defined as a reduction in airflow of ≥50% or a reduction in airflow associated with either an oxygen desaturation of >3% or arousal, also for ≥10 s. The apnea-hypopnea index (AHI) was determined as the number of apnea and hypopnea episodes per hour. Individuals with an AHI of ≥5/h were diagnosed with OSAS (*16*). The time during which nocturnal oxygen saturation (SpO_2) was <90% (oxygen desaturation time) and the lowest SpO_2 during sleep were also determined with a pulse oximeter.

Patients with OSAS were stratified according to the AHI. OSAS patients with an AHI of ≥20/h were assigned to undergo continuous positive airway pressure (CPAP) for 3 months if they agreed. Nineteen patients received CPAP (CPAP group) and 14 did not (non-CPAP group), with the latter group including nine patients treated with an oral appliance, one with nasal surgery, and four with diet alone instead of CPAP. On the night after the baseline sleep analysis, those patients assigned to receive treatment with CPAP underwent overnight titration of the pressure to adjust it so as either to abolish apnea, hypopnea, and oxygen desaturation or to determine the highest level tolerated. The patients were instructed to use the CPAP device for at least 4 h per night on 70% of nights.

Pulse Wave Analysis

The pulse waveform was obtained from the radial artery at the wrists with a transcutaneous applanation tonometer. Pulse wave analysis was performed with commercially available software (Sphygmocor PVX; AtCor Medical, Sydney, Australia). Pressure was applied to the radial artery with a probe containing a high-fidelity transducer, through which pressure waves were recorded (*17*). This technique provides intra-arterial pressure measurements similar to those obtained invasively. The central arterial pressure waveform was derived from the radial artery pressure waveform by the application of a generalized transfer function (*18*). AG, defined as the difference in pressure between the second and first systolic peaks (Fig. 1), was determined from the central arterial waveform. The aortic augmentation index (AI) was defined as the increment in pressure from the first systolic shoulder (inflection point) to the peak pressure of the aortic pressure waveform

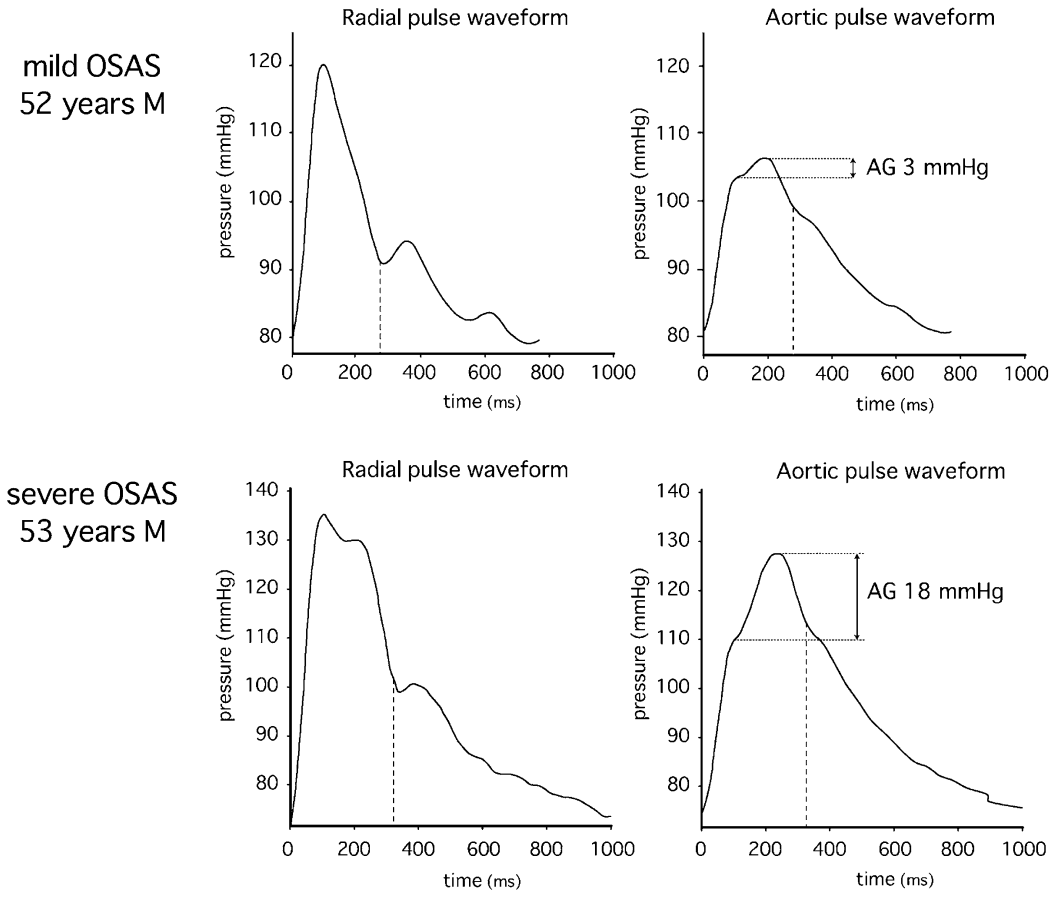

Fig. 1. *Radial and aortic pulse waveforms in representative patients with mild (upper panels) or severe (lower panels) OSAS. Augmentation (AG) is defined as the difference between the ejection peak pressure and the reflectance wave pressure of the aortic waveform. The dotted line indicates the timing of end-systole. The AG and apnea-hypopnea index (AHI) values were 3 mmHg and 11/h for the patient with mild OSAS, and 18 mmHg and 67/h in the patient with severe OSAS.*

expressed as a percentage of the peak pressure (*17*). The reproducibility of this method has been found to be acceptable, with the standard deviation of the difference between repeated measurements being 4% to 5% (*19*). For each subject, three consecutive waveform recordings were averaged to determine the mean. For sequential waveforms of $\geq$11 s, only those with a pulse wave variation of $<$10% were accepted for further analysis.

Visualization of the Vasculature and Blood Analysis

The intima-media wall thickness (IMT) of the carotid arteries was measured by ultrasonography (HDI 3000 instrument; Hitachi, Tokyo, Japan) in all patients with OSAS (*20*). It was measured at the site of greatest thickness as well as 1 cm upstream and 1 cm downstream from this site in each longitudinal projection. The three values were then averaged for each projection. The largest of the six averaged IMT values thus obtained (three for the left side and three for the right side) was used as the representative value for each subject. The serum concentrations of total cholesterol, high density lipoprotein (HDL)-cholesterol, low density lipoprotein (LDL)-cholesterol, and triglyceride, and the percentage of glycosylated hemoglobin (HbA1c) were also measured.

Statistical Analysis

Data are presented as means$\pm$SD and were compared between groups with Student's unpaired *t*-test or the χ^2 test. Pearson's correlation was used to evaluate the relation between AG and age, blood pressure, AHI, BMI, smoking, serum concentration of HDL- or LDL-cholesterol, or HbA1c. Multiple regression analysis, including age, blood pressure, AHI, BMI, smoking, serum concentrations of HDL- and LDL-cholesterol, and HbA1c, was performed with a stepwise forward procedure to identify the factors that contribute to an increased AG in OSAS patients, and partial regression coefficients were determined. All analyses were performed with the SPSS 12.0 software package (SPSS, Chicago, USA). A *p*

Table 1. Characteristics of Obstructive Sleep Apnea Syndrome (OSAS) Patients and Control Subjects

Characteristics	Controls (n=71)	OSAS (n=45)	p value
Age (years)	56.2±7.6	56.0±9.6	0.580
BMI (kg/m^2)	23.3±2.2	25.7±4.6	0.126
BSBP (mmHg)	118.8±9.9	131.4±15.1	<0.001
BDBP (mmHg)	75.9±6.6	80.6±10.2	<0.001
CSBP (mmHg)	106.2±7.5	119.3±13.9	<0.001
CDBP (mmHg)	76.0±6.3	80.7±9.5	<0.013
AG (mmHg)	6.4±3.4	9.0±4.1	<0.001
AI (%)	18.6±9.0	23.5±8.7	0.020
HR (bpm)	69.2±7.9	70.3±10.5	0.734
Smokers (%)	29.5	28.9	0.937

BMI, body mass index; BSBP, brachial systolic blood pressure; BDBP, brachial diastolic blood pressure; CSBP, central systolic blood pressure; CDBP, central diastolic blood pressure; AG, aortic pressure augmentation; AI, augmentation index, HR, heart rate.

value of <0.05 was considered statistically significant.

Results

AG and the AI were significantly greater in OSAS patients than in controls (9.0±4.1 *vs*. 6.4±3.4 mmHg, $p<0.001$; 23.5±8.7 *vs*. 18.6±9.0%, $p=0.020$, respectively) (Table 1). There was no significant difference in heart rate between OSAS patients and controls. AG was also significantly greater in hypertensive (11.4±3.5 mmHg, $n=14$, $p<0.001$) or normotensive (7.9±3.9 mmHg, $n=31$, $p=0.013$) OSAS patients than in control subjects; in addition, it was significantly greater in hypertensive OSAS patients than in normotensive OSAS patients ($p=0.032$).

There was a significant correlation between IMT and AG ($r=0.427$, $p=0.032$). AG was also significantly correlated with the AHI ($r=0.562$, $p<0.001$), age ($r=0.356$, $p=0.016$), and systolic blood pressure ($r=0.391$, $p=0.007$) but not with heart rate, the serum concentrations of HDL- and LDL-cholesterol or triglyceride, or HbA1c (Table 2). Multiple regression analysis including the AHI, age, systolic blood pressure, BMI, smoking status, the serum concentrations of HDL- and LDL-cholesterol, triglyceride, and HbA1c revealed that the AHI was the most significant contributing factor to the increased AG in OSAS patients ($\beta=0.109$, $r=0.530$, $p<0.001$) (Table 3).

Finally, there was no significant difference in the AHI between the CPAP group and non-CPAP group before treatment. AG, the AI, systolic blood pressure, and diastolic blood pressure were significantly reduced after 3 months of treatment with CPAP in the CPAP group (Table 4).

Table 2. Correlation Coefficients between Clinical Variables and Aortic Pressure Augmentation

Factor	r	p value
Age (years)	0.356	0.016
AHI (/h)	0.562	<0.001
BSBP (mmHg)	0.391	0.007
BMI (kg/m^2)	−0.066	0.670
LDL-chol. (mg/dL)	0.143	0.409
HDL-chol. (mg/dL)	−0.225	0.188
Triglyceride (mg/dL)	0.035	0.840
HbA1c (%)	0.070	0.687

AHI, apnea-hypopnea index; BSBP, brachial systolic blood pressure; BMI, body mass index; LDL-chol., low density lipoprotein-cholesterol; HDL-chol., high density lipoprotein-cholesterol; HbA1c, glycosylated hemoglobin.

Discussion

We have shown that AG was significantly increased in OSAS patients compared with healthy control subjects, and that the AHI was a significant contributing factor to the increased AG. Moreover, AG was significantly reduced in OSAS patients treated with CPAP. These results suggest that OSAS is an important risk factor for increased cardiovascular complications.

In the present study, although hypertension, hyperlipidemia, and diabetes mellitus were common complications in patients with OSAS, neither the serum concentrations of HDL- and LDL-cholesterol or triglyceride, nor HbA1c was significantly correlated with AG. Rather, the AHI was the most important contributing factor to the increased AG. The severity of sleep-disordered breathing and that of associated cardiovascular disease have been found to be important determinants of the prognosis of patients with OSAS (*21–23*). For example, the respiratory disturbance index was shown to be a significant predictor of cardiovascular mortality (*21*). We also previously showed that the prognosis of patients with OSAS complicated by cardiovascular or cerebrovascular disease was poorer than that of OSAS patients without such complications (*22*). In addition, analysis of cross-sectional data from the Sleep Heart Health Study cohort showed that the AHI was significantly associated with the prevalence of cardiovascular disease (*23*). Our present demonstration of a possible link between AG and the AHI provides important information with regard to the predisposition of OSAS patients to premature vascular disease. We propose that, in addition to lifestyle diseases such as hyperlipidemia, hypertension, and diabetes mellitus, the existence of OSAS itself might be a risk factor for cardiovascular disease.

AG was significantly greater in OSAS patients than in healthy controls regardless of the presence of concomitant hypertension. A canine model of OSAS has provided evidence

Table 3. Stepwise Multiple Regression Analysis of Factors Contributing to the Increased Aortic Pressure Augmentation in Patients with Obstructive Sleep Apnea Syndrome

Factor	β	SEM (β)	r	p value
Age (years)	0.125	0.055	0.345	0.027
AHI (/h)	0.109	0.028	0.530	<0.001
BSBP (mmHg)	0.072	0.034	0.322	0.040
BMI (kg/m^2)	−0.109	0.111	−0.155	0.332
Smoking	0.099	1.139	0.014	0.931

AHI, apnea-hypopnea index; BSBP, brachial systolic blood pressure; BMI, body mass index.

Table 4. Effects of Treatment with Continuous Positive Airway Pressure (CPAP) on Blood Pressure, Augmentation, and Sleep Parameters in Patients with Obstructive Sleep Apnea Syndrome

Characteristics	Before CPAP (n=19)	On CPAP (n=19)	p value
AHI (/h)	35.2±18.4	9.9±5.7	<0.001
Lowest SpO_2 (%)	69.8±10.6	87.7±3.6	<0.001
ODT (min)	81.5±51.1	2.3±2.5	<0.001
Arousal index (/h)	45.2±9.3	17.8±10.8	<0.001
Stage 1 sleep (%)	32.7±14.1	25.1±13.4	0.319
Stage 2 sleep (%)	50.1±10.9	48.8±13.7	0.985
Stages 3+4 sleep (%)	1.5±2.3	4.4±5.1	0.061
REM sleep (%)	9.4±5.1	17.4±6.7	0.002
BSBP (mmHg)	145.0±13.7	135.4±16.0	0.024
BDBP (mmHg)	90.5±12.3	79.7±7.3	0.005
CSBP (mmHg)	132.9±10.0	119.8±12.9	0.008
CDBP (mmHg)	87.1±11.8	81.9±9.2	0.022
AG (mmHg)	11.7±2.1	5.7±3.2	<0.001
AI (%)	25.7±10.4	16.1±8.1	0.005

AHI, apnea-hypopnea index; SpO_2, oxygen saturation; ODT, oxygen desaturation time; REM, rapid eye movement; BSBP, brachial systolic blood pressure; BDBP, brachial diastolic blood pressure; CSBP, central systolic blood pressure; CDBP, central diastolic blood pressure; AG, aortic pressure augmentation; AI, augmentation index.

that this condition can lead to a persistent increase in blood pressure not only during the night but also during daytime (*24*). We have previously shown that frequent hypoxic episodes with arousal result in an increase in nocturnal blood pressure, and may lead to sustained hypertension and left ventricular hypertrophy, in patients with OSAS (*25*, *26*). The heart rate fluctuates cyclically in response to apnea or hypopnea and subsequent hyperventilation, with the result that episodes of bradycardia and tachycardia are repeated during the night. OSAS *per se* might contribute to an altered circadian rhythm of autonomic activity that eventually leads to the development of cardiovascular disease (*27*). In addition, OSAS can precipitate myocardial ischemia or a decrease in left ventricular function, either acutely or chronically, in patients with congestive heart failure (*28*). These long-term cardiovascular complications are presumably secondary to the combined effects of an increase in left ventricular afterload during each futile inspiration caused by obstruction of the upper airway, an increase in heart rate or blood pressure on arousal, hypoxemia and hypercapnia, and the consequent activation of the sympathoadrenal system (*29*). All of these changes may also contribute to increased AG, which itself can lead to the development of cardiovascular and cerebrovascular complications.

AG, a noninvasively determined manifestation of arterial stiffening and enhanced wave reflection, is a strong and independent risk marker for premature coronary artery disease (*13*). Endothelium-dependent vasodilation in resistance vessels has been found to be impaired in patients with OSAS (*30*). Moreover, arterial stiffness increases acutely during obstructive apnea in both rapid eye movement (REM) and non-REM sleep in the absence of a measurable change in blood pressure (*31*). A meta-analysis of randomized, controlled trials showed that CPAP reduces blood pressure in patients with OSAS and helps to prevent the development of hypertension (*32*). Moreover, treatment of OSAS with CPAP has been shown to reduce the risk of fatal and nonfatal cardiovascular events (*4*). We recently showed that CPAP treatment resulted in an increase in daytime baroreflex function in addition to an improvement in sleep quality, normalization of nocturnal oxygen desaturation, an increase in plasma NO concentration, and a decrease in 24-h urinary norepinephrine excretion in OSAS patients (*2*). We have now demonstrated a direct correlation between the severity of OSAS and AG, and we have shown that AG was significantly reduced in OSAS patients treated with CPAP. Although the effects of CPAP treatment on cardiovascular alterations remain controversial, evidence suggests that changes in vascular function are ameliorated by successful long-term treatment with CPAP. Given the clinical importance of early detection of atherosclerosis for preventing cardiovascular complications, AG may prove to be a useful index in the follow-up of patients with progressive cardiovascular disease secondary to OSAS.

With regard to the limitations of our study, among the 33 patients with an AHI of ≥20/h, 14 individuals refused CPAP treatment. Thus, these patients were not randomized into groups that received CPAP for 3 months or did not receive such treatment. The remaining 19 OSAS patients in whom the effects of CPAP were evaluated in the present study may have constituted a somewhat biased group. The effect of CPAP on vascular function described in our study thus requires verification with a large-scale placebo-controlled study.

In conclusion, the severity of OSAS was found to be correlated with AG, a strong indicator of cardiovascular risk, and AG was improved by successful CPAP treatment in patients with moderate to severe OSAS. OSAS itself might therefore contribute to the development of cardiovascular and cerebrovascular complications.

References

1. Phillipson EA: Sleep apnea, in Braunwald E, Fauci AS, Kasper DL, Hauser SL, Longo DL, Jameson JL (eds): Harrison's Principles of Internal Medicine, 15th ed. New York, McGraw-Hill, 2001, pp 1520–1523.
2. Noda A, Nakata S, Koike Y, *et al*: Continuous positive airway pressure improves daytime baroreflex sensitivity and nitric oxide production in patients with moderate to severe obstructive sleep apnea syndrome. *Hypertens Res* 2007: **30**: 669–676.
3. Peppard PE, Young T, Palta M, Skatrud J: Prospective study of the association between sleep-disordered breathing and hypertension. *N Engl J Med* 2000; **342**: 1378–1384.
4. Marin JM, Carrizo SJ, Vicente E, Agusti AG: Long-term cardiovascular outcomes in men with obstructive sleep apnoea-hypopnoea with or without treatment with continuous positive airway pressure: an observational study. *Lancet* 2005; **365**: 1046–1053.
5. Yaggi H, Cancato J, Kernan W, Lichtman JH, Brass LM, Mohsenin V: Obstructive sleep apnea as a risk factor for stroke and death. *N Engl J Med* 2005; **353**: 2034–2041.
6. Peker Y, Hender J, Norman J, Kraiczi H, Carlson J: Increased incidence of cardiovascular disease in middle-aged men with obstructive sleep apnea. *Am J Respir Cir Care Med* 2002; **166**: 159–165.
7. Phillips BG, Narkiewicz K, Pesek CA, Haynes WG, Dyken ME, Somers VK: Effects of obstructive sleep apnea on endothelin-1 and blood pressure. *J Hypertens* 1999; **17**: 61–66.
8. Ohga E, Nagase T, Tomita T, *et al*: Increased levels of circulating ICAM-1, VCAM-1, and L-selectin in obstructive sleep apnea syndrome. *J Appl Physiol* 1999; **87**: 10–14.
9. Bokinsky G: Spontaneous platelet activation and aggregation during obstructive sleep-apnea and its response to therapy with nasal continuous positive air pressure. *Chest* 1995; **108**: 625–630.
10. Nichols WW, Singh BW: Augmentation index as a measure of peripheral vascular disease state. *Curr Opin Cardiol* 2002; **17**: 543–551.
11. O'Rourke MF, Staessen JA, Vlachopoulos C, Duprez D, Plante GE: Clinical applications of arterial stiffness; definitions and reference values. *Am J Hypertens* 2002; **15**: 426–444.
12. Filipovsky J, Svobodova V, Pecen L: Reproducibility of radial pulse wave analysis in healthy subjects. *J Hypertens* 2000; **18**: 1033–1040.
13. Weber T, Auer J, O'Rourke MF, *et al*: Arterial stiffness, wave reflections, and the risk of coronary artery disease. *Circulation* 2004; **109**: 184–189.
14. Chirinos JA, Zambrano JP, Chakko S, *et al*: Aortic pressure augmentation predicts adverse cardiovascular events in patients with established coronary artery disease. *Hypertension* 2005; **45**: 980–985.
15. Suzuki T, Nakano H, Maekawa J, *et al*: Obstructive sleep apnea and carotid-artery intima media thickness. *Sleep* 2004; **27**: 129–133.
16. The Report of an American Academy of Sleep Medicine Task Force. Sleep-related breathing disorders in adults: recommendations for syndrome definition and measurement techniques in clinical research. *Sleep* 1999; **22**: 667–689.
17. Kelly RP, Hayward C, Avolio A, O'Rourke M: Noninvasive determination of age-related changes in human arterial pulse. *Circulation* 1989; **80**: 1652–1659.
18. Chen CH, Nevo E, Fetics B, *et al*: Estimation of central aortic pressure waveform by mathematical transformation of radial tonometry pressure validation of generalized transfer function. *Circulation* 1997; **95**: 1827–1836.
19. Wilkinson IB, Fuchs SA, Jansen IM, *et al*: Reproducibility of pulse wave velocity and augmentation index measurement by pulse wave analysis. *J Hypertens* 1998; **16**: 2079–2084.
20. Chambless LE, Heiss G, Folsom AR, *et al*: Association of coronary heart disease incidence with carotid arterial wall thickness and major risk factors: the Atherosclerosis Risk in Communities (ARIC) Study. *Am J Epidemiol* 1997; **146**: 483–494.
21. Peker Y, Heder J, Kraiczi H, Loth S: Respiratory disturbance index. An independent predictor of mortality in coronary artery disease. *Am J Respir Crit Care Med* 2000; **162**: 81–86.
22. Noda A, Okada T, Yasuma F, Sobue T, Nakashima N, Yokota M: Prognosis of the middle-aged and aged patients with obstructive sleep apnea syndrome. *Psychiatry Clin Neurosci* 1998; **52**: 79–85.
23. Shahar E, Whitney CW, Redline S, *et al*: Sleep-disordered breathing and cardiovascular disease. *Am J Respir Crit Care Med* 2001; **163**: 19–25.
24. Brooks D, Homer RL, Kozar LF, Render-Teixeira C, Phillipson EA: Obstructive sleep apnea as a cause of systemic hypertension. Evidence from a canine model. *J Clin Invest* 1997; **99**: 106–109.
25. Noda A, Okada T, Hayashi H, Yasuma F, Yokota M: 24-Hour ambulatory blood pressure variability in obstructive sleep apnea syndrome. *Chest* 1993; **103**: 1343–1347.
26. Noda A, Okada T, Yasuma F, Nakashima N, Yokota M: Cardiac hypertrophy in obstructive sleep apnea syndrome. *Chest* 1995; **107**: 1538–1544.
27. Noda A, Yasuma F, Okada T, Yokota M: Circadian rhythm of autonomic activity in patients with obstructive sleep apnea syndrome. *Clin Cardiol* 1998; **21**: 271–276.
28. Bradley TD, Floras JS: Sleep apnea and heart failure. Part I: Obstructive sleep apnea. *Circulation* 2003; **107**: 1671–1678.
29. Narkiewicz K, Somers VK: The sympathetic nervous system and obstructive sleep apnea: implications for hypertension. *J Hypertens* 1997; **15**: 1613–1619.
30. Kato M, Roberts-Thomson P, Phillips BG, *et al*: Impaired endothelium-dependent vasodilation of resistance vessels in patients with obstructive sleep apnea. *Circulation* 2000; **102**: 2607–2610.
31. Jelic S, Bartele MN, Mateika JH, Nagai P, DeMeersman RE, Basner RC: Arterial stiffness increases during obstructive sleep apnea. *Sleep* 2002; **25**: 850–855.
32. Bazzano LA, Khan Z, Reynolds K, He J: Effect of nocturnal nasal continuous positive airway pressure on blood pressure in obstructive sleep apnea. *Hypertension* 2007; **50**: 417–423.