

## Degree of Arousal Is Most Correlated with Blood Pressure Reactivity During Sleep in Obstructive Sleep Apnea

We investigated blood pressure (BP) reactivity of obstructive sleep apnea (OSA) during rapid eye movement (REM) sleep and non-rapid eye movement (NREM) sleep. The influences on BP reactivity of degree of arousal, the lowest O<sub>2</sub> saturation (SaO<sub>2</sub>), and respiratory disturbance (RD) duration were compared. Ten normotensive or borderline hypertensive patients with OSA were studied with one-night polysomnography including non-invasive beat-to-beat BP monitoring (Finapres®). We compared baseline BP, pre-apneic BP, and post-apneic BP during both REM and NREM sleep. Also, relationships between delta BP (post-apneic BP minus pre-apneic BP) and degree of arousal, the lowest SaO<sub>2</sub>, and RD duration were examined. During both REM and NREM sleep, pre-apneic BP was elevated compared with baseline BP. Post-apneic BP elevation was noted compared with pre-apneic BP. The degree of arousal was more significantly correlated with delta BP than the lowest SaO<sub>2</sub>. RD duration was hardly correlated with delta BP. Pre-apneic BP elevation seems to result from cumulation of sympathetic activation and sympathetic nervous system resetting. The correlation between delta BP and degree of arousal suggests that sympathetic activation causing post-apneic BP elevation may result mainly from an arousal response regardless of hypoxia.

Key Words : Blood Pressure; Sleep Apnea, Obstructive; Arousal; Sympathetic Nervous System; Anoxia

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### INTRODUCTION

With a prevalence up to 2% of women and 4% of men in general (1, 2), obstructive sleep apnea (OSA) is a common disorder. Patients with OSA complain of snoring, daytime sleepiness, cognitive dysfunction, sexual dysfunction, and psychiatric disturbances such as depression and personality change (3). Well-known complications comprise cognitive impairment due to hypoxia and cardiovascular impacts, which may develop hypertension (HT), arrhythmia, heart failure, and myocardial infarction.

Among these cardiovascular complications, HT is most typical and challenging. Epidemiological studies have found that 30-35% of patients with essential HT have OSA (4-7) and 60% of patients with OSA have HT (8). This relationship between OSA and HT is strongly supported by the finding that tracheostomy or continuous positive airway pressure (CPAP), known to relieve OSA, possibly corrects HT (9, 10). To demonstrate the correlation between HT and OSA, blood pressure (BP) fluctuations during sleep in patients with OSA have been examined. Though it is not certain whether BP is decreased or increased during apnea episodes, it has been consistently found that BP is elevated at the termination of apnea episodes (11).

Several methods used to measure nocturnal BP have limitations. The commonly-used invasive method (12) disrupts the subjects' sleep by making subjects uncomfortable. The ambulatory cuff with its measurement interval up to 30 min can not pursue apnea-by-apnea BP fluctuations of patients with OSA (13). Studies using beat-to-beat and non-invasive method have been done during a fraction of nocturnal sleeping time (14).

To clarify the pathophysiology of OSA and HT, we measured BP throughout a night of nocturnal polysomnography (NPSG). We traced BP during rapid eye movement (REM) and non-rapid eye movement (NREM) sleep for the whole night, using a non-invasive beat-to-beat method. By comparing baseline, pre-apneic, and post-apneic BP, we examined BP reactivity in OSA. Among variables such as degree of arousal, hypoxia, and respiratory disturbance (RD) duration, we determined the most influential factor in BP reactivity.

### SUBJECTS AND METHODS

#### Subjects

Patients suspected of OSA were referred to the Division

of Sleep Studies, Seoul National University Hospital. After history taking, physical and neurological examinations, and one-night NPSG, we selected 10 subjects meeting the following criteria: 1) respiratory disturbance index (RDI) more than 10 RDI defined as the sum of apneas and hypopneas divided by total sleep time per hour - with central apneas excluded but mixed apneas included, reflecting obstructive component (15); 2) absence of narcolepsy or periodic limb movements during sleep (PLMS), which elevates BP (16); 3) without autonomic nervous system diseases or endocrine disorders which might influence BP; 4) without respiratory diseases; 5) normotensive or borderline hypertensive (BP was measured twice both at the day of first visit and at the NPSG night, and their BPs were not higher than 140/95 in any measurements); and 6) without usage of CPAP or surgery to relieve OSA.

## METHODS

### Sleep recording and BP measurement

We used a Grass Model 78 polysomnograph (PSG), and standard electrodes and sensors. Electroencephalography (EEG) electrodes were applied at C3/A2, O1/A2 and O2/A1, and two electrooculography (EOG) electrodes applied at both sides of eye to record horizontal and vertical eye movements. Submental electromyography (EMG) electrodes were applied at the submental muscle and EMGs of both anterior tibialis muscles recorded limb movements during sleep. We used strain gauges for recording chest and abdominal respiratory movements, and a thermocouple for recording airflow. A photoplethysmographic sensor for oxygen saturation was applied at the left index finger.

For continuous non-invasive beat-to-beat BP measurement during sleep, a Finapres<sup>®</sup> transducer (Ohmeda) was applied to the left middle finger. Finapres<sup>®</sup> is based on infrared plethysmography, measuring blood flow in proportion to infrared absorption. BP measured at the middle finger was connected to the patient interface module (PIM). For real-time downloading and storage of these BP data, we made a computer program using the C language. For time synchronization between NPSG data and BP data, the program sent a time signal to the PSG.

The height of the hand in relation to the heart gives rise to a great difference in the BP values measured with the Finapres<sup>®</sup>. To allow the subjects to sleep in comfortable state as possible, we fixed the PIM on the wrist. Using videotape records, we excluded data when the subjects lay on their sides or the hand position changed from the original. Based on the criteria of Rechtschaffen and Kales (17), we scored every epoch of 30 sec NPSG.

### Parameter definition

We defined BP variables as follows: 1) baseline BP as the mean of BP measurements during 1 min after a 15-min rest in a wakeful state; 2) pre-apneic BP as the mean of 5 BP measurements immediately before an apnea or hypopnea; 3) post-apneic BP as the mean of 5 BP measurements around the maximum BP within 20 sec after an apnea or hypopnea termination; 4) delta BP as the post-apneic BP minus pre-apneic BP.

We divided degree of arousal into 4 grades based on Rechtschaffen and Kales (17), Bonnet et al. (18), and Davies et al. (19): 1) Grade 0 - no change in EEG frequency and amplitude, and chin EMG; 2) Grade 1- when one of the following criteria was met: i) a shift in EEG frequency to theta, alpha, or frequencies greater than 16 Hz, which lasted less than 10 sec or appearance of high amplitude which lasted less than 10 sec, ii) limb or body movements which lasted less than 10 sec, iii) chin EMG change without sleep stage shift during REM sleep, and iv) K complex appearance in EEG; 3) Grade 2- when one of the following criteria was met: i) a shift in EEG frequency to theta, alpha, or frequencies greater than 16 Hz, which lasted more than 10 sec or appearance of high amplitude which lasted more than 10 sec, ii) limb or body movements which lasted more than 10 sec, and iii) chin EMG change with stage shift during REM sleep; and 4) Grade 3- shift to a wakeful epoch.

Based on airflow amplitude decreases, we manually measured RD duration in 1.5 sec units. We defined the lowest O<sub>2</sub> saturation (SaO<sub>2</sub>) as the lowest SaO<sub>2</sub> within 30 sec after an apnea or hypopnea termination.

### Statistical analysis

For statistical analysis, we used SPSS 8.0 for Windows. Using repeated measures ANOVA, we compared baseline, pre-apneic, and post-apneic BP. Paired t-test was done between 2 BPs if ANOVA showed a significance. To determine the most influential factor in post-apneic BP elevation among degree of arousal, lowest SaO<sub>2</sub>, and RD duration, stepwise multiple regression analyses were done, with delta BP as a dependent variable, and with degree of arousal, lowest SaO<sub>2</sub>, and RD duration as independent variables. All tests were two-tailed and significance was defined at  $p < 0.05$ .

## RESULTS

### Characteristics of subjects

All subjects were men, aged 31 to 69 yr. Table 1 presents daytime BP, obesity-related characteristics, and NPSG results. Subject 1 and 9 were borderline hypertensive, and the others were normotensive. All subjects weighed more than 110 % of ideal body weight except Subject 3. The fact that their

waist/hip ratios were around 1 means they were centrally obese. RDI ranged from 10.8 to 79.2, and lowest SaO<sub>2</sub> ranged from 60% to 85%. Classification of OSA severity based on RDI and lowest O<sub>2</sub> saturation revealed that it ranged from mild to severe in degree (20).

**Comparison among baseline, pre-apneic, and post-apneic BP**

Table 2 shows baseline, pre-apneic, and post-apneic systolic blood pressures (SBP). There were significant differences among 3 SBPs both during NREM and REM sleep (ANOVA, *p*<0.05, *p*<0.05, respectively). Similar results were observed when the 3 diastolic blood pressures (DBP) were compared. Paired t-tests were done as post-hoc analy-

**Table 1.** Characteristics of the subjects and results of polysomnographic study

Subj No.	BP	%IBW	BMI (kg/m <sup>2</sup> )	W/H ratio	RDI	O <sub>2</sub> saturation	
						Lowest	% time<90%
1	140/95	121	25.8	0.98	14.7	79	6.5
2	130/75	158	34.0	1.01	79.2	79	55.7
3	120/70	105	22.4	1.01	37.8	76	6.1
4	120/85	134	29.6	1.00	10.8	83	1.3
5	130/80	120	26.4	1.01	37.9	60	30.4
6	110/75	135	29.0	1.02	22.1	78	2.7
7	120/75	129	27.9	0.99	14.9	80	2.6
8	120/85	117	25.8	0.94	58.6	74	37.6
9	140/95	111	24.3	0.99	52.2	77	38.3
10	125/65	121	26.0	1.04	16.0	85	1.3

%IBW: weight/ideal body weight multiplied by 100. BMI: body mass index calculated as weight (kg)/(height (m))<sup>2</sup>. W/H: waist circumference/hip circumference. RDI (respiratory disturbance index): the total number of apneas and hypopneas divided by total sleep time (hr). % time <90%: % time when O<sub>2</sub> saturation was below 90% during total sleep time

**Table 2.** Comparison among baseline, pre-apneic, and post-apneic SBPs

Subj No.	Baseline	NREM Sleep			REM Sleep		
		Pre-apneic	Post-apneic	Delta	Pre-apneic	Post-apneic	Delta
1	136	148	171	23	165	197	32
2	123	137	154	17	168	190	22
3	110	129	152	23	132	159	27
4	113	129	143	14	141	162	21
5	117	132	156	24	132	164	32
6	99	111	123	12	112	141	29
7	120	129	150	21	131	156	25
8	128	145	162	17	152	165	13
9	131	148	173	25	158	169	11
10	117	123	148	25	136	146	10
Mean	119.4* <sup>‡</sup>	133.1* <sup>‡</sup>	153.2 <sup>‡</sup>	20.1	142.7* <sup>§</sup>	164.9 <sup>§</sup>	22.2
SD	10.82	11.75	14.34	4.75	17.7	17.4	8.36

Delta: Post-apneic SBP minus pre-apneic SBP. \**p*<0.05, <sup>‡</sup>*p*<0.05, <sup>§</sup>*p*<0.05

ses. Pre-apneic SBP was increased compared with baseline SBP during both NREM and REM sleep (*p*<0.05, *p*<0.05, respectively). Post-apneic SBP was significantly higher than pre-apneic SBP during both NREM and REM sleep (*p*<0.05, *p*<0.05, respectively). We observed the same pattern of blood pressure reactivity in DBP as in SBP (Table 3).

Comparing BP reactivity between NREM and REM sleep, pre-apneic BP was higher during REM sleep than during NREM sleep both in SBP and DBP (*p*<0.05, *p*<0.05, respectively). Post-apneic BP was higher during REM sleep than during NREM sleep both in SBP and DBP, but the difference was statistically significant only in SBP (*p*<0.05, *p*=0.052, respectively). Although comparison between delta SBP during REM and NREM sleep showed no significant difference, delta SBP tended to be higher during REM than during NREM sleep (Table 2). Delta DBP showed a similar pattern (Table 3).

**Factors influencing post-apneic blood pressure elevation**

We obtained the apnea and hypopnea episodes from all study subjects, which amounted to 1591 RDs during NREM sleep and 280 RDs during REM sleep. Based on these RD data and the BP of each RD, we did multiple regression analyses with each of delta SBP and delta DBP being a dependent variable and with degree of arousal, lowest SaO<sub>2</sub>, and RD duration being independent variables. As shown in Table 4, variances of delta SBP and delta DBP were explained by degree of arousal and lowest SaO<sub>2</sub> during both REM and NREM sleep, and these correlations were more significant during REM sleep (7.4% and 32.2% of delta SBP variance during NREM sleep and REM sleep, respectively, and 17.9% and 28.9% of delta DBP variance during NREM sleep and REM sleep, respectively). When comparing partial correla-

**Table 3.** Comparison among baseline, pre-apneic, and post-apneic DBPs

Subj No.	Baseline	NREM Sleep			REM Sleep		
		Pre-apneic	Post-apneic	Delta	Pre-apneic	Post-apneic	Delta
1	86	97	115	18	106	121	15
2	67	81	95	14	110	133	23
3	50	61	72	11	63	81	18
4	77	85	96	11	92	107	15
5	65	74	90	16	70	93	23
6	65	76	88	12	76	102	26
7	70	73	88	15	74	91	17
8	78	85	104	19	91	105	14
9	73	86	110	24	91	100	9
10	64	68	87	19	76	86	10
Mean	69.5* <sup>‡</sup>	78.6* <sup>‡</sup>	94.5 <sup>‡</sup>	15.9	84.9* <sup>§</sup>	101.9 <sup>§</sup>	17
SD	9.83	10.34	12.56	4.16	15.56	15.84	5.62

Delta: Post-apneic DBP minus pre-apneic DBP. \**p*<0.05, <sup>‡</sup>*p*<0.05, <sup>§</sup>*p*<0.05

**Table 4.** Multiple regression analysis for delta SBP and delta DBP

Predicted Parameter	Predictive Measure	Df	R <sup>2</sup> ( $p < 0.01$ )	Partial R	$p$
NREM sleep					
Delta SBP	Arousal	1, 1590	0.063	0.252	< 0.01
	Arousal	2, 1589	0.073	0.231	< 0.01
	Min SaO <sub>2</sub>			-0.107	< 0.01
	RD duration			0.013	0.616
Delta DBP	Arousal	1, 1590	0.126	0.355	< 0.01
	Arousal	2, 1589	0.179	0.320	< 0.01
	Min SaO <sub>2</sub>			-0.246	< 0.01
	RD duration			-0.037	0.142
REM sleep					
Delta SBP	Arousal	1, 279	0.235	0.485	< 0.01
	Arousal	2, 278	0.322	0.391	< 0.01
	Min SaO <sub>2</sub>			-0.336	< 0.01
	RD duration			0.100	0.97
Delta DBP	Arousal	1, 279	0.237	0.486	< 0.01
	Arousal	2, 278	0.289	0.406	< 0.01
	Min SaO <sub>2</sub>			-0.262	< 0.01
	RD duration			-0.770	0.142

RD: respiratory disturbance; SBP: systolic blood pressure; DBP: diastolic blood pressure; Delta SBP: post-apneic SBP minus pre-apneic SBP; Delta DBP: post-apneic DBP minus pre-apneic DBP; Min SaO<sub>2</sub>: lowest O<sub>2</sub> saturation during post-apneic 30 sec

tions between degree of arousal and lowest SaO<sub>2</sub>, degree of arousal was more significantly correlated with delta SBP and delta DBP during both REM and NREM sleep.

## DISCUSSION

In this study, finger BP was monitored to analyse nocturnal BP reactivity in OSA. As BP changes along the vascular tree, the BP measured on finger with Finapres<sup>®</sup> differs from the BP measured on brachial artery. In addition, shift in finger or body position during sleep may change the height of the finger in reference to the heart, changing measured BP value. Therefore, we fixed the finger position and limited data obtained from the supine body position for analysis. A beat-to-beat measurement of BPs using Finapres<sup>®</sup> provides more reliable data of relative BP changes than absolute values and thus it suited well with our study aims.

Until now, there has been no consistency in defining degree of arousal. Rechtschaffen and Kales (17) described on movement arousal using changes in EMG, EOG, and EEG, and Bohnet et al. (18) suggested a guideline for EEG arousal. Referring to these, Ringler et al. (21) divided arousal into 3 degrees. We assumed that the more finely we divided the degree of arousal, the more reliably we could establish relationship between degree of arousal and other variables. Arousal was divided into 4 degrees, based on the above-mentioned 3 papers.

Most studies on BP reactivity in OSA have been confined

to measurements during NREM sleep or only to a part of the whole night. This study observed BP reactivity during both NREM and REM sleep for the whole night. Pre-apneic BP was elevated compared with the baseline BP measured earlier in the evening. Post-apneic BP was further increased compared with pre-apneic BP. This pattern was observed both in NREM and REM sleep.

Multiple regression and partial correlation analyses showed that the degree of arousal was more influential in post-apneic BP elevation than the lowest SaO<sub>2</sub> and RD duration. These results were more prominent during REM sleep. We could easily explain it by the fact that many physiological variables change more dynamically during REM sleep than during NREM sleep.

Several studies have been done to explain post-apneic BP elevation. Using regression analysis, Shepard (22) suggested that hypoxemia could explain one third of BP elevation. Van Den Aardweg et al. (23) also argued that hypoxemia stimulated carotid body chemoreceptors, which caused vasoconstriction and BP elevation. On the contrary, Ali et al. (16) insisted that correction of hypoxemia with oxygen could not relieve BP elevations. Ringler et al. (21) found that even in hypoxemia, BP would not elevate without apnea. Davies et al. (19) stressed arousal and activation of the arousing-oriented reflex as the cause of post-apneic BP elevation. In their study, when arousal stimuli were given to normal subjects, BP was elevated in proportion to the degree of arousal. Our finding agrees with those supporting 'the arousal hypothesis': the degree of arousal was most influential in BP elevation. Sympathetic activation causing BP elevation could take place by an arousal response alone without hypoxemia.

Of interest and importance, we found that BP stayed elevated even between apnea episodes compared with BP during wakefulness. This finding could be explained as follows. First, if another RD episode began before normalization of the prior post-apneic BP elevation, BP might be still elevated. Second, more significantly, with repetitive arousal and hypoxia and consequent sympathetic stimulation, resetting of the baseline sympathetic tone might have occurred.

The mechanism by which nocturnal BP fluctuation would develop into daytime HT is not clear yet. Repetitive arousals during sleep (24) or nocturnal hypoxia (25, 26) are thought to be the culprits for daytime HT. In any event, post-apneic BP elevations should not be overlooked considering their impacts on cerebrovascular and cardiovascular systems (27). The possibility of cardiovascular and cerebrovascular complications of OSA may be increased, as the patients with OSA are under high BP for a significant time during sleep due to pre-apneic as well as post-apneic BP elevations. In addition to this sustained high BP, nocturnal BP fluctuations observed in OSA might have deleterious effects on vascular walls (14). In this respect, preventing cardiovascular complications through early treatment of OSA is very important, and methods should be developed to predict treatment effects depend-

ing on such characteristics of patients as age, obesity, and baseline BP.

In conclusion, the more significant correlation between delta BP and degree of arousal than hypoxemia suggests that sympathetic activation causing post-apneic BP elevation may result from an arousal response regardless of hypoxemia.

## REFERENCES

- Partinen M. *Epidemiology of obstructive sleep apnea syndrome. Curr Opin Pulm Med* 1995; 1: 482-7.
- Fletcher EC. *The relationship between systemic hypertension and obstructive sleep apnea: facts and theory. Am J Med* 1995; 98: 118-28.
- Guilleminault C. *Clinical features and evaluation of obstructive sleep apnea. In: Kryger MH, Roth T, Dement WC, ed. Principles and Practice of Sleep Medicine. Philadelphia, W.B. Saunders Company* 1994; 667-77.
- Fletcher EC, DeBehnke RD, Lovoi MS, Gorin AB. *Undiagnosed sleep apnea in patients with essential hypertension. Ann Intern Med* 1985; 103: 190-5.
- Jeong DU, Dimsdale JE. *Sleep apnea and essential hypertension: a critical review of the epidemiological evidence for co-morbidity. Clin Exper Hypertens [A]* 1989; 11: 1301-23.
- Kales A, Bixler EO, Cadieux RJ, Schneck DW, Shaw LC III, Locke TW, Vela-Bueno A, Soldatos CR. *Sleep apnea in a hypertensive population. Lancet* 1984; 2: 1005-8.
- Williams AJ, Houston D, Finberg S, Lam C, Kinney JL, Santiago S. *Sleep apnea syndrome and essential hypertension. Am J Cardiol* 1985; 55: 1019-22.
- Millman RP, Redline S, Carlisle CC, Assaf AR, Levinson PD. *Day-time hypertension in obstructive sleep apnea. Chest* 1991; 99: 861-6.
- Suzuki M, Otsuka K, Guilleminault C. *Long-term nasal continuous positive airway pressure administration can normalize hypertension in obstructive sleep apnea patients. Sleep* 1993; 16: 545-9.
- Wilcox I, Grunstein RR, Hender JA, Doyle J, Collins FL, Fletcher PJ, Kelly DT, Sullivan CE. *Effect of nasal continuous positive airway pressure during sleep on 24-hr blood pressure in obstructive sleep apnea. Sleep* 1993; 16: 539-44.
- Shepard JW. *Cardiorespiratory changes in obstructive sleep apnea. In: Kryger MH, Roth T, Dement WC, ed. Principles and Practice of Sleep Medicine. Philadelphia, W.B. Saunders Company* 1994; 657-66.
- Shepard JW Jr. *Gas exchange and hemodynamics during sleep. Med Clin North Am* 1985; 69: 1243-64.
- Noda A, Okada T, Hayashi H, Yasuma F, Yokota M. *24-hr ambulatory blood pressure variability in obstructive sleep apnea syndrome. Chest* 1993; 103: 1343-7.
- Davies RJO, Crosby J, Vardi-Visy K, Clarke M, Stradling JR. *Non-invasive beat to beat arterial blood pressure during non-REM sleep in obstructive sleep apnea and snoring. Thorax* 1994; 49: 335-9.
- McEvoy RD, Sharp DJ, Thornton AT. *The effect of the sleeping posture on obstructive sleep apnea. Am Rev Respir Dis* 1986; 133: 662-6.
- Ali NJ, Davies RJ, Fleetham JA, Stradling JR. *Periodic movements of the legs during sleep associated with rises in systemic blood pressure. Sleep* 1991; 14: 163-5.
- Rechtschaffen A and Kales A (eds). *A Manual of Standardized Terminology, Technique, and Scoring System for Sleep Stages of Human Subjects. Los Angeles, BIS/BRI, UCLA* 1968.
- Bonnet M, Carley D, Carskadon M, Easton P, Guilleminault C, Harper Hayes B, Hirshkowitz M, Periklis K, Keenan S, Pressman M, Rothers T, Smith J, Walsh J, Weber S, Westbrook P. *EEG arousals: scoring rules and examples. A preliminary report from the Sleep Disorders Atlas Task Force of the American Sleep Disorders Association. Sleep* 1992; 15: 173-84.
- Davies RJO, Belt PJ, Roberts SJ, Ali NJ, Stradling JR. *Arterial blood pressure responses to graded transient arousal from sleep in normal humans. J Appl Physiol* 1993; 74: 1123-30.
- He J, Kryger MH, Zorick FJ, Conway W, Roth T. *Mortality and apnea index in obstructive sleep apnea: experience in 385 male patients. Chest* 1988; 94: 9-14.
- Ringler J, Basner RC, Shannon R, Schwartzstein R, Manning H, Weinberger SE, Weiss JW. *Hypoxemia alone does not explain blood pressure elevations after obstructive apneas. J Appl Physiol* 1990; 69: 2143-8.
- Shepard JW. *Hemodynamics in obstructive sleep apnea. In: Fletcher EC, ed. Abnormalities of Respiration During Sleep. Orlando, FL: Grune and Stratton* 1986; 39-62.
- Van Den Aardweg JG, Karemaker JM. *Repetitive apneas induce periodic hypertension in normal subjects through hypoxia. J Appl Physiol* 1992; 72: 821-7.
- Loredo JS, Ziegler MG, Ancoli-Israel S, Clausen JL, Dimsdale JE. *Relationship of arousals from sleep to sympathetic nervous system activity and BP in obstructive sleep apnea. Chest* 1999; 116: 655-9.
- Peled N, Greenberg A, Pillar G, Zinder O, Levi N, Lavie P. *Contributions of hypoxia and respiratory disturbance index to sympathetic activation and blood pressure in obstructive sleep apnea syndrome. Am J Hypertens* 1998; 11: 1284-9.
- Brooks D, Horner RL, Kozar LF, Render-Teixeira CL, Phillipson EA. *Obstructive sleep apnea as a cause of systemic hypertension. Evidence from a canine model. J Clin Invest* 1997; 99: 106-9.
- Douglas NJ, Polo O. *Pathogenesis of obstructive sleep apnea/hypopnea syndrome. Lancet* 1994; 344: 653-5.