Sleep, 16(6):539–544

Hypertension and Sleep

Effect of Nasal Continuous Positive Airway Pressure During Sleep on 24-hour Blood Pressure in Obstructive Sleep Apnea

Ian Wilcox, Ronald R. Grunstein, Jan A. Hedner, Jean Doyle, Fiona L. Collins, Peter J. Fletcher, David T. Kelly and Colin E. Sullivan

Department of Medicine, University of Sydney, and Sleep Disorders Centre and Department of Cardiology, Royal Prince Alfred Hospital, Sydney, Australia

Summary: Ambulatory blood pressure (BP) was measured noninvasively (Oxford Medilog ABP) at 15-minute intervals for 24 hours before and after 8 weeks of treatment with nasal continuous positive airway pressure (nCPAP) in 19 men with obstructive sleep apnea (OSA). We included both normotensive and hypertensive patients, but hypertensives were studied after withdrawal of antihypertensive drugs. Ambulatory BP before and after treatment was compared using patients as their own controls. Treatment with nCPAP was successfully established in 14 of the 19 patients (74%). Blood pressure fell significantly in patients who were successfully treated: 24-hour mean BP (systolic/diastolic) decreased from 141 ± 18/89 ± 11 mm Hg to 134 ± 19/85 ± 13 mm Hg ($p < 0.05$). The reduction in 24-hour mean systolic BP occurred during both day and night, but a significant fall in mean diastolic BP was only observed during the day. The mean blood pressure fell in both normotensive and hypertensive patients. Patients who were inadequately treated with nCPAP had no reduction in mean 24-hour BP. Effective treatment of sleep apnea with nCPAP was associated with a significant fall in both systolic and diastolic BP independent of changes in body weight or alcohol consumption, suggesting that sleep apnea was an independent factor contributing to elevated nighttime and daytime BP in these patients. **Key Words:** Sleep apnea—Hypertension—Obesity.

An association between obstructive sleep apnea (OSA) and systemic hypertension has been identified in a number of cross-sectional studies (1–5). However, potential confounding factors such as upper body or "central" obesity and excessive alcohol intake are common in patients with OSA and it is not known whether sleep apnea causes (or contributes to) elevated blood pressure levels observed in these patients (6,7). Previous reports of reduction of daytime blood pressure in hypertensive subjects with OSA following tracheostomy (8,9) have suggested that OSA may cause or aggravate hypertension, but these studies used office blood pressure measurements, which are less reproducible than ambulatory blood pressure recordings (10). Also, these studies were not controlled for the effects of body mass changes, alcohol consumption and antihypertensive drugs.

We studied men with OSA before and after short-term treatment with nasal continuous airway pressure (nCPAP) to determine whether treatment of OSA reduced 24-hour blood pressure levels in the absence of changes in weight, alcohol consumption and concurrent antihypertensive medications. We also sought to assess whether nCPAP reduced both night and daytime blood pressure.

PATIENTS AND METHODS

Patient selection

Patients were included in the study if they had significant symptomatic obstructive sleep apnea confirmed by a full polysomnographic study. We included patients with an apnea/hypopnea index of >10/hour of sleep. Patients with a high alcohol intake (>80 g/day),

Accepted for publication March 1993.
Address correspondence and reprint requests to Dr. Ian Wilcox, David Read Laboratory, Department of Medicine, Building DO6, University of Sydney, Sydney, NSW 2006, Australia.

morbid obesity (body mass index >150% ideal) or those with significant lung disease were excluded. Patients were required to have a resting supine blood pressure of <200/120 mm Hg at entry to the study including the period off anti-hypertensive drug therapy. A total of 19 men (mean age 54 ± 9 years) were included. Most patients had at least moderate sleep apnea confirmed on a full polysomnographic study and all had significant symptoms, including repetitive snoring, witnessed apneas during sleep, excessive daytime somnolence and fatigue. Approximately half the patients (10 of 19, 53%) had either a prior history of systemic hypertension (including "borderline" hypertension) or newly diagnosed hypertension (supine blood pressure >165/95).

Study protocol

The study protocol was approved by the Ethics Review Committee of the University of Sydney. Informed consent was obtained from all patients prior to entry to the study.

A detailed history and physical examination was performed at baseline, including a careful alcohol history and anthropomorphic measurements (height, weight, neck, waist and hip measurements). All patients had comprehensive lung function tests, which included lung volumes and awake arterial blood gas analysis. A 24-hour ambulatory blood pressure recording was performed after a 3-week washout of antihypertensive medications during the patients' usual activities. After completion of these initial investigations, a full diagnostic sleep study was performed. At a second subsequent study, a nasal mask was fitted and continuous positive airway pressure applied at a sufficient pressure to prevent episodes of oxygen desaturation during sleep (11).

Patients were followed up at weekly intervals by one of the investigators. At each visit, nCPAP usage for the preceding week was charted and patients were reviewed by an experienced nCPAP technologist. In between visits, patients were encouraged to contact the sleep laboratory at any time if problems with nCPAP occurred. Patients were reinvestigated with home monitoring (MESAM 4, Madaus Medizin, Freiburg, Germany) if: 1) there was no reduction in daytime symptoms of fatigue or sleepiness, 2) the patient's bed partner reported persistent snoring or 3) if patients were using nCPAP for <5 nights per week. If the MESAM study demonstrated persistent oxygen desaturations while on nCPAP, full polysomnography was performed to reassess the nCPAP pressure. After completion of the 8-week treatment period, the ambulatory blood pressure recording was repeated and weight was remeasured. The final decision as to the success of nCPAP treatment was made by an observer blinded to the ambulatory blood pressure data (RRG) using the nCPAP compliance charts and patient records. Patients were classed as nCPAP failures if they were unable to use the treatment because of intercurrent problems or had little or no subjective improvement in daytime symptoms.

Ambulatory blood pressure recordings

Blood pressure recordings were performed using a noninvasive device (Oxford Medilog ABP, Oxford Medical Systems, Abingdon, UK), which uses a combination of the auscultatory and oscillometric methods and meets the BHS and AAMI standards for ambulatory BP equipment (12). Blood pressure was measured at 15-minute intervals for 24 hours before and after 8 weeks of treatment of sleep apnea with nCPAP. The recordings were made during the patients' usual activities out of the hospital using an appropriately sized cuff and the same arm and cuff size was used for both blood pressure recordings. A detailed log was kept of the patients' activities during the recording. Two recording periods were defined, with daytime defined as 0700–2200 hours and nighttime as 2200–0700 hours.

Polysomnography

Overnight polysomnographic studies were performed between 2200 and 0600 in all patients. The initial (diagnostic) study included electroencephalography (EEG), extraocular muscle, submental, diaphragm electromyography (EMG) and air flow measurements. Respiratory movement was measured using chest and abdominal strain gauge transducers (Respitrace, Ambulatory monitoring, Ardsley, New York). Arterial oxygen saturation (SaO_2) was measured using a pulse oximeter with an ear probe and set to its fastest response (Biox 3700E, Ohmeda). All data were recorded on a polygraph recorder (Model 78D, Grass Instruments, Quincy, Massachusetts). Sleep staging was performed according to standard criteria (13). An apnea was defined as ≥10 seconds of absent airflow in the presence of chest or abdominal wall motion and a hypopnea defined as >50% reduction in amplitude of the respitrace signal for >10 seconds. The respiratory disturbance index (RDI) was defined as the number of apneas or hypopneas/hour of sleep. Obstructive sleep apnea was considered present if an average of ≥10 respiratory events per hour of sleep were detected. The nCPAP device (Sullivan®, Rescare Ltd., Sydney, Australia) was adjusted for each patient individually during a subsequent sleep study.

TABLE 1. *Ambulatory blood pressure (BP) (24-hour mean) before and after nasal continuous positive airway pressure (nCPAP)*

	Pre-nCPAP	Post-nCPAP	p
Successful nCPAP (n = 14)			
Systolic BP	141 ± 18[a]	134 ± 19	<0.02
Diastolic BP	89 ± 11	85 ± 13	<0.05
nCPAP failures (n = 5)			
Systolic BP	129 ± 22	131 ± 19	ns[a]
Diastolic BP	84 ± 13	87 ± 15	ns

[a] All values shown are mean ± SD, ns = nonsignificant.

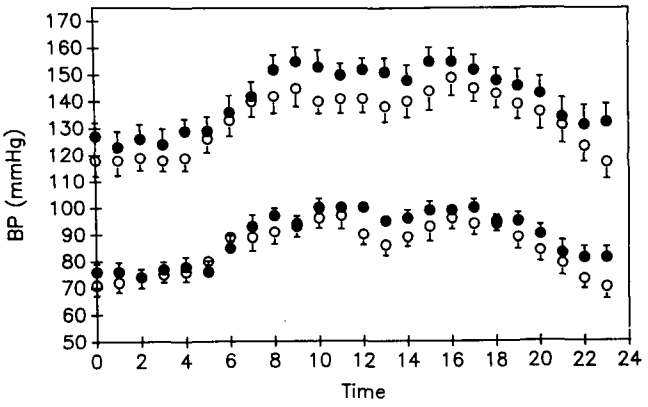

FIG. 1. Hourly blood pressure values (mean ± SEM) during ambulatory BP recordings before (closed circles) and after successful treatment of OSA with nCPAP (open circles).

Statistical analysis

All values are expressed as mean ± standard deviation unless otherwise stated. For hourly blood pressure values, the average of all recorded values in a given hour was used. Blood pressure before and after nCPAP was compared using the individual patient's mean values of all measurements taken during the relevant period. These mean values were compared using a paired *t* test. A two-tailed p value of <0.05 was considered significant. The relation between pretreatment mean ambulatory blood pressure level and the fall in blood pressure after nCPAP was examined using correlation coefficients and Spearman's rho. All statistical analysis was performed using a commercial statistical software program (SPIDA, Macquarie University Statistical Laboratory, Sydney, NSW, Australia).

RESULTS

Patients

The 19 men included were obese with a mean body mass index (BMI) of 31.5 ± 2.7 kg/m^2 (range 23.5–37.4) and had a predominantly central pattern of obesity with a mean waist/hip ratio of 1.01 ± 0.06. The patients' weight remained stable during the study. Mean BMI before treatment was 31.6 ± 4.8 kg/m^2 compared with 31.3 ± 4.5 kg/m^2 posttreatment, (p = ns). Only four of 19 patients (21%) were on antihypertensive medications prior to inclusion in the study. These included enalopril (one patient), nifedipine (one patient), atenolol (two patients), prazocin (one patient) and indapamide (one patient).

Sleep study

All patients had significant sleep apnea, with a mean of 56 ± 29 apneas per hour of sleep (range 13–118). The minimum SaO_2 during sleep was 71 ± 14% (range 45–89). During the nCPAP pressure determination study, a mean of 13 cm H_2O (range 7–20) pressure was required to maintain SaO_2 >90%. At completion of the study, nCPAP treatment was successfully achieved in 14 of 19 patients (76%). These patients reported using nCPAP for 6.4 ± 1.2 hours/night (range 4.8–8.4 hours). The reason for failure to establish nCPAP treatment in five patients was due to either recurrent nasal congestion or inability to tolerate the nCPAP mask, both common problems with nCPAP treatment.

Ambulatory blood pressure

The pretreatment 24-hour mean systolic blood pressure ranged from 100–185 mm Hg and 24-hour diastolic blood pressure from 68–115 mm Hg. Based on the 24-hour blood pressure recording, eight patients could be considered normotensive prior to commencing nCPAP treatment (daytime systolic BP <146 mm Hg and daytime diastolic BP <91 mm Hg) (14) and the remaining 11 patients were hypertensive. Average blood pressure readings during the night (2200–0700) were lower than daytime pressures, with the mean difference in systolic BP 19 ± 10 mm Hg (range −1–39) and diastolic BP 16 ± 7 mm Hg (range 3–30). The night : day pressure ratio was normal (systolic BP 0.87 ± 0.07, diastolic BP 0.82 ± 0.08 (14)).

The mean 24-hour ambulatory blood pressure before and after treatment is shown in Table 1. The change in 24-hour mean blood pressure averaged −7.5 mm Hg systolic [95% confidence interval (CI), −2.0 to −13 mm Hg, p < 0.02], and −4.1 mm Hg diastolic (95% CI, −0.4 to −7.9 mm Hg, p < 0.05). Systolic blood pressure was significantly reduced during both day (mean −7.5 mm Hg, 95% CI, −1.0 to −13.8 mm Hg, p < 0.05) and night (mean −7.5 mm Hg, 95% CI, −0.7 to −14.3 mm Hg, p < 0.05). However, a significant fall in diastolic blood pressure was present during the day (mean −5.4 mm Hg, 95% CI, −1.0 to −9.7 mm Hg, p < 0.02) but not at night (mean −2.2

TABLE 2. *Effect of nasal continuous positive airway pressure (nCPAP) on daytime and nighttime blood pressure in successfully treated patients with obstructive sleep apnea*

	Pre-nCPAP	Post-nCPAP	p
Day (0700–2200 hours)			
Systolic BP	148 ± 19[a]	140 ± 21	<0.05
Diastolic BP	95 ± 12	90 ± 13	<0.02
Heart rate (min^{-1})	78 ± 13	77 ± 11	ns[a]
Night (2200–0700 hours)			
Systolic BP	128 ± 18	121 ± 18	<0.05
Diastolic BP	78 ± 12	76 ± 12	ns
Heart rate (min^{-1})	67 ± 13	65 ± 11	ns

[a] All values are mean ± SD, ns = nonsignificant.

mm Hg, 95% CI, +2.0 to −6.4 mm Hg, p = ns) (Table 2). In contrast, the five patients who did not receive successful nCPAP had no fall in 24-hour ambulatory blood pressure.

The 24-hour blood pressure and heart rate profile of the successfully treated patients (Fig. 1) showed a normal diurnal pattern, with lower blood pressure and heart rate values recorded at night. Successful treatment of OSA with nCPAP was associated with a fall in both mean night and daytime blood pressure, but no reduction in heart rate. The reduction in blood pressure was of greater magnitude during the day than at night. These changes in blood pressure occurred independently of changes in body mass, which did not change during the study.

Although most patients successfully treated with nCPAP had a fall in blood pressure (10/14 patients, 71%), no change in blood pressure occurred in a minority (4/14 patients, 29%). The reduction in blood pressure occurred in both normotensive and hypertensive patients. There was no correlation between pretreatment ambulatory blood pressure level and the reduction in ambulatory blood pressure after nCPAP for both systolic and diastolic blood pressure (systolic BP, $r = 0.01$, p = ns or diastolic BP, $r = 0.0$, p = ns).

DISCUSSION

In the present study, we have shown that successful treatment of obstructive sleep apnea can reduce blood pressure during both the night and day. This response occurred in both normotensive and hypertensive patients and was independent of the influence of changes in body mass or antihypertensive medications. These findings suggest that sleep apnea is a causal factor in elevated blood pressure levels commonly found in this patient population.

The reduction in blood pressure was relatively modest but significant because reductions in casual blood pressure measurement of this magnitude, if maintained long term, are associated with significant reduction in cardiovascular risk at all levels of blood pressure (15). The measured fall in blood pressure may have underestimated the potential hypotensive effect of nCPAP treatment, partly because the period of observation (8 weeks) was relatively short. In addition, self-reported CPAP use tends to overestimate objective measurements of treatment usage. Furthermore, technical problems, including mask leaks and nasal obstruction due mainly to a vasomotor (nonallergic) rhinitis, sometimes delay the effective control of sleep apnea by nasal CPAP. Effective nCPAP therapy was not established in five patients (31%).

We did not include a control group of patients with OSA, who were either not treated or given nCPAP at sub-therapeutic levels ("sham control"), in the present study for several reasons. First, we were concerned about the potential risks of restricting nCPAP treatment—particularly off antihypertensive medications—for approximately 3 months in OSA patients. Second, one of the main reasons for having untreated controls would be to control for a placebo effect on blood pressure. However, the placebo effect, well recognized in studies using office blood pressure measurements, has not been observed in most studies using ambulatory blood pressure monitoring (16–19). Finally, we considered that a beneficial effect of low-pressure nCPAP on OSA, and possibly blood pressure, could not be excluded. However, the subjects in whom technical difficulties with nCPAP prevented effective treatment provided a "sham" control group, whose blood pressure did not fall over the study period.

The patients' 24-hour blood pressure profile showed a normal diurnal variation in blood pressure levels, with lower nighttime than daytime blood pressures. We have previously shown that this pattern of circadian blood pressure variation is typical of ambulatory blood pressure recordings in patients with sleep apnea (20). Following successful nCPAP treatment, both daytime (systolic and diastolic) and nighttime (systolic) blood pressure fell significantly. The beneficial effect of nCPAP on blood pressure was evident throughout the 24-hour period, suggesting that sleep apnea influenced both nighttime and daytime blood pressure. The effect of treatment with nCPAP on daytime blood pressure is not an unexpected finding because epidemiological studies suggest a link between daytime hypertension and sleep apnea (1–7). There are also well-described cyclical increases in blood pressure during apneas, changes which are abolished by treatment (20). However, blood pressure variability was not assessed adequately because of the relatively infrequent measurements during sleep compared with previous studies, which used intraarterial blood pressure recordings and continuous blood pressure measurements (20).

Patients with OSA have been reported to have in-

creased echocardiographically determined left ventricular mass, even if normotensive (21). One possible explanation of this finding is that these patients do not have the normal nocturnal fall in blood pressure (23,24) because hypertensive patients without OSA who do not have a nocturnal fall in blood pressure have greater left ventricular mass than hypertensives with a normal diurnal blood pressure profile (25). This was not the case in the present study, where average nighttime blood pressure was lower than average daytime blood pressure, findings that are similar to those we have previously reported (20). However, other potentially important influences on the development of left ventricular hypertrophy, such as increased blood pressure variability and elevated plasma catecholamines, were not measured in this study. Another potential influence on blood pressure in OSA is atrial natriuretic factor (ANF). In a previous study, we showed that ANF is released during sleep in OSA and suppressed by nCPAP (26). Atrial natriuretic factor has both vasodilator and diuretic effects, which may not only contribute to the nocturnal diuresis characteristic of OSA but may also promote a fall in blood pressure at night in OSA. Suppression of ANF release by treatment with nCPAP may explain why the effect of nCPAP treatment was less on nighttime than daytime blood pressure.

The mechanism by which OSA causes elevation of daytime blood pressure is not known, but there is accumulating evidence to suggest involvement of the sympathetic nervous system and vascular endothelial dysfunction. During sleep, high and fluctuating levels of peripheral sympathetic nerve activity occur during apneas and are associated with cyclical increases in blood pressure (27). Recently, Carlson et al. (28) demonstrated augmented muscle sympathetic nerve activity during the day in patients with OSA. We have previously demonstrated marked increases in blood pressure in response to hypoxia during the awake state in OSA (29). Abnormal endothelial function may also be a factor in a report of increased urinary excretion of endothelin in untreated patients with OSA, which is suppressed by nCPAP treatment (30). Therefore, it is possible that the effects of repetitive apneas during sleep cause altered vasoreactivity during the day, leading to sustained arterial hypertension.

Whatever the mechanisms, our data provide direct evidence that such mechanisms are indeed induced by sleep apnea and are partially reversible with nCPAP treatment.

Acknowledgements: We thank Emilia Sforza, M.D., for assistance with scoring of polysomnographic recordings. This study was supported by a project grant from the National Health and Medical Research Council of Australia and a cardiovascular research grant from the Australian Mutual Provident Society. Dr. Hedner was supported by the Swedish Medical Research Foundation (grant no. 9892) and the Swedish Heart and Lung Foundation.

REFERENCES

1. Lavie P, Rachamim B-Y, Rubin A-H E. Prevalence of sleep apnea syndrome among patients with essential hypertension. *Am Heart J* 1984;108:373–6.
2. Kales A, Bixler EO, Cadieux RJ, et al. Sleep apnoea in a hypertensive population. *Lancet* 1984;ii:1005–22.
3. Fletcher EC, DeBehnke RD, Lovoi MS, Gorin AB. Undiagnosed sleep apnea in patients with essential hypertension. *Ann Int Med* 1985;103:190–5.
4. Millman RP, Redline S, Carlisle CC, Assaf A, Levinson PD. Daytime hypertension in obstructive sleep apnea. Prevalence and contributing risk factors. *Chest* 1991;99:861–2.
5. 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.
6. Stradling JR. Sleep apnoea and systemic hypertension. *Thorax* 1989;44:984–9.
7. Jeong D-U, Dimsdale JE. Sleep apnea and essential hypertension: a critical review of the epidemiological evidence for comorbidity. *Clin Exp Hypertens [A]* 1989;A11(7):1301–23.
8. Burack B, Pollack C, Borowiecki B, Weitzman E. The hypersomnia-sleep apnea syndrome: a reversible major cardiovascular hazard. *Circulation* 1977;56:17 (abstr.).
9. Guilleminault C, Simmons FB, Motta J, Cumminskey J, Schroeder JS, Dement WC. Obstructive sleep apnea syndrome and tracheostomy. Long-term follow-up experience. *Ann Int Med* 1981;141;985–8.
10. James GD, Pickering TG, Yee LS, Harshfield GA, Riva S, Laragh JH. The reproducibility of average, ambulatory, home and clinic pressures. *Hypertension* 1988;11:545–9.
11. Sullivan CE, Issa FG, Berthon-Jones M, Eves L. Reversal of obstructive sleep apnoea by continuous positive airway pressure applied through the nares. *Lancet* 1981;i:862–5.
12. O'Brien E, O'Malley K. Twenty-four-hour blood pressure monitoring: a review of validation data. *J Hypertension* 1990;8(suppl 6):S11–S16.
13. Rechtshaffen A, Kales A, eds. *A manual of standardized terminology. Technics and scoring systems for sleep stages of normal subjects.* Bethesda, MD: National Institutes of Health, 1968 (Publication no. 204).
14. Staessen JA, Fagard RH, Lijnen PJ, Thijs L, Van Hoof R, Amery AK. Mean and range of the ambulatory pressure in normotensive subjects from a metanalysis of 23 studies. *Am J Cardiol* 1991;67:723–7.
15. MacMahon S, Peto R, Cutler J, et al. Blood pressure, stroke, and coronary heart disease. Part 1, prolonged differences in blood pressure: prospective observational studies corrected for the regression dilution bias. *Lancet* 1990;335:765–74.
16. Gould BA, Mann S, Davies AB, Altman DG, Raftery EB. Does placebo lower blood pressure? *Lancet* 1981;ii:1377–81.
17. Dupont AG, van der Niepen P, Six RO. Placebo does not lower blood pressure. *Br J Clin Pharmacol* 1987;24:106–9.
18. Conway J, Johnson J, Coats A, Somers V, Sleight P. The use of blood pressure monitoring to improve the accuracy, and reduce the number of subjects in clinical trials of anti-hypertensive agents. *J Hypertens* 1988;6:111–16.
19. Staessen JA, Fagard RH, Lijnen PJ, Thijs L, Van Hoof R, Amery AK. Ambulatory blood pressure monitoring in clinical trials. *Hypertens* 1991;9(Suppl 1):S13–S19.
20. Wilcox I, Grunstein RR, Collins FL, Doyle J, Kelly DT, Sullivan CE. Circadian variation in blood pressure in obstructive sleep apnea. *Blood Pres* 1992;1:219–22.
21. Mayer J, Becker H, Brandenburg U, Penzel T, Peter JH, v. Wichert P. Blood pressure and sleep apnea: results of long-term nasal continuous positive airways pressure therapy. *Cardiology* 1991;79:84–92.

22. Hedner JA, Ejnell H, Caidahl K. Left ventricular hypertrophy independent of hypertension in patients with obstructive sleep apnea. *J Hypertens* 1990;8:941–6.
23. Guilleminault C, Tillkan A, Dement W. The sleep apnea syndromes. *Ann Rev Med* 1976;27:465–84.
24. Warley ARH, Mitchell JH, Stradling JR. Prevalence of nocturnal hypoxaemia amongst men with mild to moderate hypertension. *Q J Med* 1988;68:637–44.
25. Verdecchia P, Schillaci G, Guerrieri M, et al. Circadian blood pressure changes and left ventricular hypertrophy in essential hypertension. *Circulation* 1990;81:528–36.
26. Krieger J, Laks L, Wilcox I, et al. Atrial natriuretic peptide release during sleep in patients with obstructive sleep apnea before and during treatment with nasal continuous positive airway pressure. *Clin Sci* 1989;77:407–11.
27. Hedner JA, Ejnell H, Sellgren J, Hedner T, Wallin G. Is high and fluctuating muscle sympathetic nerve activity in the sleep apnea syndrome, of pathogenetic importance for the development of hypertension? *J Hypertension* 1988;6:S529–31.
28. Carlson J, Hedner JA, Elam M, Ejnell H, Wallin G. Augmented sympathetic activity in awake patients with obstructive sleep apnoea. *Sleep Res* 1991;20A:297.
29. Hedner JA, Wilcox I, Grunstein RR, Laks L, Sullivan CE. A potent pressor response in awake sleep apnea patients. *Am Rev Respir Dis* 1992;146:1240–5.
30. Ehlenz K, Herzog P, von Wichert P, Kaffarnik H, Peter JH. Renal excretion of endothelin in obstructive sleep apnea syndrome. In: Gautier C, Escourrou P, Curzi-Dascalova L, eds. *Colloque INSERM*. John Libby Eurotext, Ltd., 1991;217:226.