

## High prevalence of unrecognized sleep apnoea in drug-resistant hypertension

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**Objectives** To determine the prevalence of obstructive sleep apnoea (OSA) in adult patients with drug-resistant hypertension, a common problem in a tertiary care facility.

**Design** Cross-sectional study.

**Setting** University hypertension clinic.

**Patients and methods** Adults with drug-resistant hypertension, defined as a clinic blood pressure of  $\geq 140/90$  mmHg, while taking a sensible combination of three or more antihypertensive drugs, titrated to maximally recommended doses. Each of the 41 participants completed an overnight polysomnographic study and all but two had a 24 h ambulatory blood pressure measurement.

**Results** Prevalence of OSA, defined as an apnoea-hypopnoea index of  $\geq 10$  obstructive events per hour of sleep, was 83% in the 24 men and 17 women studied. Patients were generally late middle-aged ( $57.2 \pm 1.6$  years, mean  $\pm$  SE), predominantly white (85%), obese (body mass index,  $34.0 \pm 0.9$  kg/m<sup>2</sup>) and taking a mean of  $3.6 \pm 0.1$  different antihypertensive medications daily. OSA was more prevalent in men than in women (96 versus 65%,  $P=0.014$ ) and more severe (mean apnoea-hypopnoea index of  $32.2 \pm 4.5$  versus  $14.0 \pm 3.1$  events/h,  $P=0.004$ ). There was no gender difference in body mass index or age.

### Introduction

There is compelling evidence that lowering blood pressure significantly reduces the incidence of cardiovascular disease. However, more than 75% of the hypertensive population has blood pressure readings that are above the level recommended as the goal of treatment [1]. In many cases, hypertension is unrecognized or is left untreated after detection but, disturbingly, blood pressure is uncontrolled in over one-half of patients receiving treatment for hypertension [2,3]. There are many reasons for this failure [4,5] but, even when known factors are taken into account, there is a substantial fraction of patients whose hypertension is resistant to intensive pharmacological antihypertensive therapy [5]. Prognosis for these patients is grave; they

Women with OSA were significantly older and had a higher systolic blood pressure, lower diastolic blood pressure, wider pulse pressure and slower heart rate than women without OSA.

**Conclusions** The extraordinarily high prevalence of OSA in these patients supports its potential role in the pathogenesis of drug-resistant hypertension, and justifies the undertaking of a randomized controlled trial to corroborate this hypothesis. *J Hypertens* 19:2271–2277 © 2001 Lippincott Williams & Wilkins.

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experience a high incidence of stroke, renal insufficiency and cardiovascular morbid events [6,7]. It is important therefore to search for potential underlying factors that could contribute to uncontrolled hypertension in such patients. One such factor that is frequently not considered is obstructive sleep apnoea (OSA).

Several large epidemiological studies have demonstrated convincingly that OSA is an independent risk factor for mild hypertension [8–11]. However, an association between OSA and more severe or drug-resistant forms of hypertension has not been systematically evaluated. Since OSA may cause hypertension, but is not influenced by antihypertensive drug treat-

ment [12], the aim of the present study was to determine the prevalence of OSA in adult patients with drug-resistant or refractory hypertension.

## Methods

The charts of patients referred to a university hospital hypertension clinic were reviewed to identify individuals with poorly controlled hypertension. Patients with uncontrolled hypertension despite the use of multiple antihypertensive drugs were assessed to ascertain the cause of apparent treatment resistance. Subjects with pharmacologically resistant hypertension were enrolled in the study. Patients were excluded if they had known OSA, 'white-coat' hypertension [4,13], a history of poor compliance with drug treatment, evidence of the use of exogenous substances that can raise blood pressure or interfere with the actions of antihypertensive agents, a secondary form of hypertension including renal insufficiency defined as a serum creatinine level ( $150 \mu\text{mol/l}$ ), a history of excess alcohol use or elevated liver enzyme levels (more than twice the upper limit of normal), anatomic abnormalities of the upper airways and hemodynamically significant aortic or mitral valve disease. Pregnant women were also excluded. Refractory hypertension was defined as a clinic blood pressure level of  $\geq 140/90$  mmHg, while taking a sensible combination of three or more antihypertensive drugs, titrated to maximally recommended doses [14]. Therapy included a diuretic, unless there was a specific contraindication to its use, and a low sodium diet. Eligible subjects were observed without changing their antihypertensive drug regimen for at least 1 month before entry into the study.

Ambulatory blood pressure was recorded in the non-dominant arm for 24 h at 20 min intervals during the day and every 30 min during the night, using a portable blood pressure monitoring device (model 90207, Space-Labs Medical Inc, Redmond, Washington, USA). Awake and sleep periods were determined from the diary that patients were instructed to complete. Patients were classified as dippers or non-dippers using a night-day ratio of 90% or higher for systolic blood pressure to indicate non-dipping [13]. For technical reasons, two patients with very severe hypertension were not monitored. Both were admitted to hospital for supervised administration of antihypertensive drug treatment and were found still to have persistently elevated daytime blood pressure in this setting.

All subjects had a full overnight polysomnographic study in the manner previously described [15]. At the time of the overnight sleep study, patients' weight and height were determined. Heart rate was determined from a precordial electrocardiograph. Thoraco-abdominal movements were measured by a calibrated respiratory inductance plethysmograph (Respirace,

Ambulatory Monitoring Inc., White Plains, New York, USA), and oxyhemoglobin saturation ( $\text{SaO}_2$ ) was assessed by ear oximetry (Oxysuttle, SensorMedics Corp., Anaheim, California, USA). The mean lowest  $\text{SaO}_2$  during sleep was calculated by averaging the lowest  $\text{SaO}_2$  for each 30-s epoch during sleep as previously described [15]. Obstructive apnoeas were defined as an absence of tidal volume for at least 10 s and hypopnoeas, as a  $\geq 50\%$  reduction in tidal volume from the baseline level for at least 10 s, during which there were paradoxical thoraco-abdominal movements. Patients who had 10 or more obstructive apnoeas and hypopnoeas per hour of sleep were classified as having OSA. Scoring and interpretation of sleep study data were done without knowledge of the subjects' clinical status.

Continuous variables were expressed as the mean  $\pm$  SEM and nominal variables were reported as frequencies. An unpaired Student's *t*-test was performed to compare continuous variables and Fisher's exact test was used to test for differences between categorical variables [16]. The Statistical Package for Social Sciences (SPSS, version 8, Chicago, Illinois, USA) was used for statistical analysis.  $P < 0.05$  was considered statistically significant.

## Results

Forty-one patients, 24 men and 17 women, with refractory hypertension were enrolled in this study. They were generally late middle-aged (mean age  $57.2 \pm 1.6$  years; range 35–76 years), predominantly white (85%), and obese (mean body mass index,  $34.0 \pm 0.9 \text{ kg/m}^2$ ; range 22.2–50.7  $\text{kg/m}^2$ ). Subjects were taking an average of  $3.6 \pm 0.1$  different antihypertensive medications daily and had a mean office blood pressure of  $168.1 \pm 4.4/94.0 \pm 2.3$  mmHg, mean daytime blood pressure of  $152.0 \pm 2.0/87.3 \pm 1.4$  mmHg and mean night-time blood pressure of  $141.7 \pm 2.9/77.7 \pm 1.5$ . The most frequently prescribed agents by drug class were diuretic (85%), calcium-channel blocker (83%), beta-adrenergic blocker (66%) and angiotensin converting enzyme inhibitor (63%). The use of a beta-adrenergic blocker was higher in women with OSA (82%) than in those without (67%), but the difference was not statistically significant. Four women were on hormone replacement therapy. Forty-six percent (19/41) of patients had comorbid conditions such as diabetes mellitus (22%), coronary artery disease (17%), cerebrovascular disease (7%), chronic heart failure (5%) and renal insufficiency (2%).

Table 1 shows that the overall prevalence of OSA was 83%. OSA was more prevalent in men than in women (96 versus 65%,  $P = 0.014$ ) and more severe (mean apnoea-hypopnoea index of  $32.2 \pm 4.5$  versus  $14.0 \pm 3.1$  events/h,  $P = 0.004$ ). Men, compared with women,

**Table 1** Prevalence of obstructive sleep apnoea (OSA) and mean apnoea-hypopnoea index (AHI)

	Prevalence (%)	Mean AHI $\pm$ SE (events/h)
Men	95.8*	32.2 $\pm$ 4.5†
Women	64.7*	14.0 $\pm$ 3.1†
All	82.9	24.7 $\pm$ 3.2

Data are mean  $\pm$  SEM. \*  $P < 0.05$ , Fisher's exact test; †  $P < 0.05$ , unpaired *t*-test.

had significantly more movement arousals per hour of sleep (Table 2) and longer stage I sleep time (28.0  $\pm$  2.8 versus 18.2  $\pm$  4.0 min,  $P = 0.043$ ). However, there was no gender difference in age, body mass index, blood pressure or other sleep measures.

Women with OSA were significantly older (Table 3) and had a higher systolic blood pressure (154.9  $\pm$  4.6 versus 141.2  $\pm$  3.9 mmHg,  $P = 0.086$ ), lower diastolic blood pressure (80.8  $\pm$  2.1 versus 90.0  $\pm$  2.3 mmHg,  $P = 0.02$ ), wider pulse pressure (74.1  $\pm$  5.0 versus 51.2  $\pm$  2.1 mmHg,  $P = 0.01$ ), and slower heart rate (67.9  $\pm$  4.2 versus 82.4  $\pm$  3.2 b.p.m.,  $P = 0.047$ ) than women without OSA on 24 h ambulatory blood pressure recording. There were no significant differences in body mass index, the number or types of antihypertensive medications prescribed, and total time asleep or sleep periods among women with and without OSA (Table 3). Because only one man did not have OSA, no comparisons were made between those with and without OSA were made.

Table 4 shows that 64.1% of patients with refractory hypertension were non-dippers. However, there was no difference in this prevalence or the change in blood pressure from awake to sleep periods between men and women, or between those with and without OSA. The magnitude of the fall in diastolic blood pressure during

sleep, expressed as night/day ratio, was significantly greater than that for systolic blood pressure ( $P < 0.01$ ).

## Discussion

This is the first study to demonstrate an extraordinarily high prevalence of OSA in patients with hypertension refractory to aggressive drug treatment. While others have reported an association between OSA and severe hypertension [17–20], many patients in these studies did not meet established criteria for refractory or drug-resistant hypertension [14]. In addition, unlike studies that have recruited subjects from sleep laboratories [17], who were therefore highly likely to have OSA, the participants in the present study were drawn from a specialty hypertension clinic and selected exclusively for drug-resistant hypertension, irrespective of sleep-related symptoms. Moreover, patients who were referred with known OSA were excluded. Thus, our study avoided the selection biases observed in previous reports.

In most studies, the frequency of OSA is significantly higher in hypertensive patients than in normotensive control subjects [19–23]. However, prevalence estimates vary markedly because of differences in the method to detect sleep apnoea, definitions of hypertension and OSA and demographic characteristics of the subjects studied [24]. In studies that have assessed subjects in a sleep laboratory using overnight polysomnography, the prevalence of OSA, defined as an apnoea or apnoea-hypopnoea index of 10 or more episodes per hour of sleep, ranged from 23 to 35% in relatively unselected hypertensive populations [19–23,25]. By contrast, 95.8% of men and 64.7% of women with refractory hypertension in our study had OSA, employing a similar definition of OSA and similar method to assess sleep.

**Table 2** Comparison of men and women with refractory hypertension

Factors	Men ( <i>n</i> = 24)		Women ( <i>n</i> = 17)	
	<i>n</i>	Mean $\pm$ SE	<i>n</i>	Mean $\pm$ SE
Age (years)	24	56.4 $\pm$ 1.8	17	58.3 $\pm$ 3.0
Body mass index (kg/m <sup>2</sup> )	24	33.8 $\pm$ 1.4	17	34.3 $\pm$ 1.2
No. of medications ( <i>n</i> )	24	3.6 $\pm$ 0.2	17	3.6 $\pm$ 0.2
Total time asleep (min)	24	278.9 $\pm$ 18.3	17	271.6 $\pm$ 25.1
Sleep efficiency (%)	24	69.5 $\pm$ 3.6	17	67.0 $\pm$ 5.8
Movement arousals (no./h)	24	33.3 $\pm$ 4.9*	17	18.1 $\pm$ 3.2*
Mean SaO <sub>2</sub> (%)	24	94.6 $\pm$ 0.3	17	94.1 $\pm$ 0.5
Lowest SaO <sub>2</sub> (%)	24	82.4 $\pm$ 1.6	17	86.1 $\pm$ 1.1
Office systolic blood pressure (mmHg)	24	162.2 $\pm$ 4.8	17	176.6 $\pm$ 8.0
Office diastolic blood pressure (mmHg)	24	93.7 $\pm$ 2.9	17	94.4 $\pm$ 3.7
Office pulse pressure (mmHg)	24	68.5 $\pm$ 4.4	17	82.2 $\pm$ 7.1
24 h systolic blood pressure (mmHg)	23	149.0 $\pm$ 2.6	16	150.6 $\pm$ 3.7
24 h diastolic blood pressure (mmHg)	23	86.3 $\pm$ 2.0	16	83.7 $\pm$ 1.9
24 h pulse pressure (mmHg)	23	62.7 $\pm$ 2.6	16	66.9 $\pm$ 4.4

\*  $P < 0.05$ , unpaired *t*-test.

Table 3 Comparison of women with and without obstructive sleep apnoea (OSA)

Factors	No OSA (n = 6)	OSA (n = 11)
	Mean ± SE	Mean ± SE
Age (years)	49.8 ± 5.3*	62.9 ± 2.9*
Body mass index (kg/m <sup>2</sup> )	34.5 ± 1.7	34.2 ± 1.7
AHI (events/h)	4.2 ± 0.8†	19.4 ± 3.9†
No. of medications (n)	3.3 ± 0.2	3.8 ± 0.2
Total time asleep (min)	318.8 ± 27.1	245.8 ± 34.2
Sleep efficiency (%)	79.9 ± 7.7	60.0 ± 7.2
Movement arousals (no./h)	12.0 ± 2.7	21.5 ± 4.4
Mean SaO <sub>2</sub> (%)	93.7 ± 0.6	92.6 ± 0.7
Lowest SaO <sub>2</sub> (%)	88.8 ± 0.6	84.8 ± 1.4
Office systolic blood pressure (mmHg)	179.8 ± 17.8	174.8 ± 8.5
Office diastolic blood pressure (mmHg)	103.7 ± 7.6	89.3 ± 3.2
Office pulse pressure (mmHg)	76.2 ± 10.5	85.5 ± 9.5

†P-value not determined as this variable was the basis for group categorization; AHI, apnoea-hypopnoea index. \*P < 0.05, unpaired t-test.

A major problem in determining the importance of OSA in the development of refractory hypertension is the potential confounding effect of obesity. We observed obesity, defined as a body mass index of 30 kg/m<sup>2</sup> or more, in 71% (29/41) of our study patients. This is in keeping with the observation of obesity in 60–90% of individuals assessed at sleep disorder clinics [24]. Other studies, in both clinical and general population samples, have shown a strong positive relationship between body mass index or measures of body fat distribution and the apnoea-hypopnoea index [8–10]. Obesity is also associated with an increased rate of uncontrolled hypertension and the use of higher drug doses to produce equivalent effects on blood pressure, even after statistically adjusting for the influence of age, gender and arm circumference [26].

Investigators have employed a number of different strategies to control for the confounding effect of obesity. In small clinical studies, normotensive subjects have been matched with hypertensive patients with respect to weight, age and gender [23]. In larger

studies, evaluating either clinic patients or population samples, multivariate statistical methods were used to control for a number of confounding factors simultaneously. These studies have found a significant association between OSA at night and raised daytime blood pressure or daytime hypertension, even after adjusting for body mass index or measures of body fat distribution [8–10]. While the magnitude of the effect of OSA on raising blood pressure tends to be small, its independent contribution suggests a causal effect and highlights its importance as a determinant of blood pressure variability.

Prospective data from the Wisconsin Sleep Cohort Study provide strong new evidence to support the concept of OSA as independent risk factor for hypertension [11]. In this population-based study, odds ratios of having hypertension at follow-up 4 years later, after adjusting for baseline hypertension status, age, gender, body mass index and waist and neck circumference, increased progressively from a reference value of 1 for the group with no episodes of apnoea and hypopnoea at baseline to 2.89 in the group with a baseline apnoea-hypopnoea index of 15 events or more per hour of sleep. The finding that sleep-disordered breathing preceded the diagnosis of hypertension suggests that it may play an important role in its development.

Table 4 Change in systolic and diastolic blood pressure from awake to sleep periods and prevalence of non-dipping expressed as a percentage by group. Night/day ratio values are mean (SE) adjusted for age and body mass index

Group	n	Night/day ratio (%)		Non-dipping prevalence (%)
		SBP	DBP	
All	39	93.1 (1.2)	89.1 (1.2)*	64.1
Sex				
Male	23	92.6 (1.6)	89.5 (1.6)*	65.2
Female	16	93.8 (2.0)	88.5 (1.9)*	62.5
Sleep apnoea				
Present	33	93.1 (1.4)	89.3 (1.3)*	66.7
Absent	6	93.0 (3.4)	88.4 (3.2)*	50.0

SBP, systolic blood pressure; DBP, diastolic blood pressure. \*Night/day ratios were significantly lower for DBP than for SBP in each of the four study groups (P < 0.01, paired t-tests); no significant differences were found between study groups in night/day ratio (based on unpaired t-tests) or non-dipping prevalence (based on Fisher's exact test).

Animal studies provide the most compelling evidence for a causal link between night-time obstructive apnoea and daytime hypertension, independent of obesity. In a canine model of OSA [27], airway obstruction was induced repetitively during sleep by a computer that received telemetered electroencephalographic and electromyographic signals from chronically implanted electrodes. When the computer detected sleep, it sent a signal to an occlusion valve attached to an endotracheal tube through which the dog breathed, thereby producing an obstructive apnoea and arterial O<sub>2</sub> desaturation. When the dog awoke from sleep, the occlusion was

released. Dogs subjected to long-term OSA (more than 5 weeks) gradually developed both nocturnal and daytime hypertension that resolved within one month of cessation of obstructive apnoea. These findings strongly indicate that intermittent airway obstruction during sleep causes daytime hypertension.

In our study, the prevalence of OSA and the frequency of the apneic-hypopneic episodes, a measure of OSA severity, were significantly higher in men with refractory hypertension than in women. The modifying effects of gender, however, were not explained by differences in age or body mass index. Past studies have also found a male predominance in abnormal breathing during sleep [24]. Although referral bias of men to sleep clinics for evaluation is well documented [24,28], OSA is still more common in men in community studies with population-based sampling [29,30]. Possible explanations for this difference include a larger neck girth, a more central distribution of body fat producing fat deposits around the pharynx and the effects of testosterone. These factors are also cited as reasons for the higher prevalence of hypertension and its greater severity among young and middle-aged men compared to women [31].

The women with OSA in the present study had a higher systolic blood pressure, lower diastolic blood pressure, slower heart rate and wider pulse pressure than the women without OSA; they were also significantly older. It is well known that there is a steady rise in systolic blood pressure as the population ages [32]. Diastolic blood pressure, on the other hand, increases progressively during early adulthood but plateaus around the age of 50 years and starts to decline by the age of 60 years. As a consequence, pulse pressure widens with advancing age. The likelihood of developing sleep apnoeic events also increases with age in both men and women [33–35], and even in the healthy elderly there is an age-dependent continuum in the prevalence and severity of sleep-disordered breathing [36]. The effect of age on sleep has been attributed to a greater frequency of health problems such as obesity, chronic circulatory ailments and neurological diseases. In our study, obesity did not appear to be responsible for the age effect since the women with OSA did not differ in body mass index from those without OSA. It is possible that the age-related rise in systolic blood pressure is a manifestation of arteriosclerosis and signals the presence of diffuse vascular disease [32], and this may be related to the increased risk of OSA in older women.

The differing blood pressure profiles in the women with and without OSA raise the possibility that the pathophysiology of refractory hypertension may also differ. While our study was not designed to address this issue, evidence garnered from other studies supports

this hypothesis. In a population-based study, Young *et al.* [8] demonstrated that each additional episode of apnoea or hypopnoea per hour of sleep was associated with a two-fold increase in systolic blood pressure as compared with diastolic blood pressure. In a clinical study of congestive heart failure patients with OSA, Tkacova *et al.* [37] observed that only systolic blood pressure increased significantly in conjunction with obstructive apnoeas during stage 2 non-rapid eye movement sleep, and that continuous positive airway pressure abolished OSA and significantly attenuated this increase in systolic blood pressure but had no effect on diastolic blood pressure. Subjects were also receiving optimal pharmacological treatment for their heart failure that included agents with potent blood pressure-lowering properties. Recently, we observed in a treated heart failure population that those with OSA were significantly more likely to have an elevated systolic blood pressure level than those without OSA, whereas a high diastolic blood pressure was not associated with OSA [38]. Taken together, these data suggest that OSA has a direct and disproportionate effect on systolic blood pressure that is difficult to control with pharmacological agents with hypotensive properties.

All subjects in the present study were taking blood pressure-lowering medications. Because some antihypertensive drugs may impair memory or psychomotor function [39], it has been suggested that they may also adversely affect the breathing pattern during sleep [40,41]. However, there is little evidence to support this hypothesis. In clinical studies of untreated and treated hypertensive patients, the proportion with OSA and the severity of this condition were similar in the two groups of subjects [19,23]. Likewise, in intervention studies in which patients underwent sleep studies before and after starting antihypertensive medication, there was either no change in the severity of OSA [12,42] or a significant reduction in the apnoeic index [43]. Thus, the use of antihypertensive medications does not appear to explain the high prevalence of OSA in our patients with refractory hypertension.

Treatment resistance is a common problem in a tertiary care facility and is often related to poor drug compliance or suboptimal treatment regimen [5]. In our study, patient interview was the principal method to assess medication compliance, although close monitoring of response to therapy and pill counts were employed in instances where poor compliance was suspected. In two instances, patients were admitted to hospital for supervised medication administration to confirm the diagnosis of refractory hypertension. These indirect methods, while not as sensitive or specific as direct measurement of plasma or urinary drug levels, nonetheless provide a good estimate of treatment compliance [44] and reduce the likelihood that failure to

comply with prescribed treatment was the cause of poor blood pressure control. All of our study patients were taking at least three antihypertensive medications that had been titrated to maximally recommended doses. Therapy included a diuretic, unless there was a contraindication to its use, and a low sodium diet. Thus, our patients had 'true' drug-resistant hypertension.

As a group, the prevalence of non-dipping of blood pressure in refractory hypertension was substantially higher than that reported in a working group document summarizing the experience of multiple investigators in 7320 subjects [45]. In that report, 31.8% of all subjects would be labelled as non-dippers using the same threshold as employed in our study to indicate non-dipping. In our study, the prevalence was more than twice that value with the sole exception of refractory hypertensive patients without OSA where it was 50%. Our finding is in accord with the original observation of Lugesesi *et al.* who found that the physiological decrease in systemic pressure during sleep was absent in heavy snorers with obstructive apnoea [46]. Our results of no difference in the prevalence of non-dipping or the percentage change in blood pressure between those with and without OSA differ to some extent from those of Portaluppi *et al.* [47]. In their study, they found no OSA in untreated men with essential hypertension whose blood pressure dipped normally at night. One explanation for this difference is the severity of the hypertension which was likely greater in our patients, and this has been shown to be associated with increased likelihood of OSA [17–20]. It is possible that the high prevalence of non-dipping may be one reason for the drug resistance of our hypertensive patients. However, the absence of non-dipping in more than one-third of them suggests that other factors also play a role in the pathogenesis of this condition.

This study does not address whether there is a difference in the prevalence of OSA in patients with refractory hypertension compared to those whose blood pressure is easily controlled with antihypertensive medication. Nonetheless, the results of this study and those of other epidemiological studies support an important role of OSA in the pathogenesis of severe hypertension. Since OSA is readily treatable by continuous positive airway pressure (CPAP), our results provide a compelling rationale to undertake a randomized controlled trial of CPAP in patients with drug-resistant hypertension and OSA to determine its potential for lowering blood pressure in such patients.

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