

Obstructive Sleep Apnea and Resistant Hypertension*

A Case-Control Study

Sandro Cadaval Gonçalves, MD, PhD; Denis Martinez, MD, PhD;
Miguel Gus, MD, PhD; Erlon Oliveira de Abreu-Silva, MD;
Carolina Bertoluci, MD; Isabela Dutra, MD; Thais Branchi, MD;
Leila Beltrami Moreira, MD, PhD; Sandra Costa Fuchs, MD, PhD;
Ana Cláudia Tonelli de Oliveira, MD; and Flávio Danni Fuchs, MD, PhD

Background: Obstructive sleep apnea syndrome (OSAS) has been linked to resistant hypertension, but the magnitude of this association and its independence of confounding have not been established.

Methods: Case patients were 63 patients with resistant hypertension (BP \geq 140/90 mm Hg using at least three BP-lowering drugs, including a diuretic), and control subjects were 63 patients with controlled BP receiving drug treatment. The primary outcome was the frequency of OSAS (apnea-hypopnea index [AHI] \geq 10 episodes per hour) determined with a portable home monitor. The comparison of AHI episodes in patients truly normotensive, truly hypertensive, and in patients with white coat or masked hypertension, based on BP determined at office and by ambulatory BP monitoring (ABPM) was a secondary outcome.

Results: Case patients and control subjects were well matched for confounding factors. OSAS was present in 45 case patients (71%) and in 24 control subjects (38%) [$p < 0.001$]. In a logistic regression model, OSAS was strongly and independently associated with resistant hypertension (odds ratio, 4.8; 95% confidence interval, 2.0 to 11.7). The AHI of case patients with normal BP in ABPM (white coat hypertension) and control subjects with abnormal BP in ABPM (masked hypertension) was intermediate between the AHI of individuals with normal and abnormal BP measures in both settings ($p < 0.001$).

Conclusions: The magnitude and independence of the risk of OSAS for resistant hypertension strengthen the concept that OSAS is a risk factor for resistant hypertension. Comorbid OSAS should be considered in patients with resistant hypertension.

(*CHEST* 2007; 132:1858–1862)

Key words: obstructive sleep apnea syndrome; resistant hypertension

Abbreviations: ABPM = ambulatory BP monitoring; AHI = apnea-hypopnea index; BMI = body mass index; CPAP = continuous positive airway pressure; OSAS = obstructive sleep apnea syndrome

Despite the availability of numerous effective therapies for hypertension, the proportion of patients with uncontrolled hypertension around the world is vexing.^{1–4} Among patients with uncontrolled hypertension, 15 to 20% are using at least three BP-lowering drugs, including a diuretic and, as such, are defined as patients with resistant hypertension.⁵ Obstructive sleep apnea syndrome (OSAS) may have a causative role in hypertension.^{6,7} OSAS prevalence rates up to 50% have

been described in patients with hypertension.⁸ OSAS was listed as one among the identifiable causes of hypertension, and its screening is justified in clinical practice.¹ The prevalence rates of OSAS may be higher among patients with resistant hypertension. In a case series,⁹ 83% of patients with resistant hypertension had OSAS, defined as apnea-hypopnea index (AHI) \geq 10 episodes per hour. The absence of a control group, however, precluded controlling for confounding factors such as gender,

age, and obesity. The aims of this case-control study were to investigate whether the association between OSAS and resistant hypertension is independent from confounding factors and to estimate the magnitude of risk.

MATERIALS AND METHODS

This case-control study was performed in the hypertension clinic of the Hospital de Clínicas de Porto Alegre (Porto Alegre, RS, Brazil), where a cohort study of patients with hypertension is underway.^{10–12} Case patients and control subjects were consecutively enrolled between March 2004 and June 2006. Adult patients of both genders who were 40 to 70 years of age and had body mass index (BMI) values ranging from 25 to 40 kg/m² were invited to participate. The Institutional Review Board approved the ethical and methodologic aspects of the investigation, and patients signed a written informed consent to participate.

Case patients had hypertension defined as resistant by BP \geq 140/90 mm Hg for at least two consecutive visits, and were receiving at least three antihypertensive drugs in appropriate doses, including a diuretic. Control subjects had BP < 140/90 mm Hg on at least two consecutive visits, and were receiving drug treatment for hypertension. Control subjects were matched to case patients based on age, gender, and BMI. Secondary hypertension was excluded in case patients and in control subjects by standard screening, which included renal Doppler ultrasound and renin/aldosterone ratio in suspected cases. Patients were also excluded in the presence of suspected nonadherence to pharmacologic treatment or a previous diagnosis of sleep disorders. Pregnancy, insulin-dependent diabetes, symptomatic or invasively treated coronary artery disease in the last 6 months, left ventricular systolic dysfunction, or any other disease associated with OSAS or compromising the capability to understand or to participate in the study were other criteria of exclusion.

Office BP was measured according to standard guidelines. ABPM was done using a monitor (Spacelabs 90207; Spacelabs; Redmond, WA) programmed to take measurements every 20 min from 7:00 AM to 11:00 PM and every 30 min from 11:00 PM to 7:00 AM. The cuff size was selected according to the arm circumference. Office hypertension was defined as BP \geq 140/90 mm Hg, and 24-h ambulatory BP monitoring (ABPM) hypertension was defined as BP \geq 130/80 mm Hg. All patients underwent full-

night, unattended, level III polysomnography by means of a portable monitor (Somnocheck; Weinmann GmbH; Hamburg, Germany) devoid of respiratory effort sensors. The Somnocheck device has been validated, and the results have been described in detail elsewhere.^{13,14} The studies were conducted at the domicile during each individual's usual bedtime, mostly between 11:00 PM and 7:00 AM. Respiratory parameters were assessed by nasal cannula connected to a pressure transducer within the monitor. A pulse oximeter with a finger probe was used to continuously measure arterial oxyhemoglobin saturation and pulse frequency. Body position was detected by the position sensor of the equipment. All recordings were downloaded from the monitor on the next day, stored in a computer, and scored in 5-min periods by an experienced board-certified sleep physician (D.M.) following standard rules. This investigator was blinded to the case-control status of the patient. Recordings with < 6 h of artifact-free tracings were excluded. Information from a sleep diary and the position recording were used to exclude stretches of the recording in which the subject was standing or in motion, indicating wakefulness. Apneas were defined as reductions of tidal volume and/or airflow < 10% of baseline for \geq 10 s. Hypopneas were defined as reductions of tidal volume and/or airflow < 50% of baseline for \geq 10 s, accompanied by at least 3% desaturation or at a least six-beat-per-minute increase in heart rate for 2 s in the 10 s following the event, indicating autonomic arousal. Patients provided information about their sleep quality on the monitoring night, such as lights-off and lights-on times, number of awakenings, and time out of bed. We scored as artifacts periods when the position sensor indicated upright posture or position changes and when irregular breathing and elevated heart rate revealed wakefulness. AHI was calculated as the number of apneas and hypopneas divided by number of hours of artifact-free recording.

A sample size of 62 patients per group was calculated on the basis of an estimated prevalence of OSAS of 40% among control subjects and 70% among case patients, with a power of 90% and an α error of 5%. Data are expressed as mean \pm SD. The differences between means were compared using Student *t* test. χ^2 test was used to compare proportions. To model the impact of confounding on the prediction of resistant hypertension, odds ratios were calculated in a logistic regression analysis including gender, age, BMI, AHI, and duration of hypertension as independent variables. The proportion of patients with resistant hypertension by intensity of OSAS (none, mild, moderate, and severe) was tested by means of one-way analysis of variance. We compared the proportion of patients with OSAS among patients with hypertension in the office and during ABPM (truly resistant), in patients with hypertension only in the office (white coat phenomenon), in patients with hypertension only at home (masked hypertension), and in patients with normal BP at office and at home (truly controlled). Means of AHI in these conditions were computed and tested for linear trend by means of one-way analysis of variance. Analyses were conducted using statistical software (SPSS for Windows v 13; SPSS; Chicago, IL). In all analyses, a probability of α error of < 5% was considered significant.

RESULTS

In total, 143 consecutive patients who fulfilled the criteria for enrollment were invited to participate. Ten patients refused to participate. Of the 133 patients who signed the informed consent form, 7 patients had polysomnography or ABPM measures inadequate for analysis, leaving 126 patients for effective analysis. Characteristics of case patients and

*From the Division of Cardiology and Postgraduate Program in Cardiology (Drs. Gonçalves, Martinez, Gus, de Abreu-Silva, Bertoluci, Dutra, Branchi, Oliveira, and F.D. Fuchs), Division of Clinical Pharmacology (Dr. Moreira), Hospital de Clínicas de Porto Alegre, Porto Alegre; and Department of Social Medicine (Dr. S.C. Fuchs), Universidade Federal do Rio Grande do Sul, Porto Alegre, RS, Brazil.

This study was funded by Conselho Nacional de Pesquisa, Fundação de Amparo à Pesquisa do Estado do Rio Grande do Sul, and Fundo de Incentivo à Pesquisa do Hospital de Clínicas de Porto Alegre.

This article is not under consideration elsewhere, and the authors have no potential conflicts of interest regarding this article.

Manuscript received March 13, 2007; revision accepted August 14, 2007.

Reproduction of this article is prohibited without written permission from the American College of Chest Physicians (www.chestjournal.org/misc/reprints.shtml).

Correspondence to: Flávio Danni Fuchs, MD, PhD, Serviço de Cardiologia, Hospital de Clínicas de Porto Alegre, Ramiro Barcelos, 2350, 90035-903. Porto Alegre, RS, Brazil; e-mail: ffuchs@hcpa.ufrgs.br

DOI: 10.1378/chest.07-1170

control subjects are displayed in Table 1. Gender, age, and BMI were comparable in the two groups. BP measured at office and by ABPM was obviously lower in patients with controlled BP, despite having been treated with fewer BP drugs. AHI was significantly higher in case patients than control subjects. The prevalence of OSAS was 71% in case patients and 38% in control subjects, considering AHI of 10/h as a cut-off point (Table 2). OSAS was a risk for uncontrolled hypertension in men and women (Table 2). In a logistic regression model adjusting for gender, age, BMI, and duration of hypertension, OSAS was strongly and independently associated with resistant hypertension (Fig 1). The inclusion of diabetes in the model did not change the estimates at all. The frequency of resistant hypertension increased in parallel with the increase in severity of OSAS (Fig 2). The mean low level of hemoglobin saturation was 82.8 ± 6.6 in case patients and 85.8 ± 4.5 in control subjects ($p = 0.004$).

In the control group, 11 subjects (17%) had abnormal ABPM (masked hypertension); while among case patients, 13 patients (21%) had normal ABPM (white coat hypertension). Individuals with normal BP by both methods have the lowest AHI and the lowest prevalence of OSAS (Fig 3). However, the mean of AHI and the prevalence of OSAS increased in patients with uncontrolled BP either at the office or by ABPM, and particularly in patients with uncontrolled BP in the office and by ABPM (Fig 3).

Table 1—Demographics and Other Characteristics of Case Patients and Control Subjects*

Variables	Case Patients (n = 63)	Control Subjects (n = 63)	p Value
Women	42 (67)	40 (63)	0.71
Age, yr	59 ± 7	59 ± 7	0.65
BMI, kg/m ²	30 ± 3	29 ± 4	0.31
Systolic BP in office, mm Hg	167 ± 21	127 ± 8	< 0.01
Diastolic BP in office, mm Hg	93 ± 15	79 ± 6	< 0.01
Systolic BP in ABPM over 24 h, mm Hg	141 ± 17	121 ± 10	< 0.01
Diastolic BP in ABPM over 24 h, mm Hg	84 ± 12	74 ± 7	< 0.01
Diabetes mellitus	12 (22)	12 (19)	0.19
AHI, episodes/h	21 ± 17.6	10.6 ± 9.3	< 0.001
Antihypertensive drugs	3.4 ± 0.6	2.3 ± 0.8	< 0.01
Duration of hypertension, yr	19 ± 6	16 ± 8	0.06

*Data are presented as No. (%) or mean \pm SD.

Table 2—Prevalence of AHI \geq 10 Episodes per Hour in Case Patients and Control Subjects, by Gender*

Gender	Case Patients, AHI \geq 10/h	Control Subjects, AHI \geq 10/h	p Value
Men	18/21 (86)	12/23 (52)	0.016
Women	27/42 (64)	12/40 (30)	0.002
Total	45/63 (71)	24/63 (38)	< 0.001

*Data are presented as No./total (%).

DISCUSSION

This is the first controlled study to show an independent association between OSAS and resistant hypertension. The odds ratio close to 5.0 is impressive and strengthens the concept that OSAS is a major risk factor of resistant hypertension.

The risk of OSAS for hypertension has been demonstrated in several studies.^{15–17} The association of OSAS with resistant hypertension, however, was less investigated to date. In a case series,⁹ OSAS was diagnosed in 83% of patients with resistant hypertension; this study did not have a control group and therefore could not exclude other factors associated with resistant hypertension. In another uncontrolled study,¹⁸ the AHI among patients with difficult-to-control hypertension was 26/h. In our study, case patients and control subjects were well matched for other risk factors for resistant hypertension, and the risk was independent of them in a multivariate analysis. Despite of the differences in study design, our findings in patients with resistant hypertension were similar to the prevalence described by Logan et al⁹ and to the AHI described by Martinez-Garcia et al.¹⁸ The prevalence of OSAS in case patients and control subjects among women was lower than in men, confirming the gender difference described in other studies.¹⁹ The magnitude of risk, however, was at least as strong in women as in men. The proportion of patients with masked and

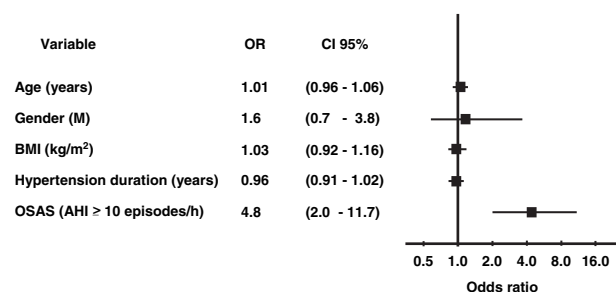


FIGURE 1. Risk factors for resistant hypertension: results of a logistic regression model. OR = odds ratio; CI = confidence interval.

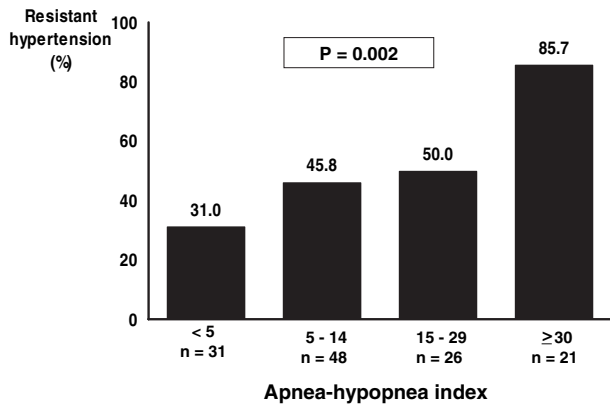


FIGURE 2. Prevalence of resistant hypertension by intensity of OSAS.

white coat hypertension in our study was higher than the prevalence described in population-based studies.^{20,21}

This is probably a consequence of the selection of patients in a tertiary center. Patients with masked or white coat hypertension have a risk for cardiovascular events intermediate between the risk of truly normotensive and truly hypertensive individuals in office and ABPM recordings.²¹ The greater AHI in our patients with uncontrolled hypertension, either by office or ABPM recordings, suggests that OSAS may be among the underlying reasons for the occurrence of white coat and masked hypertension.

Our study has limitations and strengths that deserve mention. We diagnosed OSAS using an unattended home portable sleep monitor, which does not give the whole set of parameters of full polysomnography done at the sleep laboratory. However, studies²² on sleep breathing disorders using portable monitors have giving results similar to studies in which full attended polysomnography is employed.

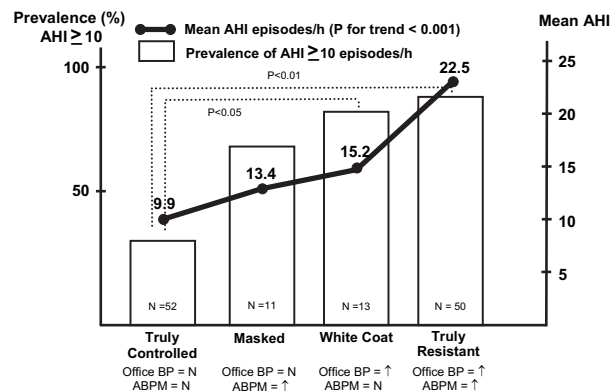


FIGURE 3. Prevalence of OSAS and frequency of AHI by hypertension defined by the combination of measurements at the office and by ABPM.

Screening devices have been recommended as an alternative method to diagnose OSAS when polysomnography is not readily available. While portable polysomnography is not currently recommended in the United States as a diagnostic tool for obstructive sleep apnea, it may be reasonable in regions where in-laboratory polysomnography is unavailable. We have not also investigated mechanisms of uncontrolled BP secondary to OSAS. Increasing in plasma aldosterone, for instance, has been related to severity of obstructive sleep apnea in subjects with resistant hypertension.²³ The controlled design is the main strength of our study. This design, together with the adequate statistical power, careful definition of case patients and control subjects, control for confounding factors, and use of ABPM suggest that our results are reliable and applicable in clinical practice. The impact of OSAS treatment with continuous positive airway pressure (CPAP) on BP in a population with resistant hypertension remains unclear. Data provided from Becker et al²⁴ showed significant reductions in BP in a small group of patients with severe OSAS receiving antihypertensive therapy and treated with CPAP. Furthermore, a recent metaanalysis²⁵ suggests small but potentially clinically significant antihypertensive effects of CPAP in patients with OSAS. Larger controlled trials are needed to confirm these findings.

In conclusion, OSAS is highly prevalent in and independently associated with resistant hypertension. Comorbid OSAS should be considered in patients with resistant hypertension.

What Is Already Known on This Subject?

The concept that OSAS is a cause of resistant hypertension is generally accepted, but the evidence comes from case series, without controlling for confounding factors.

What This Study Adds

Our study demonstrates that OSAS diagnosed by portable sleep monitors is a major and independent risk factor for hypertension.

REFERENCES

- Chobanian AV, Bakris GL, Black HR, et al. Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. National Heart, Lung, and Blood Institute; National High Blood Pressure Education Program Coordinating Committee. Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *Hypertension* 2003; 42:1206–1252
- Berlowitz DR, Ash AS, Hickey EC, et al. Inadequate control of blood pressure in a hypertensive population. *N Engl J Med* 1998; 339:1957–1963

- 3 Wang TJ, Vasan RS. Epidemiology of uncontrolled hypertension in the United States. *Circulation* 2005; 112:1651–1662
- 4 Lindholm LH. The problem of uncontrolled hypertension. *J Hum Hypertens* 2002; 16(suppl 3):S3–S8
- 5 Kaplan NM. Resistant hypertension. *J Hypertens* 2005; 23:1441–1444
- 6 Amar J, Chamontin B, Genes N, et al. Why is hypertension so frequently uncontrolled in secondary prevention? *J Hypertens* 2003; 21:1199–1205
- 7 Quan SF, Bersh BJ. Cardiovascular consequences of sleep-disordered breathing: past, present and future; report of a workshop from the National Center on Sleep Disorders Research and the National Heart, Lung, and Blood Institute. *Circulation* 2004; 109:951–957
- 8 Silverberg DS, Oksenberg A. Are sleep-related breathing disorders important contributing factors to the production of essential hypertension? *Curr Hypertens Rep* 2001; 3:209–215
- 9 Logan AG, Perlikowski SM, Mente A, et al. High prevalence of unrecognized sleep apnoea in drug-resistant hypertension. *J Hypertens* 2001; 19:2271–2277
- 10 Lubicz JN, Moreira LB, Gus M, et al. Stopping oral contraceptives: an effective blood pressure-lowering intervention in women with hypertension. *J Hum Hypertens* 2005; 19:451–455
- 11 Gus M, Fuchs FD, Pimentel M, et al. Behavior of ambulatory blood pressure surrounding episodes of headache in mildly hypertensive patients. *Arch Intern Med* 2001; 161:252–255
- 12 Fuchs FD, Gus M, Moreira WD, et al. Blood pressure effects of antihypertensive drugs and changes in lifestyle in a Brazilian hypertensive cohort. *J Hypertens* 1997; 15:783–792
- 13 Ficker JH, Wiest GH, Wilpert J, et al. Evaluation of a portable recording device (Somnocheck) for use in patients with suspected obstructive sleep apnoea. *Respiration* 2001; 68:307–312
- 14 Martinez D, Lenz MC, Lima C. Evaluation of SomnoCheck for detecting sleep apneas [abstract]. *Sleep Res Online* 1999; 2(suppl 1):399
- 15 Peppard PE, Young T, Palta M, et al. Prospective study of the association between sleep disordered breathing and hypertension. *N Engl J Med* 2000; 342:1378–1384
- 16 Nieto FJ, Young TB, Lind BK, et al. Association of sleep-disordered breathing, sleep apnea, and hypertension in a large community-based study. *JAMA* 2000; 283:1829–1836
- 17 Lavie P, Herer P, Hoffstein V. Obstructive sleep apnoea syndrome as a risk factor for hypertension: population study. *BMJ* 2000; 320:479–482
- 18 Martinez-Garcia MA, Gomez-Aldaravi R, Gil-Martinez T, et al. Sleep-disordered breathing in patients with difficult-to-control hypertension. *Arch Bronconeumol* 2006; 42:14–20
- 19 Hedner J, Bengtsson-Bostrom K, Peker Y, et al. Hypertension prevalence in obstructive sleep apnoea and sex: a population-based case-control study. *Eur Respir J* 2006; 3:564–570
- 20 Bobrie G, Chatellier G, Genes N, et al. Cardiovascular prognosis of “masked hypertension” detected by blood pressure self-measurement in elderly treated hypertensive patients. *JAMA* 2004; 291:1342–1349
- 21 Mancia G, Facchetti R, Bombelli M, et al. Long-term risk of mortality associated with selective and combined elevation in office, home, and ambulatory blood pressure. *Hypertension* 2006; 47:1–8
- 22 Flemons WW. Obstructive sleep apnea. *N Engl J Med* 2002; 347:498–504
- 23 Pratt-Ubunama MN, Nishizaka MK, Boedefeld RL, et al. Plasma aldosterone is related to severity of obstructive sleep apnea in subjects with resistant hypertension. *Chest* 2007; 131:453–459
- 24 Becker HF, Jerrentrup A, Ploch T, et al. Effect of nasal continuous positive airway pressure treatment on blood pressure in patients with obstructive sleep apnea. *Circulation* 2003; 107:68–73
- 25 Haentjens P, Van Meerhaeghe A, Moscariello A, et al. The impact of continuous positive airway pressure on blood pressure in patients with obstructive sleep apnea syndrome: evidence from a meta-analysis of placebo-controlled randomized trials. *Arch Intern Med* 2007; 167:757–764