Characteristics and Predictors of Obstructive Sleep Apnea in Patients With Systemic Hypertension

Luciano F. Drager, MD, PhD[a,*], Pedro R. Genta, MD[b], Rodrigo P. Pedrosa, MD[b], Flávia B. Nerbass, PT[b], Carolina C. Gonzaga, MD[c], Eduardo M. Krieger, MD, PhD[a], and Geraldo Lorenzi-Filho, MD, PhD[b]

Obstructive sleep apnea (OSA) is a secondary cause of hypertension and independently associated with target-organ damage in hypertensive patients. However, OSA remains largely underdiagnosed and undertreated. The aim of the present study was to evaluate the characteristics and clinical predictors of OSA in a consecutive series of patients followed up in a hypertension unit. A total of 99 patients (age 46 ± 11 years, body mass index 28.8 kg/m^2, range 25.1 to 32.9) underwent polysomnography. The clinical parameters included age, gender, obesity, daytime sleepiness, snoring, Berlin Questionnaire, resistant hypertension, and metabolic syndrome. Of the 99 patients, 55 (56%) had OSA (apnea-hypopnea index >5 events/hour). Patients with OSA were older and more obese, had greater levels of blood pressure, and presented with more diabetes, dyslipidemia, resistant hypertension, and metabolic syndrome than the patients without OSA. Of the patients with OSA, 51% had no excessive daytime sleepiness. The Berlin Questionnaire and patient age revealed a high sensitivity (0.93 and 0.91, respectively) but low specificity (0.59 and 0.48, respectively), and obesity and resistant hypertension revealed a low sensitivity (0.58 and 0.44, respectively) but high specificity (0.75 and 0.91, respectively) for OSA. Metabolic syndrome was associated with high sensitivity and specificity for OSA (0.86 and 0.85, respectively). Multiple regression analysis showed that age of 40 to 70 years (odds ratio 1.09, 95% confidence interval 1.03 to 1.16), a high risk of OSA on the Berlin Questionnaire (odds ratio 8.36, 95% confidence interval 1.67 to 41.85), and metabolic syndrome (odds ratio 19.04, 95% confidence interval 5.25 to 69.03) were independent variables associated with OSA. In conclusion, more important than the typical clinical features that characterize OSA, including snoring and excessive daytime sleepiness, the presence of the metabolic syndrome is as an important marker of OSA among patients with hypertension. **(Am J Cardiol 2010;105:1135–1139)**

Obstructive sleep apnea (OSA) is a secondary cause of hypertension,[1] highly prevalent (around 38% to 82%)[2,3] and directly related to target-organ damage and increased markers of atherosclerosis.[4,5] However, OSA remains largely underdiagnosed and, consequently, undertreated in clinical practice.[6–8] One potential limitation for the diagnosis is that the classic symptoms of snoring, breathing pauses, and daytime sleepiness are frequently subjective.[9] Furthermore, case-finding using only the typical patient characteristics (middle age, male gender, and obesity) might fail to identify women and overweight or even healthy weight patients with OSA.[9] In 1999, Netzer et al[10] validated the Berlin Questionnaire in 100 participants from a general population who simultaneously underwent portable sleep monitoring. However, this questionnaire was validated to screen OSA in a primary care population and might not be useful in other populations. Because one of the domains involves the presence of high blood pressure, the sensitivity of the Berlin Questionnaire might be low in patients with hypertension. In the present study, we explored the predictors of OSA in consecutive patients with hypertension. This population is distinct from that referred to in sleep studies, because such patients have already had sleep complaints and OSA frequency is extremely high.

Methods

We evaluated the relative importance of the traditional risk factors for OSA,[9] including age of 40 to 70 years, male gender, and the presence of snoring and obesity, in addition to daytime sleepiness somnolence, Berlin Questionnaire findings, and the presence of resistant hypertension and the metabolic syndrome. We compared these clinical parameters with data obtained from the overnight polysomnographic studies.

The local ethics committee approved the protocol, and all participants provided written informed consent. We involved consecutive patients with hypertension and no pre-

[a]Hypertension Unit and [b]Sleep Laboratory, Pulmonary Division, Heart Institute (InCor), University of São Paulo Medical School, São Paulo, São Paulo, Brazil; and [c]Department of Hypertension and Nephrology, Dante Pazzanese Institute of Cardiology, São Paulo, São Paulo, Brazil. Manuscript received October 16, 2009; revised manuscript received and accepted December 1, 2009.

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*Corresponding author: Tel: (55) 11-30695084; fax: (55) 11-30695948.

E-mail address: luciano.drager@incor.usp.br (L.F. Drager).

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Table 1
Patient characteristics

Variable	All Subjects (n = 99)	Obstructive Sleep Apnea		p Value*
		No (n = 44)	Yes (n = 55)	
Age (years)				<0.001
Mean ± SD	46 ± 11	40 ± 10	51 ± 10	
Range	19–70	19–66	22–70	
Gender				0.69
Men	52 (53%)	22 (50%)	30 (55%)	
Women	47 (47%)	22 (50%)	25 (45%)	
Whites	56 (57%)	23 (52%)	33 (60%)	0.54
Smoker	7 (7%)	2 (5%)	5 (9%)	0.46
Diabetes mellitus	19 (19%)	1 (2%)	18 (33%)	<0.001
Dyslipidemia†	49 (50%)	14 (32%)	35 (64%)	0.002
Obesity‡	43 (43%)	11 (25%)	32 (58%)	0.001
Metabolic syndrome	54 (55%)	7 (16%)	47 (86%)	<0.001
Resistant hypertension	28 (28%)	4 (9%)	24 (44%)	<0.001
Body mass index (kg/m^2)				<0.001
Median	28.8	26.9	30.9	
Interquartile range	25.1–32.9	24.1–29.9	27.9–34.1	
Range	17.1–49.2	17.1–33.9	21.4–49.2	
Neck circumference (cm)	38 (35–42)	36 (33.3–40.0)	41 (37–43)	0.001
Abdominal circumference (cm)	95 (88–107)	90 (82.3–97.3)	104 (92.5–109.0)	<0.001
Systolic blood pressure (mm Hg)	154 (132–178)	139 (128–160)	170 (140–182)	0.001
Diastolic blood pressure (mm Hg)	92 (82–106)	89 (80–106)	96 (83–108)	0.08
Heart rate (beats/min)	72 (68–78)	72 (70–79)	72 (64–78)	0.39
Antihypertensive drugs (n)	3 (2–4)	2 (1–3)	4 (3–4)	<0.001
Fasting glucose (mg/dl)	96 (90–103)	94 (88–98)	100 (92–116)	<0.001
Total cholesterol (mg/dl)	199 ± 40	192 ± 38	204 ± 41	0.13
Low-density lipoprotein (mg/dl)	124 ± 33	121 ± 32	127 ± 33	0.33
High-density lipoprotein (mg/dl)	42 (36–51)	46 (38–52)	40 (34–47)	0.025
Triglycerides (mg/dl)	134 (82–187)	98 (69–146)	152 (102–204)	0.004

Data are presented as mean ± SD for data with normal distribution, n (%), or median (interquartile range) for data with skewed distribution.

* For comparisons between patients with and without OSA.

† Disorders in the lipoprotein metabolism; classified as hypercholesterolemia, hypertriglyceridemia, combined hyperlipidemia, and low levels of high-density lipoprotein cholesterol. We also considered dyslipidemia when patients were receiving specific drug treatment.

‡ Body mass index of ≥30 kg/m^2.

vious history of OSA recruited from the Hypertension Unit, Heart Institute (InCor) (University of São Paulo Medical School, São Paulo, São Paulo, Brazil). The main reason for excluding patients with a previous diagnosis of OSA was that these patients have frequently been referred from the Sleep Clinic at the Heart Institute. All participants had an established diagnosis of hypertension according to current guidelines.[1] No patient had a history of "white-coat hypertension," because they had also performed several out-of-office blood pressure measurements. Resistant hypertension was defined as blood pressure that remained greater than the goal of <140/90 mm Hg despite the concurrent use of 3 antihypertensive agents of different classes. Ideally, 1 of the 3 agents was a diuretic, and all agents were prescribed at the optimal dosage amounts. In addition, resistant hypertension was also considered present when the blood pressure was controlled with the regular use of >3 medications.[11]

We evaluated subjective daytime sleepiness using the Epworth Sleepiness Scale. In brief, this scale was used to assess the general level of daytime sleepiness by having patients rate the likelihood of dozing during 8 different daytime situations. The scale ranges from 0 to 24, and scores >10 were considered associated with excessive daytime sleepiness.[12]

As previously described,[10] predetermination of a high risk and lower risk of OSA using the Berlin Questionnaire was determined on the basis of the responses in 3 symptom categories. In category 1, high risk was defined as persistent symptoms (>3 to 4 times/week) for ≥2 questions about snoring. In category 2, high risk was defined as persistent (>3 to 4 times/week) daytime tiredness or fatigue. In category 3, high risk was defined as a history of high blood pressure or a body mass index >30 kg/m^2. To be considered at high risk of OSA, a patient had to qualify for ≥2 symptom categories. Those who denied having persistent symptoms or who qualified for only one symptom category were placed in the lower risk group.

All participants underwent standard overnight polysomnography (EMBLA, Flaga hf. Medical Devices, Reykjavík, Iceland), as previously described.[13] OSA was considered present when the apnea-hypopnea index was >5 events/hour of sleep.

Fasting blood samples were drawn for the determination of glucose, total cholesterol, low-density lipoprotein, high-density

Table 2
Daytime sleepiness, high risk of obstructive sleep apnea (OSA), and sleep parameters determined by polysomnography

Variable	All Subjects (n = 99)	Obstructive Sleep Apnea		p Value
		No (n = 44)	Yes (n = 55)	
Excessive daytime sleepiness (Epworth Sleepiness Scale >10)	36 (36%)	9 (20%)	27 (49%)	0.003
Snoring	71 (72%)	24 (55%)	47 (85%)	0.001
High risk of obstructive sleep apnea (Berlin Questionnaire)	69 (70%)	18 (41%)	51 (93%)	<0.001
Epworth Sleepiness Scale score	9 ± 5	7 ± 5	10 ± 5	0.001
Sleep parameters				
Sleep latency (minutes)	6.3 (3.6–17.8)	5.2 (3.0–11.3)	10 (4.2–27.0)	0.06
Total sleep time (minutes)	403 ± 68	392 ± 72	412 ± 62	0.21
Sleep efficiency	89.0% (79.7–92.8)	89.8% (79.6–92.9)	88.3% (79.7–92.8)	0.81
S1	4.7% (2.6–8.8)	4.4% (2.2–7.3)	4.9% (2.8–9.1)	0.54
S2	62.7 ± 11.2%	60.6 ± 9.3%	64.9 ± 12.6%	0.12
S3-S4	13.1% (5.3–23.9)	15.4% (9.2–24.9)	11.0% (2.3–16.9)	0.03
Rapid eye movement	12.3 ± 8.1%	16.8 ± 6.8%	15.7 ± 9.4%	0.58
Apnea-hypopnea index (events/hour)	7.9 (2.3–29.1)	2.0 (0.5–3.9)	25.8 (15.5–43.4)	<0.001
Minimal oxygen saturation	86% (81–90)	90% (87.3–91.0)	82% (76.0–87.0)	<0.001
Oxygen saturation <90% (% total sleep time)	0.2% (0–2)	0% (0–0.1)	1.7% (0.2–7.1)	<0.001

Data are presented as mean ± SD for data with normal distribution, n (%), or median (interquartile range) for data with skewed distribution.

Table 3
Sensitivity, specificity, and positive and negative predictive values of traditional risk factors for obstructive sleep apnea (OSA), Epworth Sleepiness Scale, Berlin Questionnaire, resistant hypertension, and metabolic syndrome

Variable	Sensitivity (%)	Specificity (%)	Positive Predictive Value (%)	Negative Predictive Value (%)
Age 40–70 years	0.91 (79.3–96.6)	0.48 (0.33–0.63)	0.69 (0.56–0.79)	0.81 (0.60–0.93)
Male gender	0.55 (0.41–0.69)	0.50 (0.35–0.65)	0.58 (0.43–0.71)	0.47 (0.32–0.62)
Female gender	0.45 (0.32–0.59)	0.50 (0.35–0.65)	0.48 (0.37–0.58)	0.52 (0.42–0.63)
Increased neck circumference*	0.58 (0.44–0.69)	0.74 (0.55–0.87)	0.78 (0.62–0.89)	0.52 (0.37–0.66)
Increased waist circumference†	0.78 (0.65–0.88)	0.73 (0.57–0.85)	0.78 (0.65–0.88)	0.73 (0.57–0.85)
Obesity‡	0.58 (0.44–0.71)	0.75 (0.59–0.86)	0.74 (0.59–0.86)	0.59 (0.45–0.72)
Snoring	0.86 (0.73–0.93)	0.46 (0.31–0.61)	0.66 (0.54–0.76)	0.71 (0.51–0.86)
High risk of obstructive sleep apnea (Berlin Questionnaire)	0.93 (0.82–0.98)	0.59 (0.43–0.73)	0.74 (0.62–0.83)	0.87 (0.68–0.96)
Epworth Sleepiness Scale score >10	0.49 (0.36–0.63)	0.80 (0.64–0.90)	0.75 (0.57–0.87)	0.56 (0.43–0.68)
Resistant hypertension	0.44 (0.31–0.58)	0.91 (0.77–0.97)	0.86 (0.66–0.95)	0.56 (0.44–0.68)
Metabolic syndrome	0.86 (0.73–0.93)	0.85 (0.70–0.93)	0.87 (0.75–0.94)	0.82 (0.67–0.91)

Data in parentheses are 95% confidence intervals.
* Increased neck circumference ≥41 cm for men and ≥38 cm for women.
† Increased waist circumference ≥102 cm for men and ≥88 cm for women.
‡ Body mass index of ≥30 kg/m^2.

lipoprotein, and triglycerides. The metabolic syndrome was diagnosed according to the National Cholesterol Education Program, Adult Treatment Panel III,[14] if 3 of 5 factors were present as follows: (1) waist circumference (≥102 cm in men and ≥88 cm in women); (2) triglycerides ≥150 mg/dl or patient receiving specific drug treatment; (3) high-density lipoprotein cholesterol <40 mg/dl in men and <50 mg/dl in women or receiving specific drug treatment; (4) arterial blood pressure of ≥130 or 85 mm Hg systolic and diastolic blood pressure, respectively, or receiving antihypertensive drug treatment; and (5) fasting glucose of ≥100 mg/dl or receiving specific drug treatment.

The data were analyzed using the Statistical Package for Social Sciences, version 10.0, statistical software (SPSS, Chicago, Illinois). The quantitative variables are expressed as the mean ± SD. The comparison of continuous variables between patients with and without OSA was performed using the Student *t* test or Wilcoxon test, as appropriate. Categorical variables are expressed as frequency distribution and were compared using the chi-square test or Fisher's exact test. Comparing the clinical factors to the polysomnographic findings, we determined the sensitivity, specificity, positive predictive value, and negative predictive value. The odds ratio of age 40 to 70 years[9] and for other traditional risk factors for OSA (including male gender, the presence of snoring and obesity, daytime sleepiness somnolence, Berlin Questionnaire, resistant hypertension, and metabolic syndrome) were calculated using univariate logistic regression analysis. Variables with p <0.1 were included in the multivariate model.

Results

We initially selected 110 patients with established hypertension from January to July 2009. We excluded 5 who

Table 4
Odds ratio of traditional risk factors for obstructive sleep apnea (OSA), Epworth Sleepiness Scale, Berlin Questionnaire, resistant hypertension, and metabolic syndrome

Variable	OR	95% CI	p Value
Age 40–70 years	1.11	1.06–1.17	<0.001
Female gender	0.83	0.38–1.84	NS
Male gender	1.20	0.54–2.66	NS
Increased neck circumference*	1.01	0.71–1.43	NS
Increased waist circumference†	9.56	3.80–24.02	<0.001
Obesity‡	4.17	1.75–9.94	0.001
Epworth Sleepiness Scale score >10	3.75	1.52–9.25	0.004
Snoring	4.90	1.88–12.74	0.001
High risk of obstructive sleep apnea (Berlin Questionnaire)	18.42	5.65–60.05	<0.001
Resistant hypertension	7.74	2.43–24.64	0.001
Metabolic syndrome	31.05	10.32–93.4	<0.001

* Increased neck circumference ≥41 cm for men and ≥38 cm for women.

† Increased waist circumference ≥102 cm for men and ≥88 cm for women.

‡ Body mass index of ≥30 kg/m^2.

CI = confidence interval; NS = not significant; OR = odds ratio.

declined to undergo the sleep study and 6 who had a previous diagnosis of OSA. Therefore, the total study sample included 99 participants. Table 1 lists the demographic, anthropometric, and clinical characteristics of the participants. Overall, the sample included middle-age and overweight patients with a significant percentage of co-morbidities, including dyslipidemia, obesity, and metabolic syndrome. Of the 99 patients, 52 were men (~53%) and 55 (56%) had OSA. The hypertensive patients with OSA were older and more obese and had greater neck and abdominal circumferences, greater levels of blood pressure, and a greater percentage of diabetes mellitus, dyslipidemia, obesity, resistant hypertension, and metabolic syndrome. Patients with OSA also used a greater number of antihypertensive drugs.

Table 2 lists the results of the sleep questionnaires and data from the polysomnographic studies. Overall, 1/3 of the patients had excessive daytime sleepiness, and 70% of the patients with hypertension were at high risk of OSA as evaluated by the Berlin Questionnaire. Interestingly, 1/2 of the patients with OSA did not have excessive daytime sleepiness. Compared to the patients without OSA, we found that the patients with OSA showed a trend toward greater sleep latency and a reduced percentage of slow wave sleep.

Table 3 lists the sensitivity, specificity, and positive and negative predictive values of several candidate predictive factors for OSA. We observed that the high risk of OSA according to the Berlin Questionnaire and patient age had high sensitivity but low specificity for the presence of OSA. In contrast, the presence of obesity and resistant hypertension had low sensitivity but good specificity for the presence of OSA. Gender was not a good predictor of OSA in patients with hypertension. The presence of metabolic syndrome was associated with both good sensitivity and specificity for OSA. In addition, the metabolic syndrome was associated with good positive and negative predictive values (>80% for each variable).

Table 5
Independent variables associated with obstructive sleep apnea (OSA) on multiple logistic regression analysis

Variable	OR	95% CI	p Value
Age 40–70 years	1.09	1.03–1.16	0.004
High risk of obstructive sleep apnea (Berlin Questionnaire)	8.36	1.67–41.85	0.010
Metabolic syndrome	19.04	5.25–69.03	<0.001

Abbreviations as in Table 4.

The data listed in Table 4 show that the presence of OSA was associated with an increased abdominal circumference, obesity, excessive daytime sleepiness on the Epworth Sleepiness Scale, a high risk of OSA on the Berlin Questionnaire, resistant hypertension, and the metabolic syndrome. However, on multiple logistic regression analysis, only a high risk of OSA using the Berlin Questionnaire, age from 40 to 70 years old, and, mainly, the presence of the metabolic syndrome were independent predictors of OSA in patients with hypertension (Table 5).

Discussion

Our results have confirmed previous evidence suggesting that OSA is common and underdiagnosed in patients with hypertension,[2] especially in patients with resistant hypertension.[3] We have extended these findings by showing that among patients with hypertension, the presence of OSA was associated with increased age and a greater frequency of co-morbidities. More importantly, a significant proportion (~50%) of patients with OSA did not have excessive daytime somnolence. Male gender, a traditional factor associated with OSA in the general population, had a low sensitivity and specificity for OSA in patients with hypertension. In addition, a high risk of OSA from the Berlin Questionnaire findings, age from 40 to 70 years, and, mainly, the presence of the metabolic syndrome were independent predictors of OSA in patients with hypertension. However, the high sensitivity and specificity of the metabolic syndrome for the presence of OSA suggest that the diagnosis of metabolic syndrome should be considered one of the best predictive tools for the suspicion of OSA in patients with hypertension.

The present results could contribute to increase the identification of OSA among patients with hypertension. We found that the traditional methods of screening patients with OSA in the general population might not be the best option for patients with hypertension. The low specificity of the Berlin Questionnaire means that 41% of subjects with hypertension without OSA would unnecessarily be referred for a sleep study. Therefore, a high risk of OSA according to the Berlin Questionnaire findings should be interpreted with caution in patients with hypertension. Similarly, the low sensitivity observed for excessive daytime sleepiness, as determined using the Epworth Sleepiness Scale (49%), and the absence of a significant association between excessive daytime sleepiness and OSA on multivariate analysis, limits its utility for screening of OSA among patients with hypertension. Recently, Gus et al[15] investigated the accuracy of the Epworth Sleepiness Scale and the Berlin Questionnaire

to identify patients with resistant hypertension at high risk of OSA using portable sleep monitors. They found that a clinical suspicion of OSA using an Epworth Sleepiness Scale score of >10 was very low (<45% were hypersomnolent) and that the Berlin Questionnaire showed very good sensitivity (85%) for detecting OSA in patients with resistant hypertension. We have extended these findings to the general population of patients with hypertension and also included other clinical predictors of OSA. We found that patient age from 40 and 70 years and the presence of the metabolic syndrome (and not waist circumference or obesity) were predictors of OSA in patients with hypertension. In particular, there are potential explanations that justify the presence of the metabolic syndrome as one of the best predictors of OSA in this subset of patients. First, the prevalence of OSA among consecutive patients with the metabolic syndrome is extremely high. Recent evidence from our group[16,17] and others[18] has suggested that about 90% to 95% of patients had OSA (as determined by an apnea-hypopnea index of >5 events/hour). Second, previous evidence has suggested that OSA has an independent effect on each characteristic of the metabolic syndrome, including insulin resistance,[19] abdominal obesity,[20] high blood pressure,[21] and dyslipidemia.[22–24] Therefore, the role of the metabolic syndrome, which is a cluster of several risk factors for cardiovascular risk, might have a more robust effect than each criterion in isolation. This result has potential clinical implications for cardiologists and general practitioners, because the diagnosis of the metabolic syndrome is easy to determine in the clinical setting.

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