ORIGINAL ARTICLES

Sleep-Disordered Breathing in Patients With Difficult-to-Control Hypertension

M.A. Martínez-García,[a] R. Gómez-Aldaraví,[b] T. Gil-Martínez,[c] J.J. Soler-Cataluña,[a] B. Bernácer-Alpera,[c] and P. Román-Sánchez[c]

[a]Unidad de Neumología, Hospital General de Requena, Requena, Valencia, Spain.
[b]Unidad de Cardiología, Hospital General de Requena, Requena, Valencia, Spain.
[c]Servicio de Medicina Interna, Hospital General de Requena, Requena, Valencia, Spain.

OBJECTIVE: To analyze the relationship between sleep-disordered breathing and difficult-to-control arterial hypertension.

PATIENTS AND METHOD: Patients were considered to have difficult-to-control hypertension when mean systolic blood pressure was 125 mm Hg or higher and/or mean systolic blood pressure was more than or equal to 80 mm Hg (as recorded during 2 24-hour ambulatory monitoring studies) despite the use of 3 or more antihypertensive drugs. Respiratory polygraphy using the AutoSet device (ResMed Corp, Sydney, Australia) was then performed to study sleep-disordered breathing in all patients.

RESULTS: Forty-nine patients with a mean (SD) age of 68.1 (9.1) years, mean systolic and diastolic pressures of 152.5 (13)/89.2 (8.5) mm Hg, and an average of 3.5 prescribed drugs were included in the study. The mean apnea-hypopnea index (AHI) was 26.2 (19.5) and events were predominantly obstructive. Patients with severe sleep apnea-hypopnea syndrome (SAHS) (AHI ≥ 30; 40.8%) showed more uncontrolled daytime (*P*= . 017) and nighttime (*P* = .033) systolic pressure than the rest, as well as higher daytime diastolic pressure (*P* = .035) and a greater consumption of drugs than those without severe SAHS (AHI < 10; 28.6%) (*P* = .041). The study population as a whole showed a significant correlation between blood pressure and obesity. There was a significant correlation (adjusted for age and sex) with AHI only in patients with SAHS. AHI was found to be the independent predictor with the greatest effect on blood pressure in these patients.

CONCLUSIONS: Prevalence of SAHS was very high in patients with difficult-to-control hypertension. In patients with SAHS, AHI was found to be the independent predictor with the greatest affect on arterial blood pressure.

Key words: *Refractary hypertension Sleep apnea-hypopnea syndrome. Respiratory polygraphy. Cardiovascular risk factors.*

Trastornos respiratorios durante el sueño en pacientes con hipertensión arterial de difícil control

OBJETIVO: Analizar la relación existente entre los trastornos respiratorios durante el sueño y la hipertensión arterial de difícil control (HTAr).

PACIENTES Y MÉTODO: Se consideró HTAr cuando las cifras medias de la presión arterial sistólica (PAS) eran mayores o iguales a 125 mmHg y/o la diastólica (PAD) era igual o superior a 80 mmHg según el registro de 2 estudios de monitorización ambulatoria durante 24 h a pesar de la utilización de 3 o más fármacos antihipertensivos. Se realizó posteriormente una poligrafía respiratoria (Autoset) para el estudio de los trastornos respiratorios durante el sueño en todos los pacientes.

RESULTADOS: Se incluyó en el estudio a 49 pacientes con una media (± desviación estándar) de edad de 68,1 ± 9,1 años, PAS/PAD media de 152,5 ±13/89,2 ±8,5 mmHg y una media de 3,5 fármacos prescritos. El índice de apneas-hipopneas (IAH) fue de 26,2 ± 19,5, de predominio obstructivo. Los pacientes con síndrome de apneas-hipopneas durante el sueño (SAHS) grave (IAH ≥ 30; 40,8%) presentaron mayor descontrol de la PAS tanto diurna (p = 0,017) como nocturna (p = 0,033) que el resto de pacientes, así como mayor PAD diurna (p = 0,035) y toma de un mayor número de fármacos que quienes no lo presentaban (IAH < 10; 28,6%) (p = 0,041). Tomados en su conjunto, los pacientes presentaron una correlación significativa entre las cifras de la presión arterial y la obesidad, además de existir una correlación ajustada significativa con el IAH sólo en los pacientes con SAHS. El IAH se mostró como el predictor independiente que más influyó en las cifras de la presión arterial de estos pacientes.

CONCLUSIONES: En pacientes con HTAr la prevalencia de SAHS fue muy elevada. En los pacientes con SAHS, el IAH se mostró como el factor predictivo independiente más importante de las cifras de presión arterial.

Palabras clave: *Hipertensión de difícil control. Síndrome de apneas-hipopneas durante el sueño. Poligrafía respiratoria. Factores de riesgo cardiovascular.*

Introduction

Recent studies contributing a high level of scientific evidence have established that patients with sleep apnea-hypopnea syndrome (SAHS) have a higher prevalence of hypertension than the general population, even after

Correspondence: Dr. M.A. Martínez-García.
Unidad de Neumología. Servicio de Medicina Interna.
Hospital General de Requena.
Pasaje Casablanca, s/n. 46230 Requena. Valencia. España.
E-mail: med013416@saludalia.com

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adjusting for such confounding variables as body mass index (BMI), age, and sex.[1,2] Several pathophysiological mechanisms have been proposed as being responsible for a possible causal relation between the 2 entities. Perhaps the best studied of these mechanisms is an intermittent increase in nighttime sympathetic tone due to an excessive number of respiratory disturbances during sleep.[3,4] This relation seems to behave linearly, in such a way that the greater the number of respiratory disturbances during sleep (usually quantified by means of the apnea-hypopnea index [AHI]), the greater the probability of presenting hypertension[1,2] (or of developing it in the future[5]); such hypertension may sometimes be difficult to control medically even with the use of various antihypertensive drugs.[6]

More than half of patients treated for hypertension fail to bring their blood pressure under control.[7,8] Approximately 10% of them still have high blood pressure values despite treatment with a combination of 3 or more antihypertensive drugs at an adequate dose and with an adequate level of therapeutic adherence.[9] Hypertensive patients resistant to treatment are prone to a high incidence of vascular events and consequently require optimal medical control.[10] In a variable percentage of cases the reason for this failure to control blood pressure remains unknown even after all the usual causes of secondary hypertension have been ruled out.[11] Little information is available on the connection between an excessive number of respiratory disturbances during sleep and poorer control of blood pressure, but it has been suggested that SAHS may constitute a risk factor, given its high prevalence in patients with poorly controlled hypertension.[6,12,13] However, the presence of obesity (highly prevalent both in patients with SAHS and in those with hypertension) as a confounding variable[14] and the heterogeneity of definitions of hypertension used have made it difficult to compare the results of the various studies on refractory hypertension.

The objective of the present study was to analyze the association between sleep-disordered breathing and difficult-to-control hypertension (defined as blood pressure that remains elevated despite the use of 3 or more antihypertensive drugs) and to assess the influence of other confounding variables on this association.

Patients and Method

We initially included all those patients treated in our hospital with suspected difficult-to-control hypertension, that is, those patients who continued to present hypertension during routine outpatient monitoring despite receiving stable treatment with 3 or more antihypertensive drugs with adequate therapeutic adherence for at least 3 months prior to the beginning of the study. The definition of hypertension was established in accordance with the criteria of the World Health Organization, that is, systolic blood pressure of 140 mm Hg or more and/or diastolic blood pressure of 90 mm Hg or more.[15]

The exclusion criteria for our study were as follows: secondary hypertension, nonadherence to antihypertensive treatment, use of concomitant medication that could cause hypertension (such as corticosteroids or nonsteroidal anti-inflammatory drugs), changes in antihypertensive medication during the study, or previous diagnosis of SAHS. Diagnosis of secondary hypertension was established by applying a diagnostic protocol that included computed tomography angiography of the renal arteries; testing of kidney function (patients with plasma concentrations of creatinine greater than 1.5 mg/dL were excluded from the study); thyroid hormone, catecholamine, and cortisol levels in a 24-hour urine specimen; and other special tests based on clinical suspicion in specific patients. Exclusion of patients following analysis of the results of this protocol was evaluated by the appropriate specialist. Compliance with therapy was evaluated by the method proposed by Haynes and Sackett.[16] This method is based on percentage of compliance, with good compliance defined as taking at least 80% of the medication prescribed as evaluated during the last month of prescription.

In accordance with the guidelines of the European Society of Hypertension–European Society of Cardiology, difficult-to-control hypertension was considered to be mean systolic blood pressure 125 mm Hg or more and/or mean diastolic pressure 80 mm Hg or more obtained in 2 ambulatory blood pressure monitoring studies of 24 hours each (ABPM-0 and AMPM-1) carried out for each patient with no change in antihypertensive medication between the studies.[11] Of the patients with hypertension initially enrolled (blood pressure ≥ 140/80 mm Hg), those with mean blood pressure values less than 125/80 mm Hg in ABPM-0 or ABPM-1 were therefore excluded.

The study was approved by our local ethics committee and consent was obtained from all patients.

Patient Characteristics

For all patients we collected anthropometric data (including BMI and neck circumference in centimeters, and data on previous vascular events, use of antihypertensive or other medication that might affect blood pressure values (number, type, and dosage), and signs and symptoms associated with SAHS (chronic snoring, observed apneas, and daytime sleepiness evaluated by the Spanish version of the Epworth scale[17]).

Ambulatory Blood Pressure Monitoring

ABPM was carried out with the Tonoport V device (GE Marquette, Milwaukee, Wisconsin, USA). Blood pressure was measured at 20-minute intervals during the day and at 30-minute intervals at night. The following parameters were analyzed: mean daytime and nighttime systolic pressures, mean daytime and nighttime diastolic pressures, daily variability of systolic or diastolic pressure determined by analysis of standard deviations, and heart rate. The simple arithmetic mean for each pair of measurements for each parameter analyzed in the 2 ABPM studies was considered valid for subsequent calculations. Daytime and nighttime periods for blood pressure values were determined by asking patients to note the approximate time at which they fell asleep and the time at which they woke up on the days ABPM studies were carried out. We also determined the number of patients who were dippers and nondippers. Those patients whose nighttime systolic pressure decreased by at least 10% compared to daytime values were considered dippers.

Respiratory Polygraphy

All patients included in the study underwent diagnostic polygraphic testing (AutoSet Portable Plus II, ResMed Corp, Sydney, Australia) within 30 days of ABPM-1. The characteristics of the AutoSet device as well as the definitions of the nocturnal respiratory events studied have been outlined in previous publications by our group.[18] The ability of the AutoSet device to diagnose obstructive events has been adequately validated by several authors.[19-22] Thus, it was observed that for a population with a mean AHI near 30, the correlation between AHI measured by polysomnography and that measured by the AutoSet device was 0.95, with the AutoSet device detecting a mean of 4.2 events/h more than polysomnography.[20] It has also been observed that the diagnostic capability of the AutoSet device increases when it is applied in populations with an elevated mean AHI[21] or with a high pretest prevalence of SAHS.[22] All the studies were performed in our hospital in a room specially equipped for the purpose. Polygraphy was repeated for patients who either reported or were suspected (upon analysis of recorded data) of having slept fewer than 3 hours. An AHI between 10 and 29 was considered to be diagnostic of mild SAHS, and an AHI of 30 or more, diagnostic of severe SAHS. Symptoms were recorded but not taken into consideration for these definitions.

Statistical Analysis

Statistical analysis was carried out using SPSS version 11.5 software (Chicago, Illinois, USA). Quantitative variables have been presented as means (SD), while qualitative variables have been expressed as percentages of the total number of patients. For the bivariate study, normal distribution was checked using the Kolgomorov-Smirnov test. For the comparison of more than 2 means we used analysis of variance for normally distributed variables and the Friedman test for nonparametric variables with nonnormal distribution. The correlation between variables was analyzed by using the Pearson or Spearman test, depending on the distribution of the variables. We used covariate analysis, with adjustments for age and sex, to study the correlation between blood pressure and AHI and obesity. Finally, we applied a stepwise multiple linear regression analysis to determine the independent predictors of systolic and diastolic blood pressure by initially introducing into the equation age, sex, AHI, and BMI as candidates. In all cases, a *P* value less than .05 was considered significant.

Results

Initially, 65 patients were included in the study. Of these, the following were eliminated: 2 patients whose systolic pressure in ABPM-0 was less than 125 mm Hg; 7 patients who failed to undergo respiratory polygraphy or an ABPM study, or who refused to continue participating; 6 patients who failed to adhere to therapy; and 1 patient who had previously been diagnosed with SAHS and was receiving continuous positive airway pressure treatment. No cases of secondary hypertension, changes in antihypertensive medication, or new vascular events in the course of the study were observed. The final study sample thus consisted of 49 patients with a mean age of 68.1 (9.1) years, 40.8% of whom were men. Mean systolic pressure was 152.5 (13) mm Hg, and mean diastolic pressure 89.2 (8.5) mm Hg. There were 62.5% patients who had previously suffered a vascular event (35%, episodes of atrial fibrillation, 28% ischemic cardiopathy, and 5%, stroke). The mean number of drugs used was 3.5 (0.68) (range, 3-6). Eighty-six percent were taking some type of diuretic (the remaining 14% were not, because of either contraindications or adverse effects). The most frequently used drugs were angiotensin-II receptor blockers (59%), calcium channel blockers (57%), angiotensin-converting enzyme inhibitors (48%), α-blockers (47%), β-blockers (46%), and others (3%). Mean systolic pressure was 2.1 (11.5) mm Hg lower in ABPM-1 than in APBM-0, and mean diastolic pressure was 17 (5.2) mm Hg lower. This decrease was not significant. BMI and neck circumference did not vary significantly in the course of the study. Baseline patient characteristics related to anthropometric variables, signs and symptoms of SAHS, and respiratory disturbances during sleep are shown in Table 1.

Table 2 shows values for both daytime and nighttime systolic and diastolic pressures according to the number of respiratory disturbances during sleep. Patients with severe SAHS showed significantly more uncontrolled daytime systolic and nighttime systolic pressure and daytime diastolic pressure, as well as consumption of a greater number of antihypertensive drugs, than patients without SAHS. Furthermore, both daytime and nighttime systolic pressures were significantly higher in patients with severe SAHS than in those with mild SAHS. Greater variability of both systolic and diastolic pressures was associated with a greater number of respiratory disturbances during sleep, although the differences between groups were not statistically significant. Only 5 patients were dippers; 3 of them had mild SAHS, and 2 severe SAHS

In patients without SAHS (n = 14) there was a significant correlation (adjusted for age and sex)

TABLE 1
Characteristics of the 49 Patients With Difficult-to-Control Hypertension Included in the Study*

BMI, kg/m^2	34.5 (5.3)
Neck circumference, cm	40.1 (4.2)
Chronic snoring	73%
Observed apneas	10%
Epworth scale score	6.30 (4.1)
AHI	26.2 (19.5)
OAI	12.3 (16.1)
HI	11.7 (10.6)
CT90%	10.2 (10.1)
SAHS	
No	28.6%
Moderate	30.6%
Severe	40.8%
Heart rate, beats/min	72 (range, 54-101)

*Values are expressed as means (SD) unless otherwise indicated.
BMI indicates body mass index; AHI, apnea-hypopnea index; OAI, obstructive apnea index; HI, hypopnea index; CT90%, cumulative percentage of time with nighttime oxygen saturation under 90%.

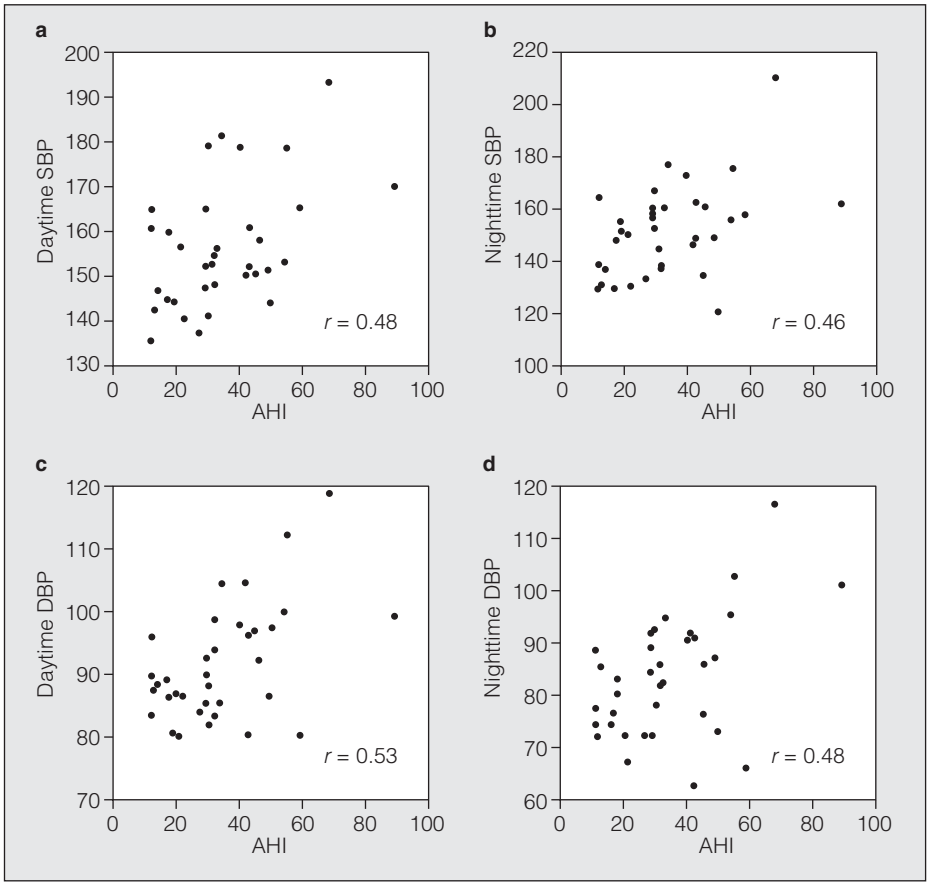

Figure. For patients with sleep apnea-hypopnea syndrome (n = 35), correlations between the apnea-hypopnea index (AHI) and (a) daytime systolic blood pressure (SBP), (b) nighttime SBP, (c) daytime diastolic blood pressure (DBP), and (d) nighttime DBP. Correlations corrected for age and sex.

between BMI and both systolic pressure (r = 0.58, P = .02) and diastolic pressure (r = 0.51, P = .04), but no correlation between AHI and systolic (r = 0.21, P = .23) or diastolic (r = 0.28, P = .32) pressure. However, in patients with SAHS (n = 35) there was a significant correlation between both BMI and systolic (r = 0.41, P = .007) and diastolic (r = 0.46, P = .009,) pressures and AHI and systolic (r = 0.47, P = .001), and diastolic (r = 0.50, P = .001) pressures, also with results adjusted for age and sex. These correlations of systolic and diastolic pressures with AHI in patients with SAHS were similar for both daytime and nighttime blood pressures (Figure). The results of the multiple regression analysis applied to patients with SAHS are summarized in Table 3. After

TABLE 2
Daytime and Nighttime Systolic and Diastolic Blood Pressure and Number of Antihypertensive Drugs Used According to Severity of SAHS*

Variable	Without SAHS (n = 14)	Mild SAHS (n = 15)	Severe SAHS (n = 20)	*P*
Age, years	66.9 (9.9)	68.1 (7.8)	69.2 (7.7)	NS
Sex, % men	35.7%	53.3%	35%	NS
Daytime SBP	148.6 (9.3)	149.4 (9.7)	161.1 (14.5)	.017†
Nighttime SBP	141.7 (10.2)	144.9 (12.7)	156.7 (19.2)	.033†
Daytime DBP	86.8 (4.2)	89.2 (8.1)	94.5 (10.7)	.035‡
Nighttime DBP	79.3 (7.4)	82.8 (9.6)	86.4 (12.9)	.23
SD for SBP	17.8 (3.8)	18.4 (2.58)	20.5 (4.1)	NS
SD for DBP	15.4 (4.4)	17.1 (3.9)	18.8 (5.2)	NS
AHI	6.3 (2.4)	19.5 (6.5)	45.3 (14.8)	.000†
BMI	33.9 (6.5)	32.9 (2.5)	36.1 (5.8)	NS
Number of drugs	3.3 (0.5)	3.5 (0.5)	3.7 (0.87)	.041‡
Number of dippers	2	3	0	NS

*Values are expressed as means (SD) unless otherwise indicated.
SAHS indicates sleep apnea-hypopnea syndrome; SBP, systolic blood pressure; DBP, diastolic blood pressure; AHI, apnea-hypopnea index; BMI, body mass index; NS, not significant.
†Significant differences between the group with severe SAHS and groups without or with mild SAHS (Bonferroni correction).
‡Significant differences between the group with severe SAHS and the group without SAHS (Bonferroni correction).

TABLE 3
Apnea-Hypopnea Index and Body Mass Index as Independent Predictors of Systolic and Diastolic Blood Pressure in Patients with Sleep Apnea-Hypopnea Syndrome (n = 35): Results of Multiple Linear Regression Analysis*

	β	SD	*P*
SBP ($r^2 = 0.28$)			
Constant	111.6	15.1	.0001
AHI	0.29	0.13	.03
BMI	0.95	0.47	.04
Age	–0.11	0.28	.69
Sex	–1.07	4.32	.81
DBP ($r^2 = 0.51$)			
Constant	55.2	7.89	.0001
AHI	0.24	0.07	.001
BMI	0.76	0.24	.004
Age	–0.09	0.16	.56
Sex	2.80	2.33	.24

*SBP indicates systolic blood pressure; AHI, apnea-hypopnea index; BMI, body mass index; DBP, diastolic blood pressure.

introducing age, sex, BMI, and AHI as independent variables into the equation, it was observed that both AHI and, to a lesser extent, BMI appeared to be the strongest independent predictors of systolic and diastolic pressures.

Discussion

Our results showed a high prevalence of sleep-disturbed breathing in patients with difficult-to-control hypertension. In patients with SAHS, AHI correlated significantly with both daytime and nighttime blood pressure, and was the predictive factor with the greatest effect on blood pressure.

There is no doubt that hypertension, especially when uncontrolled, is the most important known risk factor for vascular morbidity and mortality.[10] It is calculated that more than half of patients have above-normal blood pressure despite antihypertensive treatment.[7,8] Patients with difficult-to-control hypertension in its most severe form often remain hypertensive despite the use of several drug combinations, and in many instances the cause of this phenomenon is unknown.[23,24]

There is considerable disagreement on how to define poorly-controlled or refractory or resistant hypertension in studies dealing with the association between SAHS and poor control of blood pressure. For this reason, it is sometimes difficult to compare the results of such studies. We chose to describe blood pressure that remains high despite the use of 3 or more drugs, including a diuretic, in the context of satisfactory adherence, as difficult-to-control hypertension. We have avoided describing this clinical picture as refractory or resistant hypertension because the definition of these terms includes the use of the maximum tolerated dose of antihypertensives drugs.[11] The most frequent situation in usual clinical practice is that the physician opts for the use of a combination of various antihypertensive drugs at medium doses in an attempt to minimize the adverse effects of treatment with maximum doses without sacrificing therapeutic efficacy.

As early as 1992, Setaro and Black,[9] in an update on the subject, described SAHS as a possible cause of hypertension resistant to treatment, although recently revised international guidelines do not yet recognize it as such.[11,25] Lavie and Hofftein[6] observed that in a group of 1485 patients with SAHS, those with poorly-controlled hypertension had a significantly higher AHI than those whose blood pressure was well controlled (44 compared to 33, $P < .005$), even after results were adjusted for BMI, sex, and age. Similarly, Grote et al[13] calculated that the probability of uncontrolled hypertension increased by 2% for each unit increase in AHI. In a small study of patients with truly drug-resistant hypertension, Logan et al[12] found an 83% prevalence of SAHS. The results of the present study point in the same direction. Thus, in our study the prevalence of SAHS was 71% and SAHS was severe in 41% of patients. As there is to date no evidence that hypertension can give rise to an increased prevalence of SAHS, it can be hypothesized that an excessive number of respiratory disturbances during sleep may act as an independent risk factor for difficult-to-control hypertension. In patients with SAHS, a close association was observed between both nighttime and daytime systolic and diastolic pressures and severity of the disease, independent of other confounding variables such as age or sex. In such patients, AHI seemed to be the most important variable predictive of hypertension, independent of BMI. Greater severity of SAHS was indicative of more difficult-to-control hypertension in view of the number of antihypertensive drugs used. A global analysis of our results seems to indicate that variables affecting uncontrolled hypertension behave differently in patients with and without SAHS. Thus, in patients with a pathological AHI (≥ 10 in our study), an excessive number of respiratory disturbances during sleep, not obesity, was the factor most closely associated with difficulty in controlling hypertension, although in all patients (with or without SAHS), there was still a significant correlation with BMI, a well-known and important risk factor for both hypertension and difficulty in controlling it. Although when the 2 variables were analyzed separately AHI showed a somewhat greater explanatory value for blood pressure values in patients with SAHS than did BMI, when analyzed together in a single multivariate model both variables were able to account for only 25% of the variance in systolic pressure and slightly more than 50% in diastolic pressure. This could be explained by the many factors—some of them not measured in the present study—that can significantly modify blood pressure and that might enter into the percentage of variance not explained by AHI or BMI. In patients with SAHS, it is likely that control of obesity or dietary measures are not sufficient for optimal control of blood pressure and that a reduction in the number of respiratory disturbances during sleep is also required.

It is noteworthy that in our study we found that very few patients were dippers. This could be explained by the high prevalence of SAHS in our sample or by the poor control of blood pressure (including nighttime blood pressure) in these severe forms of hypertension, even in patients without SAHS. Of the 5 dippers, 3 were in the group of patients with mild SAHS. This phenomenon is of considerable importance, as it is well known that the presence of SAHS can change the status of a hypertensive patient from dipper to nondipper[26,27] and that nondipping status is associated with a greater number of cardiovascular events and complications,[28,29] as well as a greater probability of target-organ damage due to constantly elevated blood pressure.[30]

The association observed in our series between SAHS and difficult-to-control hypertension presented several peculiarities. Some studies have shown that the correlation between SAHS and hypertension, even in difficult-to-control forms, is usually greater in young patients and in nonobese patients,[1,13,31] although such a correlation has not been confirmed in all studies.[6] In our study, the association between an excessive number of respiratory disturbances during sleep and hypertension did not vary with age or sex, and correlation between AHI and hypertension was high for both daytime and nighttime systolic and diastolic pressures. Unlike Logan et al,[12] who found AHI to be associated mainly fundamentally with systolic pressure, we found the correlation to be somewhat higher for diastolic pressure. Finally, our patients, selected from an outpatient hypertension clinic, did not in general present noticeable signs and symptoms of SAHS, as, while more than 70% declared themselves to be habitual snorers (probably due to elevated BMI), only 10% reported observed apneas and mean Epworth sleepiness scale score was only slightly higher than 6.

We believe that the main limitation of the present study lies in the use of the AutoSet device to diagnose SAHS instead of polysomnography, which is the gold standard. However, we observed a high prevalence of sleep-disturbed breathing and the mean AHI was high, circumstances that increase the diagnostic usefulness of the AutoSet device with respect to polysomnography[21,22]; any possible error is therefore probably slight.

In view of the considerable impact of both SAHS and difficult-to-control hypertension on morbidity and mortality as well as the considerable benefit of lowering blood pressure by even only a few mm Hg in patients with difficult-to-control hypertension, we believe further studies are needed to show a possible causal relation between the 2 entities and to analyze the effect of continuous positive airway pressure treatment[32] on blood pressure in such patients.

In conclusion, we found a high prevalence of sleep-disturbed breathing in patients with difficult-to-control hypertension. In those patients with SAHS, AHI was the main predictor of blood pressure and showed a positive correlation with both daytime and nighttime mean systolic and diastolic pressures.

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